Synthesis Z.-H. Ren et al. Special Topic

Copper-Catalyzed Aerobic Oxidative Cyclization of Ketoxime Acetates with Pyridines for the Synthesis of Imidazo[1,2-*a*]pyridines

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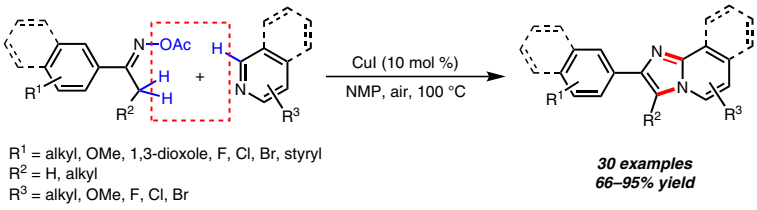

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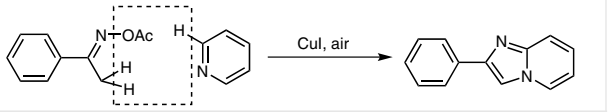
Abstract A copper(I)-catalyzed aerobic oxidative coupling of ketoxime acetates with simple pyridines for the synthesis of imidazo[1,2-*a*]pyridines has been developed. This reaction tolerates a wide range of functional groups and it affords a series of valuable imidazo[1,2-*a*]pyridines in high yields under mild conditions.

Key words copper, catalysis, pyridines, ketoxime esters, coupling, imidazopyridines

Ketoximes and their derivatives are a class of valuable chemicals[1] that are readily accessible through condensation of ketones with hydroxylammonium salts in nearly quantitative yields under mild conditions. However, in conventional synthetic chemistry, chemical transformations of ketoximes are mainly limited to Beckmann rearrangements to give amides.[2] In modern organic chemistry, transition-metal-catalyzed cross-coupling has achieved great successes, as recognized by the award of the Nobel Prize in Chemistry in 2010.[3] In this context, coupling reactions initiated by Pd(0)-catalyzed oxidative addition of ketoxime carboxylates have been developed by the groups of Abell,[4] Zhu,[5] Hartwig,[6] and Bower.[7] Cu(I)-catalyzed reductive cleavages of ketoxime carboxylates for the synthesis of various valuable compounds, such as enamides or azaheterocycles, have also been developed by us and by other groups.[8,9]

An active iminium radical and an α-carbon radical are often generated in the Cu(I)-catalyzed reductive cleavage of ketoxime carboxylates.[8,9] We therefore hypothesized that a radical-scavenger reagent might trap the iminium radical or α-carbon radical to afford valuable organic compounds. Here, we report a simple and efficient copper-catalyzed aerobic oxidative coupling of ketoxime acetates with pyridines to give imidazo[1,2-*a*]pyridines (Scheme 1).



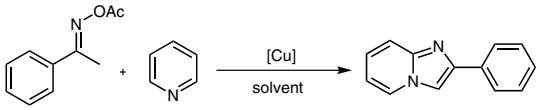
Scheme 1 Copper-catalyzed aerobic oxidative coupling of acetophenone oxime acetate with pyridine

Imidazo[1,2-*a*]pyridines are among the most important fused heterocycles, and they are present in many pharmaceuticals and biologically active compounds, such as zolpidem, alpidem, and zolimidine.[10] Conventional methods for the synthesis of imidazo[1,2-*a*]pyridines are generally based on condensations of 2-aminopyridines with α-halo ketones.[11] These methods usually have limited substrate scopes and they lack atom economy. Recently, copper-catalyzed dehydrogenative cyclizations of 2-aminopyridines with simple ketones or of pyridine with ketoxime acetates have been developed for the synthesis of imidazo[1,2-*a*]pyridines.[12] However, these methods generally give low yields, especially with substituted pyridines or propiophenone oxime acetate as substrates. Consequently, simple and practical methods for the synthesis of imidazo[1,2-*a*]pyridines remain highly desirable.

We commenced our investigation with the CuI-catalyzed coupling of acetophenone oxime acetate [**1a**; *N*-(1-phenylethylidene)acetamide] with pyridine (**2a**) in MeCN at 120 °C. 2-Phenylimidazo[1,2-*a*]pyridine (**3aa**) was obtained in 21% yield (Table 1, entry 1). Screening of various copper catalysts [CuI, CuBr, CuCl, $Cu(OAc)_2$, $CuBr_2$, and $CuCl_2$] showed that CuI is the most effective catalyst and that Cu(II) salts are inactive as catalysts (entries 2–6). Subsequently, we screened a series of solvents in an attempt to improve the reaction efficiency, and we found that DMF, *N*,*N*-dimethylacetamide (DMA), and NMP are better solvents than DCE, toluene, or DMSO for this reaction (entries 7–13). The highest yield was obtained in NMP (entry 13).

When the reaction temperature was changed to 100 °C, the yield of **3aa** increased to 95% (entry 14), whereas a 62% yield was obtained at 80 °C (entry 15).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

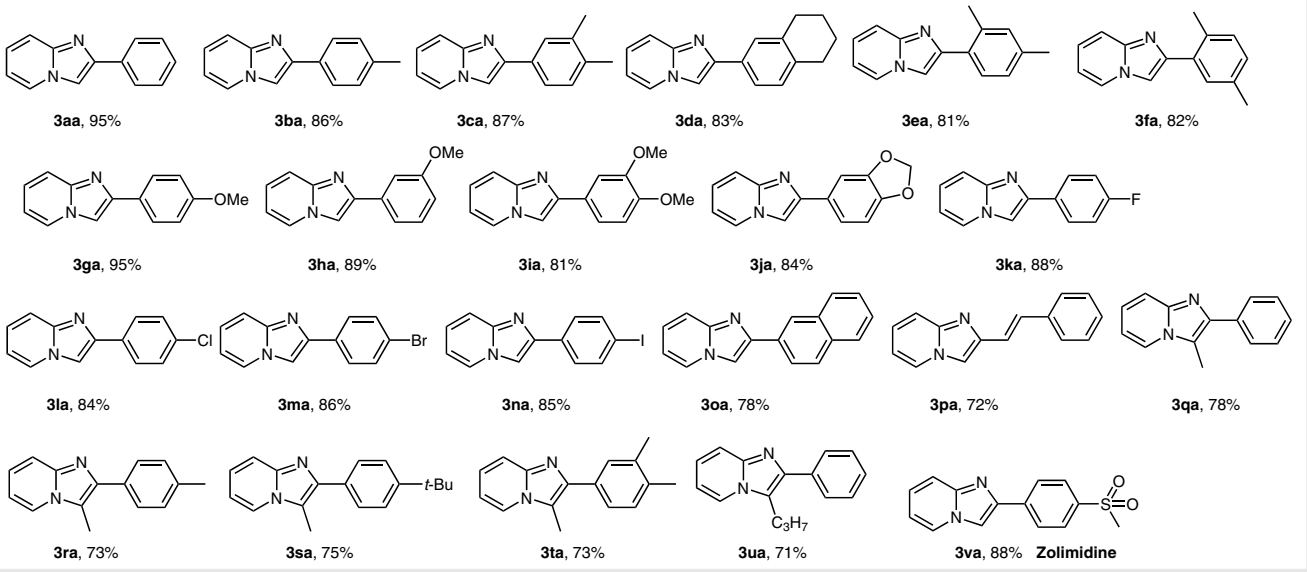
Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	CuI	MeCN	120	21
2	CuBr	MeCN	120	18
3	CuCl	MeCN	120	13
4	$Cu(OAc)_2$	MeCN	120	–
5	$CuBr_2$	MeCN	120	–
6	$CuCl_2$	MeCN	120	–
7	CuI	DCE	120	15
8	CuI	toluene	120	22
9	CuI	1,4-dioxane	120	5
10	CuI	DMF	120	67
11	CuI	DMSO	120	17
12	CuI	DMA	120	48
13	CuI	NMP	120	71
14	**CuI**	**NMP**	**100**	**95**
15	CuI	NMP	80	62

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (10 mol%), solvent (1 mL), air
[b] Isolated yield.

Having established the optimal conditions for the reaction, we next examined its scope (Scheme 2). The copper-catalyzed aerobic oxidative coupling reaction displayed a broad functional-group tolerance and proved to be a quite general method. Aryl methyl ketoxime acetates substituted on the aromatic ring with methyl, alkyl, methoxy, 1,3-dioxole, fluoro, or chloro groups, or with sensitive functional groups, such as bromo or iodo, all gave the corresponding substituted imidazo[1,2-*a*]pyridines **3aa**–**na** in 81–95% yield. Both electron-rich and electron-deficient ketoxime acetates reacted smoothly to give the desired products in high to excellent yields, implying that electronic effects of the substrates have little effect on the oxidative coupling reaction. In addition, 1-(2-naphthyl)ethanone oxime acetate (**1o**) and benzalacetone oxime acetate (**1p**) showed similar reactivities to aryl methyl ketoxime acetates, giving the corresponding 2-naphthyl- or 2-phenylethenyl-substituted imidazo[1,2-*a*]pyridines **3oa** and **3pa** in 78% and 72% yield, respectively.

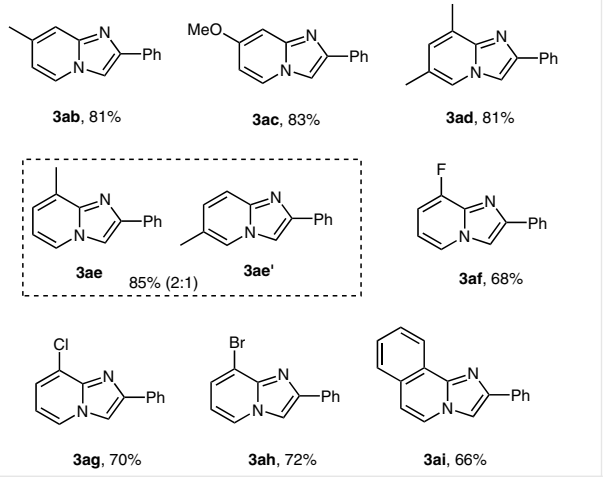
3-Substituted imidazo[1,2-*a*]pyridines, which are obtained in low yields by other methods,[12] were easily synthesized in high yields by our reaction. Aryl alkyl ketoxime acetates, such as the aryl ethyl and aryl butyl ketoxime acetates **1q**–**u**, were well tolerated in the reaction system, and gave the corresponding 3-methyl- or 3-propyl-substituted imidazo[1,2-*a*]pyridines **3qa**–**ua** in 71–78% yield. Additionally, the antiulcer drug zolimidine (**3va**) was synthesized in 81% yield on a 10 mmol scale under the standard conditions, demonstrating the synthetic utility of our method.

Next, we synthesized the substituted pyridines **2b**–**h**, which have been reported to give only low yields of the corresponding products,[12] and we used them to explore the scope of the reaction (Scheme 3). 4-Methyl-, 4-methoxy-,



Scheme 2 Synthesis of imidazo[1,2-*a*]pyridines by coupling of ketoxime acetates **1** with pyridine (**2a**). *Reaction conditions:* **1** (0.5 mmol), **2a** (0.6 mmol, 1.2 equiv), CuI (10 mol%), NMP (1.5 mL), 100 °C, air. The isolated yields are reported.

and 3,5-dimethylpyridine gave the corresponding imidazo[1,2-*a*]pyridines **3ab**–**ad** in 81–83% yield. When 3-methylpyridine was used as the substrate, two regioisomers **3ae** and **3ae'** were isolated in a 2:1 ratio and a total yield of 85%. Surprisingly, the reaction mainly occurred at the more sterically hindered 2-position of 3-methylpyridine to give 8-methyl-2-phenylimidazo[1,2-*a*]pyridine (**3ae**) as the main product. We obtained similar results when we used 3-fluoro-, 3-chloro-, or 3-bromo-substituted pyridines as the substrates. In these cases, the corresponding 8-haloimidazo[1,2-*a*]pyridines **3af**–**ah** were isolated in 68–72% yield. Moreover, isoquinoline was also tolerated in the reaction, giving 2-phenylimidazo[2,1-*a*]isoquinoline (**3ai**) in 66% yield.

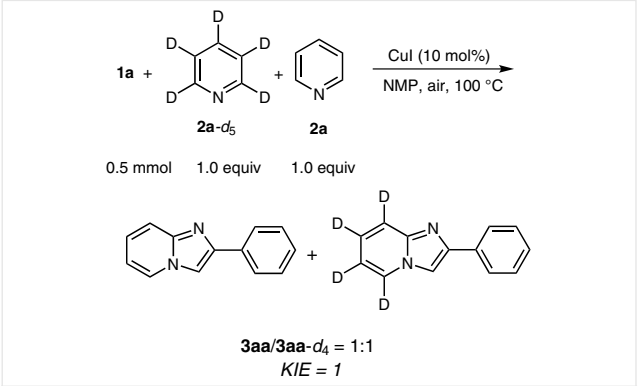


Scheme 3 Synthesis of imidazo[1,2-*a*]pyridines from ketoxime ester **1a** and pyridines **2**. *Reaction conditions*: **1a** (0.5 mmol), **2** (1.2 equiv), CuI (10 mol%), NMP (1.5 mL), 100 °C. Isolated yields are reported.

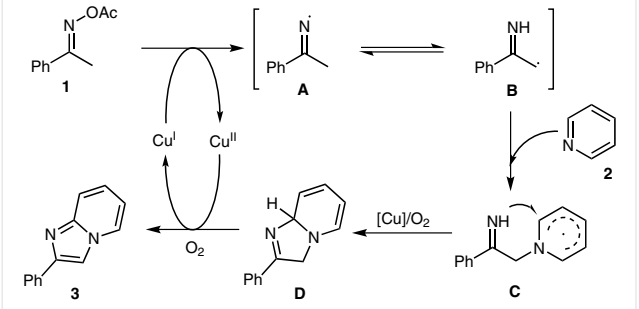
To gain insight into the mechanism of the reaction, we studied the intermolecular kinetic isotope effect (KIE) of the reaction (Equation 1). This experiment showed that cleavage of the C–H bond of the pyridine might not be the rate-determining step (KIE = 1).

Although the exact mechanism of the reaction remains unclear, a tentative mechanism for this copper-catalyzed, aerobic oxidative, coupling reaction is proposed in Scheme 4. First, reduction of ketoxime ester **1** by CuI gives the iminium radical **A**, which rapidly isomerizes to the α-carbon radical **B**.[8,9] Subsequently, radical coupling of intermediate **B** with pyridine (**2**) generates the intermediate **C**.[8,9] Intramolecular cyclization of intermediate **C** and subsequent oxidation of intermediate **D** in the presence of Cu/O_2 gives the final product, the imidazo[1,2-*a*]pyridine **3**.[12]

In summary, we have developed a simple and efficient copper-catalyzed aerobic oxidative coupling of ketoxime acetates with simple pyridines to give the corresponding



Equation 1 Kinetic isotope experiment



Scheme 4 Tentative mechanism for the CuI-catalyzed oxidative coupling of a ketoxime acetate with pyridine for the synthesis of an imidazo[1,2-*a*]pyridine

imidazo[1,2-*a*]pyridines. This copper-catalyzed, aerobic oxidative, coupling reaction tolerates a wide range of functional groups and is a reliable method for the rapid synthesis of a variety of valuable substituted imidazo[1,2-*a*]pyridines in high yields under simple and mild conditions.

Column chromatography was carried out on silica gel. ^1H NMR spectra were recorded on a Bruker NMR at 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on Bruker NMR at 100 MHz in $CDCl_3$. High-resolution mass spectra were recorded on a Bruker spectrometer in the ESI mode. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and were used without further purification. In all cases, the ketoximes were prepared from the corresponding ketones by the reported methods.[8]

Imidazo[1,2-*a*]pyridines 3; General Procedure

The appropriate ketoxime acetate **1** (0.5 mmol), CuI (10 mol%, 9.5 mg), and pyridine derivative **2** (0.6 mmol) were added successively to NMP (1.5 mL) in a 25 mL round-bottomed flask, and the mixture was stirred at 100 °C under dry air for 4–6 h. When the reaction was complete (TLC), the mixture was cooled to r.t., and the reaction was quenched with 30% aq NH_3 (5 mL). The mixture was extracted with EtOAc (10 mL), and the extracts were washed with H_2O (10 mL) and brine (10 mL). The organic layer was removed under reduced pressure to give a crude product that was further purified by chromatography (silica gel, PE–EtOAc).

2-Phenylimidazo[1,2-*a*]pyridine (3aa)

Yellow solid; yield: 92.2 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 6.4 Hz, 1 H), 7.96 (d, *J* = 7.6 Hz, 2 H), 7.82 (s, 1 H), 7.62 (d, *J* = 9.2 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.34–7.31 (m, 1 H), 7.16–7.12 (m, 1 H), 6.75–6.72 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 145.6, 133.7, 128.6, 127.9, 125.9, 125.5, 124.6, 117.4, 112.3, 108.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{11}N_2$: 195.0917; found: 195.0922.

2-(4-Tolyl)imidazo[1,2-*a*]pyridine (3ba)

Yellow solid; yield: 89.4 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 6.8 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.74 (s, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 7.12–7.08 (m, 1 H), 6.70–6.66 (m, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 145.4, 137.6, 130.8, 129.3, 125.8, 125.4, 124.4, 117.2, 112.1, 107.7, 21.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1083.

2-(3,4-Dimethylphenyl)imidazo[1,2-*a*]pyridine (3ca)

Yellow solid; yield: 96.6 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.4 Hz, 1 H), 7.75 (s, 2 H), 7.63–7.59 (m, 2 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 7.12–7.08 (m, 1 H), 6.70–6.67 (m, 1 H), 2.31 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 145.4, 136.8, 136.4, 131.1, 129.8, 127.1, 125.4, 124.3, 123.3, 117.2, 112.1, 107.6, 19.7, 19.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2$: 223.1230; found: 223.1232.

2-(5,6,7,8-Tetrahydronaphthalen-2-yl)imidazo[1,2-*a*]pyridine (3da)

Yellow solid; yield: 102.9 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.4 Hz, 1 H), 7.68 (s, 1 H), 7.65 (s, 1 H), 7.63–7.59 (m, 2 H), 7.14–7.09 (m, 2 H), 6.72–6.69 (m, 1 H), 2.82 (s, 2 H), 2.78 (s, 2 H), 1.80 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 145.4, 137.4, 137.1, 130.5, 129.4, 126.6, 125.4, 124.5, 123.1, 117.1, 112.2, 107.7, 29.3, 29.2, 23.1 (2 C).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2$: 249.1386; found: 249.1399.

2-(2,4-Dimethylphenyl)imidazo[1,2-*a*]pyridine (3ea)

Yellow solid; yield: 89.9 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (d, *J* = 6.0 Hz, 1 H), 8.13 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.25–7.21 (m, 1 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 6.87–6.84 (m, 1 H), 2.48 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.9, 144.0, 136.5, 134.9, 131.5, 130.4, 128.9, 126.7, 126.5, 126.0, 124.7, 116.5, 111.9, 21.5, 20.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2$: 223.1230; found: 223.1240.

2-(2,5-Dimethylphenyl)imidazo[1,2-*a*]pyridine (3fa)

Yellow solid; yield: 91.0 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 6.4 Hz, 1 H), 7.75 (s, 1 H), 7.68–7.65 (m, 2 H), 7.18–7.15 (m, 2 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.78–6.75 (m, 1 H), 2.49 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 144.6, 135.4, 132.8, 132.4, 130.7, 130.1, 128.5, 125.4, 124.5, 117.3, 112.2, 107.7, 21.1, 20.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2$: 223.1230; found: 223.1236.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3ga)

Yellow solid; yield: 106.4 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 6.8 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 7.74 (s, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.14–7.10 (m, 1 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 6.74–6.71 (m, 1 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 145.5, 133.6, 127.2, 126.3, 125.4, 124.3, 117.1, 114.0, 112.1, 107.1, 55.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1021.

2-(3-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3ha)

Yellow solid; yield: 34 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 6.4 Hz, 1 H), 7.85 (s, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.55 (s, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.35–7.31 (m, 1 H), 7.19–7.15 (m, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.80–6.77 (m, 1 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 145.6, 145.5, 135.1, 129.6, 125.5, 124.6, 118.4, 117.5, 114.1, 112.4, 110.9, 108.3, 55.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1031.

2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridine (3ia)

Yellow solid; yield: 102.9 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, *J* = 6.0 Hz, 1 H), 8.32 (s, 1 H), 7.57 (s, 2 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.23–7.19 (m, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.88–6.85 (m, 1 H), 3.85 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.9, 148.6, 144.6, 144.5, 126.7, 126.7, 124.7, 118.0, 116.4, 112.1, 112.0, 109.1, 108.3, 55.5, 55.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_2$: 255.1128; found: 255.1135.

2-(1,3-Benzodioxol-5-yl)imidazo[1,2-*a*]pyridine (3ja)

Yellow solid; yield: 100.0 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.0 Hz, 1 H), 7.68 (s, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.44–7.41 (m, 2 H), 7.12–7.08 (m, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.71–6.68 (m, 1 H), 5.96 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 147.4, 145.5, 145.4, 128.0, 125.4, 124.4, 119.6, 117.2, 112.2, 108.5, 107.3, 106.5, 101.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O_2$: 239.0815; found: 239.0823.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine (3ka)

Yellow solid; yield: 93.3 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 6.4 Hz, 1 H), 7.90–7.87 (m, 2 H), 7.74 (s, 1 H), 7.58 (d, *J* = 9.2 Hz, 1 H), 7.15–7.07 (m, 3 H), 6.74–6.71 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6 (d, J_{CF} = 245.5 Hz), 145.6, 144.8, 129.9, 127.6 (d, J_{CF} = 8.0 Hz), 125.5, 124.7, 117.3, 115.5 (d, J_{CF} = 21.5 Hz), 112.4, 107.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}FN_2$: 213.0823; found: 213.0825.

2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (3la)

Yellow solid; yield: 95.8 mg (84%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (d, *J* = 5.6 Hz, 1 H), 8.41 (s, 1 H), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.48 (d, *J* = 7.2 Hz, 2 H), 7.25–7.23 (m, 1 H), 6.90–6.87 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.9, 143.2, 132.8, 132.1, 128.7, 127.2, 126.9, 125.2, 116.7, 112.4, 109.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}ClN_2$: 229.0527; found: 229.0529.

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (3ma)

Yellow solid; yield: 117.0 mg (86%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.52 (d, *J* = 6.4 Hz, 1 H), 8.43 (s, 1 H), 7.92 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.27–7.23 (m, 1 H), 6.92–6.88 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.9, 143.2, 133.2, 131.6, 127.5, 127.0, 125.2, 120.7, 116.7, 112.5, 109.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}BrN_2$: 273.0022; found: 273.0031.

2-(4-Iodophenyl)imidazo[1,2-*a*]pyridine (3na)

Yellow solid; yield: 136.0 mg (85%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (d, *J* = 7.6 Hz, 1 H), 8.41 (s, 1 H), 7.78 (s, 4 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 6.91–6.88 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.8, 143.3, 137.5, 133.5, 127.6, 127.0, 125.2, 116.7, 112.5, 109.5, 93.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}IN_2$: 320.9883; found: 320.9896.

2-(2-Naphthyl)imidazo[1,2-*a*]pyridine (3oa)

Yellow solid; yield: 95.2 mg (78%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.57–8.51 (m, 3 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.98–7.95 (m, 2 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.28–7.24 (m, 1 H), 6.91–6.88 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.0, 144.3, 133.3, 132.6, 131.4, 128.2, 128.1, 127.6, 126.9, 126.4, 125.9, 125.1, 124.1, 124.0, 116.6, 112.3, 109.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{13}N_2$: 245.1073; found: 245.1071.

2-[(*E*)-2-Phenylvinyl]imidazo[1,2-*a*]pyridine (3pa)

Yellow solid; yield: 79.2 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 6.4 Hz, 1 H), 7.56–7.52 (m, 5 H), 7.37–7.33 (m, 2 H), 7.26 (d, *J* = 7.2 Hz, 1 H), 7.16–7.12 (m, 2 H), 6.74–6.71 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 144.0, 137.1, 130.5, 128.6, 127.6, 126.5, 125.4, 125.1, 119.8, 117.0, 112.2, 110.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1085.

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3qa)

Yellow solid; yield: 81.1 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 6.4 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 8.8 Hz, 1 H), 7.48–7.45 (m, 2 H), 7.36–7.33 (m, 1 H), 7.19–7.15 (m, 1 H), 6.85–6.82 (m, 1 H), 2.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 142.3, 134.7, 128.4 (2 C), 128.2, 127.2, 123.4, 122.7, 117.3, 111.9, 9.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1082.

3-Methyl-2-(4-tolyl)imidazo[1,2-*a*]pyridine (3ra)

Yellow solid; yield: 81.0 mg (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 6.4 Hz, 1 H), 7.69 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.29–7.21 (m, 3 H), 6.95–6.92 (m, 1 H), 2.62 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.4, 141.1, 136.3, 132.1, 129.1 (2 C), 127.7, 124.3, 123.7, 116.4, 111.8, 20.8, 9.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{14}N_2Na$: [M+Na] $^+$ 245.1049; found: 245.1061.

2-(4-*tert*-Butylphenyl)-3-methylimidazo[1,2-*a*]pyridine (3sa)

Yellow solid; yield: 99.0 mg (75%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.31 (d, *J* = 6.4 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.25–7.21 (m, 1 H), 6.95–6.92 (m, 1 H), 2.63 (s, 3 H), 1.32 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.5, 132.1, 127.5 (2 C), 125.2 (2 C), 124.3, 123.6, 116.5, 111.8, 34.3, 31.1, 9.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{21}N_2$: 265.1699; found: 265.1712.

2-(3,4-Dimethylphenyl)-3-methylimidazo[1,2-*a*]pyridine (3ta)

Yellow solid; yield: 86.1 mg (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (d, *J* = 6.4 Hz, 1 H), 7.60 (s, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 6.94–6.91 (m, 1 H), 2.62 (s, 3 H), 2.29 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.3, 141.2, 136.2, 135.1, 132.4, 129.6, 128.9, 125.2, 124.2, 123.6, 116.4, 115.8, 111.7, 19.5, 19.2, 9.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2$: 237.1386; found: 237.1389.

2-Phenyl-3-propylimidazo[1,2-*a*]pyridine (3ua)

Yellow solid; yield: 83.8 mg (71%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 6.8 Hz, 1 H), 7.79 (d, *J* = 7.2 Hz, 2 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.36–7.33 (m, 1 H), 7.25–7.22 (m, 1 H), 6.94–6.91 (m, 1 H), 3.11–3.07 (m, 2 H), 1.69–1.63 (m, 2 H), 0.98–0.95 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.5, 140.9, 135.0, 128.6, 127.6, 127.2, 124.4, 123.9, 120.7, 116.8, 111.9, 24.9, 20.8, 13.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2$: 237.1386; found: 237.1395.

2-[4-(Methylsulfonyl)phenyl]imidazo[1,2-*a*]pyridine (3va)

Yellow solid; 2.2 g (81%; 10 mmol scale).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.59–8.55 (m, 2 H), 8.22 (d, *J* = 8.0 Hz, 2 H), 7.99 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 9.2 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 6.95–6.92 (m, 1 H), 3.25 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.1, 142.5, 139.4, 138.8, 127.6, 127.2, 126.0, 125.7, 116.9, 112.8, 111.0, 43.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_2S$: 273.0692; found: 273.0703.

7-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3ab)

Yellow solid; yield: 84.2 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.39 (d, *J* = 6.8 Hz, 1 H), 8.29 (s, 1 H), 7.94 (d, *J* = 7.6 Hz, 2 H), 7.44–7.40 (m, 2 H), 7.35–7.28 (m, 2 H), 6.72 (d, *J* = 6.8 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.2, 144.1, 135.3, 134.1, 128.6, 127.5, 126.0, 125.5, 114.9, 114.7, 108.5, 20.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1080.

7-Methoxy-2-phenylimidazo[1,2-*a*]pyridine (3ac)

Yellow solid; yield: 93.0 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 7.6 Hz, 2 H), 8.83 (d, *J* = 7.2 Hz, 1 H), 7.61 (s, 1 H), 7.40–7.37 (m, 2 H), 7.29–7.25 (m, 1 H), 6.87 (s, 1 H), 6.44 (d, *J* = 6.8 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 147.0, 145.2, 133.7, 128.6, 127.6, 125.8, 125.7, 107.4, 106.8, 94.5, 55.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1033.

6,8-Dimethyl-2-phenylimidazo[1,2-*a*]pyridine (3ad)

Yellow solid; yield: 89.9 mg (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (s, 1 H), 8.10 (s, 1 H), 7.96 (d, *J* = 7.2 Hz, 2 H), 7.43–7.40 (m, 2 H), 7.31–7.29 (m, 1 H), 6.86 (s, 1 H), 2.48 (s, 3 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.3, 143.5, 134.2, 128.6, 127.4, 126.4, 125.4, 121.9, 121.2, 109.2, 17.5, 16.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2$: 223.1230; found: 223.1241.

8-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3ae)

Yellow solid; yield: 60.3 mg (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.6 Hz, 2 H), 7.92 (d, *J* = 6.4 Hz, 1 H), 7.78 (s, 1 H), 7.43–7.40 (m, 2 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 6.91 (d, *J* = 6.4 Hz, 1 H), 6.64–6.61 (m, 1 H), 2.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 145.1, 134.0, 128.6, 127.7, 127.4, 126.1, 123.3, 123.2, 112.2, 108.5, 17.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1084.

6-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3ae')

Yellow solid; yield: 28.1 mg (27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.6 Hz, 2 H), 7.90 (s, 1 H), 7.77 (s, 1 H), 7.54 (d, *J* = 9.2 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.34–7.30 (m, 1 H), 7.02 (d, *J* = 8.8 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 134.5, 134.0, 128.7, 127.9, 127.5, 124.2, 121.4, 116.1, 108.8, 17.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1082.

8-Fluoro-2-phenylimidazo[1,2-*a*]pyridine (3af)

Yellow solid; yield: 72.1 mg (68%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (d, *J* = 6.8 Hz, 1 H), 8.40 (d, *J* = 6.8 Hz, 1 H), 7.99 (d, *J* = 7.2 Hz, 2 H), 7.48–7.44 (m, 2 H), 7.36–7.33 (m, 1 H), 7.17–7.13 (m, 1 H), 6.90–6.85 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.4 (d, J_{CF} = 247.4 Hz), 144.6, 133.3, 128.8, 128.0, 125.7, 123.6, 111.4 (d, J_{CF} = 6.7 Hz), 110.9, 107.7 (d, J_{CF} = 16.0 Hz).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}FN_2$: 213.0823; found: 213.0831.

8-Chloro-2-phenylimidazo[1,2-*a*]pyridine (3ag)

Yellow solid; yield: 79.8 mg (70%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.52 (s, 2 H), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.47–7.43 (m, 3 H), 7.35 (d, *J* = 6.8 Hz, 1 H), 6.91–6.87 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.7, 142.0, 133.3, 128.8, 128.0, 126.1, 125.7, 124.1, 121.1, 112.1, 111.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}ClN_2$: 229.0527; found: 229.0530.

8-Bromo-2-phenylimidazo[1,2-*a*]pyridine (3ah)

Yellow solid; yield: 97.9 mg (72%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58–8.55 (m, 2 H), 7.99 (d, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 7.2 Hz, 1 H), 7.48–7.44 (m, 2 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 6.85–6.82 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.6, 142.6, 133.3, 128.8, 128.0, 127.5, 126.6, 125.7, 112.6, 111.2, 109.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{10}BrN_2$: 273.0022; found: 273.0035.

2-Phenylimidazo[2,1-*a*]isoquinoline (3ai)

Yellow solid; yield: 34 mg (66%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56 (d, *J* = 7.6 Hz, 1 H), 8.40 (s, 1 H), 8.32 (d, *J* = 6.8 Hz, 1 H), 8.03 (d, *J* = 7.6 Hz, 2 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.69–7.60 (m, 2 H), 7.48–7.44 (m, 2 H), 7.33–7.30 (m, 1 H), 7.24 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.6, 142.1, 133.9, 129.3, 128.7, 128.2, 128.1, 127.4, 127.3, 125.3, 124.2, 123.0, 122.6, 112.5, 111.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{13}N_2$: 245.1073; found: 245.1074.

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Supporting Information

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