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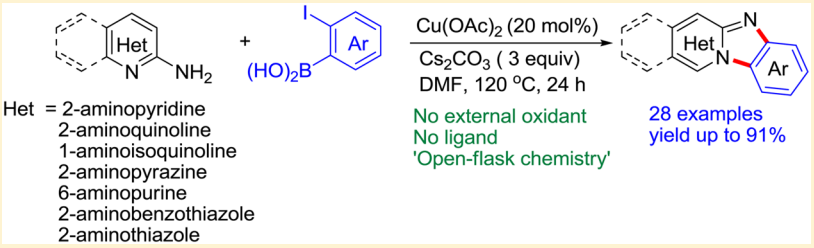
Copper-Catalyzed Inter- and Intramolecular C−N Bond Formation: Synthesis of Benzimidazole-Fused Heterocycles

Sk. Rasheed,[†,‡] D. Nageswar Rao,[†,‡] and Parthasarathi Das*[,†,‡]

[†]Jammu Campus, Academy of Scientific and Innovative Research (AcSIR), Jammu 180001, India

[‡]Medicinal Chemistry Division, Indian Institute of Integrative Medicine(CSIR), Jammu 180001, India

Supporting Information



ABSTRACT: A Cu (II)-catalyzed, inter/intramolecular C−N bond formation for the synthesis of various benzimidazole-fused heterocycles in a concise manner has been reported. The robustness of this reaction is demonstrated by the synthesis of a series of benzimidazole-fused heteroaromatics (e.g., pyrido[1,2-*a*] benzimidazole, benzimidazo[1,2-*a*]quinolines, benzimidazo [1,2-*a*]pyrazine, benzo[4,5] imidazo[2,1-*b*]thiazoles) directly from 2-aminoheteroarenens and 2-iodoarylboronic acids in one-pot. The novel cascade protocol for C−N bond formation operates via unique combination of Chan−Lam type coupling followed by Ullmann-type reaction.

Transition-metal catalyzed C−N bond coupling has been established as a useful tool in modern organic synthesis.[1] Numerous protocols for the C−N bond formations have been developed, and most of these methods involve the catalytic use of Pd complexes or Cu salts with the help of ligand and base.[2,3] Since the initial reports in 1998 independently by Chan, Lam, and Evans, the Cu-promoted coupling reaction for N/O-arylation with arylboronic acids has emerged as a powerful and useful synthetic tool for medicinal, crop protection, and material chemists.[4] The reason behind its popularity is the mild reaction conditions needed, i.e., room temperature, weak base, and ambient atmosphere ("open-flask" chemistry). Over the years, various research groups[5] including our group[6] made considerable progress in expanding the scope of this methodology. Although the Cu-catalyzed and boronic acid promoted the C−N bond cross-coupling would provide an efficient means in providing the valuable *N*-arylated heterocycles, but the use of Chan−Lam type of coupling in constructing heteroaromatic systems remain limited.[7]

The pyrido[1,2-*a*]benzimidazole core (Figure 1) is one of the most important heterocyclic systems because it has not only found widespread applications in pharmaceutical chemistry[8] but also broadly used in material science.[9] Similarly, benzimidazo-[1,2-*a*]quinoline and benzimidazo[2,1-*a*]isoquinolines are another important pharmacophore prevalent in a large number of biologically active molecules.[10] The wide range of biological properties shown by pyrido[1,2-*a*]benzimidazoles inspired organic chemists to pursue their synthesis in recent years. For the synthesis of pyrido[1,2-*a*]benzimidazole, transition-metal and metal-free catalyzed methods are reported, where mostly *N*-arylated amino-heterocycles are used as substrates (Scheme 1). Zhu and co-workers reported an elegant Cu/Fe cocatalyzed direct C−H amination of 2-(arylamino)pyridines for the synthesis of pyrido[1,2-*a*]benzimidazoles under an oxygen atmosphere.[11] The Maes group independently reported the direct C−H amination of 2-(arylamino)pyridines to access pyrido[1,2-*a*]benzimidazoles by using a catalytic amount of copper(II) acetate.[12] The metal-free synthesis of pyrido[1,2-*a*]benzimidazoles and other benzimidazole fused heterocycles promoted by hypervalent iodine(III) were independently reported by Zhu[13] and our group.[14] In another report Rossi and Cuny demonstrated a photostimulation procedure for intramolecular C−N bond in 2-(2-halophenylamino) pyridines in the presence of potassium *tert*-butoxide in liquid ammonia, which gives fused imidazo[1,2-*a*]pyridines by an $S_{RN}1$ reaction.[15] Wu et al. reported Cu-catalyzed and ligand assisted cascade method for C−N coupling in the synthesis of aza-fused benzimidazoles.[16] In most of these protocols, they require a couple of steps for the synthesis of fused-benzimidazole derivatives, including the preparation of *N*-arylated compounds from 2-amino-*N*-heterocycles. Moreover, the methods developed so far suffer from harsh conditions; narrow functional group tolerance, expensive catalysts, and ligands were required. Further, all the above-reported protocols are limited only to pyrido[1,2-*a*]benzimidazoles. Thus, finding a general/alterna-

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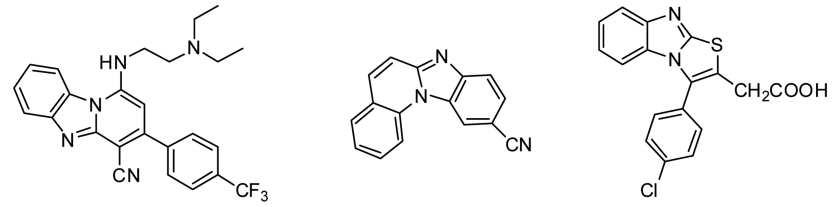
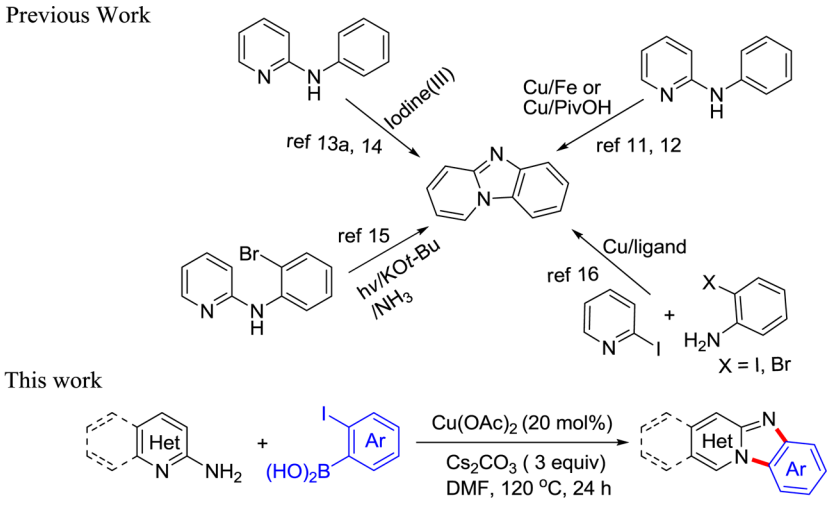


Figure 1. Medicinal interest with benzimidazole-fused heterocycles.

Scheme 1. Synthesis of Pyrido[1,2-*a*]benzimidazoles



tive protocol in synthesizing these important heterocycles will be highly desirable. Here, we report a conceptually new cascade reaction for the synthesis of pyrido[1,2-*a*]benzimidazoles and other aza-fused heterocycles catalyzed by $Cu(OAc)_2$ under ligand free conditions (Scheme 1). This cascade reaction involves sequential intermolecular C−N bond formation (Chan−Lam coupling) and intramolecular cyclization via Ullmann-type reaction.

To find an optimized protocol for synthesis of pyrido [1,2-*a*] benzimidazole, we started our experiment between 2-aminopyridine (**1a**) and 2-bromophenylboronic acid (1.1 equiv) in the presence of $Cu(OAc)_2$ (0.2 equiv) in methanol at rt, and we observed only 15% product formation (entry 1, Table 1). Next we performed the reaction with 2-iodophenylboronic acid, and the desired product was isolated in 25% yield (entry 2, Table 1). When Et_3N was added as base, the pyrido [1,2-*a*] benzimidazole was isolated in moderate yield 35% (entry 3, Table 1).

Encouraged by these findings, various base/solvent combination at different temperature/time were screened (entries 4−13, Table 1) and it was found that $Cu(OAc)_2$ (20 mol %), and Cs_2CO_3 (3 equiv) in DMF at 120 °C gave the best result (88%) in 24 h (entry 8, Table 1). Further screening of different Cu-salts such as CuI (entry 14, Table 1) and Cu_2O (entry 15, Table 1) failed to produce any coupled product, whereas $Cu(OTf)_2$ afforded **2a** in moderate yield 60% (entry 16, Table 1). When we changed the coupling partner from 2-iodophenylboronic acid to 2-bromophenylboronic acid under the same optimized conditions, the desired product isolated in 65% yield (entry 17, Table 1). Reducing the amount of Cu salt to 10 mol % has a negative impact on the isolated yield (40%) (entry18, Table 1). Further, changing the amount of base from 3 to 2 equiv gave a moderate drop in yield (75%) (entry19, Table 1). Reaction under O_2 (1 atm) atmosphere did not show any further improvement in the yield (85%) (entry 20, Table 1), while incomplete conversion and poor yield was observed under N_2 atmosphere (entry 21, Table 1).

Equipped with a set of optimized conditions, we evaluated the reactivity of various 2-amino-*N*-heterocycles with electronically diverse phenylboronic acids (Scheme 2). Gratifyingly, the reactions of 2-aminopyridine with various arylboronic acids proved to be of wide scope and furnished the desired products **2a−r** in up to a 91% yield (Scheme 2). Electronic nature or the substitution pattern did not have much effect on the cross-coupling reactions.[4c] As an example, when the reaction was carried out with simple 2-aminopyridine with phenylboronic acids bearing electron-donating (**2b−c**, **2f**) or electron-withdrawing groups (**2d−e**), the desired product isolated in excellent yields (75−91%). Bicyclic boronic acid was also investigated successfully as a example benzo[*d*][1,3]dioxol-5-ylboronic acid gave the novel tetracyclic moiety (**2g**) in good yield (76%). Then the effect of the substituent attached on the pyridine ring was examined. Pleasingly, all the substituted 2-aminopyridines underwent clean conversion with these optimized conditions and afforded the desired product (**2h−r**) in excellent yields (75−89%). Interestingly, steric congestion did not play major role as 2-amino-6-methylpyridine derivative furnished the imidazo pyridine (**2l−o**) in good yield (78−84%). Both bromo (**2q**) and cyano (**2r**) group were well tolerated under these conditions and amenable to further functional group transformation. Next, we turned our attention in synthesizing another important heterocyclic benzimidazo [1,2-*a*]pyrazine.[17] Under the optimized reaction conditions 2-

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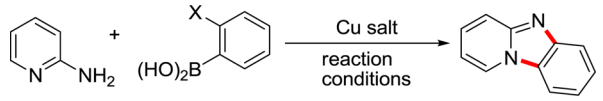
Table 1. Optimization of Reaction Conditions for the Formation of Pyrido[1,2-*a*]benzimidazole[a]



1a **2a**

entry	catalyst	X	base	solvent	temp	time (h)	yield[b]
1	$Cu(OAc)_2$	Br		MeOH	rt	12	15
2	$Cu(OAc)_2$	I		MeOH	rt	12	25
3	$Cu(OAc)_2$	I	Et_3N	MeOH	rt	12	35
4	$Cu(OAc)_2$	I	Et_3N	MeOH	80 °C	12	45
5	$Cu(OAc)_2$	I	Cs_2CO_3	MeOH	80 °C	12	60
6	$Cu(OAc)_2$	I	Cs_2CO_3	MeOH	80 °C	24	70
7	$Cu(OAc)_2$	I	Cs_2CO_3	DMF	80 °C	24	72
8	**$Cu(OAc)_2$**	**I**	**Cs_2CO_3**	**DMF**	**120 °C**	**24**	**88**
9	$Cu(OAc)_2$	I	Cs_2CO_3	DCE	120 °C	24	nr
10	$Cu(OAc)_2$	I	Cs_2CO_3	DME	120 °C	24	nr
11	$Cu(OAc)_2$	I	Cs_2CO_3	DMA	120 °C	24	40
12	$Cu(OAc)_2$	I	CsOPiV	DMF	120 °C	24	70
13	$Cu(OAc)_2$	I	Py	DMF	120 °C	24	55
14	CuI	I	Cs_2CO_3	DMF	120 °C	24	nr
15	Cu_2O	I	Cs_2CO_3	DMF	120 °C	24	nr
16	$Cu(OTf)_2$	I	Cs_2CO_3	DMF	120 °C	24	60
17	$Cu(OAc)_2$	Br	Cs_2CO_3	DMF	120 °C	24	65
18[c]	$Cu(OAc)_2$	I	Cs_2CO_3	DMF	120 °C	24	40
19[d]	$Cu(OAc)_2$	I	Cs_2CO_3	DMF	120 °C	24	75
20[e]	$Cu(OAc)_2$	I	Cs_2CO_3	DMF	120 °C	24	85
21[f]	$Cu(OAc)_2$	I	Cs_2CO_3	DMF	120 °C	24	20

[a]Reaction conditions: 2-aminopyridine (1.0 equiv), 2-halophenylboronic acid (1.1 equiv), copper-salt (20 mol %), Cs_2CO_3 (3.0 equiv) DMF (2 mL), 120 °C, 24 h, air. nr = no reaction. [b]Isolated yields [c]10 mol % $Cu(OAc)_2$ was used. [d]Cs_2CO_3 (2.0 equiv) was used. [e]Reaction performed under O_2. [f]Reaction performed under N_2 atmosphere.

aminopyrazine reacted smoothly with methoxy substituted boronic acid and afforded product 8-methoxybenzo [4,5]-imidazo[1,2-*a*]pyrazine (**2s**, 80%). Further, to establish the generality of this protocol, we focused in synthesizing another two important heterocyclic frameworks benzimidazo[2,1-*a*]-quinolines and benzimidazo[2,1-*a*]isoquinolines.[18] Benzimidazo[2,1-*a*]quinolines are privileged aza-fused heteroaromatics recently reported as topoisomerase-II inhibitors.[19] Reactivity studies with different boronic acids were performed with 2-amino quinoline and 1-aminoisoquinoline under the optimized conditions. Both electron-donating and electron-withdrawing groups afforded the cross-coupled products (**2t**−**w**) in good yields (70−76%). *N*-Arylation of DNA/RNA nucleobases at the nitrogen atom normally attached to the sugar moiety in DNA or RNA has been developed under Chan−Lam conditions.[20] Whereas arylation of nitrogen at C-NH_2 (e.g., purine) position reported rarely.[21] Thus, we applied this optimized protocol for *N*-arylation of 9-ethyl purin-6-amine, and the corresponding purine-fused polcyclics product (**2x**), isolated in good yield (70%).[22]

Both benzo[*d*]thiazolo[3,2-*a*]imidazoles and benzo[*d*]-imidazo[2,1-*b*]thiazoles are important heterocyclic class of compounds known for their interesting biological properties.[23] Despite their medicinal importance, synthesis of this heterocyclic moiety is limited.[24] To our delight, this optimized protocol successfully applied in synthesizing benzo[*d*]thiazolo-[3,2-*a*]imidazoles (**3a**−**b**) and benzo[*d*]imidazo [2,1-*b*]thiazole derivatives (**3c**−**d**) in excellent yields (75−80%)(Scheme 3).

On the basis of previous studies on Chan−Lam type coupling[25] and our experimental results, a plausible catalytic cycle was outlined in Scheme 4. In Chan−Lam type of coupling, the very first step involves the rapid coordination of Cu(II) complex with 2-aminopyridine (**1a**), forming **A** that subsequently undergoes transmetalation with phenylboronic acid to afford complex **B**. Then the Cu(II) complex (**B**) undergoes air oxidation (O_2) to provide the higher oxidation Cu(III) complex **C**, facilitating the smooth reductive elimination to furnish *N*-arylated product (**Intermediate-I**).

Now in Ullmann-type coupling, the first step involves the smooth coordination of **Intermediate-I** with Cu(I) to form complex **D**, which intramolecular oxidative addition with aryl halide furnished complex **E** and subsequently converted to complex **F**. As far as the oxidation state of the copper is concerned, these types of reactions are thus supposed to proceed via Cu(I) and Cu(III) intermediates.[1a,b,e] Now Cu(III) complex **F** on smooth reductive elimination furnished cyclized product 7-methoxybenzo [4,5]imidazo[1,2-*a*]pyridine (**2c**) with concurrent formation of Cu(I). Finally, Cu(II) is generated by O_2 (air) oxidation to complete the catalytic cycle.

In conclusion, we have developed a ligand free Cu (II)-catalyzed one-pot synthesis of benzimidazole-fused heterocycles. This protocol is an example of unique combination of Chan−Lam and Ullmann type coupling, successfully utilized sequentially in C−N bond formation in delivering aza-fused heteroaromatics. The described "open-flask" cascade chemistry is general and the low cost of the catalytic system made this process a valuable alternative compared to previously reported methods and may find useful application in medicinal chemistry.

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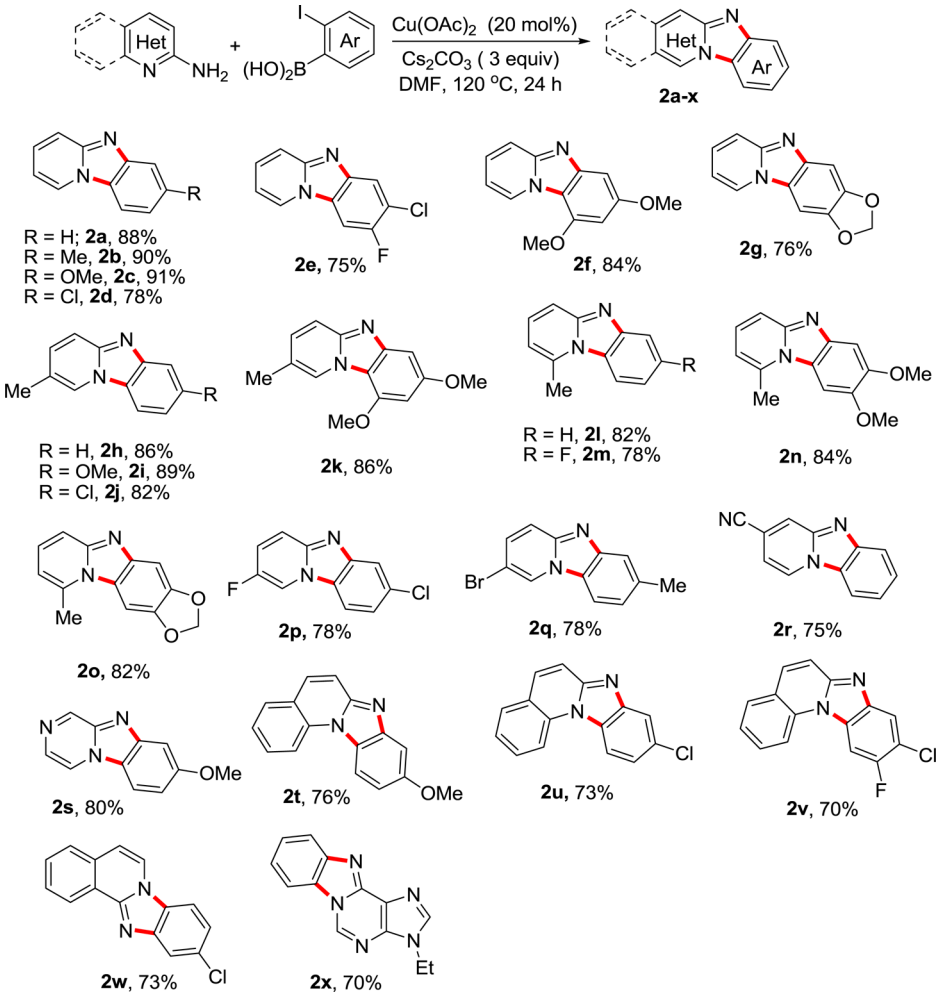
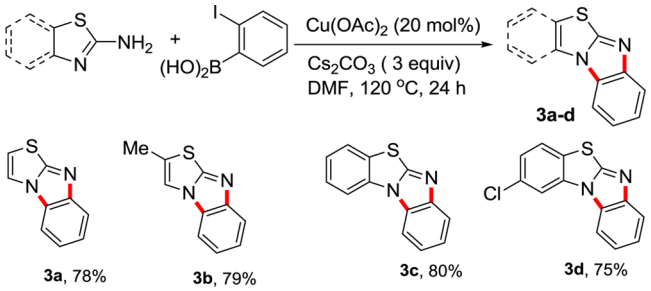
Scheme 2. Synthesis of Pyrido[1,2-*a*]benzimidazoles and Derivatives[a]



[a]Reaction conditions: amino-*N*-heterocycles (1.0 equiv), 2-iodoarylboronic acid (1.1 equiv) $Cu(OAc)_2$ (20 mol %), Cs_2CO_3 (3.0 equiv), DMF (2 mL), 120 °C, 24 h, air.

Scheme 3. Synthesis of Benzo[*d*]thiazolo[3,2-*a*]imidazole and Benzo[4,5]imidazo[2,1-*b*]thiazoles[a]



[a]Reaction conditions: 2-amino thiazole (1.0 equiv), 2-iodophenylboronic acid (1.1 equiv), $Cu(OAc)_2$ (20 mol %), Cs_2CO_3 (3.0 equiv), DMF (2 mL), 120 °C, 24 h, air.

EXPERIMENTAL SECTION

General Information. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates. TLC plates were visualized by exposing UV light or by iodine vapors or immersion in ninhydrin followed by heating on hot plate. ^1H and ^{13}C NMR spectra were recorded at 500 and 400 MHz. HRMS spectra were recorded with LCMS-QTOF (UHD) instrument. Melting points were measured in open capillary tubes and are uncorrected. Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers.

General Procedure for the Synthesis of Copper-Catalyzed Benzimidazole-Fused Heterocycles with 2-Iodophenylboronic Acids. An oven-dried round-bottom flask charged with 2-aminopyridine (1 equiv), 2-iodophenylboronic acid (1.1 equiv), copper acetate (20 mol %), cesium carbonate (3 equiv), and anhydrous DMF (2 mL), the reaction mixture was stirred at 120 °C for 24 h. The reaction was monitered by checking the TLC, and after completion, the reaction mixture was diluted with 30 mL of water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (hexane/EtOAc) to provide the desired product (**2a–x**, **3a–d**).

Benzo[4,5]imidazo[1,2-a]pyridine (**2a**).[14] Eluent: petroleum ether/ethyl acetate (4:1). Yield 79 mg (88%); white solid; mp 180–182 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 6.7 Hz, 1H), 7.86 (dd, J = 16.8, 8.2 Hz, 2H), 7.67 (d, J = 9.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.38 (m, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.81 (t, J = 6.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.0, 162.2, 143.8, 130.1, 126.9, 125.3, 120.5, 118.9, 116.9, 111.8, 110.2. HRMS (ESI): m/z calcd for $C_{11}H_9N_2$ $[M + H]^+$, 169.0760; found, 169.0752.

7-Methylbenzo[4,5]imidazo[1,2-a]pyridine (**2b**).[11] Eluent: petroleum ether/ethyl acetate (4:1). Yield 87 mg (90%); white solid; mp 150–152 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 7.0 Hz, 1H), 8.35 (d, J = 6.8 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.62 (m, 2H), 7.34 (ddd, J = 7.9, 7.0, 5.0 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (125 MHz,

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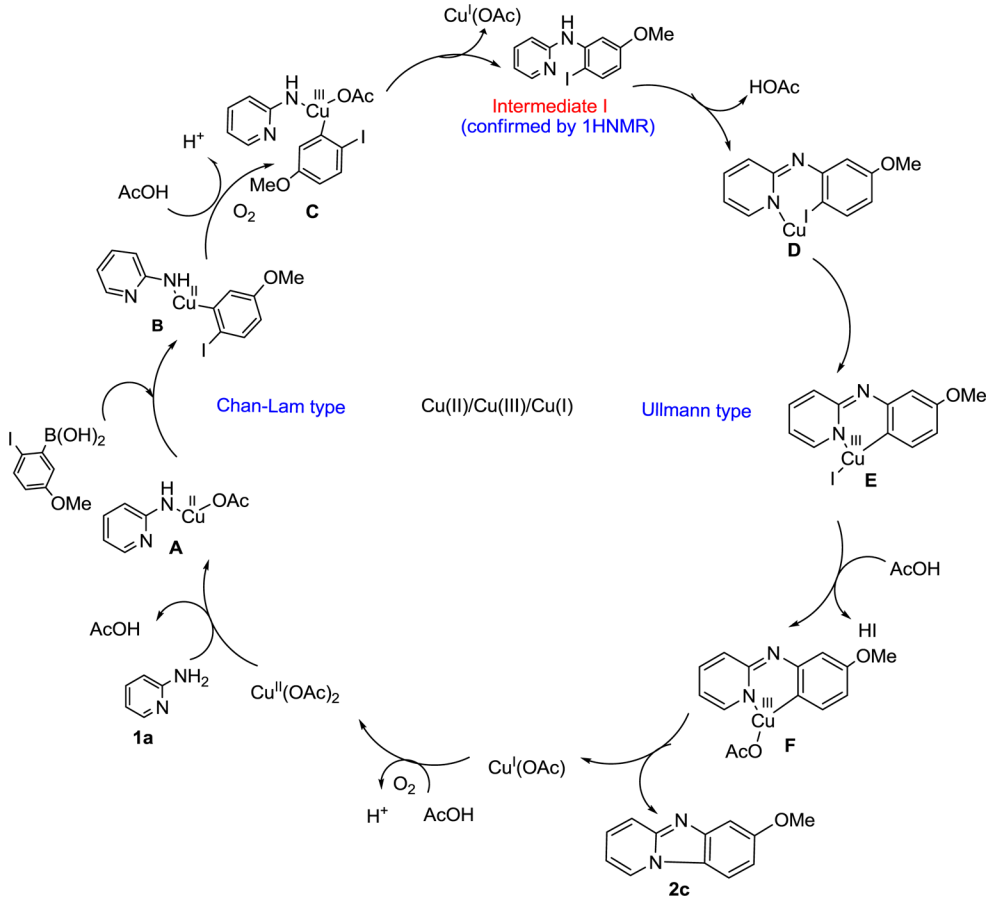
Scheme 4. Plausible Reaction Mechanism



$CDCl_3$) δ 147.5, 142.7, 129.6, 128.0, 126.1, 125.3, 121.3, 117.8, 110.7, 107.9, 17.2. HRMS (ESI): m/z calcd for $C_{12}H_{11}N_2$ $[M + H]^+$, 183.0917; found, 183.0904.

7-Methoxybenzo[4,5]imidazo[1,2-a]pyridine (**2c**).[14] Eluent: petroleum ether/ethyl acetate (4:1). Yield 95 mg (91%); white solid; mp 148−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.41(m, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.9, 2.2 Hz, 1H), 6.86 (t, J = 6.8 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 148.1, 144.2, 129.4, 125.0, 122.8, 117.0, 112.4, 111.1, 111.0, 100.2, 55.8. HRMS (ESI): m/z calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$, 199.0866; found, 199.0864.

7-Chlorobenzo[4,5]imidazo[1,2-a]pyridine (**2d**).[14] Eluent: petroleum ether/ethyl acetate (4:1). Yield 83 mg (78%); white solid; mp 208−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 6.8 Hz, 1H), 7.90 (d, J = 1.5 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 9.3 Hz, 1H), 7.47 (m, 1H), 7.33 (dd, J = 8.7, 1.7 Hz, 1H), 6.90 (t, J = 6.6 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 150.3, 146.3, 131.3, 128.6, 127.5, 121.6, 119.5, 118.2, 113.6, 113.5, 111.7. HRMS (ESI): m/z calcd for $C_{11}H_8ClN_2$ $[M + H]^+$, 203.0371; found, 203.0366.

7-Chloro-8-fluorobenzo[4,5]imidazo[1,2-a]pyridine (**2e**).[14] Eluent: petroleum ether/ethyl acetate (4:1). Yield 87 mg (75%); brown solid, mp 222−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 6.7 Hz, 1H), 8.02 (s, 1H), 7.88 (d, J = 6.6 Hz, 1H), 7.60 (dd, J = 8.4, 4.6 Hz, 1H), 7.38 (m, 1H), 6.82 (t, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 147.3, 138.6, 129.5 (d, J = 13.4 Hz), 127.1, 119.6, 118.5 (d, J = 8.7 Hz), 118.0, 114.7, 114.4 (d, J = 7.0 Hz), 110.7. HRMS (ESI): m/z calcd for $C_{11}H_7ClFN_2$ $[M + H]^+$, 221.0277; found, 221.0269.

7,9-Dimethoxybenzo[4,5]imidazo[1,2-a]pyridine (**2f**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 101 mg (84%); white solid; mp 142−144 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.03 (d, J = 6.9 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.47 (dd, J = 6.7, 1.3 Hz, 1H), 6.90 (t, J = 6.2 Hz, 1H), 6.85 (d, J = 6.1 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 4.10 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 149.2, 148.4, 129.2, 129.0, 128.5, 116.2, 110.4, 110.2, 93.8, 92.1, 55.8, 55.7. HRMS (ESI): m/z calcd for $C_{13}H_{13}N_2O_2$ $[M + H]^+$, 229.0972; found, 229.0965.

[1,3]Dioxolo[4″,5″:4′,5′]benzo[1′,2′:4,5]imidazo[1,2-a]pyridine (**2g**).[14] Eluent: petroleum ether/ethyl acetate (4:1). Yield 85 mg (76%); white solid; mp 235−237 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 6.8 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 15.3, 10.0 Hz, 3H), 6.82 (t, J = 6.6 Hz, 1H), 6.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 146.8, 126.9, 126.7, 123.1, 116.2, 110.2, 110.0, 100.6, 97.4, 89.5, 59.3. HRMS (ESI): m/z calcd for $C_{12}H_9N_2O_2$ $[M + H]^+$, 213.0659; found 213.0686.

2-Methylbenzo[4,5]imidazo[1,2-a]pyridine (**2h**).[11] Eluent: petroleum ether/ethyl acetate (4:1). Yield 72 mg (86%); white solid; mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.59 (d, J = 9.3 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.22 (dd, J = 8.8, 2.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 145.0, 133.2, 128.0, 125.4, 122.6, 120.7, 120.0, 117.2, 103.8, 21.2. HRMS (ESI): m/z calcd for $C_{12}H_{11}N_2$ $[M + H]^+$, 183.0917; found, 183.0943.

7-Methoxy-2-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2i**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 87 mg (89%); white solid; mp 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 9.3 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.26 (s, 1H), 6.98 (dd, J = 8.9, 2.3 Hz, 1H), 3.92 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 148.0, 145.7, 131.9, 123.2, 122.5, 119.9, 116.7, 111.7, 110.8, 100.6, 55.7, 18.1. HRMS (ESI): m/z calcd for $C_{13}H_{13}N_2O$ $[M + H]^+$, 213.1023; found, 213.1020.

7-Chloro-2-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2j**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 82 mg (82%); white solid; mp 156−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.29 (s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 152.6, 149.3, 143.0, 138.9, 134.6, 130.1, 127.9, 127.4, 126.0, 121.1, 117.0, 17.9. HRMS (ESI): m/z calcd for $C_{12}H_{10}ClN_2$ $[M + H]^+$, 217.0527; found, 217.0530.

7,9-Dimethoxy-2-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2k**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 96 mg (86%); white solid; mp 157−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 6.91 (d, J = 1.7 Hz, 1H), 6.41 (d, J = 1.7 Hz, 1H), 4.05 (s, 3H), 3.90 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 149.1, 147.7, 146.5, 131.5, 126.1, 119.6, 115.6, 113.5, 93.6, 92.2, 55.7, 18.2. HRMS (ESI): m/z calcd for $C_{14}H_{15}N_2O_2$ $[M + H]^+$, 243.1128; found, 243.1118.

1-Methylbenzo[4,5]imidazo[1,2-a]pyridine (**2l**).[13b] Eluent: petroleum ether/ethyl acetate (4:1). Yield 69 mg (82%); white solid; mp 106−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.60 (m, 1H), 7.53 (m, 1H), 7.37 (m, 2H), 7.07 (dd, J = 8.5, 5.2 Hz, 1H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 143.0, 138.2, 131.9, 128.4, 124.5, 121.6, 118.6, 116.2, 113.0, 109.3, 17.1. HRMS (ESI): m/z calcd for $C_{12}H_{11}N_2$ $[M + H]^+$, 183.0917; found, 183.0917.

7-Fluoro-1-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2m**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 72 mg (78%); brown solid; mp 140−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, J = 8.2 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.56 (d, J = 9.1 Hz, 1H), 7.41 (m, 1H), 7.05 (t, J = 8.9 Hz, 1H), 6.68 (d, J = 6.7 Hz, 1H), 2.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 154.4, 147.8, 139.3, 138.6 (d, J = 6.2 Hz), 130.7, 126.2 (d, J = 8.7 Hz), 123.3, 121.8 (d, J = 8.3 Hz), 114.9, 112.5, 24.0. HRMS (ESI): m/z calcd for $C_{12}H_{10}N_2F$ $[M + H]^+$, 201.0823; found, 201.0818.

7,8-Dimethoxy-1-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2n**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 94 mg (84%); white solid; mp 265−267 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.35 (s, 1H), 7.27 (t, J = 3.7 Hz, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 146.3, 137.9, 130.7, 129.4, 121.8, 121.4, 120.2, 116.4, 100.2, 92.5, 56.4, 56.2, 18.2. HRMS (ESI): m/z calcd for $C_{14}H_{15}N_2O_2$ $[M + H]^+$, 243.1128; found, 243.1114.

9-Methyl-[1,3]dioxolo[4″,5″:4′,5′]benzo[1′,2′:4,5]imidazo[1,2-a]pyridine (**2o**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 85 mg (82%); white solid; mp 193−195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 5.1 Hz, 2H), 7.21 (d, J = 13.4 Hz, 2H), 6.53 (d, J = 6.5 Hz, 1H), 6.01 (s, 2H), 2.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 143.9, 140.3, 137.5, 129.4, 127.4, 114.9, 111.1, 101.4, 98.2, 94.7, 67.7, 21.1. HRMS (ESI): m/z calcd for $C_{13}H_{11}N_2O_2$ $[M + H]^+$, 227.0815; found, 227.0810.

7-Chloro-2-fluorobenzo[4,5]imidazo[1,2-a]pyridine (**2p**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 76 mg (78%); brown solid; mp 140−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, J = 6.2 Hz, 1H), 8.37 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.76 (m, 1H), 7.49 (m, 1H), 7.37 (dd, J = 8.0, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.1, 125.1, 121.8 (d, J = 6.8 Hz), 121.4 (d, J = 7.5 Hz), 118.6, 117.7, 117.1 (d, J = 8.4 Hz), 113.6, 113.1, 110.4. HRMS (ESI): m/z calcd for $C_{11}H_7ClFN_2$ $[M + H]^+$, 221.0277; found, 221.0269.

2-Bromo-7-methylbenzo[4,5]imidazo[1,2-a]pyridine (**2q**). Eluent: petroleum ether/ethyl acetate (4:1). Yield 58 mg (78%); brown solid; mp 142−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.55 (s, 1H), 7.73 (m, 1H), 7.60 (dd, J = 12.6, 9.8 Hz, 1H), 7.44 (dd, J = 12.9, 5.4 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 132.3, 132.0, 129.5, 127.5, 124.1, 123.3, 119.5, 118.6, 117.8, 109.9, 22.0. HRMS (ESI): m/z calcd for $C_{12}H_{10}N_2Br$ $[M + H]^+$, 261.0022; found, 261.0015.

Benzo[4,5]imidazo[1,2-a]pyridine-3-carbonitrile (**2r**).[13b] Eluent: petroleum ether/ethyl acetate (4:1). Yield 61 mg (75%); white solid; mp 235−237 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.1 Hz, 1H), 8.14 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 6.99 (dd, J = 7.1, 1.3 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.1, 135.2, 130.3, 128.8, 127.3, 125.2, 123.6, 121.2, 118.1, 113.0, 112.8, 110.4. HRMS (ESI): m/z calcd for $C_{12}H_8N_3$ $[M + H]^+$, 194.0713; found, 194.0708.

8-Methoxybenzo[4,5]imidazo[1,2-a]pyrazine (**2s**). Eluent: petroleum ether/ethyl acetate (3:1). Yield 92 mg (80%); brown solid; mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.19 (s, 1H), 7.87 (m, 2H), 7.24 (d, J = 2.1 Hz, 1H), 7.19 (dd, J = 5.3, 2.5 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 157.7, 145.8, 142.7, 139.8, 133.4, 127.4, 122.5, 119.5, 119.4, 94.3, 56.3. HRMS (ESI): m/z calcd for $C_{11}H_{10}N_3O$ $[M + H]^+$, 200.0819; found, 200.0812.

9-Methyl-[1,3]dioxolo[4″,5″:4′,5′]benzo[1′,2′:4,5]imidazo[1,2-a]pyridine (**2t**).[14] Eluent: petroleum ether/ethyl acetate (3:1). Yield 65 mg (76%); brown solid; mp 120−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 9.5 Hz, 1H), 7.62 (d, J = 9.4 Hz, 1H), 7.48 (dd, J = 15.0, 7.3 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 148.5, 135.3, 130.8, 129.7, 129.5, 125.3, 124.1, 123.3, 123.2, 117.3, 115.0, 114.5, 112.9, 101.5, 55.7. HRMS (ESI): m/z calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$, 249.1023; found, 249.1013.

9-Chlorobenzo[4,5]imidazo[1,2-a]quinoline (**2u**).[14] Eluent: petroleum ether/ethyl acetate (3:1). Yield 64 mg (73%); yellow solid; mp 174−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 8.9 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.77 (dd, J = 20.0, 8.9 Hz, 2H), 7.63 (d, J = 9.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.46 (dd, J = 8.7, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 145.6, 135.3, 131.8, 130.1, 129.9, 129.7, 124.5, 123.4, 123.2, 122.9, 120.0, 117.5, 115.1, 114.6. HRMS (ESI): calcd For $C_{15}H_{10}ClN_2$ $[M + H]^+$, 253.0527; found, 253.0524.

9-Chloro-10-fluorobenzo[4,5]imidazo[1,2-a]quinoline (**2v**).[14] Eluent: petroleum ether/ethyl acetate (3:1). Yield 65 mg (70%); pale-yellow solid; mp 204−206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 9.7 Hz, 1H), 8.00 (d, J = 7.0 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.1, 149.5 (d, J = 2.6 Hz), 141.2, 135.0, 131.8, 129.9 (d, J = 21.9 Hz), 124.8, 123.4, 121.0, 117.5, 114.7, 101.8 (d, J = 28.9 Hz). HRMS (ESI): calcd For $C_{15}H_9ClFN_2$ $[M + H]^+$, 271.0433; found, 271.0428.

10-Chlorobenzo[4,5]imidazo[2,1-a]isoquinoline (**2w**).[14] Eluent: petroleum ether/ethyl acetate (3:1). Yield 64 mg (73%); brown solid; mp 149−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (t, J = 7.2 Hz 1H), 8.07 (d, J = 7.2 Hz, 1H), 7.91 (s, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.64 (m, 2H), 7.30 (dd, J = 8.6, 1.5 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 147.1, 143.3, 130.6, 129.4, 129.3, 127.4, 126.1, 124.1, 124.0, 121.3, 120.1, 118.5, 118.1, 111.0, 109.5. HRMS (ESI): calcd For $C_{15}H_{10}ClN_2$ $[M + H]^+$, 253.0527; found, 253.0526.

3-Ethyl-3H-benzo[4,5]imidazo[2,1-i]purine (**2x**).[22] Eluent: petroleum ether/ethyl acetate (1:1). Yield 51 mg (70%); brown solid; mp 219−221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.99 (m, 3H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 4.41 (q, J = 7.3 Hz, 2H), 1.62 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.3, 133.3, 132.4, 127.7, 125.7, 124.7, 121.0, 120.5, 118.6, 108.4, 37.8, 14.1. HRMS (ESI): m/z calcd for $C_{13}H_{11}N_5$ $[M + H]^+$, 238.1087; found, 238.1079.

Benzo[4,5]imidazo[2,1-b]thiazole (CAS 247-83-6) (**3a**). Eluent: petroleum ether/ethyl acetate (9:1). Yield 68 mg (78%); white solid; mp 142−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 13.9, 6.2 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 4.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 146.2, 130.9, 127.5, 124.3, 121.9, 120.7, 119.5, 110.5. HRMS (ESI): m/z calcd for $C_9H_7N_2S$ $[M + H]^+$, 175.0325; found, 175.0318.

2-Methylbenzo[4,5]imidazo[2,1-b]thiazole (CAS 16458-73-4) (**3b**). Eluent: petroleum ether/ethyl acetate (9:1). Yield 65 mg (79%); white solid; mp 156−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 6.28 (s, 1H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 143.4, 135.2, 130.0, 128.6, 122.0, 119.4, 117.9, 109.2, 21.4. HRMS (ESI): m/z calcd for $C_{10}H_9N_2S$ $[M + H]^+$, 189.0481; found, 189.0472.

Benzo[d]benzo[4,5]imidazo[2,1-b]thiazole (**3c**).[24] Eluent: petroleum ether/ethyl acetate (9:1). Yield 59 mg (80%); white solid; mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.31 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 148.2, 133.1, 128.9, 126.6,

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124.3, 124.3, 123.5, 121.9, 119.5, 112.3, 110.5. HRMS (ESI): m/z calcd for $C_{13}H_9N_2S$ $[M + H]^+$, 225.0481; found, 225.0474.

*2-Chlorobenzo[d]benzo[4,5]imidazo[2,1-b]thiazole (**3d**).*[24] Eluent: petroleum ether/ethyl acetate (9:1). Yield 52 mg (75%); white solid; mp 234−235 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 6.0 Hz, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 15.0, 7.4 Hz, 2H), 7.31 (dd, J = 7.5, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 148.0, 135.9, 132.8, 131.7, 126.3, 123.9, 123.5, 122.9, 121.2, 118.7, 111.7, 109.5. HRMS (ESI): calcd for $C_{13}H_8ClN_2S$ $[M + H]^+$, 259.0091; found, 259.0094.

*N-(2-Iodo-5-methoxyphenyl)pyridin-2-amine (**Intermediate-I**).* A oven-dried round-bottom flask charged with 2-amino pyridine (1 equiv), (2-iodo-5-methoxyphenyl)boronic acid (1.1 equiv), copper acetate (20 mol %), cesium carbonate (3 equiv), and anhydrous DMF (2 mL), the reaction mixture was stirred at 120 °C; after 6 h of cooling the reaction mixture to rt it was passed through the small silica gel pad. Eluent: petroleum ether/ethyl acetate (9:1). Colorless liquid. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.90 (s, 1H), 7.68 (s, 1H), 7.22 (m, 2H), 7.01 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 153.8, 147.8, 142.4, 138.6, 129.9, 124.1, 112.0, 108.6, 107.5, 105.4, 55.2. HRMS (ESI): calcd for $C_{12}H_{12}IN_2O$ $[M + H]^+$, 326.9988; found, 326.9990.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01396.

^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: partha@iiim.ac.in

Notes

The authors declare no competing financial interest.

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