Tetrahedron Letters 51 (2010) 3259–3262

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Convenient preparation of 4-aryl-2-(heteroarylamino)pyrimidines and 4-anilino-2-(heteroarylamino)pyrimidines

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ARTICLE INFO

Article history:
Received 29 January 2010
Revised 13 April 2010
Accepted 14 April 2010
Available online 18 April 2010

Dedicated to Asa John Livingston II (1930–2003)—teacher, mentor, inspiration and friend.

ABSTRACT

4-Aryl-2-anilinopyrimidines and 2,4-dianilinopyrimidines are privileged structures found in many drug-like molecules and biologically active compounds. A method for the quick assembly of novel 4-aryl- and 4-anilino-2-(heteroarylamino)pyrimidines via Buchwald–Hartwig N-arylations at elevated temperatures under sealed tube conditions is reported. This method's convenience and practicality is demonstrated through the preparation of several novel non-nucleoside reverse transcriptase inhibitor (NNRTI) analogues.

1. Introduction

4-Aryl-2-anilinopyrimidines **1** and 2,4-dianilinopyrimidines **2** (i.e., DAPYs)[1] represent privileged structures[2] found in an ever increasing number of drug-like molecules including VEGF and CDK inhibitors,[3] reverse transcriptase inhibitors (e.g., dapivirine **3**),[4] and tyrosine kinase inhibitors (e.g., Gleevec® **4**)[5] (Fig. 1). Traditionally, 2,4-diamino pyrimidines have been prepared from commercially available 2,4-dichloropyrimidine or 4-chloro-2-(methylsufinyl)pyrimidine by either aromatic nucleophilic substitution (S_NAr)[6] or by palladium-catalyzed arylation/amination.[7] Similarly, 2-amino-4-arylpyrimidines have been accessible via S_NAr or palladium-mediated amination of readily available 4-aryl-2-chloropyrimdines.[8] However, chloride displacement in 4-amino- and 4-aryl-2-chloropyrimidines generally requires forcing conditions which limits this chemistry to nucleophilic alkylamines and anilines.[3a]

As a result, there are few examples of 4-aryl- or 4-anilino- 2-(heteroarylamino)pyrimidines reported in the literature.[7a,b,9]

Our own research has prompted us to develop a synthetically expedient method to generate novel 4-aryl- and 4-anilino-2-(heteroarylamino)pyrimidines **5** by functionalizing readily available 4-substituted-2-chloropyrimidines with a diverse set of heteroarylamines (Fig. 2).

2. Results and discussion

Our initial and unsuccessful attempts at preparing analogues of **5** involved simple S_NAr substitution of 4-anilino-2-chloropyrimidines with heteroarylamines under both thermal[9f] and microwave[9b,10] conditions. We also explored palladium-catalyzed N-arylations[7a,9c–e] of heteroarylamines with 4-substituted-2-chloropyrimidines under standard Buchwald–Hartwig conditions (refluxing dioxane, 12–18 h) which resulted in low conversions.

Next we examined conditions used to prepare 2-aminopyrimidines via Buchwald–Hartwig N-arylations under microwave conditions.[7b,9a] Examples in the literature utilized simple 2-chloropyrimidines and relatively nucleophilic amines, in contrast to our structurally more complex 4-substituted-2-chloropyrimidines and non-nucleophilic heteroarylamines. With our substrates **6a–d**, previously reported conditions routinely provided low

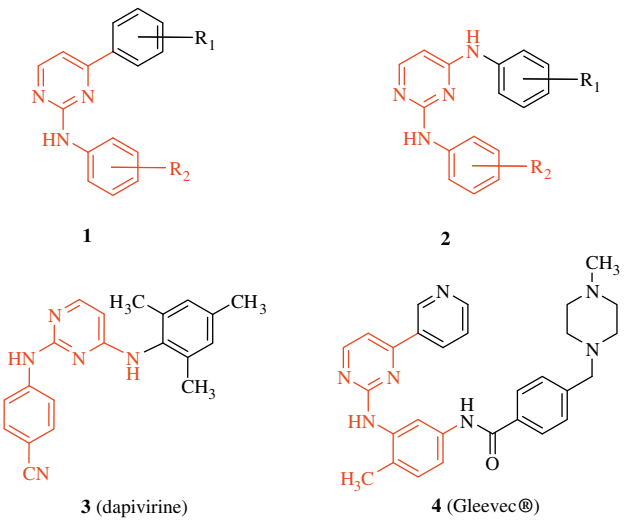

Figure 1. 4-Aryl-2-anilinopyrimidines **1** and 2,4-dianilinopyrimidines **2**.

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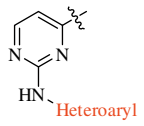
doi:10.1016/j.tetlet.2010.04.062



Heteroaryl = pyridine, pyridazine, pyrimidine, pyrazine, oxazole, isoxazole, pyrazole, imidazole, triazole, thiazole, etc.

5

Figure 2. Novel 4-substituted-2-(heteroarylamino) pyrimidines **2**.

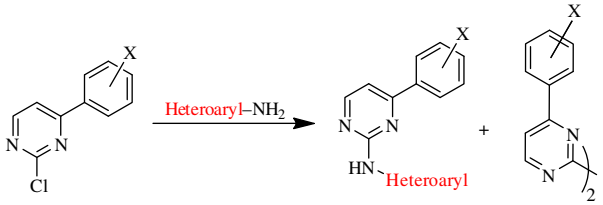
conversion (30–50%) by LC–MS analysis (UV @ 254 nm) when exposed to microwave irradiation at 120 °C. Additionally, increasing catalyst loading yielded greater amounts of unwanted homodimeric byproduct **13** (Table 1).

Based upon these initial results, we decided to focus our attention on Buchwald–Hartwig N-arylations at elevated temperature and pressure under sealed tube conditions.[11,12] Herein we describe our protocol for the convenient preparation of novel 4-aryl-2-(heteroarylamino)pyrimidines **7–12** (Table 1) and 4-anilino-2-(heteroarylamino)-pyrimidines **15–19** (Table 2).[13]

In preparing substrates **6a–d** for the N-arylation chemistry, we decided to include functionality that would allow us to probe the electronic effects imparted by the substituent located at the pyrimidine 4-position. To that end we prepared compounds that contained 4-aryl groups bearing electron-donating ($-OCH_3$) and electron-withdrawing substituents ($-CO_2CH_3$, $-NO_2$). Table 1 summarizes our efforts to prepare 4-aryl-2-(heteroarylamino)-pyrimidines **7–12**. For example, 2-aminopyrazine and 2-chloropyrimidine **6b** (Table 1, entry 3) were heated in the presence of $Pd_2(dba)_3$ and Xantphos[14] at 160 °C in a sealed tube for 6 h affording **9b** in 38% yield. 4-Aryl groups bearing electron-rich substituents tended to give slightly higher yields of coupling product than those bearing electron-withdrawing groups (Table 1). This trend is in general agreement with the observations of Buchwald and Hartwig.[15] In comparing sealed tube reactions with microwave reactions (Table 1, entries 1–3), we observed that sealed tube conditions afforded higher conversion to product as observed by LC–MS analysis, higher isolated yields and lower yields of homocoupling product **13**. Surprisingly, not all amines examined afforded product under either reaction conditions (e.g., 3-methylisoxazole-5-amine).

Control experiments were performed to confirm that the mechanism of the reaction was palladium-mediated N-arylations and not simply thermal substitutions. When 2-aminopyrazine, a relatively

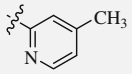
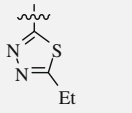
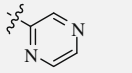
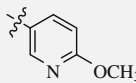
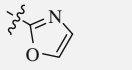
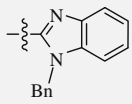
Table 1
N-Arylation of 4-aryl-2-chloropyrimidines **6a–d**



6a–d **7–12** **13**

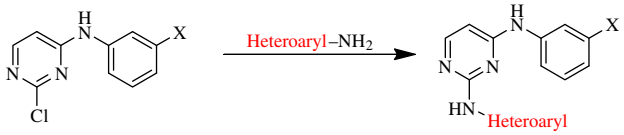
a: X = H
b: X = *p*-OCH_3
c: X = *p*-CO_2CH_3
d: X = *m*-NO_2

Sealed Tube (Δ): 1 equiv 2-chloropyrimidine; 1.2 equiv heteroarylamine; 2 equiv K_3PO_4; 0.1 equiv $Pd_2(dba)_3$; 0.3 equiv Xantphos; 160 °C, 6 h; sealed tube.
Microwave (μW): 1 equiv 2-chloropyrimidine; 1.5–2.0 equiv heteroarylamine; 2 equiv K_3PO_4; 0.1 equiv $Pd_2(dba)_3$; 0.3 equiv Xantphos; 1 h at T < 120 °C, 300 W.

Entry	Heteroaryl	Product	Δ (Yld %)[a]	μW (Yld %)[a]
1		**7a**	62%	42%
		7b	41%	33%[b]
		7c	30%	
		7d	Trace	
2		**8a**	46%	21%
		8b	48%	
		8c	35%	
		8d	Trace	
3		**9a**	45%	14%
		9b	38%	
		9c	Trace	
		9d	NR	
4		**10a**	30%	
		10b	22%	
		10c	Trace	
		10d	24%	
5		**11a**	45%	
		11b	52%	
		11c	Trace	
		11d	Trace	
6		**12a**	47%	
		12b	25%	
		12c	52%	
		12d	39%	

[a] Isolated yields.
[b] Used rac-BINAP versus Xantphos.

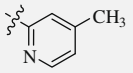
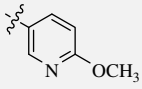
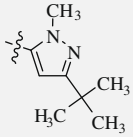
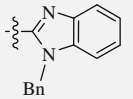
Table 2
N-Arylation of (substituted) 2-chloropyrimidines **14a–d**



14a–c **15–19**

a: X = H
b: X = F
c: X = NO_2

Sealed Tube (Δ): 1 equiv 2-chloropyrimidine; 1.2 equiv heteroarylamine; 2 equiv K_3PO_4; 0.1equiv $Pd_2(dba)_3$; 0.3 equiv Xantphos; 160°C, 6 h; sealed tube.
Microwave (μW): 1 equiv 2-chloropyrimidine; 1.5–2.0 equiv heteroarylamine; 2 equiv K_3PO_4; 0.1 equiv $Pd_2(dba)_3$; 0.3 equiv Xantphos; 1 h at T < 120 °C, 300 W.

Entry	Heteroaryl	Product	Δ (Yld %)[a]	μW (Yld %)[a]
1		**15a**	75%	
		15b	81%	65%
		15c	51%	57%
2		**16a**	Trace	
		16b	Trace	
		16c	Trace	72%
3		**17a**	63%	
		17b	40%	
		17c	45%	57%
4		**18a**	45%	
		18b	49%	37%
		18c	51%	
5		**19a**	41%	
		19b	27%	
		19c	54%	41%

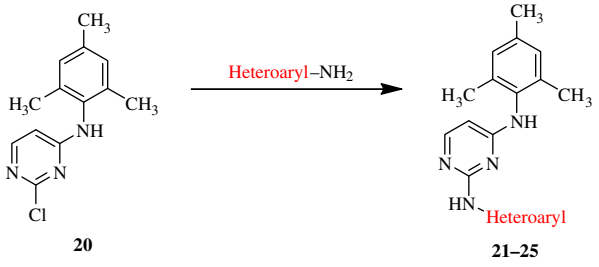
[a] Isolated yields.

nucleophilic amine,[16] was heated with 2-chloropyrimidine **6b** (Table 1, entry 3) under sealed tube reaction conditions, omitting Pd_2dba_3 yielded approximately 10% conversion to product **9b** as detected by LC–MS after 6 h at 160 °C.[17] Furthermore, when 2-aminopyrazine was heated with 2-chloropyrimidine **6b** and cesium carbonate in *n*-butanol at 160 °C for 6 h, no reaction was observed. These results indicate that the primary mode of reactivity for the formation of **9b** is via palladium-mediated N-arylation chemistry and that with our substrates **6a–d**, S_NAr plays a minor mechanistic role in overall product yields. Similar observations and mechanistic conclusions under microwave conditions have been reported.[7b]

We also prepared related substrates 4-anilino-2-chloropyrimidines **14a–c** and examined the palladium-mediated N-arylation chemistry with heteroarylamines to afford 4-anilino-2-(heteroarylamino)pyrimidines **15–19** (Table 2).

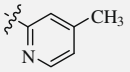
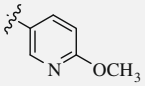
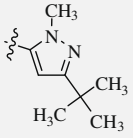
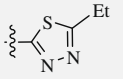
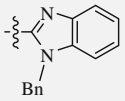
To our surprise, during the N-arylation reactions of 4-anilino-2-chloropyrimidines **14a–c** (Table 2), homodimeric byproduct formation was not observed by LC–MS analysis. Furthermore, with the noteworthy exception of **16c** (Table 2, entry 2),[18] we observed little significant advantage in terms of yield for either the thermal or microwave conditions. As was the case in Table 1, not all heteroarylamines underwent N-arylation with substrates **14a–c** under thermal conditions (e.g., 2-aminothiazole-4-carboxylic acid). Additionally, the electronics of the *para*-position substituent on **14a–c** had minimal impact on reaction yields (e.g., Table 2, entries 3 and 4). We surmise that the dominant electronic effect of the 4-anilino moiety is only marginally modulated by the presence of either electron-donating or electron-withdrawing groups on the aniline ring.

Table 3
Preparation of novel dapivirine analogues (**21–25**)



20 **21–25**

Sealed Tube: 1 equiv 2-chloropyrimidine; 1.2 equiv heteroarylamine; 2 equiv K_3PO_4; 0.1 equiv $Pd_2(dba)_3$; 0.3 equiv Xantphos; 160 °C, 6 h; sealed tube.

Entry	Heteroaryl	Product	Yield[a] (%)
1		**21**	26%
2		**22**[20]	60%
3		**23**	42%
4		**24**	Trace
5		**25**	43%

[a] Isolated yields.

As such, overall coupling yields are not materially affected by the nature of the aniline substituent in **14a–c**.

Although it is difficult to rationalize the excellent yields obtained for **16c** (Table 2, entry 2) under microwave conditions and the absence of homodimeric byproduct formation for substrates **14a–c**, our results in Tables 1 and 2 demonstrate N-arylations at elevated temperatures under sealed tube conditions are a general and practical set of conditions for the N-arylation of both 4-aryl- and 4-anilino-2-chloropyrimidines.

To illustrate the utility of our method, we prepared several analogues of the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine (**3**). Dapivirine is currently in Phase II clinical trials for the prevention of HIV infections and is expected to enter Phase III clinical trials in late 2009.[19] Novel dapivirine analogues **21–25** containing various 2-(heteroarylamines) can be prepared in two steps from the commercially available 2,4-dichloropyrimidine via readily accessible 2-chloro-*N*-mesitylpyrimidin-4-amine (**20**)[20] (Table 3).

In conclusion, we have demonstrated that non-nucleophilic heteroaryl amines can undergo Buchwald–Hartwig N-arylation with 4-aryl and 4-anilino-2-chloropyrimidines at elevated temperatures under sealed tube conditions to afford novel 4-aryl-2-(heteroarylamino)pyrimidines and 4-anilino-2-(heteroarylamino)pyrimidines. This method allows for the rapid, convenient construction, and diversification of 4-substituted-2-chloropyrimidines which is an important privileged structure found in many drug-like molecules. This method provides reproducible results in modest to good yields, affords generally higher conversion to product with 4-anilino-2-chloropyrimidines compared to previously reported Buchwald–Hartwig N-arylations under microwave conditions, and is easily amendable to parallel synthesis. The advantages and utility of this method were illustrated by the synthesis of **21–25** which are novel analogues of the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine (**3**).

Acknowledgments

The authors wish to acknowledge and thank AMRI for their financial support, Dr. Jolicia Gauuan for her encouragement and helpful discussions during the early stages of this work, and Mrs. Meagan Slater for her critical review of this Letter.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.062.

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11. For examples of 2-heteroarylaminopyrimidines prepared via alternate approaches to direct substitution of heteroarylamines onto 2-chloropyrimidines, see: (a) Schulte, J. P., II; Tweedie, S. R. *Synlett* **2007**, 2331–2336; (b) Guillaumet, G.; Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Lebret, B. *J. Org. Chem.* **2004**, *69*, 7809–7815; (c) Scott, D.; Wang, H., Wang, T. *Preparation of pyrazolylamino substituted pyrimidines as anticancer agents.* WO Patent 2006117560, November 11, 2006.
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14. BINAP has been reported to give better yields than XantPhos under Buchwald–Hartwig conditions with aminopyridines and aminopyrazines. For further discussion of catalyst selection, see Refs.[7a,7b,9e]
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16. Aminopyridines and aminopyrazines have been reported to be sufficiently nucleophilic to displace 2-chloropyrimdines under S_NAr conditions; see Ref. 9f.
17. Reactions were analyzed by LC–MS and complete conversion was generally observed after 4–6 h.
18. The surprising result reported for the formation of **16c** (Table 2, entry 2) under microwave conditions is reproducible.
19. For information on the status of Dapivirine clinical trials, see: (a) International Partnerships for Microbicides (IPM). http://www.ipm-microbicides.org (accessed October 2009); (b) U.S. National Institutes of Health. http://clinicaltrials.gov (accessed October 2009).
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