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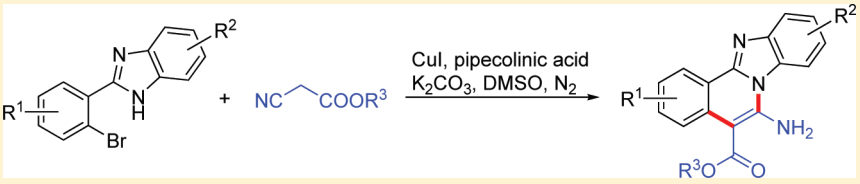
Copper-Catalyzed Cascade Synthesis of Alkyl 6-Aminobenzimidazo[2,1-*a*]isoquinoline-5-carboxylates

Juyou Lu and Hua Fu*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China

Supporting Information

ABSTRACT:



A convenient and efficient copper-catalyzed cascade method has been developed for synthesis of benzimidazoisoquinoline derivatives via reactions of readily available substituted 2-(2-halophenyl)benzoimidazoles with alkyl cyanoacetates under mild condition, and the corresponding alkyl 6-aminobenzimidazo[2,1-*a*]isoquinoline-5-carboxylates were obtained in good to excellent yields. The novel method provides diverse and useful poly *N*-heterocyclic compounds for combinatorial chemistry and medicinal chemistry.

INTRODUCTION

N-Heterocycles widely occur in natural products and biologically active molecules and play important roles in the pharmaceutical and agrochemical industries.[1] The benzimidazole derivatives have attracted much attention for their wide applications as the enzyme inhibitors,[2] drugs,[3] dyes,[4] and polymers.[5] The isoquinoline derivatives are an important class of alkaloids commonly found in natural products[6] and are often used as building blocks in pharmaceutical compounds.[7] For example, they were applied as potential PET radioligands for imaging peripheral benzodiazepine receptor[8a] and as orally bioavailable Kv1.5 antagonists for the treatment of atrial fibrillation.[8b] The hybrid structures of benzimidazole and isoquinoline frameworks, benzimidazoisoquinoline derivatives (Figure 1), show important biological activities, such as anti-HIV-1, anticancer, antimicrobial, and antifungal properties.[9] However, few syntheses of benzimidazoisoquinolines have been reported to date.[10] Dyker and co-workers have developed reactions of 2-alkynylbenzaldehydes with *o*-phenylenediamine in nitrobenzene at 150 °C for 2 d to lead to benzimidazoisoquinoline derivatives.[10a] Yanada et al. reported a palladium-catalyzed approach under microwave irradiation.[10b] The methods have harsh reaction conditions and limited substrate scopes that greatly restrict screening and discovery of potent biologically active molecules. Very recently, an efficient copper-catalyzed benzimidazoisoquinolines has been developed via reactions of various 2-ethynylbenzaldehydes and benzenediamines in the presence of NBS or I_2.[10c] We realize that the benzimidazoisoquinolines containing amino and carboxylate groups can be useful biologically active molecules and intermediates. However, there is not an efficient method for their synthesis thus far.

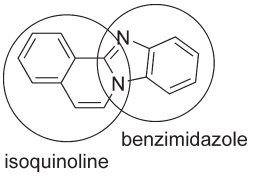


Figure 1. Benzimidazoisoquinoline as hybrid structure of isoquinoline and benzoimidazole.

Recently, there has been a great progress in copper-catalyzed cross-coupling reactions.[11,12] Their application to the construction of *N*-heterocycles has been reported by us[13] and other research groups.[14] Herein, we report a convenient and efficient copper-catalyzed cascade synthesis of alkyl 6-aminobenzimidazo[2,1-*a*]isoquinoline-5-carboxylates through reactions of substituted 2-(2-halophenyl)benzoimidazoles with alkyl cyanoacetates under mild condition.

RESULTS AND DISCUSSION

As shown in Table 1, 2-(2-bromophenyl)benzoimidazole (**1a**) and ethyl 2-cyanoacetate (**2b**) were chosen as the model substrates to optimize reaction conditions including catalysts, ligands, bases, solvents, and temperature under nitrogen atmosphere. First, copper catalysts (0.1 equiv) were investigated by using 0.2 equiv of pipecolinic acid as the ligand, 2 equiv of Cs_2CO_3 as the base, and DMSO as the solvent at 60 °C

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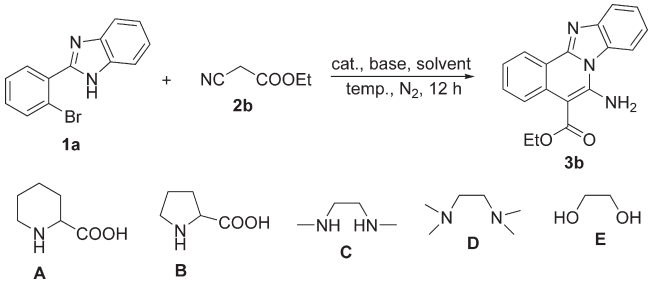
Table 1. Copper-catalyzed Cascade Synthesis of Ethyl 6-Aminobenzimidazo[2,1-*a*]isoquinoline-5-carboxylate (3b) via Reaction of 2-(2-Bromophenyl)-1*H*-benzo[*d*]imidazole (1a) with Ethyl 2-Cyanoacetate (2b): Optimization of Conditions[a]



entry	catalyst	ligand	base	solvent	temp (°C)	yield (%)[b]
1	CuI	A	Cs_2CO_3	DMSO	60	56
2	CuBr	A	Cs_2CO_3	DMSO	60	46
3	CuCl	A	Cs_2CO_3	DMSO	60	45
4	Cu_2O	A	Cs_2CO_3	DMSO	60	45
5	$Cu(OAc)_2$	A	Cs_2CO_3	DMSO	60	12
6	$CuCl_2$	A	Cs_2CO_3	DMSO	60	41
7	CuO	A	Cs_2CO_3	DMSO	60	8
8	$CuSO_4$	A	Cs_2CO_3	DMSO	60	5
9		A	Cs_2CO_3	DMSO	60	0
10	CuI	A	Cs_2CO_3	DMF	60	50
11	CuI	A	Cs_2CO_3	DMA	60	22
12	**CuI**	**A**	**K_2CO_3**	**DMSO**	**60**	**81**
13	CuI	A	$KHCO_3$	DMSO	60	27
14	CuI	A	Na_2CO_3	DMSO	60	14
16	CuI	A	Li_2CO_3	DMSO	60	20
17	CuI	A	K_3PO_4	DMSO	60	50
18	CuI	B	K_2CO_3	DMSO	60	25
19	CuI	C	K_2CO_3	DMSO	60	10
20	CuI	D	K_2CO_3	DMSO	60	5
21	CuI	E	K_2CO_3	DMSO	60	trace
22	CuI	A	K_2CO_3	DMSO	50	56
23	CuI	A	K_2CO_3	DMSO	80	63
24	CuI	A	K_2CO_3	DMSO	60	70[c]

[a] Reaction conditions: under nitrogen atmosphere, 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**1a**) (0.5 mmol), ethyl 2-cyanoacetate (**2b**) (1 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1.0 mmol), solvent (2 mL), reaction time 12 h. [b] Isolated yield. [c] CuI (0.025 mmol).

(entries 1−8). CuI provided the highest yield (entry 1), and no target product was observed in the absence of copper catalyst (entry 9). DMF and DMA were also attempted as the solvents (entries 10 and 11), and DMSO was best (compare entries 1, 10, and 11). Several bases were assayed (entries 12−17), and K_2CO_3 provided the highest yield (entry 12). Other ligands were screened (entries 18−21), and pipecolinic acid showed the highest activity (compare entries 12, 18−21). We investigated different reaction temperature (compare entries 12, 22, and 23), and 60 °C was suitable (entry 12). When 5 mol % CuI was used as the catalyst, a 70% yield was provided (entry 24).

The scope of copper-catalyzed cascade synthesis of benzimidazoisoquinoline derivatives from reactions of substituted 2-(2-halophenyl)benzoimidazoles with alkyl 2-cyanoacetates was investigated under the optimized conditions (0.1 equiv of CuI as the catalyst, 0.2 equiv of pipecolinic acid as the ligand, 2 equiv of K_2CO_3 as the base in DMSO under nitrogen atmosphere). As shown in Table 2, the tested substrates afforded good to excellent yields. The reactions provided benzimidazoisoquinolines with amino and carboxylate groups, and the functional groups are favor for further modification. In addition, the copper-catalyzed cascade reactions above could tolerate functional groups such as C−Cl bond (entries 10−17), ether (entries 7−9, 17), and ester groups (entries 1−17). We attempted scale-up reaction of 2-(2-bromophenyl)benzoimidazole (**1a**) with ethyl 2-cyanoacetate (**2b**), and a 76% yield was afforded (Scheme 1).

A possible mechanism for synthesis of benzimidazoisoquinoline derivatives was proposed in Scheme 2. First, coordination of pipecolinic acid with CuI provides complex CuL in the presence of base (K_2CO_3). Treatment of substituted 2-(2-halophenyl)-benzoimidazole (**1**) with CuL gives **I**, and oxidative addition of **I** leads to **II**. Reaction of **II** with alkyl cyanoacetate provides *C*-arylation intermediate **III**, and the intramolecular nucleophilic attack of NH of benzoimidazole to CN in **III** affords the target product (**3**).

We also attempted copper-catalyzed reaction of 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**1a**) with phenylacetylene in DMF under similar conditions, and the cascade coupling

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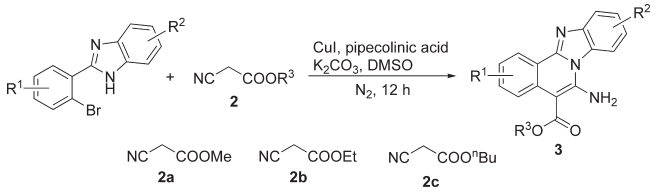
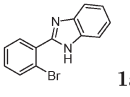
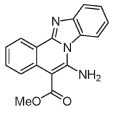
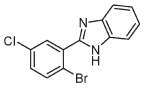
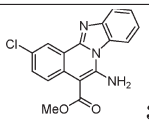
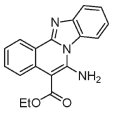
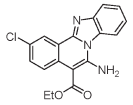
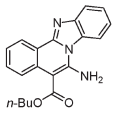
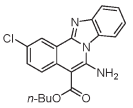
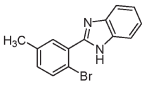
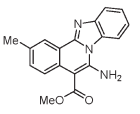
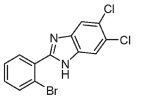
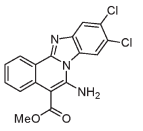
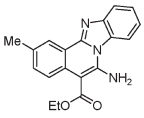
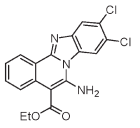
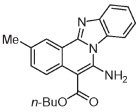
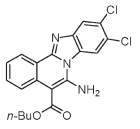
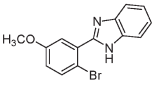
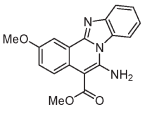
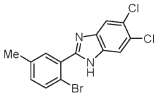
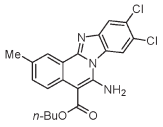
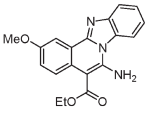
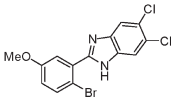
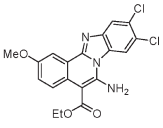
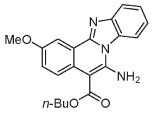
Table 2. Copper-Catalyzed Cascade Synthesis of Benzimidazoisoquinolines with Amino and Carboxylate Groups[a]



entry	1	3	yield (%)[b]	entry	1	3	yield (%)[b]
1	 1a	 3a	75	10	 1d	 3j	89
2	1a	 3b	81	11	1d	 3k	93
3	1a	 3c	78	12	1d	 3l	95
4	 1b	 3d	80	13	 1e	 3m	82
5	1b	 3e	88	14	1e	 3n	80
6	1b	 3f	71	15	1e	 3o	75
7	 1c	 3g	81	16	 1f	 3p	86
8	1c	 3h	86	17	 1g	 3q	88
9	1c	 3i	85				

[a] Reaction conditions: under nitrogen atmosphere, **1** (0.5 mmol), **2** (1.0 mmol), CuI (0.05 mmol), pipecolinic acid (0.1 mmol), K2CO3 (1.0 mmol), DMSO (2 mL), reaction time 12 h, reaction temperature 80 °C for entries 10−12; 60 °C for others. [b] Isolated yield.

provided product **4** in 65% yield (Scheme 3). Therefore, substituted 2-(2-halophenyl)benzoimidazoles (**1**) are good building blocks for synthesis of poly *N*-heterocycles under copper catalysis.

CONCLUSION

We have developed a convenient and efficient copper-catalyzed cascade method for the synthesis of benzimidazoisoquinoline derivatives. The protocol uses inexpensive CuI as the catalyst, readily available substituted 2-(2-halophenyl)benzoimidazoles (from reactions of substituted benzene-1,2-diamines with 2-haloobenzoic acids in acid medium[15]), and alkyl cyanoacetates as the starting materials. The copper-catalyzed reactions of substituted 2-(2-bromophenyl)benzoimidazoles with alkyl cyanoacetates proceeded very well under mild conditions, and the corresponding benzimidazoisoquinolines with amino and carboxylate groups were obtained in good to excellent yields. The novel method provides diverse and useful poly *N*-heterocyclic compounds for combinatorial chemistry and medicinal chemistry.

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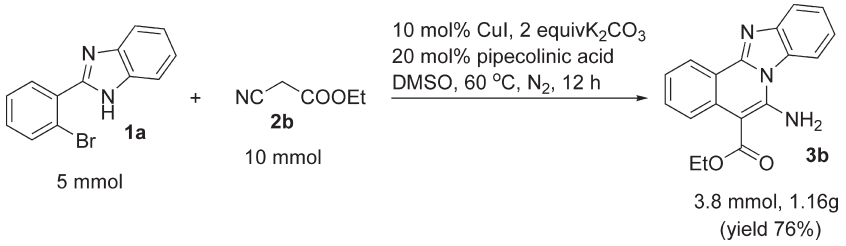
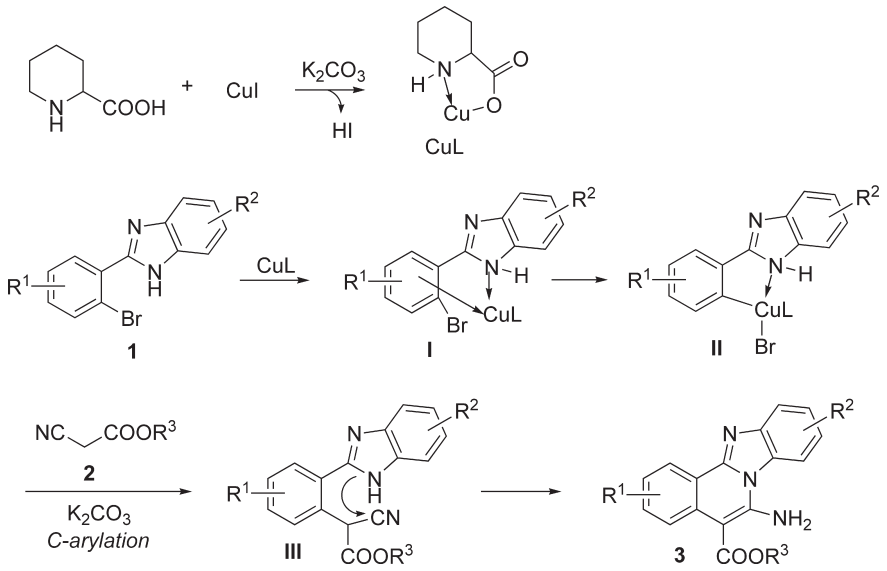
Scheme 1. Scale-up Reaction of 2-(2-Bromophenyl)benzoimidazole (1a) and Ethyl 2-Cyanoacetate (2b)



Scheme 2. Possible Copper-Catalyzed Mechanism for Synthesis of Benzimidazoisoquinoline Derivatives



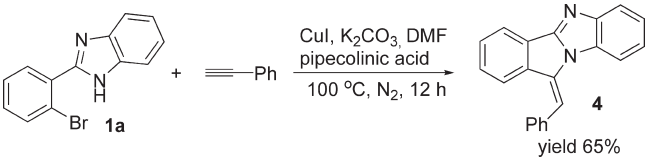
EXPERIMENTAL SECTION

General Procedure for Synthesis of Compounds 3a–q. Substituted 2-(2-halophenyl)benzoimidazole (**1**) (0.5 mmol), alkyl cyanoacetate (**2**) (1 mmol), CuI (0.05 mmol, 10 mg), pipecolinic acid (0.1 mmol, 13 mg), and K_2CO_3 (1.0 mmol, 138 mg) were added to a 10 mL two-neck round-bottom flask charged with a magnetic stirrer. The flask was evacuated and backfilled with nitrogen, and then DMSO (2.0 mL) was added to the flask under a stream of nitrogen. The mixture was stirred at 60 or 80 °C under nitrogen atmosphere for 12 h. After completion of the reaction, the resulting solution was cooled to room temperature. The solvent was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired product (**3a–q**).

3a. Eluent: petroleum ether/ethyl acetate (10:1). Yield 75% (109 mg). Yellow solid, mp 194–195 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.70 (d, 1H, J = 6.8 Hz), 8.46 (d, 1H, J = 8.6 Hz), 7.99 (s, 1H), 7.96 (s, 1H), 7.61–7.33 (m, 6H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 168.8, 148.5, 147.3, 143.8, 129.9, 129.6, 128.9, 124.3, 124.2, 124.1, 123.3, 121.4, 119.3, 117.2, 112.1, 87.6, 50.7. HR-MS $[M + H]^+$ m/z calcd for $C_{17}H_{14}N_3O_2$ 292.1086, found 292.1085.

3b. Eluent: petroleum ether/ethyl acetate (10:1). Yield 81% (124 mg). Yellow solid, mp 154–156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.52 (d, 1H, J = 7.6 Hz), 8.32 (d, 1H, J = 8.6 Hz), 7.80 (d, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 8.2 Hz), 7.45–7.09 (m, 6H), 4.33 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.2, 149.4, 148.2, 144.6, 131.0, 130.4, 129.9, 125.2, 125.1, 125.0, 124.1, 122.2, 120.1, 118.1, 113.2, 88.7, 61.0, 14.5. HR-MS $[M + H]^+$ m/z calcd for $C_{18}H_{16}N_3O_2$ 306.1243, found 306.1234.

Scheme 3. Copper-Catalyzed Reaction of 2-(2-Bromophenyl)-1*H*-benzo[*d*]imidazole (1a) with Phenylacetylene



3c. Eluent: petroleum ether/ethyl acetate (10:1). Yield 78% (130 mg). Yellow solid, mp 148–150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.60 (d, 1H, J = 7.9 Hz), 8.40 (d, 1H, J = 8.6 Hz), 7.87 (d, 1H, J = 8.2 Hz), 7.83 (d, 1H, J = 8.6 Hz), 7.52–7.18 (m, 6H), 4.33 (t, 2H, J = 6.8 Hz), 1.82–1.75 (m, 2H), 1.54–1.46 (m, 2H), 1.00 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.4, 149.5, 148.3, 144.8, 131.2, 130.5, 129.9, 125.3, 125.2, 125.1, 124.3, 122.2, 120.2, 118.2, 113.2, 88.9, 66.1, 30.8, 19.6, 14.0. HR-MS $[M + H]^+$ m/z calcd for $C_{20}H_{20}N_3O_2$ 334.1556, found 334.1553.

3d. Eluent: petroleum ether/ethyl acetate (10:1). Yield 80% (122 mg). Yellow solid, mp 216–218 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm)

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δ 8.42 (s, 1H), 8.27 (d, 1H, *J* = 8.6 Hz), 7.93−7.89 (m, 2H), 7.46 (t, 1H, *J* = 7.9 Hz), 7.34−7.26 (m, 4H), 3.94 (s, 3H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.8, 149.2, 148.4, 144.8, 134.2, 132.2, 130.0, 128.5, 125.3, 125.2, 124.8, 122.3, 120.3, 118.2, 113.3, 88.9, 51.7, 20.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{16}N_3O_2$ 306.1243, found 306.1245.

3e. Eluent: petroleum ether/ethyl acetate (10:1). Yield 88% (140 mg). Yellow solid, mp 143−145 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.38 (s, 1H), 8.30 (d, 1H, *J* = 8.6 Hz), 7.88 (t, 2H, *J* = 8.2 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.32−7.24 (m, 4H), 4.39 (q, 2H, *J* = 7.2 Hz), 2.41 (s, 3H), 1.45 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.4, 149.1, 148.3, 144.8, 134.1, 132.1, 130.0, 128.7, 125.3, 125.2, 124.7, 122.2, 120.2, 118.2, 113.3, 89.0, 61.0, 20.9, 14.5. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{19}H_{18}N_3O_2$ 320.1399, found 320.1402.

3f. Eluent: petroleum ether/ethyl acetate (10:1). Yield 71% (123 mg). Yellow solid, mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.41 (s, 1H), 8.31 (d, 1H, *J* = 8.6 Hz), 7.92−7.88 (m, 2H), 7.44 (t, 1H, *J* = 7.6 Hz), 7.34−7.23 (m, 4H), 4.35 (t, 2H, *J* = 6.5 Hz), 2.43 (s, 3H), 1.83−1.78 (m, 2H), 1.55−1.47 (m, 2H), 1.01 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.5, 149.1, 148.3, 144.8, 134.1, 132.1, 130.1, 128.7, 125.3, 124.7, 122.2, 120.2, 118.2, 113.3, 89.1, 65.0, 30.8, 20.9, 19.6, 13.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{21}H_{22}N_3O_2$ 348.1712, found 348.1715.

3g. Eluent: petroleum ether/ethyl acetate (10:1). Yield 81% (130 mg). Yellow solid, mp 206−208 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.42 (d, 1H, *J* = 9.2 Hz), 8.11−8.00 (m, 3H), 7.55 (t, 1H, *J* = 7.9 Hz), 7.40 (t, 1H, *J* = 7.9 Hz), 7.33 (s, br, 2H), 7.22 (dd, 1H, *J* = 9.2 Hz, 2.7 Hz), 4.01 (s, 3H), 3.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.9, 156.7, 148.4, 148.3, 144.8, 130.3, 127.3, 125.5, 124.9, 122.5, 121.1, 120.5, 119.5, 113.5, 105.4, 89.3, 55.8, 51.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{16}N_3O_3$ 322.1192, found 322.1191.

3h. Eluent: petroleum ether/ethyl acetate (10:1). Yield 86% (144 mg). Yellow solid, mp 189−191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.40 (d, 1H, *J* = 9.6 Hz), 8.03 (d, 1H, *J* = 2.7 Hz), 7.97 (t, 2H, *J* = 7.9 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.9 Hz), 7.21 (s, br, 2H), 7.17 (dd, 1H, *J* = 9.2 Hz, 2.7 Hz), 4.45 (q, 2H, *J* = 7.2 Hz), 3.95 (s, 3H), 1.47 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.4, 156.5, 148.2, 148.1, 144.8, 130.2, 127.1, 125.4, 125.0, 122.4, 120.9, 120.3, 119.5, 113.5, 105.2, 89.3, 61.1, 55.7, 14.5. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{19}H_{18}N_3O_3$ 336.1348, found 336.1342.

3i. Eluent: petroleum ether/ethyl acetate (10:1). Yield 85% (154 mg). Yellow solid, mp 165−166 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.47 (d, 1H, *J* = 9.2 Hz), 8.12 (d, 1H, *J* = 3.1 Hz), 8.09 (d, 1H, *J* = 8.2 Hz), 8.02 (d, 1H, *J* = 8.2 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.32 (s, br, 2H), 7.22 (dd, 1H, *J* = 9.2 Hz, 2.7 Hz), 4.45 (t, 2H, *J* = 6.5 Hz), 3.99 (s, 3H), 1.88−1.88 (m, 2H), 1.57−1.50 (m, 2H), 1.01 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.6, 156.6, 148.3, 144.9, 130.3, 127.3, 125.5, 125.1, 122.5, 121.0, 120.4, 119.6, 113.5, 105.4, 89.6, 65.1, 55.8, 30.9, 19.6, 13.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{21}H_{22}N_3O_3$ 364.1661, found 364.1662.

3j. Eluent: petroleum ether/ethyl acetate (10:1). Yield 89% (145 mg). Yellow solid, mp 246−248 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.67 (d, 1H, *J* = 2.0 Hz), 8.43 (d, 1H, *J* = 9.2 Hz), 7.99 (d, 2H, *J* = 8.2 Hz), 7.56−7.41 (m, 5H), 4.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.7, 149.8, 147.4, 130.9, 130.2, 130.1, 129.5, 127.2, 125.8, 124.5, 123.0, 120.8, 119.5, 113.2, 88.3, 52.0. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{17}H_{13}ClN_3O_2$ 326.0696, found 326.0698.

3k. Eluent: petroleum ether/ethyl acetate (10:1). Yield 93% (158 mg). Yellow solid, mp 212−214 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.54 (d, 1H, *J* = 1.7 Hz), 8.37 (d, 1H, *J* = 9.2 Hz), 7.89 (t, 2H, *J* = 7.9 Hz), 7.51−7.32 (m, 5H), 4.44 (q, 2H, *J* = 7.2 Hz), 1.47 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.0, 149.6, 147.1, 144.8, 130.7, 130.0, 129.9, 129.5, 126.9, 125.6, 124.2, 122.8, 120.6, 119.3, 113.2, 88.3, 61.2, 14.5. ESI-MS $[M + H]^+$ *m*/*z* 340.2. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{15}ClN_3O_2$ 340.0853, found 340.0852.

3l. Eluent: petroleum ether/ethyl acetate (10:1). Yield 95% (174 mg). Yellow solid, mp 208−210 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.66 (d, 1H, *J* = 2.4 Hz), 8.45 (d, 1H, *J* = 9.2 Hz), 7.97 (dd, 2H, *J* = 8.2 Hz, 2.4 Hz), 7.56−7.39 (m, 5H), 4.42 (t, 2H, *J* = 6.5 Hz), 1.86−1.81 (m, 2H), 1.56−1.51 (m, 2H), 1.02 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.3, 149.6, 147.3, 144.9, 130.8, 130.1, 130.0, 129.6, 127.1, 125.7, 124.4, 122.9, 120.7, 119.5, 113.2, 88.5, 65.2, 30.9, 19.6, 13.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{20}H_{19}ClN_3O_2$ 368.1166, found 368.1169.

3m. Eluent: petroleum ether/ethyl acetate (10:1). Yield 82% (147 mg). Yellow solid, mp 263−265 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm) δ 8.64 (s, 1H), 8.52 (d, 1H, *J* = 7.6 Hz), 8.36 (d, 1H, *J* = 8.2 Hz), 8.08 (s, 1H), 7.89 (s, br, 2H), 7.63 (t, 1H, *J* = 7.6 Hz), 7.41 (t, 1H, *J* = 7.6 Hz), 3.97 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 169.0, 150.1, 148.9, 144.5, 131.9, 131.6, 129.8, 128.4, 125.3, 124.7, 124.6, 120.5, 117.7, 117.2, 89.8, 52.3. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{17}H_{12}Cl_2N_3O_2$ 360.0307, found 360.0310.

3n. Eluent: petroleum ether/ethyl acetate (10:1). Yield 80% (149 mg). Yellow solid, mp 258−259 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.63 (d, 1H, *J* = 8.2 Hz), 8.51 (d, 1H, *J* = 8.6 Hz), 8.13 (s, 1H), 8.00 (s, 1H), 7.60 (t, 1H, *J* = 8.2 Hz), 7.44 (t, 1H, *J* = 7.2 Hz), 7.17 (s, br, 2H), 4.52 (q, 2H, *J* = 7.2 Hz), 1.51 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.1, 150.0, 148.5, 144.4, 131.3, 129.8, 129.1, 126.0, 125.6, 125.5, 124.9, 121.2, 118.2, 114.8, 90.6, 61.4, 14.5. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{18}H_{14}Cl_2N_3O_2$ 374.0463, found 374.0467.

3o. Eluent: petroleum ether/ethyl acetate (10:1). Yield 75% (150 mg). Yellow solid, mp 251−252 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.51 (d, 1H, *J* = 7.2 Hz), 8.41 (d, 1H, *J* = 8.6 Hz), 7.99 (s, 1H), 7.88 (s, 1H), 7.56 (t, 1H, *J* = 7.2 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.08 (s, br, 2H), 4.42 (t, 2H, *J* = 6.5 Hz), 1.88−1.83 (m, 2H), 1.56−1.51 (m, 2H), 1.03 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 169.1, 149.7, 148.5, 144.2, 131.2, 129.6, 128.9, 125.8, 125.5, 125.2, 124.8, 120.9, 117.9, 114.7, 90.6, 65.4, 30.8, 19.6, 13.9. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{20}H_{18}Cl_2N_3O_2$ 402.0776, found 402.0772.

3p. Eluent: petroleum ether/ethyl acetate (10:1). Yield 86% (178 mg). Yellow solid, mp 268−270 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm) δ 8.59 (s, 1H), 8.24 (d, 2H, *J* = 8.9 Hz), 8.00 (s, 1H), 7.80 (s, br, 2H), 7.40 (d, 2H, *J* = 8.2 Hz), 4.38 (t, 2H, *J* = 6.2 Hz), 2.42 (s, 3H), 1.79−1.77 (m, 2H), 1.49−1.47 (m, 2H), 0.98 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 168.7, 149.9, 148.5, 144.5, 134.0, 132.9, 129.8, 129.6, 128.2, 125.3, 124.8, 124.5, 120.3, 117.7, 117.1, 89.8, 65.0, 30.8, 20.9, 19.6, 14.0. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{21}H_{20}Cl_2N_3O_2$ 416.0933, found 416.0935.

3q. Eluent: petroleum ether/ethyl acetate (10:1). Yield 88% (177 mg). Yellow solid, mp 255−256 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm) δ 8.60 (s, 1H), 8.32 (d, 1H, *J* = 8.9 Hz), 8.04 (s, 1H), 7.88 (d, 1H, *J* = 2.7 Hz), 7.68 (s, br, 2H), 7.24 (dd, 1H, *J* = 9.6 Hz, 2.7 Hz), 4.44 (q, 2H, *J* = 7.6 Hz), 3.90 (s, 3H), 1.42 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 168.5, 156.5, 149.5, 147.7, 144.4, 129.9, 128.3, 127.3, 125.7, 124.5, 121.1, 120.3, 118.8, 117.2, 106.2, 90.1, 61.2, 55.9, 14.7. HR-MS $[M + H]^+$ *m*/*z* calcd for $C_{19}H_{16}Cl_2N_3O_3$ 404.0569, found 404.0571.

Synthesis of Compound 4. 2-(2-Bromophenyl)benzoimidazole (**1a**) (0.5 mmol, 137 mg), phenylacetylene (1 mmol, 102 mg), CuI (0.05 mmol, 10 mg), pipecolinic acid (0.1 mmol, 13 mg), and K_2CO_3 (1.0 mmol, 138 mg) were added to a 10 mL two-neck round-bottom flask charged with a magnetic stirrer. The flask was evacuated and backfilled with nitrogen, and then DMF (2.0 mL) was added to the flask under a stream of nitrogen. The mixture was stirred at 100 °C under nitrogen atmosphere for 12 h. After completion of the reaction, the resulting solution was cooled to room temperature. The solvent was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired product **4**. Eluent: petroleum ether/ethyl acetate (10:1). Yield 65% (96 mg).

Yellow solid, mp 198−200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.89 (d, 1H, J = 8.6 Hz), 7.99 (d, 1H, J = 7.9 Hz), 7.71−7.59 (m, 8H), 7.38 (t, 1H, J = 7.9 Hz), 7.00 (t, 1H, J = 8.2 Hz), 6.90 (s, 1H), 6.48 (d, 1H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 148.3, 144.3, 137.5, 134.7, 131.6, 130.7, 129.9, 129.4, 129.0, 127.9, 126.7, 125.2, 124.3, 123.0, 121.3, 119.8, 114.1, 112.6. HR-MS $[M + H]^+$ m/z calcd for $C_{21}H_{15}N_2$ 295.1235, found 295.1232.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: fuhua@mail.tsinghua.edu.cn.

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