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Easy Access to Novel Substituted 6-Aminoimidazo[1,2-*a*]pyridines Using Palladium- and Copper-Catalyzed Aminations

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Convenient and efficient methods for the preparation of novel 6-aminoimidazo[1,2-*a*]pyridine derivatives are reported that utilized palladium- or copper-catalyzed methodology. The crystal structure for 6-*N*-methylanilinoimidazo[1,2-*a*]pyridine **10** is also described.

Introduction

Despite the significant and potential biological activities of heterocycles containing a fused imidazole ring [e.g., benzodiazepine receptor ligands (Zolpidem), ligands for detecting β-amyloid plaques in the brain, p38 MAP kinase inhibitors, corticotrophin releasing factor receptor ligands],[1] reactivity of the pyridine moiety of the imidazo[1,2-*a*]pyridine core was poorly studied. The promising pharmacological activities of this nucleus have prompted us to examine new methods of functionalization that allow rapid access to a number of structure variations. Recently, we turned out our attention to palladium-catalyzed processes such as Suzuki cross-coupling, leading to new 3- or 6-(hetero)arylimidazo[1,2-*a*]pyridines.[2] We next felt it of interest to prepare variously substituted 6-aminoimidazo[1,2-*a*]pyridines. To the best of our knowledge, few examples of 6-alkyl or arylamino derivatives have been described in the literature.[3] Moreover, because of the lack of reactivity in traditional nucleophilic substitution reactions at the 6 position in this series, none of them have been obtained via the direct amination reaction of 6-halogenoimidazo[1,2-*a*]pyridines. Preparation of amine derivatives starting from 6-aminoimidazo[1,2-*a*]pyridine requires two steps to provide the starting material: (1) cyclization of 5-nitropyridin-2-amine with α-bromo-4-fluoroacetophenone in 38% yield and (2) reduction of the 6-nitro group in 52% yield (data not shown). Additionally, 6-amino-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine is of limited stability. Finally, the functionalization of the 6-amino group is only efficient if highly reactive reagants, e.g., a 1,3-diketone, an isocyanate, an isothiocyanate, or an acid chloride are used. No method allows the ready preparation of structural variants. Thus, new approaches that allow functionalization of the pyridine moiety, particularly with amino groups, are needed.

In the past few years, the palladium-catalyzed amination of aryl halides and sulfonates has been developed as a useful synthetic method.[4] More recently, it has begun to find widening application in heterocyclic chemistry as exemplified by the amination of halothiophenes,[5] halopyridines,[4a,6] β-carboline,[7] benzimidazoles,[8] and halopurines.[9,10] Moreover, libraries of heterocycles were prepared by the solid-phase aminations of substituted

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purines, pyrimidines, quinazolines, quinoxalines, pyrazines, pyridazines, and phthalazines.[10]

More recently, a simple and general procedure for the copper-catalyzed coupling of alkylamines was reported.[11] This method can be carried out in relatively mild reaction conditions and can be performed under air. This protocol was efficient for the amination of iodobenzenes and, under modified conditions, certain bromobenzenes. The only halogenated heterocycle included in this study was 3-iodopyridine.

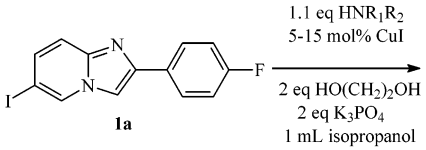
In our own work, we decided to evaluate the applicability of the palladium- and copper-catalyzed amination protocols to the combination of amines and 6-halogenoimidazo[1,2-*a*]pyridines. We also felt that it would be interesting to compare the efficiency of the Pd- and Cu-catalyzed methods.

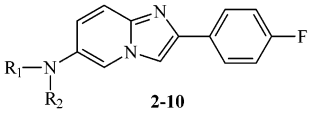
Results and Discussion

One of our initial forays was the investigation of the application of the copper-based C−N bond-forming methodology to 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a**. Indeed, compound **1a** is a very convenient starting material as it is very stable and easily obtained in one step through condensation of commercially available 5-iodopyridin-2-amine with α-bromo-4-fluoroacetophenone in refluxing ethanol in 84% yield.

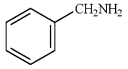
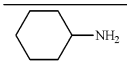
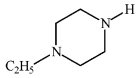
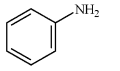
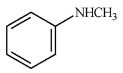
Our studies began using the reaction conditions previously described by Kwong and Buchwald (Table 1).[11] For example, the coupling reaction of benzylamine with **1a** was carried out in the presence of 5 mol % of copper(I) iodide, 2 equiv of ethylene glycol and 2 equiv of K_3PO_4 in 2-propanol (1 mL/mmol) at 85 °C for 20 h. Using this protocol, **2** was obtained in 69% yield after purification. Unfortunately, under the same reaction conditions, only 32% of the morpholino derivative **3** was formed; a significant amount of starting material remained after 20 h of heating. Considering these results and the slow rate of the reaction, we decided to optimize the process at a higher reaction temperature. We found that in refluxing toluene the coupling of benzylamine with **1a** was improved giving **2** in 79% yield. In a likewise fashion, *n*-hexylamine, cyclohexylamine, and pyrrolidine were combined with **1a** leading to compounds **4**−**6** in good yield. In contrast, using the same conditions, only moderate yields were obtained with the secondary cyclic amines, *N*-ethylpiperazine and morpholine (44 and 32% respectively). Under these conditions, all of the reactions proceeded to completion, and no starting material was

TABLE 1. Copper-Catalyzed Amination of 6-Iodo-2-(4-fluorophenyl)Imidazo[1,2-*a*]pyridine with Various Amines[a]





2-10

HNR_1R_2	Catalyst (mol%)	Temp (°C)	Time (h)	Product	Yield (%)[b]
	5	85	20		69
	5	112	20	**2**	79
	15	85	20		85
	5	85	20		32
	5	112	20	**3**	32
	15	85	20		49
	15	85	48		72
$nC_6H_{13}NH_2$	5	112	20	**4**	71
	15	85	20		59
	15	85	48		76
	5	112	20		66
	15	85	20	**5**	55
	15	85	48		72
	5	112	20	**6**	71
	15	85	20		84
	5	112	20		44
	15	85	20	**7**	49
	15	85	48		69
	15	85	20	**8**	52
	15	85	48		70
	5	85	20		30
	5	112	20	**9**	20
	15	85	20		20
	5	112	20	**10**	-

[a] Reaction conditions: 1 mmol of **1a**, 1.1 mmol of amine, 5−15 mol % of CuI, 2 mmol of K_3PO_4, 2 mmol of $HOCH_2CH_2OH$, 1 mL of 2-propanol. [b] Isolated yields.

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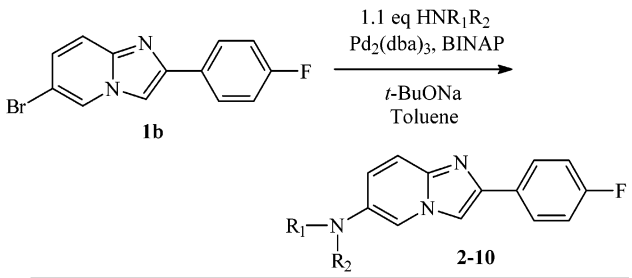
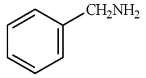
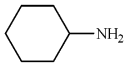
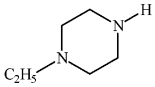
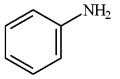
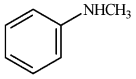
TABLE 2. BINAP/Pd Catalyzed Amination of 6-Bromo-2-(4-fluorophenyl)Imidazo[1,2-*a*]pyridine with Various Amines[a]



HNR_1R_2	Temp (°C)	Product	Yield (%)[b]
	85		40
	112	**2**	58
	112	**3**	69
$nC_6H_{13}NH_2$	112	**4**	71
	112	**5**	70
	112	**6**	85
	112	**7**	67
	85		54
	112	**9**	82
	112	**10**	55

[a] Reaction conditions: 1 mmol of **1b**, 1.1 mmol of amine, 1 mol % of $Pd_2(dba)_3$, 3 mol % of *rac*-BINAP, 1.4 mmol of *t*-BuONa, 2 mL of toluene. [b] Isolated yields.

seen after 20 h at 112 °C. Also observed was 7−15% of reduced **1a**. In the case of compounds **3** and **7**, the main side product, however, was 40−60% of 6-[(2-hydroxy)-ethoxy]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine resulting from the coupling of **1a** with ethylene glycol.

To improve the yield, we next increased the quantity of CuI from 5 mol % to 15 mol % while maintaining the reaction temperature at 85 °C. Again, a significant improvement was observed with benzylamine as substrate and **2** was isolated in 85% yield. When this reaction procedure was applied to the coupling of pyrrolidine, the yield increased from 71 to 84%. With *n*-hexylamine, cyclohexylamine, *N*-ethylpiperazine, and morpholine couplings, however, there were only slight or no improvement of the yields. Interestingly, for these reactions conducted at 85 °C, the major side product was unreacted **1a**. The ethylene glycol adduct was observed only in the coupling reaction of *N*-ethylpiperazine (11%). This indicated that an increased reaction period might be beneficial. Fortunately, by simply increasing the reaction time to 48 h, a clear increase in the yield of the desired compounds **5**, **7**, **8**, and **3** (72, 69, 70, and 72%, respectively) was seen when cyclohexylamine, *N*-ethylpiperazine, piperidine, and morpholine were used as substrates.

Finally, consistent with what had previously been reported, attempts to apply our modified protocol to the coupling of aniline and *N*-methylaniline provided only small amounts of the desired products. Then, in order to expand the range of the 6-substituted amino derivatives obtained in the imidazo[1,2-*a*]pyridine series to the aromatic amines, we decided, in the second part of this project, to evaluate the applicability of palladium-catalyzed amination protocols to the combination of amines and **1a**.

We begun by using previously described conditions (1.1 eq amine, 1 mol % $Pd_2(dba)_3$, 3 mol % *rac*-BINAP, 1.4 eq *t*-BuONa/toluene, 20 h) and applied them to the coupling of various amines with 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1b**.[2b] As for **1a**, **1b** is stable to air and light and can be obtained in 84% yield from commercial starting materials. The initial conditions for the combination of benzylamine and aniline with **1b** at 85 °C provided the products only in moderate yields, 40 and 54%, respectively. Besides the desired products **2** and **9**, starting material was recovered in both cases; a trace of reduced **1b** was also seen in the coupling of benzylamine. As before, switching to refluxing toluene as solvent increased the yield of the aniline coupling product **9**, to 82%. Surprinsingly, the coupling of benzylamine gave **2** in only 58% yield. The main side product in this case was again reduced **1b**. Subsequently, we tested the applicability of these reaction conditions to the coupling of **1b** with other primary and secondary amines. Moderate to good yields were obtained (55−85%). No starting material was recovered but small amounts of reduced compound (5−15%) were present in all cases.

Conclusions

In conclusion, we have demonstrated that both copper- and palladium-catalyzed amination can serve as a valuable tool for the functionalization of 6-haloimidazo[1,2-*a*]pyridines. Nine primary and secondary amines were coupled with **1** to provide a series of 6-aminoimidazo[1,2-*a*]pyridines in moderate to good yields (55−85%). We are currently working on the extension of this method to include other amines and to the amination of other haloimidazo[1,2-*a*]pyridines.

Experimental Section

General Procedure for Cu-Catalyzed Aminations: Method A. 6-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a** (338 mg, 1 mmol), copper (I) iodide (9.5 mg, 0.05 mmol or 29 mg, 0.15 mmol), and potassium phosphate (425 mg, 2 mmol) were added to a screw-capped test tube. The tube was evacuated and back filled with argon. Ethylene glycol (111 μL, 2 mmol), amine (1.1 mmol), and 2-propanol (1 mL) were added

successively by syringe at room temperature. The tube was sealed with a Teflon-lined cap, and the reaction mixture was heated at 85 or 112 °C for 20 or 48 h. After cooling to room temperature, the suspension was diluted with dichloromethane and was filtered through Celite. The solvent was removed with the aid of a rotary evaporator to give a brown residue which was purified by column chromatography on silica gel, eluting with dichloromethane and then a mixture of CH_2Cl_2/MeOH = 99.5/0.5 to give pure product.

General Procedure for Pd-Catalyzed Aminations: Method B. 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine[2b] **1b** (291 mg, 1 mmol), tris(dibenzylideneacetone)dipalladium (9.2 mg, 0.01 mmol), *rac*-BINAP (19 mg, 0.03 mmol), and sodium *tert*-butylate (135 mg, 1.4 mmol) were added to a screw-capped test tube. The tube was evacuated and back filled with argon. Amine (1.1 mmol) and toluene (2 mL) were added successively by syringe at room temperature. The tube was sealed with a Teflon-lined cap, and the reaction mixture was heated at 85 or 112 °C for 20 h. After cooling to room temperature, the suspension was diluted with dichloromethane and filtered through Celite. The solvent was removed with the aid of a rotary evaporator to give a brown residue which was purified by column chromatography on silica gel, eluting with dichloromethane and then CH_2Cl_2/MeOH = 99.5/0.5 to give pure product.

Crystal structure for compound 10. The structure of the anilino compound **10** was confirmed by X-ray analysis (Supporting Information).

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and X-ray crystallographic data for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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