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Copper-Catalyzed Tandem Azide–Alkyne Cycloaddition, Ullmann Type C–N Coupling, and Intramolecular Direct Arylation

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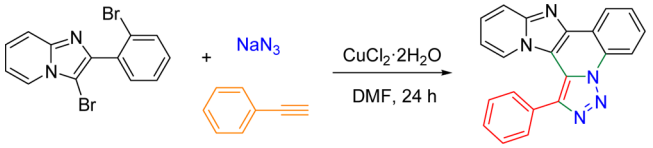
ABSTRACT



A ligand-free copper-catalyzed tandem azide–alkyne cycloaddition (CuAAC), Ullmann-type C–N coupling, and intramolecular direct arylation has been described. The designed strategy resulted in the synthesis of a novel trazole-fused azaheterocycle framework. The reaction gave good yields (59–77%) of 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines in a single step.

Transition metal-catalyzed coupling reactions play a vital role in organic and medicinal chemistry allowing construction of novel and biologically relevant molecules.[1] In particular, significant attention has been focused on copper catalysts over other expensive transition metals such as palladium, ruthenium, and rhodium for the formation of C–C and C-heteroatom bonds mainly because of their efficiency, good functional group tolerance, and economical attractiveness.[2] Tandem or cascade reactions catalyzed by copper salts serve as an efficient tool for the assembly of complex biologically active heterocyclic molecules.[3] 1,2,3-Triazoles are found to have broad range of applications in the field of synthetic, medicinal, and material chemistry.[4] Since the pioneering work by Sharpless[5] and Meldel[6] groups, copper-catalyzed azide–alkyne cycloaddition (CuAAC) has become the finest way to generate 1,4-substituted-1,2,3-triazoles. Another important copper-catalyzed reaction is Ullmann coupling.[7] The scope of Ullmann-type reactions was actively developed after the discovery of organic ligands and applied in various fields to synthesize potentially important molecules via C–C and C-heteroatom bond formation.[8] Transition metal-catalyzed direct C–H functionalization has become an alternative to traditional cross-coupling reactions that results in fabrication of complex molecular skeleton where prefunctionalization of precursors can be obviated.[9] Moreover, inexpensive copper salts have also proved to be efficient catalysts in the area of C–H activation and functionalization to assemble vital organic frameworks.[10] Recently, Ackermann et al. demonstrated

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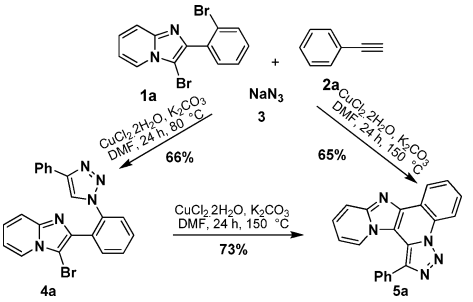
the synthesis of decorated 1,2,3-triazoles via Cu/Pd-catalyzed click reaction, direct arylation sequence.[11] Lauten et al. have described interesting results on fused 1,2,3-triazole through cycloaddition followed by direct arylations.[12] Cai et al. trapped C−Cu formed in CuAAC for intramolecular Ullmann coupling to synthesize novel fused-1,2,3-triazoles.[13] However, the combination of copper-catalyzed CuAAC, Ullmann-type coupling and C−H functionalization is rare in the literature.

There are several drugs that contain imidazo[1,2-*a*]-pyridine as the core structure such as zolpidem and alpidem (used for the treatment of anxiety and insomnia), zolimidine (used for peptic ulcers), and saripidem and necopidem (for sedative and anxiolytic effects). The derivatives of imidazo[1,2-*a*]pyridine have shown impressive biological activities such as antiinflammatory, antibacterial, antiviral, antiulcer, anti-HIV, and immunomodulatory effects.[14] On the basis of the significance of imidazo[1,2-*a*]-pyridine nucleus, we believe that further functionalization leading to fused novel heterocycles will have new and interesting properties. As a part of our continuous efforts for the synthesis of novel heterocycles containing imidazo-[1,2-*a*]pyridines,[15] herein we wish to report a ligand-free inexpensive copper-catalyzed tandem CuAAC, Ullmann type C−N coupling, and intramolecular direct arylation for the regioselective synthesis of novel 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines.

3-Bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**1a**), phenylacetylene (**2a**) and sodium azide (**3**) were chosen as model substrates for the initial investigation, and the results are summarized in Table 1. In a typical experiment, compound **1a** (1 mmol) was treated with **2a** (1.2 mmol) and **3** (1.2 mmol) in the presence of $CuCl_2 \cdot 2H_2O$ (20 mol %) and K_2CO_3 (2.5 mmol) in DMF at 80 °C for 24 h. 3-Bromo-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)imidazo[1,2-*a*]-pyridine (**4a**) (Table 1, entry 1) was obtained in 66% yield (Scheme 1). It was realized that direct Cu-catalyzed arylation product of **4a** can be achieved in one pot at higher temperature; thus, the reaction temperature was increased to 150 °C with other conditions keeping similar to entry 1. To our delight, target compound (**5a**) was obtained in 65% yield (entry 2). In the absence of copper catalyst, reaction failed to furnish tandem product, and starting materials were recovered (entry 3), whereas an inseparable mixture of compounds was observed in the absence of base (entry 4).

Scheme 1. Tandem Reaction of **1a**, **2a**, and **3** in the Presence of Copper Catalyst



To improve the yield of desired pentacyclic product **5a**, various copper salts, bases, and solvents were screened (Table 1). Use of CuI and CuO resulted in poor yields, $Cu(OAc)_2$ gave relatively better yield of desired product (entries 5, 6, and 7). At the same time $CuBr_2$, $Cu(OTf)_2$, and Cu_2O gave moderate yields of desired product **5a** (entries 9, 10, and 11), whereas $CuSO_4$ resulted in formation of **4a** (entry 8). Among all the screened catalysts, $CuCl_2 \cdot 2H_2O$ was found to give the best yield of **5a**. Next, we screened various bases such as KO*t*Bu, Cs_2CO_3, K_2CO_3, Na_2CO_3, and NaOAc (entries 12−15) with $CuCl_2 \cdot 2H_2O$ as the catalyst. Among these, K_2CO_3 turned out to be the most effective base to give **5a** (entry 2), whereas use of NaOAc resulted in formation of **4a** (entry 15). Finally, the effect of solvents was also investigated for this tandem process yielding **5a**. Aprotic polar solvents such as DMF and DMSO were found to be effective (entries 2 and 16) for this conversion. 1,4-Dioxane and toluene (entries 17 and 18) did not give any reaction. Use of acetonitrile resulted in formation of **4a** (entry 19). Moreover, use of external ligands like *N*, *N*′-dimethylethylenediamine, 1,10-phenonthroline and L-proline (40 mol %) failed to improve the yield of **5a** (entries 20, 21 and 22).

Having optimized the reaction conditions (Table 1, entry 2), we investigated the scope of this tandem reaction, and the results are summarized in Scheme 2. Various substituted phenylacetylenes smoothly reacted under the optimized conditions to give desired 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines (**5a**−**o**) in moderate to good yields. For example, phenylacetylenes with electron-donating substituents such as 4-methoxy, 4-butyl, 4-pentyl, 4-*tert*-butyl, and 3-methyl produced the corresponding 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines (**5b**−**e** and **5n**) in good yields (59−68%), and 4-fluorophenylacetylene with electron-withdrawing fluoro group underwent smooth conversion to afford 62% of 1,2,3-triazole-fused imidazo-[1,2-*a*]pyridines (**5f**). Aliphatic alkynes also efficiently participated in tandem reaction to give the corresponding

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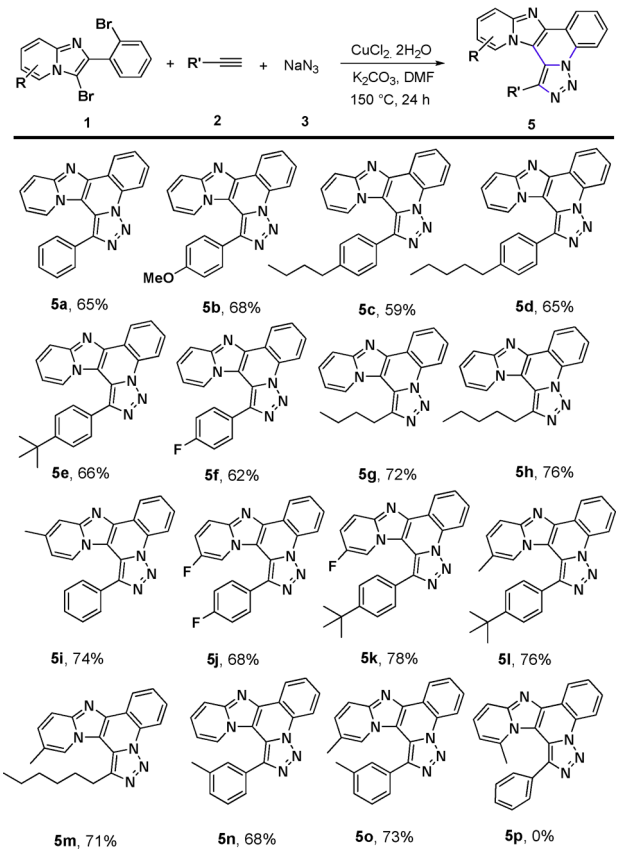
Table 1. Optimization of Reaction Conditions for the Synthesis of **5a** via Tandem Reaction[a]

entry	catalyst	base	solvent	temp (°C)	yield of **5a** (%)[b]
1	$CuCl_2 \cdot 2H_2O$	K_2CO_3	DMF	80	–[c]
2	**$CuCl_2 \cdot 2H_2O$**	**K_2CO_3**	**DMF**	**150**	**65**
3	–[d]	K_2CO_3	DMF	150	NR[e]
4	$CuCl_2 \cdot 2H_2O$	–[f]	DMF	150	–[g]
5	CuI	K_2CO_3	DMF	150	18[h]
6	CuO	K_2CO_3	DMF	150	22
7	$Cu(OAc)_2$	K_2CO_3	DMF	150	38
8	$CuSO_4$	K_2CO_3	DMF	150	–[h]
9	$CuBr_2$	K_2CO_3	DMF	150	48
10	$Cu(OTf)_2$	K_2CO_3	DMF	150	54
11	Cu_2O	K_2CO_3	DMF	150	45
12	$CuCl_2 \cdot 2H_2O$	Na_2CO_3	DMF	150	22
13	$CuCl_2 \cdot 2H_2O$	KO*t*Bu	DMF	150	50
14	$CuCl_2 \cdot 2H_2O$	Cs_2CO_3	DMF	150	46
15	$CuCl_2 \cdot 2H_2O$	NaOAc	DMF	150	–[h]
16	$CuCl_2 \cdot 2H_2O$	K_2CO_3	DMSO	150	51
17	$CuCl_2 \cdot 2H_2O$	K_2CO_3	1,4-dioxane	150	NR[e]
18	$CuCl_2 \cdot 2H_2O$	K_2CO_3	toluene	150	NR[e]
19	$CuCl_2 \cdot 2H_2O$	K_2CO_3	MeCN	150	–[h]
20	$CuCl_2 \cdot 2H_2O$[i]	K_2CO_3	DMF	150	56
21	$CuCl_2 \cdot 2H_2O$[j]	K_2CO_3	DMF	150	62
22	$CuCl_2 \cdot 2H_2O$[k]	K_2CO_3	DMF	150	traces[g]

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), NaN_3 (1.2 mmol), catalyst (0.2 mmol), base (2.5 mmol), solvent (4 mL), 24 h. [b] Isolated yields. [c] **4a** was isolated in 66% yield. [d] No copper catalyst. [e] No conversion. [f] No base was used. [g] A mixture of products was observed. [h] The major product was **4a**. [i] *N*,*N*′-Dimethylethylenediamine was used (40 mol %). [j] 1,10-Phenonthroline was used (40 mol %). [k] L-Proline was used (40 mol %).

Scheme 2. Tandem Synthesis of 1,2,3-Triazole-Fused Imidazo-[1,2-*a*]pyridines (**5**)

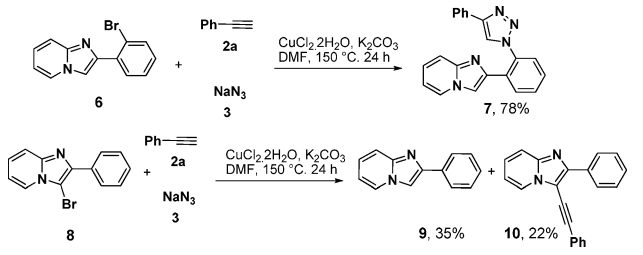


1,2,3-triazole-fused imidazo[1,2-*a*]pyridines in comparatively better yields (72%, **5g** and 76%, **5h**). Similarly, different substituted imidazo[1,2-*a*]pyridines also produced 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines in good yields (74%, **5i**; 68%, **5j** and 78%, **5k**; 76%, **5l**; 71%, **5m**; 73%, **5o**). Unfortunately, reation of 3-bromo-2-(2-bromophenyl)-5-methyl imidazo[1,2-*a*]pyridine (**1d**) with **2a** and **3** failed to give the corresponding 1,2,3-triazole-fused imidazo[1,2-*a*]-pyridine (**5p**). This may be due to the steric hindrance caused by 5-methyl in imidazo[1,2-*a*]pyridine nucleus.

Since two bromo groups are present in the starting material (**1a**–**e**), two regioisomers can be visualized for the compounds **5a**–**o** from the tandem process (explained for compound **5i** in Figure 1). To understand the reactivity of each of the bromo groups, two individual experiments were performed using the optimized reaction conditions. In the first experiment, 2-(2-bromophenyl) imidazo[1,2-*a*]-pyridine (**6**) was treated with **2a** and **3**, and the anticipated product, 2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl) phenyl)-imidazo[1,2-*a*]pyridine (**7**), was obtained via CuAAC followed by Ullmann-type coupling reaction in good yield (78%, Scheme 3). In the second experiment, 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**8**) was treated with **2a** and **3**. A mixture of products was observed in this reaction, from which two major products isolated were found to be dehalogenated starting material, i.e., 2-phenylimidazo-[1,2-*a*]pyridine (**9**), and Sonagashira-type coupling product, i.e., 2-phenyl-3-(phenylethynyl)imidazo[1,2-*a*]pyridine (**10**) (Scheme 3). In addition to these two products, formation of azide–alkyne condensation (AAC) product between **2a** and **3** was also observed in the reaction mixture. The outcome from these experiments indicates that the bromo substituent at the 2-aryl ring undergoes Ullmann-type coupling. This is due to the *ortho*-directing effect of the nitrogen atom in the imidazole moiety of imidazo[1,2-*a*]pyridine that chelates with copper and favors the C–N coupling.[15] On the other hand, the bromo on compound **8** appears to be more prone toward C–C bond formation.

On the basis of these two independent experimental results, regioisomer **A** appears to be a more logical product than the regioisomer **B** (Figure 1). But to conclusively ascertain the correct structure of the product, compound **5i** was selected for NOE studies. Compound **5i** was strategically chosen, as the CH_3 group on the pyridine ring would enable assignment of aromatic proton resonances indicated by blue and red dots in Figure 1 required to verify any NOE enhancement on the phenyl substituent on triazole ring of regioisomer **A**. For the regioisomer **B**, with phenyl group on the other side, no NOE would be expected. Focusing on the methyl group in the HMBC, the proton indicated by the blue dot was assigned to the resonance at 6.5 ppm (^{13}C shift 115 ppm from HSQC). Subsequently, from the COSY, the proton indicated by the red dot was assigned to the resonance at 7.4 ppm (^{13}C shift 127.2 ppm

Scheme 3. Reactivity of Bromo Group on Imidazo[1,*a*]pyridine



from HSQC). The ^{13}C NMR spectrum of **5i** helped in identifying symmetrical phenyl ring carbons (128.4 and 131.3 ppm), which in turn helped to (through HSQC experiment) identify the chemical shifts of proton they harbored (7.6 and 7.7 ppm; shown in black dots in Figure 1). After having identified the chemical shifts of the protons of interest, 1D NOESY experiment was run. Irradiation at frequency of the signal at δ 7.4 ppm (proton shown in red dot in Figure 1) enhanced the signal at δ 6.5 ppm (proton shown in blue dot in Figure 1), which was expected. However, there is also a significant response at a resonance involving δ 7.7 ppm, which is assigned for two of the 4 protons (shown in black dot in Figure 1) on the benzene ring substituent. If the benzene ring is on the other side (isomer **B**), then no enhancement would be expected on benzene ring substituent. Thus, on the basis of the two experiments with **6** and **8** and the NOE results, the structure of 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines were conclusively established as corresponding to regioisomer **A** (Figure 1).

Although mechanistic details are not clear at this point, on the basis of experimental observations, intermediates isolated, and the literature precedent, it has been proposed that Cu(II) can initially oxidize alkynes to result in reactive Cu(I) along with diyne.[16] Subsequently, Cu(I)-catalyzed CuAAC reaction followed by *ortho*-directed Ullman-type C−N coupling with phenyl triazole leads to intermediate **4a** (Scheme 1).

Intramolecular direct arylation of intermediate **4a** affords the desired 1,2,3-triazole-fused imidazo[1,2-*a*]pyridine (**5a**).

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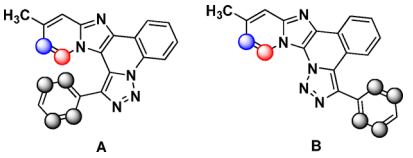

Figure 1. Possible regioisomers of compound **5i**.

There are two possible pathways for the transformation of intermediate **4a** into fused triazole **5a**: (a) direct arylation of intermediate **4a**, as reported by Ackermann group,[11a] and (b) by C−Cu trapping as reported by Cai group.[13] To clarify the mechanism of this step, isolated compound **4a** was subjected under the optimized reaction conditions (Scheme 1), which led to formation of **5a** in excellent yield (73%). This indicates that this step proceeds via direct arylation instead of C−Cu trapping.

In conclusion, we have successfully developed an efficient and simple tandem protocol for the synthesis of structurally complex and novel 1,2,3-triazole-fused imidazo-[1,2-*a*]pyridines via CuAAC, Ullmann-type C−N coupling, followed by intramolecular C−C bond formation by C−H functionalization. The reaction shows high generality and functional group tolerance. It provides a straightforward means for the preparation of fused triazoles derivatives. Attempts to understand the mechanism of the tandem reaction and its application for the synthesis of fused heterocycles are in progress in our laboratory.

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Supporting Information Available. General experimental details, copy of ^1H and ^{13}C NMR of the synthesized compounds **1a**−**e**, **5a**−**o**, **7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.