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Synthesis of Imidazo[1,2-*a*]pyridines: "Water-Mediated" Hydroamination and Silver-Catalyzed Aminooxygenation

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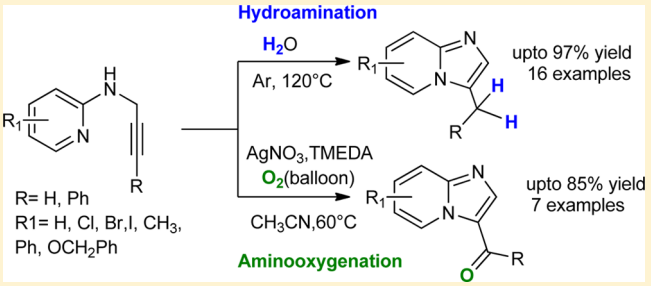
Supporting Information

ABSTRACT: Aqueous syntheses of methylimidazo[1,2-*a*]-pyridines without any deliberate addition of catalyst are reported. Imidazo[1,2-*a*]pyrazine and imidazo[2,1-*a*]-isoquinoline were also obtained in good yields under similar conditions. With acetonitrile as solvent, Ag-catalyzed intramolecular aminooxygenation produced imidazo[1,2-*a*]-pyridine-3-carbaldehydes in moderate to good yields.



Imidazo[1,2-*a*]pyridine (**IP**) scaffolds are found in many pharmacologically important compounds.[1−4] Such compounds exhibit antiviral, antibacterial, fungicidal, and anti-inflammatory properties.[5] Many commercially available drugs (Figure 1), including alpidem,[6] olprinone,[7] minodronic acid[8]

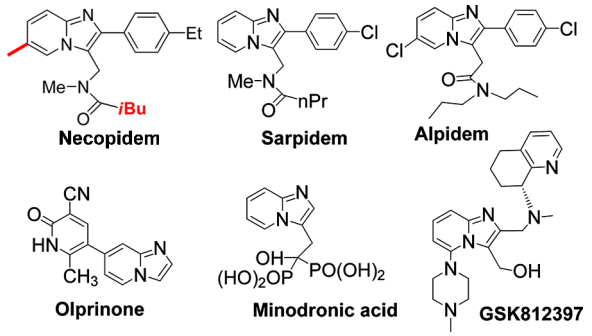
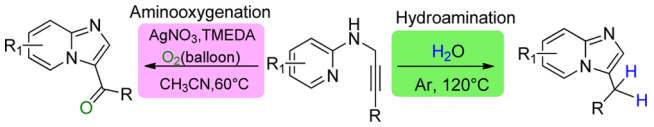


Figure 1. Imidazo[1,2-*a*]pyridine derived drugs.

(to treat anxiety, heart failure, and osteoporosis), necopidem, saripidem[9] (sedative and anxiolytic), and optically active GSK812397 candidate (HIV infection),[10] are derived from imidazo[1,2-*a*]pyridine core entities. In addition, **IP** derivatives have received considerable attention as sensor devices.[11] A variety of synthetic methods, including dehydrogenative aminooxygenation,[12] tetrabutylammonium iodide oxidative coupling,[13] copper-catalyzed aromatic amination,[14] three-component coupling,[15,16] Morita−Baylis−Hillman (MBH) reaction,[17] and silver-catalyzed oxidative cross-coupling reactions,[18] have been developed for the preparation of various **IP** derivatives. Recently, silver-catalyzed cyclization of *N*-(prop-2-yn-1-yl)pyridin-2-amine was also reported, the maximum yield achieved being 84% with 10% AgOTf.[19] It is desirable to develop benign and metal-free procedures with high yield and selectivity.

Recently, water has been employed as a solvent-cum-catalyst for the construction of heterocycles.[20,21] Aqueous reactions have attracted attention owing to the unique reactivity and selectivity observed that are difficult to achieve in conventional organic solvents.[22] Organic substrates are generally insoluble in water, but reactions have been reported to proceed "on water" to obtain desired products.[23,24] In continuation of our studies on the development of green and sustainable methods,[25−27] herein we wish to report "water-mediated" synthesis of methylimidazo[1,2-*a*]pyridines through intramolecular hydroamination under metal-free conditions. Silver-catalyzed intramolecular aminooxygenation for the syntheses of several imidazo[1,2-*a*]pyridine-3-carbaldehydes is also reported (Scheme 1). The substituted *N*-(prop-2-yn-1-yl)pyridin-2-amines **1**[28−30] starting materials were readily prepared by known methods.[31,32]

Scheme 1



Generally, hydroamination reactions were carried out using transition metal catalysts such as silver, gold, and copper.[33] In continuation of our interest on the synthesis of **IP** derivatives,[25] we performed a reaction of **1a** with $AgNO_3$ (10 mol %) as catalyst in acetonitrile, and **2a** was obtained in 86% isolated yield (Table 1, entry 1). The yields obtained were lower when

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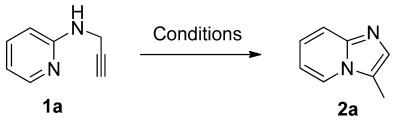
Table 1. Optimization of Reaction Conditions for 2a[a]



entry	catalyst (10 mol %)	solvent	temp (°C)	time (h)	yield (%)
1	$AgNO_3$	CH_3CN	60	4	86
2	$AgNO_3$	toluene	60	24	82
3	$AgNO_3$	DMF	60	6	38
4	$AgNO_3$	THF	60	9	65
5	$AgNO_3$	H_2O	60	9	50[b]
6	AgOTf	CH_3CN	60	4	88
7	AgOTf	H_2O	60	4	40[b]
8	–	H_2O	60	20	70
9	–	H_2O	80	6	73
10	–	H_2O	100	2	88
11	–	**H_2O**	**120**	**1**	**97**
12	–	H_2O	rt	24	trace
13	–	EtOH	100	5	87
14	–	CH_3CN	100	2	trace
15	–	DMF	100	2	trace
16	–	DMSO	100	2	trace
17	–	toluene	100	2	trace

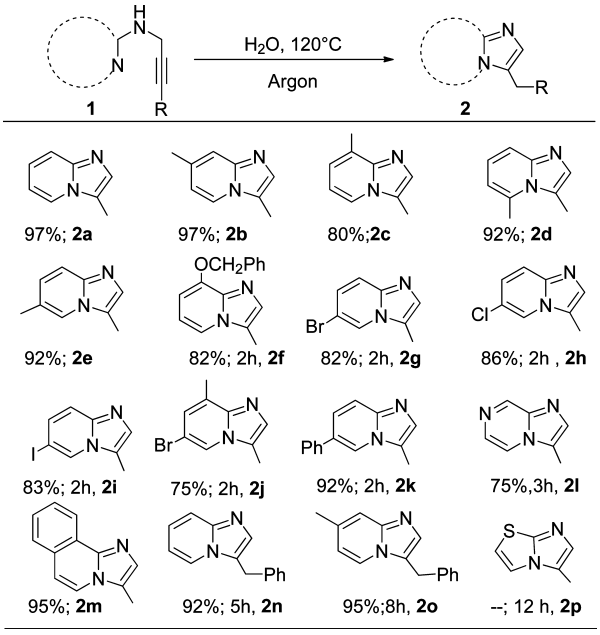
[a]Reaction conditions: **1a** (100 mg, 0.75 mmol), catalyst (0.075 mmol), solvent (4 mL), oil bath temperature under argon atmosphere in a sealed tube; entries 1–7, Ph_3P (10 mol %) used as ligand. [b]Additionally, 10% yield of imidazo[1,2-*a*]pyridine-3-carbaldehyde **3a** was observed.

the reaction was carried out in other solvents, such as toluene, DMF, THF, and H_2O, and when $AgNO_3$ was replaced with AgOTf (Table 1, entries 2–7). Surprisingly, even when the catalyst was omitted in the reaction in water at 60 °C, **2a** could be obtained in good yield (70%) (Table 1, entry 8). In this reaction, water presumably plays a dual role as a solvent and catalyst.[34] Upon varying the temperature of the reaction from 25 to 120 °C (Table 1, entries 9–12), the best yield of **2a** was obtained at 120 °C. The reaction also proceeded smoothly in ethanol (Table 1, entry 13), but in other polar and nonpolar solvents studied, there was no reaction without catalyst (Table 1, entries 14–17). To the best of our knowledge, this is the first report of efficient syntheses of **2** via intramolecular hydroamination which dispenses with metal catalyst and organic solvent.

The studies were extended to a range of substituted *N*-(prop-2-yn-1-yl)pyridin-2-amines **1**. In all cases, the reactions were conducted in water under argon atmosphere at 120 °C (Table 2). The transformation was equally efficient for *N*-(prop-2-yn-1-yl)pyridin-2-amines substituted with electron-donating (−Me, $-OCH_2Ph$) and electron-withdrawing (I, Br, Cl, and Ph) groups and generated the corresponding methylimidazo-[1,2-*a*]pyridines **2b–f** and **2g–k**, respectively, in excellent yields. The reactions were also conducted with *N*-(prop-2-yn-1-yl)pyrazin-2-amine and *N*-(prop-2-yn-1-yl)isoquinolin-1-amine. These gave **2l** and **2m** in 75 and 95% yields, respectively (Table 2). Substrates bearing phenyl substitution at the terminal alkyne position also gave excellent yields of the desired product (**2n**, **2o**). However, the present method was not suitable for thiazole substrates (**2p**), which were found to decompose under the present conditions.

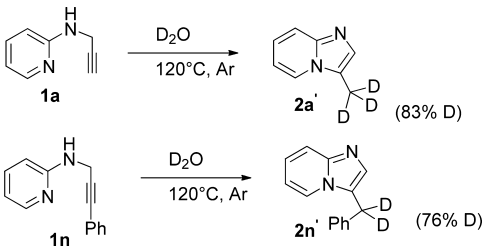
To gain insight into the reaction mechanism, we performed controlled experiments with deuterated water (Scheme 2). It

Table 2. Scope for Syntheses of 2[a]



[a]Reaction conditions: **1a** (100 mg, 0.75 mmol), H_2O (4 mL), 120 °C, oil bath under argon atmosphere in a sealed tube for 1 h (unless otherwise stated).

Scheme 2. Labeling Studies with D_2O



can be seen that, with substrate **1a**, product **2a′** was formed with mainly $-CD_3$ substituent, whereas **1n** gave product **2n′** containing $-CD_2Ph$. The observations may be rationalized through the reaction mechanism proposed in Scheme 3.

In the first step, **1a** bearing acidic protons undergoes fast deuterium exchange to yield the intermediate **I**. Subsequently, **I** undergoes intramolecular hydroamination through 5-*exo-dig* cyclization[20] to produce the vinyl intermediate **II**, incorporating a second deuterium in the process. Generally, **II** being unstable, it undergoes the rearrangement shown in step 3 during which process $-CD_3$ is formed. It would be evident that, for acetylene substituted at the terminal position, only two deuteriums can be incorporated as observed (Scheme 2).

In the course of optimization studies (Table 1, entries 5 and 7), the generation of imidazo[1,2-*a*]pyridine-3-carbaldehyde **3a** was observed via intramolecular aminooxygenation.[32,35] In view of the importance of this derivative,[12,36,37] we decided to investigate the reaction further. Screening of silver salts, ligands, and other parameters, such as solvent, temperature, atmosphere, etc., were undertaken, and the data are summarized in Table S1 (see Supporting Information). The best result was obtained using 2 mol % of $AgNO_3$ together with 10 mol % of TMEDA under oxygen atmosphere (balloon) in acetonitrile at 60 °C (Table S1, entry 18). Scheme 4 shows the reaction under optimized conditions. Note that **3a** was not produced from the

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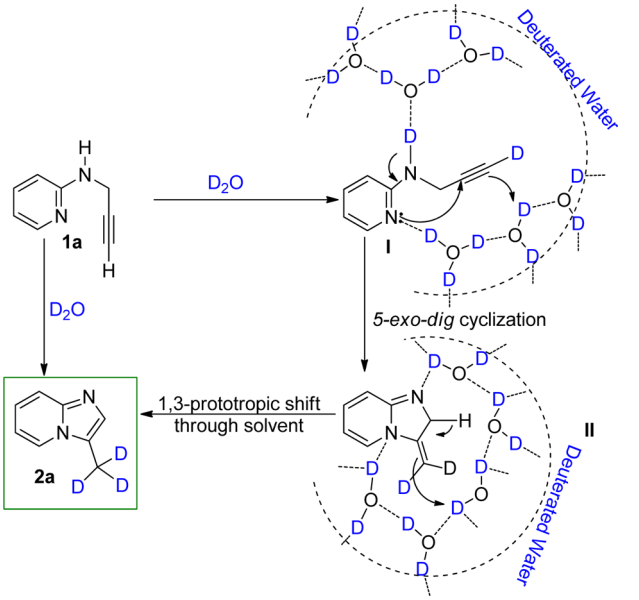
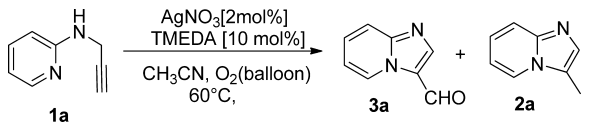
Scheme 3. Possible Mechanism for Water-Mediated Intramolecular Hydroamination



Scheme 4



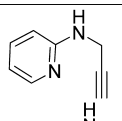
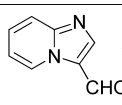
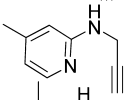
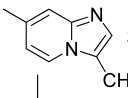
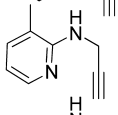
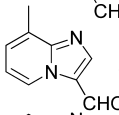
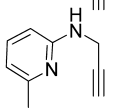
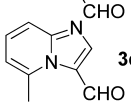
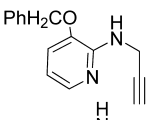
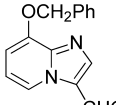
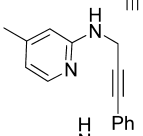
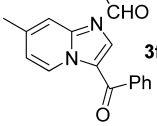
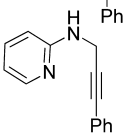
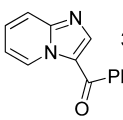
oxidation of **2a** since subjecting the latter to the same reaction conditions failed to yield the desired product.

The optimized conditions were then used to study the reactions with other substrates (Table 3). Imidazo[1,2-*a*]pyridine-3-carbaldehydes **3b**–**g** were obtained in good to moderate yields. The formation of 8-(benzyloxy)imidazo[1,2-*a*]pyridine-3-carbaldehyde **3e** was further confirmed by single-crystal XRD (Figure S1 in the Supporting Information).

To assess the plausible reaction mechanism for silver-catalyzed aminooxygenation, we performed the experiments under different atmospheres (Table S1, entries 6, 18, and 24). It can be seen that the reaction progressed best (96% yield) in O_2 atmosphere, while the yield was lower in air (78%) and negligible (11%) under argon atmosphere. Thus, based on all of the above evidence, the mechanism shown in Scheme 5 is proposed. Initially, the reaction of **1a** with metal catalyst generates metal alkyne π-complex **A**, and its cyclization leads to intermediate **B**.[20] Successively, the addition of oxygen generates organosilver peroxide intermediate **C**.[38] Aromatization of **C**→**D** and subsequent isomerization to intermediate **E**[36] and finally elimination of silver(I) species produce the desired product **3a**. From the intermediate **B**, elimination of silver species and concomitant 1,3-prototropic shift lead to the side product **2a**, which does not undergo oxidation to **3a**.

In conclusion, with water as the medium, *N*-(prop-2-yn-1-yl)pyridin-2-amines underwent clean transformation to the corresponding methylimidazo[1,2-*a*]pyridines without the deliberate addition of any catalyst or reagent. The desired products were obtained in 75–97% isolated yield. Studies with D_2O helped shed light on the likely mechanism of the reaction. The same substrates in acetonitrile medium gave imidazo[1,2-*a*]pyridine-3-carbaldehydes when the reactions were carried out

Table 3. Scope for Domino Synthesis of Imidazo[1,2-*a*]pyridine-3-carbaldehydes 3[a]

Entry	Substrate	Time(h)	Product	Yield(%)[b]
1.		4	 **3a**	85(trace)
2.		4	 **3b**	80(trace)
3[c]		2	 **3c**	67(26)
4[c]		2	 **3d**	55(37)
5		2	 **3e**	46(25)
6[d]		4	 **3f**	40(35)
7[d]		4	 **3g**	36(42)

[a]Reaction conditions: **1a** (100 mg, 0.75 mmol), $AgNO_3$ (2.0 mol %), TMEDA (10 mol %), CH_3CN (2 mL), 60 °C in an oil bath under O_2 (balloon) for 4 h, unless otherwise stated. [b]Yields in parentheses represent derivatives of **2**. [c]0.5 mol % of $AgNO_3$ used. [d]10 mol % of $AgNO_3$ used.

with 2 mol % of $AgNO_3$ and 10 mol % of TMEDA under oxygen atmosphere and at 60 °C. The carbaldehydes were, however, not obtained from the methylimidazo[1,2-*a*]pyridines and instead underwent oxidation via a separate route.

EXPERIMENTAL SECTION

General: All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded at 500/200 and 125/50 MHz, respectively. The spectra were recorded in $CDCl_3$ and CD_3OD as solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc., and coupling constants (*J*) were given in hertz. Chemical shifts are reported in parts per million relative to TMS as an internal standard. The peaks around δ values of ^1H NMR (3.2, 4.84, and 7.2) and ^{13}C NMR (49.05 and 77.0) correspond to deuterated solvents methanol and chloroform, respectively. Mass spectra were obtained using the electron impact (EI) ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified through column chromatography using silica gel 100–200 mesh size using hexane/ethyl acetate as eluent unless otherwise indicated.

General Procedure for the Synthesis of 2a:[31] In a 10 mL round bottomed flask, 100 mg (0.757 mmol) of **1a** and 4 mL of water were placed, and the flask was purged with argon gas and tightly sealed. The reaction flask was heated at 120 °C in an oil bath for 1 h. After completion of the reaction, the flask was allowed to attain room temperature; the mixture was poured into 20 mL of saturated $NaHCO_3$ solution, and the product was extracted with dichloromethane (DCM) or EtOAc (20 mL × 3). After removal of the solvent under reduced pressure, the residue left out was subjected to column chromatography on silica gel (5% CH_3OH/EtOAc). Product **2a** was obtained in 97% yield (97 mg, 0.735 mmol): ^1H NMR (500 MHz,

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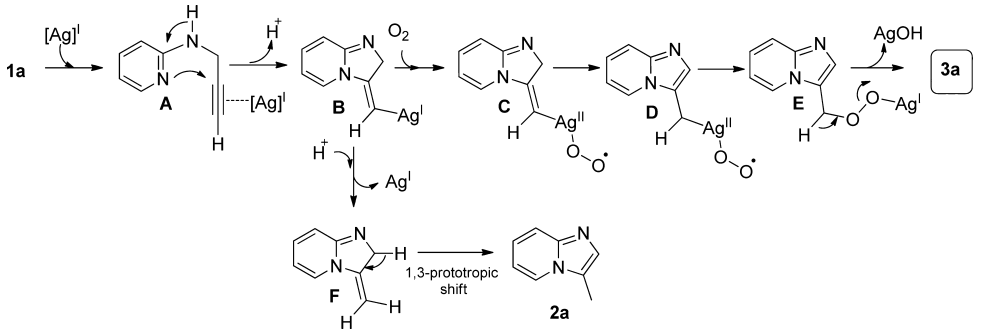
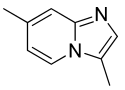
Scheme 5. Plausible Mechanism of Silver-Catalyzed Aminooxygenation of 1a



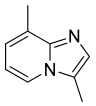
$CDCl_3$) (ppm) 2.44 (s, 3H), 6.80 (t, J = 7 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.59 (d, J = 9 Hz, 1H), 7.85 (d, J = 7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) 8.8, 111.7, 117.4, 119.6, 122.6, 122.9, 131.0, 144.9; IR (KBr) 2927, 2825, 1638,1502, 1444, 1363, 1311, 1255, 1135, 1017, 899, 843, 750, 627; MS m/z 133 [M + H]$^+$,118, 102, 95, 74.

3,7-Dimethylimidazo[1,2-*a*]pyridine (2b):[31]



(eluent, 5% CH_3OH in EtOAc); 97% yield (97 mg); ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.11 (s, 3H), 2.15 (s, 3H), 6.47 (d, J = 6.8 Hz, 1H), 6.97 (s, 2H), 7.67 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) (ppm) 8.7, 21.2, 115.6, 115. 9, 121.2, 123.9, 130.4, 136.6, 146.5; IR (KBr) 3042, 2959, 2924, 1634, 1493, 1443, 1359, 1310, 1261, 1094, 1031, 802, 746; MS m/z 147 [M + H]$^+$, 139, 129, 101, 73, 55.

3,8-Dimethylimidazo[1,2-*a*]pyridine (2c):[31]

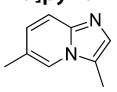


(eluent, EtOAc); 80% yield (80 mg); ^{1}H NMR (500 MHz, CD_3OD) (ppm) 2.30 (s, 3H), 2.37 (s, 3H), 6.67 (t, J = 7.0 Hz, 1H), 6.88 (d, J = 6.5 Hz,1H), 7.15 (s, 1H), 7.80 (d, J = 7.0 Hz 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.9, 16.9, 113.6, 122.2, 122.6, 124.3, 127.5, 130.3, 146.4; IR (KBr) 2924, 2856, 1634, 1551, 1493,1444, 1359, 1309, 1261, 1142, 1074, 1031, 876, 849, 800, 746; MS m/z 147 [M + H]$^+$, 132, 92, 73, 55.

3,5-Dimethylimidazo[1,2-*a*]pyridine (2d):[31]

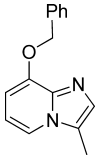
(eluent, 5% CH_3OH in EtOAc); 92% yield (92 mg); ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.62 (s, 3H), 2.70 (s, 3H), 6.40 (d, J = 6.6 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 7.07 (s, 1H), 7,18 (d, J = 9.0 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) (ppm) 13.4, 20.2, 114.2, 115.8, 123.7, 126.0, 132.8, 138.4, 148.4; IR (KBr) 3092, 2973, 2924, 2858, 1638, 1531, 1452, 1392, 1287, 1154, 1087,1044, 852, 787, 711, 643, 612, 504; MS m/z 147 [M + H]$^+$, 132, 109, 92, 73, 55.

3,6-Dimethylimidazo[1,2-*a*]pyridine (2e):[31]



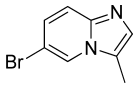
(eluent, 5% CH_3OH in EtOAc); 92% yield (92 mg); ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.11 (s, 3H), 2.20 (s, 3H), 6.88 (t, J = 9.0 Hz, 1H), 7.04 (s, 1H), 7.19 (d, J = 9.0 Hz, 1H), 7,63 (s, 1H); ^{13}C NMR (50 MHz, CD_3OD) (ppm) 8.8, 18.2, 116.5, 121.5, 122.4, 123.5, 128.4, 130.6, 145.0; IR (KBr) 2925, 2858, 2750, 1645, 1502, 1446, 1361, 1335, 1306, 1253, 1125, 1036, 851, 784., 639, 608; MS m/z 147 [M + H] $^+$, 109, 92, 73, 55.

8-(Benzyloxy)-3-methylimidazo[1,2-*a*]pyridine (2f):



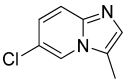
(eluent, 1:1 EtOAc/hexane); solid, 82% yield (82 mg); mp 90−95 °C; ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.36 (s, 3H), 5.18 (s, 2H), 6.64 (d, J = 7.6 Hz, 1H), 6.73 (t, J = 7.2 Hz,1H), 7.17−7.33 (m, 4H), 7.45 (d, J = 7.4 Hz, 2H), 7.67 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) 9.1, 70.5, 101.6, 111.8, 116.0, 120.8, 127.3, 127.9, 128.5, 130.3, 136.2, 139.6, 148.0; IR (KBr) 3081, 2923, 2868, 1634, 1537, 1494, 1444, 1376, 1311, 1263, 1150, 1029, 988, 926, 843, 759, 728, 698, 628; HRMS calcd for $C_{15}H_{15}N_2O$: 239.1185, found: 239.1178; MS m/z 239 [M + H] $^+$, 217, 183, 161, 147, 129, 91.

6-Bromo-3-methylimidazo[1,2-*a*]pyridine (2g):



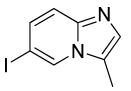
(eluent, 1:1 EtOAc/hexane); white solid; 82% yield (82 mg); mp 113.5 °C; ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.43 (s, 3H), 7.28−7.33 (m, 2H), 7.39−7.43 (m, 1H), 8.38 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.8, 108.1, 118.2, 122.9, 125.4, 128.7, 131.9, 144.6; IR (KBr) 3050, 2918, 2855, 1503, 1407, 1331, 1301, 1143, 1096, 1042, 853, 780, 728, 630; HRMS calcd for $C_8H_8BrN_2$ 210.9872, found 210.9866; MS m/z 211 [M + H] $^+$, 202, 198, 156, 147, 132, 120, 91, 79, 65.

Chloro-3-methylimidazo[1,2-*a*]pyridine (2h):[31]



(eluent, 1:1 EtOAc/hexane); 86% yield (86 mg); ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.43 (s, 3H), 7.19 (d, J = 9.6 Hz, 1H), 7.25 (s, 1H), 7.48 (d, J = 9.5 Hz, 1H) 8.30 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.8, 117.9, 121.8, 123.1, 123.2, 126.6, 132.1, 144.5; IR (KBr) 3052, 2920, 2854, 2362, 1701, 1648, 1545, 1506, 1411, 1304, 1333, 1254, 1146, 1107, 1045, 855, 781, 735, 634; MS m/z 169 [M + H]$^+$,147, 133, 109, 91, 73.

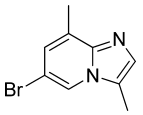
6-Iodo-3-methylimidazo[1,2-*a*]pyridine (2i):[31]



(eluent, 1:1 EtOAc/hexane); 83% yield (83 mg); ^{1}H NMR (500 MHz, CD_3OD) (ppm) 2.37 (s, 3H), 7.20−7.22 (m, 2H), 7.31−33 (m, 1H), 8.32 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.8, 76.2, 118.3, 122.3, 130.2, 131.4, 133,3, 144.6; IR (KBr) 3075, 2924, 2855, 1503, 1419, 1301, 1127, 846, 790, 728, 630; MS m/z 259 [M + H]$^+$, 239, 223, 209, 147, 132,102, 83.

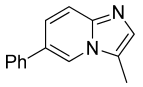
dx.doi.org/10.1021/jo3025303 | J. Org. Chem. XXXX, XXX, XXX−XXX

6-Bromo-3,8-dimethylimidazo[1,2-*a*]pyridine (2j):



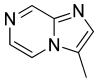
(eluent, 1:1 EtOAc/hexane); white solid; 75% yield (75 mg); mp 67.4 °C; ^{1}H NMR (500 MHz, CD_3OD) (ppm) 2.32 (s, 3H), 2.36 (s, 3H), 6.98 (s, 1H), 7.18 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.9, 16.8, 108.1, 123.0, 127.4, 128.8, 131.2, 144.8; IR (KBr) 3069, 2954, 2921, 1547, 1491, 1355, 1306, 1145, 1036, 842, 776, 746; HRMS calcd for $C_9H_{10}BrN_2$ 225.0028, found 225.0022; MS *m*/*z* 225 [M + H]$^+$, 147, 133, 109, 91,73, 55.

3-Methyl-6-phenylimidazo[1,2-*a*]pyridine (2k):[31]



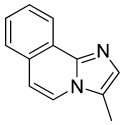
(eluent, 1:1 EtOAc/hexane); white solid; 92% yield (92 mg); ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.46 (s, 3H), 7.29−7.50 (m, 4H), 7.51 (s, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 8.25 (s, 1H); ^{13}C NMR (50 MHz, CD_3OD) (ppm) 8.8, 117.1, 121.9, 122.6, 126.0, 127.9, 128.1, 128.9, 130.1, 131.2, 138.4, 145.3; IR(KBr) 3055, 2925, 2855, 1484, 1454, 1430, 1379, 1313, 1131, 835, 763, 698; MS *m*/*z* 209 [M + H] $^+$, 172, 152, 102, 73, 55.

3-Methylimidazo[1,2-*a*]pyrazine (2l):



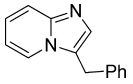
(eluent, 10% CH_3OH in EtOAc); brown solid; 76% yield (76 mg); mp 175−180 °C; ^{1}H NMR (500 MHz, CD_3OD) (ppm) 2.42 (s, 3H), 7.47 (s, 1H), 7.75 (d, *J* = 4.5 Hz, 1H), 8.13 (d, *J* = 3.5 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.4, 118.8, 124.6, 129.7, 134.4, 141.5, 143.2; IR (KBr) 3051, 3028, 2966, 1528, 1493, 1438, 1345, 1300, 1146, 1025, 891, 805, 703, 640; HRMS calcd for $C_7H_8N_3$ 134.0719, found 134.0713; MS *m*/*z* 134 [M + H] $^+$, 112, 91, 73, 55.

Methylimidazo[2,1-*a*]isoquinoline (2m):



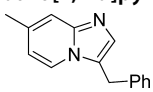
(eluent, 1:1 EtOAc/hexane); white solid; 95% yield (95 mg); mp 48 °C; ^{1}H NMR (500 MHz, CD_3OD) (ppm) 2.17 (s, 3H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.97 (s, 1H), 7.29−7.50 (m, 4H), 8.19 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 8.7, 113.9, 121.8, 123.3, 123.7, 124.1, 128.1, 128.6, 129.0, 129.1, 130.4, 143.3; IR (KBr) 3182, 2923, 2857, 1512, 1443, 1371, 1332, 1248, 844, 790, 743, 695; HRMS calcd for $C_{12}H_{11}N_2$ 183.0923, found 183.1020; MS *m*/*z* 183 [M + H]$^+$, 1175, 161, 147, 102, 91, 68. Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.09; N, 15.37; H, 5.53. Found: C, 78.82; N, 15.31; H, 5.55.

3-Benzylimidazo[1,2-*a*]pyridine (2n):[15]



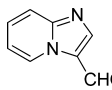
(eluent, 1:1 EtOAc/hexane); 92% yield (92 mg); ^{1}H NMR (500 MHz, CD_3OD) (ppm) 4.22 (s, 2H), 6.78 (s, 1H), 7.18−7.50 (m, 6H), 7.31 (s, 1H), 7.48 (d, *J* = 9.5 Hz, 1H), 7.97 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) (ppm) 30.6, 113.6, 117.6, 125.2, 126.0, 127.9, 129.5, 129.8, 132.0, 138.2, 146.7; IR (KBr) 3104, 3073, 3023, 2917, 2857, 1784, 1726, 1631, 1517, 1496, 1352, 1450, 1306, 1249, 1131, 1069, 1028, 865, 721, 604; MS *m*/*z* 209 [M + H]$^+$, 194,152, 128, 111, 91, 73, 55.

3-Benzyl-7-methylimidazo[1,2-*a*]pyridine (2o):



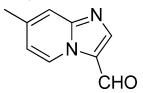
(eluent, 1:1 EtOAc/hexane); white solid; 95% yield (95 mg); mp 119.2 °C; ^{1}H NMR (200 MHz, CD_3OD) (ppm) 2.31 (s, 3H), 4.20 (s, 2H), 6.66 (d, *J* = 7.0 Hz, 1H), 7.13−7.22 (m, 7H), 7.86 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) 21.1, 30.2, 114.5, 116.1, 121.8, 122.4, 126.8, 128.2, 128.7, 131.9, 134.5, 136.7, 146.1; IR (KBr) 3053, 3025, 2919, 2854, 1643, 1495, 1437, 1311, 1119, 1030, 866, 770, 705; HRMS calcd for $C_{15}H_{15}N_2$ 223.1236, found 223.1230; MS *m*/*z* 147 [M + H]$^+$, 209, 147, 139, 109, 91, 73, 55.

General Procedure for Synthesis of Imidazo[1,2-*a*]pyridine-3-carbaldehyde 3a:[12]



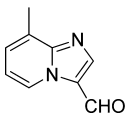
100 mg (0.757 mmol) of **1a**, $AgNO_3$ (2.5 mg, 0.015 mmol), TMEDA (8.7 mg, 0.075 mmol), and CH_3CN (2 mL) was placed in a 50 mL round bottomed flask. The mixture was heated in an oil bath at 60 °C for 4 h under oxygen atmosphere (balloon). After completion of the reaction, the flask was allowed to attain room temperature; the mixture was poured into 20 mL of saturated NaCl solution, and the product was extracted with DCM (20 mL × 3). After removal of the solvent under reduced pressure, the residue left out was subjected to column chromatography on silica gel (1:1 EtOAc/hexane). The product **3a** was obtained in 85% yield (94 mg, 0.643 mmol).^{1}H NMR (500 MHz, $CDCl_3$) (ppm) 7.15 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 8.33 (s, 1H), 9.51 (d, *J* = 7.0 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) 115.4, 117.7, 128.6, 130.1, 146.7, 149.2, 177.8; IR (KBr) 2926, 2856, 1658, 1522, 1490, 1439, 1389, 1314, 1255, 1173, 1089, 1024, 803, 768; MS *m*/*z* 147 [M + H]$^+$, 117, 93, 78, 63, 51, 39.

7-Methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3b):



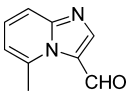
white solid; 80% yield (88 mg); mp 63.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) 2.50 (s, 3H), 6.97 (d, *J* = 6.5 Hz, 1H), 7.56 (s, 1H), 8.26 (s, 1H), 9.34 (d, *J* = 7.0 Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) 21.6, 116.4, 117.8, 124.7, 127.7, 141.9, 147.0, 149.7, 177.4; IR (KBr) 3099, 2967, 2924, 2828, 1656, 1525, 1485, 1463, 1316, 1256, 1193,1166, 1033, 854, 795, 728, 628; HRMS calcd for $C_9H_9N_2O$ 161.0716, found 161.0708; MS *m*/*z* 161 [M + H]$^+$, 142, 133, 129, 109, 102, 92, 73, 59, 55.

8-Methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3c):[12]



67% yield (73.5 mg); ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) 2.67 (s, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 9.36 (d, *J* = 6.8 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) 16.8, 115.4, 125.3, 126.3, 127.7, 129.1, 146.1, 149.4, 177.8; IR (KBr) 3105, 3029, 2962, 2837, 1653, 1516, 1486, 1430, 1314, 1252, 1159, 1081, 880, 785, 763, 638, 603; MS *m*/*z* 161 [M + H]$^+$, 142, 133, 118, 109, 100,92, 79, 65.

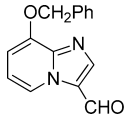
5-Methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3d):[12]



55% yield (60 mg); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) 2.92 (s, 3 H), 6.86 (d, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H), 9.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) 23.0, 115.7, 116.2, 128.1, 130.0, 140.0, 149.6, 151.9, 175.9; IR (KBr) 3925, 2925, 2885, 1631, 1542, 1490, 1423, 1378, 1304, 1279, 1159, 1083, 1031, 892, 854, 784, 633; MS *m*/*z* 161 [M + H]$^+$, 143, 133, 109, 92, 74, 55.

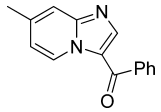
dx.doi.org/10.1021/jo3025303 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

8-(Benzyloxy)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3e):



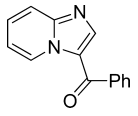
white solid; 46% yield (49 mg); mp 168.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) 5.36 (s, 2 H), 6.85−6.95 (m, 2H), 7.28−7.50 (m, 5H), 8.27 (s, 1H), 9.09 (d, J = 7.0 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) 71.5, 108.9, 115.4, 121.3, 125.8, 128.3, 128.7, 135.5, 143.4, 145.6, 147.7, 178.0; IR (KBr) 3144, 3077, 2934, 2851, 1640, 1545, 1483, 1409, 1264, 1157, 1030, 956, 789, 755, 697; MS m/z 252 $[M + H]^+$, 242, 160, 152, 91, 73; HRMS calcd for $C_{15}H_{13}N_2O_2$ 253.0978, found 253.0973.

7-Methylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (3f):



white solid; 40% yield (42 mg); mp 138.4 °C; ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) 2.51 (s, 3 H), 7.0 (d, J = 7.0 Hz, 1H), 7.52−7.60 (m, 4H), 7.88 (m, 2H), 8.15 (s, 1 H), 9.62 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) 21.5, 116.3, 117.5, 123.2, 128.0, 128.5, 128,7, 131.8, 139.3, 141.1, 145,9, 149.5, 184.5; IR (KBr) 2920, 2853, 1604, 1526, 1469, 1360, 1303, 1281, 1191, 886, 796, 711, 671, 638, 420; HRMS calcd for $C_{15}H_{13}N_2O$ 237.1029, found 237.1022; MS m/z 237 $[M + H]^+$, 208, 154, 147, 132, 91, 73.

Imidazo[1,2-*a*]pyridin-3-yl(phenyl)methanone (3g):



white solid; 36% yield (38 mg); mp 101.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) (ppm) 7.13 (t, J = 7.0 Hz, 1H), 7.48−7.59 (m, 4H), 7.71−7.87 (m, 3H), 8.19 (s, 1H), 9.74 (d, J = 6.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm) 115.0, 117.4, 123.4, 128.3, 128.7, 129.3, 131.9, 139.2, 145.6, 149.0, 184.7; IR (KBr) 3031, 2922, 1617, 1508, 1475, 1363, 1336, 1222, 1181, 885, 787, 692, 430; HRMS calcd for $C_{14}H_{11}N_2O$ 223.0872, found 223.0866; MS m/z 223 $[M + H]^+$, 208, 194, 107, 91, 73, 63.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds and HRMS spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for compound **3e** (CCDC-904111) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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