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Synthesis of 1,3-Disubstituted Imidazo[1,5-*a*]pyridines from Amino Acids via Catalytic Decarboxylative Intramolecular Cyclization

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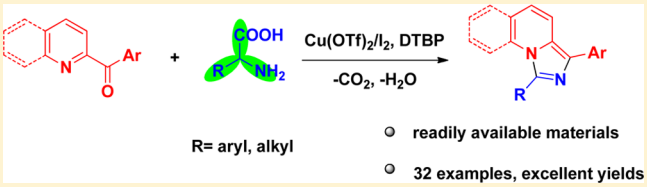
Supporting Information

ABSTRACT: A copper/iodine cocatalyzed decarboxylative cyclization of α-amino acids is described. Starting from the readily available amino acids and either 2-benzoylpyridines or 2-benzoylquinolines, 1,3-disubstituted imidazo[1,5-*a*]pyridines and 1,3-disubstituted imidazo[1,5-*a*]quinolines were prepared in excellent yields.



INTRODUCTION

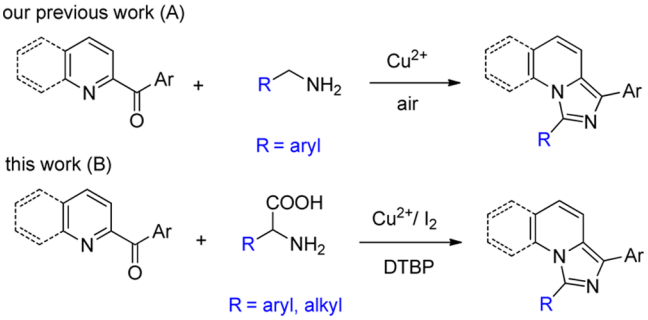
Transition-metal-catalyzed decarboxylation reactions have attracted much attention for their use in the site-specific introduction of functional groups.[1] Compared to other carboxylic acids, α-amino acids have the advantages of being naturally abundant, highly stabile, and low cost, which make them extremely promising raw materials for chemical synthesis. Therefore, α-amino acids have been widely used to construct C−C,[2] C−N,[3] and C−O[4] bonds via a decarboxylative coupling process. While various decarboxylation reaction of amino acids have been well-studied, new decarboxylative cyclization of α-amino acids for the synthesis of biologically important heterocycles, especially in a catalytic manner, is still highly desirable.

Imidazo[1,5-*a*]pyridine scaffolds are present in various drug-relevant molecules and biologically active agents.[5] Thus, method development for accessing this important structural motif is of high interest. Traditionally, imidazo[1,5-*a*]pyridines were prepared through Vilsmeier-type cyclizations or their variants.[6] Recent efforts on the oxidative cyclization reaction also provided a complementary way to access imidazo[1,5-*a*]pyridines.[7,8] However, most of these methods were ineffective for the construction of 1,3-disubstituted imidazo-[1,5-*a*]pyridines.[9] To address this limition, our group recently developed an oxidative amination method to give 1,3-diarylimidazo[1,5-*a*]pyridine in excellent yields (Scheme 1A).[10] Unfortunately, the complementary 3-alkyl derivatives were not accessible via this oxidative amination process. In continuation of our recent work on decarboxylation reaction of amino acids,[4c] we report herein an efficient decarboxylative cyclization of amino acids for the synthesis of 3-alkyl-1-arylimidazo[1,5-*a*]pyridines (Scheme 1B). To the best of our knowledge, successful examples of the synthesis of this type of scaffold are rather limited.[11]

RESULTS AND DISCUSSION

Previous work reported by Li and co-workers has shown that the combination of copper salt with peroxide was effective for the decarboxylation of amino acids.[2a] To identify the best

Scheme 1. Our Methods for the Synthesis of 1,3-Disubstituted Imidazo[1,5-*a*]pyridines



reaction conditions, the decarboxylative cyclization reaction between 2-benzoylpyridine (**1a**) and leucine (**2a**) was tested under different oxidative reaction conditions (Table 1). First, the efficiency of different copper salts was screened with molecular iodine as a cocatalyst. The results showed that $Cu(OTf)_2$ was the most efficient catalyst for this reaction (entry 1), while other copper catalysts resulted in a significant drop in yields (entries 2−5). In the absence of copper catalysts, the reaction gave the target product **3a** in 39% yield (entry 6), while only 20% yield of the desired product was obtained in the absence of molecular iodine (entry 7). Subsequently, *n*-Bu_4NI instead of molecular iodine as a catalyst was tested; however, the yield of product **3a** decreased to 51% (entry 8). Then, the influence of different peroxide on this decarboxylative cyclization reaction was investigated. The results revealed that DTBP (di-*tert*-butyl peroxide) would be the best choice for this reaction (entry 1 vs 9 and 10). Further assessment of the reaction conditions indicated that toluene was the optimal solvent, while other commonly used solvents gave lower yields (entry 1 vs 11−14). By increasing or lowing the reaction temperature, no improvement in yield was observed (entries 15 and 16).

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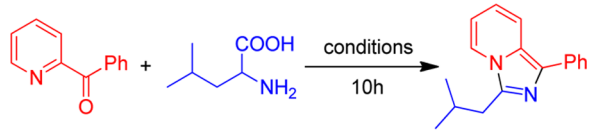
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Cu^{n+}	oxidant	solvent	yield (%)[b]
1	$Cu(OTf)_2$	DTBP	Tol	92
2	$Cu(OAc)_2$	DTBP	Tol	43
3	$CuBr_2$	DTBP	Tol	39
4	$CuCl_2$	DTBP	Tol	35
5	CuI	DTBP	Tol	29
6	–	DTBP	Tol	39
7[c]	$Cu(OTf)_2$	DTBP	Tol	20
8[d]	$Cu(OTf)_2$	DTBP	Tol	51
9	$Cu(OTf)_2$	TBHP	Tol	65
10	$Cu(OTf)_2$	BPO	Tol	56
11	$Cu(OTf)_2$	DTBP	DMF	53
12	$Cu(OTf)_2$	DTBP	dioxane	88
13	$Cu(OTf)_2$	DTBP	DCE	68
14	$Cu(OTf)_2$	DTBP	CH_3CN	69
15[e]	$Cu(OTf)_2$	DTBP	Tol	87
16[f]	$Cu(OTf)_2$	DTBP	Tol	88

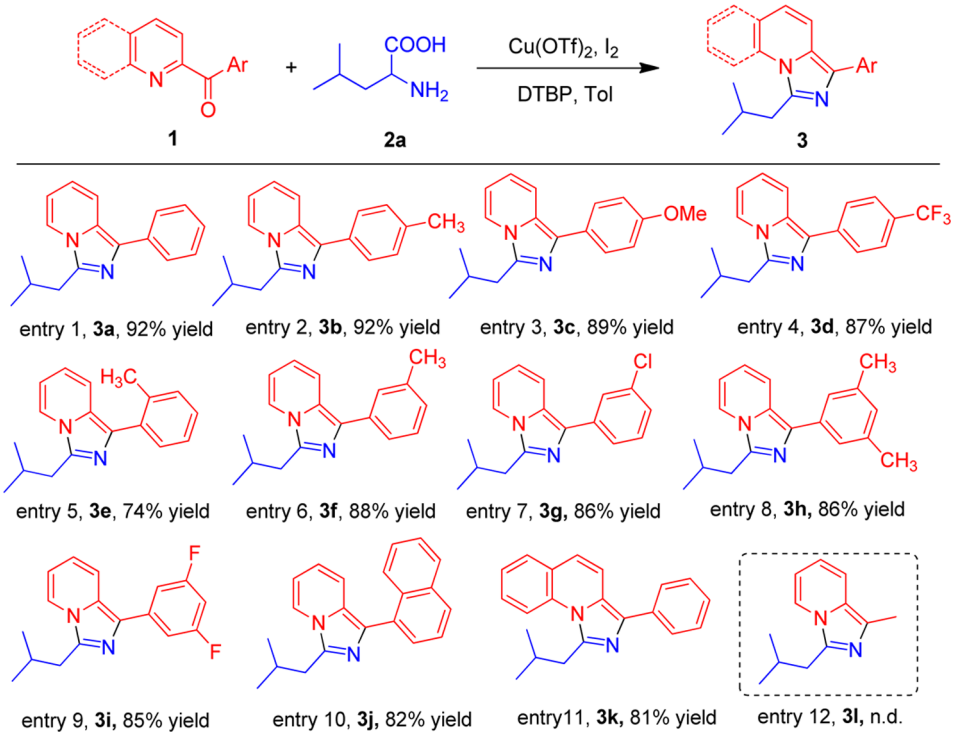
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), copper salt (0.045 mmol), I_2 (0.045 mmol), oxidant (0.75 mmol) in solvent (1 mL), 120 °C, 10 h. DTBP = di-*tert*-butyl peroxide; TBHP = *tert*-butyl hydroperoxide; BPO = dibenzoyl peroxide. Tol = toluene. [b]Isolated yield. [c]No molecular iodine was used. [d]*n*-Bu_4NI was used instead of iodine. [e]The reaction temperature was 130 °C. [f]The reaction temperature was 100 °C.

Having identified the optimal reaction conditions, we next examined the substrate scope of this decarboxylative cyclization reaction by evaluating a variety of 2-benzoylpyridine derivatives **1**. As shown in Table 2, this cyclization reaction is relatively unaffected by the nature of the aryl group, with substrates bearing electron-donating or -withdrawing functionalities demonstrating excellent efficiency (entries 1–4). However, the ortho-substituted aryl group led to a decrease in the yield (entry 5), while meta-substituted aryl groups had little influence on the yield (entries 6–9). When aryl group was replaced with the bulky 1-naphthyl group, the decarboxylation reaction furnished the cyclized product **3j** in 82% yield (entry 10). In addition, when 2-benzoylquinoline was employed as the substrate, the corresponding product **3k** was obtained in 81% yield (entry 11). However, when 1-(pyridin-2-yl)ethanone was employed as the substrate, no corresponding product was detected (entry 12).

Under the optimal reaction conditions, we next sought to establish the scope of aliphatic amino acids in this decarboxylative cyclization reaction. As shown in Table 3, a range of linear and branched amino acids were successfully employed in this reaction to give the products **4a–4d** in moderate to good yields. For the linear amino acids, alanine and norvaline provided the desired products **4a** and **4b** with a similar level of yields (entries 1 and 2), while the bulky norleucine led to a decrease of the yields (entry 3). For the branched amino acid, isoleucine was also tolerated well under the optimal reaction conditions to give product **4d** in 83% yield (entry 4).

To further extend the utility of this decarboxylative cyclization reaction, we next turned our attention to the reaction of 2-benzoylpyridines with α-aryl-substituted amino

Table 2. Substrate Scope of Pyridine Ketones[a]



entry 1, **3a**, 92% yield; entry 2, **3b**, 92% yield; entry 3, **3c**, 89% yield; entry 4, **3d**, 87% yield

entry 5, **3e**, 74% yield; entry 6, **3f**, 88% yield; entry 7, **3g**, 86% yield; entry 8, **3h**, 86% yield

entry 9, **3i**, 85% yield; entry 10, **3j**, 82% yield; entry11, **3k**, 81% yield; entry 12, **3l**, n.d.

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C, 10 h. [b]Isolated yield.

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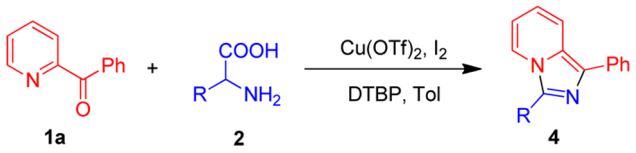
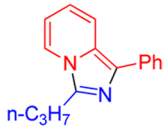
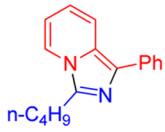
Table 3. Substrate Scope of Aliphatic Amino Acids[a]



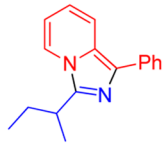
entry 1, **4a**, 73% yield



entry 2, **4b**, 72% yield



entry 3, **4c**, 66% yield



entry 4, **4d**, 83% yield

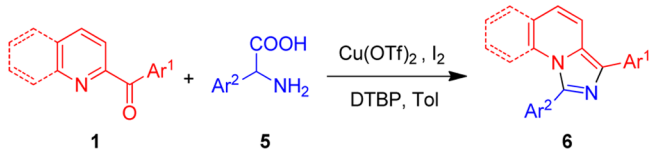
[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C, 10 h. [b]Isolated yield.

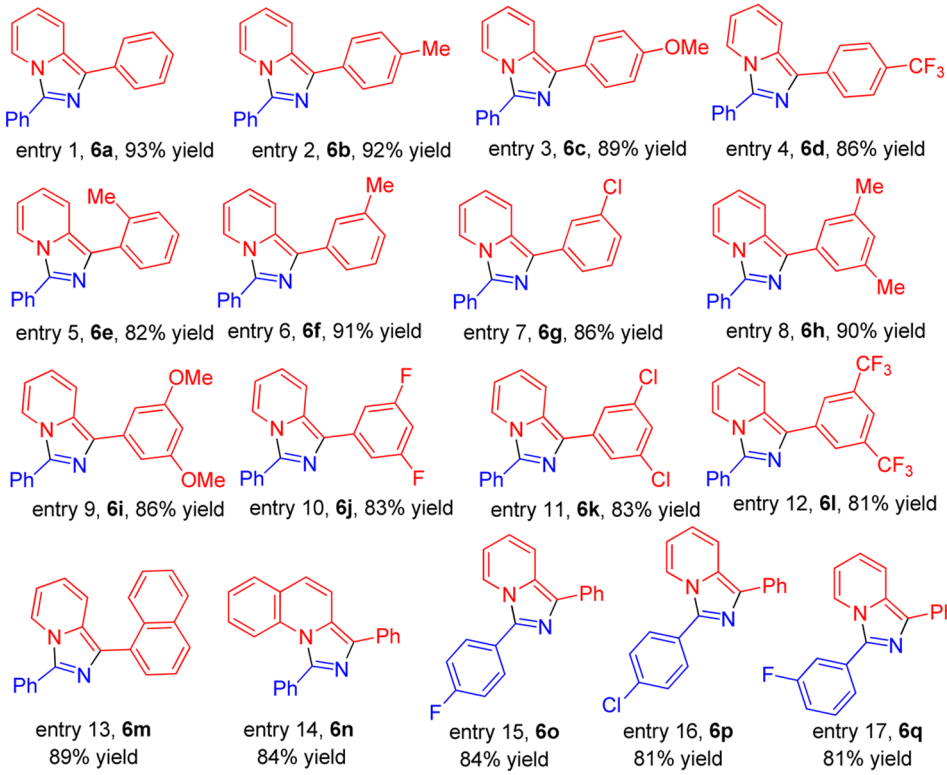
acids (Table 4). First, various 2-benzoylpyridines were employed as substrates to react with phenylglycine under the optimal conditions. The results showed that 2-benzoylpyridines were excellent substrates, regardless of the electronic nature of the aryl substituents, giving 1,3-diarylimidazo[1,5-*a*]pyridines **6a**–**6m** in good to excellent yields (entries 1–13). Besides, 2-benzoylquinoline was also successfully employed as a substrate to give the corresponding product **6n** in 84% yield (entry 14). Finally, some other α-aryl-substituted amino acids were employed as substrates to react with 2-benzoylpyridine. The results showed that para- and meta-halogenated phenylglycines were all compatible with the standard reaction conditions (entries 15–17).

To probe the nature of this decarboxylative cyclization reaction, the radical-trapping reagent (TEMPO) was subjected to the reaction of **1a** with **2a** under the standard conditions (Scheme 2). The desired product **3a** was obtained in 73% yield, suggesting that an ionic pathway was most probably involved in this decarboxylation reaction.

In our previous work, benzylamine could react with 2-benzoylpyridine to afford imidazo[1,5-*a*]pyridine.[10] To determine whether amine was the intermediate of this reaction, a competitive experiment with phenylglycine and 4-fluorobenzylamine was carried out in the same reaction flask (Scheme 3). It was found that 4-fluorobenzylamine gave the corresponding

Table 4. Substrate Scope of the Reaction between 2-Benzoylpyridines and Phenylglycine Derivatives[a]





entry 1, **6a**, 93% yield | entry 2, **6b**, 92% yield | entry 3, **6c**, 89% yield | entry 4, **6d**, 86% yield

entry 5, **6e**, 82% yield | entry 6, **6f**, 91% yield | entry 7, **6g**, 86% yield | entry 8, **6h**, 90% yield

entry 9, **6i**, 86% yield | entry 10, **6j**, 83% yield | entry 11, **6k**, 83% yield | entry 12, **6l**, 81% yield

entry 13, **6m**, 89% yield | entry 14, **6n**, 84% yield | entry 15, **6o**, 84% yield | entry 16, **6p**, 81% yield | entry 17, **6q**, 81% yield

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C, 10 h. [b]Isolated yield.

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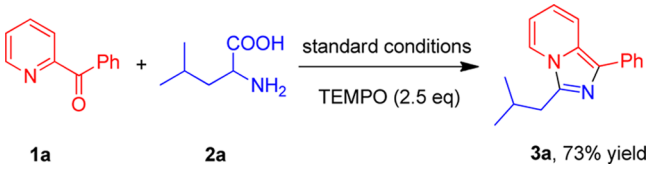
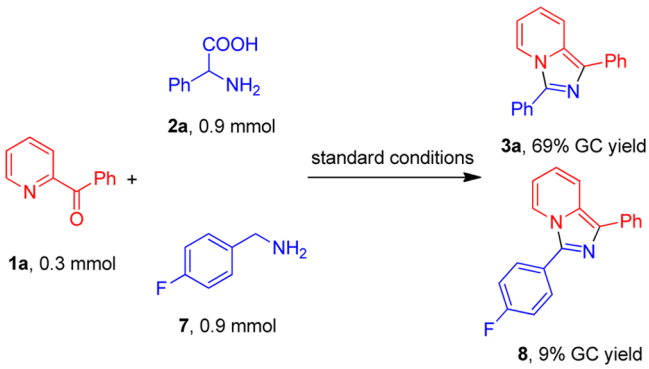
Scheme 2. Control Experiment



Scheme 3. Competitive Reaction between Phenylglycine and 4-Fluorobenzylamine



product **8** in only 9% yield, which suggested that amine was not likely to be the intermediate of this decarboxylation reaction.

On the basis of the control experiment and previous reports,[10−14] a plausible mechanism was proposed, as shown in Scheme 4. First, the condensation reaction between 2-benzoylpyridine (**1a**) and amino acid generates imine **A**. The nitrogen source in the reaction mixture (could be any of the pyridine/amine/imine species) acts as a base to deprotonate imine **A** to generate an organic acid anion, which then reacts with copper salt to give copper carboxylate **B**.[12] In the structure of intermediate **B**, two five-membered chelates were formed upon metal binding. Subsequently, intermediate **B** undergoes a decarboxylation reaction to afford intermediate **C**, which then undergoes an oxidative iodination to give intermediate **D**. With the assistance of iodide anion, the copper−carbon bond in intermediate **D** could dissociate to generate the azomethine ylide-type intermediate **E**.[2a,13] Then, the elimination of iodide anion furnishes intermediate **F**,[10,11] which could tautomerize to intermediate **G**. Intermediate **G** will not violate the geometric constrains imposed by the intermediate **F**. Finally, the intramolecular amination of intermediate **G** leads to the formation of cyclized intermediate **H**,[14] which then undergoes an oxidative dehydrogenation and rearrangement to yield product **3**.

CONCLUSION

In conclusion, we have developed an efficient copper/iodine cocatalytic system for the decarboxylative cyclization of *α*-amino acids with 2-benzoylpyridines. The present decarboxylative cyclization reaction not only provided an attractive alternative method for the synthesis of 1,3-diarylimidazo[1,5-*a*]pyridines but also opened a new route to construct 3-alkyl-1-arylimidazo[1,5-*a*]pyridines, which are difficult to access by the existing methods.

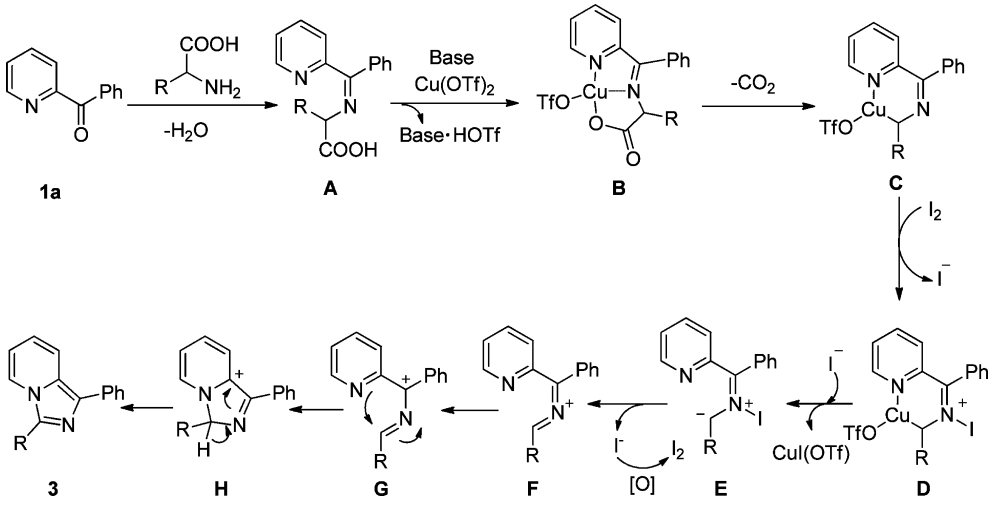
EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on 300 or 400 MHz NMR spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. HRMS was obtained by electrospray ionization (ESI) on a TOF mass analyzer. Melting points were determined on a melting point apparatus and are uncorrected. Pyridine ketones **1** were prepared by using the same methods described in our previous report.[10] Amino acids were commercially available and were used without further purification.

General Procedure for the Synthesis of 1,3-Disubstituted Imidazo[1,5-*a*]pyridines (Tables 2−4). To a sealed tube (10 mL) containing a solution of 2-benzoylpyridine (**1a**) (0.3 mmol) in Tol (1.0 mL) was added $Cu(OTf)_2$ (0.045 mmol), molecular iodine (0.045 mmol), DTBP (0.75 mmol), and amino acids (0.9 mmol) at room temperature. Then, the sealed tube was placed in an oil bath at room temperature. The oil bath was subsequently heated to 120 °C. The reaction mixture was stirred at 120 °C (oil bath temperature) for 10 h. After the reaction was completed, the resulting mixture was extracted with EtOAc (3 × 10 mL) and dried with Na_2SO_4. Then the solvent was removed under reduced pressure and purified by silica gel column chromatography (Hex:EtOAc = 15:1−2:1) to afford the desired product as a yellow solid or pale green oil.

3-Isobutyl-1-phenylimidazo[1,5-*a*]pyridine (3a).[11] Isolated yield: 92% (69 mg), pale green oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.8 Hz, 2H), 7.78−7.76 (m, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.28−7.24 (m, 1H), 6.74−6.70 (m, 1H), 6.56 (t, J = 6.8 Hz, 1H), 2.94 (d, J = 7.2 Hz, 2H), 2.31−2.23 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.3, 130.1, 128.7, 126.7, 126.4,

Scheme 4. A Plausible Mechanism for the Formation of Product 3



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126.2, 121.1, 119.1, 118.7, 112.5, 28.7, 20.7, 14.1. HRMS: calcd $C_{17}H_{19}N_2$ (M + H$^+$) 251.1548, found 251.1551.

3-Isobutyl-1-(*p*-tolyl)imidazo[1,5-*a*]pyridine (3b). Isolated yield: 92% (73 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (t, J = 8.4 Hz, 4H), 7.26 (s, 1H), 7.24 (s, 1H), 6.66 (dd, J = 9.2, 6.4 Hz, 1H), 6.51 (t, J = 6.7 Hz, 1H), 2.90 (d, J = 7.3 Hz, 2H), 2.38 (s, 3H), 2.30−2.21 (m,1H), 1.01 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 135.8, 132.5, 130.3, 129.4, 126.6, 126.1, 121.1, 119.1, 118.2, 112.3, 35.6, 27.9, 22.7, 21.3. HRMS: calcd $C_{18}H_{21}N_2$ (M + H$^+$) 265.1705, found 265.1704.

3-Isobutyl-1-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine (3c). Isolated yield: 89% (75 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.5 Hz, 2H), 7.71 (dd, J = 12.6, 8.3 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.72−6.62 (m, 1H), 6.53 (t, J = 6.7 Hz, 1H), 3.85 (s, 3H), 2.93 (d, J = 7.3 Hz, 2H), 2.33−2.20 (m, 1H), 1.02 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 138.2, 130.2, 128.2, 127.9, 125.8, 121.0, 119.1, 118.0, 114.3, 112.3, 55.4, 35.6, 28.0, 22.7. HRMS: calcd $C_{18}H_{21}N_2O$ (M + H$^+$) 281.1654, found 281.1653.

3-Isobutyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]-pyridine (3d). Isolated yield: 87% (83 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.78 (t, J = 8.8 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 6.80 (dd, J = 9.2, 6.4 Hz, 1H), 6.61 (t, J = 6.7 Hz, 1H), 2.93 (d, J = 7.3 Hz, 2H), 2.33−2.26 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.9, 128.5, 127.6 (d, $^2J_{CF}$ = 31 Hz), 127.3, 126.3, 125.7 (q, $^3J_{CF}$ = 4 Hz), 124.6 (d, $^1J_{CF}$ = 270 Hz), 121.5, 119.9, 118.7, 112.7, 35.6, 27.9, 22.7. HRMS: calcd $C_{18}H_{17}F_3N_2$ (M + H$^+$) 319.1422, found 319.1424.

3-Isobutyl-1-(*o*-tolyl)imidazo[1,5-*a*]pyridine (3e). Isolated yield: 74% (59 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 7.2 Hz, 1H), 7.45−7.43 (m, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.30 (d, J = 4.2 Hz, 1H), 7.25−7.23 (m, 2H), 6.63 (t, J = 6.6 Hz, 1H), 6.54 (t, J = 6.6 Hz, 1H), 2.92 (d, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.32−2.24 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 137.4, 134.0, 130.8, 130.4, 127.3, 127.1, 125.6, 120.8, 119.0, 117.7, 112.3, 35.6, 27.7, 22.7, 20.6. HRMS: calcd $C_{18}H_{21}N_2$ (M + H$^+$) 265.1705, found 265.1706.

3-Isobutyl-1-(*m*-tolyl)imidazo[1,5-*a*]pyridine (3f). Isolated yield: 88% (70 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (t, J = 7.3 Hz, 2H), 7.70 (s, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.68 (dd, J = 9.1, 6.5 Hz, 1H), 6.53 (t, J = 6.8 Hz, 1H), 2.91 (d, J = 7.3 Hz, 2H), 2.42 (s, 3H), 2.25−2.22 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 135.2, 130.4, 128.6, 127.5, 127.1, 126.4, 123.7, 121.2, 119.2, 118.5, 112.4, 35.6, 28.0, 22.7, 21.7. HRMS: calcd $C_{18}H_{21}N_2$ (M + H$^+$) 265.1705, found 265.1704.

1-(3-Chlorophenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3g). Isolated yield: 86% (73 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.75 (dd, J = 11.2, 7.2 Hz, 3H), 7.35 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 6.76 (dd, J = 9.2, 6.3 Hz, 1H), 6.58 (t, J = 6.8 Hz, 1H), 2.91 (d, J = 7.3 Hz, 2H), 2.27 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 137.2, 134.7, 129.9, 128.7, 126.9, 126.4, 126.1, 124.5, 121.4, 119.4, 118.8, 112.6, 35.6, 27.9, 22.8. HRMS: calcd $C_{17}H_{18}N_2Cl$ (M + H$^+$) 285.1159, found 285.1158.

1-(3,5-Dimethylphenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3h). Isolated yield: 86% (72 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (t, J = 9.4 Hz, 2H), 7.47 (s, 2H), 6.91 (s, 1H), 6.72−6.63 (m, 1H), 6.52 (t, J = 6.7 Hz, 1H), 2.91 (d, J = 7.3 Hz, 2H), 2.38 (s, 6H), 2.30−2.21 (m, 1H), 1.00 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 138.2, 135.2, 130.5, 128.1, 126.4, 124.5, 121.1, 119.3, 118.3, 112.4, 35.6, 28.0, 22.7, 21.5. HRMS: calcd $C_{19}H_{23}N_2$ (M + H$^+$) 279.1861, found 279.1860.

1-(3,5-Difluorophenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3i). Isolated yield: 85% (73 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 4 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.41−7.38 (m, 2H), 6.83−6.79 (m, 1H), 6.70−6.64 (m, 1H), 6.61 (t, J = 4 Hz, 1H), 2.90 (d, J = 7.3 Hz, 2H), 2.33−2.20 (m, 1H), 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (d, J = 244 Hz), 163.5 (d, J = 244 Hz), 139.04, 138.7 (t, J = 10.4 Hz), 127.9 (t, J = 3.2 Hz), 127.2, 121.6, 120.0, 118.6, 112.7, 108.8 (d, J = 25 Hz), 108.8 (d, J = 11 Hz), 101.1 (t, J = 26 Hz), 35.6, 27.9, 22.8. HRMS: calcd $C_{17}H_{17}F_2N_2$ (M + H$^+$) 287.1360, found 287.1359.

3-Isobutyl-1-(naphthalen-1-yl)imidazo[1,5-*a*]pyridine (3j). Isolated yield: 82% (74 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.1 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.50−7.42 (m, 2H), 7.39 (d, J = 9.2 Hz, 1H), 6.67−6.58 (m, 1H), 6.54 (t, J = 6.7 Hz, 1H), 2.97 (d, J = 7.3 Hz, 2H), 2.32 (td, J = 13.7, 6.9 Hz, 1H), 1.06 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 134.3, 132.2, 132.1, 129.7, 128.2, 127.9, 127.7, 127.6, 126.6, 126.0, 125.7, 125.4, 120.9, 119.0, 118.1, 112.5, 35.7, 27.8, 22.8. HRMS: calcd $C_{21}H_{21}N_2$ (M + H$^+$) 301.1705, found 301.1707.

1-Isobutyl-3-phenylimidazo[1,5-*a*]quinoline (3k). Isolated yield: 81% (72 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.61 (dd, J = 13.0, 8.6 Hz, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 9.5 Hz, 1H), 3.32 (d, J = 7.0 Hz, 2H), 2.45 (dt, J = 13.3, 6.7 Hz, 1H), 1.11 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 135.0, 133.2, 132.3, 128.7, 128.5, 127.8, 127.4, 126.7, 126.3, 126.0, 124.8, 121.1, 117.6, 116.6, 41.1, 26.6, 22.7. HRMS: calcd $C_{21}H_{21}N_2$ (M + H$^+$) 301.1705, found 301.1704.

3-Methyl-1-phenylimidazo[1,5-*a*]pyridine (4a).[11] Isolated yield: 73% (45 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 6.74 (dd, J = 9.1, 6.5 Hz, 1H), 6.59 (t, J = 6.7 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 135.0, 130.0, 128.8, 126.6, 126.5, 126.3, 121.1, 119.1, 118.7, 112.6, 12.6. HRMS: calcd $C_{14}H_{13}N_2$ (M + H$^+$) 209.1079, found 209.1081.

1-Phenyl-3-propylimidazo[1,5-*a*]pyridine (4b). Isolated yield: 72% (51 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.0 Hz, 2H), 7.78−7.71 (m, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.27−7.23 (m, 1H), 6.72−6.68 (m, 1H), 6.54 (t, J = 6.6 Hz, 1H), 2.99 (t, J = 7.6 Hz, 2H), 1.94−1.82 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.3, 130.1, 128.7, 126.7, 126.5, 126.2, 121.1, 119.1, 118.7, 112.5, 28.7, 20.7, 14.1. HRMS: calcd $C_{16}H_{17}N_2$ (M + H$^+$) 237.1392, found 237.1394.

3-Butyl-1-phenylimidazo[1,5-*a*]pyridine (4c). Isolated yield: 66% (50 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.82 (m, 2H), 7.75 (dd, J = 13.1, 8.2 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.30−7.20 (m, 1H), 6.71 (dd, J = 9.2, 6.4 Hz, 1H), 6.55 (t, J = 6.7 Hz, 1H), 3.06−3.01 (m, 2H), 1.88−1.80 (m, 2H), 1.53−1.44 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 135.4, 130.1, 128.8, 126.7, 126.5, 126.2, 121.1, 119.1, 118.7, 112.5, 29.4, 26.6, 22.8, 14.0. HRMS: calcd $C_{17}H_{19}N_2$ (M + H$^+$) 251.1548, found 251.1550.

3-(*sec*-Butyl)-1-phenylimidazo[1,5-*a*]pyridine (4d). Isolated yield: 83% (62 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.8 Hz, 2H), 7.74 (t, J = 8.2 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.26−7.22 (m, 1H), 6.76−6.59 (m, 1H), 6.51 (t, J = 6.7 Hz, 1H), 3.11 (dd, J = 13.8, 6.9 Hz, 1H), 2.02 (dt, J = 14.3, 7.2 Hz, 1H), 1.79 (dt, J = 14.0, 7.1 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 135.5, 130.1, 128.7, 126.8, 126.4, 126.1, 121.0, 119.1, 118.6, 112.3, 33.1, 28.3, 18.3, 12.2. HRMS: calcd $C_{17}H_{19}N_2$ (M + H$^+$) 251.1548, found 251.1550.

1,3-Diphenylimidazo[1,5-*a*]pyridine (6a).[10,11,15] Isolated yield: 93% (75 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28−8.15 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 9.1, 2.0 Hz, 3H), 7.52 (t, J = 7.5 Hz, 2H), 7.49−7.40 (m, 3H), 7.29 (t, J = 7.4 Hz, 1H), 6.83−6.71 (m, 1H), 6.60−6.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 135.0, 132.0, 130.2, 129.1, 128.9, 128.8, 128.4, 127.8, 126.9, 126.6, 121.8, 119.8, 119.2, 113.3. MS (EI): m/z 270 (M$^+$). Mp: 111−112 °C.

3-Phenyl-1-(*p*-tolyl)imidazo[1,5-*a*]pyridine (6b).[10,11] Isolated yield: 92% (78 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 7.2 Hz, 1H), 7.84−7.80 (m, 5H), 7.54−7.50 (m, 2H), 7.46−7.42 (m, 1H), 7.28−7.25 (m, 2H), 6.77−6.73 (m, 1H), 6.56−6.52 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.2,

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132.1, 132.0, 130.2, 129.4, 129.0, 128.8, 128.4, 127.4, 126.7, 121.7, 119.4, 119.3, 113.2, 21.3. MS (EI): m/z 284 (M^+). Mp: 133−134 °C.

1-(4-Methoxyphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6c).[10,11] Isolated yield: 89% (80 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22−8.20 (d, J = 7.2 Hz, 1H), 7.87−7.76 (m, 5H), 7.55−7.41 (m, 3H), 7.03−7.00 (d, J = 8.4 Hz, 2H), 6.76−6.71 (m, 1H), 6.56−6.52 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 137.8, 132.0, 130.2, 129.0, 128.7, 128.3, 128.1, 127.7, 127.1, 121.6, 119.2, 119.2, 114.2, 113.2, 55.4. MS (EI): m/z 300 (M^+). Mp: 115−116 °C.

3-Phenyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]-pyridine (6d).[9a,10,11] Isolated yield: 86% (87 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.86−7.81 (m, 3H), 7.69 (d, J = 8.2 Hz, 2H), 7.57−7.44 (m, 3H), 6.89−6.84 (m, 1H), 6.60 (t, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.7, 131.4, 130.3, 130.0, 129.2, 128.5, 128.4, 128.2 (d, J = 40 Hz), 126.6, 125.7 (q, J = 4 Hz), 124.6 (d, J = 270 Hz), 122.2, 121.0, 118.8, 113.6. MS (EI): m/z 338 (M^+). Mp: 184−185 °C.

3-Phenyl-1-(*o*-tolyl)imidazo[1,5-*a*]pyridine (6e).[10,11] Isolated yield: 82% (70 mg), green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28−8.25 (m, 1H), 7.87−7.84 (m, 2H), 7.53−7.49 (m, 3H), 7.44−7.39 (m, 2H), 7.33−7.31 (m, 1H), 7.27−7.25 (m, 2H), 6.71−6.67 (m, 3H), 6.57−6.53 (m, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.40, 137.39, 133.6, 132.8, 130.8, 130.4, 129.9, 128.6, 128.5, 128.1, 127.4, 125.6, 121.4, 119.1, 118.8, 113.2, 20.6. MS (EI): m/z 284 (M^+). Mp: 118−119 °C.

3-Phenyl-1-(*m*-tolyl)imidazo[1,5-*a*]pyridine (6f).[10,11] Isolated yield: 91% (77 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23−8.21 (d, J = 7.2 Hz, 1H), 7.85−7.80 (m, 4H), 7.72−7.70 (d, J = 8.1 Hz, 1H), 7.56−7.50 (m, 2H), 7.47−7.44 (m, 1H), 7.38−7.33 (t, J = 15.3 Hz,1H), 7.13−7.10 (d, J = 7.5 Hz, 1H), 6.80−6.74 (m, 1H), 6.60−6.63 (m, 1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.1, 134.8, 132.2, 130.2, 129.0, 128.8, 128.6, 128.4, 127.6, 127.4, 123.8, 121.7, 119.6, 119.3, 113.2, 21.6. MS (EI): m/z 284 (M^+). Mp: 111−112 °C.

1-(3-Chlorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6g).[10,11] Isolated yield: 86% (78 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27−8.24 (d, J = 7.2 Hz, 1H), 7.96 (s, 1H), 7.85−7.82 (m, 4H), 7.57−7.36 (m, 4H), 7.26 (s, 1H), 6.88−6.83 (m, 1H), 6.64−6.59 (t, J = 13.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 136.9, 134.7, 130.4, 129.9, 129.9, 129.1, 129.0, 128.4, 128.0, 126.6, 126.4, 124.6, 121.9, 120.4, 118.8, 113.4. HRMS: calcd $C_{19}H_{14}ClN_2$ ($M + H^+$) 305.0846, found 305.0848. Mp: 131−132 °C.

1-(3,5-Dimethylphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6h).[10] Isolated yield: 90% (80 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24−8.21 (d, J = 7.2 Hz, 1H), 7.86−7.83 (m, 3H), 7.56−7.44 (m, 5H), 6.95 (s, 1H), 6.80−6.75 (m, 1H), 6.59−6.54 (m, 1H), 2.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 138.0, 134.8, 132.3, 130.2, 129.0, 128.8, 128.4, 127.6, 124.7, 121.7, 119.4, 119.4, 113.2, 21.5. MS (EI): m/z 298 (M^+). Mp: 125−126 °C.

1-(3,5-Dimethoxyphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6i).[10] Isolated yield: 86% (85 mg), green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.24 (d, J = 7.2 Hz, 1H), 7.88−7.85 (m, 3H), 7.57−7.53(m, 2H), 7.49−7.45 (t, J = 14.8 Hz, 1H), 7.13−7.12 (d, J = 2.4 Hz, 2H), 6.84−6.80 (m, 1H), 6.63−6.60 (t, J = 13.2 Hz, 1H), 6.46−6.45 (t, J = 4 Hz, 1H), 3.89 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 137.9, 136.7, 131.7, 130.0, 129.1, 128.9, 128.4, 127.9, 121.8, 120.0, 119.2, 113.4, 104.9, 99.2, 55.5. MS (EI): m/z 330 (M^+). Mp: 178−179 °C.

1-(3,5-Difluorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6j).[10] Isolated yield: 83% (76 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28−8.25 (d, J = 7.2 Hz, 1H), 7.84−7.82 (m, 3H), 7.58−7.50 (m, 5H), 6.93−6.88 (m, 1H), 6.75−6.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (d, J = 245 Hz), 163.5 (d, J = 245 Hz), 138.5, 138.3, 129.8, 129.6, 129.2, 129.1, 128.4, 128.3, 122.2, 121.0, 118.6, 113.5, 109.1, 109.0, 108.9, 108.8, 101.4 (t, J = 25.5 Hz). MS (EI): m/z 306 (M^+). Mp: 164−165 °C.

1-(3,5-Dichlorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6k).[10] Isolated yield: 83% (84 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28−8.25 (d, J = 7.2 Hz, 1H), 7.85−7.81 (m, 4H), 7.58−7.48 (m, 4H), 6.93−6.88 (m, 1H), 6.67−6.62 (t, J = 13.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.0, 135.3, 129.8, 129.2, 129.1, 129.0, 128.4, 126.0, 124.6, 122.2, 121.1, 118.6, 113.5. MS (EI): m/z 339 (M^+). Mp: 188−189 °C.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylimidazo[1,5-*a*]-pyridine (6l).[10] Isolated yield: 81% (98 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 2H), 8.31−8.28 (d, J = 6.9 Hz, 1H), 7.85−7.83 (m, 3H), 7.75 (s, 1H), 7.60−7.48 (m, 3H), 7.00−6.94 (m, 1H), 6.71−6.66 (t, J = 13.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 137.3, 132.0 (q, J = 33 Hz), 129.6, 129.4, 129.2, 128.7, 128.5, 126.1, 123.6 (d, J = 277 Hz), 122.4, 121.8, 119.4 (q, J = 3.8 Hz), 118.2, 113.7. MS (EI): m/z 406 (M^+). Mp: 134−135 °C.

1-(Naphthalen-1-yl)-3-phenylimidazo[1,5-*a*]pyridine (6m).[10] Isolated yield: 89% (85 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39−8.36 (m, 1H), 8.31−8.29 (d, J = 7.2 Hz, 1H), 7.92−7.85 (m, 4H), 7.75−7.73 (m, 1H), 7.58−7.41 (m, 7H), 6.71−6.66 (m, 1H), 6.59−6.54 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 134.2, 132.1, 131.8, 131.7, 130.3, 129.3, 129.0, 128.7, 128.2, 127.7, 128.6, 126.1, 125.8, 125.4, 121.6, 119.2, 119.2, 113.4. MS (EI): m/z 320 (M^+). Mp: 118−119 °C.

1,3-Diphenylimidazo[1,5-*a*]quinoline (6n).[10] Isolated yield: 84% (81 mg), green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 7.4 Hz, 2H), 7.72−7.64 (m, 3H), 7.61 (d, J = 7.6 Hz, 1H), 7.56−7.51 (m, 3H), 7.47 (t, J = 7.9 Hz, 3H), 7.36−7.28 (m, 2H), 7.16 (dd, J = 11.6, 4.2 Hz, 1H), 7.07 (d, J = 9.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 134.2, 133.7, 133.4, 132.5, 129.9, 129.7, 129.1, 128.8, 128.6, 127.7, 127.6, 127.2, 126.5, 125.8, 125.4, 122.4, 117.8, 117.5. MS (EI): m/z 320 (M^+). Mp: 136−137 °C.

3-(4-Fluorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6o).[10,11] Isolated yield: 84% (73 mg), green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.2 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.87−7.74 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.26−7.20 (m, 2H), 6.78 (dd, J = 9.0, 6.5 Hz, 1H), 6.57 (t, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (d, J = 250 Hz), 137.3, 135.0, 132.1, 130.4 (d, J = 8.3 Hz), 128.9, 127.8, 126.9, 126.7, 126.50 (d, J = 3.2 Hz), 121.6, 119.8, 119.3, 116.2 (d, J = 22 Hz), 113.5. HRMS: calcd $C_{19}H_{14}FN_2$ (M^+) 289.1141, found 289.1139. Mp: 168−169 °C.

3-(4-Chlorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6p).[10,11,16] Isolated yield: 81% (74 mg), green-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21−8.18 (d, J = 6.6 Hz, 1H), 7.94−7.79 (m, 5H), 7.53−7.45 (m, 4H), 7.33−7.26 (m, 1H), 6.85−6.79 (m, 1H), 6.64−6.60 (t, J = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 134.7, 134.7, 132.3, 129.5, 129.3, 128.8, 128.6, 127.9, 126.8, 126.7, 121.5, 119.9, 119.3, 113.6. MS (EI): m/z 304 (M^+). Mp: 172−173 °C.

3-(3-Fluorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6q). Isolated yield: 81% (70 mg), green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 7.1 Hz, 1H), 7.92 (d, J = 7.4 Hz, 2H), 7.85 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 9.5 Hz, 1H), 7.48 (dt, J = 13.5, 7.9 Hz, 3H), 7.31 (t, J = 7.3 Hz, 1H), 7.20−7.08 (m, 1H), 6.87−6.73 (m, 1H), 6.61 (t, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, J = 250 Hz), 136.8 (d, J = 3 Hz), 134.9, 132.5, 132.4 (d, J = 8 Hz), 130.8 (d, J = 8 Hz), 128.9, 128.1, 126.9, 126.8, 123.8 (d, J = 3 Hz), 121.7, 120.1, 119.4, 115.8 (d, J = 21 Hz), 115.4 (d, J = 23 Hz), 113.8. HRMS: calcd $C_{19}H_{14}FN_2$ ($M + H^+$) 289.1141, found 289.1140. Mp: 150−151 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00343.

^{1}H and ^{13}CNMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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