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A general and efficient method for the copper-catalyzed cross-coupling of amides and thiophenols with 6-halogenoimidazo[1,2-*a*]pyridines

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Abstract—Convenient and efficient methods for the preparation of novel 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridine derivatives that utilize copper-catalyzed methodologies are reported. These methods are particularly noteworthy because of their experimental simplicity and the low cost of the catalyst system.

1. Introduction

During the course of our work to evaluate the applicability of metallo-catalyzed cross-coupling reactions in the imidazo[1,2-*a*]pyridine series, we previously reported on the reactivity of this nucleus towards Suzuki type cross-coupling,[1] and copper- or palladium-catalyzed coupling reactions with amines and azoles.[2] From a diversity-targeting perspective, we were then interested in developing the 6-amido or 6-phenylsulfanylimidazo[1,2-*a*]pyridine series since no broadly applicable methods for the synthesis of these classes of compounds exist in the literature. To the best of our knowledge, few examples of 6-amidoimidazo[1,2-*a*]pyridines have been described in the literature and were prepared starting from 6-nitroimidazo[1,2-*a*]pyridines in two steps: reduction of the nitro group and reaction with an isocyanate or a carboxylate derivative.[3] Concerning the thioether compounds, two recent publications have related their preparation on the 6-position of the imidazo[1,2-*a*]pyridine through nucleophilic substitution with sodium thiolate or halogen–metal exchange and addition of a thiophenol.[4] Nevertheless, no experimental data were given and these procedures are incompatible with sensitive functionalities.

The formation of aryl C–X bonds (X=N, S, O, etc.) via copper-catalyzed coupling between aryl halides and hetero-centered nucleophiles has drawn a great deal of attention in the past few years.[5] The high stability and low costs of copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium-catalyzed processes. Concerning the Goldberg reaction,[6] recent developments dramatically simplified this classical amidation reaction. The enhanced version of the Goldberg coupling was reported using CuI and chelating 1,2-diamine in combination with K_3PO_4, K_2CO_3, or Cs_2CO_3.[7] Application of this methodology to various heteroaromatic compounds is still a relatively unexplored process. Only a few examples of copper-catalyzed *N*-arylations of amides with furan, thiophene, quinoline, and pyrimidine were reported in the literature.[7,8]

New methods for the copper-catalyzed formation of aryl–sulfur bonds, which are analogous to the Ullmann biaryl ether synthesis,[9] were recently reported by Palomo and co-workers in 2000,[10] and concomitantly by Venkataraman et al.,[11] and Buchwald and Kwong[12] in 2002. The Buchwald methodology is the most attractive from an economic standpoint using CuI in the presence of ethylene glycol and K_2CO_3. Only two examples of application to heterocycles were given in this publication. The Venkataraman methodology using neocuproine as ligand was extended to 8-mercaptoadenine.[13]

Because of the lack of a general protocol for their synthesis, we felt that the copper-based protocols may be readily extended to the synthesis of 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridines. Herein, we detail our copper-catalyzed C–N cross-coupling results using 6-halogeno-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridines with a broad

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selection of useful amido substrates, and we report the copper-based protocol for the cross-coupling of 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine with thiophenols.

2. Results and discussion

2.1. Copper-catalyzed carbon–nitrogen bond formation

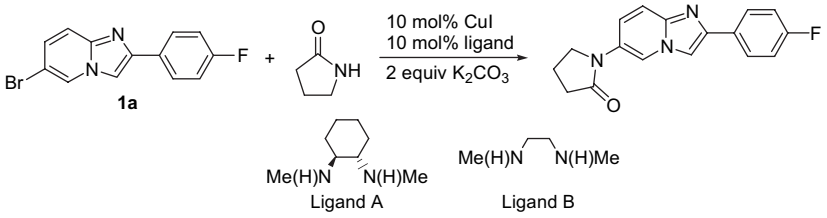
In our initial screening experiments, 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a** and pyrrolidinone were used as model substrates to evaluate suitable reaction conditions for the lactam cross-coupling (Table 1). Indeed, compound **1** is a very convenient starting material as it is very stable and easily obtained in one-step through condensation of commercially available 5-halogenopyridin-2-amine with α-bromo-4-fluoroacetophenone.

Two commercially available ligands were evaluated for the coupling reaction: *trans*-*N*,*N*′-dimethyl-1,2-cyclohexyldiamine (ligand A, entries 1 and 2) and *N*,*N*′-dimethylethylenediamine (ligand B, entries 3 and 4). Reactions were performed in two different solvents, toluene (entries 1 and 3) and dioxane (entries 2 and 4). In all cases, the coupling product was obtained in good yields (75–92%). Optimized reaction conditions utilized 10 mol % CuI, K_2CO_3 (2 equiv), and 10 mol % ligand B in toluene at 110 °C.

In the first part of this study, these reaction conditions were applied to the coupling of various lactams. As shown in Table 2, the process is also efficient when the size of the lactam ring is varied. Of particular interest is the result in entry 2, in which it appears that steric hindrance has no adverse effect on the success of the couplings.

The scope of this copper-catalyzed *N*-arylation of lactams was then extended to the use of amides, carbamate, and urea (Table 3). The heteroarylation of acetamide proved to be successful, starting from the iodinated substrate **1b** (85% yield, entry 2). *N*-Benzylformamide could also be coupled to **1a** and **1b** but in only 48% yield in both cases (entries 3 and 4). The use of ligand A in the presence of K_2CO_3 or K_3PO_4 was then evaluated. As can be seen, the reaction of *N*-benzylformamide with **1b** proceeded in 71% yield using ligand A and K_3PO_4 (entry 6). These modified conditions were also efficient in the *N*-arylation of benzamide (99% yield, entry 8) and to a lesser extent, phenylurea (58% yield, entry 10). The *N*-(*tert*-butyloxycarbonyl)aniline remained a problematic substrate in the catalyst systems evaluated, resulting in only poor yields.

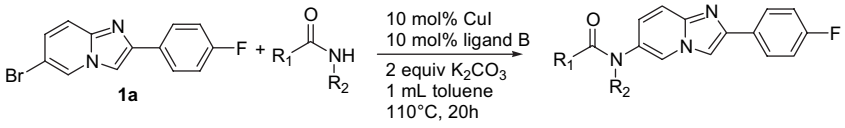
Table 1. Optimization studies on the copper-catalyzed cross-coupling of **1a** with pyrrolidinone[a]

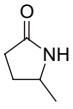
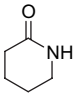


Entry	Ligand	Solvent, temperature	Yield, %[b]
1	A	Toluene, 110 °C	88
2	A	Dioxane, 100 °C	83
3	B	Toluene, 110 °C	92
4	B	Dioxane, 100 °C	75

[a] Reaction conditions: 1 mmol **1a**, 1.2 mmol lactam, 10 mol % CuI, 10 mol % ligand, 2 mmol K_2CO_3, 1 mL solvent, and 20 h.
[b] Isolated yields.

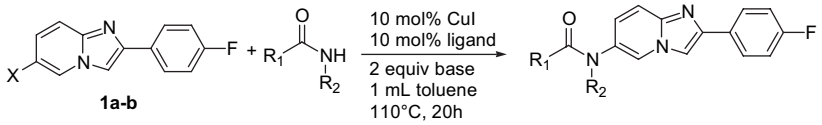
Table 2. Copper-catalyzed cross-coupling of **1a** with various lactams[a]



Entry	Lactam	Yield, %[b]	Entry	Lactam	Yield, %[b]
1		83	3		80
2		87	4		75

[a] Reaction conditions: 1 mmol **1a**, 1.2 mmol lactam, 10 mol % CuI, 10 mol % ligand B, 2 mmol K_2CO_3, 1 mL toluene, and 20 h at 110 °C.
[b] Isolated yields.

Table 3. Copper-catalyzed cross-coupling of **1a–b** with various amides, carbamate, and urea[a]



Entry	Amido substrate	X	Ligand	Base	Yield, %[b]
1	CH_3CONH_2	Br	B	K_2CO_3	NI[c]
2		I	B	K_2CO_3	85
3		Br	B	K_2CO_3	48
4	$C_6H_4CH_2NHCHO$	I	B	K_2CO_3	48
5		I	A	K_2CO_3	43
6		I	A	K_3PO_4	71
7	$C_6H_4CONH_2$	I	B	K_2CO_3	NI[c]
8		I	A	K_3PO_4	99
9	$C_6H_4NHCONH_2$	I	B	K_2CO_3	NI[c]
10		I	A	K_3PO_4	58
11		Br	B	K_2CO_3	5
12	$C_6H_4NHCO_2C(CH_3)_3$	I	B	K_2CO_3	27
13		I	A	K_2CO_3	Traces
14		I	A	K_3PO_4	23

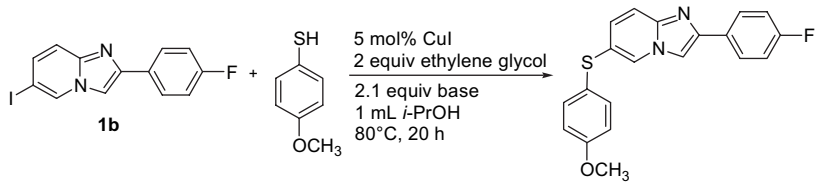
[a] Reaction conditions: 1 mmol **1a–b**, 1.2 mmol amides, carbamate, and urea, 10 mol % CuI, 10 mol % ligand, 2 mmol base, 1 mL toluene, and 20 h at 110 °C.
[b] Isolated yields.
[c] NI=not isolated.

2.2. Copper-catalyzed carbon–sulfur bond formation

The reaction conditions for the C–S couplings were optimized using 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine and 4-methoxythiophenol as substrates (Table 4). Attempts to use brominated starting materials were unsuccessful. The conditions developed by Buchwald and Kwong[12] were applied using 5 mol % CuI and ethylene glycol (2 equiv) in isopropanol. From the different bases evaluated, the use of K_2CO_3 resulted in the best coupling yields (94%, entry 3). The coupling also proceeded in good yield using the procedure described for the *N*-arylation of amide: 5 mol % CuI, 15 mol % ligand A, and K_3PO_4 (2.1 equiv) in toluene (entry 1).

To investigate the scope of the reaction, various substituted thiophenols were included in this study (Table 5). From the results obtained with different methoxythiophenols, the substituent position appears to influence the coupling efficacy, with the *ortho*-methoxythiophenol the least reactive reagent. In this case, attempts to use increased catalyst loading met with good success. However, traces of starting material in the coupling product were very difficult to remove. We were not able to isolate the product. We then introduced a higher amount of thiophenol in order to consume all the starting material. The excess thiophenol present at the end of the reaction was easily eliminated by washing with aqueous sodium hydroxide solution. Using these modified conditions, the 2-methoxythiophenol could be coupled in 67% yield (entry 6), while the coupling of 3-methoxythiophenol took place in 98% yield (entry 2). The 4-aminothiophenol also necessitated the use of an excess of thiophenol and led to the 4-aminophenylsulfanylderivative in 95% yield (entry 9). To the best of our knowledge, the aminothiophenol counterpart has never been previously evaluated in copper-based coupling reaction. Finally, the reaction of **1b** with

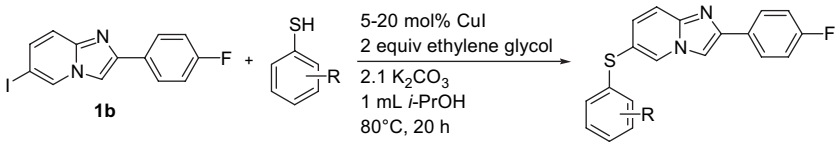
Table 4. Optimization studies on the copper-catalyzed cross-coupling of **1b** with 4-methoxythiophenol[a]



Entry	Base	Yield, %[b]
1	K_3PO_4	88[c]
2	K_3PO_4	83
3	K_2CO_3	94
4	Cs_2CO_3	84

[a] Reaction conditions: 1 mmol **1b**, 1 mmol thiol, 5 mol % CuI, 2 mmol ethylene glycol, 2.1 mmol base, 1 mL isopropanol, and 20 h at 80 °C.
[b] Isolated yields.
[c] Reaction was carried out in the presence of ligand A (15 mol %) in toluene at 110 °C.

Table 5. Copper-catalyzed cross-coupling of **1b** with various thiophenols[a]



Entry	R	CuI (mol %)	Yield, %[b]
1	3-OCH_3	5	NI[c]
2		20	98[d]
3	2-OCH_3	5	NI
4		15	NI
5		20	NI
6		20	67[e]
7	4-Cl	5	83
8	4-NH_2	5	22
9		20	95[d]
10	4-OH	5	96

[a] Reaction conditions: 1 mmol **1b**, 1 mmol thiol, 5–20 mol % CuI, 2 mmol ethylene glycol, 2.1 mmol base, 1 mL isopropanol, and 20 h at 80 °C.
[b] Isolated yields.
[c] Not isolated.
[d] Thiol (1.5 mmol) was used.
[e] Thiol (2 mmol) was used.

4-chlorothiophenol proceeded in 83% yield (entry 7) and in 96% yield with 4-hydroxythiophenol (entry 10).

3. Conclusion

In summary, we have developed a mild and efficient copper-catalyzed system for the amidation of 6-halogeno-imidazo[1,2-*a*]pyridines. Lactams of different sizes, amides, urea, and *N*-BOC aniline were thus introduced in the 6-position of this nucleus using the inexpensive and air-stable copper(I) iodide along with commercially available *N*,*N*′-dimethylated 1,2-diamine ligands in the presence of potassium carbonate or potassium phosphate. The best results were obtained with lactams that could be introduced on the 6-bromoimidazo[1,2-*a*]pyridine. In the other cases, the iodinated starting material was required.

We have also reported a general synthetic protocol for the cross-coupling of various thiophenols with 6-iodoimidazo[1,2-*a*]pyridine using copper(I) iodide, ethylene glycol, and potassium carbonate in isopropanol. In some cases, an excess of thiophenol was required but was easily eliminated at the end of the reaction via a basic treatment.

In both cases, our protocols are palladium-free and avoid the use of expensive and air sensitive ligands. They constitute the first convenient and flexible routes to new 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridines.

4. Experimental

4.1. General

Unless otherwise noted, all chemicals were used as received. 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a**[1b] and 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1b**[2a] were prepared according to literature procedures. All new compounds were fully characterized by ^1H, ^{13}C, and elemental analysis. NMR spectra were run at 200 or 300 MHz (^1H) and 50, 75 or 125 MHz (^{13}C) in $CDCl_3$ with chemical shifts reported relative to residual deuterated solvent peaks. Possible inversion of two values in the ^{13}C NMR spectra is expressed by an asterisk. Mps were determined in a capillary apparatus and are uncorrected.

4.2. General procedure for copper-catalyzed carbon–nitrogen bond formation

6-Halogeno-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1** (1 mmol), copper(I) iodide (19 mg, 0.1 mmol), amide when solid (1.2 mmol), and base (2 mmol) were added to a screw-capped test tube. The tube was evacuated and back filled with argon. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.1 mmol) or racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), amide when liquid (1.2 mmol), and solvent (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 110 °C for 20 h. After cooling to room temperature, the suspension was diluted with dichloromethane (15 mL), 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 to give pure product.

4.2.1. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-pyrrolidinone (Table 1, entry 3). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-pyrrolidinone (91 μL, 1.2 mmol) in toluene. Column chromatography on alumina, eluting with ethyl acetate afforded 270 mg (92% yield) of the title compound, mp 235 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (dd, 1H, J=2.1–0.8 Hz, H-5), 7.90 (dd, 2H, J=9–5.4 Hz, F–Ph-2,6), 7.81 (s, 1H, H-3), 7.58 (d, 1H, J=9.6 Hz, H-8), 7.27 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.12

(t, 2H, J=9 Hz, F–Ph-3,5), 3.88 (t, 2H, J=7.2 Hz, CH_2), 2.64 (t, 2H, J=7.8 Hz, CH_2), 2.22 (m, 2H, CH_2). ^{13}C NMR (75 MHz) δ 174.6 (CO), 162.9 (F–Ph-4), 145.8 (C-2*), 143.6 (C-8a*), 130.1 (F–Ph-1), 127.8 (F–Ph-2,6), 127.2 (C-6), 119.4 (C-7), 118.1 (C-5), 117.2 (C-8), 115.9 (F–Ph-3,5), 108.9 (C-3), 48.8 (CH_2), 32.5 (CH_2), 18.2 (CH_2). Anal. Calcd for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78. Found: C, 69.05; H, 5.16.

4.2.2. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-3-methyl-2-pyrrolidinone (Table 2, entry 1). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 3-methyl-2-pyrrolidinone (88 μL, 120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 258 mg (83% yield) of the title compound, mp 223 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, 1H, J=2.1 Hz, H-5), 7.89 (dd, 2H, J=9–5.7 Hz, F–Ph-2,6), 7.78 (s, 1H, H-3), 7.62 (d, 1H, J=9.6 Hz, H-8), 7.28 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.10 (t, 2H, J=9 Hz, F–Ph-3,5), 3.81 (dd, 2H, J=9–5.4 Hz, CH_2), 2.71 (m, 1H, CH), 2.44 (m, 1H, CH), 1.83 (m, 1H, CH), 1.33 (d, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (75 MHz) δ 177.6 (CO), 163.4 (F–Ph-4), 146.1 (C-2*), 144.0 (C-8a*), 130.4 (F–Ph-1), 128.5 (F–Ph-2,6), 128.0 (C-6), 119.8 (C-7), 118.3 (C-5), 117.7 (C-8), 116.3 (F–Ph-3,5), 109.5 (C-3), 47.1 (CH_2), 38.6 (CH_3), 27.7 (CH), 16.8 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.66; H, 5.34.

4.2.3. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-5-methyl-2-pyrrolidinone (Table 2, entry 2). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 5-methyl-2-pyrrolidinone (106 μL, 120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 268 mg (87% yield) of the title compound, mp 179 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H, H-5), 7.86 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.61 (d, 1H, J=9.6 Hz, H-8), 7.07 (t, 2H, J=8.7 Hz, F–Ph-3,5), 4.24 (m, 1H, CH), 2.58 (m, 2H, CH_2), 2.37 (m, 1H, CH), 1.75 (m, 1H, CH), 1.21 (d, 3H, J=6.3 Hz, CH_3). ^{13}C NMR (75 MHz) δ 174.6 (CO), 162.8 (F–Ph-4), 145.7 (C-2*), 143.9 (C-8a*), 129.9 (F–Ph-1), 127.8 (F–Ph-2,6), 124.7 (C-6), 122.2 (C-7*), 122.1 (C-5*), 117.4 (C-8), 115.7 (F–Ph-3,5), 108.8 (C-3), 55.7 (CH_2), 31.1 (CH_2), 26.7 (CH_3), 20.4 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.57; H, 5.46.

4.2.4. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-azetidinone (Table 2, entry 3). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-azetidinone (85 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 235 mg (80% yield) of the title compound, mp 238 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (m, 1H, H-5), 7.88 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.75 (s, 1H, H-3), 7.63 (d, 1H, J=9.6 Hz, H-8), 7.16 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.10 (t, 2H, J=8.8 Hz, F–Ph-3,5), 3.68 (t, 2H, J=4.5 Hz, CH_2), 3.18 (t, 2H, J=4.5 Hz, CH_2). ^{13}C NMR (125 MHz) δ 165.1 (CO), 163.4 (F–Ph-4), 146.2 (C-2*), 144.0 (C-8a*), 130.4 (F–Ph-1), 128.3 (F–Ph-2,6), 127.5 (C-6), 118.5 (C-7), 117.0 (C-8), 116.4 (F–Ph-3,5), 114.3 (C-5), 109.3 (C-3), 39.3 (CH_2), 37.4 (CH_2). Anal. Calcd for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30. Found: C, 68.23; H, 4.66.

4.2.5. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-piperidinone (Table 2, entry 4). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-piperidinone (120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 233 mg (75% yield) of the title compound, mp 233 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (m, 1H, H-5), 7.89 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.62 (d, 1H, J=9.3 Hz, H-8), 7.10 (t, 2H, J=8.7 Hz, F–Ph-3,5), 7.09 (dd, 1H, J=9.3–2.1 Hz, H-7), 3.67 (m, 2H, CH_2), 2.59 (m, 2H, CH_2), 1.97 (m, 4H, $2CH_2$). ^{13}C NMR (125 MHz) δ 170.8 (CO), 162.9 (F–Ph-4), 146.0 (C-2*), 144.5 (C-8a*), 130.4 (C-6), 130.0 (F–Ph-1), 127.9 (F–Ph-2,6), 124.9 (C-7), 123.8 (C-5), 117.7 (C-8), 115.8 (F–Ph-3,5), 108.7 (C-3), 52.3 (CH_2), 33.0 (CH_2), 23.7 (CH_2), 21.5 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.78; H, 4.91.

4.2.6. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]acetamide (Table 3, entry 2). The general procedure was followed using compound **1b** (338 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and acetamide (71 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (90/10) afforded 229 mg (85% yield) of the title compound, mp 233 °C. ^1H NMR (200 MHz, DMSO-d_6) δ 9.22 (m, 1H, H-5), 8.47 (s, 1H, H-3), 7.97 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.58 (d, 1H, J=9.5 Hz, H-8), 7.28 (t, 2H, J=8.7 Hz, F–Ph-3,5), 7.17 (dd, 1H, J=9.5–1.6 Hz, H-7), 2.11 (s, 3H, CH_3), NH not found. ^{13}C NMR (50 MHz, DMSO-d_6) δ 170.7 (CO), 163.1 (F–Ph-4), 130.2 (F–Ph-1), 127.9 (F–Ph-2,6), 127.1 (C-6), 121.7 (C-7), 117.5 (C-5), 115.9 (C-8), 115.6 (F–Ph-3,5), 110.2 (C-3), 22.5 (CH_3). Anal. Calcd for $C_{15}H_{12}FN_3O$: C, 66.91; H, 4.49. Found: C, 66.77; H, 4.57.

4.2.7. *N*-Benzyl-*N*-[2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridin-6-yl]formamide (Table 3, entry 6). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and *N*-benzylformamide (162 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 245 mg (71% yield) of the title compound, mp 132 °C. ^1H NMR (300 MHz, $CDCl_3$) δ rotamer A 8.43 (s, 1H, CHO), 7.87 (dd, 2H, J=8.8–5.5 Hz, F–Ph-2,6), 7.81 (d, 1H, J=1.8 Hz, H-5), 7.74 (s, 1H, H-3), 7.60 (d, 1H, J=9.5 Hz, H-8), 7.27 (m, 5H, Ph), 7.11 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.01 (dd, 1H, J=9.5–1.8 Hz, H-7);

rotamer B 8.59 (s, 1H, CHO), 7.87 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.85 (d, 1H, *J*=1.8 Hz, H-5), 7.70 (s, 1H, H-3), 7.57 (d, 1H, *J*=9.5 Hz, H-8), 7.27 (m, 5H, Ph), 7.11 (t, 2H, *J*=8.8 Hz, F–Ph-3,5), 7.01 (dd, 1H, *J*=9.5–1.8 Hz, H-7). ^{13}C NMR (125 MHz) δ 163.1 (F–Ph-4), 162.2 (CO), 146.5 (C-2*), 144.4 (C-8a*), 136.1 (C-6), 129.6 (F–Ph-1), 129.1 (Ph), 128.7 (Ph), 128.3 (Ph-1), 128.2 (Ph-4), 128.0 (F–Ph-2,6), 123.9 (C-7), 122.8 (C-5), 118.3 (C-8), 116.0 (F–Ph-3,5), 108.9 (C-3), 49.6 (CH_2). Anal. Calcd for $C_{21}H_{16}FN_3O$: C, 73.03; H, 4.67. Found: C, 73.28; H, 4.46.

4.2.8. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-benzamide (Table 3, entry 8). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and benzamide (145 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99/1) afforded 327 mg (99% yield) of the title compound, mp 262 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.47 (s, 1H, NH), 9.39 (s, 1H, H-5), 8.55 (s, 1H, H-3), 7.97 (m, 4H, F–Ph-2,6, Ph-2,6,), 7.66 (d, 1H, *J*=9.3 Hz, H-8), 7.57 (m, 5H, Ph-3,4,5, H-7, H-8), 7.30 (t, 2H, *J*=8.8 Hz, F–Ph-3,5). ^{13}C NMR (125 MHz) δ 166.9 (CO), 162.9 (F–Ph-4), 144.7 (C-2*), 143.7 (C-8a*), 135.4 (Ph-1), 133.0 (Ph-4), 131.6 (F–Ph-1), 129.6 (Ph-3,5), 128.8 (Ph-2,6), 128.5 (F–Ph-2,6), 127.7 (C-6), 122.8 (C-7), 118.4 (C-5), 117.5 (C-8), 116.8 (F–Ph-3,5), 111.3 (C-3). Anal. Calcd for $C_{20}H_{16}FN_3O$: C, 72.50; H, 4.26. Found: C, 72.72; H, 4.56.

4.2.9. *N*-Phenyl-*N*′-[2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridin-6-yl]urea (Table 3, entry 10). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and phenylurea (163 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (90/10) afforded 200 mg (58% yield) of the title compound, mp>260 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 (s, 1H, H-5), 8.76 (s, 1H, NH), 8.71 (s, 1H, NH), 8.39 (s, 1H, H-3), 7.94 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.51 (d, 1H, *J*=9.6 Hz, H-8), 7.45 (d, 2H, *J*=8.1 Hz, Ph-2,6), 7.29–7.21 (m, 4H, F–Ph-3,5, Ph-3,5), 7.07 (dd, 1H, *J*=9.6–2.1 Hz, H-7), 6.96 (t, 1H, *J*=7.5 Hz, Ph-4). ^{13}C NMR (50 MHz) δ 161.7 (F–Ph-4), 152.7 (CO), 143.5 (C-2*), 142.3 (C-8a*), 139.5 (Ph-1), 130.6 (F–Ph-1), 128.8 (Ph-3,5), 127.2 (F–Ph-2,6), 126.9 (C-6), 122.0 (Ph-4), 121.0 (C-7), 118.3 (Ph-2,6), 116.5 (C-5), 115.6 (F–Ph-3,5), 114.9 (C-8), 109.8 (C-3). Anal. Calcd for $C_{20}H_{15}FN_4O$: C, 69.35; H, 4.37. Found: C, 69.62; H, 4.14.

4.2.10. 6-[*N*-(*tert*-Butyloxycarbonyl)-*N*-phenylamino]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (Table 3, entry 12). The general procedure was followed using compound **1b** (338 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and *N*-(*tert*-butyloxycarbonyl)aniline (232 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5) afforded 118 mg (27% yield) of the title compound, mp 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H, H-5), 7.91 (dd, 2H, *J*=9–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.65 (d, 1H, *J*=9.6 Hz, H-8), 7.37 (m, 2H, Ph-2,6), 7.25 (m, 3H, Ph-3,4,5), 7.18 (dd, 1H, *J*=9.6–2.1 Hz, H-7), 7.12 (t, 2H, *J*=9 Hz, F–Ph-3,5), 1.50 (s, 6H, *t*-Bu). ^{13}C NMR (125 MHz) δ 163.2 (F–Ph-4), 154.0 (CO), 145.9 (C-2*), 144.1 (C-8a*), 142.7 (Ph-1*), 131.2 (C-6*), 129.9 (F–Ph-1), 129.5 (Ph-2,6), 128.2 (F–Ph-2,6), 127.1 (Ph-3,5), 126.7 (Ph-4*), 126.6 (C-7*), 124.1 (C-5), 117.1 (C-8), 116.1 (F–Ph-3,5), 108.9 (C-3), 82.5 ($C(CH_3)_3$), 28.6 ($3CH_3$). Anal. Calcd for $C_{24}H_{22}FN_3O_2$: C, 71.45; H, 5.50. Found: C, 71.48; H, 5.71.

4.3. General procedure for copper-catalyzed carbon–sulfur bond formation

6-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1b** (338 mg, 1 mmol), copper(I) iodide (9.5 mg, 0.05 mmol to 38 mg, 0.2 mmol), potassium carbonate (290 mg, 2.1 mmol), and thiophenol when solid, were added to a screw-capped test tube. The tube was evacuated and back filled with argon. Ethylene glycol (111 μL, 2 mmol), thiophenol when liquid, and isopropanol (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 80 °C for 20 h. After cooling to room temperature, the suspension was diluted with ethyl acetate (15 mL) and washed three times with 10 N aqueous sodium hydroxide. After drying ($MgSO_4$), the solvent was removed with the aid of a rotary evaporator to give a brown residue that was purified by column chromatography to give pure product.

4.3.1. 2-(4-Fluorophenyl)-6-(4-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 4, entry 3). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-methoxythiophenol (123 μL, 1 mmol). Column chromatography on silica gel eluting with dichloromethane afforded 327 mg (94% yield) of the title compound, mp 134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1H, *J*=1.8–0.6 Hz, H-5), 7.89 (dd, 2H, *J*=8.7–5.4 Hz, F–Ph-2,6), 7.72 (s, 1H, H-3), 7.51 (d, 1H, *J*=9.3 Hz, H-8), 7.37 (d, 2H, *J*=8.8 Hz, CH_3O–Ph-2,6), 7.12 (t, 2H, *J*=8.7 Hz, F–Ph-3,5), 7.09 (dd, 1H, *J*=9.3–1.8 Hz, H-7), 6.89 (d, 2H, *J*=8.8 Hz, CH_3O–Ph-3,5), 3.81 (s, 3H, CH_3). ^{13}C NMR (125 MHz) δ 162.9 (F–Ph-4), 159.9 (CH_3O–Ph-4), 145.6 (C-2*), 144.7 (C-8a*), 133.8 (CH_3O–Ph-2,6), 129.9 (F–Ph-1), 128.6 (CH_3O–Ph-1), 127.8 (F–Ph-2,6), 126.2 (C-7), 125.0 (C-6), 122.3 (C-5), 117.7 (C-8), 115.9 (F–Ph-3,5), 115.3 (CH_3O–Ph-3,5), 108.1 (C-3), 55.6 (CH_3O). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 68.57; H, 4.45.

4.3.2. 2-(4-Fluorophenyl)-6-(3-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 2). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 3-methoxythiophenol (185 μL, 1.5 mmol). After washing with 10 N aqueous sodium hydroxide, 347 mg (98% yield) of the title compound were obtained without further purification, mp 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (m, 1H, H-5), 7.95 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.82 (s, 1H, H-3), 7.62 (d, 1H, *J*=9.4 Hz, H-8), 7.30–7.13 (m, 4H, CH_3O–Ph-5, F–Ph-3,5, H-7), 6.90–6.78 (m, 3H, CH_3O–Ph-2,4,6), 3.79 (s, 1H, CH_3). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 160.6

(CH_3O–Ph-3), 146.1 (C-2*), 145.1 (C-8a*), 137.7 (CH_3O–Ph-1), 130.6 (CH_3O–Ph-5*), 130.5 (C-7*), 130.0 (F–Ph-1), 129.1 (C-5), 128.2 (F–Ph-2,6), 121.7 (CH_3O–Ph-6), 119.5 (C-6), 118.2 (C-8), 116.2 (F–Ph-3,5), 115.0 (CH_3O–Ph-2), 112.9 (CH_3O–Ph-4), 108.5 (C-3), 55.7 (OCH_3). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 68.59; H, 4.37.

4.3.3. 2-(4-Fluorophenyl)-6-(2-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 6). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 2-methoxythiophenol (243 μL, 2 mmol). Column chromatography on silica gel eluting with a mixture of diethyl ether–petroleum ether (70/30) afforded 235 mg (67% yield) of the title compound, mp 149 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (m, 1H, H-5), 7.98 (dd, 2H, J=8.8–5.3 Hz, F–Ph-2,6), 7.82 (s, 1H, H-3), 7.70 (d, 1H, J=9.4 Hz, H-8), 7.30 (m, 2H, CH_3O–Ph-6, H-7), 7.18 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.11 (dd, 1H, J=7.5–1.5 Hz, CH_3O–Ph-4), 6.94 (m, 2H, CH_3O–Ph-3,5), 3.94 (s, 1H, CH_3). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 157.1 (CH_3O–Ph-2), 145.8 (C-2*), 145.1 (C-8a*), 130.8 (CH_3O–Ph-6), 130.3 (CH_3O–Ph-4), 129.8 (F–Ph-1), 129.2 (C-5), 128.7 (C-7), 128.2 (F–Ph-2,6), 124.6 (C-6), 121.8 (CH_3O–Ph-5), 119.0 (CH_3O–Ph-1), 117.9 (C-8), 116.2 (F–Ph-3,5), 111.3 (CH_3O–Ph-3), 108.4 (C-3), 56.3 (OCH_3). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 66.32; H, 4.51.

4.3.4. 2-(4-Fluorophenyl)-6-(4-chlorophenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 7). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-chlorothiophenol (145 μL, 1 mmol). Column chromatography on silica gel eluting with dichloromethane afforded 294 mg (83% yield) of the title compound, mp 181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (m, 1H, H-5), 7.91 (dd, 2H, J=9–5.4 Hz, F–Ph-2,6), 7.78 (s, 1H, H-3), 7.58 (d, 1H, J=9.3 Hz, H-8), 7.27 (d, 2H, J=8.9 Hz, Cl–Ph-2,6), 7.19 (d, 2H, J=8.9 Hz, Cl–Ph-3,5), 7.14 (dd, 1H, J=9.3–1.5 Hz, H-7), 7.13 (t, 2H, J=9 Hz, F–Ph-3,5). ^{13}C NMR (125 MHz) δ 162.8 (F–Ph-4), 145.9 (C-2*), 144.7 (C-8a*), 134.6 (Cl–Ph-1), 133.0 (Cl–Ph-4), 130.3 (Cl–Ph-2,6), 129.7 (C-7), 129.6 (F–Ph-1), 129.5 (Cl–Ph-3,5), 128.9 (C-5), 127.8 (F–Ph-2,6), 118.7 (C-6), 118.1 (C-8), 115.9 (F–Ph-3,5), 108.2 (C-3). Anal. Calcd for $C_{19}H_{12}ClFN_2S$: C, 64.31; H, 3.41. Found: C, 64.27; H, 3.64.

4.3.5. 2-(4-Fluorophenyl)-6-(4-aminophenylsulfanyl)imidazo[1,2-*a*]pyridine (Table 5, entry 9). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 4-aminothiophenol (188 mg, 1.5 mmol). Column chromatography on silica gel eluting with CH_2Cl_2 and then with ether, afforded 317 mg (95% yield) of the title compound, mp 154 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (m, 1H, H-5), 7.92 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.74 (s, 1H, H-3), 7.53 (d, 1H, J=9.4 Hz, H-8), 7.32 (d, 2H, J=8.7 Hz, NH_2–Ph-2,6), 7.15 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.12 (d, 1H, J=9.4 Hz, H-7), 6.70 (d, 2H, J=8.7 Hz, NH_2–Ph-3,5), 3.85 (s, 2H, NH_2). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 147.5 (NH_2–Ph-4), 145.5 (C-2*), 144.8 (C-8a*), 135.1 (NH_2–Ph-2,6), 130.1 (F–Ph-1), 128.4 (C-7), 128.1 (F–Ph-2,6), 125.2 (C-5), 124.2 (NH_2–Ph-1*), 121.1 (C-6*), 117.6 (C-8), 116.3 (NH_2–Ph-3,5), 116.1 (F–Ph-3,5), 108.3 (C-3). Anal. Calcd for $C_{19}H_{14}FN_3S$: C, 68.04; H, 4.21. Found: C, 68.12; H, 4.33.

4.3.6. 2-(4-Fluorophenyl)-6-(4-hydroxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 10). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-hydroxythiophenol (121 μL, 1 mmol). After washing with 10 N aqueous sodium hydroxide, 312 mg (96% yield) of the title compound was obtained without further purification, mp>250 °C. ^{1}H NMR (200 MHz, CD_3OD) δ 8.05 (m, 1H, H-5), 8.03 (s, 1H, H-3), 7.92 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.42 (d, 1H, J=9.4 Hz, H-8), 7.26 (d, 2H, J=8.6 Hz, HO–Ph-2,6), 7.17 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.16 (dd, 1H, J=9.4–1.9 Hz, H-7), 6.70 (d, 2H, J=8.6 Hz, HO–Ph-3,5), 4.91 (s, 1H, OH). ^{13}C NMR (50 MHz) δ 169.1 (HO–Ph-4), 163.1 (F–Ph-4), 144.6 (C-2*), 144.4 (C-8a*), 136.4 (HO–Ph-2,6), 130.1 (F–Ph-1), 127.9 (F–Ph-2,6), 127.7 (C-7), 127.4 (C-6), 123.4 (C-5), 120.4 (HO–Ph-3,5), 115.6 (C-8), 115.5 (F–Ph-3,5), 113.2 (HO–Ph-1), 109.3 (C-3). Anal. Calcd for $C_{19}H_{13}FN_2OS$: C, 67.84; H, 3.90. Found: C, 67.98; H, 3.89.

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