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One-Pot Two-Step Microwave-Assisted Reaction in Constructing 4,5-Disubstituted Pyrazolopyrimidines

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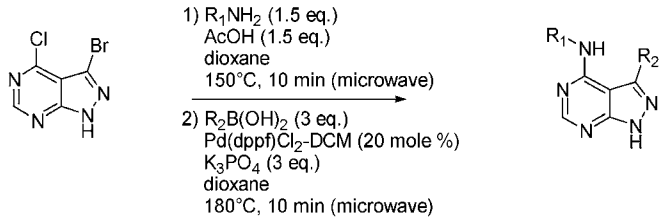
ABSTRACT



A microwave-assisted reaction was developed to facilitate the construction of 4,5-disubstituted pyrazolopyrimidines. This one-pot two-step process involves a sequential S_NAr displacement of the C4 chloro substituent with various anilines and amines, followed by a Suzuki coupling reaction with different boronic acids. Using microwave irradiation leads to high product conversion, low side product formation, and shorter reactions.

Microwave radiation is used as an alternative thermal energy source to conventional heating. The use of microwave irradiation in organic synthesis has been applied to a wide range of reaction types, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions.[1,2] Many of these reactions have been demonstrated to result in higher yield and/or selectivity under microwave irradiation compared to using a heat bath. Herein, we apply this method to the efficient synthesis of 4,5-disubstituted pyrazolopyrimidines.

Heterocyclic small molecules with a fused 5,6-membered ring represent excellent scaffolds for targeting the protein kinase family due to their structural similarity to the adenine moiety of ATP. Among these scaffolds, the pyrazolopyrimidine has been shown to have activity against multiple kinase subfamilies. Different substitution pattern around the scaffold result in selective inhibition of KDR,[3] Src,[4] and EGFR[5] kinase families. Some of these pyrazolopyrimidines have been shown to have antiproliferative activities and are being developed as antitumor agents.[6] Hence, the pyrazolopyrimidines represent an attractive scaffold for development of kinase inhibitors with interesting biological activities.

Previous published synthetic approaches toward making 4,5-disubstituted pyrazolopyrimidines have utilized a 3-(phenyl)-5-amino-4-cyanopyrazole (**2**) as the common in-

(1) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(2) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283.

(3) Fraley, M. E.; Rubino, R. S.; Hoffman, W. F.; Hambaugh, S. R.; Arrington, K. L.; Hungate, R. W.; Bilodeau, M. T.; Tebben, A. J.; Rutledge, R. Z.; Kendall, R. L.; McFall, R. C.; Huckle, W. R.; Coll, K. E.; Thomas, K. A. *Bio. Org. Med. Lett.* **2002**, *12*, 3537−3541.

(4) Hanke, J. H.; Gardner, J. P.; Dow, R. L.; Changelian, P. S.; Brissette, W. H.; Weringer, E. J.; Pollok, B. A.; Connelly, P. A. *J. Biol. Chem.* **1996**, *271*, 695−701.

(5) Caravatti, G.; Bruggen, J.; Buchdunger, E.; Cozens, R.; Furet, P.; Lydon, N.; O'Reilly, T.; Traxler, P. *Pyrrolo[2,3-d]pyrimidine and Pyrazolo-[3,4-d]pyrimidine Derivatives as Selective Inhibitors of the EGF Receptor Tyrosine Kinase*; Ojima, I., Vite, G. D., Altmann, K.-H., Eds.; ACS Symposium Series 796; American Chemical Society: Washington, DC, 2001; pp 231−244.

(6) Hirst, G. C.; Rafferty, P.; Ritter, K.; Calderwood, D.; Wishart, N.; Arnold, L. D.; Friedman, M. M. U.S. Patent 2002156081 A1, 2001; WO Patent 200280926 A1, 2002.

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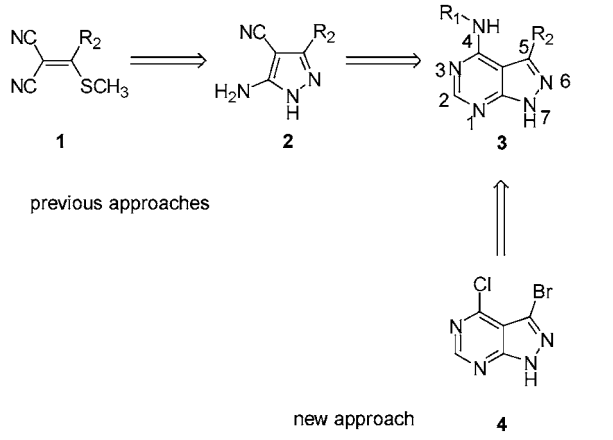
termediate, which is synthesized from 3-(phenyl)-2-cyano-3-(methylthio)-acrylonitrile (**1**) (Scheme 1).[7−9] This route

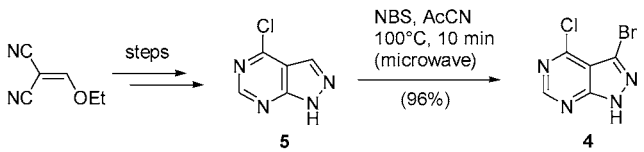
Scheme 1. Strategies of Making 4,5-Disubstituted Pyrazolopyrimidines



involves at least five sequential reaction steps, but more importantly, the R_2 substituent is introduced in the first step. Therefore, the generation of analogues with varying C5 substituents is inefficient. Moreover, bulky R_2 substituents often prevent efficient cyclization to form **2**, thereby limiting the diversity at this position. Finally, compound **1** and its R_2 precursors have limited commercial sources and the synthesis of **1** is a multistep task itself. We have devised an extremely convergent route for making 4,5-disubstituted pyrazolopyrimidines. This route involves the synthesis of a common intermediate, 4-chloro-5-bromopyrazolo-pyrimidine (**4**), that allows rapid derivatization of the heterocyclic core scaffold in two steps. Furthermore, a one-pot two-step process was developed using microwave irradiation to combine these two reactions with enhanced yield and efficiency.

The common intermediate, 4-chloro-5-bromopyrazolo-pyrimidine (**4**), was synthesized from the known compound 4-chloropyrazolopyrimidine[10] (**5**) on a multigram scale by treatment with *N*-bromosuccinimide in acetonitrile (Scheme 2). The corresponding 4-chloro-5-iodopyrazolopyrimidine

Scheme 2. Synthesis of Common Intermediate **4** Using Microwave Irradiation



was also synthesized using *N*-iodosuccinimide; however, due to its poor solubility in organic solvents, it was not utilized as the common intermediate for subsequent derivatization of the scaffold.

Starting from compound **4**, a two-step derivatization process was developed. Initially, it was found that aromatic displacement of the C4 chloro substituent by 3-chloroaniline is the most efficient under acidic conditions. Treatment of **4** with 1.5 equiv of the aniline and 1.5 equiv of acetic acid in dioxane for 10 min at 150 °C using a microwave heat source resulted in nearly quantitative conversion. Under basic conditions such as DIEA or K_3PO_4, the reaction is more sluggish. After the reaction was cooled to ambient temperature, 3-aminophenyl boronic acid (3 equiv), Pd(dppf)Cl_2·DCM (20 mol %), and K_3PO_4 (3 equiv) were added to the crude reaction mixture as solids. The reaction was heated to 180 °C for another 10 min using microwave irradiation, which again afforded the desired product (**5**) with nearly quantitative conversion. The extremely high starting material to product conversion ratio during the first aromatic displacement step also makes the Suzuki coupling a very high-yielding reaction. Reversal of the reaction sequence gave significantly lower yields due to the fact that the palladium catalyst can undergo oxidative addition to the C4 chlorine under such forcing conditions. A diverse set of substituents was tested for this one-pot two-step reaction (Table 1). Boronic acids and anilines containing hydroxyl, amino, amide, ketone, ester, and chloro groups were well tolerated, albeit those containing an electron-withdrawing group typically gave lower yields (50−70%). Secondary and primary amines were also excellent substrates for this reaction, giving nearly quantitative yields regardless of the presence of electron-withdrawing substituents. All of the microwave-assisted reactions were performed in an Emrys Optimizer microwave reactor (Personal Chemistry, Inc.) at the specified temperature using the standard mode of operation.

It is worthwhile to compare this new approach to 4,5-disubstituted pyrazolopyrimidines with previous approaches. This one-pot two-step process represents a much more convergent route by utilizing a common intermediate and introducing the diversity elements in the last step. Moreover, since the previous strategies involve exposing the R_2 substituents to a series of condensation reactions under strong acidic and strong basic conditions, sensitive functional groups (e.g., $-NH_2$, $-OH$, $-COOR$) on R_2 are not tolerated and must be protected. The mild acidic (acetic acid) and basic (K_3PO_4) condensation employed here, together with the shorter reaction times used in the one-pot two-step microwave-assisted reaction, allowed the tolerance of relatively reactive functional groups such as ketone, amine, amide, alcohol, ester, etc. Under conventional thermal heating conditions, longer reaction times are necessary, which would lead to significant decomposition of the desired product. For example, transformation of **4** to **5** in entry **7** would require 12

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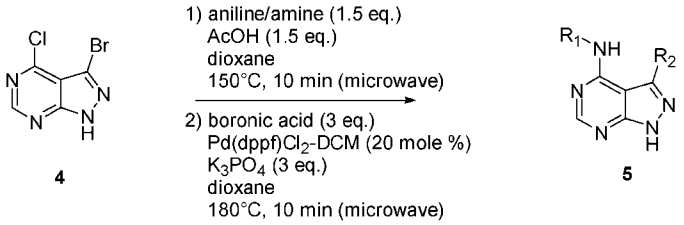
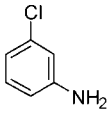
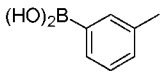
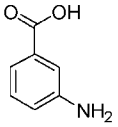
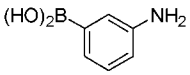
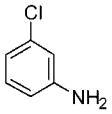
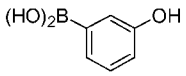
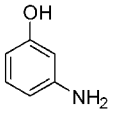
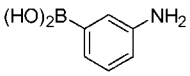
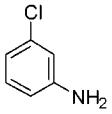
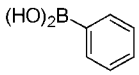
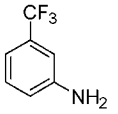
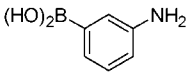
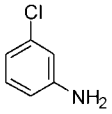
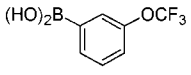
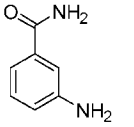
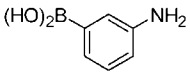
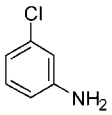
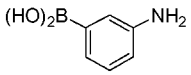
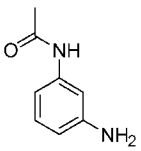
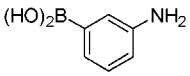
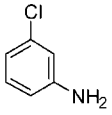
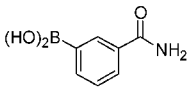
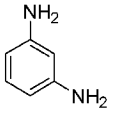
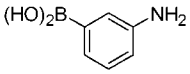
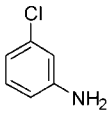
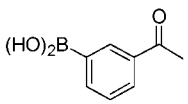
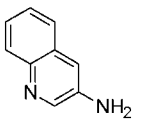
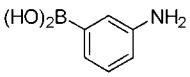
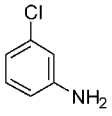
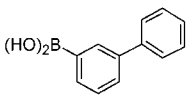
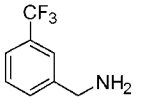
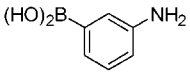
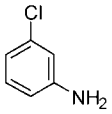
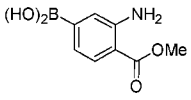
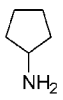
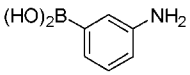
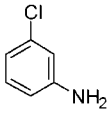
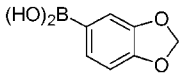
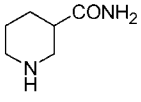
(10) Robins, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 784−790.

Table 1. R_1 and R_2 Substituents Tested for the One-Pot Two-Step Microwave-Assisted Reaction



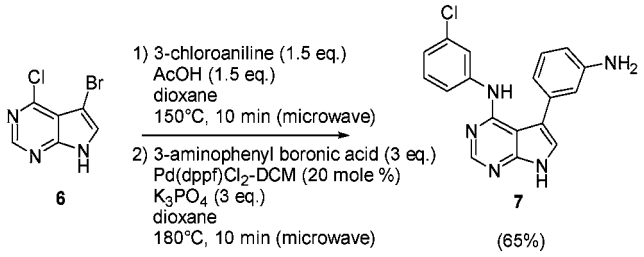
4 **5**

entry	aniline/amine	boronic acid	isolated yield	entry	aniline/amine	boronic acid	isolated yield
1			96	**12**			67
2			75	**13**			92
3			87	**14**			92
4			98	**15**			83
5			97	**16**			87
6			56	**17**			96
7			73	**18**			77
8			98	**19**			93
9			63	**20**			96
10			76	**21**			80
11			82	**22**			90

h of heating at 100 °C for both steps, and the yield of the desired product is estimated at <50%.

The use of microwave irradiation to cleanly generate intermediates that can be directly used in a subsequent

Scheme 3. Synthesis 4,5-Disubstituted Pyrrolopyrimidine Using Microwave Irradiation



reaction step was also tested on other heterocyclic scaffolds. For example, 4,5-disubstituted pyrrolopyrimidine (**7**) could also be synthesized in high yield from the corresponding 4-chloro-5-bromopyrrolopyrimidine (**6**) using the same reaction conditions (Scheme 3). This further demonstrates the generality of this microwave-assisted reaction to generate two diversity elements on a heterocyclic scaffold in one pot, without intermediate workup and purification.

Heterocycles constitute an important class of compounds for use as pharmaceutical agents. The one-pot two-step microwave-assisted reaction described here should facilitate the synthesis of heterocyclic small molecules.

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Supporting Information Available: LCMS and ^{1}H NMR of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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