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Phenoxide leaving group S_NAr strategy for the facile preparation of 7-amino-3-aryl pyrazolo[1,5-*a*]pyrimidines from a 3-bromo-7-phenoxypyrazolo[1,5-*a*]pyrimidine intermediate

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ABSTRACT

We have discovered a 3-bromo-7-phenoxypyrazolo[1,5-a]pyrimidine intermediate that allows for the direct sequential funtionalization of the 3-position and 7-position of a pyrazolo[1,5-a]pyrimidine scaffold. The intermediate and general method described herein offer an improvement over prior methods, particularly in cases where multiple unique 3-aryl substituents are to be incorporated in conjunction with multiple unique 7-amino substituents.

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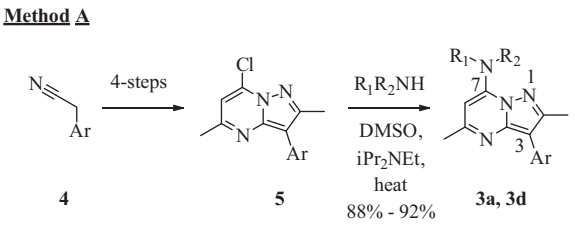
Introduction

The pyrazolo[1,5-*a*]pyrimidine heterocyclic core is an important scaffold for medicinal chemists. In particular, 7-amino-3-aryl-pyrazolo[1,5-*a*]pyrimidine derivatives have found utility as agents against NYP1, CRF, kinases, and other targets.[1–4]

A common method utilized for synthesizing 7-amino-3-aryl pyrazolo[1,5-*a*]pyrimidines employs aryl-substituted acetonitrile precursors such as **4** (Scheme 1).[1–4] Intermediates **4** are converted to 7-chloro-3-aryl precursors **5** in four steps and then subsequently treated with amines to give final targets **3**. Method A is quite efficient for derivatization of the 7-amino position in cases where the 3-aryl substituent is held constant. The utility of this method is greatly reduced, however, in cases where 7-amino substitution and 3-aryl substitution need to be explored concurrently, for example when multiple unique 3-aryl substituents will be studied in conjunction with multiple unique 7-amino substituents.

Another general method employed to synthesize 7-amino-3-aryl pyrazolo[1,5-*a*]pyrimidines analogs is shown in Scheme 2. Upon preliminary inspection, intermediate **6**[5] would appear to be an ideal precursor for the sequential funtionalization of the 3-position and 7-position of a pyrazolo[1,5-*a*]pyrimidine core. Unfortunately, direct conversion of intermediate **6** to intermediates **5** via Suzuki conditions proved to be problematic. Palladium-catalyzed coupling of **6** with aryl boronic acids/esters often resulted in substitution at both the 7-chloro and 3-bromo functionalities and gave complex mixtures of regioisomers as well as bis-substituted products. Intermediate **6** was, however, effectively reacted with amines to achieve precursors **7**. Regrettably, direct conversions of **7** to **3** under Suzuki conditions were often also problematic. Other researchers appear to have had similar problems with Suzuki chemistry on these substrates and have employed a *t*-butylcarbamate protection scheme to facilitate the desired coupling.[6] In our hands, Boc-protected intermediates **8** readily reacted with aryl boronic acids/esters to give intermediates



Scheme 1. 7-Amino-3-aryl pyrazolo[1,5-*a*]pyrimidines from aryl-substituted acetonitrile precursors. Experimental details included in Supplemental material.

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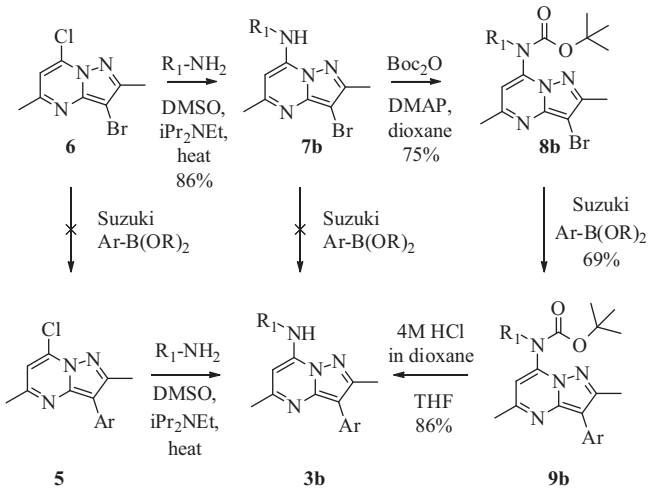


Scheme 2. 7-Amino-3-aryl pyrazolo[1,5-*a*]pyrimidines from 3-bromo-7-chloropyrazolo[1,5-*a*]pyrimidine precursor. Experimental details included in Supplemental material.

9. Deprotection under acidic conditions then provided desired products **3**. Method B allowed for efficient derivatization at the 3-position with a 2-step enumeration from intermediate **8**. As with method A, however, the utility of method B is greatly diminished when both the 7-amino position and the 3-aryl position need to be derivatized in direct sequence.

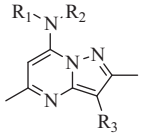
Neither method A nor method B was very efficient for successive functionalization at the 3-aryl and 7-amino positions. For method A, the 3-aryl substituent is incorporated in the first step of the 5 step sequence. For method B, the 7-amino substituent is incorporated in the first step of the respective 4 step sequence. As such, we desired a late-stage intermediate with reactive groups at the 3-position and 7-position that could be functionalized in direct succession.

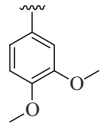
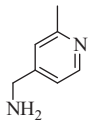
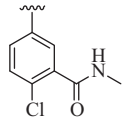
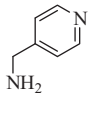
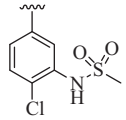
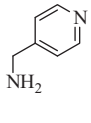
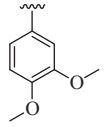
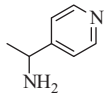
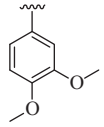
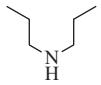
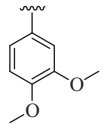
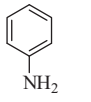
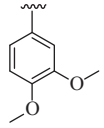
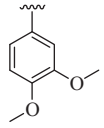
Useful bifunctional intermediate for the facile preparation of 7-amino-3-aryl-pyrazolo[1,5-*a*]pyrimidine derivatives

Phenoxy is an atypical leaving group for S_NAr reactions and has been utilized sparingly for these types of displacements. Use of phenoxy as a leaving group at the 7-position of a pyrazolo[1,5-*a*] pyrimidine core, such as for intermediate **10**, has not been previously reported. Intermediate **6** was readily converted to the 7-phenoxy intermediate **1** by displacement of chloro with phenoxide ion. As expected, intermediate **1** readily reacted with boronic acids/esters under Suzuki conditions to give clean substitution at the 3-position. Phenoxide was then displaced by amines to give desired products **3**. In this manner, method C initially generated the three compounds **3a**–**3c** (Table 1). Each analog required just two steps from common intermediate **1**, which equated to 6 total chemistry experiments for all three compounds. For comparison, method A and method B minimally required a total of 15 and 12 chemistry experiments respectively to achieve the same three compounds. The benefit of method C over method A and method B increases as arrays become larger.

We additionally synthesized compounds **3d**–**3h** (Table 1) by method C in order to more thoroughly explore the reactivity and limitations of the phenoxide displacement. In general, the phenoxide leaving group was readily displaced by unbranched **3a**–**d** and moderately branched **3e** amines. Phenoxide displacements to achieve **3a**–**3e** were largely complete in a few hours between 80 °C and 90 °C, although we regularly allowed the displacement

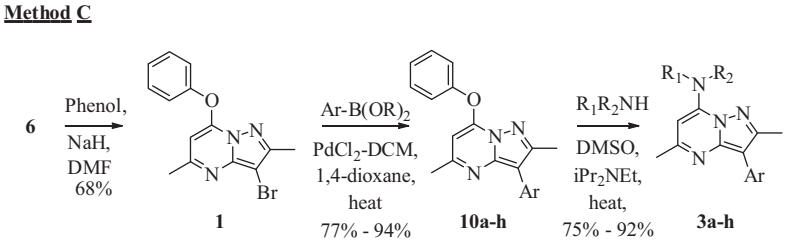
Table 1
7-Amino-3-aryl pyrazolo[1,5-*a*]pyrimidines analogs



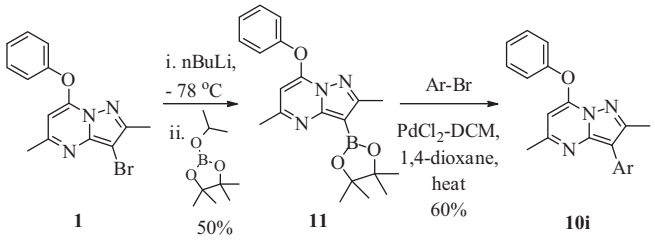
Compound	R_1R_2NH	R_3	Method (% yield)[a]
3a			A [5 steps from 4] (86%) C [2 steps from 1] (89%)
3b			B [4 steps from 6] C [2 steps from 1] (92%)
3c			C (76%)
3d			A (92%) C (88%)
3e			C (82%)
3f			C (86%)
3g			C (85%)
3h			C (75%)

[a] Isolated yield of amine displacement product in final step of the respective method. Experimental details included in Supplemental material.

reaction to run overnight without observing decomposition or by-products. The secondary amine **3f**, aniline **3g**, and sterically encumbered *t*-butylamine **3h** proved significantly less reactive during the phenoxy displacements and required higher temperatures, additional reagent, and prolonged reaction times to give roughly the same conversion. Phenoxide displacement with aniline gave no conversion at 90 °C. However, upon increasing the temperature to 130 °C and adding an extra equivalent of aniline, the displacement was complete within 36 hours to form **3g** in good yield. Reaction of **10** with dipropylamine was also sluggish at 90 °C and required additional reagent, time, and heat to effect displacement of the phenoxide, but ultimately gave **3f** in good yield. Displacement of phenoxide **10** with *t*-butylamine did proceed slowly at 90 °C, but ultimately required additional amine, higher temperature, and longer reaction times to achieve conversion to **3h**. Significant decomposition impurities were not observed at elevated temperatures or prolonged reaction times and therefore



Scheme 3. 7-Amino-3-aryl pyrazolo[1,5-*a*]pyrimidines from a 3-bromo-7-phenoxypyrazolo[1,5-*a*]pyrimidine precursor. Experimental details included in Supplemental material.



Scheme 4. 7-Phenoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyrimidine precursor. Experimental details included in Supplemental material. Ar = 3-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfonyl)-4-chlorophenyl.

we believe that the reaction times might be reduced simply by increasing temperature, amine equivalents, and/or reaction mixture concentration. We also considered that an electron deficient phenoxy moiety might potentially be a more reactive leaving group, but ultimately did not explore this possibility.

It is interesting to note that intermediate **1** was also readily converted to the boronic ester **11** (Scheme 4) and subsequently reacted with aryl bromides via a 'reverse' Suzuki reaction to give penultimate intermediate **10**. Intermediate **11** was a convenient starting point when the desired aryl boronic acids/esters used for the Suzuki reaction in Scheme 3 were not readily available. Yield and scope of the 'reverse' Suzuki illustrated in Scheme 4 compared satisfactorily to the Suzuki reactions exemplified in Scheme 3.

Conclusion

We have discovered a useful approach using intermediate **1** to achieve direct sequential functionalization at the 3-position and 7-position of a pyrazolo[1,5-*a*]pyrimidine scaffold. The intermediate and method are robust with few limitations and offers a significant improvement over previous methods where larger sets of diverse 7-amino-3-aryl-pyrazolo[1,5-*a*]pyrimidines were produced.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and analytical data for intermediates and products found in Schemes 1–4 and Table 1) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.068. These data include MOL files and InChiKeys of the most important compounds described in this article.

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