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Regioselective synthesis of C-2 substituted imidazo[4,5-*b*]pyridines utilizing palladium catalysed C–N bond forming reactions with enolizable heterocycles

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ABSTRACT

In this Letter we report a rapid and facile access to C2-substituted imidazo[4,5-*b*]pyridine analogues utilizing palladium mediated Buchwald–Hartwig cross-coupling reactions. The use of enolizable heterocycles as cross-coupling partners resulted in a wide range of imidazo[4,5-*b*]pyridine analogues which are prone to have medicinal relevance. Xantphos and $Pd(OAc)_2$ were found to be more effective for the coupling of 2-halo imidazo[4,5-*b*]pyridines with pyridone nucleophiles. A regioselective approach for the synthesis of 2-substituted 3*H*-imidazo[4,5-*b*]pyridine and 1*H*-imidazo[4,5-*b*]pyridine is also reported.

Imidazo[4,5-*b*]pyridines are an important class of heterocycles that have been widely studied for biological activity.[1] The reason why imidazo[4,5-*b*]pyridines have a broad pharmacological profile lies in their similarity and isosterism to purines.[2] A combination of biologically relevant heterocyclic systems and their further derivatization is of immense interest due to the novelty and therapeutic potential of the developed heterocycles.[3] As part of our research on imidazo[4,5-*b*]pyridine core[4] we were interested in the C2-amination[5] of this pharmaceutically relevant molecule.

The introduction of amino moiety at this position is well documented in the literature for benzimidazoles.[6] In our previous work we have successfully demonstrated the synthesis of 2-amino-1-methyl-6-phenylimi-dazo[4,5-*b*]pyridine (PHIP) and 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine (DMIP), which involves an optimized palladium mediated Buchwald cross coupling reaction of 2-halo-3-alkylimidazo[4,5-*b*]pyridine with benzophenone imine.[4a] The C2-amination of this heterocyclic core can lead to more diverse 2-amino deazapurine analogues[7] which can be a better substitute to the benzimidazole[8] analogues leading to more potential drug candidate. The 2-amino deazapurine analogues have better aqueous solubility and may have a better biological profile compared to benzimidazole ring derived analogues.

Palladium-catalysed C-N bond forming reactions of heteroaryl halides has rapidly emerged as a valuable tool in the field of heterocyclic chemistry for the construction of (hetero) aryl amines.[9] During the preparation of this Letter, Clark et al.[7a] reported the synthesis of 2-amino-imidazo[4,5-*b*]pyridines via nucleophilic substitution (S_NAr) with functionalized primary and secondary amines. As part of our research work on biologically relevant imidazo[4,5-*b*]pyridine based structures, we were interested in introducing some pyridone analogues at C2 position of this heterocyclic core. Unfortunately, our initial efforts to introduce pyridones via nucleophilic substitution (S_NAr) were not promising as we did not observe any product formation (Table 1). Our subsequent efforts were to employ palladium mediated C-N bond forming conditions to cross-couple a wide range of enolizable heterocycles with this heterocyclic core. The development of more efficient ligands (Brettphos, S-phos, *t*-BuXphos, RuPhos etc.) by Buchwald[10] prompted us to study the reactivity of 2-halo imidazopyridines using various palladium catalyst/ligand combinations.

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Table 1
Effect of bases on cross-coupling of **3** with **2a**

Entry	Base (3 equiv)	Conditions	Solvent	[i]Yield[a] (%)
1	KO*t*Bu	90 °C, 15 h	1,4-Dioxane	0
2	NaO*t*Bu	90 °C, 15 h	1,4-Dioxane	Traces
3	K_3PO_4	90 °C, 15 h	1,4-Dioxane	0
4	Na_2CO_3	90 °C, 15 h	1,4-Dioxane	0
5	CsOAc	90 °C, 15 h	1,4-Dioxane	Traces
6	Cs_2CO_3	90 °C, 15 h	1,4-Dioxane	Traces

[a] Method A: Base (3 equiv), **3** (1 equiv), **2a** (1.3 equiv), sealed vial, 90 °C, 15 h, 1,4-dioxane.

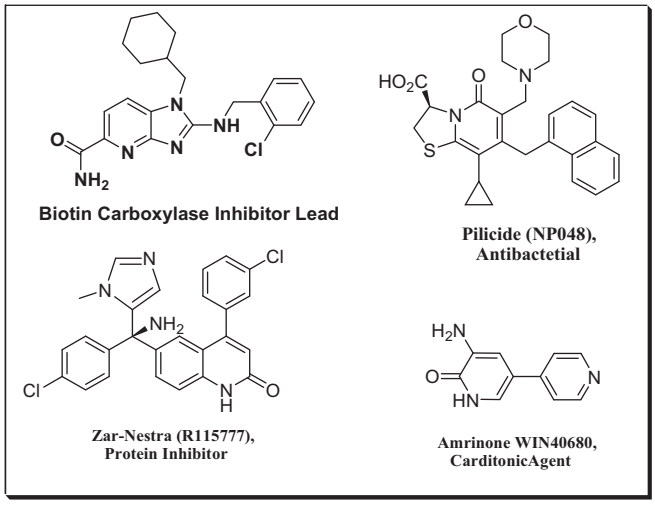
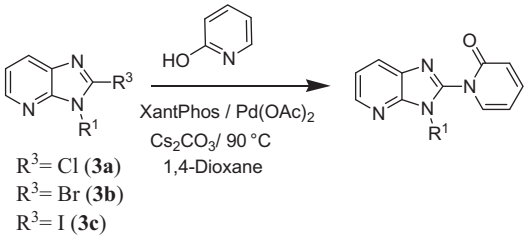


Figure 1. Pharmacologically relevant imidazo[4,5*b*]pyridines.



Scheme 1. Synthesis of substituted imidazo[4,5-*b*]pyridin-2-yl)pyridin-2(1*H*)-one.

The presence of substituted pyrid-2-ones in biologically relevant analogues (Fig. 1) has attracted synthetic organic chemists and hence an efficient protocol to access these compounds is of high relevance.[9a] The presence of these N-alkylated heterocycles in both natural products and pharmacologically relevant molecules renders them as useful synthons in the field of medicinal chemistry. Moreover, enolizable heterocycles[11] such as 2-hydroxypyridine,[11c] 4-hydroxypyrimidine and 3-hydroxypyridazine have provoked great interest in biological and chemical fields as a result of their ability to serve as models for hydrogen bonding[12] tautomerization[12] and proton shuttling[12] in both chemical and biological processes. These data directed our studies towards the synthesis of diversely substituted pyridone analogues at the C-2 position of imidazo[4,5-*b*]pyridine core.

Optimization of the reaction parameters was performed with **3a** to stabilize an effective catalytic system for Buchwald cross-coupling of imidazo[4,5-*b*]pyridine core. Chloro, bromo and iodo azoles (**3a**, **3b** and **3c**) were used as electrophiles and their synthesis was performed as described in reference.[4a–c] Our initial attempts to cross-couple **3c** with pyridone (**2a**) using $Pd(OAc)_2$/BINAP, KO*t*Bu in 1,4-dioxane were unsuccessful as we could see major dehalogenation of **3c**. The use of weaker bases like K_2CO_3 and Cs_2CO_3 also did not provide any fruitful results. Probably, iodo analogue becomes too labile, as it is flanked between two nitrogen atoms and hence highly reactive.[13]

An attempt was made on the use of **3a** and **3b** for cross-coupling with **2a** (Scheme 1). We could obtain 30% product by using **3b** along with $(PdOAc)_2$/BINAP and Cs_2CO_3 in 1,4-dioxane. A base screening was conducted and the results are shown in Table 2. The isolated yields of the coupled products were still not promising. Failure of the aforementioned conditions prompted us to screen various ligands for the cross-coupling of **3b** with pyridone (Table 3). To our delight, we could isolate 94% of pyridone coupled product using $(PdOAc)_2$/xantphos and Cs_2CO_3 as base. Identical result was observed when chloro intermediate (**3a**) was the cross coupling partner (Scheme 1). The effect of solvents on the reaction was studied and the results are presented in Table 4. Applying these optimized conditions to a series of diversely substituted 2-hydroxypyridines, allowed the rapid synthesis of N-alkylated pyridines in excellent yields (Table 5). For substrates bearing electron-withdrawing groups (Table 5, **4o**) longer reaction times were required and low yields of the coupled products were obtained. The electron withdrawing groups on pyridone reduce the nucleophilicity of the nitrogen thereby making the reactions very sluggish. To extend the scope of this methodology, we screened a variety of heterocycles containing more than one nitrogen atom (Table 5, **4p**, **4q** and **4r**). The formation of the products under these optimized conditions was confirmed by ^{1}H NMR and LCMS. The final coupled products show characteristic IR absorption bands of pyridone at 1715 cm^{-1}.

The overall efficiency of a cross-coupling process is significantly affected by the structure of the ligand (see Fig. 2) and catalyst. Therefore the use of ligand with appropriate steric and electronic properties is very crucial in dealing with problematic and specific substrates in this area. To extend the scope of this methodology in the regioselective synthesis of 2-substituted 3*H*-imidazo[4,5-

Table 2
Effect of bases on cross-coupling of **3b** with **2a**

Entry	Catalytic system	Base (**3** equiv)	Conditions	Solvent	[i]Yield[a] (%)
1	$Pd_2(dba)_3$/BINAP	KO*t*Bu	90 °C, 15 h	1,4-Dioxane	0
2	$Pd_2(dba)_3$/BINAP	KOAc	90 °C, 15 h	1,4-Dioxane	0
3	$Pd_2(dba)_3$/BINAP	K_3PO_4	90 °C, 15 h	1,4-Dioxane	Traces
4	$Pd_2(dba)_3$/BINAP	Na_2CO_3	90 °C, 15 h	1,4-Dioxane	Traces
5	$Pd_2(dba)_3$/BINAP	CsOAc	90 °C, 15 h	1,4-Dioxane	25
6	$Pd_2(dba)_3$/BINAP	Cs_2CO_3	90 °C, 15 h	1,4-Dioxane	30

[a] Method A: 4 mol % $Pd_2(dba)_3$, 8 mol % BINAP, Base (3 equiv), **3b** (1 equiv), **2a** (1.3 equiv), sealed vial, 90 °C, 15 h, 1,4-dioxane.
[i] Isolated yields.