Copper(I)-Catalyzed, One-Pot Synthesis of Multisubstituted Indoles from 2-Iodoanilines and Ethyl Buta-2,3-dienoate

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Abstract: Reactions of 2-iodoanilines with ethyl buta-2,3-dienoate catalyzed by potassium carbonate and CuI in one pot generate the corresponding ethyl 2-methyl-1*H*-indole-3-carboxylate products in moderate yields under mild conditions.

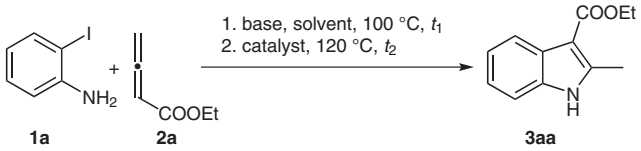
Key words: indoles, aniline, allenes, copper, catalysis

The indole moiety exists in a wide range of natural products and pharmaceuticals.[1] Their importance in medicinal chemistry has stimulated considerable interest from organic chemists, and has encouraged the development of new synthetic methods to prepare these compounds.[2] Many strategies for the synthesis of the indole moiety,[3] in addition to the classical Fisher indole synthesis,[4] have already been reported. Recent progress in metal-catalyzed construction of the indole skeleton[5] has achieved remarkable improvements regarding efficiency and functional group compatibility. In particular, the palladium-catalyzed ring-closing reaction of aniline derivatives with alkynes was been widely investigated and can efficiently produce multisubstituted indoles.[6] In addition, transition-metal-catalyzed intermolecular cyclization of *N*-(2-haloaryl)enamine or *N*-aryl enamine, derived from alkynes or acyclic β-diketones, has been used in the synthesis of multisubstituted indoles.[7] Direct construction of multi-substituted indoles from allenes has received less attention. Only Mukai and Takahashi synthesized 2,3-disubstituted indoles with *N*-acyl-2-iodoanilines and the 1-(tributylstannyl)-1-substituted allenes.[8] In this reaction, a tin reagent was used as substrate that is not readily accessible and is harmful to environment. Therefore, methods of synthesis of multisubstituted indoles with allenes need improvement. As a part of our continuing study on the use of copper catalysis in the synthesis of heterocycles,[9] herein, we report a straightforward, one-pot synthesis of multisubstituted indoles from 2-iodoanilines and ethyl buta-2,3-dienoate.

Our initial study began with the reaction of 2-iodoaniline (**1a**) and ethyl buta-2,3-dienoate (**2a**) in the presence of 1.5 equivalents of K_2CO_3 in 1,4-dioxane at 120 °C. The desired ethyl 2-methyl-1*H*-indole-3-carboxylate (**3aa**) was obtained in 32% conversion and 28% yield in the reaction catalyzed by CuI after 12 hours (Table 1, entry 1).

When a mixture of **1a** and **2a** in dioxane was heated (100 °C, 8 h; t_1) and cooled to room temperature, then a catalytic amount of CuI was added and the mixture again heated (120 °C, 7 h; t_2), to our delight, **3aa** was obtained

Table 1 Survey of Catalysts, Bases, and Solvent Effects in the Reaction of **1a** with **2a**[a]



1a **2a** **3aa**

Entry	Base	t_1 (h)	Catalyst	t_2 (h)	Solvent	Conv. (%)[b]	Yield (%)[c]
1	K_2CO_3	0	CuI	12	1,4-dioxane	32	28
2	K_2CO_3	8	CuI	7	1,4-dioxane	100	70
3	K_2CO_3	4	CuI	7	1,4-dioxane	51	45
4[d]	K_2CO_3	8	CuI	7	1,4-dioxane	100	72
5[e]	K_2CO_3	8	CuI	7	1,4-dioxane	100	70
6	K_2CO_3	8	–	7	1,4-dioxane	100	0
7	K_2CO_3	8	Cu_2O	7	1,4-dioxane	100	44
8	K_2CO_3	8	CuBr	7	1,4-dioxane	100	40
9	K_2CO_3	8	$Cu(OAc)_2$	7	1,4-dioxane	100	50
10	K_2CO_3	8	[Cu][f]	7	1,4-dioxane	100	53
11	K_2CO_3	8	CuI	7	THF	80	30
12	K_2CO_3	8	CuI	7	DMSO	0	0
13	K_2CO_3	8	CuI	7	DMF	70	36
14	K_2CO_3	8	CuI	7	NMP	0	0
15	Na_2CO_3	8	CuI	7	1,4-dioxane	63	34
16	Cs_2CO_3	8	CuI	7	1,4-dioxane	26	20
17	KOH	8	CuI	7	1,4-dioxane	40	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol) and base (0.3 mmol) in solvent (0.9 mL), 100 °C for t_1, then cooled to r.t. and catalyst (0.02 mmol) was added and the mixture was heated at 120 °C for t_2.
[b] Conversions are given for **1a**.
[c] Isolated yield.
[d] Reaction was carried out with 2 equiv base.
[e] Reaction was carried out with 1.5 equiv base under nitrogen.
[f] [Cu] = CuI-phenanthroline.

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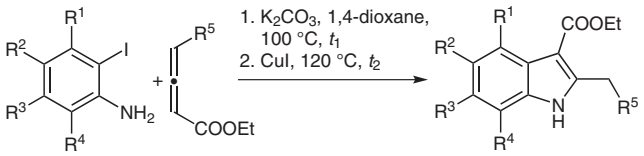
in 100% conversion and 70% yield (Table 1, entry 2). When t_1 was reduced, a lower conversion of **3aa** was obtained (Table 1, entry 3). By increasing the base loading to two equivalents, the conversion of **3aa** changed only slightly (Table 1, entry 4).

A range of copper salts such as Cu_2O, CuBr, $Cu(OAc)_2$ and CuI-phenanthroline were then examined (Table 1, entries 7–10), but no better results were obtained. In addition, in the absence of metal salts, no desired product was found, but ethyl 3-(2-iodophenylamino)but-2-enoate was detected (Table 1, entry 6). Among the solvent systems examined, changing the solvent to THF, DMSO, DMF, or NMP did not improve the conversions or yields (Table 1, entries 11–14). The results indicated that the choice of 1,4-dioxane as solvent was crucial for the reaction. Other bases such as Na_2CO_3, Cs_2CO_3, and KOH were also evaluated (Table 1, entries 15–17), and K_2CO_3 was found to provide the product in good yield. It is worth mentioning that when the reaction was carried out under nitrogen, product **3aa** was also obtained in 70% yield (Table 1, entry 5). Thus, the most suitable reaction conditions for the formation of **3aa** was found to be 1.5 equivalent of K_2CO_3, 1,4-dioxane, and 10 mol% CuI (Table 1, entry 2), which provided product **3aa** in good yield.

Under the optimized reaction conditions, we then attempted to extend the scope of this reaction to test the generality of this method; the results are illustrated in Table 2. Generally, reaction of 2-iodoanilines with ethyl buta-2,3-dienoate proceeded smoothly and led to the desired multisubstituted indoles in moderate yields. Thankfully, the reaction was found to tolerate a range of functionalities, including alkyl-substituted, cyano-substituted, keto-

Table 2 Synthesis of Ethyl 2-Methyl-1*H*-indole-3-carboxylate

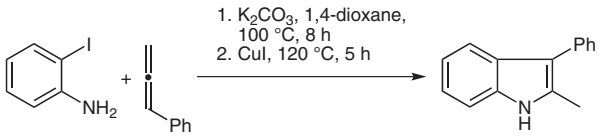


Entry	1	R^1	R^2	R^3	R^4	2	R^5	t_1 (h)	t_2 (h)	Product	Conv. (%)[a]	Yield (%)[b]
1	**1a**	H	H	H	H	**2a**	H	8	7	**3aa**	100	70
2	**1a**	H	H	H	H	**2b**	Me	8	7	**3ab**	84	51
3	**1a**	H	H	H	H	**2c**	E[c]	8	7	**3ac**	83	50
4	**1a**	H	H	H	H	**2d**	F[c]	8	7	**3ad**	80	46
5	**1a**	H	H	H	H	**2e**	G[c]	6	4	**3ae**	100	56
6	**1b**	H	Me	H	H	**2a**	H	8	7	**3ba**	100	72
7	**1c**	H	Et	H	H	**2a**	H	7	7	**3ca**	100	76
8	**1d**	H	Me_2CH	H	H	**2a**	H	7	7	**3da**	100	81
9	**1e**	H	H	Me	H	**2a**	H	8	7	**3ea**	100	71
10	**1f**	H	Cl	H	H	**2a**	H	8	7	**3fa**	60	43
11	**1g**	H	Br	H	H	**2a**	H	8	7	**3ga**	65	47
12	**1h**	H	I	H	H	**2a**	H	8	7	**3ha**	61	44
13	**1i**	H	Ac	H	H	**2a**	H	8	7	**3ia**	51	37
14	**1j**	H	CN	H	H	**2a**	H	16	7	**3ja**	62	31
15	**1k**	H	Me	Me	H	**2a**	H	5.5	7	**3ka**	100	82
16	**1l**	H	I	Me	Me	**2a**	H	7	7	**3la**	100	74
17	**1m**	H	I	H	Me	**2a**	H	8	7	**3ma**	60	45
18	**1n**	Me	I	H	Me	**2a**	H	8	7	**3na**	54	43
19	**1o**	H	I	H	Et	**2a**	H	8	7	**3oa**	62	40
20	**1p**	$-(CH{=}CH)_2-$		H	H	**2a**	H	8	7	**3pa**	80	52

[a] Conversions are given for **1**.
[b] Isolated yield.
[c] E = *n*-Bu; F = *i*-Pr; G = COOEt.

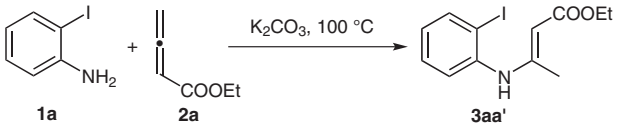
substituted, and halogenated 2-iodoanilines. Good conversions and yields of indole products **3** were usually obtained with 2-iodoanilines containing electron-donating substituents (Table 2, entries 6–9 and 15). In addition, the conversions and yields of *para*- and *meta*-substituted 2-iodoanilines changed only slightly (Table 2, entries 6 and 9).

Under the same experimental conditions, 2-iodoanilines with electron-withdrawing substituents gave lower conversions and yields (Table 2, entries 10–14). Spatial effects had little impact on the conversions or yield of the reaction (Table 2, entries 12 and 16–19). 2-Iodoanilines bearing benzo rings, such as 1-iodonaphthalen-2-amine could also react to give **3pa** in 52% yield (Table 2, entry 20). Further investigations demonstrated that allenes with electron-withdrawing substituents gave higher yields than those with electron-donating groups (Table 2, entries 2–5). To our delight, **3af** was also obtained in 65% yield (Equation 1).

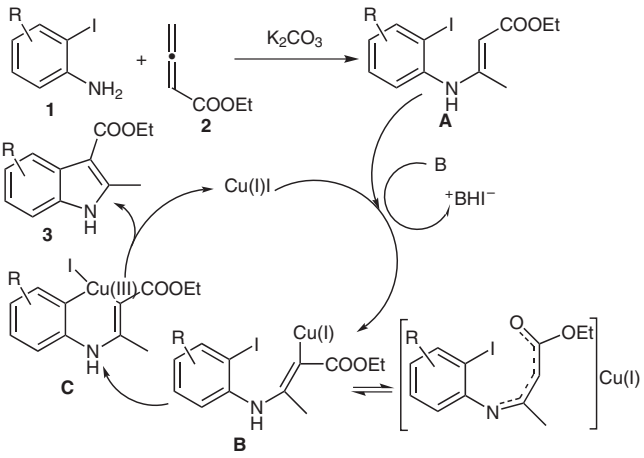


Equation 1 Reactions of **1a** and **2f** to give **3af**

The reaction of **1a** and **2a** in the presence of K_2CO_3 afforded ethyl 3-(2-iodophenyl-amino)but-2-enoate (**3aa′**; Scheme 1),[10] which was detected by NMR analysis. On the basis of the results obtained above, a plausible pathway for this reaction is illustrated in Scheme 2. The reaction consists of a Michael addition reaction and an intramolecular Heck coupling reaction of 2-iodoanilines and ethyl buta-2,3-dienoate. The reaction of **1** and **2** in the presence of K_2CO_3 leads to the formation of intermediate **A**. The next step involves initial coordination of carbon with copper (Scheme 2). The resulting complex **B** undergoes an oxidative addition of the C–X bond[7e] to copper to obtain the Cu(III) intermediate **C**. Reductive elimination of **C** then releases the desired product with concomitant regeneration of the Cu(I) species. Another possible mechanism involves the formation of **C** through oxidative addition of the C–I bond to CuI to produce a Cu(II) intermediate, which is followed by nucleophilic displacement of iodide by the anionic fragment. However, neither **2** nor the byproducts of **2** were found at the end of the reaction; this may be because unreacted **2** decomposes.



Scheme 1 Reactions of **1a** and **2a** in the presence of K_2CO_3 at 100 °C



Scheme 2 Possible reaction pathway

In summary, we have developed a novel methodology for the synthesis of 2-methyl-1*H*-indole-3-carboxylates, based on the addition of 2-iodoaniline and ethyl buta-2,3-dienoate followed by intramolecular cyclization, in the presence of a common and inexpensive catalyst. In addition, several multisubstituted indoles were synthesized in a one-pot process that consist of a Michael addition reaction and a Heck coupling reaction of 2-iodoanilines with ethyl buta-2,3-dienoate. Further application of this method to the synthesis of bioactive compounds and natural products with the indole skeleton as a core framework will be reported in due course.

NMR spectra were recorded at 400 (^{1}H) and 100 MHz (^{13}C) with a Bruker ARX 400 spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. IR spectra were recorded with an FT-IR spectrometer and only major peaks are reported. Melting points were determined with a microscopic apparatus and are uncorrected. All new products were further characterized by HRMS analysis. For product purification by flash column chromatography, silica gel (200–300 mesh) was used. Petroleum ether (PE), where used, had a boiling range 30–60 °C. Allenes were prepared according to the literature.[11] Multisubstituted 2-iodoanilines were prepared according to the literature.[12]

Ethyl 2-Methyl-1*H*-indole-3-carboxylate (3aa); Typical Procedure

A mixture of **1a** (43.8 mg, 0.2 mmol) and **2a** (26.9 mg, 0.24 mmol) in 1,4-dioxane (0.9 mL) was heated at 100 °C for 8 h in a sealed reaction tube. After cooling to r.t., CuI (3.8 mg, 0.02 mmol) was added and the mixture was heated at 120 °C for 7 h. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc–PE, 1:6) to give **3aa**.

Yield: 28.5 mg (70%); white solid; mp 135–136 °C.

IR (KBr): 3301, 2291, 1660, 1456, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (br, 1 H), 8.11 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 6.8 Hz, 1 H), 7.21 (m, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 143.9, 134.5, 127.2, 122.3, 121.7, 121.3, 110.5, 104.7, 59.5, 14.6, 14.2.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{12}H_{13}NO_2$: 204.1025; found: 204.1019.

Ethyl 2-Ethyl-1*H*-indole-3-carboxylate (3ab)
Yield: 22.0 mg (51%); colorless solid; mp 104–106 °C.

IR (KBr): 3303, 2978, 1665, 1456, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (br, 1 H), 8.15 (d, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 4.8 Hz, 1 H), 7.20 (m, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 3.21 (q, *J* = 7.6 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 149.5, 134.5, 127.3, 122.3, 121.7, 121.5, 110.6, 103.7, 59.4, 21.3, 14.6, 13.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_2$: 218.1181; found: 218.1179.

Ethyl 2-Pentyl-1*H*-indole-3-carboxylate (3ac)
Yield: 26.0 mg (50%); white solid; mp 49–51 °C.

IR (KBr): 3298, 2957, 2930, 1664, 1458, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (br, 1 H), 8.13 (d, *J* = 7.2 Hz, 1 H), 7.29 (m, 1 H), 7.21 (m, 2 H), 4.40 (q, *J* = 6.8 Hz, 2 H), 3.16 (t, *J* = 7.6 Hz, 2 H), 1.74 (m, 2 H), 1.45 (t, *J* = 6.8 Hz, 3 H), 1.36 (m, 4 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 148.6, 134.5, 127.2, 122.2, 121.6, 121.4, 110.6, 103.8, 59.5, 31.6, 29.0, 28.0, 22.4, 14.5, 13.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NO_2$: 282.1465; found: 282.1461.

Ethyl 2-Isobutyl-1*H*-indole-3-carboxylate (3ad)
Yield: 22.5 mg (46%); yellow solid; mp 74–75 °C.

IR (KBr): 3326, 2956, 1676, 1660, 1441, 1190, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br, 1 H), 8.14 (m, 1 H), 7.32 (m, 1 H), 7.22 (m, 2 H), 4.39 (q, *J* = 6.8 Hz, 2 H), 3.03 (d, *J* = 7.2 Hz, 2 H), 2.12 (m, 1 H), 1.45 (t, *J* = 7.2 Hz, 3 H), 0.97 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 147.6, 134.5, 127.3, 122.3, 121.6, 121.5, 110.6, 104.5, 59.5, 37.0, 29.2, 22.5, 14.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_2$: 268.1308; found: 268.1306.

Ethyl 2-(2-Ethoxy-2-oxoethyl)-1*H*-indole-3-carboxylate (3ae)
Yield: 30.8 mg (56%); yellow oil.

IR (KBr): 3321, 3061, 2982, 1691, 1457, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.83 (br, 1 H), 8.14 (t, *J* = 4.0 Hz, 1 H), 7.38 (m, 1 H), 7.25 (m, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.37 (s, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 1.48 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 165.7, 138.7, 134.8, 126.4, 122.8, 121.8, 121.5, 111.1, 105.2, 61.5, 59.7, 32.3, 14.5, 14.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}NO_4$: 276.1236; found: 276.1240.

2-Methyl-3-phenyl-1*H*-indole (3af)
Yield: 26.9 mg (65%); colorless oil.

IR (KBr): 3401, 1603, 1496, 1459, 1258, 908, 748, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (br, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.54 (m, 4 H), 7.35 (m, 2 H), 7.19 (m, 2 H), 2.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 135.1, 131.4, 129.4, 128.5, 127.7, 125.7, 121.4, 119.9, 118.7, 114.3, 110.3, 12.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N$: 208.1126; found: 208.1124.

Ethyl 2,5-Dimethyl-1*H*-indole-3-carboxylate (3ba)
Yield: 31.2 mg (72%); white solid; mp 177–178 °C.

IR (KBr): 3292, 2977, 2922, 1656, 1457, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (br, 1 H), 7.92 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 2.48 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 143.8, 132.7, 131.1, 127.5, 123.7, 121.08, 110.1, 104.2, 59.4, 21.7, 14.6, 14.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_2$: 218.1181; found: 218.1176.

Ethyl 5-Ethyl-2-methyl-1*H*-indole-3-carboxylate (3ca)
Yield: 35.1 mg (76%); white solid; mp 131–132 °C.

IR (KBr): 3299, 2966, 2926, 1658, 1433, 783 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (br, 1 H), 7.97 (s, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 2.79 (q, *J* = 7.6 Hz, 2 H), 2.71 (s, 3 H), 1.49 (t, *J* = 7.2 Hz, 3 H), 1.33 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 144.0, 137.8, 131.0, 127.5, 122.7, 119.8, 110.3, 104.2, 59.4, 29.2, 16.4, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_2$: 232.1338; found: 232.1333.

Ethyl 5-Isopropyl-2-methyl-1*H*-indole-3-carboxylate (3da)
Yield: 39.7 mg (81%); white solid; mp 154–155 °C.

IR (KBr): 3287, 2958, 1652, 1455, 812 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br, 1 H), 8.01 (s, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 3.10 (m, 1 H), 2.71 (s, 3 H), 1.48 (t, *J* = 7.2 Hz, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 144.0, 142.5, 133.1, 127.4, 121.3, 118.3, 110.3, 104.2, 59.4, 34.3, 24.5, 14.5, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}NO_2$: 246.1494; found: 246.1490.

Ethyl 2,6-Dimethyl-1*H*-indole-3-carboxylate (3ea)
Yield: 30.8 mg (71%); white solid; mp 191–192 °C.

IR (KBr): 3371, 2976, 2918, 1656, 1408, 801 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (br, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 2.71 (s, 3 H), 2.45 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 143.4, 134.9, 132.1, 124.9, 123.3, 120.9, 110.5, 104.4, 59.4, 21.5, 14.6, 14.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_2$: 218.1181; found: 218.1177.

Ethyl 5-Chloro-2-methyl-1*H*-indole-3-carboxylate (3fa)
Yield: 20.4 mg (43%); white solid; mp 181–182 °C.

IR (KBr): 3286, 2978, 2921, 1663, 1453, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br, 1 H), 8.08 (s, 1 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 7.15 (d, *J* = 8.8 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.75 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 145.0, 132.8, 128.3, 127.6, 122.7, 121.0, 111.4, 104.7, 59.7, 14.6, 14.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}ClNO_2$: 238.0635; found: 238.0633.

Ethyl 5-Bromo-2-methyl-1*H*-indole-3-carboxylate (3ga)
Yield: 26.4 mg (47%); gray-green solid; mp 163–165 °C.

IR (KBr): 3282, 2975, 2921, 1665, 1455, 779 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (br, 1 H), 8.24 (s, 1 H), 7.29 (d, *J* = 8.8 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.75 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 144.8, 133.1, 128.9, 125.3, 124.0, 115.2, 111.8, 104.6, 59.7, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}BrNO_2$: 282.0130; found: 282.0127.

Ethyl 5-Iodo-2-methyl-1*H*-indole-3-carboxylate (3ha)
Yield: 29.0 mg (44%); white solid; mp 185–186 °C.

IR (KBr): 3384, 3268, 2922, 1652, 1429, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.40 (br, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.74 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 144.4, 133.6, 130.8, 130.2, 129.5, 112.3, 104.2, 85.8, 59.7, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}INO_2$: 329.9991; found: 329.9987.

Ethyl 5-Acetyl-2-methyl-1*H*-indole-3-carboxylate (3ia)
Yield: 18.1 mg (37%); white solid; mp 180–181 °C.

IR (KBr): 3219, 3187, 3044, 2976, 2924, 1685, 1650, 1473, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (br, 1 H), 8.78 (s, 1 H), 7.91 (q, *J* = 8.4 Hz, 1 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 2.78 (s, 3 H), 2.70 (s, 3 H), 1.50 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 165.6, 145.3, 137.3, 131.5, 126.9, 123.6, 122.5, 110.6, 105.9, 59.8, 26.6, 14.5, 14.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_3$: 246.1130; found: 246.1136.

Ethyl 5-Cyano-2-methyl-1*H*-indole-3-carboxylate (3ja)
Yield: 14.1 mg (31%); white solid; mp 245–246 °C.

IR (KBr): 3276, 2984, 2922, 2853, 2217, 1665, 1467 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (br, 1 H), 8.46 (s, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 8.46 (q, *J* = 7.2 Hz, 2 H), 2.80 (s, 3 H), 1.49 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165, 145.9, 136.2, 127.0, 126.8, 125.6, 120.5, 105.6, 105.0, 60.0, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_2O_2$: 229.0977; found: 229.0980.

Ethyl 2,5,6-Trimethyl-1*H*-indole-3-carboxylate (3ka)
Yield: 37.9 mg (82%); colorless solid; mp 196–197 °C.

IR (KBr): 3275, 2922, 1653, 1416, 778 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (br, 1 H), 7.89 (s, 1 H), 7.04 (s, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 2.69 (s, 3 H), 2.38 (s, 3 H), 2.35 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 143.1, 133.4, 131.1, 130.3, 125.5, 121.3, 111.0, 103.9, 59.4, 20.3, 20.2, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_2$: 232.1338; found: 232.1332.

Ethyl 5-Iodo-2,6,7-trimethyl-1*H*-indole-3-carboxylate (3la)
Yield: 52.8 mg (74%); white solid; mp 230–232 °C.

IR (KBr): 3339, 2985, 2925, 1696, 1659, 1441, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1 H), 8.15 (br, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 2.75 (s, 3 H), 2.53 (s, 3 H), 2.45 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 143.7, 134.5, 131.5, 129.3, 126.8, 118.2, 104.3, 95.1, 59.6, 24.8, 15.0, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}INO_2$: 358.0304; found: 358.0301.

Ethyl 5-Iodo-2,7-dimethyl-1*H*-indole-3-carboxylate (3ma)
Yield: 30.9 mg (45%); colorless solid; mp 226–227 °C.

IR (KBr): 3299, 2976, 2923, 1665, 1444, 867 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 8.27 (br, 1 H), 7.31 (s, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 2.43 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 143.9, 133.2, 131.3, 128.9, 127.9, 121.7, 104.5, 85.9, 59.7, 16.1, 14.6, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}INO_2$: 344.0147; found: 344.0145.

Ethyl 5-Iodo-2,4,7-trimethyl-1*H*-indole-3-carboxylate (3na)
Yield: 30.7 mg (43%); brown-black solid; mp 55–56 °C.

IR (KBr): 3313, 2976, 2923, 1672, 1439, 1088, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br, 1 H), 7.48 (s, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 2.63 (s, 3 H), 2.38 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 141.0, 134.2, 133.4, 131.2, 125.5, 119.0, 107.5, 94.9, 60.2, 26.8, 15.6, 14.4, 14.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}INO_2$: 358.0304; found: 358.0300.

Ethyl 7-Ethyl-5-iodo-2-methyl-1*H*-indole-3-carboxylate (3oa)
Yield: 28.6 mg (40%); colorless solid; mp 179–180 °C.

IR (KBr): 3298, 2970, 2929, 1666, 1446, 860 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 2 H), 7.32 (s, 1 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 2.80 (q, *J* = 7.6 Hz, 2 H), 2.76 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 143.8, 132.5, 129.5, 129.1, 127.9, 104.6, 86.3, 59.7, 23.50, 14.6, 14.2, 13.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}INO_2$: 358.0304; found: 358.0302.

Ethyl 2-Methyl-3*H*-benzo[*e*]indole-1-carboxylate (3pa)
Yield: 26.3 mg (52%); white solid; mp 174–175 °C.

IR (KBr): 3327, 2984, 2905, 1669, 1439, 804 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (d, *J* = 8.8 Hz, 1 H), 8.56 (br, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 4.4 Hz, 1 H), 7.58 (m, 1 H), 7.46 (m, 2 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 2.72 (s, 3 H), 1.49 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 140.2, 131.6, 130.6, 128.6, 128.1, 126.1, 125.6, 124.5, 123.8, 111.7, 108.3, 60.1, 15.3, 14.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}NO_2$: 254.1181; found: 254.1175.

Ethyl 3-[(2-Iodophenyl)amino]but-2-enoate (3aa′)
Yellow oil.

IR (KBr): 3458, 3363, 3061, 2979, 1613, 1478, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (br, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 6.94 (t, *J* = 8.0 Hz, 1 H), 4.78 (s, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 1.87 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 158.1, 141.3, 139.4, 128.7, 127.2, 126.8, 97.7, 86.9, 58.86, 20.1, 14.5.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{12}H_{14}INO_2$: 332.0147; found: 332.0144.

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