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Ultrasound-Promoted and Base-Mediated Regioselective Bromination of Imidazo[1,2-*a*]pyridines with Pyridinium Tribromide

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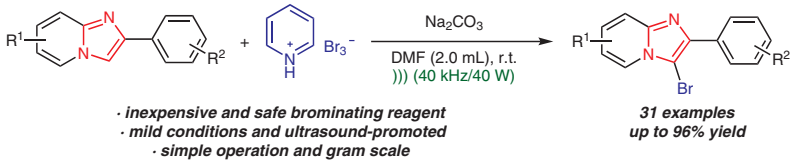

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Abstract By using pyridinium tribromide as the bromo source, an efficient and practical protocol for the synthesis of C3-brominated imidazo[1,2-*a*]pyridines through ultrasound-promoted and Na_2CO_3-mediated regioselective bromination of imidazo[1,2-*a*]pyridines has been developed. This method effectively avoids the use of metal catalysts and harsh reaction conditions, and shows attractive characteristics such as operational simplicity, broad substrate scope with good to excellent yields, ease of scale-up and high energy efficiency.

Key words bromination, pyridinium tribromide, metal-free synthesis, regioselectivity, imidazopyridines, ultrasonic irradiation, base mediated

Imidazo[1,2-*a*]pyridines have been recognized as a class of privileged heterocyclic scaffolds and are widely applied in the organic synthesis, biological and pharmaceutical fields.[1] In particular, C3-brominated imidazo[1,2-*a*]pyridines have been commonly applied as the important skeletons or precursors for artificial alpidem, zolpidem, necopidem, saripidem and GSK812397, thus attracting tremendous attention over the past decades (Figure 1).[2] Traditional methods for the synthesis of C3-brominated imidazo[1,2-*a*]pyridines constitute oxidative reactions of alkynes with 2-aminopyridines or enamides with pyridines, and tandem cyclization/bromination between 2-bromoacetophenones and 2-aminopyridines.[3] Recently, substantial efforts toward the regioselective synthesis of imidazo[1,2-*a*]pyridines have been mainly focused on the C3 position, using arylation,[4] alkenylation,[5] carbonylation,[6] sulfenylation[7] and so on.[8] Thus, direct CH bond activation of imidazo[1,2-*a*]pyridines and then bromination is a straightforward strategy to synthesize C3-brominated imidazo[1,2-*a*]pyridines.[9] Although these methodologies are highly demanded for the regioselective synthesis of C3-brominated imidazo[1,2-*a*]pyridines, most of them suffer from some limitations such as limited substrate scope, involvement of transition metals, and stoichiometric oxidants, as well as high reaction temperature along with the use of hazardous and corrosive and toxic Br_2 as bromination reagent. Therefore, the development of novel, general and efficient synthetic methods to brominate imidazo[1,2-*a*]pyridines is of great interest.

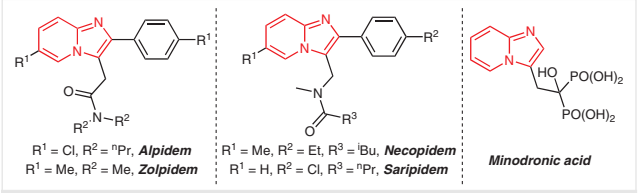

Figure 1 Biologically active imidazo[1,2-*a*]pyridines

Here, we evaluate the commercially available and inexpensive pyridinium tribromide as bromination reagent for the synthesis of a series of imidazo[1,2-*a*]pyridine derivatives. Pyridinium tribromide is a red solid that can be weighed in air and easily handled. In recent years, pyridinium tribromide has been utilized in brominations of indoles, purines and other aryl compounds.[10] To the best of our

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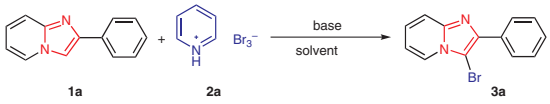
knowledge, there are no reports so far on the bromination of imidazo[1,2-*a*]pyridines using pyridinium tribromide as the bromo source under eco-friendly reaction conditions.

Ultrasound-accelerated organic reactions have drawn an increasing attention in recent years.[11] Compared with traditional mechanical agitation, ultrasonic irradiation has the advantages of elevated reaction rate, low reaction temperature, reduced energy consumption, minimized side reactions, and enhanced selectivity and yield. In light of the above-mentioned points and also in continuation of our ongoing research in green organic synthesis,[12] we now report for the first time the ultrasound-promoted and Na_2CO_3-mediated bromination of imidazo[1,2-*a*]pyridines using pyridinium tribromide as the bromo source, which afforded the corresponding C3-brominated imidazo[1,2-*a*]pyridines in good yields.

Initially, we conducted the bromination of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) using pyridinium tribromide as the bromination reagent in the presence of base (Na_2CO_3) at room temperature, and a 50% yield of 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**3a**) was achieved after 12 hours (Table 1, entry 1). Under the same conditions, the reaction was also carried out in alternative solvents, other than acetonitrile, including toluene, DMSO, DMF, DCM, THF and EtOAc (entries 2–7); the best result was obtained with DMF as the solvent. Further investigation indicated that the employment of other inorganic bases (K_2CO_3, $NaHCO_3$) or organic bases (Et_3N, DBU) produced **3a** in slightly lower yields (entries 8–11). In addition, no higher yield was gained by increasing the temperature or time (entry 12). It was found that conventional stirring was not ideal to improve the efficiency of this chemical process. By employing Na_2CO_3 as the base and DMF as the solvent, the bromination reaction was further optimized under ultrasonic irradiation, beginning at 25 °C. To our delight, ultrasonic irradiation (40 kHz/40 W) employed under the same reaction parameters for 30 minutes resulted in a 95% yield of **3a** (entry 13). This preferable result may be attributed to the cavitation effect of ultrasonic irradiation. Subsequent evaluation of the effect of ultrasonic power and frequency revealed that the reaction is sensitive to the ultrasonic irradiation energy (entries 14–17), and 40 kHz/40 W was the appropriate energy for this bromination reaction. No reaction took place without Na_2CO_3, suggesting that base is essential

Table 1 Optimization of the Reaction Conditions[a]



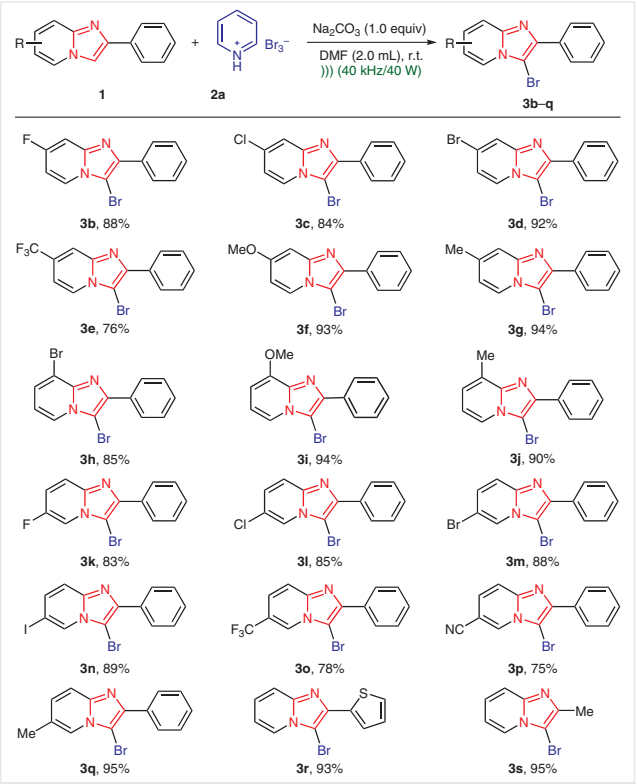
1a 2a 3a

Entry	Base (equiv)	Solvent (mL)	Conditions	Yield (%)[b]
1	Na_2CO_3 (1)	CH_3CN (2)	stirring, r.t., 12 h	50
2	Na_2CO_3 (1)	toluene (2)	stirring, r.t., 12 h	n.r.
3	Na_2CO_3 (1)	DMSO (2)	stirring, r.t., 12 h	67
4	Na_2CO_3 (1)	DMF (2)	stirring, r.t., 12 h	80
5	Na_2CO_3 (1)	DCM (2)	stirring, r.t., 12 h	65
6	Na_2CO_3 (1)	THF (2)	stirring, r.t., 12 h	73
7	Na_2CO_3 (1)	EtOAc (2)	stirring, r.t., 12 h	65
8	K_2CO_3 (1)	DMF (2)	stirring, r.t., 12 h	75
9	$NaHCO_3$ (1)	DMF (2)	stirring, r.t., 12 h	78
10	Et_3N (1)	DMF (2)	stirring, r.t., 12 h	67
11	DBU (1)	DMF (2)	stirring, r.t., 12 h	70
12	Na_2CO_3 (1)	DMF (2)	stirring, 43 °C, 24 h	80
13	**Na_2CO_3 (1)**	**DMF (2)**	**US (40 KHz/40 W), 25–43 °C, 30 min**	**95**
14	Na_2CO_3 (1)	DMF (2)	US (40 KHz/50 W), 25–51 °C, 30 min	95
15	Na_2CO_3 (1)	DMF (2)	US (40 KHz/30 W), 25–38 °C, 30 min	90
16	Na_2CO_3 (1)	DMF (2)	US (28 KHz/40 W), 25–43 °C, 30 min	76
17	Na_2CO_3 (1)	DMF (2)	US (68 KHz/40 W), 25–43 °C, 30 min	87
18	–	DMF (2)	US (40 KHz/40 W), 25–43 °C, 30 min	n.r.
19	Na_2CO_3 (1)	DMF (2)	stirring, r.t., 30 min	18

[a] Reaction conditions, unless otherwise specified: **1a** (0.2 mmol), **2a** (0.2 mmol), base (0.2 mmol), solvent (2.0 mL), in a Schlenk tube, r.t.; US = ultrasound irradiation.
[b] Isolated yield.

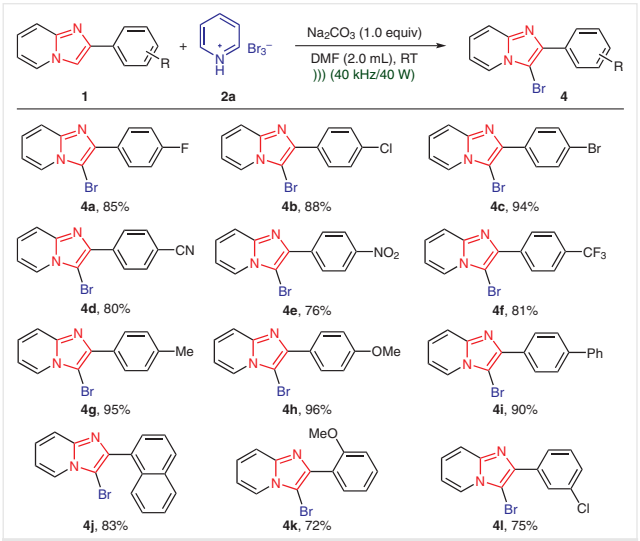
for this conversion (entry 18). Moreover, **3a** was obtained in 18% yield when ultrasonic irradiation was replaced by stirring at room temperature for 30 minutes (entry 19).

With optimal reaction conditions in hand, we explored the substrate scope of this ultrasound-promoted and base-mediated regioselective bromination reaction. Substrates with different substituent positions on the pyridyl ring were firstly examined (Scheme 1). Both electron-withdrawing groups (F, Cl, Br, I, CF_3, CN) and electron-donating groups (Me, OMe) at different positions on the pyridyl ring (C6, C7, C8) of 2-phenylimidazo[1,2-*a*]pyridine derivatives afforded the desired products **3b**–**3q** in good to excellent yields (75–95%). With 2-(thien-2-yl)imidazo[1,2-*a*]pyridine and 2-methylimidazo[1,2-*a*]pyridine as starting materials, we were glad to discover that they could also be smoothly brominated under our conditions, producing products **3r** and **3s** in 93% and 95% yield, respectively (Scheme 1).



Scheme 1 Scope of the pyridyl ring of imidazo[1,2-*a*]pyridines. *Reagents and conditions*: **1** (0.2 mmol), **2a** (0.2 mmol), Na_2CO_3 (0.2 mmol), DMF (2.0 mL), in a Schlenk tube, ultrasound irradiation. Isolated yields.

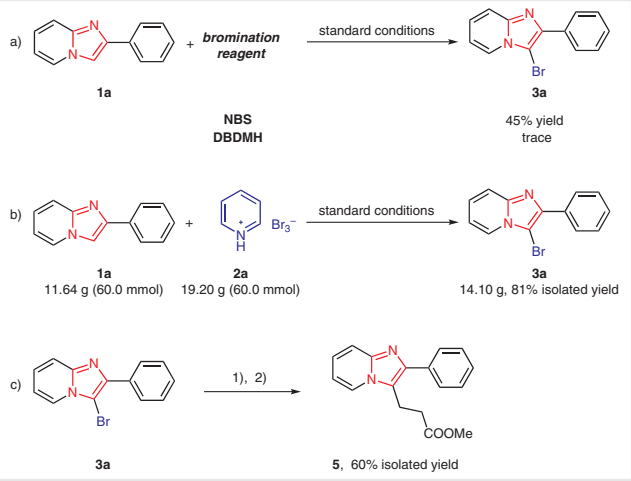
To extend the scope of the present methodology, we investigated different substituents on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridines (Scheme 2). Imidazo[1,2-*a*]pyridines bearing a halogen substituent (F, Cl, Br) at the *para*-position of the C2 phenyl ring reacted with pyridinium tribromide efficiently to afford the desired products **4a**–**4c** in good yields. Imidazo[1,2-*a*]pyridines bearing an electron-withdrawing group such as CN, NO_2 and CF_3 at the C2 phenyl could also deliver the corresponding bromination products **4d**–**4f** in up to 81% yield. Meanwhile, the presence of an electron-donating substituent like the methyl or methoxy group was able to give products **4g** and **4h** in up to 96% yield. Moreover, the substrates bearing a biphenyl or naphthyl group provided a good reactivity (**4i**, **4j**). It is noteworthy that steric hindrance in the aryl ring exerted an obvious effect on the reaction, as exemplified by the lower yields that were observed with regard to *ortho*- and *meta*-substituted substrates (**4k**, **4l**).



Scheme 2 Scope of the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridines. *Reagents and conditions*: **1** (0.2 mmol), **2a** (0.2 mmol), Na_2CO_3 (0.2 mmol), DMF (2.0 mL), in a Schlenk tube, ultrasound irradiation. Isolated yields.

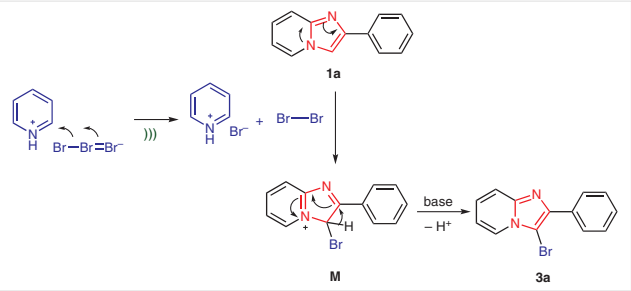
Furthermore, two alternative bromination reagents, *N*-bromosuccinimide (NBS) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), were utilized, but pyridinium tribromide was determined to be the optimal reagent under the standard conditions (Scheme 3a). To further highlight the applicability and efficiency of this strategy, a 300-fold scaled up experiment over the initial screening pursuant to the conditions outlined in Scheme 3b was conducted, and this large-scale reaction afforded the target product **3a** in 86% isolated yield within 30 minutes. Downstream functionalization of prepared synthons was also attempted. A palladium-catalyzed cross-coupling of **3a** and methyl acrylate afforded the derivatized product **5** (Scheme 3c).

On the basis of results from control experiments and those in the literature,[7d,f,8d] a plausible reaction mechanism is proposed for this transformation (Scheme 4). Initially, Br_2 is in situ generated from pyridinium tribromide by ultrasonic irradiation. Subsequently, the generated Br_2



Scheme 3 Gram-scale reaction and synthetic application. c) *Reagents and conditions*: 1) methyl acrylate (3.0 equiv), $Pd(PPh_3)_2Cl_2$ (20 mol%), TBAI (2.0 equiv), 1,4-dioxane/*N*,*N*-diisopropylethylamine (1:1, v/v; 2.0 mL), N_2, 90 °C; 2) $NaBH_4$ (3.0 equiv), $NiCl_2{\cdot}6H_2O$ (1 mol%), MeOH (2.0 mL), r.t.

undergoes electrophilic addition with imidazopyridine **1a** to produce intermediate **M**. Finally, the desired product **3a** is obtained from intermediate **M** via proton transfer using base.



Scheme 4 Possible reaction mechanism

In summary, we have demonstrated that pyridinium tribromide is an efficient bromination reagent for the synthesis of C3-brominated imidazo[1,2-*a*]pyridines under ultrasonic irradiation. Moreover, this method, which demonstrated good functional group tolerance, was also shown to be applicable in an efficient gram-scale preparation of the desired compound.

All reactions were carried out in anhydrous solvent and commercially available reagents were used as received unless otherwise stated. Analytical TLC was performed on precoated aluminum-backed silica gel 60 F_{254} plates (EMD Millipore, 200 µm thickness). TLC plates were visualized with ultraviolet light and by treatment with $KMnO_4$ or vanillin stain followed by heating. Flash column chromatography was performed using Tsingdao silica gel (200–300 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DRX-400 spectrometers; chemical shifts (δ) are given in ppm and calibrated using the signal of residual nondeuterated solvent as internal reference ($CHCl_3$: δ_H = 7.26 ppm, δ_C = 77.00 ppm). NMR data are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant(s) (Hz), integration. HRMS data were recorded MAT 95XP (ESI). Melting points were determined on a SGWX-4 apparatus.

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

A mixture of a 2-bromoacetophenone (10.0 mmol, 1.0 equiv), a 2-aminopyridine (12.5 mmol, 1.25 equiv) and $NaHCO_3$ (15.6 mmol, 1.56 equiv) was stirred in EtOH (150 mL) at r.t. for 6 h. After completion of the reaction, the resulting mixture was diluted with water (30 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (25 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to give the analytically pure imidazopyridine.

3-Bromo-2-phenylimidazo[1,2-*a*]pyridine (3a); Typical Procedure

A mixture of 2-phenylimidazo[1,2-*a*]pyridine (**1a**; 38.8 mg, 0.20 mmol), pyridinium tribromide (**2a**; 63.9 mg, 0.20 mmol) and Na_2CO_3 (21.2 mg, 0.2 mmol) in DMF (2.0 mL) in a Schlenk tube at r.t. was subjected to ultrasonic irradiation JP-120ST(Skymen) for 30 min. After the reaction was complete, the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 200–300 mesh) to give desired product **3a**.

Yield: 51.68 mg (95%); yellow solid; mp 85 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 6.8 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 2 H), 7.68 (d, *J* = 8.2 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.30–7.26 (m, 1 H), 6.95 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.39, 142.58, 132.73, 128.46, 128.32, 127.89, 125.19, 123.97, 117.58, 113.11, 91.75.

3-Bromo-7-fluoro-2-phenylimidazo[1,2-*a*]pyridine (3b)

Yield: 51.23 mg (88%); yellow solid; mp 111 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (t, *J* = 6.8 Hz, 3 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 1 H), 7.30–7.26 (m, 1 H), 6.81 (td, *J* = 7.2, 2.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.36, 159.69, 145.48 (d, *J* = 18.0 Hz), 143.39, 132.60, 128.61 (d, *J* = 6.0 Hz), 127.85, 125.55 (d, *J* = 14.0 Hz), 105.70 (d, *J* = 40.0 Hz), 101.47 (d, *J* = 32.0 Hz), 91.31.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9BrClN_2$ $[M + H]^+$: 306.9632; found: 306.9646.

3-Bromo-7-chloro-2-phenylimidazo[1,2-*a*]pyridine (3c)

Yield: 51.67 mg (84%); yellow solid; mp 169 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.1–8.0 (m, 3 H), 7.64 (s, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.41–7.38 (m, 1 H), 6.90 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.15, 143.68, 132.52, 131.82, 128.70, 128.66, 127.96, 124.37, 116.51, 114.83, 92.11.

3,7-Dibromo-2-phenylimidazo[1,2-*a*]pyridine (3d)

Yield: 64.77 mg (92%); brown solid; mp 79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.12 (m, 2 H), 8.02 (d, *J* = 7.2 Hz, 1 H), 7.85 (t, *J* = 3.0 Hz, 1 H), 7.54–7.50 (m, 2 H), 7.46–7.41 (m, 1 H), 7.02 (dd, *J* = 7.2, 2.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.29, 143.32, 132.33, 128.47, 128.42, 127.77, 124.08, 119.67, 118.77, 116.83, 91.96.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9Br_2N_2$ $[M + H]^+$: 350.9127; found: 350.9142.

3-Bromo-2-phenyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridine (3e)

Yield: 51.85 mg (76%); yellow solid; mp 79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.2 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 2 H), 8.01 (s, 1 H), 7.56 (t, *J* = 7.6 Hz, 2 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.15 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.89, 143.53, 132.09, 130.86, 128.86, 128.61, 127.95, 124.76, 115.54 (q, *J* = 18.0 Hz), 109.01, 108.99, 93.72.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_9BrF_3N_2$ $[M + H]^+$: 340.9896; found: 340.9910.

3-Bromo-7-methoxy-2-phenylimidazo[1,2-*a*]pyridine (3f)

Yield: 56.38 mg (93%); green solid; mp 105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.17 (m, 2 H), 7.78 (dd, *J* = 6.8, 0.8 Hz, 1 H), 7.47–7.44 (m, 2 H), 7.38–7.34 (m, 1 H), 6.78 (t, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 7.2 Hz, 1 H), 4.01 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.01, 142.00, 139.90, 132.84, 128.38, 128.26, 128.12, 116.98, 113.01, 101.42, 92.73, 56.16.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}BrN_2O$ $[M + H]^+$: 303.0128; found: 303.0144.

3-Bromo-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (3g)

Yield: 53.98 mg (94%); red solid; mp 97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (t, *J* = 7.2 Hz, 2 H), 8.04 (d, *J* = 6.8 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.41–7.36 (m, 2 H), 6.76 (dd, *J* = 6.8, 1.2 Hz, 1 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.79, 142.28, 136.17, 132.99, 128.40, 128.12, 127.77, 123.10, 115.99, 115.64, 90.78, 21.32.

3,8-Dibromo-2-phenylimidazo[1,2-*a*]pyridine (3h)

Yield: 59.85 mg (85%); brown solid; mp 83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.14 (m, 3 H), 7.54–7.50 (m, 3 H), 7.45–7.41 (m, 1 H), 6.83–6.78 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.45, 143.06, 132.32, 128.48, 128.38, 128.11, 127.42, 123.31, 112.93, 111.58, 93.36.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9Br_2N_2$ $[M + H]^+$: 350.9127; found: 350.9141.

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

Yield: 56.99 mg (94%); brown solid; mp 79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.10 (m, 2 H), 7.97 (d, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 6.94 (d, *J* = 7.4 Hz, 1 H), 6.63 (dd, *J* = 7.6, 2.4 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.51, 146.57, 141.76, 132.69, 128.44, 128.14, 127.59, 124.38, 108.26, 94.74, 89.97, 55.72.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}BrN_2O$ $[M + H]^+$: 303.0128; found: 303.0144.

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

Yield: 51.69 mg (90%); brown solid; mp 81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.16 (m, 2 H), 8.09 (d, *J* = 6.8 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.09 (d, *J* = 6.8 Hz, 1 H), 6.88 (t, *J* = 6.8 Hz, 1 H), 2.72 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.70, 142.12, 133.04, 128.40, 128.10, 128.02, 127.59, 123.84, 121.79, 112.99, 92.01, 16.54.

3-Bromo-6-fluoro-2-phenylimidazo[1,2-*a*]pyridine (3k)

Yield: 48.33 mg (83%); yellow solid; mp 99 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.4 Hz, 3 H), 7.65 (dd, *J* = 8.6, 4.8 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.23–7.18 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.53, 152.95, 143.96 (d, *J* = 4.0 Hz), 142.97, 132.49, 128.46 (d, *J* = 6.0 Hz), 127.71, 118.13 (d, *J* = 12.0 Hz), 117.11 (d, *J* = 34.0 Hz), 110.92 (d, *J* = 56.0 Hz), 92.92.

3-Bromo-6-chloro-2-phenylimidazo[1,2-*a*]pyridine (3l)

Yield: 52.29 mg (85%); yellow solid; mp 102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.14 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.81, 143.69, 132.39, 128.58, 128.54, 127.83, 126.57, 121.95, 121.57, 118.00, 92.19.

3,6-Dibromo-2-phenylimidazo[1,2-*a*]pyridine (3m)

Yield: 61.96 mg (88%); white solid; mp 155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.42–7.38 (m, 1 H), 7.31 (dd, *J* = 7.6, 1.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.84, 143.42, 132.31, 128.59, 128.55, 128.50, 127.81, 124.09, 118.17, 107.93, 91.96.

3-Bromo-6-iodo-2-phenylimidazo[1,2-*a*]pyridine (3n)

Yield: 71.03 mg (89%); yellow solid; mp 112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.11 (d, *J* = 7.6 Hz, 2 H), 7.48 (t, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.00, 143.03, 133.15, 132.26, 128.96, 128.57, 128.52, 127.87, 118.51, 91.49, 76.04.

3-Bromo-2-phenyl-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine (3o)

Yield: 53.22 mg (78%); yellow solid; mp 130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 8.13–8.08 (m, 2 H), 7.77 (d, *J* = 8.6 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 2 H), 7.44–7.41 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.20, 144.60, 132.07, 128.85, 128.59, 127.92, 124.27, 123.09 (q, *J* = 6.0 Hz), 122.47, 121.01 (q, *J* = 2.0 Hz), 118.33, 117.58 (q, *J* = 136.0 Hz), 93.38.

3-Bromo-2-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile (3p)

Yield: 44.72 mg (75%); brown solid; mp 110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.13–8.11 (m, 2 H), 7.72 (d, *J* = 8.2 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 7.46–7.42 (m, 1 H), 7.37 (dd, *J* = 9.2, 1.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.09, 144.65, 131.60, 130.01, 129.16, 128.67, 127.96, 124.94, 118.54, 116.23, 99.46, 93.35.

3-Bromo-6-methyl-2-phenylimidazo[1,2-*a*]pyridine (3q)

Yield: 54.56 mg (95%); yellow solid; mp 111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 2 H), 7.92 (s, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.08 (dd, *J* = 8.2, 1.2 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.39, 142.22, 132.92, 128.35, 128.21, 128.07, 127.70, 122.82, 121.55, 116.80, 91.18, 18.29.

3-Bromo-2-(thien-2-yl)imidazo[1,2-*a*]pyridine (3r)

Yield: 51.92 mg (93%); yellow solid; mp 105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 6.8 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.45 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.32–7.28 (m, 1 H), 7.21–7.13 (m, 1 H), 6.97 (td, *J* = 8.8, 0.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.26, 138.35, 135.71, 127.70, 126.20, 125.58, 125.45, 123.78, 117.30, 113.22, 90.82.

3-Bromo-2-methylimidazo[1,2-*a*]pyridine (3s)

Yield: 40.10 mg (95%); brown solid; mp 40 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 6.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.14–7.10 (m, 1 H), 6.80 (td, *J* = 6.8, 0.8 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.02, 141.80, 124.10, 123.44, 116.83, 112.38, 92.74, 13.44.

3-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (4a)

Yield: 49.49 mg (85%); white solid; mp 110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (dt, *J* = 8.0, 1.8 Hz, 1 H), 8.20–8.15 (m, 2 H), 7.72 (d, *J* = 8.2 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.27–7.21 (m, 2 H), 7.03 (td, *J* = 6.8, 1.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.13, 161.66, 145.42, 141.82, 129.75 (d, *J* = 16.0 Hz), 128.90 (d, *J* = 6.0 Hz), 125.35, 124.00, 117.56, 115.47 (d, *J* = 44.0 Hz), 113.23.

3-Bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (4b)

Yield: 54.13 mg (88%); white solid; mp 88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 6.8 Hz, 1 H), 8.13–8.11 (m, 2 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.49–7.47 (m, 2 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 6.97 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.38, 141.41, 134.20, 131.25, 129.03, 128.65, 125.40, 123.95, 117.55, 113.23, 91.77.

3-Bromo-2-(4-bromophenyl)imidazo[1,2-*a*]pyridine (4c)

Yield: 66.18 mg (94%); white solid; mp 88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.2 Hz, 1 H), 8.07–8.05 (m, 2 H), 7.69–7.63 (m, 3 H), 7.34–7.30 (m, 1 H), 6.99 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.39, 141.41, 131.62, 129.35, 129.33, 125.48, 124.00, 122.54, 117.57, 113.30, 91.84.

4-(3-Bromoimidazo[1,2-*a*]pyridin-2-yl)benzonitrile (4d)

Yield: 47.70 mg (80%); white solid; mp 175 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.0 Hz, 2 H), 8.19 (d, *J* = 6.8 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.34–7.30 (m, 1 H), 6.99 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.70, 140.53, 137.32, 132.26, 128.20, 125.96, 124.13, 118.83, 117.93, 113.71, 111.72, 92.96.

3-Bromo-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (4e)

Yield: 48.36 mg (76%); yellow solid; mp 121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41–8.36 (m, 4 H), 8.26 (d, *J* = 6.8 Hz, 1 H), 7.72 (d, *J* = 9.2 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 7.05 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.34, 145.69, 140.11, 139.16, 128.30, 126.16, 124.18, 123.80, 117.93, 113.84, 93.41.

3-Bromo-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridine (4f)

Yield: 55.26 mg (81%); white solid; mp 121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.0 Hz, 2 H), 8.24 (d, *J* = 7.2 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.38–7.34 (m, 1 H), 7.03 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.53, 141.03, 136.26, 130.16, 129.94, 127.99, 125.73, 125.42 (q, *J* = 6.0 Hz), 124.09, 117.79, 113.52, 92.57.

3-Bromo-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (4g)

Yield: 54.56 mg (95%); yellow solid; mp 105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.16 (m, 1 H), 8.07 (d, *J* = 7.6 Hz, 2 H), 7.68–7.65 (m, 1 H), 7.32 (t, *J* = 6.8 Hz, 2 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 6.92 (t, *J* = 7.0 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.30, 142.66, 138.18, 129.87, 129.16, 127.79, 124.99, 123.86, 117.44, 112.94, 91.38, 21.33.

3-Bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (4h)

Yield: 58.20 mg (96%); brown solid; mp 77 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (dt, *J* = 8.6, 2.8 Hz, 1 H), 8.11–8.08 (m, 2 H), 7.65 (dt, *J* = 8.2, 2.8 Hz, 1 H), 7.28–7.25 (m, 1 H), 7.05–7.02 (m, 2 H), 6.93 (td, *J* = 8.4, 2.8 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.71, 145.25, 142.42, 129.15, 125.25, 125.02, 123.83, 117.28, 113.88, 112.92, 90.91, 55.27.

2-(1,1′-Biphenyl-4-yl)-3-bromoimidazo[1,2-*a*]pyridine (4i)

Yield: 62.86 mg (90%); white solid; mp 113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.4 Hz, 2 H), 8.24 (d, *J* = 6.8 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 7.6 Hz, 3 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.34–7.30 (m, 1 H), 6.99 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.40, 142.15, 140.96, 140.61, 131.67, 128.77, 128.18, 127.41, 127.14, 127.04, 125.25, 123.93, 117.53, 113.13, 91.79.

3-Bromo-2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridine (4j)

Yield: 53.65 mg (83%); yellow solid; mp 155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1 H), 8.17 (dd, *J* = 8.8, 2.0 Hz, 1 H), 8.04 (d, *J* = 6.8 Hz, 1 H), 7.84 (dd, *J* = 8.6, 4.0 Hz, 2 H), 7.77–7.71 (m, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.45–7.36 (m, 2 H), 7.2–7.16 (m, 1 H), 6.85–6.81 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.25, 142.15, 133.23, 133.08, 129.81, 128.44, 128.05, 127.61, 127.20, 126.36, 126.21, 125.54, 125.38, 123.93, 117.32, 113.28, 92.16.

3-Bromo-2-(2-methoxyphenyl)imidazo[1,2-*a*]pyridine (4k)

Yield: 43.65 mg (72%); brown solid; mp 101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.8 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.90 (t, *J* = 6.8 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.09, 145.19, 141.77, 131.88, 130.05, 124.51, 123.81, 121.89, 120.45, 117.67, 112.84, 111.05, 94.69, 55.45.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}BrN_2O$ $[M + H]^+$: 303.0128; found: 303.0141.

3-Bromo-2-(3-chlorophenyl)imidazo[1,2-*a*]pyridine (4l)

Yield: 46.14 mg (75%); gray solid; mp 118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.15 (m, 2 H), 8.05–8.02 (m, 1 H), 7.63 (d, *J* = 8.2 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.31–7.26 (m, 1 H), 6.96 (dt, *J* = 6.8, 0.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.49, 141.25, 134.70, 134.54, 129.69, 128.32, 127.87, 125.89, 125.43, 124.03, 117.77, 113.31, 92.08.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9BrClN_2$ $[M + H]^+$: 306.9632; found: 306.9645.

Methyl 3-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)propanoate (5)

Yield: 33.64 mg (60%); brown solid; mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.8 Hz, 1 H), 7.78–7.76 (m, 2 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 8.2 Hz, 1 H), 7.20–7.16 (m, 1 H), 6.84 (td, *J* = 6.8, 1.2 Hz, 1 H), 3.65 (s, 3 H), 3.47 (m, 2 H), 2.70–2.66 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.63, 144.54, 142.70, 132.42, 128.56, 128.04, 127.60, 123.94, 122.89, 118.36, 117.62, 112.26, 51.86, 32.07, 19.19.

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Supporting Information

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