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Ipso- or *Cine*-Substitutions of 6-Haloimidazo[1,2-*a*]pyridine Derivatives with Different Azoles Depending on the Reaction Conditions

Cécile Enguehard,[†] Hassan Allouchi,[‡] Alain Gueiffier,*[,†] and Stephen L. Buchwald[§]

EA 3247, Laboratoire de Chimie Thérapeutique, and Laboratoire de Chimie Physique, UFR des Sciences Pharmaceutiques, 31 Avenue Monge, 37200 Tours, France, and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

gueiffier@univ-tours.fr

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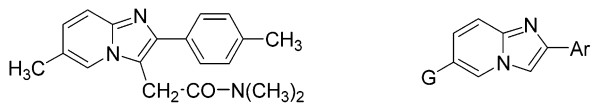
The reactivity of 6-haloimidazo[1,2-*a*]pyridine toward different azoles is reported. The process was shown to be highly dependent on the reaction conditions. Using copper(I) catalyst, the product of *ipso* substitution was obtained. In the absence of copper, with cesium carbonate in *N*,*N*-dimethylformamide, a *cine* substitution took place.

The commercialization of the imidazo[1,2-*a*]pyridine derivative zolpidem **I** (Figure 1) as a hypnotic[1] demonstrated the pharmacological potential of fused imidazole heterocycles with bridgehead nitrogens. Surprisingly, despite the interest in the imidazo[1,2-*a*]pyridine series in medicine,[2] few studies on the reactivity of the pyridinyl moiety have been reported. In the course of our work evaluating the chemical and pharmacological properties of fused imidazolic derivatives with bridgehead nitrogens,[3] we have recently reported on the reactivity of 6-haloimidazo[1,2-*a*]pyridines **II** in Suzuki cross-coupling reactions and palladium- or copper-catalyzed aminations.[4] In further pursuing investigations on methods of functionalization which allow the rapid preparation of a number of structural variants, we became interested in the preparation of 6-azolyl derivatives; our results in this area are the subject of this manuscript.



I = Zolpidem

II G = halogen
III G = R

FIGURE 1. Structure of zolpidem and related compounds.

The use of high temperatures and an excess of aryl halide required in traditional Ullmann coupling procedures[5,6] is incompatible with the sensitive nature of **II** and **III**. Recently, Ullmann-type methods for the *N*-arylation of imidazoles[7] as well as copper- and palladium-catalyzed arylations of indole[8] and other *N*-heterocycles have been reported.[9] We chose to apply the copper-catalyzed procedure to the reaction of **1**. In our first attempts, the 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridine **1a** was reacted with 1 equiv of azole in the presence of 5 mol % of copper(I) iodide, 15 mol % of *rac-trans*-*N*,*N*′-dimethyl-1,2-diaminocyclohexane (ligand A), and 2.1 equiv of potassium phosphate in toluene (1 mL/mmol) at 112 °C for 24 h (Table 1). Under these

* To whom correspondence should be addressed. Fax: +33(0)2 47 36 72 88.

† Laboratoire de Chimie Thérapeutique, UFR des Sciences Pharmaceutiques.

‡ Laboratoire de Chimie Physique, UFR des Sciences Pharmaceutiques.

§ Massachusetts Institute of Technology.

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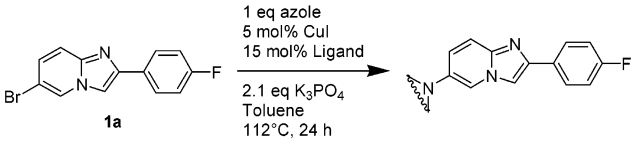
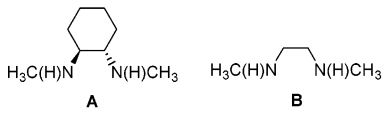
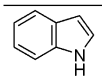
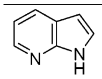
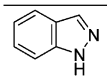
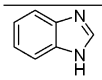
TABLE 1. Copper-Catalyzed Couplings of 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine 1a with Various Azoles in Toluene[a]





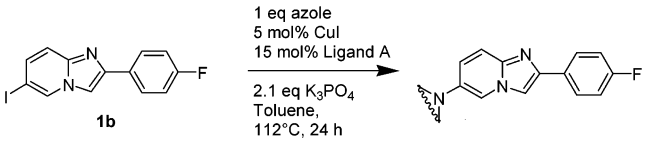
Azole	Ligand	Product	Yield (%)
	A	**2**	**72**
	B		70
	A	**3**	**94**
	B		29
	A	**4a-b**	**52**
			4a/4b **70/30**
	A	**5**	**44**
	A		20[b]
	A	**6**	**42**
	A	**7**	**18**
	A	**8**	**-**
	A	**9**	-
	A	**10**	-

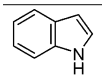
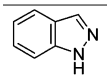
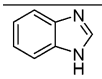
[a] All reactions: [**1a**] = 1 M in toluene. [b] Reaction was run using K_2CO_3 as base.

conditions, indole and 7-azaindole were efficiently *N*-arylated giving the desired products **2** and **3** in 72 and 94% yield, respectively. Likewise, indazole, pyrazole, and pyrrole were coupled in moderate yield (42−52%) while the imidazole derivative **7** was formed in only 18% yield. No reaction was found when using 1,2,3- and 1,2,4-triazoles and benzimidazole. In the case of the indazole coupling reaction, we observed the formation of the two regioisomers **4a** and **4b** in a 70/30 ratio with the *N*-1 derivative **4a** as the major compound. Attempts to change the base to potassium carbonate in the case of the pyrazole reaction according to the literature[9a] did not improve the coupling yield.

In consideration of the good results obtained with indole and 7-azaindole, we decided to study the applicability of *N*,*N*′-dimethyl-1,2-ethylenediamine, a commercially available ligand (ligand B). With ligand B, indole was arylated in a similar yield as before while a significant decrease in yield was found for 7-azaindole (Table 1).

TABLE 2. Copper-Catalyzed Couplings of 6-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine 1b with Various Azoles in Toluene[a]



Azole	Product	Yield (%)
	**2**	74
	**4a-b**	86
		4a/4b 97/3
	**5**	79
	**6**	76
	**7**	55
	**9a-b**	-
	**10**	9

[a] All reactions: [**1b**] = 1 M in toluene.

In an attempt to increase the efficiency of these processes, we performed the reaction with the more reactive 6-iodoimidazopyridine derivative **1b**.[4b] Using **1b**, no significant change in the coupling yield was observed for the reaction of indole (Table 2). However, with indazole, the yield of the coupling was increased from 52% to 86%. Additionally, the process occurred with a much improved regioselectivity, 97:3 in favor of the *N*-1 derivative **4a**. The *N*-arylations of pyrazole and pyrrole were also more efficient with **1b** providing **5** and **6** in 79 and 76% yields, respectively. The imidazole derivative **7** was obtained in 55% yield. However, the benzimidazole **10** was isolated in only 9% yield. As previously observed, the 1,2,3-triazole was unreactive.

At this point in our study, the coupling reactions of 1,2,4-triazole, 1,2,3-triazole, imidazole, and benzimidazole needed to be improved. In our first attempt, we decided to change to a more polar solvent, DMF (Table 3). With this change, the 1,2,4-triazolyl derivative **8** was obtained from **1b** in nearly 30% yield. Reaction with the 1,2,3-triazole gave a mixture of *N*-1 and *N*-2 derivatives **9a**,**b** in 59% yield in a ratio 44/56, the *N*-2 derivative **9b** predominating. In a second attempt, we investigated the use of stronger base cesium carbonate. The reaction of 1,2,4-triazole using cesium carbonate in DMF led to the 6-derivative **8** in 45% yield.

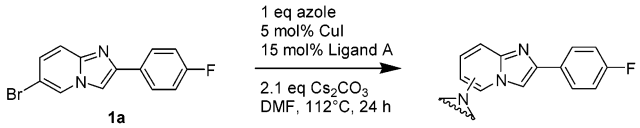
Remarkably, the reaction of imidazole and **1a** in DMF gave, in addition to expected product **7** in 31% yield, the 5-(imidazol-1-yl)-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine derivative **11** in 37% yield (Table 4). The structure of the latter compound was easily demonstrated by the

TABLE 3. Copper-Catalyzed Couplings of 6-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine 1b with Triazoles in DMF[a]

Azole	Base	Product	Yield (%)
	K_3PO_4	**8**	31
	Cs_2CO_3		45
	K_3PO_4	**9a-b**	59
			9a/9b 44/56

[a] All reactions: [**1b**] = 1 M in DMF.

TABLE 4. Copper-Catalyzed Couplings of 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine 1a with Imidazole and Benzimidazole in DMF[a]



Azole	7	11
	31	37

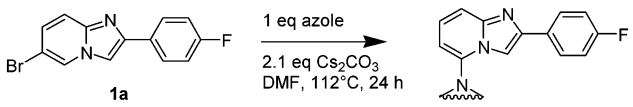
Azole	10	12
	12	21

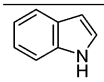
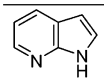
[a] All reactions: [**1a**] = 1 M in DMF.

disappearance of the H-5 resonance and the presence of a signal for H-6 as a doublet of doublets in the ^{1}H NMR spectrum. The structure of the 6-imidazolyl compound **7** was ascertained by X-ray crystallography study. In the case of benzimidazole, cesium carbonate also led to the formation of the C-6- and C-5-substituted derivatives **10** and **12** (12% and 21% yields. respectively).

We were then interested in the mechanistic pathway leading to the 5-substituted derivatives. To determine the role of the copper catalyst, we ran the reaction with **1a** in the absence of CuI with cesium carbonate in DMF at 112 °C for 24 h. Under these conditions, the 5-imidazolyl compound **11** was isolated in 58% yield along with 25% of unreacted starting material (Table 5). No trace of the 6-substituted derivative was found. These results demonstrated the formation of **11** was not copper dependent. An attempt to increase the efficiency of the *cine* substitution using 6-iodoimidazopyridine **1b** as starting material was unsuccessful leading to compound **11** in only 38%

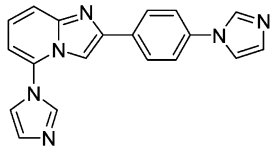
TABLE 5. *Cine* Substitutions on the 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine 1a in DMF[a]



Azole	Product	Yield (%)
	**11**	58
		37[b]
	**13**	59
	**14**	40
	**15**	52
	**16**	55

[a] All reactions: [**1a**] = 1 M in DMF. [b] Reaction was run at 140 °C.

SCHEME 1. Structure of the Diimidazolyl Side Product 17



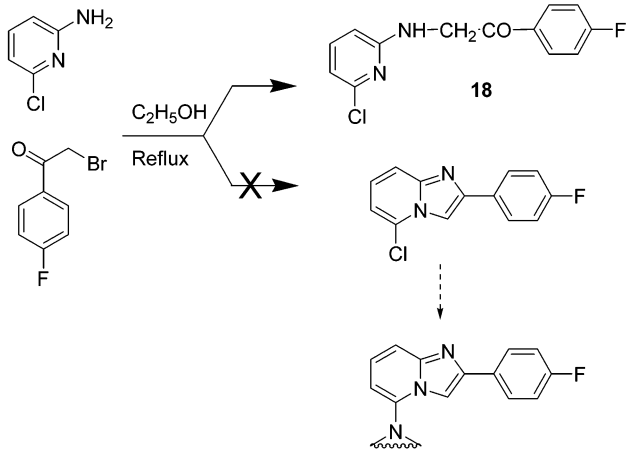
17

yield (data not shown). With the previous conditions, we were able to obtain the 5-substituted derivatives using pyrazole, pyrrole, indole, and 7-azaindole leading to compounds **13**−**16** in reasonable yields (40−59%). Only the 1,2,3- and 1,2,4-triazoles were unreactive. Since a significant amount of starting material was recovered in the imidazole coupling, we decided to run the reaction in the presence of imidazole at 140 °C. In this case, the yield decreased from 58% to 37% and the formation of the diimidazolyl compound **17** was observed in 20% yield (Scheme 1).

To the best of our knowledge, no *cine* substitution has been reported to date for the imidazo[1,2-*a*]pyridine series.[10] Only one example of *tele*-amination has been described with 3-bromo derivatives.[11] This unique *cine* substitution represents the first methodology that allows the direct preparation of 5-functionalized-2-arylimidazo-[1,2-*a*]pyridine derivatives. Thus, our attempts to form the 5-halo-2-phenylimidazo[1,2-*a*]pyridine failed to give the desired product required for the catalytic amination chemistry. When 2-amino-6-chloropyridine was allowed to react with the appropriate phenacyl bromide derivatives, none of the desired imidazopyridine was formed. Instead, attack of the phenacyl bromide by the anilino NH_2 gave the corresponding secondary amine **18** in moderate yield (Scheme 2).

(10) Suwinski, J.; Swierczek, K. *Tetrahedron*. **2001**, *57*, 1639.
(11) Hand, E. S.; Paudler, W. W. *J. Org. Chem*. **1978**, *43*, 2900.

SCHEME 2. Condensation of 2-Amino-6-chloropyridine with α-Bromo-4-fluoroacetophenone



It is interesting to consider whether this reaction occurs through an addition−elimination mechanism or an aryne mechanism. While we have no evidence, considering the nature of the base, we feel that the intermediary of an aryne is unlikely.

In conclusion, the coupling of various azoles with 6-bromo- or 6-iodoimidazo[1,2-*a*]pyridine provided 5- or 6-substituted derivatives depending on the reaction conditions. Using a copper(I) catalyst in toluene gave *ipso* substitution, while treatment with cesium carbonate in *N*,*N*-dimethylformamide led to *cine* substitution. Further studies are in progress to ascertain the mechanistic pathway and determine the scope and limitations of this reaction and its applicability to the preparation of other heterocycles containing bridgehead nitrogen.

Experimental Section

General Considerations. Unless otherwise noted, all chemicals were used as received. *trans*-*N*,*N*′-Dimethyl-1,2-diaminocyclohexane,[9b] 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridine,[4a] and 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine[4b] were prepared according to a literature procedure. All materials were weighed in an air atmosphere.

General Procedure for Cu-Catalyzed Arylations. Method A. A screw-cap test tube was charged with 6-halogeno-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a**,**b** (1.00 mmol), base (2.10 mmol), copper(I) iodide (9.5 mg, 0.050 mmol), and azole (1.00 mmol). A Teflon septum was attached, the tube was evacuated and back-filled with argon, and the evacuated/backfilled sequence was repeated an additional time. Ligand (0.15 mmol) and solvent (1 mL) were added by syringe under argon. The screw-cap test tube was sealed with a cap, and the reaction mixture was stirred magnetically at 112 °C (oil bath) for 24 h. After cooling, the suspension was diluted with dichloromethane and filtered through Celite. The filtrate was concentrated and the residue chromatographed to afford pure product.

General Procedure for *Cine* Substitutions. Method B. A screw-cap test tube was charged with 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a** (291 mg, 1.00 mmol), cesium carbonate (684 mg, 2.10 mmol), and azole (1.00 mmol). A Teflon septum was attached, the tube was evacuated and back-filled with argon, and the evacuated/backfield sequence was repeated an additional time. *N*,*N*-Dimethylformamide (1 mL) was added by syringe under argon. The screw-cap test tube was sealed with a cap, and the reaction mixture was stirred magnetically at 112 °C (oil bath) for 24 h. After cooling, the suspension was diluted with dichloromethane and filtered through Celite. The filtrate was washed with water, dried over magnesium sulfate, and concentrated under vacuo. The crude product was chromatographed to afford pure product.

Crystal Structure for Compound 7. The structure of the imidazolyl compound **7** was confirmed by X-ray analysis (Supporting Information).

Acknowledgment. S.L.B. thanks the US National Institutes of Health (GM58160), Merck, Pfizer, and Bristol-Myers-Squibb for funding. We are grateful to Dr. Jon C. Antilla for helpful advice and suggestions.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and X-ray crystallographic data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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