Synthesis of Imidazo[1,2-*a*]pyridines by the Bis(acetyloxy)(phenyl)-λ^3-iodane-Mediated Oxidative Coupling of 2-Aminopyridines with β-Keto Esters and 1,3-Diones

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Abstract: Imidazo[1,2-*a*]pyridine-3-carboxylates can be prepared directly from 2-aminopyridines and β-keto esters by using bis(acetyloxy)(phenyl)-λ^3-iodane as an oxidant and boron trifluoride etherate as a catalyst. The amount of catalyst plays a key role in determining the course of the reaction. Whereas the use of 0.2 equivalents of catalyst ensures the generation of imidazo[1,2-*a*]pyridines, raising the amount of catalyst to 1.0 equivalents results in exclusive α-acetoxylation of the β-keto esters. 2-Aminopyridines can also react with 1,3-diones to afford 3-acylimidazo[1,2-*a*]pyridines.

Key words: heterocycles, polycycles, cyclization, oxidation, coupling

Imidazo[1,2-*a*]pyridine is an important ring system that forms the core structure of many pharmacologically important compounds.[1,2] Unsurprisingly, many efforts have been made to gain access to imidazo[1,2-*a*]pyridine rings with a range of substituents, and several approaches that employ various strategies and precursors are now available.[1,2] The condensation of 2-aminopyridines with α-halocarbonyl compounds provides a conventional but simple method.[3] Recent studies have demonstrated that the synthesis can also be achieved by a three-component reaction.[2,4] Although the latter strategy is attractive in terms of its efficiency, the reaction of 2-aminopyridines with α-halocarbonyl compounds offers a practical synthetic route and is the method most frequently used in medicinal chemistry.[5]

Hypervalent iodine(III) reagents such as bis(acetyloxy)(phenyl)-λ^3-iodane (DIB or PIDA), bis(trifluoroacetyloxy)(phenyl)-λ^3-iodane (BTI or PIFA), and hydroxy(phenyl)(tosyloxy)-l^3-iodane (HTIB, Koser's reagent) are very useful oxidants in organic synthesis.[6] One synthetic application of hypervalent iodine(III) reagents is in effecting the α-functionalization of carbonyl groups. As such, α-acetoxylation and α-tosylation of ketones have been realized by using PIDA or HTIB, respectively, as the oxidant.[7] A reagent combination of iodosylbenzene and 4-toluenesulfonic acid oxidizes alcohols to the corresponding α-tosyloxy ketones. The products react with 2-aminopyridines to afford imidazo[1,2-*a*]pyridines in moderate-to-good yields.[8] A modification of this procedure, which features the use of *N*-ethyl-*N*-methylimidazolium tosylate as the reaction medium with iodobenzene and 4-chloroperbenzoic acid (MCPBA) as the oxidizing system, has been developed to enable the synthesis to be performed in a one-pot manner.[9] In an attempt to extend the synthetic utility of hypervalent iodine(III) reagents in the synthesis of imidazo[1,2-*a*]pyridines, we hypothesized that imidazo[1,2-*a*]pyridine-3-carboxylates **3** might be obtained from 2-aminopyridines and β-keto esters through a PIDA-mediated direct oxidative coupling (Scheme 1).[10] Compounds **3** have been previously synthesized from 2-aminopyridines and α-bromo β-keto esters, but the yields were not high.[11] We hoped that our protocol would not only help simplify the synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates, but would also improve their yields.

To achieve this goal, pyridin-2-amine (**1a**) and ethyl 2-benzoylacetate (**2a**) were used as substrates, and the reaction was performed by stirring a mixture of one equivalent each of **1a**, **2a**, and PIDA in dichloromethane at room temperature (7 °C) for several hours. However, no reaction occurred. To effect the reaction, 1 equivalent of boron trifluoride etherate ($BF_3{\cdot}Et_2O$) was added to the mixture. One hour later, the formation of a product was indicated by thin-layer chromatography; this product was identified as the keto ester **4a** (Table 1, entry 2). This result was not unexpected, as Lewis acids can catalyze the α-acetoxylation of carbonyl compounds.[7a] We speculated that the unwanted reaction might be restrained by reducing the amount of $BF_3{\cdot}Et_2O$. In our previous studies on the applications of hypervalent iodine in heterocycle synthesis,[12] we found that a catalytic amount of $BF_3{\cdot}Et_2O$ was capable of promoting hypervalent iodine-mediated coupling reactions. We therefore adjusted the amount of $BF_3{\cdot}Et_2O$ in the reaction system to examine whether the course of the reaction could be changed (entries 2–6). To our delight, when 0.2 equivalents of $BF_3{\cdot}Et_2O$ were used, the desired ethyl 2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (**3a**) was obtained as the major product in 80% yield (entry 3). The reaction was complete in one hour. The use of 0.5 equivalents or more of $BF_3{\cdot}Et_2O$ reduced the yield of **3a** and resulted in the formation of **4a** (entries 5 and 6).

The yield of **3a** was also influenced by the reaction temperature. When the reaction was performed at 25 °C, the yield of **3a** was reduced to 45% (entry 4).

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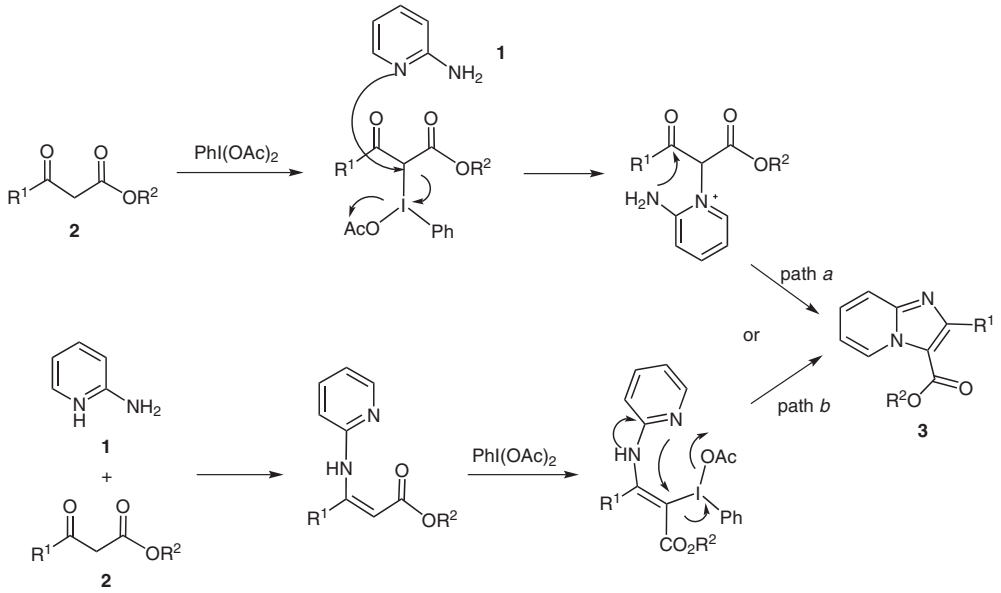
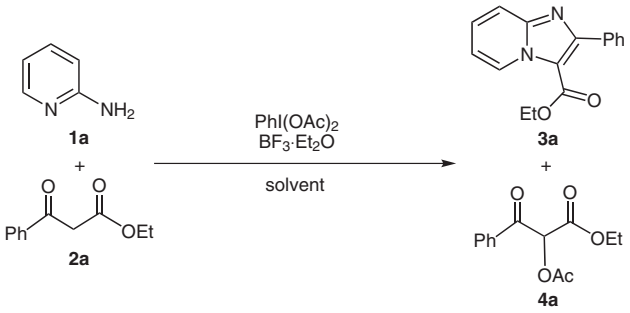


Scheme 1

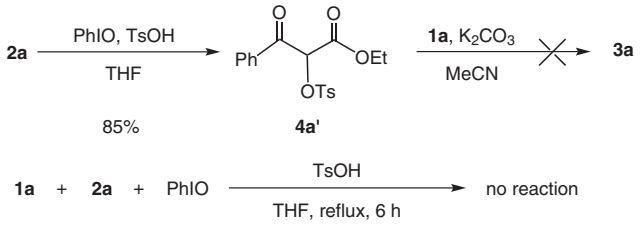
Table 1 Screening of the Reaction Conditions



Entry[a]	Solvent	$BF_3{\cdot}Et_2O$ (equiv)	Yield (%) of **3a**[b]	Yield (%) of **4a**[b]
1	CH_2Cl_2	0	–[c]	–[c]
2	CH_2Cl_2	1.0	0	45
3	CH_2Cl_2	0.2	80	0
4	CH_2Cl_2	0.2	45[d]	0[d]
5	CH_2Cl_2	0.5	52	21
6	CH_2Cl_2	1.5	0	75
7	MeOH	0.2	39	0
8	EtOH	0.2	32	0
9	THF	0.2	86	0
10	toluene	0.2	47	28
11	MeCN	0.2	37	19

[a] **1a** (1 mmol), **2a** (1 mmol), PIDA (1 mmol), and $BF_3{\cdot}Et_2O$ in solvent (5 mL). The temperature was 7 °C unless otherwise specified.
[b] Isolated yield.
[c] No reaction occurred.
[d] At 25 °C.

Compound **4a** could not react with **1a** to generate **3a** under these conditions. This result is consistent with our initial hypothesis about the reaction process (Scheme 1), and is different from that reported by Togo and co-workers.[8] In their synthesis of imidazo[1,2-*a*]pyridines from acetophenones and 2-aminopyridines, acetophenones were initially converted into their a-tosylated counterparts by the action of iodosylbenzene and 4-toluenesulfonic acid. As a matter of fact, when ethyl 2-{[(4-methylphenyl)sulfonyl]oxy}-3-oxo-3-phenylpropanoate (**4a¢**) was treated with **1a** under the reported conditions,[8] **3a** was not obtained, and most of the starting materials decomposed. Furthermore, a one-pot operation involving refluxing of a mixture of **1a**, **2a**, iodosylbenzene, and 4-toluenesulfonic acid in tetrahydrofuran failed to effect a reaction (Scheme 2).



Scheme 2

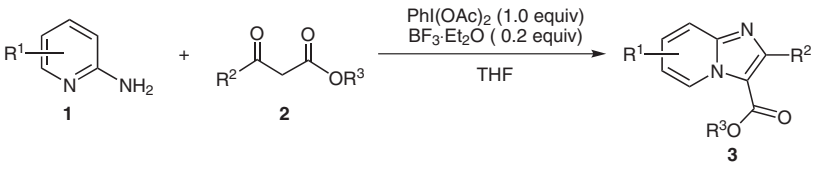
To gain more insight into the reaction mechanism, a control experiment was conducted by stirring a mixture of **1a**, **2a**, and $BF_3{\cdot}Et_2O$ in tetrahydrofuran in the absence of PIDA. No reaction product was found after one day, and no reaction occurred at an elevated temperature. This showed that path *b* shown in Scheme 1 is unlikely to account for the formation of **3a**. We therefore assumed that the reaction probably proceeds by the mechanism shown in path *a*.

It is interesting to note that whereas the PIDA-mediated reaction of **1a** and **2a** is promoted by a catalytic amount of $BF_3{\cdot}Et_2O$, the use of 1.0 equiv. of $BF_3{\cdot}Et_2O$ prevents the reaction occurring. Acids have been frequently used to facilitate reactions involving PIDA by enhancing its electrophilic capacity and by promoting the elimination of iodobenzene and acetic acid.[6] The finding that the amount of acid determined the course of the reaction is an exception to this general rule, and might be explained by the fact that pyridin-2-amine (**1a**) is a base that can interact with the $BF_3{\cdot}Et_2O$ and the acetic acid generated during the reaction. The use of too much $BF_3{\cdot}Et_2O$ hampers the function of **1a** as a nucleophile, and this leads to the formation of **4a**. The later process is disfavored compared with path *a* in Scheme 1 when only 0.2 equivalents of $BF_3{\cdot}Et_2O$ are used.

The reaction was also performed with tetrahydrofuran, methanol, methanol, acetonitrile, or toluene as a solvent (Table 1 entries 6–10). Of these solvents, tetrahydrofuran showed the best performance, giving **3a** in a yield of 86% (Table 1, entry 8). The results with the other solvents were less satisfactory.

Having determined the optimal reaction conditions (Table 1, entry 8), we next examined the scope of the reaction. As summarized in Table 2, a variety of substituted imidazo[1,2-*a*]pyridine-3-carboxylates **3** could be prepared by our new protocol. The results were generally good for 2-aryl substituted products. The reaction could be carried out on a gram scale without an apparent decrease in yield. Compared with the previously reported synthesis of 2-aryl imidazo[1,2-*a*]pyridine-3-carboxylates from 2-aminopyridines and 2-benzoyl-2-bromoacetates,[11] our new method not only eliminated the need for previous halogenation of the β-keto esters, but also gave better yields. The method was also effective for the synthesis of 2-alkylimidazo[1,2-*a*]pyridine-3-carboxylates, albeit in lower yields. In the case of **3s** and **3t**, the reaction proceeded poorly in tetrahydrofuran, but when refluxing toluene was used as the solvent, complete conversion occurred and the products were obtained in yields of 46% and 66%, respectively (Table 2, entries 19 and 20).

Table 2 Synthesis of Imidazo[1,2-*a*]pyridine-3-carboxylates



1 **2** **3**

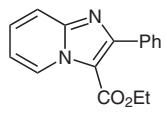
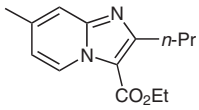
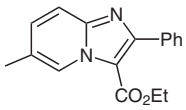
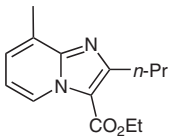
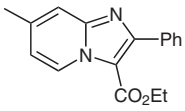
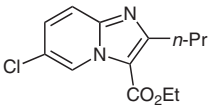
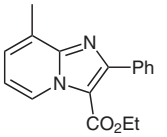
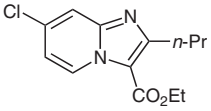
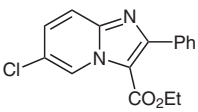
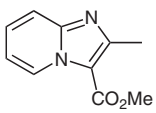
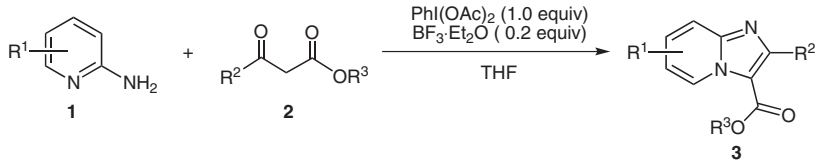
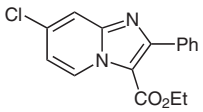
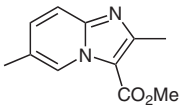
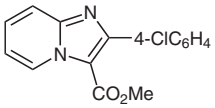
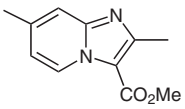
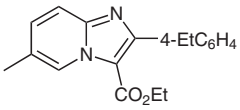
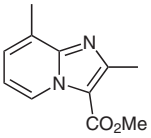
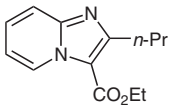
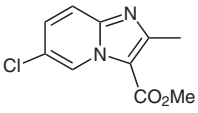
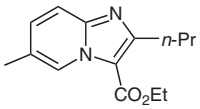
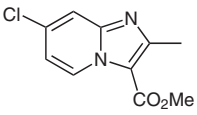
Entry[a]	Time	Product	Yield (%)[b]	Entry	Time	Product	Yield (%)[b]
1	2 h	 **3a**	86	11	overnight	 **3k**	63
2	2 h	 **3b**	85	12	overnight	 **3l**	57
3	2 h	 **3c**	75	13	overnight	 **3m**	57
4	2 h	 **3d**	89	14	overnight	 **3n**	72
5	2 h	 **3e**	60	15	overnight	 **3o**	58

Table 2 Synthesis of Imidazo[1,2-*a*]pyridine-3-carboxylates (continued)



1 2 3

Entry[a]	Time	Product	Yield (%)[b]	Entry	Time	Product	Yield (%)[b]
6	2 h	 **3f**	87	16	overnight	 **3p**	51
7	2 h	 **3g**	82	17	overnight	 **3q**	52
8	2 h	 **3h**	83	18	overnight	 **3r**	30
9	overnight	 **3j**	71	19	24 h[c]	 **3s**	46
10	overnight	 **3j**	67	20	24 h[c]	 **3t**	66

[a] The reaction was carried out in THF at 7 °C unless otherwise specified; **2** (1.2 equiv) and PIDA (1.2 equiv) were used for the synthesis of **3o–t**.
[b] Isolated yield.
[c] The reaction was carried out in refluxing toluene.

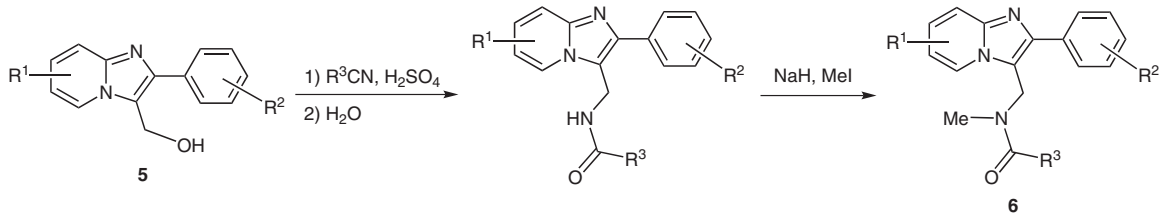
Compounds **3** are useful intermediates for the synthesis of pharmaceutically important compounds. Reduction of compounds **3** give the corresponding (imidazo[1,2-*a*]pyridin-3-yl)methanols (**5**),[13] which can be used as precursors for the synthesis of the *N*-methylcarboxamides **6** (Scheme 3).[14]

Carboxylates **3** can also be reduced by means of a recently reported procedure using sodium borohydride.[15] Thus, **3g** and **3h** were reduced to **5g** and **5h,** respectively, which can be converted into the anxiolytic drugs saripidem and necopidem, respectively, in two more steps (Scheme 4).[14]

Compounds **5** are also useful in the synthesis of some antiviral agents.[16]

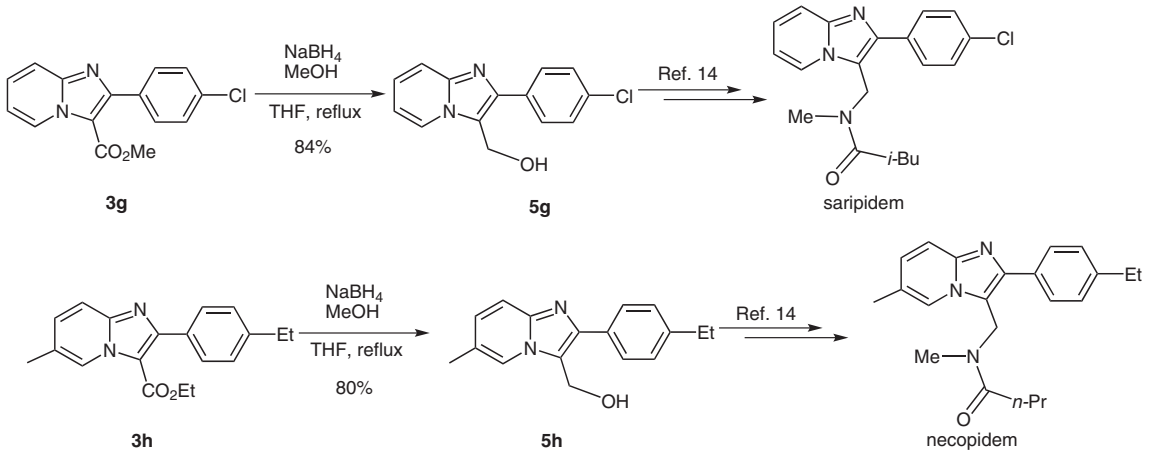
The protocol could be extended to the reactions of 2-aminopyridines with 1,3-diones such as **7** to give the corresponding 3-acylimidazo[1,2-*a*]pyridines **8** (Scheme 5).[5a,17]

When asymmetric 1,3-diones were used as the substrates, the products were obtained as the mixture of two imidazo[1,2-*a*]pyridine isomers. For example, 1-phenylbutane-1,3-dione (**9**) reacted with 2-aminopyridines **1** to afford products **10** and **11**, with the 2-methyl isomer **10** as the major product (Scheme 6).

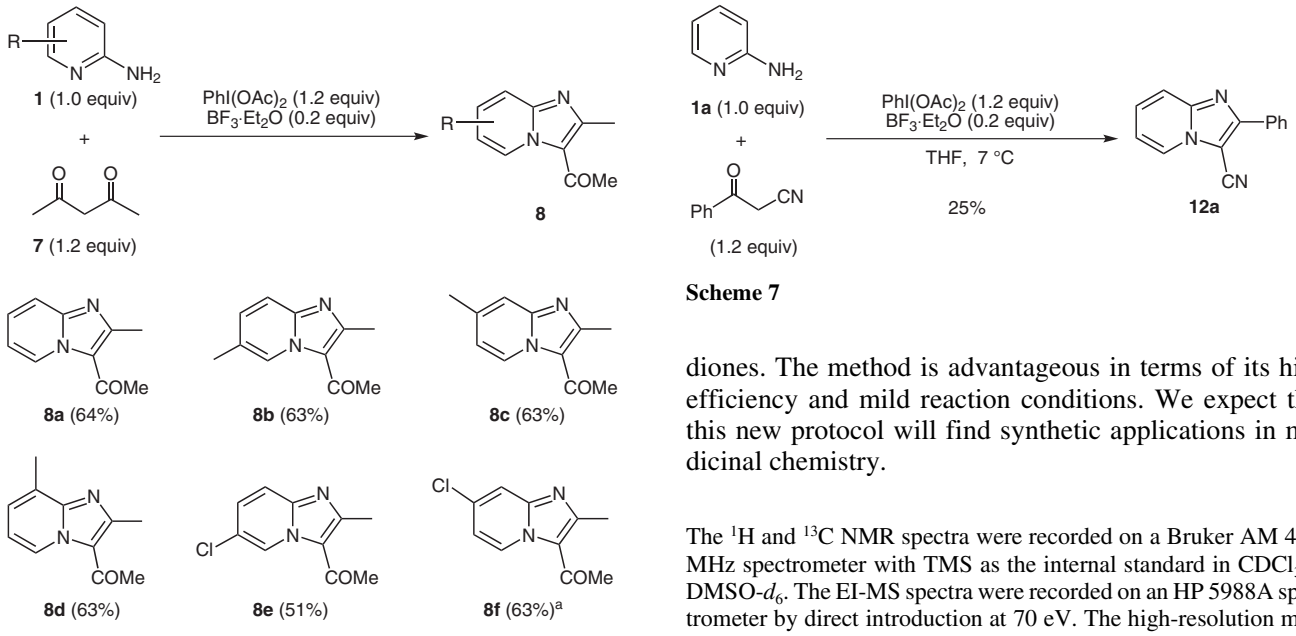


5 6

Scheme 3



Scheme 4



Scheme 5 The reactions were performed in THF at 7 °C unless otherwise specified. [a]The reaction was performed in toluene at refluxing temperature.

On the other hand, PIDA was not as effective in promoting the coupling/condensation of **1a** with benzoylacetonitrile. The expected imidazo[1,2-*a*]pyridine product **12a** was obtained in only 25% yield (Scheme 7).

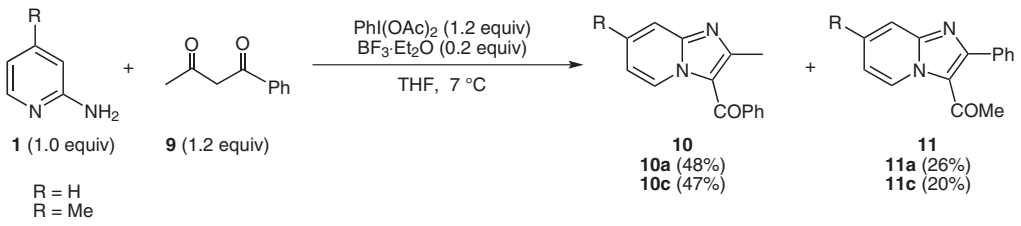
In summary, we have developed a new method for the synthesis of imidazo[1,2-*a*]pyridines by bis(acetyloxy)(phenyl)-λ^3-iodane-mediated direct oxidative coupling of pyridine-2-amines and β-keto esters or 1,3-diones. The method is advantageous in terms of its high efficiency and mild reaction conditions. We expect that this new protocol will find synthetic applications in medicinal chemistry.

Scheme 7

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400-MHz spectrometer with TMS as the internal standard in $CDCl_3$ or DMSO-d_6. The EI-MS spectra were recorded on an HP 5988A spectrometer by direct introduction at 70 eV. The high-resolution mass spectra were recorded on a Bruker Daltonics APEX II 47e spectrometer. Melting points were measured on an XT-4 melting point apparatus and are uncorrected.

2-Substituted Imidazo[1,2-*a*]pyridine-3-carboxylates (3); General Procedure

Keto ester **2** (1.0 mmol), $PhI(OAc)_2$ (0.322 g, 1.0 mmol), and $BF_3{\cdot}Et_2O$ (26 μL) were added successively to a 10-mL round-bottomed flask containing THF (5 mL) and 2-aminopyridine **1** (1.0 mmol), and the mixture was stirred at 7 °C until the reaction was complete (TLC). The mixture was then poured into sat. aq $NaHCO_3$ (15 mL) and extracted with EtOAc (10 × 3 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by



Scheme 6

chromatography (silica gel). For the synthesis of **3o**–**3t**, 1.2 equiv each of **2** and PIDA were used. The synthesis of compounds **3s** and **3t** was performed in refluxing toluene for 24 h.

Ethyl 7-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (3c)[11b]
White solid; mp 90–91 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (t, 3 H, *J* = 7.2 Hz), 2.46 (s, 3 H), 4.29 (q, 2 H, *J* = 7.2 Hz), 6.86 (dd, 1 H, *J* = 6.8 Hz, *J* = 1.6 Hz), 7.40–7.44 (m, 3 H), 7.48 (s, 1 H), 7.75–7.77 (m, 2 H), 9.27 (d, 1 H, *J* = 6.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 21.3, 60.2, 111.4, 116.0, 116.5, 127.3, 127.4, 128.5, 130.1, 134.5, 139.2, 147.5, 153.6, 161.1.

EI-MS: *m/z* (%) = 280 (54) [M$^+$], 208 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1282.

Ethyl 8-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (3d)[11b]
White solid; mp 113–114 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, 3 H, *J* = 7.2 Hz), 2.68 (s, 3 H), 4.28 (q, 2 H, *J* = 7.2 Hz), 6.94 (t, 1 H, *J* = 7.0 Hz), 7.22 (dd, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz) 7.40–7.45 (m, 3 H), 7.74–7.76 (m, 2 H), 9.27 (d, 1 H, *J* = 6.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 17.1, 60.3, 112.3, 114.0, 126.0, 126.7, 127.4, 127.5, 128.4, 130.2, 134.9, 147.3, 153.2, 161.2.

EI-MS: *m/z* (%) = 280 (53) [M$^+$], 208 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1286.

Ethyl 6-Chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (3e)[11b]
White solid; mp 117–119 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, 3 H, *J* = 7.2 Hz), 4.32 (q, 2 H, *J* = 7.2 Hz), 7.40–7.46 (m, 4 H), 7.68 (d, 1 H, *J* = 9.2 Hz), 7.74–7.76 (m, 2 H), 9.52 (d, 1 H, *J* = 1.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 60.7, 112.3, 117.7, 122.4, 126.3, 127.6, 128.9, 129.2, 130.1, 134.0, 145.3, 154.0, 160.9.

EI-MS: *m/z* (%) = 302 (17), 300 (54) [M$^+$], 230 (28), 228 (100), 174 (42), 159 (66), 149 (36).

Ethyl 7-Chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (3f)
White solid; mp 116–118 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, 3 H, *J* = 7.2 Hz), 4.31 (q, 2 H, *J* = 7.2 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 7.43–7.47 (m, 3 H), 7.72–7.76 (m, 3 H), 9.36 (d, 1 H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 60.6, 112.0, 115.5, 116.4, 127.6, 128.6, 128.9, 130.1, 133.9, 134.5, 146.9, 154.2, 160.8.

EI-MS: *m/z* (%) = 302 (20), 300 (50) [M$^+$], 230 (32), 228 (100), 149 (42), 57 (35).

HRMS (ESI): [M + H]$^+$ calcd for $C_{16}H_{14}ClN_2O_2$: 301.0738; found: 301.0736.

Methyl 2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine-3-carboxylate (3g)
White solid; mp 130–132 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 7.02 (dt, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.39–7.44 (m, 3 H), 7.70 (d, 3 H, *J* = 8.4 Hz), 9.37 (dd, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.2, 111.6, 114.2, 117.4, 127.8, 128.1, 128.3, 131.3, 132.8, 134.7, 147.1, 152.3, 161.1.

EI-MS: *m/z* (%) = 288 (37), 286 (100) [M$^+$], 273 (17), 271 (60), 242 (18), 240 (42), 230 (23), 228 (73), 149 (59).

HRMS (ESI): [M + H]$^+$ calcd for $C_{15}H_{12}ClN_2O_2$: 287.0582; found: 287.0579.

Ethyl 2-(4-Ethylphenyl)-6-methylimidazo[1,2-*a*]pyridine-3-carboxylate (3h)
White solid; mp 60–62 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, 3 H, *J* = 7.2 Hz), 1.27 (t, 3 H, *J* = 7.6 Hz), 2.41 (s, 3 H), 2.71 (q, 2 H, *J* = 7.6 Hz), 4.31 (q, 2 H, *J* = 7.2 Hz), 7.26 (d, 3 H, *J* = 8.4 Hz), 7.62 (d, 1 H, *J* = 8.8 Hz), 7.70 (d, 2 H, *J* = 8.0 Hz), 9.22 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 15.5, 18.4, 28.7, 60.2, 111.4, 116.6, 123.7, 126.2, 127.0, 130.1, 130.7, 131.8, 144.7, 146.1, 153.5, 161.3.

EI-MS: *m/z* (%) = 308 (71) [M$^+$], 236 (100), 221 (47).

HRMS (ESI): [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1591.

Ethyl 2-Propylimidazo[1,2-*a*]pyridine-3-carboxylate (3i)
White solid; mp 24–26 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (t, 3 H, *J* = 7.2 Hz), 1.42 (t, 3 H, *J* = 7.0 Hz), 1.75–1.84 (m, 2 H), 3.06 (t, 2 H, *J* = 7.6 Hz), 4.41 (q, 2 H, *J* = 7.2 Hz), 6.95 (t, 1 H, *J* = 6.8 Hz), 7.35 (t, 1 H, *J* = 8.4 Hz), 7.62 (d, 1 H, *J* = 9.2 Hz), 9.31 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 14.3, 22.9, 32.2, 60.2, 112.2, 113.5, 116.8, 127.4, 128.0, 146.9, 156.9, 161.4.

EI-MS: *m/z* (%) = 232 (21) [M$^+$], 204 (67), 132 (100), 78 (20).

HRMS (ESI): [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_2$: 233.1285; found: 233.1280.

Ethyl 6-Methyl-2-propylimidazo[1,2-*a*]pyridine-3-carboxylate (3j)
Pale yellow solid; mp 31–33 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (t, 3 H, *J* = 7.2 Hz), 1.44 (t, 3 H, *J* = 7.0 Hz), 1.74–1.84 (m, 2 H), 2.38 (s, 3 H), 3.05 (t, 2 H, *J* = 7.6 Hz), 4.42 (q, 2 H, *J* = 7.2 Hz), 7.23 (dd, 1 H, *J* = 9.2 Hz, *J* = 1.6 Hz), 7.54 (d, 1 H, *J* = 9.2 Hz), 9.15 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 14.4, 18.4, 22.9, 32.2, 60.1, 111.9, 116.0, 123.4, 126.0, 130.4, 145.9, 156.6, 161.5.

EI-MS: *m/z* (%) = 246 (20) [M$^+$], 218 (61), 146 (100), 92 (14).

HRMS (ESI): [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1441; found: 247.1449.

Ethyl 7-Methyl-2-propylimidazo[1,2-*a*]pyridine-3-carboxylate (3k)
White solid; mp 52–54 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, 3 H, *J* = 7.2 Hz), 1.36 (t, 3 H, *J* = 7.0 Hz), 1.68–1.77 (m, 2 H), 2.34 (s, 3 H), 2.98 (t, 2 H, *J* = 7.8 Hz), 4.42 (q, 2 H, *J* = 7.2 Hz), 6.70 (d, 1 H, *J* = 7.2 Hz), 7.30 (s, 1 H), 9.09 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 14.2, 21.1, 22.8, 32.0, 59.9, 111.6, 115.3, 115.8, 127.0, 138.6, 147.2, 156.8, 161.2.

EI-MS: *m/z* (%) = 246 (21) [M$^+$], 218 (61), 146 (100), 92 (16).

HRMS (ESI): [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1441; found: 247.1436.

Ethyl 6-Chloro-2-propylimidazo[1,2-*a*]pyridine-3-carboxylate (3m)
Orange solid; mp 91–93 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (t, 3 H, *J* = 7.2 Hz), 1.44 (t, 3 H, *J* = 7.2 Hz), 1.76–1.81 (m, 2 H), 3.05 (t, 2 H, *J* = 7.8 Hz), 4.43 (q, 2 H, *J* = 7.2 Hz), 7.33 (dd, 1 H, *J* = 9.2 Hz, *J* = 2.0 Hz), 7.56 (dd, 1 H, *J* = 9.2 Hz, *J* = 2.4 Hz), 9.41 (d, 1 H, *J* = 2.0 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 14.3, 22.8, 32.1, 60.5, 112.7, 117.0, 121.8, 126.0, 128.7, 145.2, 157.3, 161.2.

EI-MS: *m/z* (%) = 268 (6), 266 (17) [M$^+$], 240 (21), 238 (72), 168 (32), 166 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{13}H_{16}ClN_2O_2$: 267.0895; found: 267.0900.

Ethyl 7-Chloro-2-propylimidazo[1,2-*a*]pyridine-3-carboxylate (3n)
White solid; mp 61–63 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (t, 3 H, *J* = 7.2 Hz), 1.43 (t, 3 H, *J* = 7.0 Hz), 1.73–1.82 (m, 2 H), 3.04 (t, 2 H, *J* = 7.8 Hz), 4.41 (q, 2 H, *J* = 7.2 Hz), 6.94 (dd, 1 H, *J* = 7.2 Hz, *J* = 2.0 Hz), 7.60 (d, 1 H, *J* = 2.0 Hz), 9.25 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 14.3, 22.8, 32.1, 60.4, 112.4, 114.9, 115.8, 128.2, 134.1, 146.8, 157.6, 161.2.

EI-MS: *m/z* (%) = 268 (6), 266 (19) [M$^+$], 240 (22), 238 (69), 168(33), 166 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{13}H_{16}ClN_2O_2$: 267.0895; found: 267.0893.

Methyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (3o)
Pale yellow solid; mp 103–105 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.72 (s, 3 H), 3.97 (s, 3 H), 6.99 (t, 1 H, *J* = 6.8 Hz), 7.39 (t, 1 H, *J* = 7.2 Hz), 7.63 (d, 1 H, *J* = 9.2 Hz), 9.31 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 51.3, 112.4, 113.7, 116.6, 127.7, 127.9, 146.9, 152.8, 161.8.

EI-MS: *m/z* (%) = 190 (100) [M$^+$], 159 (83), 132 (68), 131 (24), 90 (28).

HRMS (ESI): [M + H]$^+$ calcd for $C_{10}H_{11}N_2O_2$: 191.0815; found: 191.0817.

Methyl 2,6-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (3p)
Pale yellow solid; mp 47–49 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.37 (s, 3 H), 2.67 (s, 3 H), 3.94 (s, 3 H), 7.21 (d, 1 H, *J* = 8.8 Hz), 7.49 (d, 1 H, *J* = 8.8 Hz), 9.09 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.6, 18.3, 51.2, 112.1, 115.8, 123.4, 125.9, 130.5, 145.9, 152.6, 161.9.

EI-MS: *m/z* (%) = 204 (100) [M$^+$], 173 (73), 146 (68), 145 (21), 104 (13).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0972; found: 205.0974.

Methyl 2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (3q)
White solid; mp 36–38 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H), 2.65 (s, 3 H), 3.92 (s, 3 H), 6.77 (dd, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.32 (s, 1 H), 9.11 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 21.3, 51.1, 111.9, 115.3, 116.0, 127.0, 139.0, 147.3, 152.9, 161.8.

EI-MS: *m/z* (%) = 204 (100) [M$^+$], 173 (71), 146 (76), 145 (33), 104 (13).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0972; found: 205.0979.

Methyl 2,8-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (3r)
White solid; mp 99–100 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.62 (s, 3 H), 2.72 (s, 3 H), 3.95 (s, 3 H), 6.87 (t, 1 H, *J* = 7.0 Hz), 7.16 (d, 1 H, *J* = 6.8 Hz), 9.15 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 17.0, 51.2, 112.8, 113.6, 125.7, 126.4, 126.8, 147.0, 152.1, 161.9.

EI-MS: *m/z* (%) = 204 (100) [M$^+$], 173 (65), 146 (65), 145 (20).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0972; found: 205.0976.

Methyl 6-Chloro-2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (3s)
Khaki solid; mp 99–101 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.67 (s, 3 H), 3.95 (s, 3 H), 7.32 (dd, 1 H, *J* = 9.2 Hz, *J* = 2.0 Hz), 7.51 (d, 1 H, *J* = 9.2 Hz), 9.33 (d, 1 H, *J* = 1.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 51.4, 112.9, 116.8, 121.9, 125.9, 128.8, 145.1, 153.2, 161.4.

EI-MS: *m/z* (%) = 226 (31), 224 (100) [M$^+$], 195 (30), 193 (91), 168 (23), 166 (71), 165 (20), 124 (28).

HRMS (ESI): [M + H]$^+$ calcd for $C_{10}H_{10}ClN_2O_2$: 225.0425; found: 225.0433.

Methyl 7-Chloro-2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (3t)
White solid; mp 141–143 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.69 (s, 3 H), 3.96 (s, 3 H,), 6.96 (dd, 1 H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.59 (d, 1 H, *J* = 2.0 Hz), 9.23 (d, 1 H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 51.5, 112.7, 115.1, 115.7, 128.1, 134.3, 146.8, 153.6, 161.6.

EI-MS: *m/z* (%) = 226 (13), 224 (100) [M$^+$], 195 (27), 193 (80), 168 (25), 166 (77), 165 (29), 124 (25).

HRMS (ESI): [M + H]$^+$ calcd for $C_{10}H_{10}ClN_2O_2$: 225.0425; found: 225.0422.

2-Aryl-3-methoxymethylimidazo[1,2-*a*]pyridine; General Procedure[15]
Finely powdered $NaBH_4$ (96%, 0.74 g, 0.019 mol, 5.8 equiv) was stirred in refluxing THF containing carboxylate **3g** (0.92 g, 3.2 mmol) or **3h** (0.99 g, 3.2 mmol) for 15 min. MeOH (6 mL) was then added dropwise over 15 min, and the mixture was stirred and refluxed for 1 h. At the end of reaction (TLC), the mixture was cooled to rt and the reaction was quenched with sat. aq NH_4Cl (10 mL) for a further 1.5 h. The organic layer was then separated and the aqueous phase was extracted with EtOAc (70 × 3 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure. The product was further purified by column chromatography [silica gel, EtOAc–MeOH (10:1 to pure MeOH)]. Yield for **5h**: 0.68 g, 80%.

[2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methanol (5g)
White solid; yield: 0.69 g (84%); mp 204–206 °C.

^{1}H NMR (DMSO, 400 MHz): δ = 4.91 (d, 2 H, *J* = 5.2 Hz), 5.46 (t, 1 H, *J* = 5.2 Hz), 6.99 (dt, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.32 (ddd, 1 H, *J* = 9.2 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.55 (dd, 2 H, *J* = 6.8 Hz,

J = 2.0 Hz), 7.62 (d, 1 H, J = 9.2 Hz), 7.87 (dd, 2 H, J = 6.8 Hz, J = 2.0 Hz), 8.46 (d, 1 H, J = 7.2 Hz).

^{13}C NMR (DMSO, 100 MHz): δ = 52.0, 112.2, 116.7, 120.8, 125.2, 128.6, 129.7, 132.4, 133.3, 141.6, 144.0.

EI-MS: *m/z* (%) = 260 (15), 258 (49) [M$^+$], 243 (33), 242 (40), 241 (100), 206 (35), 205 (35), 57 (37), 44 (40).

HRMS (ESI): [M + H]$^+$ calcd for $C_{14}H_{12}ClN_2O_1$: 259.0633; found: 259.0635.

[2-(4-Ethylphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl]methanol (5h)[14]

White solid; yield: 0.69 g (84%); mp 195–197 °C.

^{1}H NMR (DMSO, 400 MHz): δ = 1.22 (t, 3 H, J = 7.6 Hz), 2.33 (s, 3 H), 2.65 (q, 2 H, J = 7.6 Hz), 4.88 (d, 2 H, J = 5.2 Hz), 5.38 (t, 1 H, J = 5.2 Hz), 7.14 (dd, 1 H, J = 9.2 Hz, J = 1.2 Hz), 7.31 (d, 2 H, J = 8.0 Hz), 7.51 (d, 1 H, J = 9.2 Hz), 7.74 (d, 2 H, J = 8.4 Hz), 8.25 (s, 1 H).

^{13}C NMR (DMSO, 100 MHz): δ = 15.6, 17.8, 27.9, 52.2, 116.0, 120.0, 121.0, 122.5, 127.7, 127.9, 128.1, 132.0, 142.8, 143.0, 143.1.

EI-MS: *m/z* (%) = 266 (11) [M$^+$], 149 (64), 57 (61), 44 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_1$: 267.1492; found: 267.1494.

3-Acylimidazo[1,2-*a*]pyridines 8, 10, and 11; General Procedure

Dione **7** or **9** (1.2 mmol), $PhI(OAc)_2$ (0.386 g, 1.2 mmol), and $BF_3{\cdot}Et_2O$ (26 μL) were added successively to a 10-mL round-bottomed flask containing THF (5 mL) and 2-aminopyridine **1**, and the mixture was stirred at 7 °C overnight. When the reaction was complete (TLC), the mixture was poured into sat. aq $NaHCO_3$ (15 mL) and the product was extracted with EtOAc (10 × 3 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel). For the synthesis of **8f**, the reaction was performed in refluxing toluene for 24 h. Compound **12a** was prepared by a similar procedure.

1-(2-Methylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8a)[5a,17a]

White solid; mp 105–106 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.55 (s, 3 H), 2.72 (s, 3 H), 6.94 (t, 1 H, J = 7.2 Hz), 7.38 (t, 1 H, J = 7.6 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 9.65 (dd, 1 H, J = 7.2 Hz, J = 0.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.2, 30.1, 114.3, 116.2, 121.6, 128.8, 128.9, 146.7, 152.6, 187.4.

EI-MS: *m/z* (%) = 174 (69) [M$^+$], 159 (100), 131 (17), 90 (33).

1-(2,6-Dimethylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8b)

Pale yellow solid; mp 101–103 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H), 2.61 (s, 3 H), 2.78 (s, 3 H), 7.31 (d, 1 H, J = 9.2 Hz), 7.53 (d, 1 H, J = 9.2 Hz), 9.55 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.3, 30.2, 115.5, 121.6, 124.3, 127.0, 131.8, 145.7, 152.5, 187.5.

EI-MS: *m/z* (%) = 188 (55) [M$^+$], 173 (100), 104 (14).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_1$: 189.1022; found: 189.1026.

1-(2,7-Dimethylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8c)

White solid; mp 137–138 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.43 (s, 3 H), 2.57 (s, 3 H), 2.74 (s, 3 H), 6.82 (dd, 1 H, J = 6.8 Hz, J = 1.2 Hz), 7.36 (s, 1 H), 9.56 (d, 1 H, J = 6.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.3, 21.4, 30.0, 115.1, 116.8, 121.5, 128.2, 140.6, 147.2, 152.9, 187.2.

EI-MS: *m/z* (%) = 188 (67) [M$^+$], 173 (100), 145 (17).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O$: 189.1022; found: 189.1026.

1-(2,8-Dimethylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8d)

White solid; mp 156–157 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (s, 3 H), 2.62 (s, 3 H), 2.79 (s, 3 H), 6.90 (t, 1 H, J = 7.2 Hz), 7.23 (d, 1 H, J = 7.2 Hz), 9.58 (d, 1 H, J = 6.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.9, 18.4, 30.3, 114.4, 122.1, 126.1, 126.8, 128.1, 146.9, 152.1, 187.6.

EI-MS: *m/z* (%) = 188 (63) [M$^+$], 173 (100), 104 (13).

HRMS (ESI): [M + H]$^+$ calcd for $C_{11}H_{13}N_2O$: 189.1022; found: 189.1024.

1-(6-Chloro-2-methylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8e)[17c]

White solid; mp 169–170 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (s, 3 H), 2.76 (s, 3 H), 7.39 (dd, 1 H, J = 9.6 Hz, J = 2.0 Hz), 7.53 (d, 1 H, J = 9.6 Hz), 9.78 (d, 1 H, J = 1.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.3, 30.3, 116.6, 122.0, 122.7, 127.0, 130.1, 145.0, 153.0, 187.8.

EI-MS: *m/z* (%) = 210 (18), 208 (58) [M$^+$], 195 (36), 193 (100), 124 (27).

1-(7-Chloro-2-methylimidazo[1,2-*a*]pyridin-3-yl)ethanone (8f)

Khaki solid; mp 157–159 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (s, 3 H), 2.77 (s, 3 H), 6.97 (dd, 1 H, J = 7.6 Hz, J = 2.0 Hz), 7.59 (d, 1 H, J = 2.0 Hz), 9.64 (d, 1 H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.2, 30.2, 115.5, 115.7, 121.8, 129.2, 135.5, 146.8, 153.4, 187.6.

EI-MS: *m/z* (%) = 210 (10), 208 (58) [M$^+$], 195 (32), 193 (100), 124 (21).

HRMS (ESI): [M + H]$^+$ calcd for $C_{10}H_{10}ClN_2O$: 209.0476; found: 209.0479.

(2-Methylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (10a)

White solid; mp 82–84 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13 (s, 3 H), 7.00 (t, 1 H, J = 6.8 Hz), 7.42–7.48 (m, 3 H), 7.52–7.55 (m, 1 H), 7.62–7.64 (m, 3 H), 9.46 (d, 1 H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.4, 114.2, 116.4, 121.2, 128.2, 128.4, 128.5, 129.1, 131.6, 140.2, 147.3, 153.3, 186.8.

EI-MS: *m/z* (%) = 236 (60) [M$^+$], 235 (100), 159 (28), 90 (14), 77(13).

HRMS (ESI): [M + H]$^+$ calcd for $C_{15}H_{13}N_2O$: 237.1022; found: 237.1026.

(2,7-Dimethylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (10c)

White solid; mp 149–151 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.12 (s, 3 H), 2.47 (s, 3 H), 6.87 (d, 1 H, J = 6.8 Hz), 7.40 (s, 1 H), 7.46–7.50 (m, 2 H), 7.54–7.58 (m, 1 H), 7.64 (d, 2 H, J = 7.6 Hz), 9.38 (d, 1 H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.6, 21.6, 115.4, 116.8, 121.2, 127.9, 128.3, 128.6, 131.5, 140.6, 140.9, 148.1, 153.9, 186.7.

EI-MS: *m/z* (%) = 250 (67) [M$^+$], 249 (100), 173 (23), 77 (13).

HRMS (ESI): [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1179; found: 251.1176.

1-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)ethanone (11a)
White solid; mp 110–112 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.19 (s, 3 H), 7.08 (dt, 1 H, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.48–7.53 (m, 4 H), 7.57–7.60 (m, 2 H), 7.74 (d, 1 H, *J* = 8.8 Hz), 9.76 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.8, 114.8, 117.2, 121.3, 128.4, 129.0, 129.1, 129.3, 129.7, 135.2, 146.8, 155.3, 189.1.

EI-MS: *m/z* (%) = 236 (74) [M$^+$], 235 (42), 221 (100), 192 (25).

HRMS (ESI): [M + H]$^+$ calcd for $C_{15}H_{13}N_2O$: 237.1022; found: 237.1024.

1-(7-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethanone (11c)
White solid; mp 108–110 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.16 (s, 3 H), 2.48 (s, 3 H), 6.91 (dd, 1 H, *J* = 6.8 Hz, *J* = 1.6 Hz), 7.47–7.48 (m, 4 H), 7.56–7.58 (m, 2 H), 9.63 (d, 1 H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 29.7, 115.8, 117.2, 121.1, 128.2, 128.3, 129.0, 129.7, 135.4, 140.9, 147.2, 155.5, 188.7.

EI-MS: *m/z* (%) = 250 (76) [M$^+$], 249 (36), 235 (100).

HRMS (ESI): [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1179; found: 251.1174.

2-Phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (12a)
White solid; mp 144–146 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.10 (dt, 1 H, *J* = 6.8 Hz, *J* = 0.8 Hz), 7.45–7.55 (m, 4 H), 7.77 (d, 1 H, *J* = 9.2 Hz), 8.18–8.21 (m, 2 H), 8.37 (d, 1 H, *J* = 6.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 93.8, 112.8, 114.7, 118.2, 125.6, 127.3, 128.7, 129.0, 130.1, 131.2, 146.8, 153.4.

EI-MS: *m/z* (%) = 219 (100) [M$^+$], 218 (20), 149 (11), 78 (16).

HRMS (ESI): [M + H]$^+$ calcd for $C_{14}H_{10}N_3$: 220.0869; found: 220.0863.

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

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