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Rapid construction of imidazopyridines from *ortho*-haloaminopyridines

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ABSTRACT

A practical strategy for the preparation of imidazopyridine derivatives from *ortho*-haloaminopyridines utilizing a two-step C–N coupling/cyclization reaction sequence has been developed. This procedure provides rapid and efficient access to many medicinally interesting imidazopyridine compounds and related imidazopyrazine/purine heterocycles.

Imidazopyridine[1] derivatives are of great importance for their diverse biological properties, which may be related to their structural similarity to purines and indole/azaindole derivatives, the important building blocks of DNA/RNA and the basic heterocyclic structure found in numerous alkaloids. Many imidazopyridine derivatives possess interesting biological activities and therefore are used as antibacterial[2], antivirus[3], anti-inflammatory[4], and antitumor agents.[5] They have also found utility as herbicides and fungicides.[6]

During lead optimization of a drug discovery program, a novel analog containing an imidazopyridine core was identified and found to significantly improve the in vitro potency as well as the in vivo efficacy compared with the original purine leads. Our initial imidazopyridine alkylation approach resulted in very low yield (~15%) of desired product due to poor N3/N1 selectivity. Alternative route from readily available aminopyridine was then devised which utilized ortho nitration as the first transformation.[7] Although this route selectively introduced alkyl group to the N3 nitrogen, it was inefficient for SAR studies because of the large number of steps (6 steps) required to build up the imidazole ring. Recognizing the limitations of this route, we explored a conceptively more efficient C–N coupling route (Scheme 1). Herein we report the optimization and scope of the rapid construction of imidazopyridines via the C–N coupling of alkyl amine derivatives with *ortho*-haloaminopyridines[8] followed by ring closure.

Although significant advances in the field of C–N coupling of amines with aromatic halides have been reported[9], there are few reports of C–N couplings of 2-haloaniline or *ortho*-haloaminopyridines[10] with amine derivatives, which was required for our method. Copper catalyzed C–N couplings of 2-iodoanilines with primary amines have been reported with limited substrate scope and success.[11] In addition to S_NAr[12] or harsh copper catalyzed conditions (200 °C, ~10% yield)[13] for introducing an alkylamino group ortho to a NH_2 on pyridines, the palladium catalyzed C–N couplings of *ortho*-haloaminopyridine with alkylamines has been reported in two cases.[14] In the first case[14a], a Pd/BINAP system was used to affect the coupling of 3-bromo-4-aminopyridine in low yield (~14%). Of most relevance to the present disclosure, Minatti[14b] and coworkers recently reported a BrettPhos precatalyst/LiHMDS conditions for the amination of 2-aminopyridine scaffolds with synthetically useful yields.

We began our investigation by screening conditions for C–N coupling of 4-amino-3-bromopyridine with benzylamine (Table 1). The best catalyst and base were BrettPhos and LiHMDS as shown in entry 1 (82% yield). Alternative catalysts (such as ^{t}BuXPhos, XPhos, RuPhos, or XantPhos) did not afford the desired product in useful yield (Table 1, entry 4–8). Surprisingly, BrettPhos G1 precatalyst outperformed BrettPhos G3 precatalyst (45% yield, Table 1, entry 2) and $Pd(OAc)_2$/BrettPhos (12% yield, Table 1, entry 3). The choice of LiHMDS as base[15] was found to be critical for achieving high

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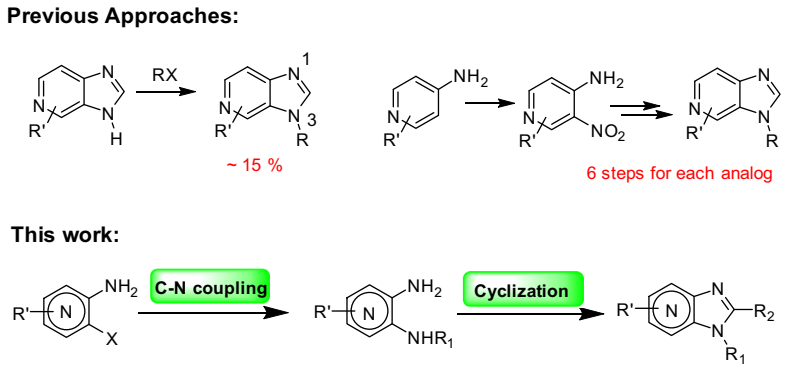
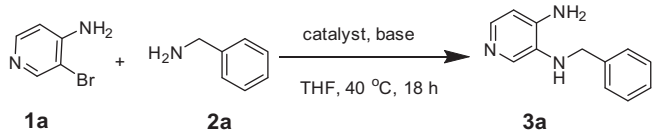
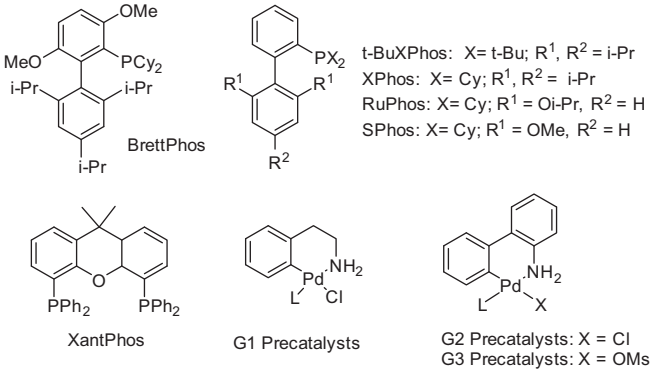


Scheme 1. Routes to imidazopyridine derivatives.

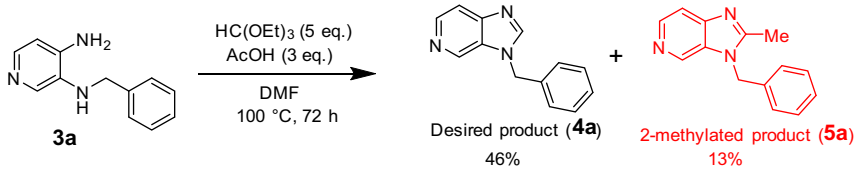
Table 1
Optimization of C–N coupling[a]



Entry	Catalyst (6 mol%)	Base (2.5 equiv)	Conc (M)	Yield (%)
1	**BrettPhos G1 Prec.**	**LiHMDS**	**0.2**	**82**
2	BrettPhos G3 Prec.	LiHMDS	0.2	45
3	BrettPhos + $Pd(OAc)_2$	LiHMDS	0.2	12
4	t-BuXPhos G1 Prec.	LiHMDS	0.2	16
5	XPhos G1 Prec.	LiHMDS	0.2	12
6	RuPhos G2 Prec.	LiHMDS	0.2	5
7	SPhos G1 Prec.	LiHMDS	0.2	3
8	XantPhos G2 Prec.	LiHMDS	0.2	0
9	BrettPhos G1 Prec.	NaHMDS	0.2	33
10	BrettPhos G1 Prec.	KHMDS	0.2	14
11	BrettPhos G1 Prec.	NaO^tBu	0.2	5
12	BrettPhos G1 Prec.	LiO^tBu	0.2	3
13	BrettPhos G1 Prec.	Cs_2CO_3	0.2	7
14	**BrettPhos G1 Prec.**	**LiHMDS**	**0.4**	**94**
15	BrettPhos G1 Prec.	LiHMDS	0.1	46
16	BrettPhos G1 Prec.	LiHMDS	0.05	7

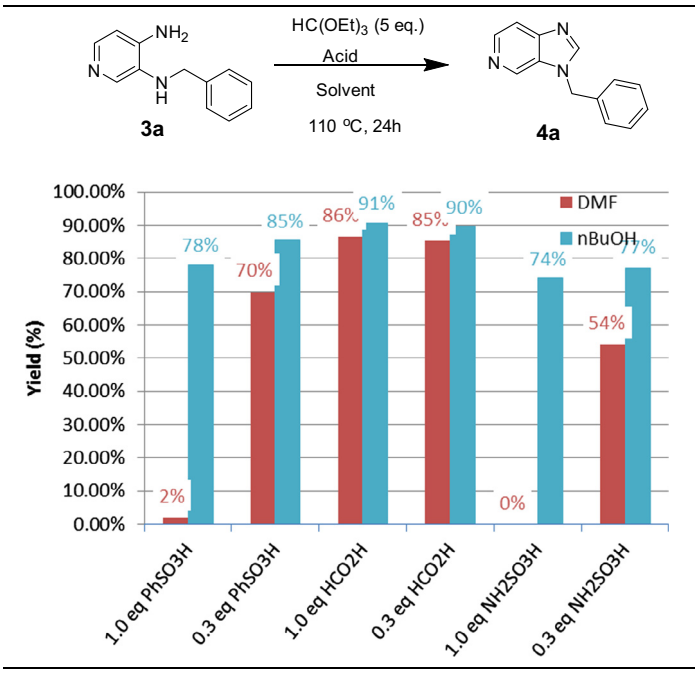


[a] All the reactions were carried out using bromide (**1a**) and benzylamine (**2a**, 1.5 equiv) with Pd catalyst (6 mol%) in THF (0.2 M) in a sealed microtube and the yields were determined based on quantitative HPLC analysis.[16]



Scheme 2. Initial attempt for cyclization.

Table 2
Optimization of cyclization[a]



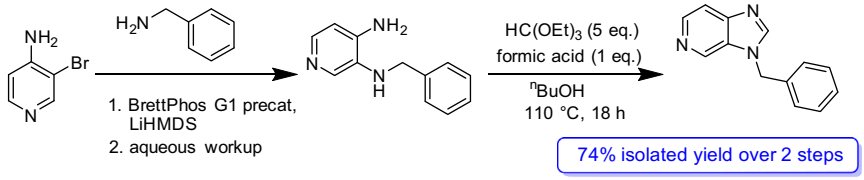
[a] The yields were determined based on quantitative HPLC analysis.[15]

yield while none of the other bases (Table 1, entry 9–13) examined gave more than 35% yield. Additional variables including solvent, concentration, catalyst loading, equivalents of base, and temperatures were also examined. While these parameters did not impact the reaction as profoundly as the catalyst and the base, we did observe that the reaction was more efficient at higher concentrations (Table 1, entry 1 and 14–16) and the yield was slightly improved to 94% at 0.4 M concentration compared with 0.2 M. After examining multiple parameters for the model substrate, we concluded the following reaction conditions as optimal for the C–N coupling: BrettPhos G1 precatalyst (6 mol%), LiHMDS (2.5 equiv), THF (0.4 M), 40 °C. In addition, we also examined 4-amino-3-iodopyridine and 4-amino-3-chloropyridine as the halide coupling partner and found that the former showed comparable reactivity (85% yield) while the chloride had inferior performance (47% yield).

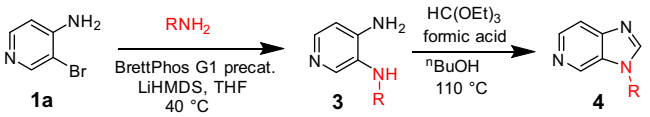
With optimal C–N coupling conditions identified, we turned our attention to the cyclization step. Our first attempt using triethyl orthoformate and acetic acid as the promoter afforded the desired product in 46% yield (isolated) together with 13% yield of 2-methyl imidazopyridine as side product, indicating the participation of acetic acid (Scheme 2). Encouraged by this, we examined alternative acids and solvents for optimization (Table 2). The protic solvent *n*-BuOH generally outperformed DMF and gave moderate to good yields of the cyclized product. The best conditions for the cyclization afforded the product in 91% yield using 1 equiv of formic acid in *n*-BuOH. A surprising observation from these experiments was the exclusive formation of the ethylpyridinium salt in either $PhSO_3H$/DMF or NH_2SO_3H/DMF combinations suggesting the potential generation of electrophilic ethyl equivalent in the reaction media when strong acid and polar aprotic solvent were used.[17]

After the two individual steps (C–N coupling and cyclization) were optimized, it was realized that purification of extremely polar C–N coupled diamine was difficult with standard silica gel column chromatography techniques. Therefore, we decided to compare three different work-up procedures: (1) purification of diaminopyridine intermediate by silica gel column chromatography followed by cyclization; (2) aqueous workup of the C–N coupling reaction and use of the crude diaminopyridine in the next step; and (3) one-pot sequence of the two steps. Among the three options, procedure 2 afforded a 74% isolated yield over two steps while the yields for other two procedures were less than 40% (see Scheme 3).

After establishing an optimized two step procedure for the imidazopyridine synthesis, the scope of the alkyl amine component was examined. Primary amines without steric hindrance at the alpha position all provided the desired products in moderate to good yield (**4a**–**e**, **4g**–**h**). However, with sterically hindered amines, lower reactivity was observed (**4i**) and no desired product was observed for tert-butylamine (**4k**). The lower reactivity for **4f** may be attributed to the chelation behavior of the amine. On the other hand, the relatively lower yield of **4j** might be related to the instability of N-Boc functionality in the second step (see Scheme 4).



Scheme 3. Two step/single purification procedure for Imidazopyridine synthesis.



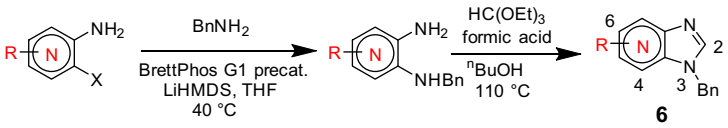
product	R	Yield (2 steps)	product	R	Yield (2 steps)
4a	Ph	74%	4g	iPr	72%
4b	OMe	68%	4h	Cy	63 %
4c	nHex	76%	4i	Ph	57%
4d	Cy	68 %	4j	N–Boc	42%
4e	Ph	86%	4k	tBu	0%
4f	OMe	39%			

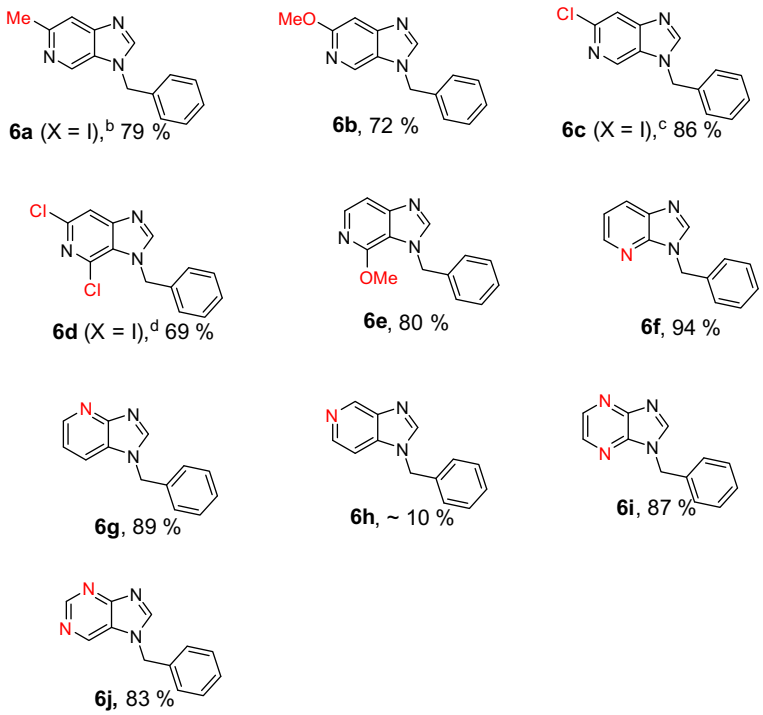
Scheme 4. Scope of primary amine. Step 1: RNH_2 (1-1.5 equiv), BrettPhos G1 Precat. (6 mol%), LiHMDS (2.5 equiv), 40 °C, 4–18 h. Step 2: triethylorthoformate (5 equiv), formic acid (1 equiv), ^{n}BuOH, 110 °C, 18–24 h, yield as isolated after two steps.

Having explored the scope and limitation of the primary amine component, we turned our attention to variation of the pyridine core using benzylamine as the C–N coupling partner. In this context, we intended to explore various substitution patterns on the pyridine core, as well as pyrazine and pyrimidine derivatives. As summarized in Scheme 5, electron donating and withdrawing substituents on the 4 or 6 position[18] of the pyridine ring were both tolerated (**6a–e**). For most cases, either bromide or iodide substrate worked similarly for the C–N coupling except for **6c** and **6d**, where the iodo derivative was chosen intentionally to minimize bis/tris C–N coupling. To our delight, in addition to the 4-amino-3-bromopyridine, two other regioisomers: 3-amino-2-bromopyridine (**6f**) and 2-amino-3-bromopyridine (**6g**) both worked well with this sequence and gave the products in good yields. Although the reaction of 4-bromo-3-aminopyridine and benzylamine did not yield product (**6h**) in a productive way (only ~10%), the value of this novel two-step protocol was further demonstrated in the case of pyrazine and pyrimidine based systems, where imidazopyrazine (**6i**) and purine (**6j**) were efficiently prepared.

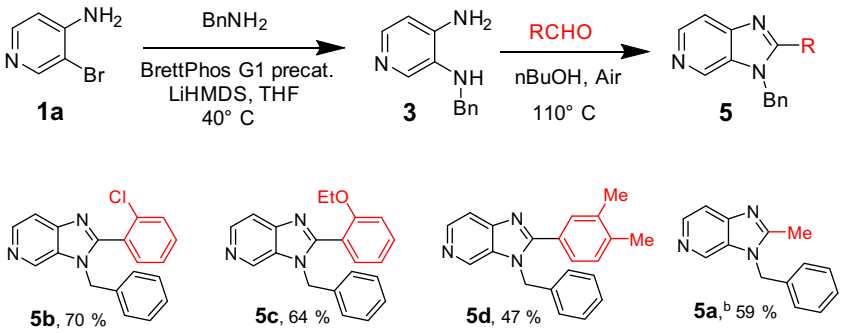
To further expand the substrate scope of this procedure, the preparation of 2-substituted imidazopyridines was next investigated. When the intermediate diamine **3** was reacted with different aromatic aldehydes under aerobic oxidation condition[19] at elevated temperature, the corresponding 2-aryl substituted derivatives **5b–d** were obtained in moderate yields. Taking note of our previous experience (Scheme 2), triethyl orthoacetate was used as cyclization reagent to generate the 2-Me substituted product **5a** in 59% isolated yield (see Scheme 6).

In summary, we have developed a practical[20] strategy for the preparation of imidazopyridine derivatives from *ortho*-haloaminopyridines utilizing a two-step C–N coupling/cyclization reaction sequence. The scope and limitations of this sequence has been explored. This procedure provides rapid and efficient access





Scheme 5. Pyridine core variations.[a] [a]Step 1: RNH_2 (1-1.5 equiv), BrettPhos G1 Precat. (6 mol%), LiHMDS (2.5 equiv), 40 °C, 4–18 h. Step 2: triethylorthoformate (5 equiv), formic acid (1 equiv), ^{n}BuOH, 110 °C, 18–24 h, yield as isolated after two steps. [b]5-iodo-2-methylpyridin-4-amine was used as starting material. [c]2-chloro-5-iodopyridin-4-amine was used as starting material. [d]2,6-dichloro-3-iodo-4-aminopyridine was used as starting material.



Scheme 6. Synthesis of 2-substituted imidazopyridines.[a] [a]Step 1: $BnNH_2$ (1.5 equiv), BrettPhos G1 Precat. (6 mol%), LiHMDS (2.5 equiv), 40 °C, 4–18 h. Step 2: RCHO (2 equiv), *n*BuOH, air, 110 °C, 18–24 h. [b]For Step 2: triethylorthoacetate (5 equiv), acetic acid (1 equiv), *n*-BuOH, 110 °C, 24 h, yield as isolated after two steps.

to many medicinally interesting imidazopyridine compounds and related imidazopyrazine/purine heterocycles. We anticipate further utilization of this method in the chemical community.

Acknowledgements

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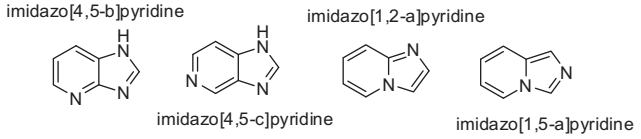
Supplementary data

Supplementary data (1H and 13C NMR spectra of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.118.

References and notes

1. Imidazopyridine derivatives comprise four unique isomers: imidazo[4,5-b] pyridine, imidazo[4,5-c]pyridine, imidazo[1,2-a]pyridine and imidazo[1,5-a] pyridine. Only the first two isomers are related to this study.



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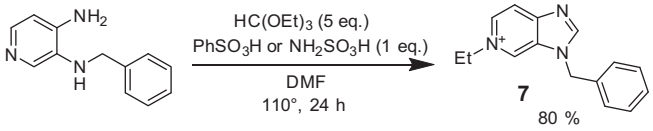
16. The HPLC yields refer to quantitative HPLC analysis of crude reaction mixtures using an analytically pure standard.
17. See SI for the characterization of ethylpyridinium product **7** of this reaction.



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20. We have carried out 2 g scale reaction between substrate **1a** and benzylamine, which gave comparable (75%) yield.