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Rapid Construction of an Imidazo[4,5-*b*]pyridine Skeleton from 2-Chloro-3-nitropyridine via Tandem Reaction in H_2O-IPA Medium

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Supporting Information

ABSTRACT: A highly efficient, clean, and simple procedure for the synthesis of a privilege imidazo[4,5-*b*]pyridine scaffold from 2-chloro-3-nitropyridine in combination with environmentally benign H_2O-IPA as a green solvent is presented. The scope of the novel method has been demonstrated through the tandem sequence of S_NAr reaction with substituted primary amines followed by the in situ nitro group reduction and subsequent heteroannulation with substituted aromatic aldehydes to obtain functionalized imidazo[4,5-*b*]pyridines with only one chromatographic purification step. The synthesis pathway appears to be green, simple, and superior compared with other already reported procedures, with the high abundance of reagents and great ability in expanding the structural diversity.

INTRODUCTION

Highly diverse polyheterocyclic ring systems have played a crucial role in medicinal chemistry, which may facilitate the discovery of novel biologically active molecules.[1] These heterocyclic small molecules modulate the functions of receptors or enzymes in living systems, which is very important for studying biology and their treatment of disease.[2] Imidazo[4,5-*b*]pyridines are an important class of heterocycles which have gained much attention in recent years owing to the broad spectrum of their bioactivities.[3] Imidazo[4,5-*b*]pyridines were reported as dual inhibitors of FLT3/aurora kinases for the treatment of acute myeloid leukemia (**A**) as well as a potent angiotensin II type I receptor blocker (**B**) with partial peroxisome proliferator-activated receptor-γ agonism.[4] Similarly, 2-phenyl-3*H*-imidazo[4,5-*b*]pyridine-3-acetamide (**C**) has been reported as nonbenzodiazepine anticonvulsants and anxiolytics, whereas an imidazo[4,5-*b*]pyridine-based drug, sulmazole (**D**), acts as a cardiotonic agent (Figure 1).[5]

Besides this, imidazo[4,5-*b*]pyridine derivatives also possess the potential for numerous applications of proton- and charge-transfer processes in organometallic chemistry and in material science owing to their special structural characteristics.[6] In recent years, some novel synthesis strategies have been reported for the synthesis of imidazo[4,5-*b*]pyridine derivatives via N−C−N or N−C−N−C bond formation reaction. The first method for imidazo[4,5-*b*]pyridine derivatives via the N−C−N bond formation involves the reaction of diamines with aldehydes or excess of carboxylic acids in the presence of $FeCl_3$ or aerial oxidation under heating.[7] Recently, Pitchumani and co-workers have published the use of a recyclable Al^{3+}-exchanged K10 clay as solid acids catalyzed synthesis of 2-substituted 3-ethyl-3*H*-imidazo[4,5-*b*]pyridines.[8] The second method involves the N−C−N−C bond formation, which occurs via Pd- or Cu-catalyzed regiospecific cyclization of 2-halo-3-acylaminopyridines with amines, Pd-catalyzed amidation of 2-chloro-3-amino-substituted pyridines, and Cu- and Pd-catalyzed amidation reaction of 3-amino-*N*-Boc-4-chloropyridine using ligands (Scheme 1).[9]

Blagg et al. reported the synthesis of substituted imidazo[4,5-*b*]pyridines via Pd-catalyzed regioselective C2-arylation reaction.[10] Similarly, Soural and his colleagues described the solid-supported synthesis of imidazo[4,5-*b*]pyridines, where the polymer-supported amines reacted with the pyridine moiety followed by S_NAr reaction with amines, nitro group reduction, and cyclization using aldehydes.[11] In the case of imidazo[4,5-*b*]pyridines, most of the methods are based on Pd- or Cu-catalyzed amidation reaction of 2-halo-3-acylaminopyridines with amines. However, in spite of uniqueness and diversity of the reported methods, there are several drawbacks associated with them, which include the participation of toxic and costly Pd or Cu catalyst in the presence of specific and costly ligands and appropriate bases, narrow substrate scope and use of toxic solvent, harsh reaction condition, and longer reaction time with laborious workup procedures. Thus, the construction of the imidazo[4,5-*b*]pyridine scaffold bearing a diverse range of substituents at the N-1 and the C-2 positions poses a synthetic challenge. In this context, it is requisite to develop a simple and efficient strategy for the synthesis of biologically important substituted imidazo[4,5-*b*]pyridines. In recent times, the synthesis of active pharmaceutical analogues in water as the

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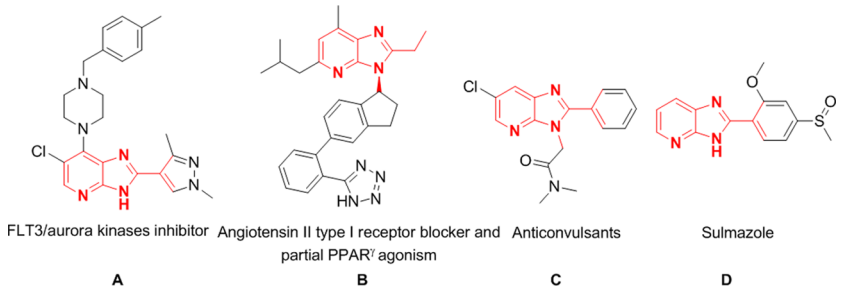
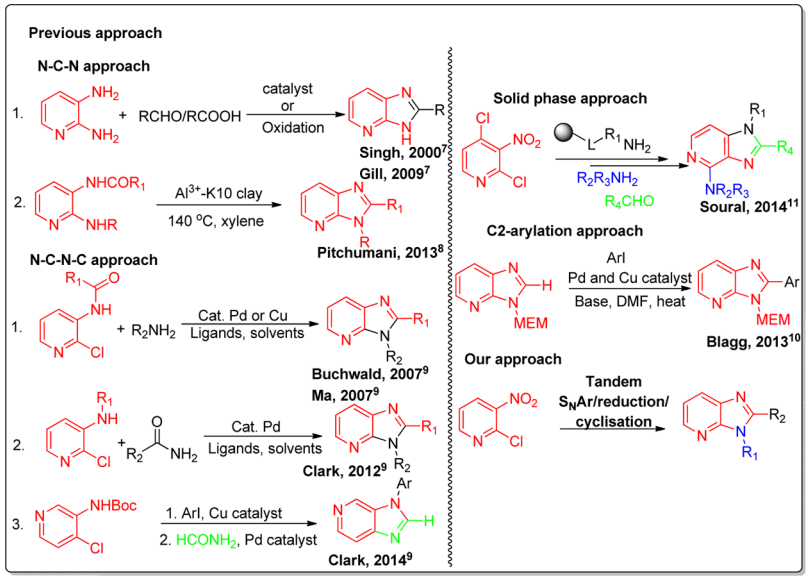


Figure 1. Biologically active imidazo[4,5-*b*]pyridine derivatives.

Scheme 1. Strategies for the Synthesis of Substituted Imidazo[4,5-*b*]pyridines



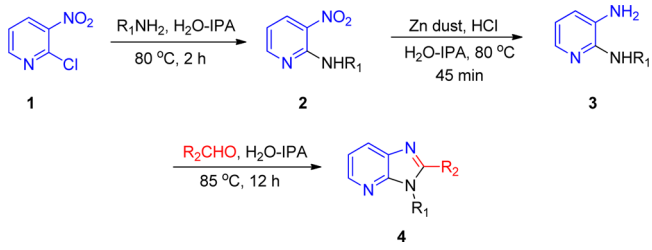
solvent has attracted considerable attention owing to the nontoxic, nonflammable nature of water, which further fulfills all green principles.[12] The poor solubility of organic compounds in water has been overcome by the use of an organic cosolvent.

A tandem reaction is an important tool for the diversity-oriented synthesis of heterocyclic small molecules to meet the demands of high-throughput screening for drug discovery research.[13] Using the H_2O-IPA as the preferred reaction medium in the design of green chemical syntheses, we therefore wished to develop a convenient catalyst-free tandem synthesis of imidazo[4,5-*b*]pyridines. In comparison to the already reported synthesis protocols, the present methodology offers several advantages such as the application of a tandem process by circumventing the classical step-by-step approaches of using toxic transition-metal catalysts, H_2O-IPA as the green and ecofriendly solvent, excellent yields with high purity, and a broad substrate scope. In continuation of our quest for the development of newer synthesis methodologies for the bioactive heterocycles,[14] we aim to utilize the tandem reaction in a green solvent for the synthesis of imidazo[4,5-*b*]pyridines from readily available chemicals with excellent yields.

RESULTS AND DISCUSSION

Our work started with the alkyl amination step, which is crucial in introducing the substituents of the disubstituted imidazo[4,5-*b*]pyridine scaffold. The new metal- and base-free route for the relevant C−N bond forming step involved the nucleophilic substitution reaction of 2-chloro-3-nitropyridine **1** with primary amines in refluxing dichloromethane as the solvent for 72 h to obtain the N-substituted pyridine-2-amine **2** (Scheme 2).

Scheme 2. Synthesis of Imidazo[4,5-*b*]pyridine from 2-Chloro-3-nitro Pyridine



Nevertheless, to speed up the process, we attempted the S_NAr reaction of 2-chloro-3-nitropyridine **1** with primary amines under refluxing 1,2-dichloroethane solvent for 24 h for completion. However, the H_2O-IPA-assisted aromatic nucleophilic substitution of 2-chloro-3-nitropyridine with diverse amines at 80 °C greatly reduced the reaction time to 2 h to form the intermediate N-substituted pyridine-2-amine **2**. The introduction of common linear-chain aliphatic amines as the first diversity point in the skeleton furnished the targeted compounds in excellent yields. Subsequently, our next step in the synthesis sequence involved the reduction of the nitro group, which was carried out using Zn/$HCOONH_3$ in the

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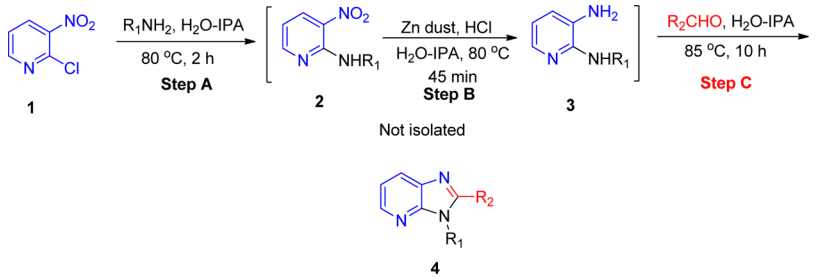
Scheme 3. One-Pot Three-Step Reaction toward Imidazo[4,5-*b*]pyridine Compounds 4



methanol solvent at room temperature. However, it took almost 24 h to complete under room-temperature condition to furnish the substituted pyridine-2,3-diamine **3**. Upon changing the solvent system to H_2O-IPA as the reaction medium using Zn/AcOH as the reducing agent at 80 °C, the reaction took 12 h for completion. Nonetheless, to hasten the reduction step, instead of using Zn/AcOH as the reducing agent,[15] we tried Zn/HCl at 80 °C to obtain the substituted pyridine-2,3-diamine **3** in 45 min with excellent yields. The use of Zn/HCl as the reducing agent in H_2O-IPA as the reaction medium greatly reduced the reaction time to minutes, which further justifies the green chemistry principles. To introduce the second diversity point in the imidazo[4,5-*b*]pyridine ring, pyridine-2,3-diamines **3** were subjected to heterocyclization with substituted aldehydes under H_2O-IPA at room temperature, which took almost 2 days for completion.

To facilitate the synthesis of the target compounds swiftly, we conducted the same reaction at 85 °C for completion in 10 h to yield substituted 2-aryl imidazo[4,5-*b*]pyridines **4**. However, in an attempt to diversify the synthesis methodology, we envisioned that the imidazo[4,5-*b*]pyridine ring **4** could be constructed by a one-pot tandem process involving S_NAr reaction−reduction−heterocyclization reaction. The initial investigation toward the synthesis of *N*-aryl alkyl/alkyl-2-alkyl/aryl/heteroaryl imidazo[4,5-*b*]pyridines using the tandem process has been performed (Scheme 3). Thus, 2-chloro-3-nitropyridine **1** was subjected to the S_NAr reaction with different amines in H_2O-IPA as the reaction medium at 80 °C for 2 h, and the in situ formed N-substituted products **2** were treated with Zn dust (1 equiv) and concd HCl (0.5 equiv) at 80 °C and stirred for another 45 min. The N-substituted pyridine-2,3-diamines **3** were obtained in 90% yield. However, the use of HOAc instead of aq. HCl afforded 50% yield of **3**. The formation of the amine products **3** could also be confirmed by the color change of the reaction mixture from yellow to blue along with the change in the chemical shifts of aromatic regions in the ^1H NMR spectra of the crude products. After the reaction was completed, Zn dust was filtered off and the preformed **3** were next treated with aldehydes in H_2O-IPA without any metal catalyst for 10 h to obtain the substituted imidazo[4,5-*b*]pyridines **4** in excellent yield. However, the use of polar protic solvents such as MeOH or EtOH gave good yields, whereas the aprotic solvents such as toluene, 1,4-dioxane, tetrahydrofuran, and 1,2-dichloroethane under similar conditions obtained lower yields, which demonstrates the advantage of using H_2O-IPA in the condensation stage.

Notably, because the three steps (A, B, and C) were all performed in H_2O-IPA, the whole procedure can be completed in one pot without isolating the intermediates. These findings highlighted the indispensable role of H_2O-IPA in promoting the S_NAr reaction−reduction−heterocyclization step for the diversity-oriented one-pot synthesis of disubstituted imidazo-[4,5-*b*]pyridines. With the one-pot reaction conditions for the preparation of **4** in hand, we set out to investigate the substrate scope for a range of primary amines and aldehydes. Generally, the use of substituted aldehydes bearing electron-donating or electron-withdrawing substituents or heteroaromatic aldehydes provided the corresponding imidazo[4,5-*b*]pyridines in higher yields. All these reactions were performed under an open atmosphere. Table 1 demonstrates the excellent results for general applicability of the diversity-oriented synthesis of 1,2-disubstituted imidazo[4,5-*b*]pyridines.

Table 1. Diversity-Oriented Synthesis of 1,2-Disubstituted Imidazo[4,5-*b*]pyridines

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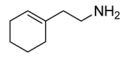
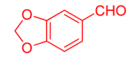
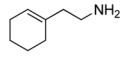
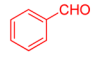
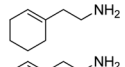
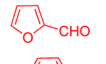
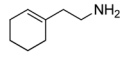
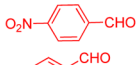
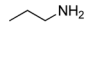
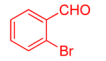
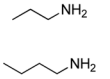
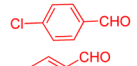
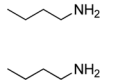
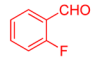
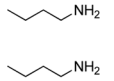
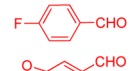
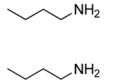
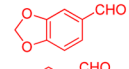
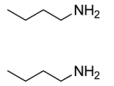
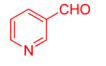
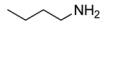
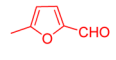
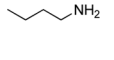
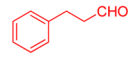
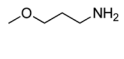
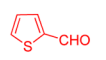
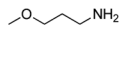
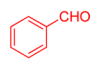
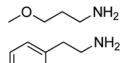
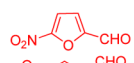
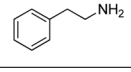
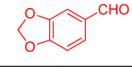
4a			347	95
4b			303	92
4c			293	93
4d			348	96
4e			315	90
4f			271	91
4g			269	92
4h			269	95
4i			295	97
4j			252	91
4k			255	90
4l			279	91
4m			273	92
4n			267	96
4o			302	90
4p			343	97

[a]LRMS were detected with an electron ionization source. [b]Yield of the isolated product.

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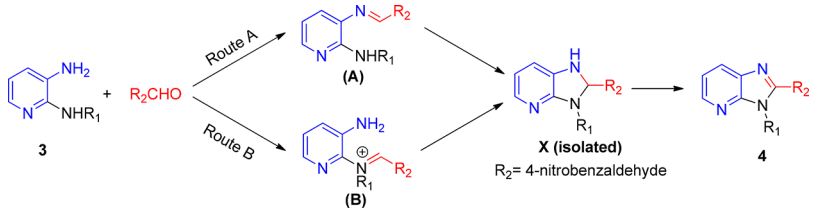
Scheme 4. Possible Routes of the Heterocyclization Step for the Synthesis of 1,2-Disubstituted Imidazo[4,5-*b*]pyridine



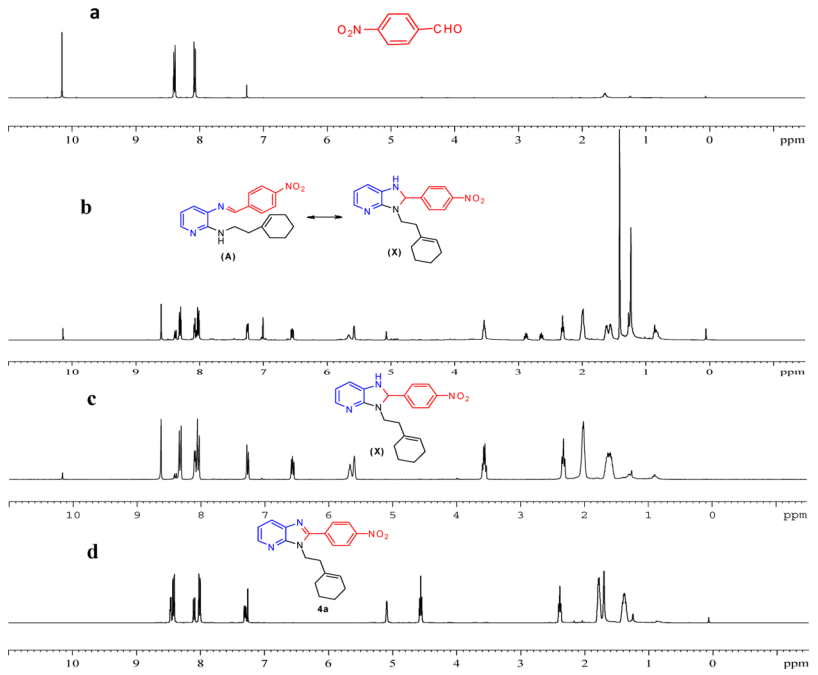
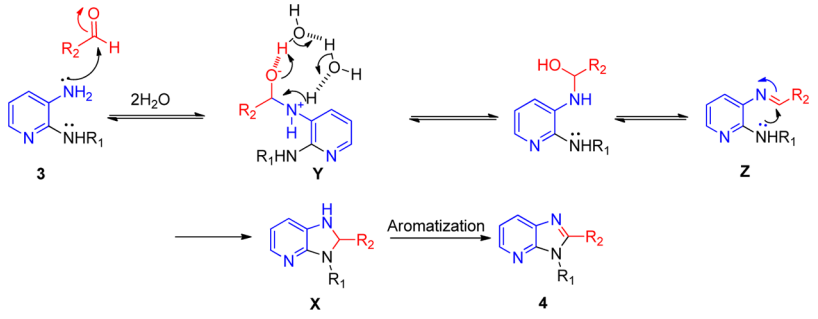


Figure 2. Time-dependent ^{1}H NMR study for reaction of **3a** with 4-nitrobenzaldehyde in H_2O-IPA (5 mL): (a) 4-nitrobenzaldehyde; (b) reaction mixture after 10 min; (c) reaction mixture after 1 h; and (d) reaction mixture after 10 h.

Scheme 5. Plausible Heteroannulation Mechanism toward the Formation of Imidazo[4,5-*b*]pyridine in Aqueous Medium



After completion of the reaction, the corresponding 1,2-disubstituted imidazo[4,5-*b*]pyridine derivatives **4** were obtained with excellent yields, followed by a simple work-up involving removal of solvents under reduced pressure, extraction, and solvent evaporation. Finally, the crude products were purified by column chromatography, followed by spectroscopic characterization using ^{1}H NMR, ^{13}C NMR, and mass spectroscopy (MS). There are two possible pathways such as the formation of imine intermediate (A) or the immonium intermediate (B) in the heterocyclization step through which 1,2-disubstituted imidazo[4,5-*b*]pyridines are obtained, as outlined in Scheme 4.

However, to understand whether the reaction proceeds through "route A" or "route B", we monitored the progress of the reaction of **3a** with 4-nitrobenzaldehyde in H_2O-IPA by ^{1}H NMR (Figure 2).

The appearance of the signals at δ 7.00 ppm and δ 8.60 ppm in the reaction mixture after 10 min of reaction suggested the simultaneous formation of imine **A** and cyclized intermediate **X**, respectively. However, after 1 h of reaction, disappearance of the signal at δ 7.00 ppm indicates the exclusive formation of intermediate **X**. Finally, after 10 h of reaction, the cyclized intermediate **X** aromatized to the imidazo[4,5-*b*]pyridine **4** as obtained from ^{1}H NMR spectra. The time-dependent ^{1}H NMR study further confirms that the reaction proceeds via route A, which involved the formation of imines followed by subsequent cyclization and aromatization to obtain the imidazo[4,5-

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b]pyridine derivatives. A plausible mechanistic pathway for this heteroannulation reaction is outlined in Scheme 5.

It is assumed that the water molecule plays an important role in the heteroannulation step because of its ability to activate both the electrophile and nucleophile simultaneously.[16] It activates the oxygen atom of the C═O group and hydrogen atom of the NH_2 group via hydrogen bonds through the transient species Y to form the imine Z. Subsequent intramolecular nucleophilic attack of the adjacent NH group to the C═ N moiety resulted in the formation of disubstituted dihydro imidazo[4,5-*b*]pyridine derivatives **X**, which, on further aromatization, resulted in the disubstituted imidazo[4,5-*b*]-pyridine **4**. The intermediate **X** was isolated and characterized by mass, IR, and NMR (^{1}H and ^{13}C) spectroscopies.

Finally, imidazo[4,5-*b*]pyridine derivatives were screened for in vitro antimicrobial activity against Gram-negative (*Escherichia coli* and *Klebsiella*) and Gram-positive (*Staphylococcus aureus*) bacteria by the conventional serial dilution method. The in vitro antimicrobial assay was performed at a drug concentration of 0 to 250 μM. Minimum inhibitory concentration (MIC) values were evaluated for all compounds. None of the compounds displayed promising antibacterial activities with MIC values less than 40 μM (see Supporting Information Table 1 for complete assay).

CONCLUSIONS

In summary, we have developed a distinct tandem protocol toward rapidly accessing disubstituted imidazo[4,5-*b*]pyridine derivatives by employing 2-chloro-3-nitropyridine and primary amines as the starting materials. Significantly, upon rational design, after treatment of the in situ formed N-substituted pyridine-2,3-diamine with aldehydes, a novel annulations occurs through the simultaneous electrophile−nucelophilie activation ability of water. Further aromatization results in the formation of imidazo[4,5-*b*]pyridine compounds. In general, the sequential transformations can be simply manipulated in a one-pot tandem process. The H_2O-IPA-assisted tandem S_NAr reaction−reduction−condensation chemistry provides green procedures for the novel base-free one-pot synthesis of imidazo[4,5-*b*]pyridine derivatives in excellent yields.

EXPERIMENTAL SECTION

Dichloromethane and methanol were distilled from calcium hydride before use. All chemicals were purchased from Sigma-Aldrich. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F254 plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230−400 mesh). ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on a Bruker DRX 300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. High-resolution mass spectrometry (HRMS) spectra were recorded on a JEOL TMS-HX 110 mass spectrometer.

General Procedure for the Synthesis of 3-(Alkyl/Aralkyl)-2-aryl/heteroaryl-3*H*-imidazo[4,5-*b*]pyridine. To a solution of 2-chloro-3-nitropyridine **1** (1 equiv) in H_2O-IPA (5 mL, 1:1) was added primary amine (1 equiv) and was stirred for 5 min at room temperature, and then the reaction mixture was heated at 80 °C for 2 h to obtain the intermediate **2** as monitored by TLC. After completion of the reaction, to the same reaction mixture was added Zn (1 equiv) and concd HCl (0.5 equiv), and the reaction mixture was heated for 45 min at 80 °C to obtain the diamine derivatives **3**. After completion, the reaction mixture was then subjected to centrifugation to remove Zn dust; to the same reaction mixture was added substituted aldehydes (1 equiv); and the reaction mixture was heated for 10 h at 85 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (10 mL, twice). The combined organic layer was dried over anhydrous $MgSO_4$. The combined filtrate was subjected to evaporation to obtain the crude compound, which was purified over silica gel column (60−120 mesh) using 15% ethyl acetate in hexane as the eluent to obtain the corresponding 3-(alkyl/aralkyl)-2-aryl/heteroaryl-3*H*-imidazo-[4,5-*b*]pyridine **4** derivatives in excellent yields.

2-(Benzo[*d*][1,3]dioxol-5-yl)-3-(2-(cyclohex-1-en-1-yl)-ethyl)-3*H*-imidazo[4,5-*b*]pyridine (4a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (dd, J = 4.8, 1.4 Hz, 1H), 7.80 (dd, J = 7.9, 1.4 Hz, 1H), 7.25−7.23 (m, 2H), 7.21 (dd, J = 8.0, 2.5 Hz, 1H), 6.94 (dd, J = 7.9, 1.4 Hz, 1H), 6.05 (s, 2H), 5.12 (m, 1H), 4.49 (t, J = 7.1 Hz, 2H), 2.37 (t, J = 7.1 Hz, 2H), 1.81−1.76 (m, 4H), 1.48−1.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 149.6, 149.2, 148.5, 143.9, 135.5, 133.8, 127.2, 124.6, 123.8, 118.8, 109.8, 109.0, 102.0, 42.7, 38.0, 28.5, 25.5, 22.9, 22.4; IR (KBr, cm^{-1}): 3048, 2927, 1727, 1598, 1467, 1035 cm^{-1}; MS (EI) m/z: 347.1 (M^+); HRMS (EI, m/z): calcd for $C_{21}H_{21}N_3O_2$, 347.1634; found, 347.1629 (M^+).

3-(2-(Cyclohex-1-en-1-yl)ethyl)-2-phenyl-3*H*-imidazo-[4,5-*b*]pyridine (4b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (dd, J = 4.8, 1.5 Hz, 1H), 8.03 (dd, J = 7.7, 1.5 Hz, 1H), 7.75 (dd, J = 3.7, 1.5 Hz, 2H), 7.52−7.50 (m, 3H), 7.22 (dd, J = 7.7, 4.8 Hz, 1H), 5.09 (m, 1H), 4.50 (t, J = 7.2 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.75−1.73 (m, 4H), 1.37−1.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 149.1, 144.1, 135.6, 133.8, 130.9, 130.5, 129.5, 129.2, 127.5, 124.6, 118.8, 42.7, 38.1, 28.4, 25.5, 22.9, 22.3; IR (KBr, cm^{-1}): 2927, 1727, 1598, 1469, 1380, 1284, cm^{-1}; MS (EI) m/z: 303.1 (M^+); HRMS (EI, m/z): calcd for $C_{20}H_{21}N_3$, 303.1735; found, 303.1741 (M^+).

3-(2-(Cyclohex-1-en-1-yl)ethyl)-2-(furan-2-yl)-3*H*-imidazo[4,5-*b*]pyridine (4c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (dd, J = 4.5, 1.3 Hz, 1H), 8.00 (d, J = 1.3 Hz, 1H), 7.94 (dd, J = 7.9, 1.3 Hz, 1H),7.54 (s, 1H), 7.15 (m, 1H), 6.97 (s, 1H), 5.25 (m, 1H), 4.44 (t, J = 6.2 Hz, 2H), 2.38 (t, J = 6.2 Hz, 2H), 1.92−1.90 (m, 2H), 1.79−1.77 (m, 2H), 1.48−1.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 149.1, 144.1, 135.6, 133.8, 130.9, 130.5, 129.5, 129.2, 127.5, 124.6, 118.8, 42.7, 38.1, 28.4, 25.5, 22.9, 22.3; IR (KBr, cm^{-1}): 2927, 1727, 1598, 1469, 1380, 1284.36, cm^{-1}; MS (EI) m/z: 293 (M^+); HRMS (EI, m/z): calcd for $C_{18}H_{19}N_3O$, 293.1528; found, 293.1535 (M^+).

3-(2-(Cyclohex-1-en-1-yl)ethyl)-2-(4-nitrophenyl)-3*H*-imidazo[4,5-*b*]pyridine (4d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, J = 4.4 Hz, 1H), 8.34 (d, J = 8.0 Hz, 2H), 8.02 (dd, J = 8.0, 4.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.24 (dd, J = 8.0, 4.4 Hz, 1H), 5.03 (s, 1H), 4.49 (t, J = 7.6 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 1.72−1.71 (m, 4H), 1.34−1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 148.8, 148.6, 144.8, 136.8, 135.2, 133.1, 130.0, 127.7, 124.6, 124.0, 119.0, 42.6, 37.8, 28.1, 25.1, 22.5, 21.9; IR (KBr, cm^{-1}): 2924, 1593, 1516, 1340 cm^{-1}; MS (EI) m/z: 349 (MH^+); HRMS (ESI, m/z): calcd for $C_{20}H_{21}N_4O_2$, 349.1665; found, 349.1668 (MH^+).

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2-(2-Bromophenyl)-3-propyl-3*H*-imidazo[4,5-*b*]-pyridine (4e). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.45−8.43 (m, 1H), 8.10 (m, 1H), 7.78 (d, J = 8 Hz, 1H), 7.52−7.43 (m, 3H), 7.40 (m, 1H), 4.167 (t, J = 7.2 Hz, 2H), 1.75 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CdCl_3$): δ 153.3, 147.7, 144.1, 134.8, 134.1, 133.0, 132.0, 131.7, 127.7, 127.5, 123.6, 118.5, 45.2, 22.9, 11.2; IR (KBr, cm^{-1}): 2962, 2927, 1712, 1604, 1456, 1381, 1278, cm^{-1}; MS (EI) m/z: 315 (M^+); HRMS (ESI, m/z): calcd for $C_{15}H_{14}BrN_3$, 315.0371; found, 316.0448 (MH^+).

2-(4-Chlorophenyl)-3-propyl-3*H*-imidazo[4,5-*b*]-pyridine (4f). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.42 (m, 1H), 8.08 (t, J = 7.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.26 (m, 1H), 4.36 (t, J = 7.6 Hz, 2H), 1.89 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CdCl_3$): δ 152.3, 147.7, 143.0, 138.3, 135.5, 134.1, 129.4, 128.2, 126.3, 117.7, 44.3, 22.2, 10.1; IR (KBr, cm^{-1}): 2924, 1728, 1604, 1482, 1284, 1232 cm^{-1}; MS (EI) m/z: 271 (M^+); HRMS (ESI, m/z): calcd for $C_{15}H_{15}ClN_3$, 272.0955; found, 272.0958 (MH^+).

3-Butyl-2-(2-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine (4g). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.37 (dd, J = 4.7, 1.4 Hz, 1H), 8.02 (dd, J = 7.9, 1.4 Hz, 1H), 7.60 (dt, J = 7.4, 1.5 Hz, 1H), 7.49−7.43 (m, 1H), 7.29−7.15 (m, 3H), 4.23 (t, J = 7.3 Hz, 2H), 1.68 (quint, J = 7.3 Hz, 2H), 1.15−1.11 (m, 2H), 0.71 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 162.0, 158.7, 150.3, 148.6, 144.4, 135.7, 132.4, 127.8, 125.1, 118, 116.6, 116.3, 43.7, 31.7, 20.1, 13.9; IR (KBr, cm^{-1}): 3035, 2960, 2867, 1592, 1523, 1471 cm^{-1}; MS (EI) m/z: 269 (M^+); HRMS (EI, m/z): calcd for $C_{16}H_{18}FN_3$, 269.1328; found, 269.1320 (M^+).

3-Butyl-2-(4-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine (4h). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.42 (dd, J = 4.7, 1.5 Hz, 1H), 8.08 (dd, J = 8.0, 1.5 Hz, 1H), 7.80−7.76 (m, 2H), 7.29−7.23 (m, 3H), 4.40 (t, J = 7.6 Hz, 2H), 1.80 (quint, J = 7.6 Hz, 2H), 1.36−1.24 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 165.8 (d, J_{CF} = 247.5 Hz), 153.8, 148.9, 144.2, 135.5, 131.0 (d, J_{CF} = 15 Hz), 127.5, 127.0 (d, J_{CF} = 3.3 Hz), 118.9, 116.5 (d, J_{CF} = 3.3 Hz), 43.8, 32.2, 20.2, 13.9; IR (KBr, cm^{-1}): 2958, 2869, 1604, 1525, 1487, 1409 cm^{-1}; MS (EI) m/z: 269 (M^+); HRMS (EI, m/z): calcd for $C_{16}H_{18}FN_3$, 269.1328; found, 269.1324 (M^+).

2-(Benzo[*d*][1,3]dioxol-5-yl)-3-butyl-3*H*-imidazo[4,5-*b*]pyridine (4i). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.38 (dd, J = 4.8, 1.4 Hz, 1H), 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.28−7.20 (m, 3H), 6.95 (d, J = 8.5 Hz, 1H), 6.07 (s, 2H), 4.38 (t, J = 7.6 Hz, 2H), 1.81 (quint, J = 7.6 Hz, 2H), 1.35−1.23 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 154.6, 149.7, 149.1, 148.5, 143.9, 135.5, 127.3, 124.5, 123.9, 118.8, 109.8, 109.1, 102.0, 43.9, 32.2, 20.3, 13.9; IR (KBr, cm^{-1}): 2962, 2869, 1598, 1486, 1477 cm^{-1}; MS (EI) m/z: 295 (M^+); HRMS (EI, m/z): calcd for $C_{17}H_{17}N_3O_2$, 295.1321; found, 295.1324 (M^+).

3-Butyl-2-(pyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine (4j). ^{1}H NMR (300 MHz, $CdCl_3$): δ 9.00 (s, 1H), 8.75 (d, J = 4.4 Hz, 1H), 8.40 (d, J = 4.4 Hz, 1H), 8.11−8.04 (m, 2H), 7.47 (dd, J = 7.5, 4.9 Hz, 1H), 7.23 (dd, J = 7.5, 4.9 Hz, 1H), 4.38 (t, J = 7.6 Hz, 2H), 1.82 (quint, J = 7.6 Hz, 2H), 1.33−1.23 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 151.7, 151.4, 149.9, 148.9, 144.7, 137.0, 135.6, 127.8, 127.2, 124.1, 119.2, 43.9, 32.4, 20.3, 13.9; IR (KBr, cm^{-1}): 2958, 2869, 1604, 1525, 1460, 1455 cm^{-1}; MS (EI) m/z: 269 (M^+); HRMS (EI, m/z): calcd for $C_{15}H_{16}N_4$, 252.1375; found, 252.1370 (M^+).

3-Butyl-2-(5-methylfuran-2-yl)-3*H*-imidazo[4,5-*b*]-pyridine (4k). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.35 (dd, J = 4.7, 1.0 Hz, 1H), 8.00 (dd, J = 7.9, 1.0 Hz, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 7.11 (d, J = 3.3 Hz, 1H), 6.23 (d, J = 3.3 Hz, 1H), 4.59 (t, J = 7.6 Hz, 2H), 2.46 (s, 3H), 1.90 (quint, J = 7.6 Hz, 2H), 1.49−1.39 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 155.4, 148.7, 145.7, 143.9, 135.6, 126.9, 118.9, 114.7, 108.9, 43.7, 32.5, 20.6, 14.3, 14.1; IR (KBr, cm^{-1}): 2958, 2867, 1596, 1558, 1468, 1429, 1384 cm^{-1}; MS (EI) m/z: 255 (M^+); HRMS (EI, m/z): calcd for $C_{15}H_{17}N_3O$, 255.1372; found, 255.1374 (M^+).

3-Butyl-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridine (4l). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.34 (d, J = 4.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.34−7.18 (m, 6H), 4.14 (t, J = 7.5 Hz, 2H), 3.30−3.16 (m, 4H), 1.72 (quint, J = 7.5 Hz, 2H), 1.39−1.29 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 155.9, 148.4, 143.5, 141.1, 134.9, 129.1, 128.8, 126.9, 126.8, 118.4, 42.6, 34.1, 32.4, 30.4, 20.5, 14.1; IR (KBr, cm^{-1}): 3058, 2958, 2863, 1724, 1600, 1502, 1398 cm^{-1}; MS (EI) m/z: 279 (M^+); HRMS (EI, m/z): calcd for $C_{18}H_{21}N_3$, 279.1735; found, 279.1734 (M^+).

3-(3-Methoxypropyl)-2-(thiophen-2-yl)-3*H*-imidazo-[4,5-*b*]pyridine (4m). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.38 (dd, J = 4.8, 1.2 Hz, 1H), 8.04 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 5.4 Hz, 1H), 7.26 (dd, J = 4.0, 1.2 Hz, 1H), 7.25−7.21 (m, 1H), 4.70 (t, J = 6.7 Hz, 2H), 3.47 (t, J = 6.7 Hz, 2H), 3.32 (s, 3H), 2.27−2.17 (m, 2H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 149.1, 148.9, 144.2, 135.6, 132.9, 129.6, 128.7, 128.6, 127.2, 119.2, 69.9, 59.2, 41.4, 30.3; IR (KBr, cm^{-1}): 2928, 1730, 1600, 1552, 1467, 1387 cm^{-1}; MS (EI) m/z: 273 (M^+); HRMS (EI, m/z): calcd for $C_{14}H_{15}N_3OS$, 273.0936; found, 273.0948 (M^+).

3-(3-Methoxypropyl)-2-phenyl-3*H*-imidazo[4,5-*b*]-pyridine (4n). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.40 (dd, J = 4.7, 1.1 Hz, 1H), 8.07 (dd, J = 6.8, 1.1 Hz, 1H), 7.83−7.79 (m, 2H), 7.56−7.54 (m, 3H), 7.26 (m, 1H), 4.55 (t, J = 7.2 Hz, 2H), 3.32 (t, J = 7.2 Hz, 2H), 3.18 (s, 3H), 2.14 (quint, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 155.0, 149.1, 144.2, 135.6, 130.6, 129.3, 129.0, 127.6, 118.9, 69.7, 58.9, 41.5, 30.1; IR (KBr, cm^{-1}): 2936, 1597, 1458, 1384 cm^{-1}; MS (EI) m/z: 267 (M^+); HRMS (EI, m/z): calcd for $C_{16}H_{17}N_3O$, 267.1372; found, 267.1367 (M^+).

3-(3-Methoxypropyl)-2-(5-nitrofuran-2-yl)-3*H*-imidazo[4,5-*b*]pyridine (4o). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.50 (dd, J = 4.7, 1.4 Hz, 1H), 8.10 (dd, J = 8.1, 1.4 Hz, 1H), 7.53−7.49 (m, 2H), 7.34 (dd, J = 8.1, 4.7 Hz, 1H), 4.87 (t, J = 6.8 Hz, 2H), 3.52 (t, J = 6.8 Hz, 2H), 3.27 (s, 3H), 2.24 (quint, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 148.4, 147.5, 146.3, 142.3, 135.6, 128.3, 128.1, 120.0, 115.1, 113.4, 70.1, 58.1, 42.2, 30.7; IR (KBr, cm^{-1}): 3057, 2927, 1732, 1593, 1470, 1423 cm^{-1}; MS (EI) m/z: 302 (M^+); HRMS (EI, m/z): calcd for $C_{14}H_{14}N_4O_4$, 302.1015; found, 302.0980 (M^+).

2-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenethyl-3*H*-imidazo-[4,5-*b*]pyridine (4p). ^{1}H NMR (300 MHz, $CdCl_3$): δ 8.42 (dd, J = 4.8, 1.4 Hz, 1H), 8.05 (dd, J = 7.9, 1.4 Hz, 1H), 7.36−33 (m, 1H), 7.29−7.19 (m, 3H), 7.01−6.87 (m, 5H), 6.06 (s, 2H), 4.62 (t, J = 7.5 Hz, 2H), 3.16 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CdCl_3$): δ 154.9, 149.5, 149.0, 148.3, 144.1, 138.0, 135.6, 129.2, 128.9, 127.4, 124.2, 123.8, 118.9, 109.9, 108.8, 101.9, 45.5, 35.9; IR (KBr, cm^{-1}): 3111, 2830, 1535, 1500, 1364, 1346 cm^{-1}; MS (EI) m/z: 302 (M^+); HRMS (EI, m/z): calcd for $C_{21}H_{17}N_3O_2$, 343.1321; found, 343.1532 (M^+).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00426.

Analytical data of intermediate X **S2**; copies of ^{1}H and ^{13}C NMR, HRMS, and IR spectra of compounds **4** and X **S3**−**S36**; and antibacterial assay of compounds **4 S37**−**S39** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated to Prof. Chung Ming Sun for his enormous contribution in combinatorial chemistry.

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