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Synthesis of Pyridopyrimidines by Palladium-Catalyzed Isocyanide Insertion

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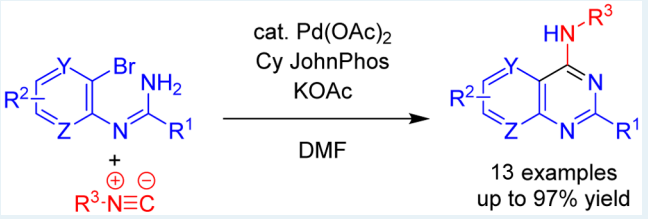
Supporting Information

ABSTRACT: A new synthetic approach to 4-aminopyrido[2,3-*d*]pyrimidines and 4-aminopyrido[3,2-*d*]pyrimidines based on palladium-catalyzed reaction of isocyanides with readily available *N*-(bromopyridyl)amidines is reported. The target heterocycles were obtained in generally good to excellent yield. For the two regioisomeric pyrimidopyrimidines, we compared our approach involving oxidative addition with the analogous C−H activation protocol because both methods have been reported for the synthesis of 4-aminoquinazolines. We found that the C−H activation protocol does not allow one to obtain the target pyridopyrimidines, but the imidoylative cross-coupling protocol provided a new entry to the synthesis of these medicinally important scaffolds.

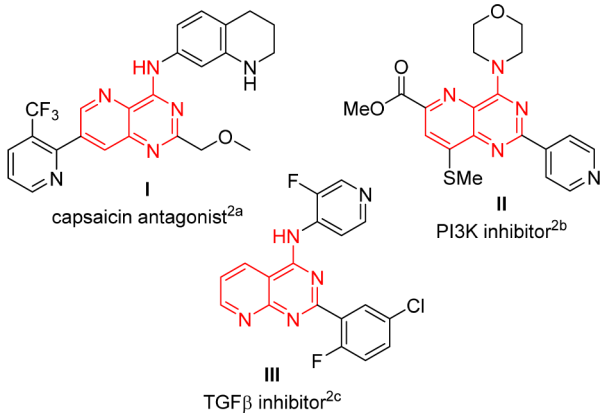


KEYWORDS: *palladium, isocyanides, heterocycles, insertion reactions, homogeneous catalysis, cross-coupling*

INTRODUCTION

Nitrogen-rich fused heterocycles are of paramount importance in medicinal chemistry, not the least owing to their typical affinity for ATP binding sites in kinases and other pharmaceutically relevant enzyme targets.[1] 5,6-Fused pyrimidines such as pyrido[3,2-*d*]pyrimidines (**1**) and pyrido[2,3-*d*]pyrimidines (**2**) are prime example of such N-heterocycles that inhibit an array of disease-related kinases (Chart 1).[2] The synthesis of these compounds is typically achieved by construction of the heterocyclic core by classical methods using harsh conditions, followed by stepwise introduction of the substituents by cross-coupling or S_NAr reactions.

Chart 1. Pharmaceutically Relevant Pyrido[3,2-*d*]pyrimidines (I and II) and Pyrido[2,3-*d*]pyrimidines (III)



Palladium-catalyzed cross-coupling reactions have become commonplace in medicinal chemistry for the decoration of preconstructed scaffold structures.[3] However, their utilization in an integral approach to the de novo synthesis of highly functionalized heterocycles is currently still underdeveloped. On the other hand, many palladium-catalyzed cascade reactions toward complex cyclic molecular scaffolds continue to be developed.[4] Among these reactions, the palladium-catalyzed migratory insertion of isocyanides is currently emerging as a highly efficient strategy for the construction of densely and diversely functionalized heterocycles.[5]

Recently, we reported the Pd-catalyzed intramolecular imidoylative cross-coupling of *N*-(2-bromoaryl)amidines to give 4-amino-2-arylquinazolines (Scheme 1, pathway A).[6] Independently, Zhu et al. developed a similar oxidative cross-coupling involving C−H activation (pathway B).[7] Although the latter method provides some clear advantages with respect to atom economy and synthetic accessibility of the starting materials, it suffers from regioselectivity issues that can be avoided using our approach. Moreover, we anticipated that our method would be a more general approach to the synthesis of 4-aminopyrimidines fused with nonbenzenoid (e.g., pyridine) rings (pathway C), since C−H activation is likely not easily

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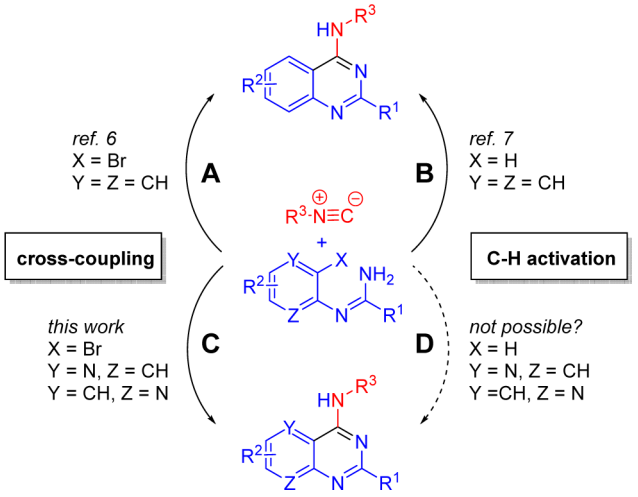
Scheme 1. Pd-Catalyzed Synthesis of Fused 4-Aminopyrimidines



transferred from an arene to an azine system (pathway D). We therefore set out to investigate the palladium-catalyzed insertion of isocyanides into several *N*-(bromopyridyl)amidines as a new entry to pharmaceutically relevant 5,6-fused 4-aminopyrimidines and compare it to the oxidative approach using *N*-(pyridyl)amidines.

RESULTS AND DISCUSSION

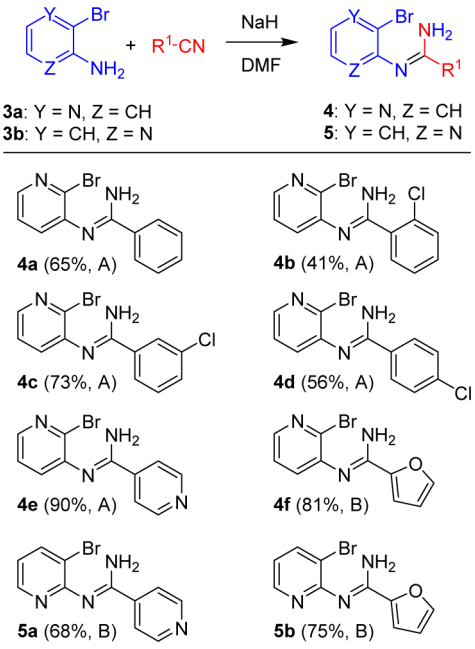
We started our investigations with the synthesis of a range of amidines **4** and **5** starting from commercially available 3-amino-2-bromopyridine (**3a**) and 2-amino-3-bromopyridine (**3b**), respectively, using a literature procedure[8] (method A) or a slightly adapted protocol (method B, Scheme 2). Without optimization, we readily prepared a set of diversely substituted *N*-(bromopyridyl)amidines **4** and **5** (Scheme 2).

These amidines were then subjected to our previously optimized conditions for Pd-catalyzed intramolecular imidoylation [3 mol % $Pd(OAc)_2$, 6 mol % Cy JohnPhos, 1.5 equiv of isocyanide, 3 equiv of KOAc, DMF, 120 °C, 7 h].[6] To our delight, all amidines were smoothly converted to the corresponding 4-aminopyridopyrimidines **1** (Scheme 3) and **2** (Scheme 4). The pyrido[3,2-*d*]pyrimidines **1a−i** were generally obtained in fair to good yield, although we found that a higher catalyst loading and temperature were required compared with our previous study on aminoquinazolines (5 mol % Pd, 160 °C). The presence of chloro substituents was tolerated (**1b−d**, **1h**), although the 2-chlorobenzamidine derivative **4b** led to a lower yield, possibly for steric reasons. Heterocyclic substituents such as 4-pyridyl (**1e**, **1i**) and 2-furyl (**1f**) are also allowed. *tert*-Butyl isocyanide, as the benchmark isocyanide, was most efficiently inserted, although cyclohexyl isocyanide could also be used with slightly diminished efficiency.

Gratifyingly, amidines **5** underwent Pd-catalyzed isocyanide insertion much more efficiently than amidines **4**. The pyrido[2,3-*d*]pyrimidines **2a−d** were obtained in good to excellent yield, even with lower catalyst loading (3 mol % Pd) and at substantially lower temperature (120 °C). Both *tert*-butyl and cyclohexyl isocyanide were in this case inserted with high efficiency, as exemplified by the combination with amidines featuring heterocyclic substituents (4-pyridyl and 2-furyl).

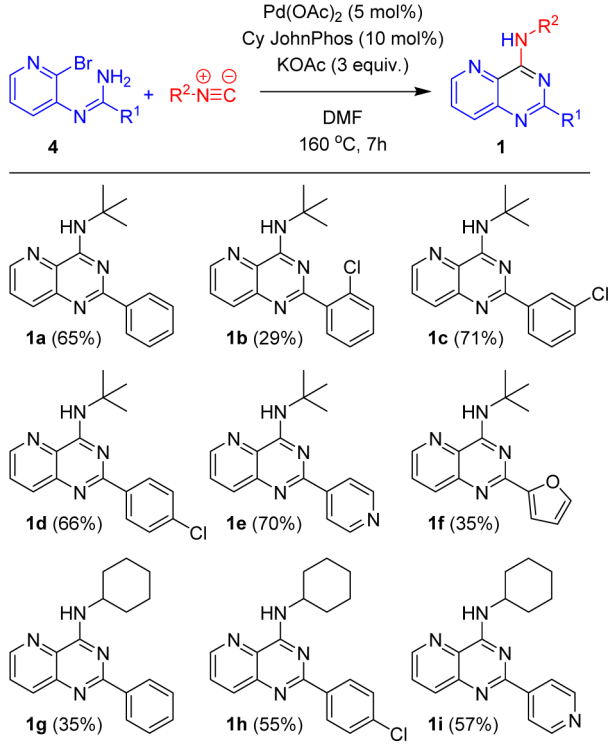
We then set out to confirm our hypothesis that these scaffolds are presumably not accessible via the C−H activation

Scheme 2. Synthesis of *N*-(Bromopyridyl)amidines



Method A: A solution of **3a** (1.1 equiv) and the appropriate nitrile (1.0 equiv) in dry DMF was added at 0 °C to a suspension of NaH (1.5 equiv, washed with pentane) in dry DMF, then stirred overnight at RT. Method B: **3a** or **3b** (1.1 equiv) was added at 0 °C to a suspension of NaH (1.5 equiv, washed with pentane) in dry DMF and stirred at 0 °C for 10 min before the addition of a solution of the appropriate nitrile (1.0 equiv) in dry DMF. The resulting mixture was stirred overnight at RT.

Scheme 3. Synthesis of Pyrido[3,2-*d*]pyrimidines (1)



protocol described by Zhu et al. for the synthesis of 4-aminoquinazolines.[7] As anticipated, the amidines **6** and **7** were not converted to the corresponding pyridopyrimidines **1a** and

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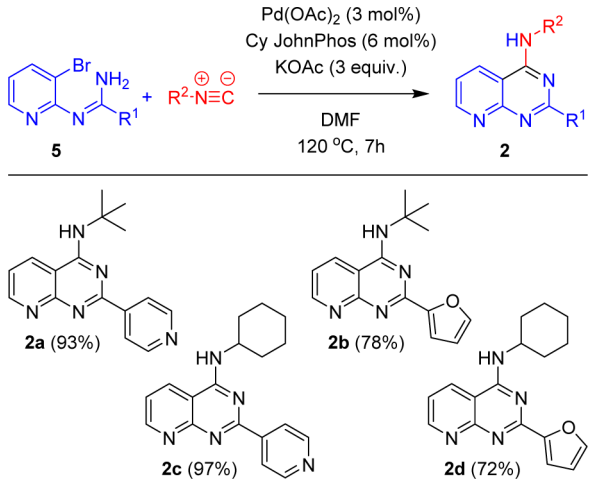
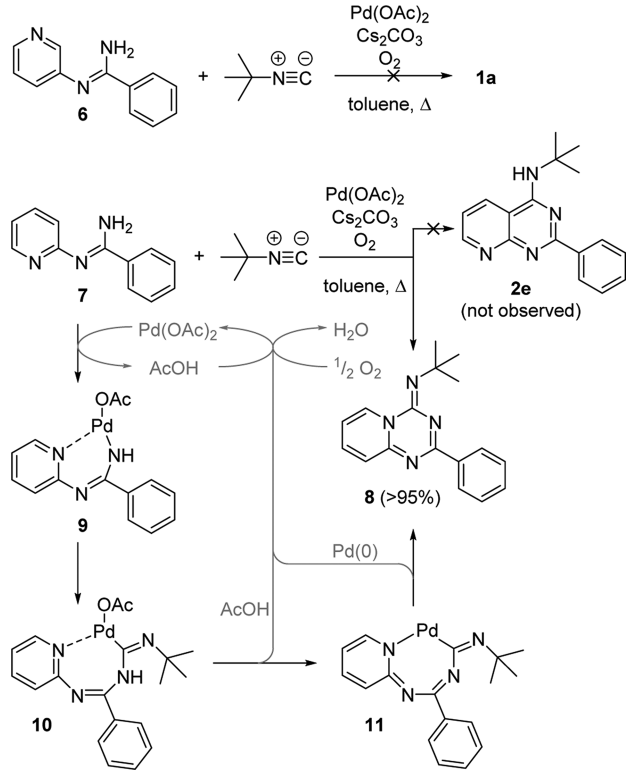
Scheme 4. Synthesis of Pyrido[2,3-*d*]pyrimidines (2)



Scheme 5. Attempted Synthesis of Pyridopyrimidines by C–H Activation and Unexpected Formation of 8



2e under the reaction conditions reported (5 mol % $Pd(OAc)_2$, 1.5 equiv of Cs_2CO_3, 1 atm O_2, toluene, reflux, 3 h). In the case of **6**, incomplete conversion of the starting amidine and a complex mixture of unidentified products was observed. A trace peak with m/z corresponding to the pyridopyrimidine **1a** was observed during ESI-MS analysis of the reaction mixture. However, the reaction did not afford an isolable amount of **1a** or an isomer. Surprisingly, amidine **7** was completely and selectively converted to a single new product under these conditions. MS and NMR analysis revealed that this product was not pyridopyrimidine **2e**, but an isomer. After extensive 1D and 2D NMR studies, we were able to assign structure **8** to this unexpected reaction product. Remarkably, this product was formed very fast (within 1 h) and in very high yield compared with the formation of 4-aminoquinazolines reported by Zhu et al.[7] The mechanism we propose for the formation of this species is analogous to the oxidative isocyanide insertion of *o*-phenylenediamines and related compounds we recently reported.[9] Amidine **7** can be regarded as an excellent bidentate ligand for Pd(II). After coordination and insertion of the isocyanide to the Pd(II) complex **11**, reductive elimination of Pd(0) affords the observed product **8**. Reoxidation of Pd(0) by O_2 completes the catalytic cycle (Scheme 5).

CONCLUSIONS

We report the use of Pd-catalyzed intramolecular imidoylative cross-coupling reactions to efficiently access nitrogen-rich, fused, bicyclic heteroaromatics that are of significant interest in medicinal chemistry. The reaction proceeds with a range of *N*-(bromopyridyl)amidines in combination with secondary and tertiary aliphatic isocyanides under mild conditions, allowing straightforward incorporation of (acid-)labile functional groups, which are incompatible with the majority of currently used methods for the preparation of these classes of compounds.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Pyrido[3,2-*d*]pyrimidines 1. A round-bottomed flask was charged with Pd $(OAc)_2$ (5 mol %) and Cy JohnPhos (10 mol %), followed by 5 mL of dry DMF. The mixture was flushed with N_2 for 10 min. In another round-bottomed flask, KOAc (3 equiv), the appropriate amidine (1 equiv), and isocyanide (1.5 equiv) were weighed. To this mixture, the Pd catalyst solution was added, and the flask was flushed with N_2. Then, the mixture was stirred and heated at 160 °C for 7 h. After cooling to room temperature, the resulting mixture was filtered over a pad of Celite and rinsed with ethyl acetate. The solvent was removed under reduced pressure, and the obtained residue was purified by flash column chromatography on silica gel using the appropriate solvent mixture as the eluent.

General Procedure for the Synthesis of Pyrido[2,3-*d*]pyrimidines 2. A round-bottomed flask was charged with Pd $(OAc)_2$ (3 mol %) and Cy JohnPhos (6 mol %), followed by 5 mL of dry DMF. The mixture was flushed with N_2 for 10 min. In another round-bottomed flask, KOAc (3 equiv), the appropriate amidine (1 equiv), and isocyanide (1.5 equiv) were weighed. To this mixture, the Pd catalyst solution was added, and the flask was flushed with N_2. Then, the mixture was stirred and heated at 120 °C for 7 h. After cooling to room temperature, the resulting mixture was filtered over a pad of Celite and rinsed with ethyl acetate. The solvent was removed under reduced pressure, and the obtained residue was purified by flash column chromatography on silica gel using the appropriate solvent mixture as the eluent.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interests.

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■ ABBREVIATIONS

ATP,adenosine triphosphate; Cy Johnphos,2-(dicyclohexylphosphino)biphenyl; PI3K,phosphoinositide-3-kinase; TGF,transforming growth factor (tumor growth factor); XPhos,2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl

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