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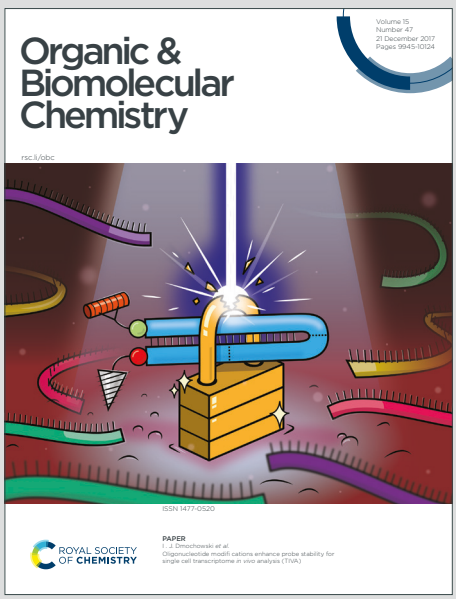

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Copper- and DMF-Mediated Switchable Oxidative C-H Cyanation and Formylation of Imidazo[1,2-a]pyridines Using Ammonium Iodide

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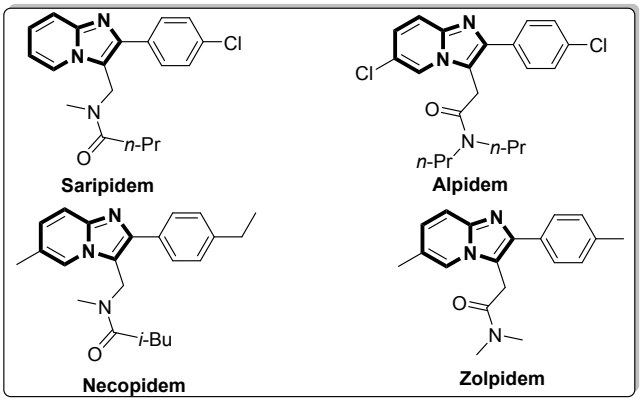
The cyanation and formylation of imidazo[1,2-*a*]pyridines were developed under copper-mediated oxidative conditions using ammonium iodide and DMF as nontoxic combined cyano-group source and DMF as formylation reagent. Mechanistic studies indicate that the cyanation of imidazo[1,2-*a*]pyridines proceeds through a two-step sequence: initial iodination and then cyanation. The cyanation has a high broad substrate scope, high functional group tolerance, and can be safely conducted on gram scale. A novel copper-mediated formylation using the widely available DMF as the formylation reagent and environmentally friendly molecular oxygen as the oxidant has also been developed. This protocol also provided a convenient approach for the synthesis of clinically used Saripidem.

Introduction

Imidazo[1,2-*a*]pyridines are an important class of heterocycles in medicinal chemistry and have attracted critical attention of chemists for their application value.[1] A number of clinically used drugs and clinical candidates contain the core structure of imidazo[1,2-*a*]pyridine, such as Saripidem, Necopidem, Alpidem, and Zolpidem (Figure 1).[2] It is not surprising, therefore, that great efforts have been directed toward developing synthetic methods for the construction of this privileged scaffold. Recently, Cao et al. reported a number of successful synthetic strategies for the construction of functionalized imidazo[1,2-*a*]pyridines.[3] Jiang and Zhu et al. also described efficient and elegant transformations to prepare imidazo[1,2-*a*]pyridines.[4]

Figure 1. Structures of Several Commercial Drugs Containing Imidazo[1,2-*a*]pyridine Skeletons.



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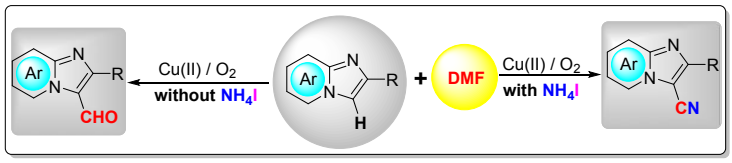
Aryl nitriles are an ubiquitous structural motif frequently found in natural products, pharmaceuticals, agricultural chemicals, materials, and dyes.[5] Cyano unit is a key precursor for diverse functional groups including amines, amidines, amides, tetrozoles, aldehydes, or other carboxy derivatives.[6] In the early years, the methods to introduce a cyano group onto an aromatic ring were limited.[7] As a result, a variety of new procedures have been extensively investigated for the synthesis of aryl nitriles.[8] In particular, metal-catalyzed cyanation of aryl halides or (hetero)arenes with metal cyano reagents, such as CuCN, KCN, NaCN, $Zn(CN)_2$, TMSCN, and $K_2Fe(CN)_4$, is considered to be highly promising.[9] Despite of their attractive features, these methods have some drawbacks: 1) the employed cyano-group sources are highly toxic; 2) in order to prevent the generation of hazardous HCN gas, careful handling is generally needed; 3) metal waste is unavoidably produced in stoichiometric amounts; 4) a careful control of the cyanide concentration is required to maintain the catalyst activity. Owing to the concept of "*green chemistry*", the use of nonmetallic cyano-group sources, especially combined cyano-group sources generated in situ, has been scrutinized as an alternative approach in recent years.[10]

On the other hand, formylation of (hetero)arenes has attracted the interest of organic chemists due to their remarkable application value in synthetic chemistry. The traditional formylation methods such as Vilsmeier-Haack, Reimer-Tiemann or Rieche and Friedel-Crafts acylations are routinely employed for the preparation of formylheteroarenes, which generally require the use of excess strong bases or acids, high temperatures, and strict exclusion of moisture.[11] Owing to the harsh reaction conditions, the development of more efficient and facile formylation methods remains highly desirable. In recent years, many elegant formylation processes have been developed using DMSO, DMF, TMEDA, and anilines as the carbonyl sources.[12]

Although significant progress has been made in these reasearch fields, direct copper-mediated cyanation and formylation of imidazo[1,2-*a*]pyridine using ammonium iodide and DMF as nontoxic combined cyano-group source and DMF as formylation

reagent have not been described yet. DMF is not only a common solvent and industrial raw material but also an important carbon source for C=O, CH_3, CH_2, CH and -CN formation.[13] Owing to our continuing interest in the construction of functionalized compounds by employing simple and readily available starting materials,[14] we disclosed an efficient protocol on copper-mediated cyanation of imidazo[1,2-*a*]pyridine C-H bonds using ammonium iodide and DMF as the source of nitrogen and carbon atom of the cyano unit, respectively. Meanwhile, we have also developed a convenient and general method for C-3 formylation of imidazo[1,2-*a*]pyridines using DMF as formylation reagent (Scheme 1).

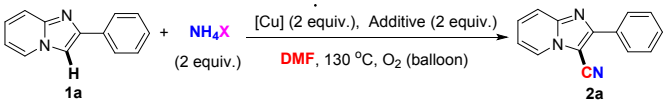
Scheme 1. Copper-Mediated Cyanation and Formylation of Imidazo[1,2,*a*]pyridine.



Results and discussion

Using 2-phenylimidazo[1,2-*a*]pyridine (**1a**) as a test substrate, optimal conditions were first sought for the cyanation (Table 1). After intensive screening of copper salts, we are pleased to find that $Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv to **1a**) was most effective for the cyanation (Table 1, entries 1-5). For further investigation, we focused on testing various additives to improve the product yield. Fortunately, high yield was observed when acetic acid was used as an additive (Table 1, entries 6-8). Interestingly, similar efficiency was also obtained by the combined use of NH_4OAc and I_2, which provided an important clue for the mechanistic details (Table 1, entry 9). Furthermore, the temperature was found to be vital to the reaction system, higher temprature or relatively lower temprature was ineffective for the reaction (Table 1, entries 10-12). In addition, when the copper salt loading was reduced to 1 equiv, **2a** could be obtained only in 65% yield (Table 1, entry 13). Then the reaction was performed under air atmosphere, the desired product was observed with lower yield (Table 1, entry 14).

Table 1. Optimization of Reaction Conditions [a]



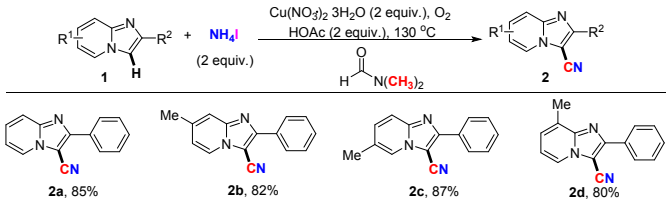
entry	[Cu]	NH_4X	additive	T (°C)	yield[b] (%)
1	$Cu(OAc)_2$	NH_4I	----	130	15
2	$CuBr_2$	NH_4I	----	130	0
3	CuI	NH_4I	----	130	0
4	$CuCl_2$	NH_4I	----	130	0
5	$Cu(NO_3)_2.3H_2O$	NH_4I	----	130	60
6	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	130	85
7[c]	$Cu(NO_3)_2.3H_2O$	NH_4I	K_2CO_3	130	0
8	$Cu(NO_3)_2.3H_2O$	NH_4I	TFA	130	50
9	$Cu(NO_3)_2.3H_2O$	NH_4OAc	I_2	130	82
10	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	140	0
11	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	110	23
12	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	100	0
13[c]	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	130	65
14[d]	$Cu(NO_3)_2.3H_2O$	NH_4I	HOAc	130	41

[a]Reaction conditions: **1a** (0.2 mmol), [Cu] (2.0 equiv), NH_4X (2.0 equiv), addtive (2.0 equiv), and DMF (2.0 mL) were added under O_2 balloon. [b]Isolated yield. [c][Cu] loading is 1.0 equiv. [d]Under air atmosphere.

With the optimal conditions in hand, we next explored the scope and limitations of our method (Table 2). In general, reaction of imidazo[1,2-*a*]pyridines bearing electron-donating groups gave slightly higher product yields than those containing electron-withdrawing moieties (**2a-2o**). It is notable that a wide range of functional groups were compatible with the optimal conditions. Imidazo[1,2-*a*]pyridine substituted at different positions, having 6-CH_3, 7-CH_3, 8-CH_3 substitution, were all smoothly cyanated in good yields (**2b-2d**). Polyaryl substrates such as 2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine was readily cyanated (**2p**). Much to our satisfaction, heteroaryl substrates and imidazo[1,2-*a*]pyridine underwent the reaction in moderate yields (**2q-2t**). It was worth noting that this cyanation process can be safely conducted on gram scale when using substrate bearing electron-donating group as starting material.

In continuation of our interest in preparing imidazo[1,2-*a*]pyridine derivatives by direct C-H functionalization, we next explored a novel and facile copper-mediated C-3 formylation of imidazo[1,2-*a*]pyridines utilizing DMF as formylation reagent and molecular oxygen as the terminal oxidant (Table 3). A variety of substituted imidazo[1,2-*a*]pyridines were tested under the optimized conditions. Much to our satisfaction, the substrates with functional groups such as fluoro, chloro, and bromo all gave the corresponding products in moderate yields (**3d-3f**, **3j** and **3k**). To our delight, the substrates with naphthalene, heterocyclic ring and 2-unsubstituted imidazo[1,2-*a*]pyridine were also tolerated in the reaction system (**3n-3p**). Furthermore, methyl imidazo[1,2-*a*]pyridine-2-carboxylate also gave the desired product in 22% yield (**3q**). 2-Chloroimidazo[1,2-*a*]pyridine and 2-bromoimidazo[1,2-*a*]pyridine also gave the corresponding products in 30% and 27% yields (**3r**, **3s**).

Table 2. Copper-Mediated Cyanation of Imidazo[1,2-*a*]pyridines [a,b]



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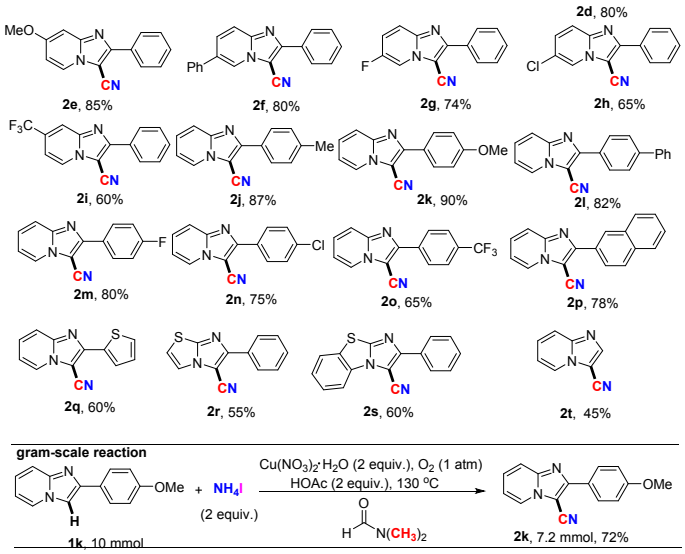
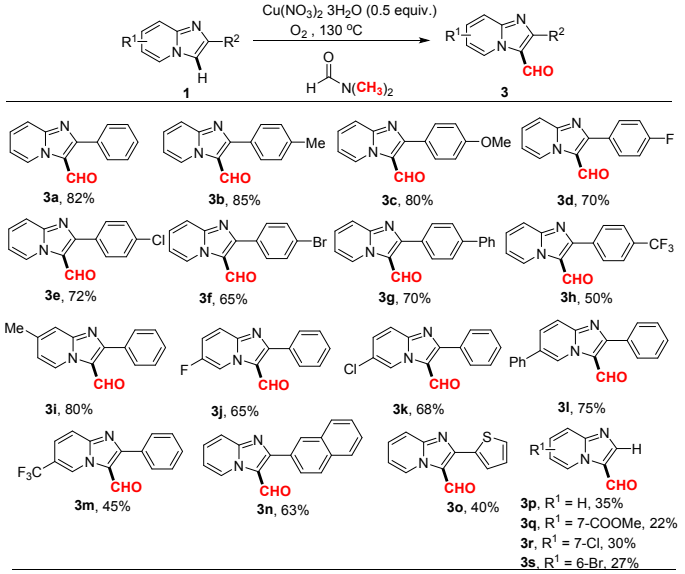


[a]Reaction conditions: a mixture of **1** (0.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (2.0 equiv), NH_4I (2.0 equiv), HOAc (2.0 equiv) and DMF (2.0 mL) were added at 130 °C under O_2 balloon. [b]Yields referred to isolated yields.

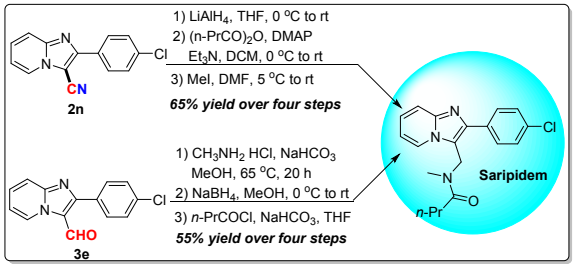
Table 3. Copper-Mediated Formylation of Imidazo[1,2-*a*]pyridines *a,b*



[a]Reaction conditions: a mixture of **1** (0.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.5 equiv), and DMF (2.0 mL) were added at 130 °C under O_2 balloon. [b]Yields referred to isolated yields.

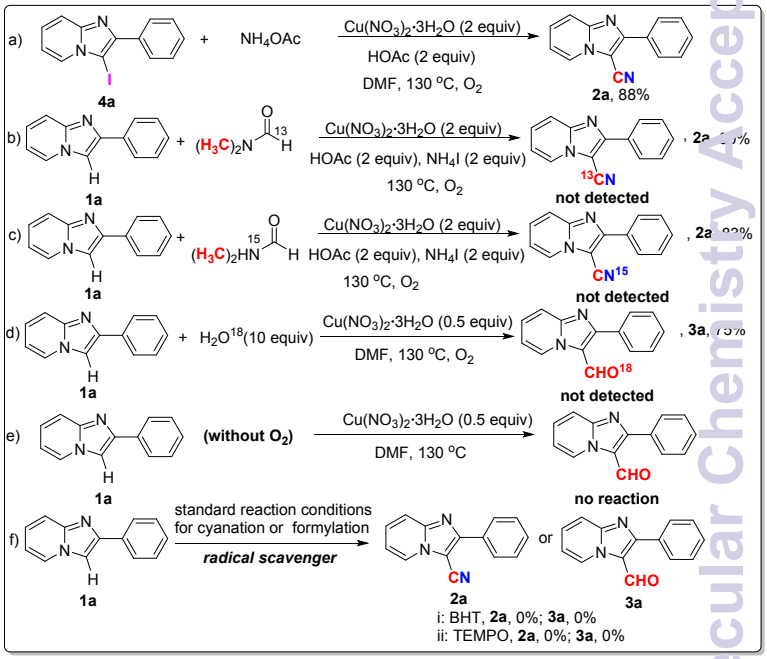
As a synthetic application of this method, we successfully converted our products **2n** and **3e** to the clinically used Saripidem with 65% and 55% overall yields (Scheme 2). Compared with previously reported procedures for the synthesis of Saripidem,[15] our synthetic strategy is much facile and convenient.

Scheme 2. Synthesis of Saripidem



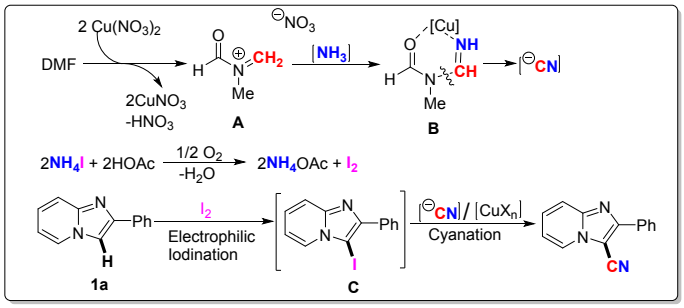
To gain insight into the mechanism of the reaction, a variety of control experiments were conducted as shown in Scheme 3. First, separately prepared 3-iodo-2-phenylimidazo[1,2-*a*]pyridine (**4a**) underwent the cyanation with 88% yield when ammonium acetate instead of its iodide salt was used to react under the otherwise identical conditions (Scheme 3a). This result demonstrated that the reaction proceeded in two steps via initial iodination and subsequent cyanation. To probe the mechanism of the conversion of DMF into a -CN unit, a series of labeling experiments were next carried out, indicating that ammonium iodide plays a dual role to supply iodide and nitrogen atom of the cyano unit (Scheme 3b, 3c). The results of ^{18}O-labeling experiments proved that the oxygen atom in the carbonyl group should be originated from molecular oxygen (Scheme 3d and 3e). In addition, no products were obtained in the presence of radical scavenger, such as BHT (2,6-di-tert-butyl-4-methylphenol) and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), which suggesting that the reaction probably proceeds through a radical pathway (Scheme 3f).

Scheme 3. Control Experiments

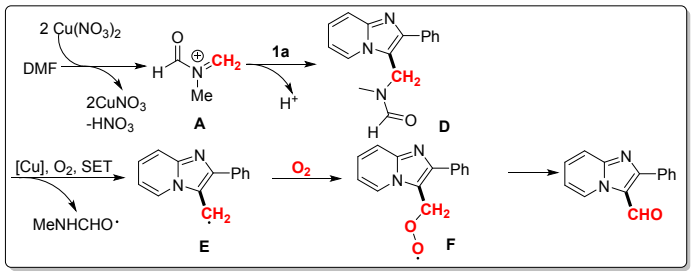


The above results led us to propose a sequential cyanation pathway that substrates are first iodinated and then cyanated under the copper-mediated conditions (Scheme 4).[16] It is assumed that DMF is initially oxidized to intermediate **A** upon the reduction of Cu(II) to Cu(I). Then, the reaction of **A** with ammonia can lead to the formation of amidinyl species **B**, which is envisioned to release the cyanide ion. On the other hand, an electrophilic substitution is believed to involve the iodination of **1a** giving intermediate **C**. Finally, cyanation of intermediate **C** would take place presumably upon the reaction with naked cyanide anion. The role of additive is assumed to capture the released ammonia leading to its acetate salt. A plausible mechanism of the formylation reaction has also been proposed in Scheme 5. First, nucleophilic addition of **1a** to species **A** produced intermediate **D**, which was further oxidated into intermediate **E** via a single electron-transfer (SET) process. Intermediate **E** is trapped by dioxygen to give peroxy radical **F**. Finally, intermediate **F** is converted into the desired formylation product.

Scheme 4. Plausible Mechanism for Cyanation.



Scheme 5. Plausible Mechanism for Formylation.



Conclusions

In summary, we have developed a new procedure of copper-mediated cyanation of imidazo[1,2-*a*]pyridine using ammonium iodide and DMF as nontoxic combined cyano-group source and DMF as formylation reagent. Ammonium iodide plays a dual role to supply iodide and nitrogen atom of the cyano unit. The reaction features excellent functional group tolerance and can be safely conducted on gram scale. This protocol is also recognized as a convenient approach for the synthesis of Saripidem, which is sedative and anxiolytic drug. Advantageously, the employment of O_2 as a clean oxidant and DMF as formylation reagent significantly improved the practicality of this C-H formylation transformation. Our method is more convenient and environmentally friendly compared to the traditional methods for the preparation of 3-formylimidazo[1,2-*a*]pyridines. A detailed mechanistic investigation and further application of DMF are currently underway in our laboratory.

Experimental section

General Information

All purchased reagents and solvents were used without further purification unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX-400 or Bruker DRX-600 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively. TLC was performed by using commercially prepared 100-400 mesh silica gel plates and visualization was effected at 254 nm.

General Procedure for Cyanation

The mixture of **1** (0.2 mmol, 1.0 equiv), NH_4I (0.4 mmol, 2.0 equiv), $Cu(NO_3)_2.3H_2O$ (0.4 mmol, 2.0 equiv) and HOAc (0.4 mmol, 2.0 equiv) was stirred in DMF (2.0 mL/mmol) in an oil bath at 130 °C in a 20 mL tube with a balloon O_2. After the reaction was completed (monitored by TLC), the resulting mixture were cooled to room temperature and diluted with EtOAc and aqueous NH_3 solution (3 M). Two layers were separated and aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum. The desired products **2** were obtained in the corresponding yields after purified by column chromatography on silica gel with mixture of petroleum ether and ethyl acetate.

General Procedure for Formylation

The mixture of **1** (0.2 mmol, 1.0 equiv) an $Cu(NO_3)_2.3H_2O$ (0.1 mmol, 0.5 equiv) was stirred in DMF (2.0 mL) in an oil bath at 130 °C in a 20 mL tube with a balloon O_2. After the reaction was completed (monitored by TLC), the resulting mixture were cooled to room temperature and extracted with EtOAc (3×10 mL). The combined organic layers were evaporated under vacuum. The desired products **3** were obtained in the corresponding yields after purified by column chromatography on silica gel with mixture of petroleum ether and ethyl acetate. General Procedure for Synthesis of **3**

Experimental Procedure for Gram Scale Reaction.

A mixture of 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **1k** (10.0 mmol, 1.0 equiv), NH_4I (20 mmol, 2.0 equiv), $Cu(NO_3)_2.3H_2O$ (20 mmol, 2.0 equiv) and HOAc (20 mmol, 2.0 equiv) was stirred in DMF (50 mL/mmol) at 130 °C in a 100 mL round-bottom flask with a balloon O_2. After the reaction was completed (monitored by TLC), the resulting mixture were cooled to room temperature and diluted with EtOAc and aqueous NH_3 solution. Two layers were separated and aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum. The desired products **2k** were obtained in 72% yield after purified by column chromatography on silica gel with mixture of petroleum ether and ethyl acetate.

2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2a): Yield 37.2 mg (85%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 6.8 Hz, 1H), 8.10 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 9.1 Hz, 1H), 7.40 (m, 4H), 6.98 (t, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 145.8, 130.2, 129.1, 128.0, 127.7, 126.3, 124.6, 117.1, 113.7, 111.8, 92.8. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}N_3$ $[M+H]^+$, 220.0869; Found 220.0873.

7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2b): Yield 38.2 mg (82%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 14.3, 7.2 Hz, 3H), 7.55-7.25 (m, 4H), 6.80 (d, J = 6.9 Hz, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.5, 147.3, 140.4, 131.4, 130.0, 129.0, 127.3, 124.7, 117.3, 116.8, 113.1, 93.3, 21.6. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_3$ $[M+H]^+$, 234.1026; Found 234.1028.

6-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2c): Yield 40.5 mg (87%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5 Hz, 2H), 8.04 (s, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.47-7.31 (m, 3H), 7.19 (d, J = 8.9 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.0, 145.8, 131.8, 131.4, 130.0, 129.0, 127.2, 125.0, 123.5, 117.4, 113.0, 93.5, 18.2. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{11}N_3Na$ $[M+Na]^+$, 256.0845; Found 256.0847.

8-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2d): Yield 37.2 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.3 Hz, 3H), 7.53 (t, J = 7.3 Hz, 2H), 7.49 (d, J = 6.7 Hz, 1H), 7.24 (d, J = 7.0 Hz, 1H), 6.99 (t, J = 6.8 Hz, 1H), 2.71 (s, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.8, 147.2, 131.5, 130.0,

129.0, 128.7, 127.4, 127.4, 123.3, 114.7, 113.1, 94.2, 16.9, 16.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_3$ $[M+H]^+$, 234.1026; Found 234.1024.

7-methoxy-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2e): Yield 42.3 mg (85%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 10.7, 8.0 Hz, 3H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.47 (d, *J* = 6.8 Hz, 1H), 7.02 (s, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7, 153.8, 148.7, 131.4, 130.0, 129.0, 127.1, 125.8, 113.2, 109.4, 95.9, 92.7, 55.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_3O$ $[M+H]^+$, 250.0975; Found 250.0975.

2,6-diphenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2f): Yield 47.2 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.20-8.10 (m, 2H), 7.75 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.64 (dd, *J* = 9.3, 1.8 Hz, 1H), 7.57-7.50 (m, 2H), 7.49-7.36 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.7, 145.1, 134.9, 130.2, 129.2, 128.5, 128.4, 128.4, 128.0, 127.7, 126.3, 126.1, 121.7, 116.9, 111.9, 93.2. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{20}H_{14}N_3$ $[M+H]^+$, 296.1182; Found 296.1180.

6-fluoro-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2g): Yield 35.1 mg (74%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 2H), 7.73 (dd, *J* = 9.8, 4.8 Hz, 1H), 7.56-7.44 (m, 3H), 7.37 (t, *J* = 9.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.3 (d, $J_{C\text{-}F}$ = 241 Hz), 154.1, 144.4, 131.0, 130.3, 129.1, 127.2, 120.7 (d, $J_{C\text{-}F}$ = 24 Hz), 118.8 (d, $J_{C\text{-}F}$ = 9 Hz), 113.0 (d, $J_{C\text{-}F}$ = 51 Hz), 112.2, 95.2. ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.7. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_9FN_3$ $[M+H]^+$, 238.0775; Found 238.0773.

6-chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (2h): Yield 32.9 mg (65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.15 (d, *J* = 7.3 Hz, 2H), 7.68 (d, *J* = 9.5 Hz, 1H), 7.50 (q, *J* = 8.5, 7.7 Hz, 3H), 7.41 (d, *J* = 9.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 145.2, 130.8, 130.4, 130.2, 129.1, 127.3, 123.6, 123.2, 118.4, 112.2, 94.3. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_9ClN_3$ $[M+H]^+$, 254.0480; Found 254.0487.

2-phenyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2i): Yield 34.4 mg (60%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 7.0 Hz, 1H), 8.25-8.12 (m, 2H), 8.04 (s, 1H), 7.52 (m, 3H), 7.25 (d, *J* = 6.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.7, 145.1, 130.7, 130.7(q, $J_{C\text{-}F}$ = 44 Hz), 130.5, 129.2, 127.4, 126.4, 122.6 (q, $J_{C\text{-}F}$ = 339 Hz), 116.0 (q, $J_{C\text{-}F}$ = 5 Hz), 111.9, 110.6 (q, $J_{C\text{-}F}$ = 4 Hz), 95.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ-64.0. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_9F_3N_3$ $[M+H]^+$, 288.0743; Found 288.0743

2-(p-tolyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2j): Yield 40.5 mg (87%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 6.4 Hz, 0H), 8.09 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 0H), 7.44 (t, *J* = 7.9 Hz, 0H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 6.6 Hz, 0H), 2.43 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 146.8, 140.5, 129.7, 128.7, 128.4, 127.2, 125.6, 118.1, 114.6, 113.0, 93.5, 21.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_3$ $[M+H]^+$, 234.1026; Found 234.1029.

2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2k): Yield 44.8 mg (90%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, *J* = 6.7 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 6.8 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 161.2, 152.6, 146.9, 130.2, 128.8, 127.3, 124.2, 117.7, 115.5, 115.1, 113.6, 92.7, 55.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{11}N_3ONa$ $[M+Na]^+$, 272.0794; Found 272.0799.

2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2l): Yield 48.4 mg (82%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 6.8 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 8.5 Hz, 3H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 3H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 6.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 146.9, 142.9, 140.3, 130.1, 128.9, 128.8, 127.8, 127.7, 127.6, 127.1, 125.6, 118.2, 114.8, 112.9, 93.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{20}H_{14}N_3$ $[M+H]^+$, 296.1182; Found 296.1179.

2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2m): Yield 37.9 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 6.2 Hz, 1H), 8.23-8.15 (m, 2H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 6.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $J_{C\text{-}F}$ = 249 Hz), 152.4, 146.8, 129.3 (d, $J_{C\text{-}F}$ = 9 Hz), 128.9, 127.5, 125.7, 118.1, 116.2 (d, $J_{C\text{-}F}$ = 21 Hz), 114.9, 112.7, 93.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ-109.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_9FN_3$ $[M+H]^+$, 238.0775; Found 238.0776.

2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2n): Yield 37.9 mg (75%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.4 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 6.9 Hz, 3H), 7.10 (t, *J* = 6.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 146.8, 136.2, 129.7, 129.3, 129.0, 128.5, 125.7, 118.2, 114.9, 112.6, 93.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_9ClN_3$ $[M+H]^+$, 254.0480; Found 254.0484.

2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2o): Yield 37.3 mg (65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.8 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 3H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.5, 146.9, 134.6, 131.7 (q, $J_{C\text{-}F}$ = 33 Hz), 129.1, 127.5, 126.0 (q, $J_{C\text{-}F}$ = 4 Hz), 125.7, 123.9 (q, $J_{C\text{-}F}$ = 271 Hz), 118.4, 115.2, 112.3, 94.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ-62.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_9F_3N_3$ $[M+H]^+$, 288.0743; Found 288.0742

2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2p): Yield 41.9 mg (78%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.27 (d, *J* = 6.7 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.82-7.76 (m, 1H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.44 (d, *J* = 5.3 Hz, 2H), 7.37 (t, *J* = 8.1 Hz, 1H), 6.98 (t, *J* = 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.3, 146.9, 134.1, 133.3, 128.9, 128.8, 128.6, 127.8, 127.2, 127.2, 126.7, 125.6, 124.2, 118.2, 114.8, 112.9, 94.1. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{18}H_{11}N_3Na$ $[M+Na]^+$, 292.0845; Found 292.0842.

2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (2q): Yield 27.0 mg (60%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.6 Hz, 1H), 7.91 (d, *J* = 3.7 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 5.0 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 4.4 Hz, 1H), 7.08 (t, *J* = 6.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.5, 146.8, 134.4, 129.0, 128.4, 127.3, 125.6, 117.9, 114.86, 112.3, 92.7. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{12}H_8N_3S$ $[M+H]^+$, 226.0433; Found 226.0433.

6-phenylimidazo[2,1-*b*]thiazole-5-carbonitrile (2r): Yield 24.7 mg (55%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 4.4 Hz, 1H), 7.38 (dt, *J* = 15.3, 7.2 Hz, 3H), 6.98 (d, *J* = 4.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.8, 153.0, 131.5, 129.81, 129.0, 127.0, 126.7, 118.5, 115.1, 112.7, 94.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{12}H_8N_3S$ $[M+H]^+$, 226.0433; Found 226.0436.

2-phenylbenzo[d]imidazo[2,1-*b*]thiazole-3-carbonitrile (2s): Yield 33.0 mg (60%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 8.06-7.99 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.53-7.31 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.1, 151.5, 132.0, 131.3, 130.1, 129.9, 129.0, 127.1, 126.7, 126.2, 124.5, 113.5, 113.2, 94.6. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{16}H_{10}N_3S$ $[M+H]^+$, 276.0590; Found 276.0589.

imidazo[1,2-*a*]pyridine-3-carbonitrile (2t): Yield 12.9 mg (45%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.19 (s, 1H), 7.80 (dt, *J* = 9.2, 1.1 Hz, 1H), 7.49 (ddd, *J* = 9.1, 6.9, 1.2 Hz, 1H), 7.14 (td, *J* = 6.9, 1.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.2, 142.4, 128.3, 125.7, 118.7, 115.1, 111.1, 98.3. HRMS Calcd (ESI-TOF) m/z: calcd for $C_8H_6N_3$ $[M+H]^+$, 144.0556; Found 144.0553.

2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3a): Yield 36.4 mg (82%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 9.65 (d, *J* = 6.8 Hz, 1H), 7.86-7.76 (m, 3H), 7.61-7.54 (m, 1H), 7.52 (m, 3H), 7.11 (t, *J* = 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.6, 179.5, 158.3, 147.7, 132.4, 130.4, 129.8, 128.9, 128.8, 120.7, 117.4, 115.3. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}N_2ONa$ $[M+Na]^+$, 245.0685; Found 245.0688.

2-**(p-tolyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3b):** Yield 40.1 mg (85%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.65 (d, *J* = 6.7 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 6.9 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.6, 158.4, 147.7, 140.1, 130.4, 129.7, 129.6, 129.5, 128.8, 120.7, 117.4, 115.2, 21.4. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_2ONa$ $[M+Na]^+$, 259.0842; Found 259.0846.

2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3c): Yield 40.3 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.56 (d, *J* = 6.8 Hz, 1H), 7.79-7.62 (m, 3H), 7.48 (t, *J* = 8.2 Hz, 1H), 7.14-6.79 (m, 3H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 161.1, 158.2, 147.8, 131.2, 130.4, 128.8, 124.8, 120.5, 117.2, 115.1, 114.4, 55.4. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_2O_2Na$ $[M+Na]^+$, 275.0791; Found 275.0786.

2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3d): Yield 33.6 mg (70%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.66 (d, *J* = 6.8 Hz, 1H), 7.89-7.75 (m, 3H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 8.5 Hz, 2H), 7.14 (t, *J* = 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.2, 163.9 (d, $J_{C\text{-}F}$ = 311 Hz), 157.2, 147.7, 131.7 (d, $J_{C\text{-}F}$ = 10 Hz), 130.6, 128.8, 128.5 (d, $J_{C\text{-}F}$ = 5 Hz), 120.7, 117.4, 116.1 (d, $J_{C\text{-}F}$ = 28 Hz), 115.4. ^{19}F NMR (471 MHz, $CDCl_3$) δ-110.7. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}FN_2O$ $[M+H]^+$, 241.0772; Found 241.0771.

2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3e): Yield 36.8 mg (72%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 9.65 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.84-7.74 (m, 3H), 7.60 (ddd, *J* = 8.8, 7.0, 1.4 Hz, 1H), 7.55-7.49 (m, 2H), 7.15 (td, *J* = 6.9, 1.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.1, 156.8, 147.7, 136.3, 131.0, 130.8, 130.6, 129.2, 128.8, 120.8, 117.5, 115.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}ClN_2O$ $[M+H]^+$, 257.0476; Found 257.0476.

2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3f): Yield 39.1 mg (65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 9.66 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.82 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.76-7.58 (m, 5H), 7.16 (td, *J* = 6.9, 1.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.1, 156.8, 147.7, 132.2, 131.2, 131.1, 130.7, 128.8, 124.6, 120.7, 117.5, 115.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}BrN_2O$ $[M+H]^+$, 300.9971; Found 300.9970.

2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3g): Yield 41.7 mg (70%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 9.67 (d, *J* = 6.8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.85-7.71 (m, 3H), 7.63 (dd, *J* = 29.4, 8.2 Hz, 3H), 7.43 (d, *J* = 34.3 Hz, 3H), 7.12 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 157.9, 147.8, 142.7, 140.2, 131.3, 130.5, 130.3, 128.9, 128.8, 127.9, 127.6, 127.18, 120.8, 117.4, 115.3. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{20}H_{14}N_2ONa$ $[M+Na]^+$, 321.0998; Found 321.0995.

2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3h): Yield 29.0 mg (50%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.67 (d, *J* = 6.9 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 2H), 7.88-7.71 (m, 3H), 7.63 (t, *J* = 8.2 Hz, 1H), 7.18 (t, *J* = 7.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.0, 156.3, 147.7, 135.9, 131.7 (q, $J_{C\text{-}F}$ = 33 Hz), 130.8, 130.1, 128.8, 125.8 (q, $J_{C\text{-}F}$ = 4 Hz), 123.9 (q, $J_{C\text{-}F}$ = 335 Hz), 121.0, 117.6, 115.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ-62.7. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{10}F_3N_2O$ $[M+H]^+$, 291.0740; Found 291.0737.

7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3i): Yield 37.8 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 0H), 9.51 (d, *J* = 6.8 Hz, 0H), 7.87-7.78 (m, 1H), 7.61-7.47 (m, 1H), 6.96 (d, *J* = 6.9 Hz, 0H), 2.51 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.2, 158.5, 148.2, 142.3, 132.4, 129.8, 128.9, 128.0, 120.6, 117.7, 116.2, 21.8. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{12}N_2ONa$ $[M+Na]^+$, 259.0842; Found 259.0847.

6-fluoro-2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3j): Yield 31.2 mg (65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.66 (dd, *J* = 4.4, 2.5 Hz, 1H), 7.88-7.69 (m, 3H), 7.60-7.38 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.7, 158.6 (d, $J_{C\text{-}F}$ = 4 Hz), 154.5 (d, $J_{C\text{-}F}$ = 239 Hz), 145.2, 132.1, 130.0, 129.7, 129.0, 126.2, 121.7 (d, $J_{C\text{-}F}$ = 31 Hz), 117.7 (d, $J_{C\text{-}F}$ = 9 Hz), 116.1 (d, $J_{C\text{-}F}$ = 43 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ-135.2. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}FN_2O$ $[M+H]^+$, 241.0772; Found 241.0771.

6-chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3k): Yield 34.8 mg (68%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (d, *J* = 2.0 Hz, 1H), 9.74 (s, 1H), 7.85-7.79 (m, 2H), 7.74 (d, *J* = 9.4 Hz, 1H), 7.61-7.44 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.7, 179.7, 158.4, 146.0, 131.6, 130.1, 129.8, 129.0, 126.8, 123.5, 120.8, 117.6. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{14}H_{10}ClN_2O$ $[M+H]^+$, 257.0476; Found 257.0476.

2,6-diphenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (3l): Yield 44.7 mg (75%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.81 (t, *J* = 1.4 Hz, 1H), 7.80-7.73 (m, 4H), 7.58-7.53 (m, 2H), 7.49-7.39 (m, 5H), 7.38-7.32 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.6, 158.5, 146.9, 136.4, 132.3, 130.7, 130.0, 129.9, 129.8, 129.3, 128.9, 128.4, 127.2, 126.2, 121.0, 117.2. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{20}H_{15}N_2O$ $[M+H]^+$, 299.1179; Found 299.1177.

2-phenyl-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3m): Yield 26.1 mg (45%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 9.77 (d, *J* = 7.1 Hz, 1H), 8.10 (s, 1H), 7.84 (dd, *J* = 6.4, 3.3 Hz, 2H), 7.56 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.29 (dd, *J* = 7.2, 1.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.2, 158.9, 146.1, 131.8 (q, $J_{C\text{-}F}$ = 34 Hz), 131.7, 130.3, 129.8, 129.6, 129.5, 129.1, 122.7 (q, $J_{C\text{-}F}$ = 271 Hz), 121.2, 115.2 (q, $J_{C\text{-}F}$ = 5 Hz), 111.0 (q, $J_{C\text{-}F}$ = 3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ-64.0.

HRMS Calcd (ESI-TOF) m/z: calcd for $C_{15}H_{10}F_3N_2O$ $[M+H]^+$, 291.0740; Found 291.0736.

2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3n): Yield 34.2 mg (63%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 9.69 (d, *J* = 6.8 Hz, 1H), 8.31 (s, 1H), 8.04-7.94 (m, 3H), 7.93-7.89 (m, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.65-7.49 (m, 3H), 7.15 (td, *J* = 6.9, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.7, 158.0, 147.7, 133.9, 133.2, 130.6, 129.9, 129.6, 128.9, 128.8, 128.6, 127.8, 127.2, 126.8, 126.7, 121.0, 117.4, 115.4. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{18}H_{13}N_2O$ $[M+H]^+$, 273.1022; Found 273.1021.

2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (3o): Yield 18.2 mg (40%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.64 (d, *J* = 6.8 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.62-7.53 (m, 2H), 7.21 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.12 (td, *J* = 6.9, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.5, 151.2, 147.7, 134.7, 130.8, 129.2, 129.0, 128.8, 128.3, 120.0, 117.2, 115.4. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{12}H_9N_2OS$ $[M+H]^+$, 229.0430; Found 229.0428.

imidazo[1,2-*a*]pyridine-3-carbaldehyde (3p): Yield 10.2 mg (35%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.50 (d, *J* = 6.8 Hz, 1H), 8.34 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.58 (ddd, *J* = 8.8, 7.0, 1.3 Hz, 1H), 7.15 (t, *J* = 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.9, 149.4, 146.7, 130.2, 128.7, 125.0, 117.9, 115.5. HRMS Calcd (ESI-TOF) m/z: calcd for $C_8H_6N_2ONa$ $[M+Na]^+$, 169.0372; Found 169.0379.

methyl 3-formylimidazo[1,2-*a*]pyridine-7-carboxylate (3q): Yield 8.9 mg (22%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 9.53 (d, *J* = 7.0 Hz, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.71 (dd, *J* = 7.1, 1.7 Hz, 1H), 4.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.4, 164.7, 148.5, 147.5, 131.1, 128.3, 125.5, 120.0, 114.7, 53.0. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{10}H_9N_2O_3$ $[M+H]^+$, 205.0608; Found 205.0610.

7-chloroimidazo[1,2-*a*]pyridine-3-carbaldehyde (3r): Yield 10.8 mg (30%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.43 (d, *J* = 7.2 Hz, 1H), 8.32 (s, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.27 (s, 0H), 7.13 (dd, *J* = 7.2, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.9, 149.4, 147.3, 136.8, 128.8, 125.0, 117.1, 117.0. HRMS Calcd (ESI-TOF) m/z: calcd for $C_8H_6ClN_2O$ $[M+H]^+$, 181.0163; Found 181.0165.

6-bromoimidazo[1,2-*a*]pyridine-3-carbaldehyde (3s): Yield 12.0 mg (27%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.68 (d, *J* = 1.8 Hz, 1H), 8.31 (s, 1H), 7.70 (d, *J* = 9.4 Hz, 1H), 7.63 (dd, *J* = 9.4, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.0, 147.7, 146.6, 133.5, 128.8, 124.9, 118.4, 110.4. HRMS Calcd (ESI-TOF) m/z: calcd for $C_8H_6BrN_2O$ $[M+H]^+$, 224.9658; Found 224.9661.

Saripidem from 2n: Yield 44.3 mg (65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 9.1, 6.7 Hz, 1H), 6.84 (t, *J* = 6.8 Hz, 1H), 5.18 (s, 2H), 2.60 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.68 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 145.2, 144.7, 134.1, 132.7, 130.1, 128.9, 125.5, 125.4, 117.3, 116.1, 112.8, 38.6, 35.4, 33.6, 18.5, 13.9. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{19}H_{21}ClN_3O$ $[M+H]^+$, 342.1368; Found 342.1389.

Saripidem from 3e: Yield 37.5 mg (55%, white solid).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.51-7.40 (m, 2H), 7.27-7.20 (m, 1H), 6.83 (t, *J* = 6.9 Hz, 1H), 5.17 (s, 2H), 2.59 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.67 (h, J = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 145.2, 144.8, 134.1, 132.8, 130.0, 128.9, 125.5, 125.4, 117.3, 116.0, 112.8, 38.6, 35.4, 33.6, 18.5, 13.9.

2k from gram-scale: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 6.7 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.47 (ddd, *J* = 8.6, 6.9, 1.3 Hz, 1H), 7.17-6.93 (m, 3H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.2, 153.4, 146.9, 128.8, 128.7, 125.6, 123.9, 117.9, 114.5, 114.4, 113.2, 93.0, 55.4.

3-iodo-2-phenylimidazo[1,2-*a*]pyridine (4a): Yield 51.0 mg (80%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 6.9 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 2H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.33-7.26 (m, 1H), 6.94 (t, *J* = 6.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.1, 148.0, 133.5, 128.6, 128.4, 126.6, 125.7, 117.6, 113.3, 59.6. HRMS Calcd (ESI-TOF) m/z: calcd for $C_{13}H_{10}IN_2$ $[M+H]^+$, 320.9883; Found 320.9881.

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