Synthesis of 3-Arylimidazo[1,2-*a*]pyridines by a Catalyst-Free Cascade Process

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Abstract: A simple and efficient protocol to synthesize 3-arylimidazo[1,2-*a*]pyridines by a catalyst-free cascade process from 2-aminopyridine and 1-bromo-2-phenylacetylene or 1,1-dibromo-2-phenylethene in yields up to 86% is described.

Key words: heterocycle, catalyst-free, cascade process

3-Aryl-substituted imidazo[1,2-*a*]pyridines are often used as core structures to construct many bioactive molecules including $GABA_A$ agonist **1**,[1] CXCR3 antagonists **2**,[2] positive allosteric modulators (PAMs) of mGluR2 **3**,[3] and the liver X receptor (LXR) agonists **4** (Figure 1).[4] Considerable attention has also recently been paid to their photoluminescent properties.[5] The normal approach to the synthesis of 3-substituted imidazo[1,2-*a*]pyridine is based on the condensation of 2-aminopyridine and α-bromoaldehyde; however, this method usually suffers from substrate complexity or poor selectivity.[3,6] An alternative protocol was recently reported that relies on palladium-catalyzed C–C bond cross-coupling reactions, however, the tedious multi-step sequence involved and the considerable cost of the catalyst restricts its application.[7] In light of this, a general and straightforward methodology that can be used to prepare such molecules is still required.

On the other hand, transition-metal-catalyzed cycloisomerization of propargylpyridines has gained considerable attention over the past decade as an effective method for creating nitrogen-fused heterocycles such as indolizinones, pyrroloquinolines, pyrroloisoquinolines, as well as indolizines.[8] An elegant protocol for the synthesis of imidazopyridines by the copper-catalyzed three-component coupling reaction of 2-aminopyridine, aldehydes, and alkynes is also reported.[9] Furthermore, ynamines and ynamides have recently been reported to be synthesized by the coupling of 1-bromoalkynes with nitrogen-containing heterocycles or amides.[10] Inspired by these reports, and in a continuation of our endeavors in the synthesis of heterocyclic compounds,[11] we envisioned that 2-aminopyridine could couple with 1-bromo-2-phenylacetylene to give alkynylamine **6**, which could isomerize to **7** and undergo subsequent intramolecular nucleophilic addition in generate the desired product 3-phenylimidazo[1,2-*a*]pyridine **8** as shown in Scheme 1.

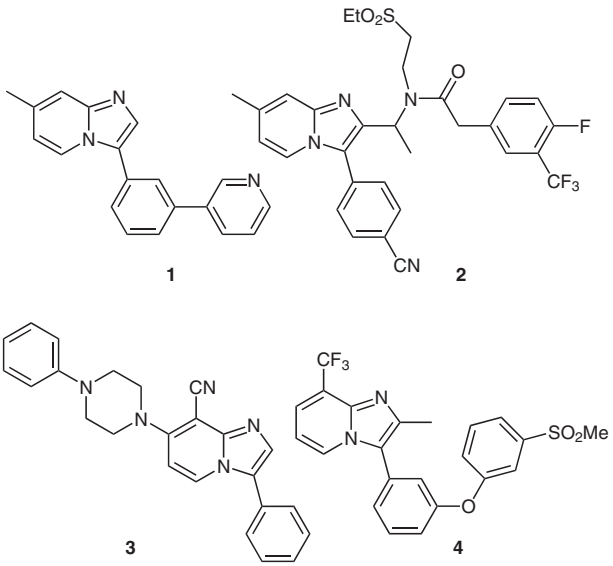
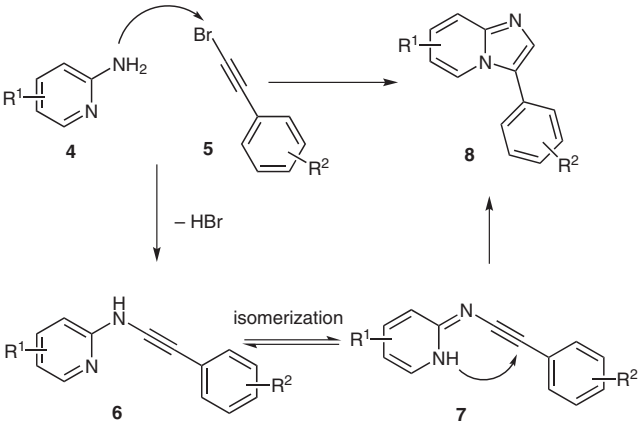


Figure 1 Structure of bioactive 3-aryl imidazo[1,2-*a*]pyridines



Scheme 1 Proposed synthesis of 3-aryl imidazo[1,2-*a*]pyridines

At first, 2-aminopyridine (**4a**) and 1-bromo-2-phenylacetylene (**5a**) were employed as model substrates, as indicated in Table 1. Gratifyingly, the reaction worked well in the absence of any catalyst to give the desired product **8a** in 32% yield in 24 hours at 100 °C (Table 1, entry 1).[12] The reaction conditions were then optimized. Among several bases examined, use of the weak inorganic base NaOAc and $NaHCO_3$ led to better results, giving yields 65% and 66%, respectively, while use of stronger bases such as Cs_2CO_3 decreased the yield to only 17% (Table 1, entries 2–8). After studying the influence of reaction time,

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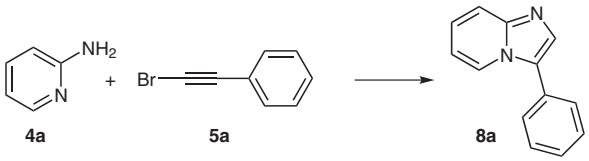
it was found that 24 hours was optimal for the catalysis; only 50% yield was obtained after 12 hours (Table 1, entry 9). Further investigations revealed that the yield increased to 76% at an elevated temperature of 120 °C (Table 1, entry 10). It is worth mentioning that the reaction also worked well in dimethylsulfoxide (DMSO) or xylene, although slightly lower yields were obtained (Table 1, entries 11 and 12).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Additives	Temp (°C)	Time (h)	Yield (%)[b]
1	DMF	–	100	24	32
2	DMF	K_2CO_3	100	24	50
3	DMF	Cs_2CO_3	100	24	17
4	DMF	NaOAc	100	24	65
5	DMF	$NaHCO_3$	100	24	66
6	DMF	Et_3N	100	24	19
7	DMF	pyridine	100	24	38
8	DMF	HOAc	100	24	39
9	DMF	$NaHCO_3$	100	12	50
10	**DMF**	**$NaHCO_3$**	**120**	**24**	**76**
11	DMSO	$NaHCO_3$	120	24	70
12	Xylene	$NaHCO_3$	120	24	69

[a] Reaction conditions: 2-aminopyridine (0.5 mmol), 1-bromo-2-phenylacetylene (0.6 mmol), solvent (0.5 mL).
[b] Isolated yield.

Next, under the optimized conditions, the scope of this new protocol was investigated. Table 2 lists the results of the reactions between a range of substituted 2-aminopyridines and 1-bromo-2-phenylacetylenes.

In general, substituted 1-bromo-2-phenylacetylenes bearing either electron-donating or electron-withdrawing groups were able to react with 2-aminopyridine in moderate to good yields ranging from 61 to 86%; electron-withdrawing substituents were found to be beneficial to the reaction (Table 2, entries **8a–e**). For example, 1-bromo-2-(4-chlorophenyl)acetylene gave the desired product in 86% yield, whereas only 61% yield was obtained in the case of 1-bromo-2-(4-methylphenyl)acetylene. This result might, in part, be caused by the fact that electron-rich substrates were unfavorable for the nucleophilic addition step proposed in Scheme 1. Substituents on the 2-aminopyridines had less influence on the results, with yields using such substrates ranging from 62 to 71% (Table 2, entries **8f–j**). Figure 2 shows the X-ray crystal structure of the product **8c**.

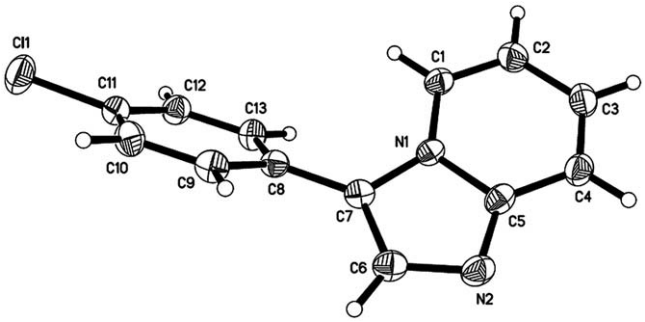
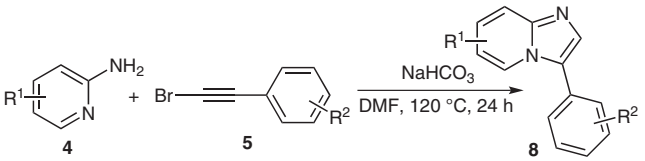


Figure 2 X-ray crystal structure of the product **8c**

Table 2 Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines from Substituted 1-Bromo-2-phenylacetylenes[a]



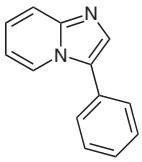
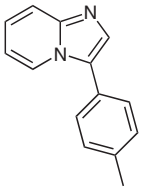
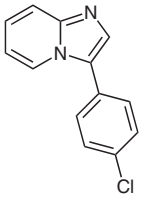
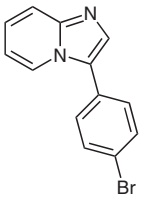
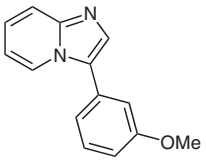
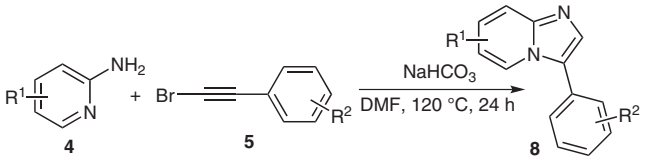
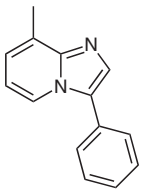
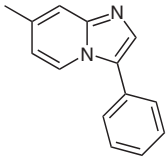
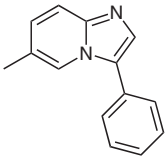
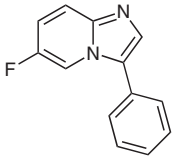
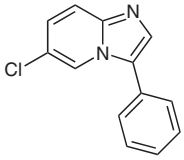
Entry	Product		Yield (%)[b]
1	**8a**		76
2	**8b**		61
3	**8c**		86
4	**8d**		82
5	**8e**		70

Table 2 Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines from Substituted 1-Bromo-2-phenylacetylenes[a] (continued)



4 5 8

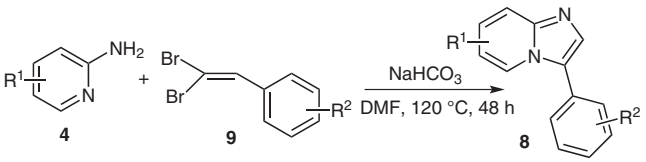
Entry	Product		Yield (%)[b]
6	**8f**		63
7	**8g**		69
8	**8h**		71
9	**8i**		68
10	**8j**		62

[a] Reaction conditions: 2-aminopyridine (0.5 mmol), 1-bromo-2-phenylacetylene (0.6 mmol), $NaHCO_3$ (1 mmol), DMF (0.5 mL), 120 °C, 24 h.
[b] Isolated yield.

In an endeavor to expand the application of this protocol, we tried to use 1,1-dibromo-2-phenylethenes directly as substrates in this reaction, which were known to be able to form 1-bromo-2-phenylacetylenes through use of the Ramirez and Corey–Fuchs procedures.[13,14] To our delight, all the substituted 1,1-dibromo-2-phenylethenes worked well under the standard conditions, and afforded comparable yields with 1-bromo-2-phenylacetylenes, as shown in Table 3.

In summary, we have developed a novel synthetic protocol for the efficient assembly of 3-aryl imidazo[1,2-*a*]pyridines by a catalyst-free cascade process. The efficiency and substituent-tolerance of this procedure have been demonstrated by synthesizing a number of functionalized imidazo[1,2-*a*]pyridines. Considering the simple reaction conditions and the convenient availability of the starting materials, this approach is a necessary complement to the other existing methods for producing substituted imidazo[1,2-*a*]pyridines. Further studies and applications of this methodology are currently underway in our laboratory.

Table 3 Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines from Substituted 1,1-Dibromo-2-phenylethenes[a]



4 9 8

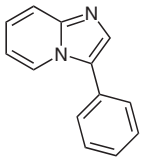
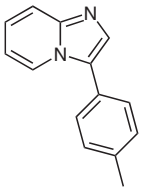
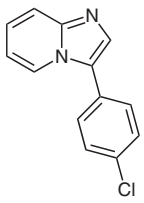
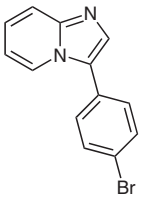
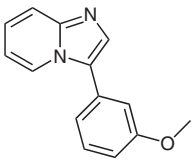
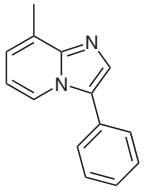
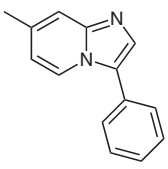
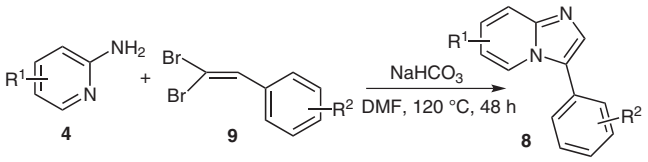
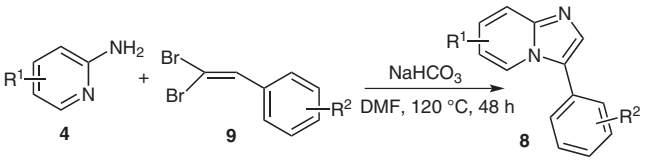
Entry	Product		Yield (%)[b]
1	**8a**		76 (trace)[c]
2	**8b**		58
3	**8c**		80
4	**8d**		77
5	**8e**		71
6	**8f**		63
7	**8g**		69

Table 3 Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines from Substituted 1,1-Dibromo-2-phenylethenes[a] (continued)



Entry	Product	Yield (%)[b]
8	**8h**	71
9	**8i**	68
10	**8j**	62
11	**8k**	76
12	**8l**	63
13	**8m**	63
14	**8n**	27
15	**8o**	63

Table 3 Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines from Substituted 1,1-Dibromo-2-phenylethenes[a] (continued)



Entry	Product	Yield (%)[b]
16	**8p**	30
17	**8q**	33
18	**8r**	60

[a] Reaction conditions: 2-aminopyridine (0.5 mmol), 1,1-dibromo-2-phenylethene (0.6 mmol), $NaHCO_3$ (1 mmol), DMF (0.5 mL), 120 °C, 48 h.
[b] Isolated yield.
[c] In the absence of $NaHCO_3$.

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF254 plates. Column chromatography was performed using silica gel (200–300 mesh) eluting with EtOAc and petroleum ether (60–90 °C). All products were characterized by NMR and MS analyses. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker DPX) with $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm using TMS as internal standard.

Synthesis of 3-Aryl Imidazo[1,2-*a*]pyridines; Typical Procedure

A mixture of 2-aminopyridine (0.5 mmol), 1-bromo-2-phenylacetylene (0.6 mmol), $NaHCO_3$ (1 mmol), and DMF (0.5 mL) was heated at 120 °C for 24 h. The mixture was then allowed to cool to r.t., diluted with H_2O (15 mL) and then extracted with EtOAc (3 × 20 mL). The organic extracts were combined and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography to afford the corresponding product.

3-Phenylimidazo[1,2-*a*]pyridine (8a)

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 6.8 Hz, 1 H), 7.69–7.65 (m, 2 H), 7.55–7.47 (m, 4 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.03, 131.32, 128.22, 127.19, 127.01, 124.71, 123.31, 122.32, 117.15, 111.57.

MS (EI): *m*/*z* = 194 [M$^+$].

3-(4-Methylphenyl)imidazo[1,2-*a*]pyridine (8b)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.2 Hz, 1 H), 7.59 (d, *J* = 9.2 Hz, 1 H), 7.58 (s, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.11–7.06 (m, 1 H), 6.71 (t, *J* = 7.2 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.94, 137.13, 131.21, 128.88, 126.97, 125.28, 124.72, 123.00, 122.34, 117.16, 111.37, 20.29.

MS (EI): *m*/*z* = 208 [M$^+$].

3-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (8c)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 6.8 Hz, 1 H), 7.69 (d, *J* = 7.2 Hz, 2 H), 7.49 (s, 4 H), 7.24–7.20 (m, 1 H), 6.85 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.24, 134.03, 132.69, 129.50, 129.19, 127.72, 124.50, 123.15, 118.31, 112.83.

MS (EI): *m*/*z* = 228 [M$^+$].

3-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (8d)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 6.8 Hz, 1 H), 7.62–7.56 (m, 4 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.17–7.12 (m, 1 H), 6.78 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.28, 131.64, 131.46, 128.43, 127.16, 123.54, 122.13, 121.14, 117.34, 111.87.

MS (EI): *m*/*z* = 273 [M$^+$].

3-(3-Methoxylphenyl)imidazo[1,2-*a*]pyridine (8e)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 7.2 Hz, 1 H), 7.70 (s, 1 H), 7.68 (d, *J* = 9.2 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.21–7.14 (m, 2 H), 7.08 (s, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.82 (t, *J* = 6.8 Hz, 1 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.21, 146.17, 132.58, 130.57, 130.31, 125.61, 124.27, 123.53, 120.26, 118.26, 113.75, 113.54, 112.57, 55.39.

MS (EI): *m*/*z* = 224 [M$^+$].

8-Methyl-3-phenylimidazo[1,2-*a*]pyridine (8f)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.2 Hz, 1 H), 7.68 (s, 1 H), 7.55–7.47 (m, 4 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 6.99 (d, *J* = 6.8 Hz, 1 H), 6.72 (t, *J* = 6.8 Hz, 1 H), 2.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.49, 131.79, 129.57, 129.19, 128.06, 127.90, 126.15, 123.12, 121.27, 112.60, 17.10.

MS (EI): *m*/*z* = 208 [M$^+$].

7-Methyl-3-phenylimidazo[1,2-*a*]pyridine (8g)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.2 Hz, 1 H), 7.52 (s, 1 H), 7.45–7.37 (m, 4 H), 7.32–7.27 (m, 2 H), 6.54 (d, *J* = 6.8 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.56, 134.19, 131.07, 128.44, 128.15, 126.91, 126.79, 124.16, 121.55, 115.47, 114.14, 20.18.

MS (EI): *m*/*z* = 208 [M$^+$].

6-Methyl-3-phenylimidazo[1,2-*a*]pyridine (8h)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.63 (s, 1 H), 7.58–7.49 (m, 5 H), 7.42 (t, *J* = 7.2 Hz, 1 H), 7.05 (d, *J* = 9.2 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.22, 132.34, 129.54, 129.21, 128.06, 127.44, 125.41, 122.17, 120.93, 117.51, 18.38.

MS (EI): *m*/*z* = 208 [M$^+$].

6-Fluoro-3-phenylimidazo[1,2-*a*]pyridine (8i)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (m, 1 H), 7.64 (s, 1 H), 7.58–7.54 (m, 1 H), 7.45–7.44 (m, 4 H), 7.37–7.35 (m, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.75, 151.40, 142.76, 132.64, 128.36, 127.77, 127.52, 126.82, 126.03, 117.68, 117.59, 115.42, 115.16, 109.21, 108.80.

MS (EI): *m*/*z* = 212 [M$^+$].

6-Chloro-3-phenylimidazo[1,2-*a*]pyridine (8j)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 7.62 (s, 1 H), 7.55 (d, *J* = 9.6 Hz, 1 H), 7.46 (d, *J* = 4.4 Hz, 4 H), 7.39–7.34 (m, 1 H), 7.09 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.36, 132.24, 128.38, 127.62, 127.55, 127.04, 125.27, 124.61, 120.21, 120.01, 117.55.

MS (EI): *m*/*z* = 228 [M$^+$].

3-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine (8k)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.8 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.14–7.08 (m, 3 H), 6.74 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.73, 160.26, 145.00, 131.45, 129.02, 128.94, 124.30, 123.64, 123.26, 122.06, 117.24, 115.43, 115.21, 111.64.

MS (EI): *m*/*z* = 212 [M$^+$].

3-(4-Methoxylphenyl)imidazo[1,2-*a*]pyridine (8l)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 6.8 Hz, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.63 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.18–7.14 (m, 1 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 6.79 (t, *J* = 6.8 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.59, 145.78, 132.01, 129.62, 125.49, 123.91, 123.26, 121.54, 118.15, 114.67, 112.34, 55.39.

MS (EI): *m*/*z* = 224 [M$^+$].

3-(3-Methylphenyl)imidazo[1,2-*a*]pyridine (8m)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 6.8 Hz, 1 H), 7.59 (s, 1 H), 7.58 (d, *J* = 6.8 Hz, 1 H), 7.32–7.25 (m, 3 H), 7.14 (d, *J* = 6.8 Hz, 1 H), 7.10–7.06 (m, 1 H), 6.71 (t, *J* = 6.8 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.00, 137.98, 131.34, 128.13, 128.06, 127.94, 127.66, 124.81, 123.98, 123.12, 122.41, 117.14, 111.42, 20.45.

MS (EI): *m*/*z* = 208 [M$^+$].

3-(2-Chlorophenyl)imidazo[1,2-*a*]pyridine (8n)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 6.8 Hz, 1 H), 7.64 (s, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.41–7.30 (m, 3 H), 7.30–7.15 (m, 1 H), 6.76 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.79, 133.66, 132.57, 131.75, 129.30, 129.20, 127.08, 126.20, 123.51, 123.40, 121.88, 116.96, 111.23.

MS (EI): *m*/*z* = 228 [M$^+$].

5-Methyl-3-phenylimidazo[1,2-*a*]pyridine (8o)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.8 Hz, 1 H), 7.44 (s, 1 H), 7.34–7.28 (m, 5 H), 7.03–6.99 (m, 1 H), 6.40 (d, *J* = 6.8 Hz, 1 H), 2.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.97, 135.37, 133.36, 130.90, 130.57, 127.40, 126.37, 125.19, 123.25, 115.06, 112.25, 20.76.

MS (EI): *m*/*z* = 208 [M$^+$].

Methyl 3-Phenylimidazo[1,2-*a*]pyridine-6-carboxylate (8p)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 7.70 (d, *J* = 9.2 Hz, 1 H), 7.68 (s, 1 H), 7.62 (d, *J* = 9.2 Hz, 1 H), 7.51–7.46 (m, 4 H), 7.41–7.37 (m, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.40, 145.40, 132.93, 128.45, 127.73, 127.27, 126.75, 125.96, 122.86, 116.53, 115.76, 51.45.

MS (EI): *m*/*z* = 252 [M$^+$].

3-(1-Naphthalenyl)imidazo[1,2-*a*]pyridine (8q)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.86 (m, 2 H), 7.71 (s, 1 H), 7.68–7.62 (m, 2 H), 7.52–7.42 (m, 4 H), 7.36 (t, *J* = 6.8 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.64 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.78, 132.88, 132.69, 130.99, 128.60, 128.11, 127.69, 125.94, 125.37, 125.22, 124.59, 124.17, 123.35, 123.07, 122.64, 116.96, 111.28.

MS (EI): *m*/*z* = 244 [M$^+$].

7-Methyl-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (8r)
White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.8 Hz, 1 H), 7.60 (s, 1 H), 7.45 (s, 4 H), 7.41–7.40 (m, 1 H), 6.65 (d, *J* = 7.2 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.80, 135.41, 133.70, 132.51, 129.43, 128.96, 127.98, 124.00, 122.38, 116.66, 115.41, 21.23.

MS (EI): *m*/*z* = 242 [M$^+$].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis

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