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Microwave-assisted synthesis of 2,5-disubstituted pyrimidine derivatives *via* Buchwald-Hartwig amination

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Graphical Abstract

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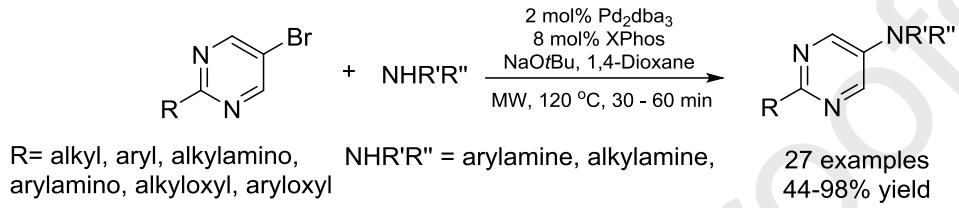

R= alkyl, aryl, alkylamino, arylamino, alkyloxyl, aryloxyl

NHR'R" = arylamine, alkylamine,

27 examples
44-98% yield

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ABSTRACT

Various 2,5-disubstituted pyrimidine derivatives were synthesized under microwave irradiation *via* Buchwald-Hartwig amination. This concise approach provides interesting scaffolds in good to high yields and with large functional group compatibility. These novel chemical entities could be used as building blocks in drug design.

1. Introduction

Pyrimidines are one of two biologically important families of nitrogenous bases, which include cytosine and thymine in DNA and cytosine and uracil in RNA. Substituted pyrimidines have been found in a large variety of biologically active natural and synthetic products [1–3], and are also used as building blocks for a number of commercial drugs including the tyrosine kinase inhibitor Gleevec® [4], the HMG-CoA reductase inhibitor Crestor® [5], the 5-HT1A receptor agonist Buspirone [6], and the dihydrofolate reductase inhibitor Trimethoprim [7]. Several pyrimidine derivatives possess medicinal properties such as anti-cancer [1], anti-bacterial [8], antiviral [9], anti-inflammatory [10], anti-arthritic [11], anti-diabetic [12], antihypertensive [13], anti-analgesic [14], antipyretic [15] and antiplatelet activities [16]. Among them, 2,5-disubstituted pyrimidine-containing small molecules have also attracted significant attention due to their interesting pharmacological activities (Fig. 1) [5, 17–21].

Our interest in the development of 2,5-disubstituted pyrimidine scaffolds prompted us to develop a scalable method for their synthesis. Despite the simple structural features of these scaffolds, our synthetic efforts encountered major setbacks, due to low reactivity at the 5 position of the pyrimidine ring. A review of the literature for the Pd-catalyzed amination of aryl halides and heteroaryl halides provided few successful examples of C-N cross-couplings with 2-substituted-5-bromopyrimidines, which have been less explored and usually gave modest yields [22].

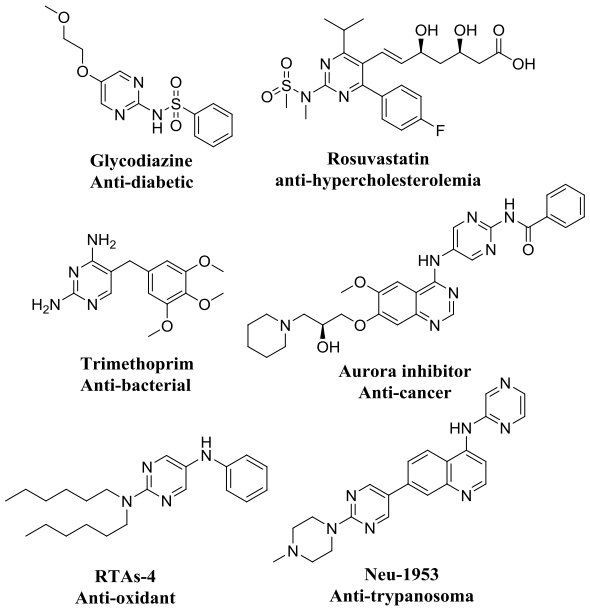

Figure 1. Selected bioactive compounds containing 2,5-disubstituted pyrimidine frameworks.

In recent decades, palladium-catalyzed C-N coupling under microwave (MW) irradiation has become a powerful technique for the synthesis of various heterocyclic compounds [23, 24]. Herein, we report optimized conditions, substrate scope, and

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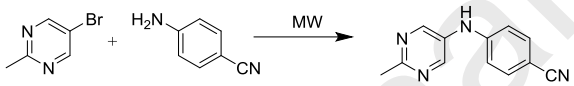
applications of the Pd-catalyzed C-N cross-coupling of 2-substituted-5-bromo-pyrimidines under MW irradiation, which provided facile access to these compounds with good to high yields.

2. Results and Discussion

Initially, the palladium-catalyzed C-N cross-coupling reaction of commercially available 5-bromo-2-methylpyrimidine **1a** with 4-aminobenzonitrile was selected as a model reaction to optimize the MW conditions. Upon performing the reaction in a sealed tube, we noted that the optimal yields were achieved when the reaction was performed at 120 °C. The reaction time was adjusted to 1 h in order to obtain maximum conversion without causing decomposition of the products. Then, we examined the reaction in the presence of different palladium catalysts using XPhos and Cs_2CO_3 in 1,4-dioxane (Table 1, entries 1–3). We were delighted to find that the reaction successfully proceeded with Pd_2dba_3 as the Pd source and furnished the desired cross-coupling product **2a** in 65% yield (Table 1, entry 3). We subsequently investigated the effect of various ligands and bases on the yield; however, the results were not satisfactory and SPhos, XantPhos, BINAP and $P(tBu)_3$ all gave lower yields (Table 1, entries 4–7). Sodium *tert*-butoxide was superior to all of the other bases tested (Table 1, entries 7–9). Strong bases such as NaOtBu promoted the reaction affording product **2a** in 92% yield, whereas weak bases such as K_3PO_4 and Cs_2CO_3 were less favorable for the reaction yield. In addition, we used different organic solvents (Table 1, entries 9, 11–12) and identified 1,4-dioxane as the most effective solvent which gave a better yield (Table 1, entry 9) in comparison with toluene and DMF (Table 1, entries 11 and 12). Finally, the reaction with Pd/XPhos (1:1) resulted in a reduced yield (Table 1, entry 10).

Table 1
Optimization of the C-N-coupling conditions.



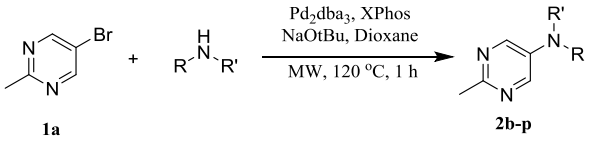
1a **2a**

Entry	Catalyst	Ligand	Base	Solvent	Yield **2a** [%][a,b]
1	$Pd(PPh_3)_4$	XPhos	Cs_2CO_3	1,4-Dioxane	12
2	$Pd(OAc)_2$	XPhos	Cs_2CO_3	1,4-Dioxane	29
3	Pd_2dba_3	XPhos	Cs_2CO_3	1,4-Dioxane	65
4	Pd_2dba_3	SPhos	Cs_2CO_3	1,4-Dioxane	26
5	Pd_2dba_3	XantPhos	Cs_2CO_3	1,4-Dioxane	14
6	Pd_2dba_3	BINAP	Cs_2CO_3	1,4-Dioxane	9
7	Pd_2dba_3	$P(tBu)_3$	Cs_2CO_3	1,4-Dioxane	15
8	Pd_2dba_3	XPhos	K_3PO_4	1,4-Dioxane	45
9	Pd_2dba_3	XPhos	NaOtBu	1,4-Dioxane	92
10	Pd_2dba_3	XPhos[c]	NaOtBu	1,4-Dioxane	76
11	Pd_2dba_3	XPhos	NaOtBu	Toluene	57
12	Pd_2dba_3	XPhos	NaOtBu	DMF	trace

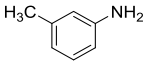
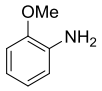
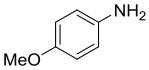
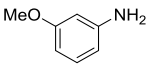
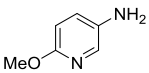
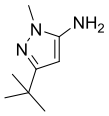
[a] Reagents and conditions: **1a** (0.3 mmol), 4-aminobenzonitrile (0.33 mmol), Pd-catalyst (2 mol%), L/Pd = 2/1, base (0.42 mmol), solvent (2 mL), 1 h, 120 °C.
[b] Isolated yield.
[c] L/Pd = 1/1

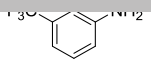
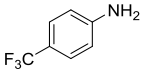
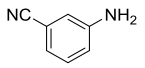
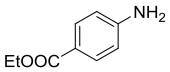
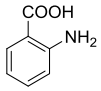
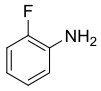
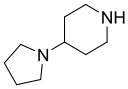
With the optimized conditions in hand (Table 1, entry 9), we explored the substrate scope of the amine to assess the generality of the reaction (Table 2). Firstly, electron-donating groups (EDGs) on the aromatic ring of different arylamines, such as *m*-methyl (Table 2, entry 1), *o*-methoxy (Table 2, entry 2), *p*-methoxy (Table 2, entry 3) and *m*-methoxy groups (Table 2, entry 4) provided the desired products **2b–e** in high yields. Heteroarylamines with EDGs such as methoxy (Table 2, entry 5) and alkyl groups (Table 2, entry 6) reacted with 5-bromo-2-methylpyrimidine **1a**, affording the corresponding products **2f–g** in 64−84% yield. Aniline reacted well with 2-methyl-5-bromopyrimidine (Table 2, entry 7) giving the corresponding product **2h** in 82% yield. On the other hand, the arylamines bearing strong electron withdrawing groups (EWGs) including *m*-CF_3 (Table 2, entry 8), *p*-CF_3 (Table 2, entry 9) and *m*-CN (Table 2, entry 10) were tolerated, leading to the corresponding products **2i–k** in 59−82% yield. In addition, the arylamine bearing *o*-CO_2H also reacted well with **1a** affording the desired product **2m** in 67% yield (Table 2, entry 12). The reaction of 4-aminobenzoate ester with **1a** gave a mixture of the desired product and its hydrolyzed compound with a poor yield. When the MW irradiation time was shortened to 30 minutes, we were pleased to obtain the product in 55% yield. In particular, arylamines bearing an inductive electron-withdrawing *o*-F group (Table 2, entry 13) gave the desired product in a nearly quantitative yield. Finally, the substrate scope of the amine was also extended to several secondary amines such as morpholine (Table 2, entry 14) and a piperidine derivative (Table 2, entry 15), providing the desired coupling products in good to excellent yields.

Table 2
Preparation of 2-methyl-5-substituted pyrimidines **2b–p**.



1a **2b-p**

Entry	RR'NH	Product	Yield [%][a,b]
1		**2b**	85
2		**2c**	86
3		**2d**	81
4		**2e**	83
5		**2f**	64
6		**2g**	84
7		**2h**	82

8		**2i**	82
9		**2j**	59
10		**2k**	69
11		**2l**	55[c]
12[c]		**2m**	67
13		**2n**	98
14		**2o**	93
15		**2p**	77

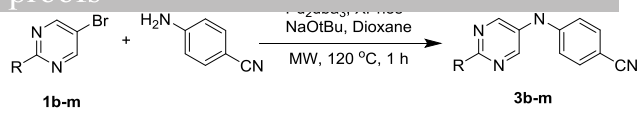
[a] Reagents and conditions: **1a** (0.3 mmol), RR'NH (0.33 mmol), Pd_2dba_3 (2 mol%), XPhos (8 mol %), NaO*t*Bu (0.42 mmol), 1,4-dioxane (2 mL), 1 h, 120 ºC;

[b] Isolated yield;

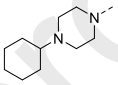
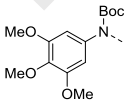
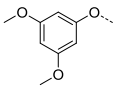
[c] Reaction time 30 min.

Next, we extended the Pd-catalyzed amination to 5-bromopyrimidines bearing a variety of substituents at the 2-position (**1b**–**m**, Table 3). These substrates reacted well with 4-aminobenzonitrile and provided the corresponding products in rather good to excellent yields (**3b**–**m,** Table 3). Notably, the reaction of 5-bromopyrimidine with 4-aminobenzonitrile proceeded well giving **3b** in 84% yield, which is better than that obtained using Okada's method [25]. 5-Bromopyrimidine substituted by phenyl or *p*-methoxyphenyl groups (Table 3, entries 2–3) afforded the corresponding products in high yields. In addition, 5-bromopyrimidines substituted by a secondary amino group (alkyl, cyclic and phenylalkyl amino) provided the desired products in 81–99% yield (Table 3, entries 5–8). In contrast, a primary amino group at the 2-position of 5-bromopyrimidine resulted in a lower yield. Indeed, 2-methylamino-5-bromopyrimidine gave the corresponding product in 44% yield (Table 3, entry 4), while 2-phenylamino-5-bromopyrimidine led to low conversion (data not shown). Thus, the arylamino group at the 2-position of 5-bromopyrimidine was protected with Boc and then reacted with 4-aminobenzonitrile, giving the product **3j** in 62% yield. This was subsequently treated with TFA leading to the deprotected product **3j'** (Table 3, entry 9). On the other hand, 5-bromopyrimidine substituted by alkyloxy, phenyloxy and aryloxy groups were also suitable for this reaction, with the target compounds **3k–m** formed in 51–65% yield (Table 3, entries 10–12).

Table 3.
Preparation of various 2,5-disubstituted pyrimidines **3b-m**.



1b-m **3b-m**

Entry	R	Product	Yield [%][a,b,c]
1	H	**3b**	84
2		**3c**	86
3		**3d**	90
4	CH_3NH--	**3e**	44
5	$(CH_3)_2N$--	**3f**	81
6		**3g**	99
7		**3h**	89
8		**3i**	93
9		**3j (3j')**[b]	62 (52)
10	CH_3O--	**3k**	65
11		**3l**	55
12		**3m**	51

[a] Reagents and conditions: **1b–m** (0.3 mmol), 4-aminobenzonitrile (0.33 mmol), Pd_2dba_3 (2 mol%), XPhos (8 mol %), NaO*t*Bu (0.42 mmol), 1,4-dioxane (2 mL), 1 h, 120 ºC;

[b] Isolated yield;

[c] **3j** was treated with TFA to give **3j'**, yield in parentheses was calculated for **3j'** over two steps. **3j'**, 4-((2-((3,4,5-trimethoxyphenyl)amino) pyrimidin-5-yl)amino)benzonitrile.

3. Conclusion

A concise approach was developed for the synthesis of 2,5-disubstituted pyrimidine derivatives *via* palladium catalyzed C-N coupling under microwave irradiation in good to high yields. This coupling reaction has a wide range of substrate scope and good functional group tolerance, leading to versatile building blocks for assembling interesting heterocyclic molecules. We believe that this study would supply new chemical entities (*NCEs*) for drug discovery.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (experimental and spectral data for compounds) to this article can be found online at http://doi.org/.....

References

[1] Prachayasittikul S, Pingaew R, Worachartcheewan A, Sinthupoom N, Prachayasittikul V, Ruchirawat S, Prachayasittikul V. *Mini. Rev. Med. Chem*. **2017**; 17: 869–901.
[2] Radi M, Schenone S, Botta M. *Org Biomol. Chem*. **2009**; 7: 2841–2847.
[3] Kim J, Jung J, Koo J, Cho W, Lee WS, Kim C, Park W, Park SB. *Nat. Commun*. **2016**; 7: 13196
[4] Campiotti L, Suter MB, Guasti L, Piazza R, Gambacorti-Passerini C, Grandi AM, Squizzato A. *Eur. J. Cancer*. **2017**; 77: 48–56.
[5] Husain I, Khan S, Khan S, Madaan T, Kumar S, Najmi AK. *Clin. Exp. Pharmacol. P*. **2019**; 46: 283–291.
[6] Mula M. *Expert. Opin. Pharmacother*. **2018**; 19: 1867–1874.
[7] Palomino JC, Martin A. *Future Microbiol*. **2016**; 11: 539–547.
[8] Abdellatif K R A, Bakr R B. *Bioorg. Chem*. **2018**; 78: 341–357.
[9] Balzarini J, McGuigan C. *J. Antimicrob. Chemother*. **2002**; 50: 5–9.
[10] Falcão E P da S, de Melo S J, Srivastava R M, Catanho M T J de A, Do Nascimento S C. *Eur. J. Med. Chem*. **2006**; 41: 276–282.
[11] Vega S, Alonso J, Diaz J A, Junquera F. *J. Heterocyclic Chem*. **1990**; 27: 269–273.
[12] Fang Y, Xu J, Li Z, Yang Z, Xiong L, Jin Y, Wang Q, Xie S, Zhu W, Chang S. *Bioorg. Med. Chem*. **2018**; 26: 4080–4087.
[13] Bukhari S N A, Butt A M, Amjad M W B, Ahmad W, Shah V H, Trivedi A R. *Pak. J. Biol. Sci*. **2013**; 16: 1368–1372.
[14] Sabiniarz A, Sladowska H, Filipek B, Sapa J, Dudek M, Slepokura K. *Acta. Pol. Pharm*. **2007**; 64: 369–376.
[15] Nam T, Nara S J, Zagol-Ikapitte I, Cooper T, Valgimigli L, Oates J A, Porter N A, Boutaud O, Pratt D A. *Org. Biomol. Chem*. **2009**; 7: 5103–5112.
[16] Bruno O, Brullo C, Schenone S, Bondavalli F, Ranise A, Tognolini M, Ballabeni V, Barocelli E. *Bioorg. Med. Chem*. **2004**; 12: 553–561.
[17] Ben Amara H, Kacem A, Gaigi I, Dakhli S, Ben Mami F, Achour A. *Tunis Med*. **2008**; 86: 957–959.
[18] Duployez C, Robert J, Vachée A. *Med. Mal. Infect*. **2018**; 48: 410–413.
[19] Heron N M, Anderson M, Blowers D P, Breed J, Eden J M, Green S, Hill G B, Johnson T, Jung F H, McMiken H H J, Mortlock A A, Pannifer A D, Pauptit R A, Pink J, Roberts N J, Rowsell S. *Bioorg. Med. Chem. Lett*. 2006; 16: 1320–1323.
[20] Mehta N, Ferrins L, Leed S E, Sciotti R J, Pollastri M P. *ACS. Infect. Dis*. **2018**; 4: 577–591.
[21] Shah R, Haidasz E A, Valgimigli L, Pratt D A. *J. Am. Chem. Soc*. **2015**; 137: 2440–2443.
[22] Lach F, Pasquet M-J, Chabanne M. *Tetrahedron Lett*. **2011**; 52: 1882–1887.
[23] Loupy A, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2002**
[24] Dao P, Garbay C, Chen H. *Tetrahedron*. **2012**; 68: 3856–3860.
[25] Okada M, Yoden T, Kawaminami E, Shimada Y, Kudoh M, Isomura Y. *Chem. Pharm. Bull*. **1997**; 45: 482 – 486.

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- A practical procedure was developed to prepare 2,5-disubstituted pyrimidines.
- The method has a wide range of substrate scope and good functional group tolerance.
- The reaction occurred generally in good to excellent yields.
- The products of this reaction could be used as the building blocks in drug design.