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Visible-Light-Induced Regioselective Cyanomethylation of Imidazopyridines and Its Application in Drug Synthesis

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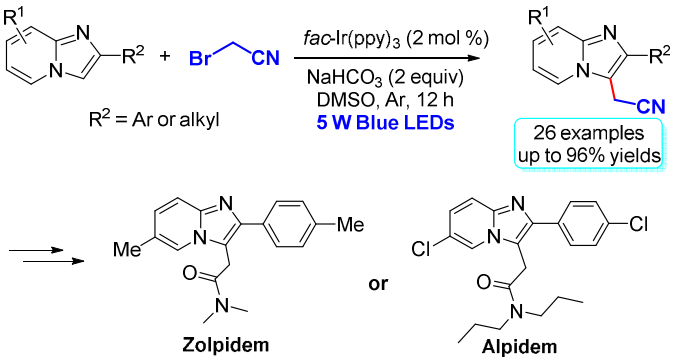


ABSTRACT: 3-Cyanomethylated imidazopyridines were synthesized *via* a visible light-promoted reaction of imidazopyridines with bromoacetonitrile or iodoacetonitrile catalyzed by *fac*-Ir(ppy)$_3$ under mild conditions. For the substrates with various substituents on benzene or pyridine ring, the reaction proceeded smoothly to give the corresponding products in moderate to good yields. The synthetic utility of this visible-light-induced reaction has been illustrated in the efficient synthesis of zolpidem and alpidem.

■ INTRODUCTION

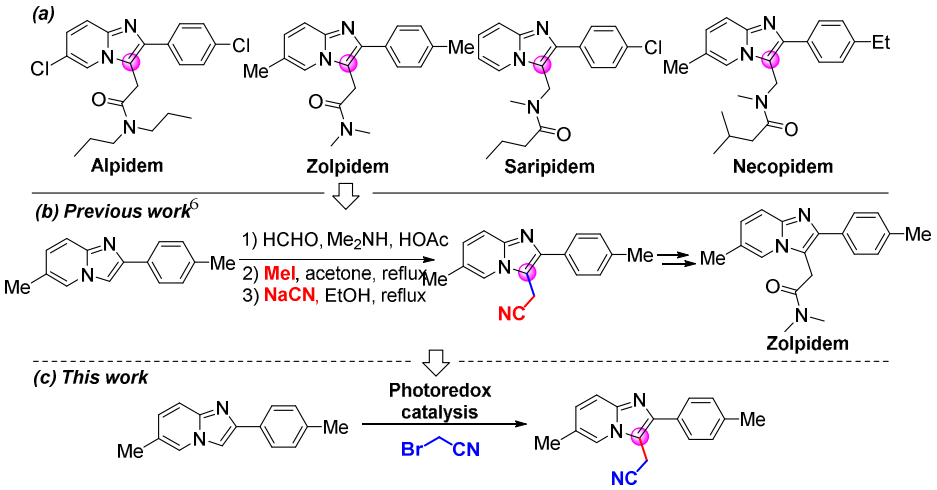
Imidazo[1,2-*a*]pyridine is considered as "drug bias" skeleton in drug discovery and has aroused great attention.[1] Imidazo[1,2-*a*]pyridines show an impressively wide range of biological activities, such as anti-inflammatory,[2] antiviral activity,[3] antiprotozoal agents,[4] inhibitors of cyclin-dependent kinases,[5] *etc*. Some marketed drugs containing imidazo[1,2-*a*]pyridine cycle and amide group are shown in Scheme 1-a, which include anxiolytic drugs alpidem, saripidem and

necopidem. The top-selling blockbuster drug zolpidem was used to treat insomnia in the imidazopyridines family. The general procedures to synthesize zolpidem involved a Mannich reaction to give *N*,*N*-dimethyl amino imidazopyridine derivative, followed by the reaction with methyl iodide to form a quaternary ammonium salt, and the nucleophilic substitution with the toxic sodium cyanide. Zolpidem was finally obtained by the hydrolysis and amination of the 3-cyanomethylated imidazo[1,2-*a*]pyridine derivative (Scheme 1-b).[6] In 2010, Gevorgyan and co-workers explored an efficient one pot copper-catalyzed three-component coupling reaction of 2-amino-5-methylpyridine, *p*-tolualdehyde and *N*,*N*-dimethylpropiolamide to access zolpidem in a glovebox.[7] *N*,*N*-Dimethyl-4-oxo-4-tolylbutanamide, MBH acetates of nitroalkenes and xanthates were also used as the substrates for the assembly of zolpidem by several groups.[8] Despite the significant advances have been made in this field, establishing more straightforward methods as well as developing environmentally friendly reaction conditions to prepare diverse imidazo[1,2-*a*]pyridine derivatives are still highly desirable.

The majority of imidazo[1,2-*a*]pyridine-based drugs feature C3 substituents, and many successful examples of the direct C3 functionalization of imidazo[1,2-*a*]pyridine are reported in recent years.[9] In our previous works, the regioselective C3-fluorination and -alkoxycarbonylation of imidazoheterocycles were successfully achieved using selectfluor and carbazates respectively.[10] As an effective means of organic synthesis, visible-light-induced organic reaction has aroused much attention in recent years since these reactions can take place under very mild reaction conditions with low photocatalyst-loadings.[11] In 2015, Hajra et al demonstrated the C3-thiocyanation of imidazoheterocycles *via* visible light photoredox catalysis using eosin Y as a photocatalyst.[12] Successively, in the report by Fu, Xu and co-workers, the 2,2,2-trifluoroethyl group was introduced in C3-position of imidazo[1,2-*a*]pyridines by using 1,1,1-trifluoro-2-iodoethane based on a similar photoredox process in the presence of *fac*-Ir(ppy)$_3$.[13] It is well known that cyano is a versatile group in organic synthesis, especially in drug synthesis since it can be converted into a variety of useful functional groups,[14] therefore the cyanation of organic compounds is continuously the attractive research subject to organic chemists. Cheap bromoacetonitrile was successfully used as a cyanomethyl radical source for the preparation of nitriles.[15] As the continuous study of our group on the synthesis of functionalized heterocyclic compounds *via* C−H bond functionalization, we now wish to report the efficient

visible-light-promoted cyanomethylation of imidazopyridines using bromoacetonitrile as the reaction partner. The products could be conveniently transformed into zolpidem, alpidem and other related compounds (Scheme 1).

Scheme 1. Examples of Imidazo[1,2-*a*]pyridine-Based Drugs and Synthetic Routes of Zolpidem

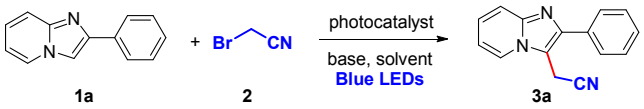


■ RESULTS AND DISCUSSION

Initially, we selected 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and bromoacetonitrile (**2**) as model substrates to test the feasibility of the cyanomethylation reaction (Table 1). Gratifyingly, the reaction indeed occurred in the presence of 2 mol % *fac*-Ir(ppy)$_3$ as the photocatalyst and 2 equiv Et_3N as a base under 5 W blue light-emitting diode (LED) bulb irradiation in CH_3CN at room temperature, and gave the cyanomethylated imidazopyridine **3a** in 70% yield (entry 1). When this reaction was performed in the absence of base, only trace amount of product was observed and most of the imidazopyridine **1a** was recovered (entry 2). Several commonly used bases, such as *N*,*N*-diisopropylethylamine (DIPEA), *N*,*N*-dicyclohexylmethylamine (Cy_2NMe), $NaHCO_3$, NaOAc were also successful for this transformation and the highest yield of 85% was obtained through the use of $NaHCO_3$ (entries 3–6). Solvent had evident influence on this cyanomethylation reaction and DMSO outperformed other solvents such as CH_3CN, DMF, H_2O and toluene to give the best result (entries 5, 7−10). A series of photocatalysts were then screened, and the results

revealed that $Ru(bpy)_3Cl_2·6H_2O$ only gave the product in 11% yield, while organic photocatalyst such as eosin Y and rhodamine B did not showed any catalytic activity to this reaction (entries 11-13). In addition, no desired product was observed with the control experiments lacking either the photocatalyst or visible light irradiation (entries 14, 15). The formation of product **3a** drastically decreased when the reaction was performed under air instead of argon (entry 16). It should be noted that the use of iodoacetonitrile instead of bromoacetonitrile delivered the product in a comparable yield (entry 17). The highest yield was achieved when 4 equiv bromoacetonitrile was used. Reduced it to 3 equiv led to a lower yield of 68% (entry 18).

Table 1. Optimization of Reaction Conditions[a]



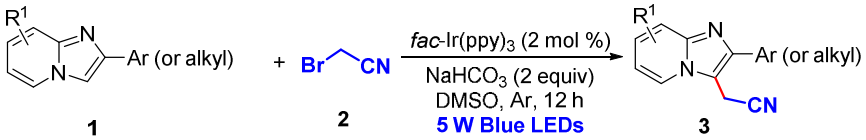
1a 2 3a

entry	photocatalyst	base	solvent	yield (%)
1	*fac*-Ir(ppy)$_3$	NEt_3	MeCN	70
2	*fac*-Ir(ppy)$_3$	–	MeCN	trace
3	*fac*-Ir(ppy)$_3$	DIPEA	MeCN	65
4	*fac*-Ir(ppy)$_3$	Cy_2NMe	MeCN	82
5	*fac*-Ir(ppy)$_3$	$NaHCO_3$	MeCN	85
6	*fac*-Ir(ppy)$_3$	NaOAc	MeCN	81
7	***fac*-Ir(ppy)$_3$**	**$NaHCO_3$**	**DMSO**	**87**
8	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMF	65
9	*fac*-Ir(ppy)$_3$	$NaHCO_3$	H_2O	54
10	*fac*-Ir(ppy)$_3$	$NaHCO_3$	toluene	50
11	$Ru(bpy)_3Cl_2·6H_2O$	$NaHCO_3$	DMSO	11
12	eosin Y	$NaHCO_3$	DMSO	trace
13	rhodamine B	$NaHCO_3$	DMSO	0
14	–	$NaHCO_3$	DMSO	0
15[b]	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMSO	0
16[c]	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMSO	12
17[d]	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMSO	86
18[e]	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMSO	68

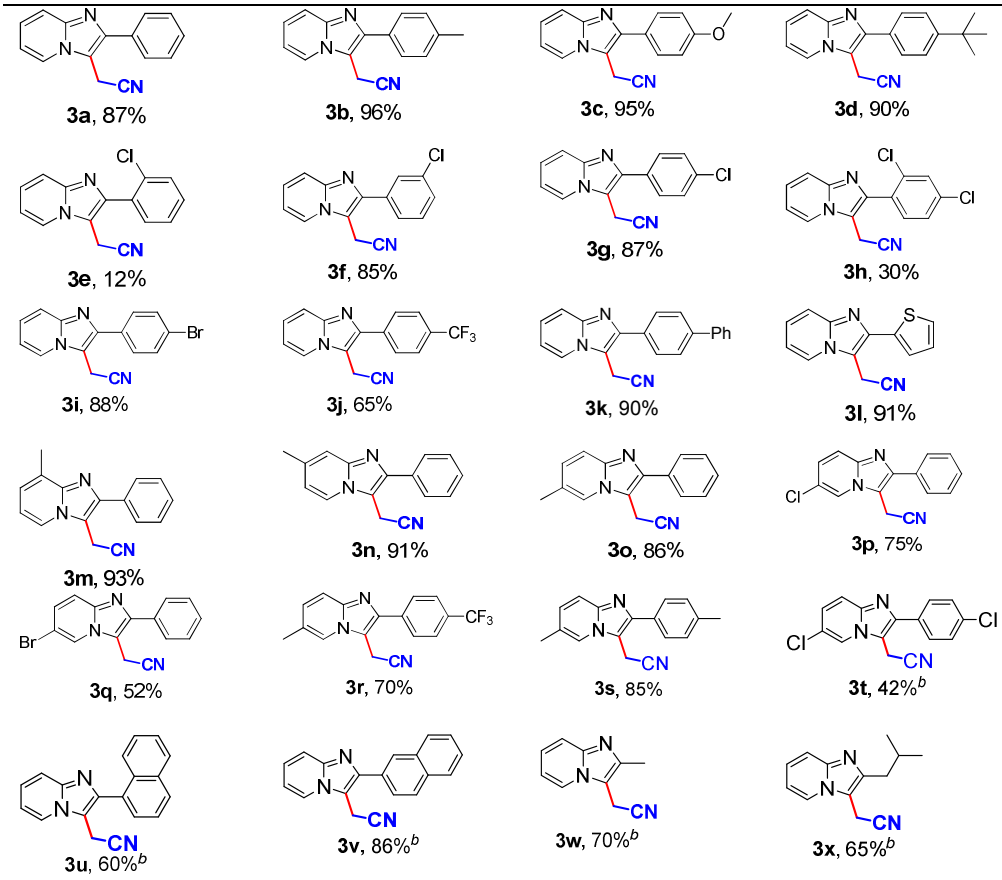
[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), **2** (0.8 mmol), base (0.4 mmol), photocatalyst (2 mol %) and solvent (2 mL) were carried out in a sealed tube under Ar atmosphere upon irradiation of 5 W blue LEDs for 12 h. [b]In the dark. [c]Under air. [d]Iodoacetonitrile was used instead of bromoacetonitrile. [e]Reduced the amount of **2** to 0.6 mmol (3 equiv).

With the optimized conditions in hand, we next investigated the generality and scope of the reaction with a series of imidazopyridines (Table 2). 2-Aryl substituted imidazopyridines were firstly examined. Electron-donating groups such as methyl, methoxyl and *tert*-butyl on the benzene ring were tolerated and the reactions selectively gave the desired products in excellent yields (**3b**−**3d**). Substrates bearing electron withdrawing groups Cl or Br on the *para*- or *meta*-position of the benzene ring also gave high yields (**3f**, **3g** and **3i**), whereas *ortho*-Cl seemed not suitable to the reaction well and lower yields were obtained (**3e** and **3h**). The presence of strong electron-withdrawing substituent CF_3 lowered the yield to 65% (**3j**). The reaction of imidazopyridine with biphenyl or thienyl on 2-position also proceeded smoothly and gave high yields (**3k** and **3l**). The substrates with various substituents on pyridine ring were then employed. The methyl at different position on the pyridine ring of imidazopyridines had no evident effect on the reaction and the corresponding cyanomethylated products were obtained in good yields (**3m**–**3o**, **3s**). The existence of Cl or Br group on the pyridine ring reduced the reactivity of the substrates, and the reaction provided moderate yields (**3p**, **3q** and **3t**). Notablely, for 2-α-naphthyl substituted reactant, a very low yield (less than 20%) was obtained probably due to steric hindrance. To improve the yields for some substrates, iodoacetonitrile was used instead of bromoacetonitrile. With α- and β-naphthyl substituted imidazopyridines, 60% and 86% yields were obtained respectively (**3u** and **3v**). In addition, the reaction of 2-alkyl substituted imidazopyridines could react with iodoacetonitrile to give the corresponding 3-cyanomethylated products in satisfactory yields (**3w** and **3x**).

Table 2. Visible-Light-Induced Synthesis of Cyanomethylated Imidazopyridines[a]



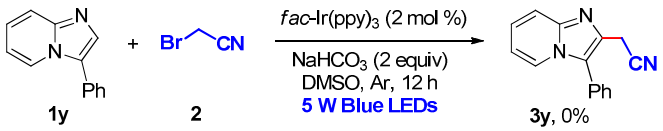
1 **2** **3**



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), *fac*-Ir(ppy)$_3$ (2 mol %), $NaHCO_3$ (0.4 mmol), DMSO (2 mL), irradiation under Ar atmosphere at room temperature using 5 W blue LEDs for 12 h. All yields are isolated ones. [b]Iodoacetonitrile was used instead of bromoacetonitrile.

It was interesting that for a 3-position substituted reactant 3-phenylimidazo[1,2-*a*]pyridine (**1y**), no 2-cyanomethylated product was generated under the standard conditions. This result illustrated that the reaction regioselectively took place at 3-position (Scheme 2).

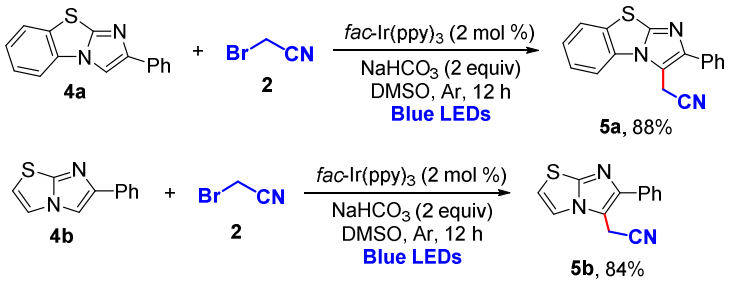
Scheme 2. Regioselectivity of Cyanomethylation Reaction



Furthermore, the visible-light-induced cyanomethylation reaction could also regioselectively occur on imidazo ring for other imidazoheterocycles substrates such as

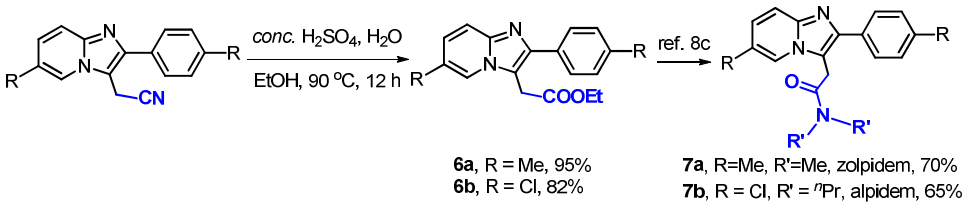
2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (**4a**) and 6-phenylimidazo[2,1-*b*]thiazole (**4b**), which provided the cyanomethylated products in 88% and 84% yields (**5a** and **5b**) respectively under the same reaction conditions (Scheme 3).

Scheme 3. Regioselective Cyanomethylation of Imidazoheterocycles



We then decided to use this convenient cyanomethylation in the synthesis of some drugs. The 3-cyanomethylated derivative **3s** or **3t** was treated with concentrated sulfuric acid in EtOH to give the corresponding ester (**6**). Zolpidem (**7a**) and alpidem (**7b**) were then obtained by the hydrolysis of imidazopyridine esters and subsequent amidation (Scheme 4).[8c]

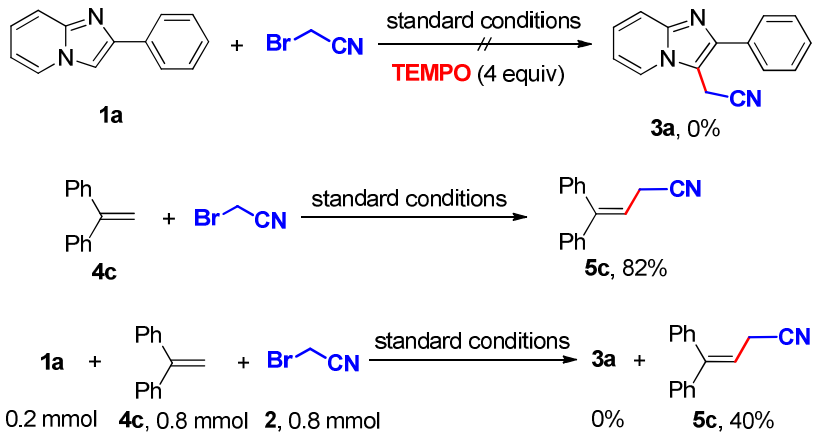
Scheme 4. Synthesis of Zolpidem and Alpidem



The control experiments were performed to study the mechanism of this visible light-promoted cyanomethylation of imidazopyridines (Scheme 5). The results showed that this visible-light-promoted cyanomethylation reaction was obviously suppressed upon addition of a radical scavenge 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and the substrate **1a** was recovered, which suggested that the reaction probably proceeded *via* a radical pathway. To further verify the presence of the radical in this transformation, another radical scavenge 1,1-diphenylethene (**4c**) was used to trap the cyanomethyl radical. As that was expected, the

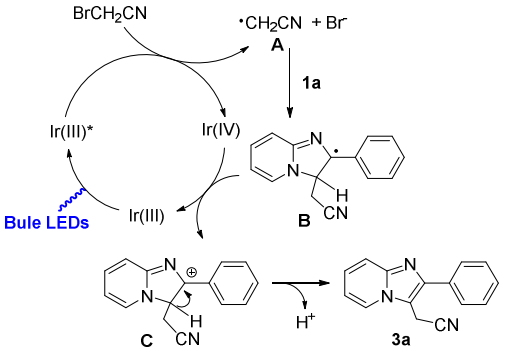
formation of product **3a** was suppressed, and the coupling product 4,4-diphenylbut-3-enenitrile (**5c**) was obtained.

Scheme 5. Control Experiments



Based on the above results and related reports,[13] a possible mechanism for the visible-light photoredox cyanomethylation reaction is proposed in Scheme 6. Initially, the *fac*-Ir(III)$(ppy)_3$ was converted to the excited state upon the irradiation of visible light (blue LEDs). The formation of cyanomethyl radical **A** and [*fac*-Ir(IV)$(ppy)_3$]$^+$ was established by the single electron transfer (SET) from the excited Ir^{III}-photocatalyst to bromoacetonitrile.[15] The regioselective addition of the electron-deficient radical **A** to the electron-rich position of imidazopyridine **1a** furnished the radical **B**, which was oxidized by the [*fac*-Ir(IV)$(ppy)_3$]$^+$ to generate the carbocation **C** *via* another SET process and regenerate the Ir^{III}-photocatalyst. Finally, the deprotonation of **C** with the aid of a base produced the desired product **3a**.

Scheme 6. Proposed Reaction Mechanism



■ CONCLUSIONS

In summary, we have successfully explored a regioselective cyanomethylation reaction of imidazopyridines using available bromoacetonitrile or iodoacetonitrile as the cyanomethyl source under visible light photoredox catalysis. Both electron-donating and electron-withdrawing groups on the imidazopyridines are tolerated in the reaction and the corresponding products were obtained in moderate to excellent yields. This new protocol features short synthetic route, low cost and mild reaction conditions, which makes it attractive for the synthesis of the drug zolpidem and alpidem, as well as other related compounds.

■ EXPERIMENTAL SECTION

General. Chemicals were commercially available and were used without purification. Imidazo[1,2-*a*]pyridines were prepared according to the literature procedures.[16] The NMR spectra were recorded at 400 MHz (^{1}H), 100 MHz (^{13}C NMR) and 376 MHz (^{19}F) in $CDCl_3$ or d_6-DMSO using TMS as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, td = triplet of doublet, q = quartet, m = multiplet. Q-TOF was used for the HRMS measurements. Melting points are uncorrected.

General Experimental Procedure for Cyanomethylation Reaction.

An oven-dried Schlenk tube (25 mL) was equipped with a magnetic stir bar and charged with 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 38.8 mg, 0.2 mmol), bromoacetonitrile (96.0 mg, 55.7 μL, 0.8 mmol), *fac*-Ir(ppy)$_3$ (2 mol %, 2.6 mg) and $NaHCO_3$ (33.6 mg, 0.4 mmol). The flask was evacuated and backfilled with argon for 3 times, DMSO (2 mL) was then added. The mixture was

stirred under 5 W blue LEDs strip irradiation for 12 h. When the reaction was completed, the mixture was diluted with water (10 mL) and extracted with DCM (15 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by silica gel chromatography using petroleum ether/EtOAc (2:1, v/v) as eluent to afford the pure product **3a**.

2-(2-Phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3a**).[17] Colorless solid (40.6 mg, 87% yield); mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (dt, J = 6.9, 1.1 Hz, 1H), 7.75–7.68 (m, 3H), 7.55–7.49 (m, 2H), 7.47–7.41 (m, 1H), 7.33 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 7.00 (td, J = 6.8, 1.1 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 145.1, 133.1, 129.0, 128.6, 128.6, 125.4, 122.9, 118.0, 115.0, 113.4, 107.8, 13.9.

2-(2-(p-Tolyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3b**).[17] Colorless solid (47.5 mg, 96% yield); mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.37–7.30 (m, 3H), 7.00 (td, J = 6.8, 1.0 Hz, 1H), 4.16 (s, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.3, 145.2, 138.5, 130.2, 129.7, 128.4, 125.3, 122.9, 117.9, 115.1, 113.3, 107.5, 21.4, 14.0.

2-(2-(4-Methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3c**).[17] Colorless solid (50.0 mg, 95% yield); mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 9.1 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.37–7.32 (m, 1H), 7.07–6.99 (m, 3H), 4.16 (s, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 160.0, 145.3, 145.0, 129.8, 125.5, 125.3, 122.8, 117.8, 115.0, 114.5, 113.3, 107.2, 55.4, 14.0.

2-(2-(4-(tert-Butyl)phenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3d**). Colorless solid (52.1 mg, 90% yield); mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.67–7.64 (m, 2H), 7.56–7.54 (m, 2H), 7.33–7.29 (m, 1H), 6.98 (td, J = 6.8, 1.1 Hz, 1H), 4.17 (s, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 151.7, 145.4, 145.2, 130.2, 128.2, 126.0, 125.2, 122.9, 117.9, 115.1, 113.3, 107.6, 34.7, 31.3, 14.0; HRMS (ESI) m/z: calcd for $C_{19}H_{20}N_3$ $[M + H]^+$ 290.1652, found 290.1650.

2-(2-(2-Chlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3e**). Yellow solid (6.4 mg, 12% yield); mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12 (d, J = 6.9 Hz, 1H), 7.73 (d, J = 9.1 Hz, 1H), 7.63–7.57 (m, 1H), 7.55–7.49 (m, 1H), 7.44–7.32 (m, 3H), 7.03 (td, J = 6.8, 1.0 Hz, 1H), 4.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 142.5, 133.2, 132.7, 132.1, 130.3,

129.9, 127.2, 125.4, 123.1, 118.2, 114.7, 113.6, 109.6, 14.3; HRMS (ESI) m/z: calcd for $C_{15}H_{11}ClN_3$ $[M + H]^+$ 268.0636 and 270.0607, found 268.0637 and 270.0606.

2-(2-(3-Chlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3f**). Colorless solid (45.5 mg, 85% yield); mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (dd, J = 6.8, 1.0 Hz, 1H), 7.71–7.68 (m, 2H), 7.53 (dd, J = 7.3, 1.5 Hz, 1H), 7.44–7.31 (m, 3H), 7.02–6.98 (m, 1H), 4.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 143.6, 135.0, 134.9, 130.2, 128.6, 128.6, 126.5, 125.8, 123.0, 118.0, 114.8, 113.7, 108.2, 13.9; HRMS (ESI) m/z: calcd for $C_{15}H_{11}ClN_3$ $[M + H]^+$ 268.0636 and 270.0607, found 268.0636 and 270.0606.

2-(2-(4-Chlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3g**).[17] Yellow solid (46.6 mg, 87% yield); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (d, J = 6.9 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.40–7.33 (m, 1H), 7.03 (td, J = 6.8, 0.6 Hz, 1H), 4.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 144.0, 134.7, 131.6, 129.7, 129.2, 125.7, 122.9, 118.0, 114.8, 113.7, 107.9, 13.9.

2-(2-(2,4-Dichlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3h**). Brown solid (18.1 mg, 30% yield); mp 217−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (d, J = 6.9 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.57–7.56 (m, 2H), 7.43–7.37 (m, 2H), 7.08 (td, J = 6.8, 0.8 Hz, 1H), 3.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 141.4, 135.7, 133.9, 133.5, 130.6, 129.7, 127.6, 125.7, 123.0, 118.3, 114.4, 113.8, 109.7, 14.3; HRMS (ESI) m/z: calcd for $C_{15}H_{10}Cl_2N_3$ $[M + H]^+$ 302.0246 and 304.0217, found 302.0246 and 304.0222.

2-(2-(4-Bromophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3i**). Colorless solid (54.9 mg, 88% yield); mp 128–130 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 8.58 (d, J = 6.9 Hz, 1H), 7.78–7.75 (m, 2H), 7.74–7.68 (m, 3H), 7.43–7.38 (m, 1H), 7.12 (td, J = 6.8, 1.2 Hz, 1H), 4.65 (s, 2H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ (ppm) 144.9, 142.2, 133.1, 132.2, 130.4, 126.2, 125.1, 121.9, 117.5, 117.2, 113.5, 110.3, 13.6; HRMS (ESI) m/z: calcd for $C_{15}H_{11}BrN_3$ $[M + H]^+$ 312.0131 and 314.0110, found 312.0131 and 314.0109.

2-(2-(4-(Trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3j**). Yellow solid (39.2 mg, 65% yield); mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09 (d, J = 6.9 Hz, 1H), 7.84–7.73 (m, 5H), 7.38 (ddd, J = 9.0, 6.8, 1.0 Hz, 1H), 7.04 (td, J = 6.8, 1.0 Hz, 1H), 4.18 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.6, 143.6, 136.7, 130.4 (q, $^2J_{C\text{-}F}$ = 32.5), 128.8, 126.0 (q, $^3J_{C\text{-}F}$ = 3.7), 125.9, 124.0 (q, $^1J_{C\text{-}F}$ = 270.5), 123.0, 118.2, 114.7, 113.9, 108.6, 13.9; ^{19}F NMR

(376 MHz, $CDCl_3$): δ (ppm) -62.5; HRMS (ESI) m/z: calcd for $C_{16}H_{11}F_3N_3$ $[M + H]^+$ 302.0900, found 302.0899.

2-(2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3k**). Yellow solid (55.7 mg, 90% yield); mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, J = 6.8 Hz, 1H), 7.77 (ddd, J = 11.3, 8.8, 3.5 Hz, 5H), 7.71–7.64 (m, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.44–7.31 (m, 2H), 7.00 (td, J = 6.8, 0.9 Hz, 1H), 4.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.5, 144.7, 141.3, 140.3, 132.0, 128.9, 128.9, 127.7, 127.1, 125.5, 122.9, 118.0, 115.1, 113.5, 107.8, 14.0; HRMS (ESI) m/z: calcd for $C_{21}H_{16}N_3$ $[M + H]^+$ 310.1339, found 310.1338.

2-(2-(Thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3l**). Yellow solid (43.6 mg, 91% yield); mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.48–7.42 (m, 2H), 7.36–7.31 (m, 1H), 7.20 (dd, J = 5.2, 3.6 Hz, 1H), 7.01 (td, J = 6.8, 0.8 Hz, 1H), 4.27 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.4, 139.3, 135.7, 128.0, 126.8, 125.8, 125.7, 122.8, 117.9, 114.6, 113.6, 107.1, 13.8; HRMS (ESI) m/z: calcd for $C_{13}H_{10}N_3S$ $[M + H]^+$ 240.0590, found 240.0590.

2-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3m**). Colorless solid (46.0 mg, 93% yield); mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, J = 6.8 Hz, 1H), 7.72–7.70 (m, 2H), 7.54–7.50 (m, 2H), 7.45–7.42 (m, 1H), 7.13 (d, J = 6.9 Hz, 1H), 6.92 (t, J = 6.8 Hz, 1H), 4.14 (s, 2H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.9, 144.7, 133.4, 129.0, 128.7, 128.4, 128.2, 124.1, 120.7, 115.2, 113.4, 108.1, 17.1, 14.0; HRMS (ESI) m/z: calcd for $C_{16}H_{14}N_3$ $[M + H]^+$ 248.1182, found 248.1182.

2-(7-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3n**). Gray solid (45.0 mg, 91% yield); mp 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 6.9 Hz, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.52–7.40 (m, 4H), 6.82 (dd, J = 6.8, 1.2 Hz, 1H), 4.13 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.9, 144.8, 136.5, 133.3, 128.9, 128.5, 128.4, 122.1, 116.4, 116.0, 115.2, 107.1, 21.4, 13.9; HRMS (ESI) m/z: calcd for $C_{16}H_{14}N_3$ $[M + H]^+$ 248.1182, found 248.1182.

2-(6-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3o**).[17] Colorless solid (42.5 mg, 86% yield); mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.68–7.59 (m, 3H), 7.50–7.42 (m, 3H), 7.17 (d, J = 8.0 Hz, 1H), 4.13 (s, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.7, 144.4, 134.4, 133.1, 129.0, 128.7, 128.5, 123.4, 120.6, 117.2, 115.2, 107.5,

18.4, 14.0.

2-(6-Chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3p**).[17] Colorless solid (40.2 mg, 75% yield); mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12 (d, J = 1.1 Hz, 1H), 7.71–7.67 (m, 3H), 7.56–7.51 (m, 2H), 7.49–7.44 (m, 1H), 7.31 (dd, J = 9.5, 1.9 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 146.0, 143.7, 132.6, 129.1, 128.9, 128.8, 128.5, 126.9, 121.8, 120.8, 118.4, 114.6, 108.4, 13.9.

2-(6-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3q**). Colorless solid (32.5 mg, 52% yield); mp 185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.22 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.41 (dd, J = 9.6, 1.6 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.9, 143.9, 132.6, 129.1, 129.0, 128.9, 128.5, 123.0, 118.7, 114.6, 108.3, 108.2, 13.9; HRMS (ESI) m/z: calcd for $C_{15}H_{11}BrN_3$ $[M + H]^+$ 312.0131 and 314.0110, found 312.0131 and 314.0108.

2-(6-Methyl-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3r**). Colorless solid (44.1 mg, 70% yield); mp 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85–7.82 (m, 3H), 7.77 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 9.2 Hz, 1H), 7.23 (dd, J = 9.2, 1.2 Hz, 1H), 4.15 (s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.6, 143.3, 136.9, 130.3 (q, $^2J_{C\text{-}F}$ = 32.4), 129.1, 128.7, 125.9 (q, $^3J_{C\text{-}F}$ = 3.7), 124.1 (q, $^1J_{C\text{-}F}$ = 270.5), 123.8, 120.6, 117.5, 114.8, 108.1, 18.5, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) -62.5; HRMS (ESI) m/z: calcd for $C_{17}H_{13}F_3N_3$ $[M + H]^+$ 316.1056, found 316.1057.

2-(6-Methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3s**).[17] Colorless solid (44.4 mg, 85% yield); mp 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (s, 1H), 7.62 (d, J = 9.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 9.2 Hz, 1H), 4.15 (s, 2H), 2.44 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.5, 144.2, 138.5, 129.9, 129.7, 128.8, 128.4, 123.5, 120.6, 117.0, 115.1, 107.3, 21.3, 18.5, 14.0.

2-(6-Chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3t**).[17] Colorless solid (25.4 mg, 42% yield); mp 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13 (s, 1H), 7.70 (d, J = 9.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.35 (dd, J = 9.6, 1.6 Hz, 1H), 4.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.0, 143.9, 135.0, 131.1, 129.7, 129.4, 127.2, 122.1, 120.8, 118.5, 114.4, 108.5, 13.9.

2-(2-(Naphthalen-1-yl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3u**). Brown solid (34.0 mg, 60%

yield); mp 75–77 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 8.64 (d, J = 6.8 Hz, 1H), 8.05 (t, J = 9.2 Hz, 3H), 7.78 (d, J = 8.8 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.60–7.57 (m, 2H), 7.54–7.46 (m, 2H), 7.20 (td, J = 6.8, 1.2 Hz, 1H), 4.39 (s, 2H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ (ppm) 144.6, 143.0, 133.9, 132.1, 130.7, 129.3, 128.7, 128.7, 126.9, 126.6, 126.4, 126.3, 125.9, 125.3, 117.4, 117.0, 113.6, 112.1, 13.5; HRMS (ESI) m/z: calcd for $C_{19}H_{14}N_3$ $[M + H]^+$ 284.1182, found 284.1182.

2-(2-(Naphthalen-2-yl)imidazo[1,2-a]pyridin-3-yl)acetonitrile (**3v**). Colorless solid (48.7 mg, 86% yield); mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (s, 1H), 8.06 (d, J = 6.8 Hz, 1H), 8.00–7.94 (m, 2H), 7.91–7.84 (m, 2H), 7.76 (d, J = 9.2 Hz, 1H), 7.57–7.53 (m, 2H), 7.36–7.32 (m, 1H), 7.00 (td, J = 6.8, 1.2 Hz, 1H), 4.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.5, 145.1, 133.4, 133.1, 130.5, 128.8, 128.3, 127.8, 127.7, 126.6, 126.6, 126.1, 125.5, 122.9, 118.0, 115.1, 113.5, 108.1, 14.0; HRMS (ESI) m/z: calcd for $C_{19}H_{14}N_3$ $[M + H]^+$ 284.1182, found 284.1186.

2-(2-Methylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3w**).[18] Brown solid (24.0 mg, 70% yield); mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.30–7.26 (m, 1H), 6.95 (td, J = 6.8, 0.8 Hz, 1H), 4.00 (s, 2H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.0, 141.8, 124.8, 122.5, 117.2, 114.7, 112.9, 107.7, 13.3, 12.9.

2-(2-Isobutylimidazo[1,2-a]pyridin-3-yl)acetonitrile (**3x**). Yellow liquid (27.7 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.28–7.23 (m, 1H), 6.93 (t, J = 6.8 Hz, 1H), 3.99 (s, 2H), 2.62 (d, J = 7.2 Hz, 2H), 2.20–2.10 (m, 1H), 0.96 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 145.3, 145.1, 124.8, 122.6, 117.3, 114.8, 112.9, 108.2, 36.7, 29.3, 22.5, 13.0; HRMS (ESI) m/z: calcd for $C_{13}H_{16}N_3$ $[M + H]^+$ 214.1339, found 214.1335.

2-(2-Phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)acetonitrile (**5a**).[19] Colorless solid (50.9 mg, 88% yield); mp 189–190 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 8.15 (d, J = 8.0 Hz, 1H), 8.09 (dd, J = 8.0, 0.8 Hz, 1H), 7.70–7.68 (m, 2H), 7.64–7.60 (m, 1H), 7.54–7.46 (m, 3H), 7.44–7.39 (m, 1H), 4.74 (s, 2H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ (ppm) 147.9, 145.1, 133.4, 132.5, 129.8, 129.3, 128.3, 128.1, 127.2, 125.7, 125.6, 117.7, 114.2, 114.1, 15.2.

2-(6-Phenylimidazo[2,1-b]thiazol-5-yl)acetonitrile (**5b**).[20] Yellow solid (40.2 mg, 84% yield); mp 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (d, J = 7.4 Hz, 2H), 7.54–7.45 (m, 3H),

7.39 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 4.5 Hz, 1H), 4.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 150.0, 146.0, 133.2, 129.0, 128.2, 127.8, 116.8, 115.4, 113.8, 109.5, 14.7.

4,4-Diphenylbut-3-enenitrile (**5c**).[21] (1,1-Diphenylethene (**4c**) was added to the reaction mixture) Yellow solid (35.9 mg, 82% yield); mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48–7.38 (m, 3H), 7.36–7.30 (m, 3H), 7.28–7.18 (m, 4H), 6.06 (t, J = 7.4 Hz, 1H), 3.18 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 147.5, 140.7, 138.0, 129.4, 128.8, 128.4, 128.2, 128.2, 127.5, 118.2, 115.5, 18.4.

Procedure for the Hydrolysis of 3s or 3t.

To a 25 mL flask were sequentially added EtOH (4 mL), *conc.* H_2SO_4 (1.5 mL), 4 drops of H_2O and 2-(6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)acetonitrile (**3s**, 130.7 mg, 0.5 mmol). The reaction mixture was refluxed at 90 ^{o}C for 12h. After cooling to room temperature, the reaction mixture was quenched with *sat.* $NaHCO_3$ aq. to wipe off excessive acid and extracted with DCM (15 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography using hexane/EtOAc (2:1, v/v) as eluent to afford the product **6a**.

Ethyl 2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetate (**6a**).[8c] Colorless solid (146.3 mg, 95% yield); mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 9.2 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.04 (s, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.6, 144.4, 144.0, 137.6, 131.3, 129.3, 128.4, 127.6, 122.0, 121.3, 116.8, 112.4, 61.6, 30.9, 21.3, 18.5, 14.2.

Ethyl 2-(6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)acetate (**6b**).[8c] Colorless solid (142.7 mg, 82% yield); mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.26 (s, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 9.3 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 9.2 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.03 (s, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 168.7, 143.3, 142.8, 134.8, 129.9, 129.2, 127.2, 122.0, 121.6, 117.6, 113.9, 62.1, 30.7, 14.2.

Zolpidem and alpidem were synthesized according to the procedure of Namboothiri and co-workers.[8c]

N,N-Dimethyl-2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamide (**7a**, zolpidem).[7, 8c] Colorless solid (43.0 mg, 70% yield); mp 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96

(s, 1H), 7.53 (dd, J = 8.6, 4.0 Hz, 3H), 7.25 (d, J = 7.9 Hz, 2H), 7.05 (dd, J = 9.1, 0.8 Hz, 1H), 4.06 (s, 2H), 2.94 (s, 3H), 2.90 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 168.2, 143.7, 143.2, 137.6, 131.2, 129.3, 128.3, 127.9, 122.2, 122.0, 116.2, 113.8, 37.5, 35.8, 30.1, 21.3, 18.4.

2-(6-Chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-dipropylacetamide (**7b**, alpidem).[8c] Colorless solid (52.6 mg, 65% yield); mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.27 (d, J = 1.2 Hz, 1H), 7.63–7.57 (m, 3H), 7.48–7.43 (m, 2H), 7.20 (dd, J = 9.5, 1.9 Hz, 1H), 4.07 (s, 2H), 3.35–3.29 (m, 2H), 3.19–3.13 (m, 2H), 1.62–1.47 (m, 4H), 0.88 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 167.2, 143.5, 143.4, 134.2, 132.4, 129.8, 129.0, 126.2, 122.6, 120.7, 117.6, 115.6, 49.9, 48.0, 30.0, 22.2, 20.9, 11.3, 11.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra for all products (PDF).

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Notes

The authors declare no competing financial interest.

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