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Copper-Catalyzed One-Pot Synthesis of Imidazo/Benzoimidazoquinazolinones by Sequential Ullmann-Type Coupling and Intramolecular C–H Amidation

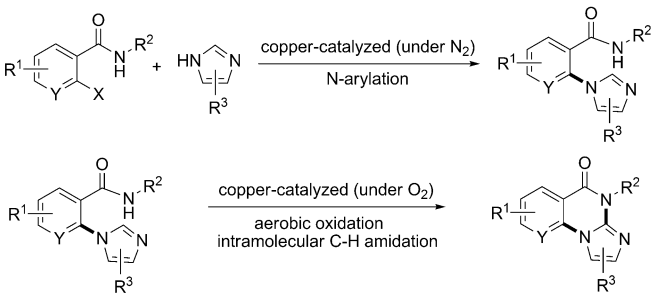
Hao Xu [a, b] and Hua Fu *[a, b]

Abstract: A simple, practical, and highly efficient copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones has been developed. The procedure is based on a sequential copper-catalyzed Ullmann-type N-arylation and aerobic oxidative intramolecular C–H amidation. This method should provide a new and useful strategy for construction of N-heterocycles.

Keywords: aerobic oxidation · C–H amidation · copper · heterocycles · Ullmann-type coupling

Introduction

Nitrogen heterocycles are widespread in various natural products and biologically active molecules.[1] They have been assigned as privileged structures in drug development,[2] therefore, their construction is an important goal in organic synthesis. Fused quinazolinone derivatives attract much attention because of their diverse biological activity. For example, the quinazolinone derivatives have been used as antibacterial, antihypertensive, antitoxoplasmatic, and antihistaminic agents, as well as phosphodiesterase inhibitors.[3] Imidazoquinazolinone derivatives have shown important biological activities, for example, as antiallergens and antivirals.[4] Unfortunately, only limited approaches to imidazoquinazolinones have been developed thus far.[4,5] Although the reported methods are effective, the tedious procedures required greatly limit the construction of diverse molecules, which prevents the development of potent biologically active molecules. The transition-metal-catalyzed formation of N-heterocycles continues to be an active area of research.[6] Traditional methods for the synthesis of N-heterocycles substituted with functional groups require the use of prefunctionalized precursors. Recently, there have been great advances in the direct functionalization of C–H bonds,[7] and some N-heterocycles (for example, benzimidazoles,[8] carbazoles,[9] indazoles,[10] *N*-methoxylactams,[11] and indolines[12]) have been synthesized through C–H activation/C–N bond-formation sequences, in which expensive palladium-, rhodium-, and ruthenium-based catalysts are usually required. In recent decades, there has been remarkable progress in copper-catalyzed cross-couplings with inexpensive, low-toxicity copper catalysts, and wide applications with good functional group tolerance have been investigated.[13,14] Recently, several examples for efficient copper-catalyzed sp^2-C–H amination/amidation have been reported,[15] and some heterocycles have been constructed through copper-promoted arene sp^2-C–H activation[16] by using air/O_2 as the ideal oxidant.[17] Herein, we report a convenient and efficient copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones by sequential Ullmann-type coupling and aerobic oxidative intramolecular C–H amidation. As shown in Scheme 1, our strategy for copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones is divided into the following reactions: copper-catalyzed N-arylation of imidazole derivatives under nitrogen atmosphere and subsequent aerobic oxidative intramolecular C–H amidation.



Scheme 1. Our strategy for copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones.

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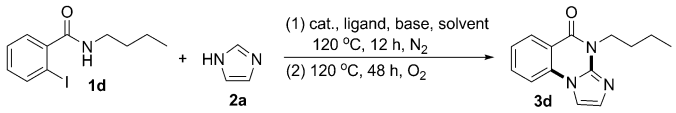
Results and Discussion

N-Butyl-2-iodobenzamide (**1d**) and imidazole (**2a**) were used as model substrates to optimize the reaction conditions (catalyst, ligand, base, solvent, temperature, reaction time). As shown in Table 1, copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones involved two sequential reactions: intermolecular N-arylation and intramolecular C–H amidation. The N-arylation was performed at 120 °C for 12 h under N_2 and the C–H amidation was carried out at 120 °C for 48 h under O_2. Seven copper catalysts (20 mol %) were tested in the reaction with L-proline (40 mol %) as the ligand and Cs_2CO_3 (2 equiv) as the base in dry DMSO (Table 1, entries 1–7). CuI showed the highest activity (Table 1, entry 1) and no target product **3d** was observed in the absence of copper catalyst (Table 1, entry 8). Other ligands were examined (Table 1, entries 9–11) but were inferior to L-proline (Table 1, entry 1 versus entries 9–11). A 47 % yield was achieved in the absence of any ligand (Table 1, entry 12). The effect of the base was also investigated (Table 1, entry 1 versus entries 13–16) and Cs_2CO_3 showed the highest efficiency. We screened various solvents and dry DMSO was superior (Table 1, entry 1 versus entries 17–19). Oxygen afforded a better result than air in the copper-catalyzed aerobic oxidative intramolecular C–H amidation (Table 1, entry 1 versus 20).

Table 1. Optimization of the conditions for copper-catalyzed one-pot synthesis of **3d** by coupling of **1d** with **2a**.[a]

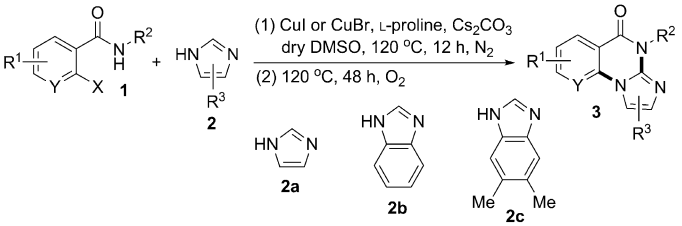


Entry	Cat.	Ligand	Base	Solvent	Yield [%][b]
1	CuI	L-proline	Cs_2CO_3	DMSO	66
2	CuBr	L-proline	Cs_2CO_3	DMSO	59
3	CuCl	L-proline	Cs_2CO_3	DMSO	28
4	Cu_2O	L-proline	Cs_2CO_3	DMSO	25
5	CuO	L-proline	Cs_2CO_3	DMSO	28
6	$Cu(OAc)_2$	L-proline	Cs_2CO_3	DMSO	24
7	Cu	L-proline	Cs_2CO_3	DMSO	58
8	–	L-proline	Cs_2CO_3	DMSO	0
9	CuI	DMEDA[c]	Cs_2CO_3	DMSO	40
10	CuI	phenanthroline	Cs_2CO_3	DMSO	55
11	CuI	pipecolic acid	Cs_2CO_3	DMSO	30
12	CuI	–	Cs_2CO_3	DMSO	47
13	CuI	L-proline	K_2CO_3	DMSO	28
14	CuI	L-proline	K_3PO_4	DMSO	47
15	CuI	L-proline	NaOAc	DMSO	trace
16	CuI	L-proline	KOC_4H_9	DMSO	33
17	CuI	L-proline	Cs_2CO_3	DMF	50
18	CuI	L-proline	Cs_2CO_3	THF	trace
19	CuI	L-proline	Cs_2CO_3	dioxane	18
20	CuI	L-proline	Cs_2CO_3	DMSO	44[d]

[a] Reaction conditions: **1d** (0.5 mmol), **2a** (1 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (1 mmol), solvent (1.5 mL), under nitrogen atmosphere for the first step, under oxygen balloon (1 atm.) for the second step. [b] Isolated yield. [c] Dimethylethylenediamine. [d] Under air for the second step.

The scope of the copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones was investigated and the products were obtained in good to excellent yields (Table 2). For substituted 2-halo-N-alkylbenzamides (**1**), the aryl halides that contained electron-withdrawing groups had higher reactivity than those with electron-donating groups. 5-Chloro-substituted substrates **1i** and **1l** led to the target

Table 2. Copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones by sequential Ullmann-type coupling and aerobic oxidative intramolecular C–H amidation.[a]



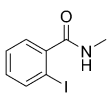
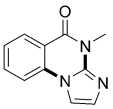
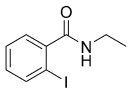
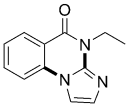
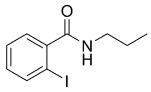
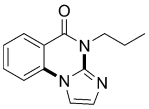
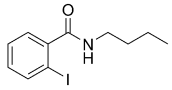
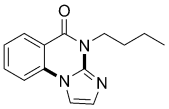
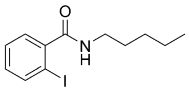
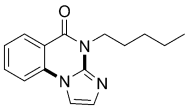
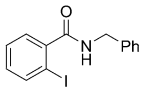
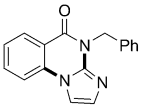
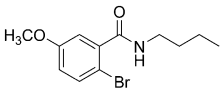
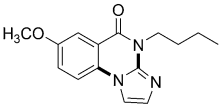
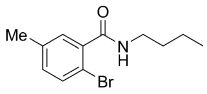
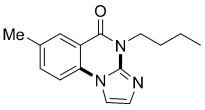
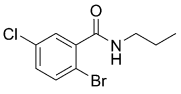
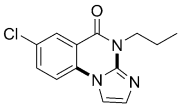
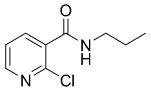
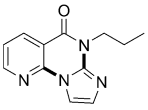
Entry	**1**	**3**	Yield [%][b]
1		**1a** 	**3a** 78
2		**1b** 	**3b** 72
3		**1c** 	**3c** 72
4		**1d** 	**3d** 66
5		**1e** 	**3e** 65
6		**1f** 	**3f** 62
7		**1g** 	**3g** 53
8		**1h** 	**3h** 54
9		**1i** 	**3i** 98[c]
10		**1j** 	**3j** 55

Table 2. (Continued)

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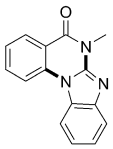
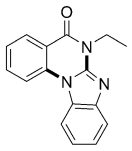
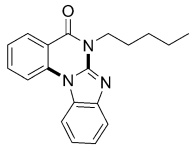
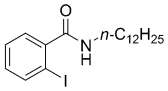
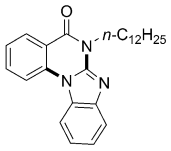
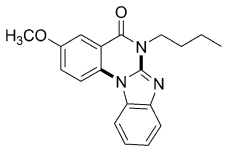
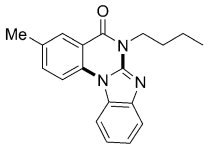
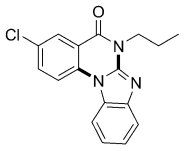
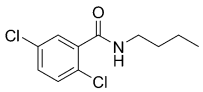
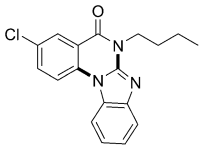
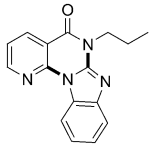
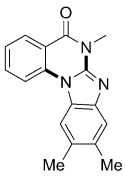
11	**1a**		**3k** 91
12	**1b**		**3l** 95
13	**1e**		**3m** 98
14		**1k** 	**3n** 80
15	**1g**		**3o** 75
16	**1h**		**3p** 98
17	**1i**		**3q** 98[c]
18		**1l** 	**3r** 80[c]
19	**1j**		**3s** 65
20	**1a**		**3t** 92

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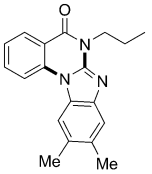
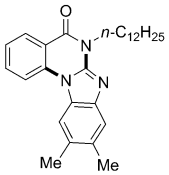
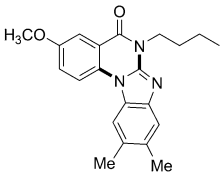
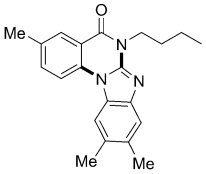
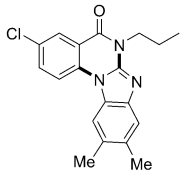
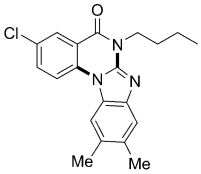
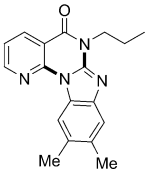
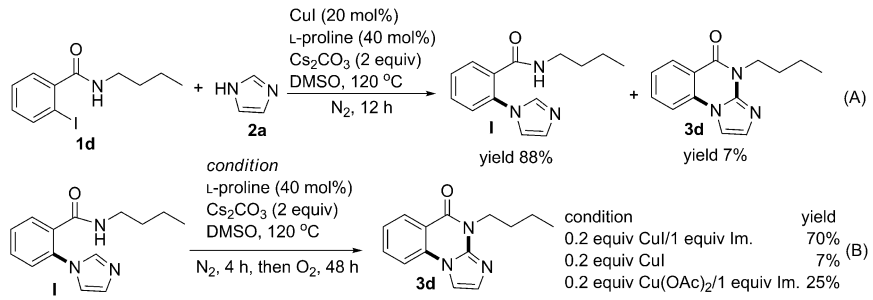
21	**1c**		**3u** 98
22	**1k**		**3v** 75
23	**1g**		**3w** 98
24	**1h**		**3x** 98
25	**1i**		**3y** 98[c]
26	**1l**		**3z** 84[c]
27	**1j**		**3a′** 54

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), CuI or CuBr (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (1 mmol), DMSO (1.5 mL), 120 °C, 12 h under nitrogen atmosphere; then 120 °C, 48 h under oxygen balloon (1 atm). CuI was used as the catalyst for substrate **2a**; CuBr was used as the catalyst for substrates **2b** and **2c**. [b] Isolated yield. [c] In the absence of ligand.

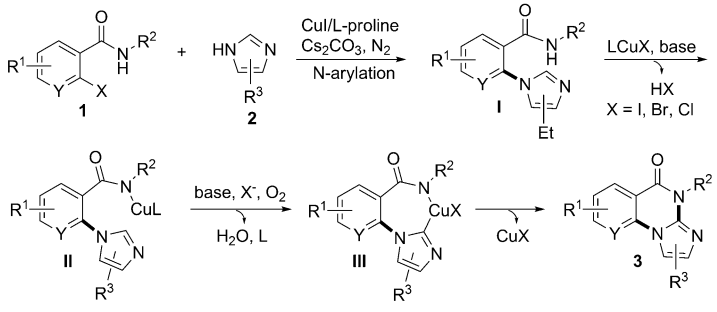
products in high yields without the assistance of a ligand (Table 2, entries 9, 17, 18, 25, and 26). 2-Chloro-*N*-propylpyridine-3-carboxamide (**1j**) also displayed moderate reactivity (Table 2, entries 10 and 27). Benzoimidazole derivatives exhibited higher reactivity than imidazole derivatives. The reactions shown in Table 2 could tolerate some functionality in the substrate, for example, a methyl ether (Table 2, entries 7 and 23), a C–Cl bond (Table 2, entries 9,



Scheme 2. a) Copper-catalyzed coupling of **1d** with **2a** under N_2; b) copper-catalyzed aerobic oxidative intramolecular C–H amidation of **I** under O_2.

17, 18, 25, and 26), N-heterocycles (Table 2, entries 10 and 27), and the amide bond.

To investigate the reaction mechanism of this synthesis of imidazo/benzoimidazoquinazolinones, we performed the following control experiments. Copper-catalyzed coupling of **1d** with **2a** under N_2 provided N-arylation product **I** in 88% yield, alongside a small amount of **3d** (Scheme 2a). We attempted copper-catalyzed aerobic oxidative intramolecular C–H amidation of **I** under different conditions and found that pre-treatment of the copper-catalyst system under nitrogen (about 4 h) before addition of oxygen to the Schlenk apparatus promoted the reaction efficiency. Product **3d** was obtained in 70% yield in the presence of **2a** (1 equiv) by using CuI (20 mol%) as the catalyst and L-proline (40 mol%) as the ligand. Only a small amount of **3d** was observed in the absence of **2a**, thus the imidazole could act as an additive in the copper-catalyzed aerobic oxidative C–H amidation (Scheme 2b). A low yield (25%) was achieved when $Cu(OAc)_2$ replaced CuI as the catalyst. A possible mechanism for the copper-catalyzed synthesis of imidazo/benzoimidazoquinazolinones is suggested in Scheme 3. Ullmann-type coupling of substituted 2-halo-N-alkylbenzamides or 2-chloro-*N*-propylpyridine-3-carboxamides (**1**) with an imidazole derivative **2** provides N-arylation product **I**. Treatment of CuX with L-proline forms complex LCuX. Coordination of intermediate **I** to LCuX gives **II** in the presence of base, then **II** furnishes **III** under O_2 in the presence of base. Reductive elimination of **III** leads to the target product **3** and regenerates the catalyst, CuX.



Scheme 3. Possible mechanism for synthesis of imidazo/benzoimidazoquinazolinones **3**.

Conclusion

We have developed a simple, practical, highly efficient copper-catalyzed one-pot method for synthesis of imidazo/benzoimidazoquinazolinones. The protocol uses readily available substituted 2-halo-N-alkylbenzamides, 2-chloro-*N*-propylpyridine-3-carboxamide, imidazole, and benzimidazole derivatives as the starting materials, inexpensive CuI/L-proline as the catalyst system, and economical and environmentally friendly oxygen gas as the oxidant. The imidazo/benzoimidazoquinazolinones were obtained in good to excellent yields. The procedure involved sequential copper-catalyzed Ullmann-type N-arylation and aerobic oxidative intramolecular C–H amidation. This inexpensive, convenient, highly efficient approach to N-heterocycles should attract much attention in academic and industrial research as a new and useful strategy for the construction of N-heterocycles.

Experimental Section

General: ^1H and ^{13}C NMR were recorded in $CDCl_3$ (^1H NMR referenced to TMS at $\delta = 0.00$ ppm, $CHCl_3$ at $\delta = 7.26$ ppm; ^{13}C NMR referenced to $CDCl_3$ at $\delta = 77.2$ ppm). DMSO was dried over CaH_2.

General procedure for the synthesis of compounds 3a–3a′: A Schlenk tube (10 mL) was charged with a magnetic stirrer, dry DMSO (1.5 mL), **1** (0.5 mmol), **2** (1 mmol), L-proline (0.2 mmol, 23 mg), and Cs_2CO_3 (1 mmol, 326 mg). The mixture was stirred for 20 min under nitrogen atmosphere, then CuI or CuBr (0.1 mmol) was added. The N-arylation reaction was performed at 120 °C for 12 h under nitrogen atmosphere, then the nitrogen atmosphere was replaced with an oxygen atmosphere (other conditions were kept). The aerobic oxidative intramolecular C–H amidation was carried out at 120 °C for 48 h. The resulting mixture was filtered and the solid was washed with EtOAc (2×3 mL). The combined filtrates were concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the target product.

Compound 3a: Eluent: petroleum ether/EtOAc (2:1). White solid, 78 mg (78%). M.p. 108–110 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 7.9$ Hz, 1H), 7.79–7.71 (m, 1H), 7.60–7.40 (m, 3H), 7.18 (s, 1H), 3.77 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.3$, 142.8, 134.8, 134.5, 129.8, 128.8, 125.5, 116.9, 114.1, 109.6, 29.5 ppm; MS (ESI): *m/z*: 200.1 $[M+H]^+$, 222.1 $[M+Na]^+$.

Compound 3b:[18] Eluent: petroleum ether/EtOAc (2:1). White solid, 77 mg (72%). M.p. 156–158 °C (ref. [litr18>] 176–178 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.36$ (d, $J = 7.9$ Hz, 1H), 7.77–7.69 (m, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.49 (s, 1H), 7.45–7.39 (m, 1H), 7.18 (s, 1H), 4.41 (q, $J = 7.2$ Hz, 2H), 1.43 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.7$, 142.1, 134.9, 134.4, 129.8, 128.8, 125.4, 117.1, 114.1, 109.4, 38.3, 12.9 ppm; MS (ESI): *m/z*: 214.3 $[M+H]^+$, 236.1 $[M+Na]^+$.

Compound 3c: Eluent: petroleum ether/EtOAc (2:1). White solid, 82 mg (72%). M.p. 102–104 °C; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.39$–8.37 (m, 1H), 7.76–7.73 (m, 1H), 7.56 (d, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 1.4$ Hz, 1H), 7.45–7.42 (m, 1H), 7.18 (d, $J = 1.7$ Hz, 1H), 4.33–4.29 (m, 2H), 1.93–1.86 (m, 2H), 1.04 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$

159.0, 142.5, 134.9, 134.4, 129.9, 128.8, 125.5, 117.1, 114.2, 109.4, 44.8, 20.9, 11.4 ppm; MS (ESI): m/z: 228.3 $[M+H]^+$, 250.2 $[M+Na]^+$.

Compound 3d: Eluent: petroleum ether/EtOAc (2:1). White solid, 79 mg (66%). M.p. 59–61°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.41–8.38 (m, 1H), 7.77–7.73 (m, 1H), 7.57 (d, J=8.3 Hz, 1H), 7.49 (d, J=1.4 Hz, 1H), 7.46–7.43 (m, 1H), 7.19 (d, J=1.4 Hz, 1H), 4.37–4.33 (m, 2H), 1.87–1.81 (m, 2H), 1.51–1.44 (m, 2H), 0.98 ppm (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.0, 142.4, 134.9, 134.4, 129.9, 128.9, 125.5, 117.1, 114.2, 109.4, 43.1, 29.7, 20.3, 13.9 ppm; MS (ESI): m/z: 242.3 $[M+H]^+$, 264.1 $[M+Na]^+$.

Compound 3e: Eluent: petroleum ether/EtOAc (2:1). White solid, 83 mg (65%). M.p. 40–42°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.41–8.36 (m, 1H), 7.78–7.71 (m, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.50–7.41 (m, 2H), 7.18 (d, J=1.7 Hz, 1H), 4.37–4.30 (m, 2H), 1.90–1.78 (m, 2H), 1.46–1.34 (m, 4H), 0.90 ppm (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.0, 142.5, 135.0, 134.5, 130.0, 128.9, 125.5, 117.2, 114.2, 109.4, 43.4, 29.1, 27.4, 22.6, 14.1 ppm; MS (ESI): m/z: 256.4 $[M+H]^+$.

Compound 3f: Eluent: petroleum ether/EtOAc (2:1). White solid, 85 mg (62%). M.p. 154–156°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.35 (d, J=7.9 Hz, 1H), 7.72–7.56 (m, 3H), 7.51–7.34 (m, 3H), 7.33–7.20 (m, 3H), 7.17 (m, 1H), 5.53 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.1, 142.5, 136.5, 135.0, 134.6, 130.0, 129.1, 128.9, 128.5, 127.8, 125.5, 117.1, 114.2, 109.6, 46.3 ppm; MS (ESI): m/z: 276.3 $[M+H]^+$, 298.1 $[M+Na]^+$.

Compound 3g: Eluent: petroleum ether/EtOAc (2:1). White solid, 72 mg (53%). M.p. 116–118°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.82 (d, J=2.8 Hz, 1H), 7.51 (d, J=8.9 Hz, 1H), 7.45 (d, J=1.4 Hz, 1H), 7.35–7.32 (m, 1H), 7.18 (d, J=1.4 Hz, 1H), 4.36 (t, J=7.6 Hz, 2H), 3.93 (s, 3H), 1.87–1.81 (m, 2H), 1.52–1.44 (m, 2H), 0.99 ppm (t, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=158.9, 157.3, 141.9, 129.2, 128.5, 123.6, 118.1, 115.8, 110.6, 109.3, 56.0, 43.3, 29.8, 20.3, 13.9 ppm; MS (ESI): m/z: 272.3 $[M+H]^+$.

Compound 3h: Eluent: petroleum ether/EtOAc (2:1). White solid, 68 mg (54%). M.p. 98–100°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.16 (s, 1H), 7.56–7.51 (m, 1H), 7.47–7.42 (m, 2H), 7.16 (d, J=1.4 Hz, 1H), 7.23–7.15 (m, 1H), 4.34 (t, J=7.6 Hz, 2H), 2.47 (s, 3H), 1.90–1.77 (m, 2H), 1.53–1.39 (m, 2H), 0.98 ppm (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.1, 142.3, 135.5, 135.4, 132.9, 129.6, 128.6, 116.9, 114.1, 109.3, 43.1, 29.7, 21.0, 20.3, 13.9 ppm; MS (ESI): m/z: 256.3 $[M+H]^+$, 278.2 $[M+Na]^+$.

Compound 3i: Eluent: petroleum ether/EtOAc (2:1). White solid, 128 mg (98%). M.p. 165–167°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.29 (d, J=2.1 Hz, 1H), 7.70–7.64 (m, 1H), 7.51 (d, J=8.6 Hz, 1H), 7.45 (d, J=1.4 Hz, 1H), 7.17 (d, J=1.4 Hz, 1H), 4.28 (t, J=7.6 Hz, 2H), 1.94–1.79 (m, 2H), 1.03 ppm (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.8, 142.2, 134.5, 133.4, 131.3, 129.4, 129.1, 118.3, 115.8, 109.5, 44.9, 20.8, 11.4 ppm; MS (ESI): m/z: 262.3 $[M+H]^+$.

Compound 3j: Eluent: petroleum ether/EtOAc (2:1). White solid, 63 mg (55%). M.p. 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.75–8.71 (m, 1H), 8.68–8.63 (m, 1H), 7.85 (d, J=1.7 Hz, 1H), 7.46–7.40 (m, 1H), 7.17 (d, J=1.7 Hz, 1H), 4.34–4.27 (m, 2H), 1.96–1.83 (m, 2H), 1.04 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.8, 153.7, 146.1, 142.6, 138.8, 128.7, 121.5, 112.5, 110.1, 44.9, 20.9, 11.4 ppm; MS (ESI): m/z: 229.3 $[M+H]^+$.

Compound 3k: Eluent: petroleum ether/EtOAc (4:1). White solid, 113 mg (91%). M.p. 198–200°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.41–8.37 (m, 1H), 8.10–8.05 (m, 1H), 7.92–7.87 (m, 1H), 7.82–7.75 (m, 1H), 7.73–7.68 (m, 1H), 7.45–7.26 (m, 3H), 3.81 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.6, 147.1, 142.5, 136.7, 134.9, 134.8, 130.7, 130.0, 124.9, 124.3, 122.4, 119.3, 116.6, 114.2, 112.4, 30.0 ppm; MS (ESI): m/z: 250.5 $[M+H]^+$, 272.3 $[M+Na]^+$.

Compound 3l: Eluent: petroleum ether/EtOAc (4:1). White solid, 125 mg (95%). M.p. 168–170°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.35–8.30 (m, 1H), 7.96 (d, J=8.3 Hz, 1H), 7.79 (d, J=7.9 Hz, 1H), 7.74–7.63 (m, 2H), 7.37–7.18 (m, 3H), 4.44 (q, J=7.2 Hz, 2H), 1.46 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.0, 146.4, 142.6, 136.7, 134.6, 130.5, 129.9, 124.7, 124.1, 122.1, 119.1, 116.8, 114.1, 112.3, 38.8, 12.9 ppm; MS (ESI): m/z: 264.4 $[M+H]^+$, 286.2 $[M+Na]^+$.

Compound 3m: Eluent: petroleum ether/EtOAc (4:1). White solid, 150 mg (98%). M.p. 124–126°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.32 (d, J=8.3 Hz, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.78 (d, J=8.3 Hz, 1H), 7.71–7.67 (m, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.35–7.31 (m, 1H), 7.29–7.25 (m, 1H), 7.23–7.19 (m, 1H), 4.36 (t, J=7.6 Hz, 2H), 1.91–1.84 (m, 2H), 1.48–1.37 (m, 4H), 0.92 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.2, 146.6, 142.6, 136.6, 134.5, 130.5, 129.9, 124.6, 124.0, 122.0, 119.1, 116.7, 114.1, 112.2, 43.6, 29.1, 27.2, 22.6, 14.1 ppm; MS (ESI): m/z: 306.2 $[M+H]^+$, 328.1 $[M+Na]^+$.

Compound 3n: Eluent: petroleum ether/EtOAc (4:1). White solid, 161 mg (80%). M.p. 80–82°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.46–8.42 (m, 1H), 8.17 (d, J=8.3 Hz, 1H), 7.98 (d, J=7.6 Hz, 1H), 7.86–7.75 (m, 2H), 7.48–7.29 (m, 3H), 4.44 (t, J=7.9 Hz, 2H), 1.95–1.84 (m, 2H), 1.53–1.20 (m, 18H), 0.90–0.83 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.4, 146.9, 142.8, 136.9, 134.8, 130.8, 130.2, 124.9, 124.2, 122.2, 119.4, 116.9, 114.3, 112.5, 43.8, 32.0, 29.7, 29.6, 29.5, 29.4, 27.6, 27.0, 22.8, 14.2 ppm; MS (ESI): m/z: 404.3 $[M+H]^+$.

Compound 3o: Eluent: petroleum ether/EtOAc (4:1). White solid, 120 mg (75%). M.p. 159–160°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.06 (d, J=8.9 Hz, 1H), 7.90 (d, J=8.3 Hz, 1H), 7.84 (d, J=2.8 Hz, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.38–7.34 (m, 2H), 7.32–7.28 (m, 1H), 4.45 (t, J=7.6 Hz, 2H), 3.91 (s, 3H), 1.91–1.86 (m, 2H), 1.54–1.47 (m, 2H), 1.00 ppm (t, J=7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.3, 156.6, 146.4, 142.5, 131.0, 130.5, 123.9, 123.2, 122.0, 119.2, 117.9, 115.8, 112.1, 111.2, 55.9, 43.6, 29.6, 20.3, 14.0 ppm; MS (ESI): m/z: 322.6 $[M+H]^+$, 344.5 $[M+Na]^+$.

Compound 3p: Eluent: petroleum ether/EtOAc (4:1). White solid, 150 mg (98%). M.p. 154–156°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.16 (d, J=1.4 Hz, 1H), 7.96 (d, J=8.6 Hz, 1H), 7.88 (d, J=7.6 Hz, 1H), 7.74–7.70 (m, 1H), 7.57–7.52 (m, 1H), 7.37–7.24 (m, 2H), 4.41 (t, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.93–1.80 (m, 2H), 1.55–1.42 (m, 2H), 0.99 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.5, 146.7, 142.7, 135.5, 134.8, 134.7, 130.7, 129.8, 123.9, 122.0, 119.2, 116.6, 114.1, 112.3, 43.5, 29.6, 20.9, 20.3, 14.0 ppm; MS (ESI): m/z: 306.4 $[M+H]^+$, 328.3 $[M+Na]^+$.

Compound 3q: Eluent: petroleum ether/EtOAc (2:1). White solid, 152 mg (98%). M.p. 165–167°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.38 (d, J=2.8 Hz, 1H), 8.08 (d, J=8.6 Hz, 1H), 7.89 (d, J=7.9 Hz, 1H), 7.79–7.72 (m, 2H), 7.42–7.29 (m, 2H), 4.39 (t, J=7.6 Hz, 2H), 1.99–1.85 (m, 2H), 1.06 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.4, 146.6, 142.7, 135.3, 134.7, 130.7, 130.5, 129.7, 124.4, 122.5, 119.5, 118.3, 115.7, 112.2, 45.4, 20.8, 11.4 ppm; MS (ESI): m/z: 312.2 $[M+H]^+$.

Compound 3r: Eluent: petroleum ether/EtOAc (2:1). White solid, 130 mg (80%). M.p. 163–165°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.34 (d, J=2.4 Hz, 1H), 8.02 (d, J=8.9 Hz, 1H), 7.83 (d, J=7.9 Hz, 1H), 7.74–7.69 (m, 2H), 7.38–7.28 (m, 2H), 4.39 (t, J=7.6 Hz, 2H), 1.91–1.79 (m, 2H), 1.54–1.40 (m, 2H), 0.98 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.3, 146.5, 142.6, 135.2, 134.7, 130.6, 130.4, 129.6, 124.4, 122.5, 119.5, 118.2, 115.7, 112.2, 43.7, 29.5, 20.3, 13.9 ppm; MS (ESI): m/z: 326.2 $[M+H]^+$.

Compound 3s: Eluent: petroleum ether/EtOAc (2:1). White solid, 90 mg (65%). M.p. 168–170°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.76–8.72 (m, 1H), 8.60–8.55 (m, 2H), 7.65 (d, J=7.9 Hz, 1H), 7.37–7.23 (m, 3H), 4.35 (t, J=7.6 Hz, 2H), 2.00–1.86 (m, 2H), 1.07 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.4, 153.7, 148.2, 146.4, 142.1, 138.3, 130.2, 124.6, 122.7, 120.5, 118.4, 115.3, 111.9, 45.1, 20.8, 11.4 ppm; MS (ESI): m/z: 279.2 $[M+H]^+$, 301.1 $[M+Na]^+$.

Compound 3t: Eluent: petroleum ether/EtOAc (4:1). White solid, 128 mg (92%). M.p. 236–238°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.41 (d, J=7.9 Hz, 1H), 8.13–8.05 (m, 1H), 7.87–7.78 (m, 1H), 7.67 (d, J=3.4 Hz, 1H), 7.49–7.39 (m, 2H), 3.81 (s, 3H), 2.43 (s, 3H), 2.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=159.6, 146.6, 140.9, 136.9, 134.7, 133.1, 131.2, 130.0, 129.1, 124.6, 119.6, 116.6, 114.2, 112.9, 30.0, 20.8, 20.4 ppm; MS (ESI): m/z: 278.3 $[M+H]^+$, 300.2 $[M+Na]^+$.

Compound 3u: Eluent: petroleum ether/EtOAc (4:1). White solid, 150 mg (98%). M.p. 172–174°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.44–8.40 (m, 1H), 8.13 (d, J=8.6 Hz, 1H), 7.86–7.79 (m, 1H), 7.71 (s, 1H),

7.51 (s, 1H), 7.46–7.40 (m, 1H), 4.39 (t, J=7.6 Hz, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 2.00–1.85 (m, 2H), 1.06 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.5, 146.3, 141.1, 137.0, 134.7, 132.9, 131.0, 130.0, 129.1, 124.5, 119.6, 116.8, 114.2, 113.0, 45.1, 20.8, 20.3, 11.4 ppm; MS (ESI): m/z: 306.5 $[M+H]^+$, 328.4 $[M+Na]^+$.

Compound 3v: Eluent: petroleum ether/EtOAc (4:1). White solid, 161 mg (75%). M.p. 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.43–8.37 (m, 1H), 8.09 (d, J=8.3 Hz, 1H), 7.83–7.75 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.44–7.36 (m, 1H), 4.40 (t, J=7.6 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H), 1.93–1.81 (m, 2H), 1.37–1.18 (m, 18H), 0.87 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.4, 146.3, 141.1, 137.0, 134.5, 132.9, 130.9, 130.0, 129.1, 124.4, 119.6, 116.8, 114.2, 112.9, 43.7, 32.0, 29.7, 29.6, 29.5, 29.4, 27.5, 27.0, 22.8, 20.7, 20.3, 14.2 ppm; MS (ESI): m/z: 432.4 $[M+H]^+$.

Compound 3w: Eluent: petroleum ether/EtOAc (4:1). White solid, 171 mg (98%). M.p. 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.96 (d, J=8.9 Hz, 1H), 7.80 (d, J=2.8 Hz, 1H), 7.57 (s, 1H), 7.47 (s, 1H), 7.37–7.30 (m, 1H), 4.41 (t, J=7.6 Hz, 2H), 3.91 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H), 1.93–1.80 (m, 2H), 1.56–1.42 (m, 2H), 0.99 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.3, 156.3, 145.8, 140.9, 132.6, 131.1, 130.7, 128.8, 123.1, 119.5, 117.7, 115.6, 112.5, 111.0, 55.9, 43.5, 29.6, 20.8, 20.3, 14.0 ppm; MS (ESI): m/z: 350.5 $[M+H]^+$, 372.4 $[M+Na]^+$.

Compound 3x: Eluent: petroleum ether/EtOAc (4:1). White solid, 163 mg (98%). M.p. 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.19 (d, J=1.7 Hz, 1H), 7.98 (d, J=8.6 Hz, 1H), 7.66 (s, 1H), 7.62–7.56 (m, 1H), 7.49 (s, 1H), 4.42 (t, J=7.6 Hz, 2H), 2.48 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H), 1.92–1.81 (m, 2H), 1.56–1.42 (m, 2H), 0.98 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.5, 146.2, 141.0, 135.5, 134.8, 134.5, 132.7, 130.8, 129.8, 129.0, 119.5, 116.6, 114.1, 112.8, 43.4, 29.6, 21.0, 20.8, 20.3, 20.2, 14.0 ppm; MS (ESI): m/z: 334.5 $[M+H]^+$, 356.5 $[M+Na]^+$.

Compound 3y: Eluent: petroleum ether/EtOAc (2:1). White solid, 166 mg (98%). M.p. 192–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.30 (s, 1H), 7.85 (d, J=8.9 Hz, 1H), 7.66 (s, J=8.3 Hz, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 4.30 (t, J=7.6 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 1.94–1.80 (m, 2H), 1.03 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.2, 145.7, 140.9, 135.1, 134.4, 133.2, 131.2, 130.1, 129.4, 128.6, 119.7, 118.0, 115.5, 112.5, 45.2, 20.8, 20.3, 11.4 ppm; MS (ESI): m/z: 340.2 $[M+H]^+$.

Compound 3z: Eluent: petroleum ether/EtOAc (2:1). White solid, 139 mg (79%). M.p. 226–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.33 (s, 1H), 7.96 (d, J=8.3 Hz, 1H), 7.72 (s, J=8.9 Hz, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 4.38 (t, J=6.5 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.91–1.76 (m, 2H), 1.55–1.39 (m, 2H), 0.99 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=58.3, 145.9, 141.0, 135.3, 134.5, 133.2, 131.3, 130.2, 129.5, 128.7, 119.8, 118.1, 115.6, 112.6, 43.6, 29.5, 20.8, 20.3, 13.9 ppm; MS (ESI): m/z: 354.4 $[M+H]^+$, 376.3 $[M+Na]^+$.

Compound 3a′: Eluent: petroleum ether/EtOAc (2:1). White solid, 83 mg (54%). M.p. 212–214 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.77–8.73 (m, 1H), 8.59–8.53 (m, 1H), 8.30 (s, 1H), 7.39 (s, 1H), 7.36–7.29 (m, 1H), 4.33 (t, J=7.2 Hz, 2H), 2.37 (s, 3H), 2.34 (s, 3H), 1.98–1.84 (m, 2H), 1.05 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.3, 153.6, 148.2, 145.9, 140.4, 138.2, 133.3, 131.6, 128.4, 120.2, 118.8, 115.5, 111.9, 45.1, 20.8, 20.5, 11.4 ppm; MS (ESI): m/z: 307.2 $[M+H]^+$.

Synthesis of compound I: A two-neck round-bottom flask was charged with a magnetic stirrer then evacuated and backfilled with nitrogen. Benzamide **1d** (0.5 mmol, 152 mg), **2a** (1 mmol, 68 mg), Cs_2CO_3 (1 mmol, 326 mg), CuI (0.1 mmol, 19 mg), and DMSO (1.5 mL) were added to the flask under nitrogen atmosphere. The mixture was allowed to stir under nitrogen atmosphere at 120 °C for 12 h. The resulting solution was concentrated by using a rotary evaporator and the residue was purified by column chromatography on silica gel (EtOAc) to provide **I** as a white solid, (106 mg, 88%). M.p. 43–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.64–7.59 (m, 1H), 7.55–7.42 (m, 3H), 7.33–7.26 (m, 1H), 7.12 (s, 1H), 7.04 (s, 1H), 6.41 (s, 1H), 3.20 (t, J=6.9 Hz, 2H), 1.41–1.28 (m, 2H), 1.28–1.13 (m, 2H), 0.86 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.7, 137.2, 134.2, 133.4, 130.9, 129.7, 129.4, 128.7, 126.0, 120.5, 39.7, 31.2, 20.0, 13.7 ppm; MS (ESI): m/z: 244.2 $[M+H]^+$, 266.1 $[M+Na]^+$.

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