ORGANIC LETTERS

2005
Vol. 7, No. 19
4113−4116

Expedient Parallel Synthesis of 2-Amino-4-heteroarylpyrimidines

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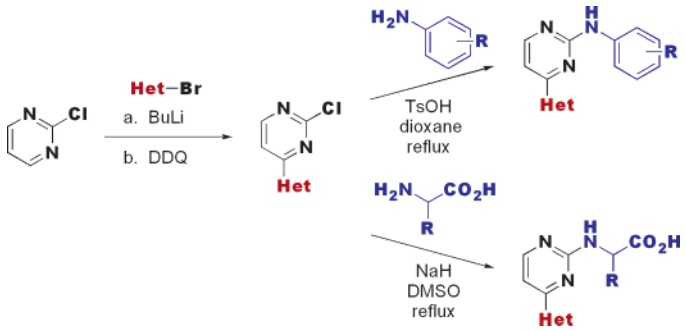
Received June 8, 2005

ABSTRACT



An expedient synthesis of diverse 2-amino-4-heteroarylpyrimidines via a 2-chloropyrimidine intermediate is described. A series of potentially biologically active analogues have been synthesized in two parallel steps to afford focused arrays.

In our efforts to pursue leads generated via HTS campaigns, we have focused on developing expedient parallel syntheses. Following one such HTS campaign, we needed to develop a straightforward synthesis to both 2-anilino-4-heteroarylpyrimidines **1** and 2-amino acid-4-heteroaryl pyrimidines **2**.[1]

Traditional approaches (Figure 1) suggested synthesis via condensation of ketone **3** with either guanidine **4** or **5**.[2] Unfortunately, formation of arylguanidine **4** and subsequent cyclization is nontrivial as specific conditions are required for guanidine formation with individual anilines—seemingly counterproductive to developing an expedient parallel synthesis.[3] Synthesis of **2** via amino acid guanidine formation and subsequent cyclization is also nontrivial, affording complex reaction mixtures.

To develop an expedient parallel synthesis that explored both the pyrimidine 2-amino- and 4-heterocycle substituent we envisioned forming these two key bonds sequentially utilizing all commercially available starting materials (Figure 2). Key to our envisioned parallel synthesis was the initial selective formation of the 4-pyrimidine−heteroaromatic bond. Subsequently, we needed to develop methods for

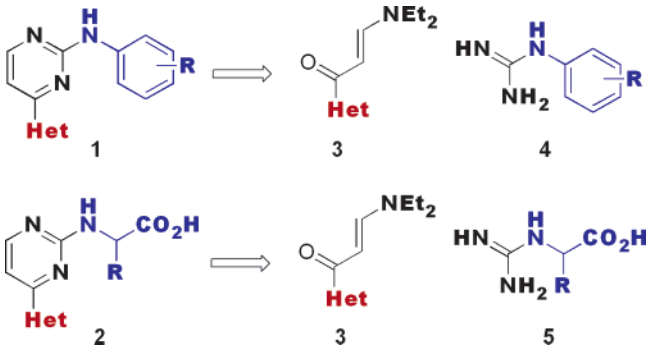


Figure 1. Traditional retrosynthetic analysis of 2-anilino-4-heteroaromatic pyrimidines.

(1) For a review of bioactive pyrimidines, see: Fabbro, D.; Ruetz, S.; Buchdunger, E.; Cowan-Jacob, S. W.; Fendrich, G.; Liebetanz, J.; Mestan, J.; O'Reilly, T.; Traxler, P.; Chaudhuri, B.; Fretz, H.; Zimmermann, J.; Meyer, T.; Caravatti, G.; Furet, P.; Manley, P. W. *Pharmacol. Therapeut.* **2002**, *93*, 79 and references contained therein. Tavares, F. X.; Boucheron, J. A.; Dickerson, S. H.; Griffin, R. J.; Preugschat, F.; Thomson, S. A.; Wang, T. Y.; Zhou, H.-Q. *J. Med. Chem.* **2004**, *47*, 4716.

10.1021/ol051339z CCC: $30.25
Published on Web 08/17/2005

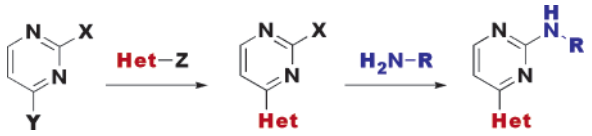
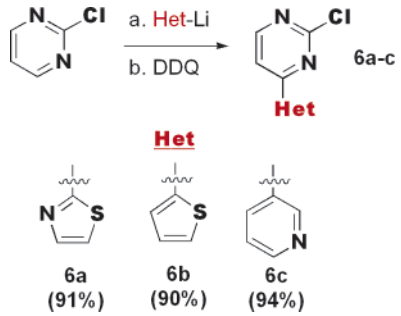


Figure 2. Envisioned 2-amino-4-heteroaromatic pyrimidine formation.

generating the 2-aminopyrimidine bond. Accomplishing these two goals would provide a general, expedient route to a potentially biologically important 2,4-disubstituted pyrimidine scaffold.

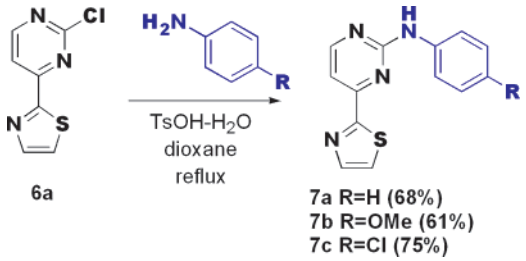
We decided to focus our efforts on the synthesis and subsequent nucleophilic displacement of 2-chloro-4-heteroarylpyrimidines **6**. We initially investigated Suzuki reactions with 2,4-dichloropyrimidine to afford **6**[4] but found this reaction to be unsatisfactory with heteroarylboronic acids. Fortunately, we were able to generate this key intermediate via the method of Strekowski and co-workers.[5] Nucleophilic attack with several different heteroaryllithium anions generated in situ on commercially available 2-chloropyrimidine afforded **6a**−**c** after subsequent oxidative workup with DDQ (Scheme 1).

Scheme 1



With the key intermediates **6a**−**c** in hand, we focused on identifying conditions to generate the 2-aminopyrimidine bond with anilines. We investigated a variety of conditions including bases, solvents, additives, extended reaction times, temperatures, and microwave irradiation. Several of these conditions afforded some conversion of the starting materials to the desired product but suffered from issues of generality and reproducibility. After a more thorough literature investigation, we identified an acid-mediated approach to synthesize 2-anilinopyrimidines.[6] We found that refluxing **6a** with 1.2 equiv of several anilines in the presence of 0.8 equiv *p*-TsOH in dioxane afforded the desired 2-aniline products **7a**−**c** in good yields after isolation via flash chromatography (Scheme 2). Furthermore, this acid-mediated procedure appeared to be general, reproducible, and amenable to parallel synthesis.

Scheme 2



To demonstrate the scope of the acid-mediated, nucleophilic displacement of 2-chloro-4-heteroarylpyrimidines with a variety of anilines, the compounds in Table 1 were prepared. All three 4-heteroarylpyrimidines **6a**−**c** were successfully coupled with a variety of anilines. In addition to reactions with aniline to give **7a**,**j**,**s** in good yields, couplings of anilines containing electron-donating groups to give **7b**,**i**,**k**,**r**,**t**,**z** went in high yields as determined by LC/MS. Good isolated yields of these products were also obtained. Whereas displacement reactions of 2-chloropyrimidines with weakly nucleophilic anilines are problematic under basic conditions, anilines with strong *p*-electron-withdrawing groups gave good yields of 2-amino-4-heteroarylpyrimidines under the *p*-TsOH conditions (**7d**,**f**,**g**,**m**,**o**−**q**,**v**,**x**,**y**). Ortho substitution on the aniline also appears to be tolerated as *o*-toluidine couples effectively to give **7e**,**n**,**w**.

We also wanted to synthesize 2-amino acid-4-heteroarylpyrimidines. There are limited literature reports on this type of biologically interesting scaffold.[7] To our knowledge, there is no literature procedure available to rapidly access analogues of this scaffold. Our initial efforts to synthesize this scaffold utilizing aminoguanidines (Figure 1) failed miserably leading to complex reaction mixtures. Nucleophilic displacement of 2-chloro-4-heteroarylpyrimidines with amino acids under the acidic *p*-TsOH procedure also did not work. We then investigated a variety of conditions including bases,

(2) Paul, R.; Hallett, W. A.; Hanifin, J. W.; Reich, M. F.; Johnson, B. D.; Lenhard, R. H.; Dusza, J. P.; Kerwar, S. S.; Lin, Y. I.; Pickett, W. C.; Seifert, C. M.; Torley, L. W.; Tarrant, M. E.; Wrenn, S. *J. Med. Chem.* **1993**, *36*, 2716. Drager, G.; Solodenko, W.; Messinger, J.; Schon, U.; Kirschning, A. *Tetrahedron Lett.* **2002**, *43*, 1401. For other methods to potentially access 2-amino-4-heteroarylpyrimidines, see: Collis, A. J.; Foster, M. L.; Halley, F.; Maslen, C.; McLay, I. M.; Page, K. M.; Redford, E. J.; Souness, J. E.; Wilsher, N. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 693. Manley, P. J.; Balitza, A. E.; Bilodeau, M. T.; Coll, K. E.; Hartman, G. E.; McFall, R. C.; Rickert, K. W.; Rodman, L. D.; Thomas, K. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1673. Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; VanRens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; Brown, K. K.; Juergens, K.; Taiwo, Y. O.; Janusz, M. J. *J. Med. Chem.* **2004**, *47*, 2724.

(3) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.

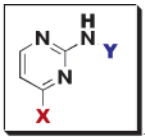
(4) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829.

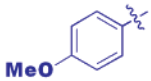
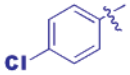
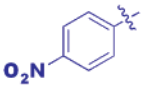
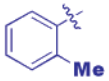
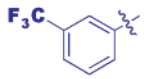
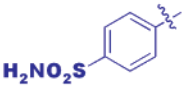
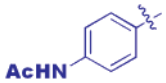
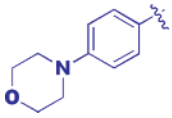
(5) Harden, D. B.; Mokrosz, M. J.; Strekowski, L. *J. Org. Chem.* **1988**, *53*, 4137. Strekowski, L.; Harden, D. B.; Grubb, W. B., III; Patterson, S. E.; Czarny, A.; Mokrosz, M. J.; Cegla, M. T.; Wydra, R. L. *J. Heterocycl. Chem.* **1990**, *27*, 1393.

(6) Hattinger, G.; Stanetty, P.; Eberle, M. GB 2369359, 2002.

(7) A SciFinder search of the generic 2-amino acid-4-cyclic-pyrimidine scaffold identified a total of only 18 patents and 2 publications. In ref 2, Clark et al., one of the 30 compounds exemplified was a 2-Phe-OMe-4-cyclic-pyrimidine.

Table 1. 2-Amino-4-heteroarylpyrimidines Prepared via Schemes 1 and 2[a]



	**7a** 93%(68%)*	**7j** 96% (56%)	**7s** 100% (60%)
	**7b** 94% (61%)*	**7k** 97% (61%)	**7t** 93% (60%)
	**7c** 100% (75%)*	**7l** 97% (51%)*	**7u** 99% (45)*
	**7d** 88% (61%)	**7m** 95% (63%)	**7v** 61%
	**7e** 97%(55%)	**7n** 100% (67%)	**7w** 96%
	**7f** 100% (65%)	**7o** 100% (72%)	**7x**94% (61%)
	**7g** 62%	**7p** 100%	
	**7h** 34%	**7q** 100% (59%)	**7y** 50%
	**7i** 100% (70%)	**7r** 100%	**7z** 87% (67%)

[a] Reported yields determined via LC/MS analysis of the crude reaction mixture using an internal standard. Yields in parentheses are isolated yields after RP-HPLC purification using a Gilson HPLC instrument. Yields with * are isolated yields after flash chromatography.

solvents, additives, extended reaction times, microwave irradiation, and temperatures. We found that heating **6a** with 1.5 equiv of the amino acid and 4 equiv of NaH in DMSO afforded the desired 2-amino acid product **8** in moderate yields and appeared to be general, reproducible, and amenable to parallel synthesis (Scheme 3).

A simple 2 × 2 library was prepared via nucleophilic displacement of 2-chloro-4-heteroarylpyrimidines with amino

Scheme 3

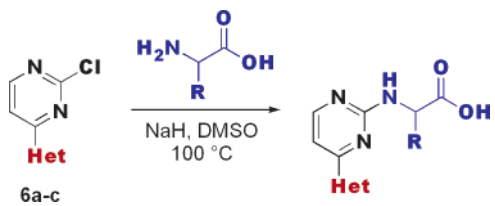
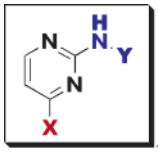
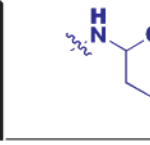
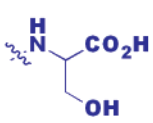


Table 2. 2-Amino acid-4-heteroarylpyrimidines Prepared via Schemes 1 and 3[a]







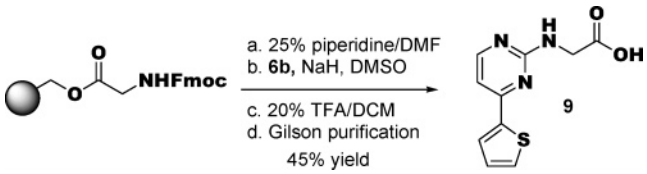
	**8a** 31% (27%)	**8c** 74% (27%)
	**8b** 27% (25%)	**8d** 87% (34%)

[a] Reported yields determined via LC/MS analysis of the crude reaction mixture using an internal standard. Yields in parentheses are isolated yields after RP-HPLC purification using a Gilson HPLC instrument.

acids (Table 2). Both 4-heteroarylpyrimidines **6a** and **6c** were successfully coupled with racemic leucine and serine to afford **8a**−**d**.[8] The yields with the more sterically encumbered leucine (**8a** and **8b**) were only moderate as determined by LC/MS, but the yields with the less sterically encumbered, more highly functionalized serine (**8c** and **8d**) were good. While the yields are good to moderate at best for **8a**−**d**, this synthetic strategy allows rapid, straightforward access to potentially biologically interesting scaffolds for which there are no efficient procedures known in the literature.

We also found the 2-amino acid-4-heteroarylpyrimidine chemistry to be amenable to solid-phase techniques (Scheme 4) utilizing an Fmoc-Gly Wang resin. The Fmoc group was

Scheme 4



first removed to unmask the amino acid. Subsequent heating of this resin with NaH and the desired 2-chloropyrimidine in DMSO afforded, after acidic cleavage, the desired 2-amino acid-4-heteroarylpyrimidine **9**. Purification of this relatively clean product via preparative HPLC afforded the desired compound in moderate yield and excellent purity. One can imagine cleavage of the product from the Wang resin under different conditions to incorporate another site of diversity, e.g., to produce amide analogues as well.[9] Thus, in a single

(8) Resynthesis of **8a** and **8c** with the enantiomerically pure amino acids and subsequent purification via preparatory HPLC revealed a minimal degree of epimerization. The desired products **8a** and **8c** were isolated in 93% and 76% respective chiral purity.

(9) Barn, D. R.; Morphy, J. R.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3213.

on-resin transformation multiple arrays of this potentially biologically interesting scaffold could be generated with three points of diversity.

In summary, we have developed an expedient parallel synthesis to diverse 2-amino-4-heteroarylpyrimidines. These potentially biologically important targets can be obtained in two straightforward steps utilizing commercially available starting materials. Synthetic arrays of both 2-anilino- and 2-amino acid-pyrimidines can be derived from the same key 2-chloro intermediate. We have also shown the utility of a solid phase supported functionalization protocol for the 2-amino acid-pyrimidine derivatives. We are currently investigating other syntheses utilizing this key 2-chloro-4-heteroarylpyrimidine intermediate to access other biologically interesting targets.

Acknowledgment. We thank Michael Kelly for helpful discussions and insights on RP-HPLC purification using a Gilson HPLC instrument. We also thank Mairead Young for chiral sample analysis.

Supporting Information Available: Experimental procedures and ^{1}H NMR and LC/MS data for intermediates and final products of chemistry validation and LC/MS data for parallel synthesis array. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051339Z