Tetrahedron Letters 57 (2016) 2708–2712

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid construction of imidazopyridines from *ortho*-haloaminopyridines

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ARTICLE INFO

Article history:
Received 16 March 2016
Revised 21 April 2016
Accepted 27 April 2016
Available online 9 May 2016

Keywords:
Imidazopyridine
Ortho-haloaminopyridine
C–N coupling
Imidazopyrazine
Purine

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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http://dx.doi.org/10.1016/j.tetlet.2016.04.118
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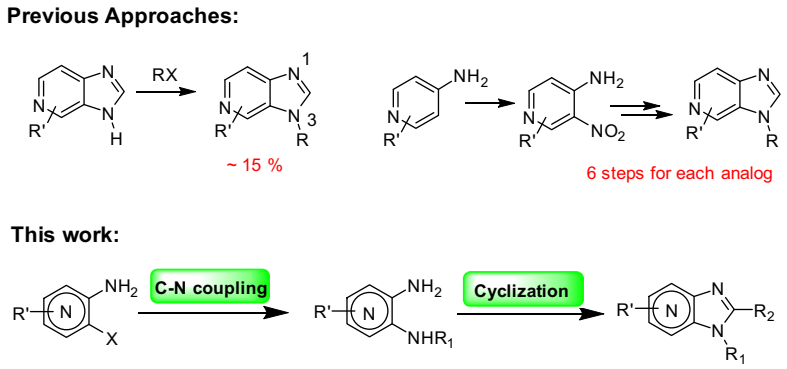
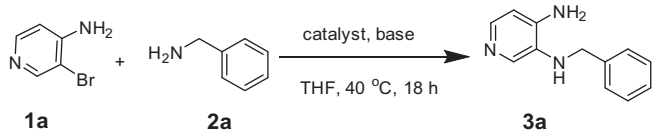
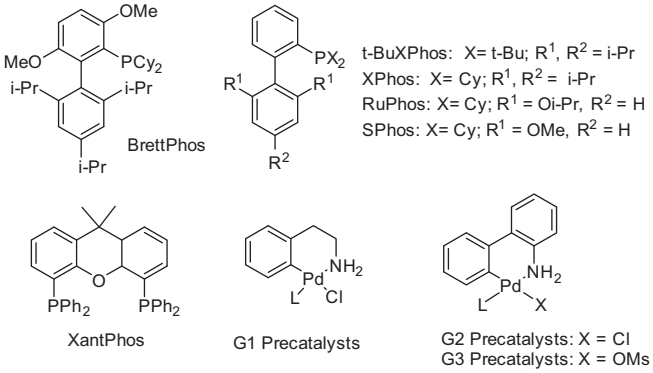


Scheme 1. Routes to imidazopyridine derivatives.

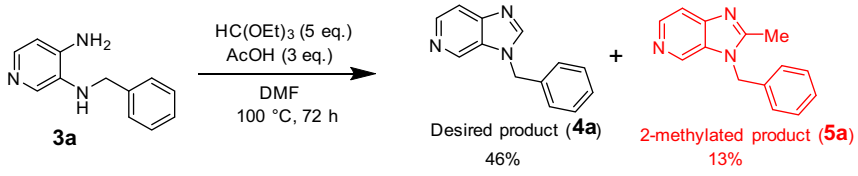
Table 1
Optimization of C–N coupling[a]



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.