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Copper-Promoted Double Oxidative C−H Amination Cascade for the Synthesis of Imidazo[1,5-*a*]quinolines

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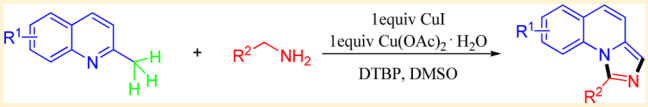
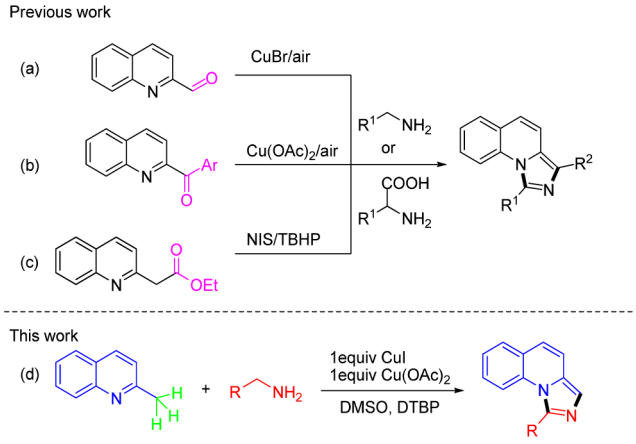
Supporting Information

ABSTRACT: A copper-promoted cascade reaction of 2-methylazaarenes and benzylamines has been developed via sequential double oxidative C(sp^3)−H aminations. This protocol provides straightforward access to imidazo[1,5-*a*]quinoline derivatives without employing prefunctionalized substrates.



Imidazo[1,5-*a*]quinolines are an important class of fused N-heterocyclic compounds due to their wide applications in medicinal chemistry (e.g., NK1 receptor ligands).[1] A great deal of attention has been paid to synthesize imidazo[1,5-*a*]quinoline derivatives.[2] The most popular strategy for the synthesis of imidazo[1,5-*a*]quinolines is Vilsmeier-type cyclizations, which involved the use of *N*-2-pyridylmethylamides as substrates.[3] Another attractive tool is C−H amination based strategy. Zeng[4] (Scheme 1a) and Xu[5] (Scheme 1b) have respectively developed interesting copper catalyzed oxidative tandem cyclization reactions of N-heteroaryl aldehydes or ketones with alkylamines to construct imidazo[1,5-*a*]-quinolines. Recently, Wang has reported a novel protocol to synthesize imidazo[1,5-*a*]pyridines and -quinolines via sequential dual oxidative amination of C(sp3)−H bonds in the presence of stoichiometric *N*-iodobutanimide (Scheme 1c).[6a] Later, the same reaction was performed employing CuI as catalyst by Adimurthy.[6b] However, electron-withdrawing substituents on the carbon are necessary for these reactions. Moreover, the amination of 2-alkylazaarenes with aliphatic primary amines is difficult because of oxidative olefination reactions.[7] The development of efficient methods for the synthesis of imidazo[1,5-*a*]quinolines from 2-methylquinolines without an activating group or prefunctionalization still remains a significant challenge.[8]

Scheme 1. C−H Amination Based Strategies for the Synthesis of Imidazo[1,5-*a*]quinolines



2-Alkylazaarenes, which are inexpensive and broadly available, have emerged as a useful class of building blocks mainly in the form of a nucleophilic coupling partner for syntheses of various important organic compounds.[9] The additions of 2-alkylazaarenes to a series of unsaturated bonds, including C═N double bond,[10a] C═C double bond,[10b] C═O double bond,[10c] N═N double bond,[10d] have been developed mostly to form acyclic compounds, while the cascade reactions of 2-alkylazaarenes to synthesize heterocyclic compounds have not been extensively studied. Metal catalyzed intermolecular direct oxidative aminations of the sp^2 C−H bond have been well established in recent years.[11] As 2-methyquinoline can be isomerized to a nonaromatic emamine intermediate in the presence of transition metal,[9] we hypothesized that metal catalyzed or promoted dual C(sp^3)−H amination of 2-methylazaarenes with alkylamines might be doable to construct heterocyclic compounds. In continuation of our interest in the quinoline-based synthesis of heterocycles,[12] herein, we describe the direct synthesis of imidazo[1,5-*a*]quinoline derivatives from commercially accessible 2-methylazaarenes and benzylamines (Scheme 1d).

We began to study the dual C(sp^3)−H amination reaction utilizing 2-methylquinoline **1a** and benzylamine **2a** as model substrates to optimize the reaction conditions (Table 1). When the reaction was performed in DMF in the presence of 1 equiv of CuI and 2 equiv of di-*t*-butyl peroxide (DTBP) for 12 h at 110 °C, the desired 1-phenylimidazo[1,5-*a*]quinoline **3aa** was obtained in a 35% yield (Table 1, entry 1). The effect of solvents for this cascade reaction was examined. DMSO was

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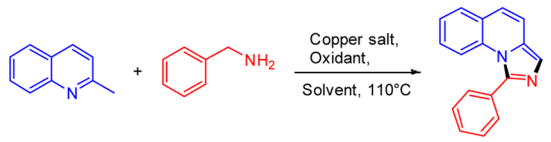
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	Cu salt	oxidant	solvent	yield (%)[b]
1	CuI	DTBP	DMF	35
2	CuI	DTBP	DMSO	57
3	CuI	DTBP	DMA	41
4	CuI	DTBP	EtOH	trace
5	CuI	DTBP	H_2O	12
6	CuI	DTBP	PhMe	nd
7	CuI	TBHP	DMSO	36
8	CuI	$K_2S_2O_8$	DMSO	trace
9	CuI	I_2	DMSO	trace
10	CuI	DDQ	DMSO	trace
11	CuI	O_2	DMSO	38
12	CuBr	DTBP	DMSO	26
13	CuCl	DTBP	DMSO	40
14	$Cu(OAc)_2·H_2O$	DTBP	DMSO	45
15	CuI_2	DTBP	DMSO	17
16	–	DTBP	DMSO	nd
17[c]	CuI	DTBP	DMSO	68
18[d]	$CuI/Cu(OAc)_2·H_2O$	DTBP	DMSO	83
19[e]	$Cu(OAc)_2·H_2O$	DTBP	DMSO	34

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Cu salt (0.2 mmol), DTBP (0.4 mmol), solvent (1.5 mL), 110 °C, 24 h. [b]Isolated yield. [c]2 equiv of CuI were used. [d]CuI (0.2 mmol) and $Cu(OAc)_2·H_2O$ (0.2 mmol) were used. [e]2 equiv of $Cu(OAc)_2·H_2O$ were used.

found to be the optimal solvent to give **3aa** in a 57% yield (Table 1, entry 2). When other solvents (polar protic solvents or nonpolar solvents) were utilized, inferior results were obtained (Table 1, entries 3–6). A screening of oxidants, including DTBP, O_2, TBHP, I_2, $K_2S_2O_8$ and DDQ, showed that DTBP was still to be the best choice (Table 1, entries 7–11). Subsequently, we turned our attention to the effect of copper salts. Among the tested copper salts, such as CuCl, CuBr, $Cu(OAc)_2·H_2O$, CuI and CuI_2, CuI afforded **3aa** in the highest yield (Table 1, entries 12–15). The reaction did not proceed at all in the absence of a copper salt (Table 1, entry 16). When the amount of CuI was increased to 2 equiv, a positive result was observed and the yield of **3aa** was improved to 68% (Table 1, entry 17). Recently, Zhang found that the combination of 1 equiv of CuCl and 1 equiv of $Cu(OAc)_2·H_2O$ could mediate annulation of alkyl ketones with α,β-unsaturated carboxylic acids to afford furan products.[13] Inspired by this results, we carried out our reaction in the presence of 1 equiv of CuI and 1 equiv of $Cu(OAc)_2·H_2O$, the yield of **3aa** was increased to 83% (Table 1, entry18). When 2.0 equiv of $Cu(OAc)_2·H_2O$ was used, the yield of **3aa** was decreased to 34% (Table 1, entry19). On the basis of these results, the optimized reaction conditions of 100 mol % CuI, 100 mol % $Cu(OAc)_2·H_2O$, and 200 mol % DTBP in DMSO at 110 °C were used for further investigation.

With the optimal conditions in hand, the substrate scope of the double oxidative C–H amination cascade was investigated. As showed in Table 2, a series of aliphatic amines **2** were employed to react with 2-methylquinoline **1a** under the optimized reaction conditions. Benzylamine derivatives with both electron-donating (4-Me, 4-OMe) and electron-withdrawing (4-CF_3) groups on the aromatic ring proceeded in this reaction smoothly to afford the desired products **3** in good to excellent yields. Generally, electron-withdrawing substituents on the aromatic ring have negative effect on the yield. Halogen substituted benzylamine derivatives, including fluorobenzylamines, chlorobenzylamines, or bromobenzylamine, were also well tolerated in this cascade reaction (Table 2, **3ah–3am**), which provides the possibility to allow additional coupling reactions. Interestingly, 2-chlorobenzylamines gave the corresponding product in 85% yield (Table 2, **3aj**). Steric effects had a little influence on the reaction since 2-methylbenzylamine gave similar yield than 4-methylbenzylamine (Table 2, **3ab** and **3ad**). Notably, the ring-fused and heterocyclic derived substrates also amenable to current reaction conditions to deliver the corresponding products (**3an–3ap**) in good yields (41–89%). Additionally, the present system is applicable to simple aliphatic amine, and the corresponding imidazo[1,5-*a*]quinoline (Table 2, **3aq**) was obtained in moderate yield.

Next, we turned our attention to the scope of various 2-methylquinoline derivatives to prove the general applicability of the reaction and the results were summarized in Table 3. The reaction is sensitive to the electronic effect of the aromatic ring. 2-Methylquinoline derivatives with electron-donating groups such as –Me, –OMe and –OEt successfully gave the desired imidazo[1,5-*a*]quinolines in good yields (Table 3, **3ba–3fa**). Electron-withdrawing substituents such as $-NO_2$ (**3ka**) and –Ph (**3ga**) also had deleterious effect on this reaction. Halogen-substituted 2-methylquinolines (Table 3, **3ha–3ja**) were tolerated. Moreover, 4-methyl-2-phenylquinazoline also was found to be a suitable substrate and afforded the desired product (**3la**). However, the present system is not applicable for 2-methylpyridine (Table 3, **3ma**), most of 2-methylquinoline remained unconsumed.

To establish a possible mechanism of the copper-promoted oxidative C–H amination cascade, some control experiments were carried out. First of all, traces of 2-methylquinoline **1a** were converted into quinoline-2-carbaldehyde **4a** in the absence of **2a** under standard conditions, and most of 2-methylquinoline **1a** remained unconsumed (Scheme 2, eq 1). When quinoline-2-carbaldehyde **4a** was allowed to react with **2a**, the target product **3aa** was obtained in 57% yield (Scheme 1, eq 2). The reaction course through formation of aldehyde **4a** cannot be excluded. In order to confirm whether the reaction process was performed via a radical pathway, **1a** and **2a** were subjected to the standard conditions using TEMPO as radical scavenger (Scheme 2, eq 3). As expected, only 12% yield of target product **3aa** was obtained, which suggested that the reaction presumably proceeded through a radical formation pathway.

On the basis of results described above and literature reports,[9] a plausible mechanism was proposed (Scheme 3). Initially, 2-methylquinoline **1a** is involved a hydrogen abstraction to form a carbon-centered radical **A**. The reaction of **A** with copper(II) gives a benzylic carbocation **B** via a single-electron-transfer (SET) process. The nucleophilic addition of benzylamine **2a** to **B** provides intermediate **C** (path I). Furthermore, another pathway may occur according to previous reports.[14,15] A nitrogen centered radical **I** is generated by oxidation of benzylamine **2a**. The addition of the nitrogen radical **I** to the enamine intermediate **H** which is formed from 2-methylquinoline **1a** through the copper-promoted isomerization, afford another intermediate **J**. Then, the intermediate **J** could generate intermediate **C** by the action of copper and

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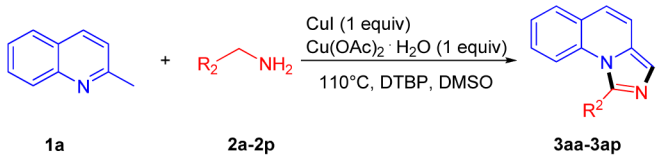
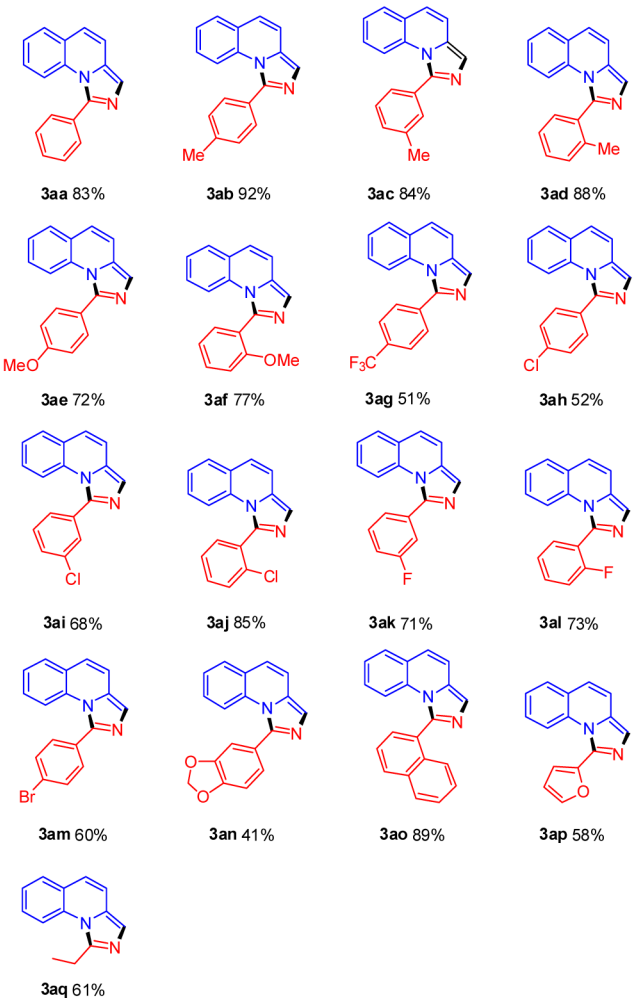
Table 2. Scope of Benzylamines[a]





[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), CuI (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol), DTBP (0.4 mmol), DMSO (1.5 mL), 110 °C, 24 h. Isolated yield.

DTBP (path II). The intermediate **C** can be oxidated to imine intermediate **D**, which is converted into carbocation **E** by oxidative dehydrogenation in the presence of copper and oxidant. And intermediate **E** can be cyclized by an intramolecular nucleophilic addition to provide intermediate **G**, which can undergo oxidative aromatization to afford imidazo[1,5-*a*]quinoline **3aa**.

In summary, we have developed a copper-promoted tandem cyclization reaction via sequential intermolecular oxidative amination, intramolecular oxidative amination and oxidative aromatization to construct imidazo[1,5-*a*]quinoline derivatives from 2-methylquinolines and benzylamines. This protocol can tolerate a broad range of functional groups. In particular, substrate prefunctionalization was not required in the reaction, which avoided the need of extra preparation steps for active precursors.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$, using tetramethylsilane (TMS) as internal reference. HRMS were recorded using ESI-TOF techniques. Products were purified by flash chromatography on 200−300 mesh silica gels using petroleum ether/ethyl acetate as eluent.

General Procedure for the Synthesis of 3. CuI (38.1 mg, 0.2 mmol) and $Cu(OAc)_2 \cdot H_2O$ (39.9 mg, 0.2 mmol) was dissolved in a reaction tube using 1.5 mL of DMSO, and then benzylamine **2a** (65.6 μL, 0.6 mmol), 2-methylquinoline **1a** (27.1 μL, 0.2 mmol) and DTBP (73.3 μL, 0.4 mmol) were added, sequentially. The mixture was stirred at 110 °C for 24 h, and the reaction process was monitored by TLC. After the reaction was completed, The reaction system was allowed to attain room temperature and extracted with ethyl acetate (3 × 20 mL), and then the organic layer was washed with brine (2 × 10 mL) and dried with anhydrous Na_2SO_4. Subsequently, the solvent was removed under reduced pressure and the remaining crud product was purified by column chromatography over silica gel (PE/EtOAc = 3:1) to afford

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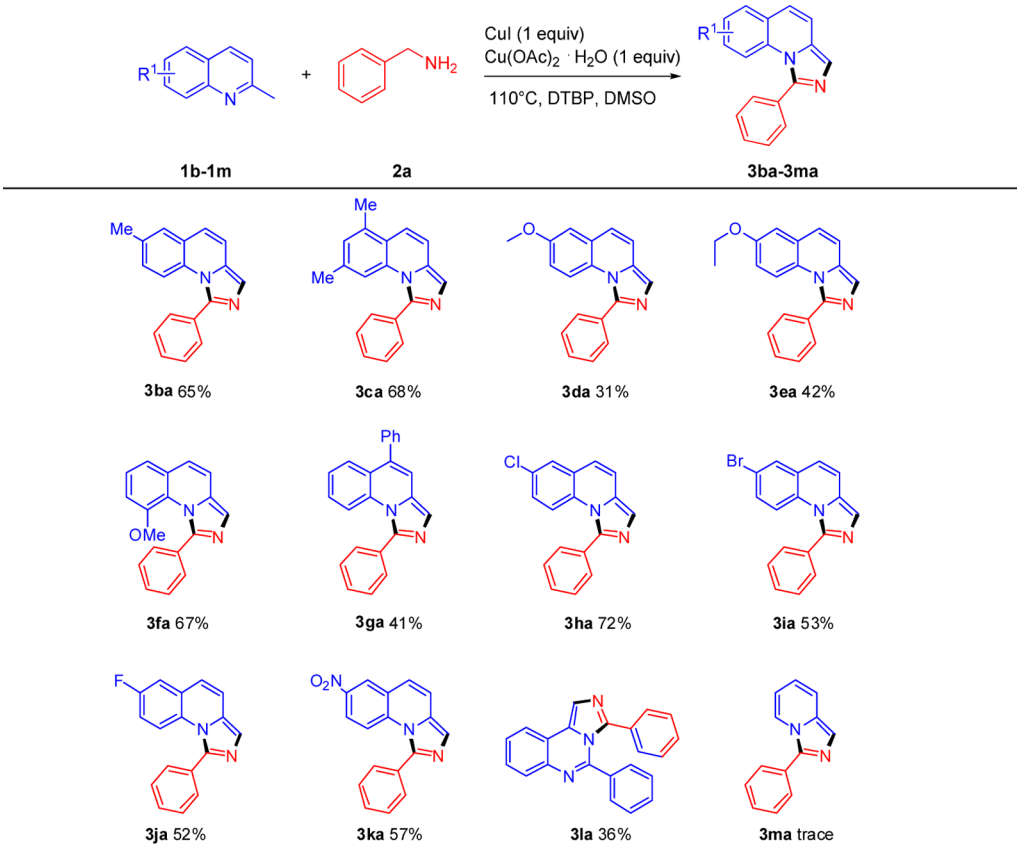
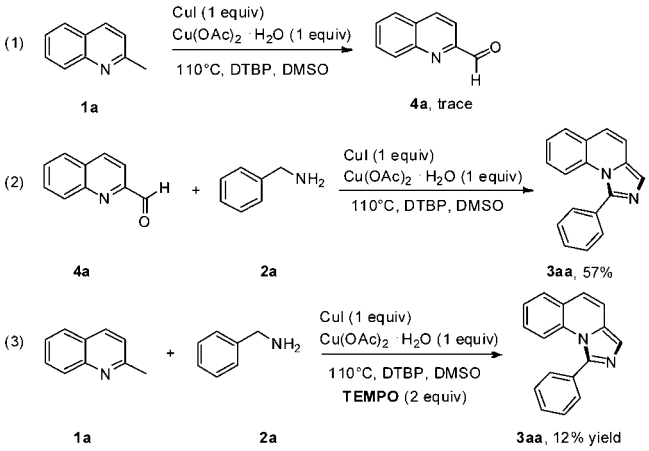
Table 3. Scope of 2-Methylquinolines[a]

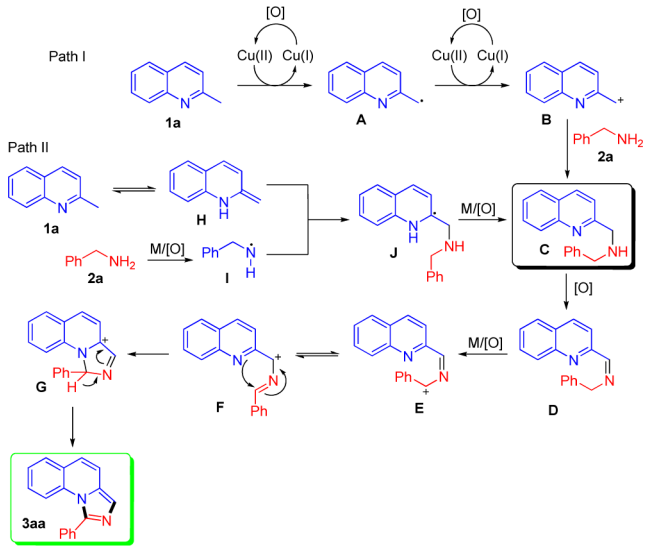


[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), CuI (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol), DTBP (0.4 mmol), DMSO (1.5 mL), 110 °C, 24 h. Isolated yield.

Scheme 2. Control Experiments for Mechanism



Scheme 3. Plausible Mechanism



1-phenylimidazo[1,5-*a*]quinoline (**3aa**) (40.5 mg, 83%) as a yellow solid.

*1-Phenylimidazo[1,5-a]quinoline (**3aa**).*[2d] Yellow solid (40.5 mg, 83%), melting point 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.65 (m, 3H), 7.55−7.52 (m, 5H), 7.34−7.28 (m, 2H), 7.19−7.16 (m, 1H), 7.03−7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 133.8, 132.3, 130.6, 129.6, 129.3, 128.7, 128.6, 127.3, 125.6, 125.1, 122.4, 121.4, 117.4, 117.1. HRMS(ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{13}N_2$ 245.1073, found 245.1076.

*1-(p-Tolyl)imidazo[1,5-a]quinoline (**3ab**).* Yellow solid (47.5 mg, 92%), melting point 121−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.54 (m, 5H), 7.35−7.28 (m, 4H), 7.22−7.18 (m, 1H), 7.02 (d, *J* = 9.3 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 139.2, 132.5, 130.9, 130.5, 129.4, 128.5, 127.2, 125.6, 125.0, 122.3, 121.2, 117.4, 117.2, 21.5. HRMS(ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}N_2$ 259.1237, found 259.1235.

*1-(m-Tolyl)imidazo[1,5-a]quinoline (**3ac**).* Yellow solid (43.3 mg, 84%), melting point 134−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.54 (m, 3H), 7.50 (s, 1H), 7.44−7.38 (m, 2H), 7.34−7.27 (m, 3H), 7.19−7.15 (m, 1H), 6.99 (d, *J* = 9.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 138.6, 133.7, 132.4, 130.5, 130.2, 130.0, 128.5, 128.5, 127.2, 126.5, 125.6, 125.0, 122.3, 121.3, 117.4,

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117.1, 21.4. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2$ 259.1234, found 259.1235.

*1-(o-Tolyl)imidazo[1,5-a]quinoline (**3ad**).* Yellow oil (45.4 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.49−7.46 (m, 2H), 7.39−7.34 (m, 3H), 7.31−7.27 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.16−7.12 (m, 1H), 7.02 (d, J = 9.3 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.4, 133.9, 132.6, 130.5, 130.4, 129.9, 129.8, 128.5, 127.8, 126.4, 125.3, 125.0, 122.0, 121.2, 117.2, 115.9, 19.57. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2$ 259.1233, found 259.1235.

*1-(4-Methoxyphenyl)imidazo[1,5-a]quinoline (**3ae**).* Yellow solid (39.5 mg, 72%), melting point 117−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (m, 4H), 7.53 (s, 1H), 7.33−7.28 (m, 2H), 7.21−7.19 (m, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 9.3 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 142.3, 132.5, 130.9, 130.4, 128.5, 127.2, 126.1, 125.6, 125.0, 122.2, 121.2, 117.3, 117.2, 114.2, 55.3. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1182, found 275.1184.

*1-(2-Methoxyphenyl)imidazo[1,5-a]quinoline (**3af**).* Yellow solid (42.2 mg, 77%), melting point 118−122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.59 (m, 3H), 7.57−7.52 (m, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 9.3 Hz, 1H), 7.32−7.28 (m, 1H), 7.20−7.14 (m, 2H), 7.03 (d, J = 8.9 Hz, 2H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 139.3, 133.0, 131.9, 131.1, 130.3, 128.2, 127.3, 125.2, 124.8, 123.3, 122.1, 121.2, 121.0, 117.2, 116.4, 111.0, 55.3. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1182, found 275.1184.

*1-(4-(Trifluoromethyl)phenyl)imidazo[1,5-a]quinoline (**3ag**).* Yellow solid (31.8 mg, 51%), melting point 152−156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.79 (m, 4H), 7.69 (d, J = 7.7 Hz, 1H), 7.60 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.40−7.37 (m, 2H), 7.29−7.25 (m, 1H), 7.11 (d, J = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 137.2, 132.0, 131.2, 131.1, 130.9, 129.8, 128.9, 128.0, 127.5, 125.7, 125.7, 125.6, 125.5, 125.3, 123.0, 122.6, 121.9, 117.3, 117.1. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}N_2F_3$ 313.0951, found 313.0953.

*1-(4-Chlorophenyl)imidazo[1,5-a]quinoline (**3ah**).* Yellow solid (29.0 mg, 52%), melting point 148−151 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64−7.61 (m, 3H), 7.56−7.51 (m, 4H), 7.37−7.35 (m, 2H), 7.28−7.23 (m, 1H), 7.06 (d, J = 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.3, 132.2, 132.2, 130.9, 130.8, 129.0, 128.7, 127.4, 125.6, 125.3, 122.7, 121.6, 117.3, 117.1. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Cl$ 279.0689, found 279.0687.

*1-(3-Chlorophenyl)imidazo[1,5-a]quinoline (**3ai**).* Yellow solid (37.9 mg, 68%), melting point 149−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.55−7.43 (m, 5H), 7.35−7.32 (m, 2H), 7.25−7.21 (m, 1H), 7.04 (d, J = 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.4, 134.7, 132.1, 130.8, 129.9, 129.7, 129.4, 128.8, 127.7, 127.5, 125.6, 125.3, 122.7, 121.7, 117.3, 117.0. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Cl$ 279.0688, found 279.0689.

*1-(2-Chlorophenyl)imidazo[1,5-a]quinoline (**3aj**).* Yellow solid (47.4 mg, 85%), melting point 121−124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.46 (m, 6H), 7.40−7.32 (m, 2H), 7.28−7.19 (m, 2H), 7.08 (d, J = 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.3, 133.6, 132.4, 132.4, 131.0, 130.3, 129.8, 128.6, 127.9, 127.3, 125.3, 125.2, 122.3, 121.6, 117.0, 115.9. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Cl$ 279.0687, found 279.0689.

*1-(3-Fluorophenyl)imidazo[1,5-a]quinoline (**3ak**).* Yellow solid (37.2 mg, 71%), melting point 102−105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.65 (m, 1H), 7.57−7.45 (m, 4H), 7.41−7.35 (m, 3H), 7.28−7.22 (m, 2H), 7.08−7.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.0−161.5 (d, $^1J_{C-F}$ = 246.2 Hz), 140.9, 135.8−135.7 (d, $^3J_{C-F}$ = 8.3 Hz), 132.1, 130.8, 130.4−130.3 (d, $^3J_{C-F}$ = 8.3 Hz), 128.7, 127.5, 125.6, 125.4 (d, $^4J_{C-F}$ = 3.0 Hz), 125.3, 122.6, 121.7, 117.3, 117.1, 116.8−116.6 (d, $^2J_{C-F}$ = 22.3 Hz), 116.4−116.2 (d, $^2J_{C-F}$ = 21.0 Hz). HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2F$ 263.0982, found 263.0985.

*1-(2-Fluorophenyl)imidazo[1,5-a]quinoline (**3al**).* Yellow solid (38.3 mg, 73%), melting point 102−104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.68 (m, 1H), 7.64−7.61 (m, 2H), 7.56−7.55 (m, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.38−7.31 (m, 3H), 7.28−7.24 (m, 2H), 7.05 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ161.9−159.4 (d, $^1J_{C-F}$ = 248.2 Hz), 136.3, 132.4, 132.1 (d, $^4J_{C-F}$ = 1.6 Hz), 131.5−131.4 (d, $^3J_{C-F}$ = 8.0 Hz), 130.7, 128.5, 127.7, 125.3, 125.2, 124.7 (d, $^3J_{C-F}$ = 3.5 Hz), 122.6, 122.4−122.2 (d, $^2J_{C-F}$ = 15.2 Hz), 121.7, 116.9, 116.1−115.9 (d, $^2J_{C-F}$ = 20.9 Hz), 116.0. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2F$ 263.0984, found 263.0985.

*1-(4-Bromophenyl)imidazo[1,5-a]quinoline (**3am**).* Yellow solid (38.8 mg, 60%), melting point 138−140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (m, 3H), 7.57−7.53 (m, 4H), 7.38−7.33 (m, 2H), 7.28−7.25 (m, 1H), 7.08−7.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 137.9, 132.7, 132.0, 131.1, 129.6, 128.7, 127.4, 125.6, 125.3, 123.5, 122.7, 121.6, 117.3, 117.2. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Br$ 323.0183, found 323.0184.

*1-(Benzo[d][1,3]dioxol-5-yl)imidazo[1,5-a]quinoline (**3an**).* Yellow solid (23.6 mg, 41%), melting point 115−119 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 2H), 7.52 (s, 1H), 7.35−7.32 (m, 2H), 7.28−7.23 (m, 1H), 7.14 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.09−7.08 (m, 1H), 7.02 (d, J = 9.3 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 147.9, 141.9, 132.4, 130.4, 128.6, 127.3, 125.6, 125.1, 123.7, 122.2, 121.3, 117.4, 117.1, 110.0, 108.7, 101.4. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{13}N_2O_2$ 289.0975, found 289.0977.

*1-(Naphthalen-1-yl)imidazo[1,5-a]quinoline (**3ao**).* Yellow solid (52.3 mg, 89%), melting point 199−201 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 6.9 Hz, 1H), 7.71 (s, 1H), 7.68−7.60 (m, 2H), 7.53−7.50 (m, 1H), 7.44 (d, J = 9.4 Hz, 1H), 7.41−7.33(m, 2H), 7.24−7.21 (m, 1H), 7.09 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.95−6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 133.7, 132.6, 132.3, 131.6, 130.3, 130.0, 128.8, 128.4, 128.4, 127.6, 127.1, 126.4, 125.6, 125.5, 125.4, 124.9, 122.5, 121.5, 117.2, 117.0. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{15}N_2$ 295.1234, found 295.1235.

*1-(Furan-2-yl)imidazo[1,5-a]quinoline (**3ap**).* Yellow solid (27.1 mg, 58%), melting point 90−94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 2H), 7.57 (s, 1H), 7.40−7.33 (m, 3H), 7.22−7.20 (m, 1H), 7.09 (d, J = 9.3 Hz, 1H), 6.88 (d, J = 3.2 Hz, 1H), 6.68−6.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 143.2, 132.4, 132.1, 131.0, 128.6, 128.1, 125.4, 122.7, 122.2, 116.8, 112.8, 111.8. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{11}N_2O$ 235.0870, found 235.0871.

*1-Ethylimidazo[1,5-a]quinoline (**3aq**).* Yellow oil (24.1 mg, 61%), ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.54−7.52 (m, 1H), 7.43−7.39 (m, 1H), 7.30−7.27 (m, 2H), 7.18−7.15 (m, 1H), 3.31 (q, J = 7.3 Hz, 2H), 1.49 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 132.1, 129.3, 127.5, 126.6, 124.7, 123.7, 119.6, 119.5, 116.3, 115.5, 24.8, 10.7. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{13}N_2$ 197.1079, found 197.1083.

*7-Methyl-1-phenylimidazo[1,5-a]quinoline (**3ba**).* Yellow solid (33.5 mg, 65%), melting point 117−120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.53 (s, 4H), 7.42 (s, 2H), 7.34−7.31 (m, 1H), 7.02−6.97 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 134.8, 133.9, 130.5, 130.3, 129.6, 129.2, 128.7, 128.5, 128.4, 125.6, 122.3, 121.3, 117.2, 117.1, 20.8. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2$ 259.1236, found 259.1235.

*6,8-Dimethyl-1-phenylimidazo[1,5-a]quinoline (**3ca**).* Yellow solid (35.4 mg, 65%), melting point 104−107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H), 7.43−7.39 (m, 4H), 7.22−7.17 (m, 1H), 7.11−7.08 (m, 2H), 6.90 (s, 1H), 2.47 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 136.8, 135.3, 134.0, 132.5, 130.6, 129.5, 129.1, 128.6, 127.8, 121.9, 121.7, 117.6, 116.2, 115.7, 21.6, 19.9. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2$ 273.1393, found 273.1392.

*7-Methoxy-1-phenylimidazo[1,5-a]quinoline (**3da**).* Yellow oil (17.0 mg, 31%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 3.5 Hz, 2H), 7.55−7.53 (m, 4H), 7.46 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 9.3 Hz, 1H), 7.07 (s, 1H), 6.98 (d, J = 9.3 Hz, 1H), 6.78 (dd, J_1 = 9.1 Hz, J_2 = 2.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.9, 133.8, 130.3, 129.6, 129.2, 128.7, 126.9, 126.6, 122.5, 121.1,

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118.6, 117.6, 114.8, 110.8, 55.5. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1183, found 275.1184.

*7-Ethoxy-1-phenylimidazo[1,5-a]quinoline (**3ea**).* Yellow solid (24.2 mg, 42%), melting point 113−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 7.55−7.52 (m, 4H), 7.44 (d, J = 9.1 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 7.06 (s, 1H), 6.96 (d, J = 9.2 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 4.07 (q, J = 6.3 Hz, 2H), 1.43 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 141.9, 133.8, 130.3, 129.6, 129.2, 128.7, 126.9, 126.5, 122.5, 121.2, 118.6, 117.5, 115.3, 111.6, 63.8, 14.8. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$ 289.1342, found 289.1341.

*9-Methoxy-1-phenylimidazo[1,5-a]quinoline (**3fa**).*[2d] Yellow solid (36.7 mg, 67%), melting point 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.43−7.41 (m, 2H), 7.28−7.15 (m, 5H), 7.09 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 9.2 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 146.7, 136.4, 131.7, 128.5, 128.0, 127.5, 125.9, 125.0, 122.9, 122.4, 120.8, 119.5, 117.7, 109.8, 53.6. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179, found 275.1177.

*1,5-Diphenylimidazo[1,5-a]quinoline (**3ga**).* Yellow solid (26.2 mg, 41%), melting point 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.71 (m, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.60 (s, 1H), 7.55−7.47 (m, 8H), 7.32−7.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 138.8, 133.8, 133.4, 132.5, 130.2, 129.6, 129.5, 129.2, 128.8, 128.6, 127.8, 127.4, 127.3, 125.3, 124.9, 122.9, 117.8, 117.0. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{17}N_2$ 321.1393, found 321.1392.

*7-Chloro-1-phenylimidazo[1,5-a]quinoline (**3ha**).* Yellow solid (40.1 mg, 72%), melting point 151−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.55 (m, 7H), 7.46 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.14 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H), 6.96 (d, J = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 133.4, 130.8, 130.5, 130.3, 129.5, 129.5, 128.9, 127.7, 127.2, 127.1, 123.0, 120.3, 118.7, 118.5. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Cl$ 279.0688, found 279.0689.

*7-Bromo-1-phenylimidazo[1,5-a]quinoline (**3ia**).*[2d] Yellow solid (34.2 mg, 53%), melting point 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 1.6 Hz, 1H), 7.65−7.63 (m, 2H), 7.59−7.55 (m, 4H), 7.41−7.35 (m, 2H), 7.29−7.25 (m, 1H), 6.96−6.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 133.4, 131.2, 130.8, 130.3, 130.1, 129.6, 129.5, 129.0, 127.5, 123.1, 120.2, 119.0, 118.5, 118.3. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2Br$ 323.0178, found 323.0175.

*7-Fluoro-1-phenylimidazo[1,5-a]quinoline (**3ja**).* Yellow solid (27.2 mg, 52%), melting point 113−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.53 (m, 2H), 7.50−7.39 (m, 5H), 7.30 (d, J = 9.3 Hz, 1H), 7.22−7.18 (m, 1H), 6.87 (d, J = 9.4 Hz, 1H), 6.83−6.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.7−158.2 (d, $^1J_{C-F}$ = 244.1 Hz), 142.4, 133.5, 130.3, 129.6, 129.5, 129.0, 128.8 (d, $^4J_{C-F}$ = 2.1 Hz), 127.4 (d, $^3J_{C-F}$ = 8.4 Hz), 123.0, 120.6 (d, $^4J_{C-F}$ = 2.5 Hz), 119.1 (d, $^3J_{C-F}$ = 8.1 Hz), 118.5, 114.9−114.7 (d, $^2J_{C-F}$ = 23.5 Hz), 113.8−113.5 (d, $^2J_{C-F}$ = 22.3 Hz). HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_2F$ 263.0986, found 263.0985.

*7-Nitro-1-phenylimidazo[1,5-a]quinoline (**3ka**).* Yellow solid (32.9 mg, 57%), melting point 200−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 2.4 Hz, 1H), 8.0 (dd, J_1 = 9.3 Hz, J_2 = 2.5 Hz, 1H), 7.66−7.49 (m, 7H), 7.5 (d, J = 9.4 Hz, 1H), 7.12 (d, J = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 143.5, 136.0, 132.9, 130.4, 130.0, 129.4, 129.2, 126.0, 123.8, 123.6, 121.9, 120.5, 119.6, 118.0. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{12}N_3O_2$ 290.0931, found 290.0930.

*3,5-Diphenylimidazo[1,5-c]quinazoline (**3la**).*[8] Yellow solid (23.1 mg, 36%), melting point 142−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.04 (m, 2H), 7.94−7.92 (m, 1H), 7.60−7.57 (m, 2H), 7.35 (d, J = 7.4 Hz, 2H), 7.28−7.02 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 142.7, 138.1, 133.8, 131.5, 130.3, 129.9, 129.2, 128.6, 128.4, 128.2, 128.0, 127.7, 127.4, 121.7, 120.6, 119.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_3$ 322.1339, found 322.1338.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00569.

^{1}H NMR and ^{13}C NMR spectra for all the products. (PDF)

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Notes

The authors declare no competing financial interest.

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