A Practical Synthesis of 2-Aroylindoles from *N*-(2-Formylphenyl)trifluoroacetamides in PEG-400

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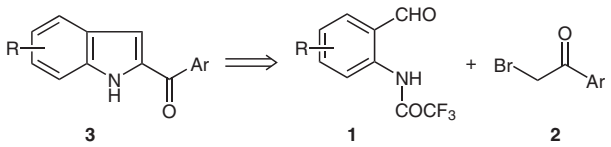
Abstract: A one-pot and environmentally benign approach to the synthesis of highly functionalized 3-unsubstituted 2-aroylindoles is described. Moderate to good yields were obtained through the reaction of easily accessible *N*-(2-formylphenyl)trifluoroacetamides and α-bromoacetophenones in the presence of K_2CO_3. PEG-400 was found to be an efficient and reusable solvent in the process.

Key words: 2-aroylindoles, PEG-400, *N*-(2-formylphenyl)trifluoroacetamides, heterocycles, cyclization

The indole skeleton has been referred to as a 'privileged structure' owing to its diverse biological activities.[1] Particularly, free-NH 3-unsubstituted 2-aroylindoles were reported to be highly potent tubulin polymerization inhibitors,[2] histone deacetylase class I/II inhibitors,[3] platelet-derived growth factor (PDGF) receptor kinase inhibitors,[4] peroxisome proliferator-activated receptor (PPAR) agonists,[5] and cyclooxygenase-2 (COX-2) inhibitors.[6] Different methods have been developed for their syntheses. Among these transformations, addition of acyl electrophiles to 2-lithioindole species[7] and palladium-catalyzed coupling reactions[8] are widely used processes. In other cases, isatins also lead to 2-aroylindoles.[9] Jones reported the preparation of 2-benzoylindole by reaction of 2-aminobenzaldehyde ethylene acetal with α-bromoacetophenone.[10a] However, these synthetic approaches sometimes suffer from harsh reaction conditions, the need for transition-metal assistance, poor availability of starting materials, or long reaction steps. In light of these challenges, a direct and practical method for the formation of 3-unsubstituted 2-aroylindoles is still in demand.

o-Aminoacetophenones reacted readily with α-bromoacetophenones to afford 3-methyl-2-aroylindoles.[10] However, the reaction was limited to *o*-aminoacetophenones in substrate scope, and *o*-aminobenzaldehyde failed to generate 3-unsubstituted aroylindoles.[10a] Our preliminary experiments also showed the failure of this reaction.[11] In a recent patent report, pyrrolo[2,3-*d*]pyrimidines were prepared from 4-(phenylamino)pyrimidine-5-carbaldehydes and α-bromoactophenones.[12] To the best of our knowledge, there is no other report on the analogous indole formation from *o*-aminobenzaldehyde and α-bromoacetophenone.

Herein, we report a convenient and environmentally benign method for the construction of 3-unsubstituted 2-aroylindoles **3** from *N*-(2-formylphenyl)trifluoroacetamides **1**, which can be readily prepared from *o*-aminobenzaldehydes with trifluoroacetic anhydride, and α-bromoacetophenones **2** in PEG-400 (Scheme 1).



Scheme 1 Approach to synthesis of 2-aroylindoles.

N-(2-Formylphenyl)trifluoroacetamide (**1a**) and α-bromoacetophenone (**2a**) were used as model compounds to assess the feasibility of the method. A variety of reaction conditions were examined and the results are shown in Table 1.

When a mixture of **1a** and **2a** was heated in the presence of K_2CO_3 in DMF and PEG-400, 2-benzoylindole (**3a**) was obtained in moderate yields. Moreover, use of PEG-400 as the solvent gave the highest yield (Table 1, entries 1–5). Cs_2CO_3 and K_3PO_4 performed poorly under the reaction conditions (entries 6 and 7). Upon adjusting the ratio of **1a** to **2a** to 1:1.2, an improved yield was observed (entries 5, 8, and 9). Further investigation of reaction time and temperature showed that three hours and 100 °C offered the best result for this transformation (entries 10–13). Thus, the optimized reaction conditions for the formation of **3a** were established (Table 1, entry 8).

PEG-400 is inexpensive and is known to be thermally stable, non-toxic, and is often used as a recyclable reaction medium.[13] Thus, the reusability of PEG-400 in the reaction was examined. After the initial reaction with **1a** and **2a**, the reaction mixture was extracted with diethyl ether and the PEG-400 layer was subjected to a subsequent reaction run by adding further substrates (**1a**, **2a**, and K_2CO_3).[14] The results of the initial and the subsequent three runs of the reaction were consistent in yields (**3a**; 77, 76, 75, and 75%).

Various *N*-(2-formylphenyl)trifluoroacetamides **1** and α-bromoacetophenones **2** were then applied to investigate

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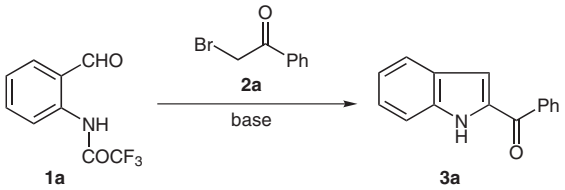
the reaction scope under the optimized reaction condition; the results were shown in Table 2. This method was suitable for a variety of substrates, giving the desired functionalized 2-aroylindoles in moderate to good yields. No obvious electronic effects were observed with either **1** or **2**. Both electron-donating (**1b–d**, **2g**, and **2h**) and electron-withdrawing (**1e**, **1f**, and **2i–k**) substituents on the aromatic rings in these two components were accommodated (Table 2, entries 1–10). The *ortho*-substitution of α-bromoacetophenones (**2m** and **2n**) provided the corresponding products **3m** and **3n** in good yields (67 and 72%, respectively). Steric hindrance at the *ortho*-position of **2** was tolerated. In addition, when the aromatic ring of **2** was substituted with methoxy groups at various positions, similar yields were observed (Table 2, entries 7, 11, and 12). It was presumed that the acidic nature of the NH group, caused by the withdrawing effect of the trifluoacetyl group of **1**, is strong enough to counteract the electronic influence of the substituents of **1** and/or **2** in the reaction.

Table 1 Screen and Optimization of the Reaction Conditions[a]



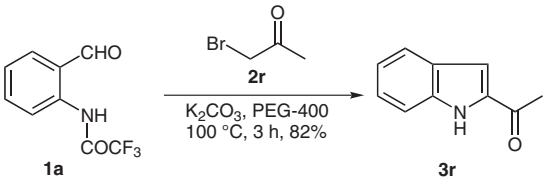
Entry	Solvent	Ratio (**1a**/**2a**)	Base	Temp (°C)	Yield (%)[b]
1	acetone	1:1.1	K_2CO_3	reflux	trace
2	acetonitrile	1:1.1	K_2CO_3	reflux	8
3	toluene	1:1.1	K_2CO_3	100	12[c]
4	DMF	1:1.1	K_2CO_3	100	68
5	PEG-400	1:1.1	K_2CO_3	100	74
6	PEG-400	1:1.1	Cs_2CO_3	100	30
7	PEG-400	1:1.1	K_3PO_4	100	61
8	PEG-400	1:1.2	K_2CO_3	100	77
9	PEG-400	1:1.3	K_2CO_3	100	71
10	PEG-400	1:1.2	K_2CO_3	100	75[d]
11	PEG-400	1:1.2	K_2CO_3	100	65[e]
12	PEG-400	1:1.2	K_2CO_3	80	62
13	PEG-400	1:1.2	K_2CO_3	110	64

[a] Reaction conditions: *N*-(2-formylphen-yl)trifluoroacetamide (100 mg, 0.46 mmol), α-bromoactophenone, base (3.0 equiv), solvent (5 mL), 3 h (unless noted otherwise), under nitrogen.
[b] Isolated yield.
[c] 100 °C for 8 h.
[d] 100 °C for 2 h.
[e] 100 °C for 10 h.

The reaction sequence presumably involves three steps: (1) N-alkylation of the trifluoroacetamide, (2) intramolecular condensation followed by dehydration, and (3) deprotection of the *N*-trifluoroacetyl group. Moreover, we explored the reactions **1a** with various 2-bromo-1-(2-heteroaryl)-ethanones and found that 2-(2-bromoacetyl)naphthalene (**2o**), 2-(2-bromoacetyl)furan (**2p**), and 2-(2-bromoacetyl)thiophene (**2q**) were also compatible in the reactions, providing the desired 2-heteroaroylindoles in fair to good yields (entries 14–16).

Finally, we applied this procedure to α-bromoacetone (**2r**) and **1a**. The reaction proceeded smoothly under the above optimized reaction conditions and provided 2-acetylindole (**3r**) in satisfactory yield (Schemes 2, 82%). This result further extends the application of this method to the preparation of 2-alkoyl-indoles.

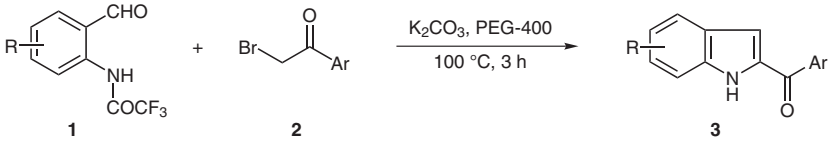
In conclusion, we have developed a simple and practical method to synthesize 3-unsubstituted 2-aroylindoles through the reaction of *N*-(2-formylphenyl)trifluoroacetamides and α-bromoacetophenones in PEG-400 in moderate to good yields. Our approach is characterized by some features: (1) free (NH)-aroylindoles were obtained directly under one-pot, catalyst-free conditions; (2) PEG-400 was used as an efficient and reusable solvent; (3) starting materials are readily available, and (4) the reaction is tolerant of various functional groups. The method provides a valuable alternative for the preparation of 3-unsubstituted 2-aroylindoles.



Scheme 2 Synthesis of 2-acetylindole

Reagents and solvents were purchased from commercial sources and were used as received without additional purification unless mentioned otherwise. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} glass plates. Melting points are uncorrected. NMR spectra were recorded with a Bruker AV400 or a Bruker AV500 spectrometer. Chemical shifts are given as values in ppm relative to the residual solvent peak as the internal reference [$CDCl_3$: δ = 7.26 ppm (^{1}H NMR), δ = 77.0 ppm (^{13}C NMR); DMSO-d_6: δ = 2.50 ppm (^{1}H NMR)], coupling constants are given in Hertz. Mass spectra were recorded with an Agilent1200/MSD LC-MS spectrometer. High-resolution mass spectra were performed with Kompact Axima-CFR MALDI mass spectrometers. Elemental analysis was performed with an Elementar vario EL analyzer. Petroleum ether (PE) refers to the fraction boiling between 60–90 °C.

Table 2 Substrate Scope of the 2-Aroylindole Synthesis[a]



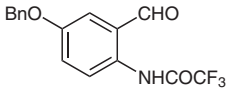
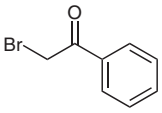
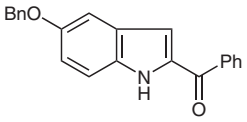
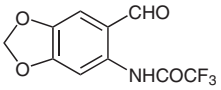
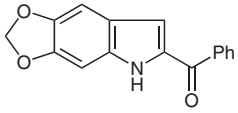
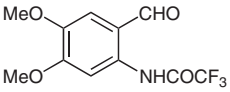
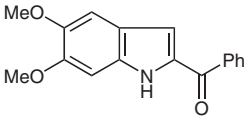
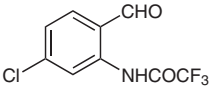
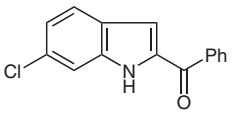
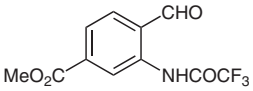
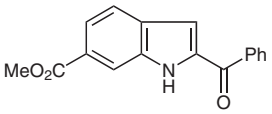
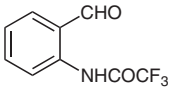
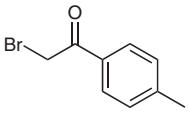
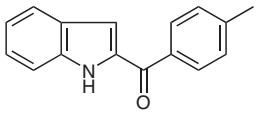
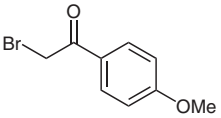
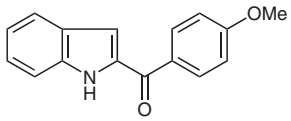
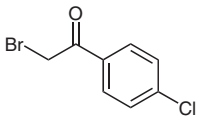
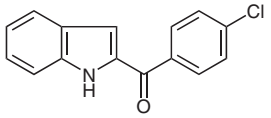
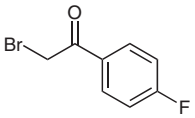
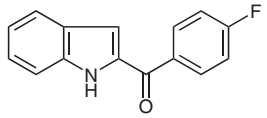
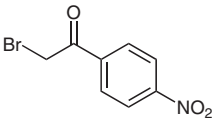
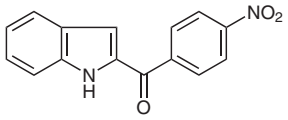
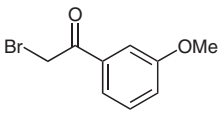
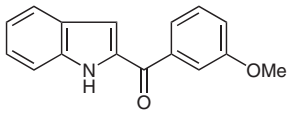
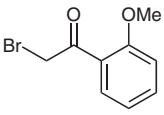
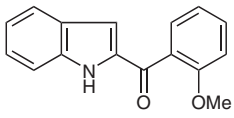
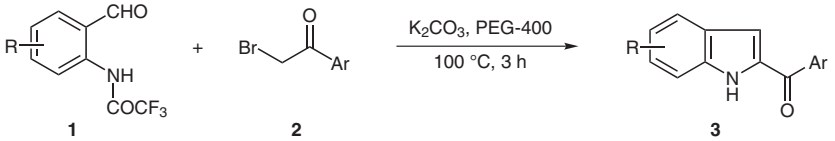
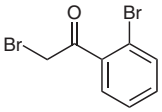
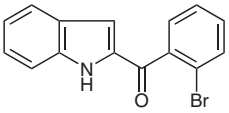
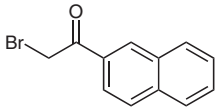
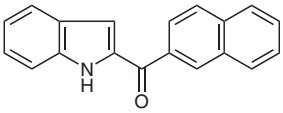
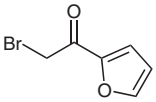
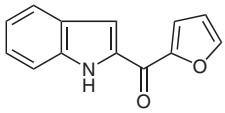
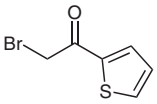
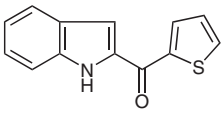
Entry	Substrate **1**	Substrates **2**	Product	Yield (%)[b]
1	**1b** 	**2a** 	**3b** 	60
2	**1c** 	**2a**	**3c** 	52
3	**1d** 	**2a**	**3d** 	71
4	**1e** 	**2a**	**3e** 	79
5	**1f** 	**2a**	**3f** 	64
6	**1a** 	**2g** 	**3g** 	57
7	**1a**	**2h** 	**3h** 	69
8	**1a**	**2i** 	**3i** 	78
9	**1a**	**2j** 	**3j** 	64
10	**1a**	**2k** 	**3k** 	50
11	**1a**	**2l** 	**3l** 	70
12	**1a**	**2m** 	**3m** 	67

Table 2 Substrate Scope of the 2-Aroylindole Synthesis[a] (continued)



Entry	Substrate **1**	Substrates **2**	Product	Yield (%)[b]
13	**1a**	**2n** 	**3n** 	72
14	**1a**	**2o** 	**3o** 	64
15	**1a**	**2p** 	**3p** 	77
16	**1a**	**2q** 	**3q** 	85

[a] Rection conditions (0.36–0.5 mmol scale): *N*-(2-formylphenyl)trifluoroacetamide (1.0 equiv), α-bromoacetophenone (1.2 equiv), K_2CO_3 (3.0 equiv), PEG-400 (5 mL), 100 °C, 3 h, under nitrogen.
[b] Isolated yield.

Synthesis of *N*-(2-Formylphenyl)trifluoroacetamides (1a–f); General Procedure

To a cold solution of *o*-aminobenzaldehyde (5.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added anhydrous pyridine (0.8 mL, 10 mmol), followed by dropwise addition of TFAA (0.9 mL, 6.4 mmol). After the addition was complete, the reaction mixture was warmed to r.t. and further stirred at r.t. for 3–4 h. H_2O (15 mL) was added to the reaction mixture, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with 1 M HCl (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to afford *N*-(2-formylphenyl)trifluoroacetamide **1**.

2,2,2-Trifluoro-*N*-(2-formylphenyl)acetamide (1a)

Following the general procedure, the reaction was performed with *o*-aminobenzalidehyde (0.6 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (20:1).

Yield: 1.04 g (95%); white solid; mp 72–73 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.19 (br s, 1 H), 9.98 (s, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 7.79 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.73–7.69 (m, 1 H), 7.41 (td, *J* = 7.6, 0.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 155.8 ($^2J_{C–F}$ = 38.2 Hz), 138.2, 136.3, 135.9, 125.2, 122.7, 120.4, 117.0 ($^1J_{C–F}$ = 288.7 Hz).

MS (ESI): *m*/*z* = 216 $(M – H)^-$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_9H_7F_3NO_2$: 218.0423; found: 218.0421.

***N*-[4-(Benzyloxy)-2-formylphenyl]-2,2,2-trifluoroacetamide (1b)**

Following the general procedure, the reaction was performed with 2-amino-5-(benzyloxy)benzaldehyde (1.13 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (9:1).

Yield: 1.55 g (96%); white solid; mp 112–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.91 (br s, 1 H), 9.90 (s, 1 H), 8.62 (d, *J* = 9.0 Hz, 1 H), 7.45–7.34 (m, 5 H), 7.33 (d, *J* = 3.0 Hz, 1 H), 7.30 (dd, *J* = 9.0, 3.0 Hz, 1 H), 5.15 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 155.9, 155.4 ($^2J_{C–F}$ = 38.0 Hz), 136.0, 131.7, 128.8, 128.4, 127.4, 123.7, 122.6, 122.1, 121.5, 115.7 ($^1J_{C–F}$ = 288.5 Hz), 70.8.

MS (ESI): *m*/*z* = 322 $[M – H]^-$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}F_3NO_3$: 324.0842; found: 324.0843.

2,2,2-Trifluoro-*N*-(6-formylbenzo[*d*][1,3]dioxol-5-yl)acetamide (1c)

Following the general procedure, the reaction was performed with 6-aminobenzo[*d*][1,3]dioxole-5-carbaldehyde (0.83 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (9:1).

Yield: 1.24 g (95%); pale-yellow solid; mp 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.52 (br s, 1 H), 9.72 (s, 1 H), 8.23 (s, 1 H), 7.10 (s, 1 H), 6.12 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0, 155.7 ($^2J_{C–F}$ = 38.1 Hz), 154.0, 144.9, 136.1, 116.9, 115.5 ($^1J_{C–F}$ = 288.2 Hz), 113.2, 102.8, 101.8.

MS (ESI): *m*/*z* = 260 $[M – H]^-$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_7F_3NO_4$: 262.0322; found: 262.0321.

2,2,2-Trifluoro-*N*-(2-formyl-4,5-dimethoxyphenyl)acetamide (1d)

Following the general procedure, the reaction was performed with 2-amino-4,5-dimethoxybenzaldehyde (0.9 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (5:1).

Yield: 1.36 g (98%); white solid; mp 187–188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.38 (br s, 1 H), 9.78 (s, 1 H), 8.32 (s, 1 H), 7.12 (s, 1 H), 3.99 (s, 3 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 155.7 ($^2J_{C–F}$ = 47.8 Hz), 155.6, 146.2, 134.4, 116.8, 115.7, 115.6 ($^1J_{C–F}$ = 288.5 Hz), 103.8, 56.5, 56.4.

MS (ESI): *m*/*z* = 276 [M – H]$^-$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}F_3NO_4$: 278.0635; found: 278.0635.

***N*-(5-Chloro-2-formylphenyl)-2,2,2-trifluoroacetamide (1e)**
Following the general procedure, the reaction was performed with 2-amino-4-chlorobenzaldehyde (0.78 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (9:1).

Yield: 1.20 g (96%); white solid; mp 63–64 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.24 (br s, 1 H), 9.94 (d, *J* = 0.4 Hz, 1 H), 8.74 (d, *J* = 1.6 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.38 (dd, *J* = 8.0, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2, 155.8 ($^2J_{C–F}$ = 38.3 Hz), 143.1, 139.0, 136.7, 125.5, 121.0, 120.7, 115.4 ($^1J_{C–F}$ = 288.4 Hz).

MS (ESI): *m*/*z* = 250 [M – H]$^-$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_9H_6ClF_3NO_2$: 252.0034; found: 252.0033.

Methyl 4-Formyl-3-(2,2,2-trifluoroacetamido)benzoate (1f)
Following the general procedure, the reaction was performed with methyl 3-amino-4-formylbenzoate (0.9 g, 5.0 mmol). Eluent for chromatography: PE–EtOAc (5:1).

Yield: 1.36 g (99%); yellow solid; mp 120–121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.10 (br s, 1 H), 10.06 (s, 1 H), 9.28 (s, 1 H), 8.06 (dd, *J* = 8.0, 1.6 Hz), 7.88 (d, *J* = 8.0 Hz, 1 H), 3.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 165.2, 155.8 ($^2J_{C–F}$ = 38.2 Hz), 138.1, 136.8, 135.8, 126.0, 124.8, 121.4, 115.4 ($^1J_{C–F}$ = 286.2 Hz), 52.9.

MS (ESI): *m*/*z* = 274 [M – H]$^-$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9F_3NO_4$: 276.0478; found: 276.0480.

Synthesis of 2-Aroylindoles (3a–s); General Procedure
To a stirring mixture of *N*-(2-formylphenyl)trifluoroacetamide **1** (100 mg) and α-bromoacetophenone **2** (1.2 equiv) in PEG-400 (5 mL), was added solid K_2CO_3 (3.0 equiv). The resulting reaction mixture was heated to 100 °C in an oil-bath for 3 h under a nitrogen atmosphere. The reaction was cooled to r.t. and the black mixture was extracted with Et_2O (3 × 20 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to afford **3.**

(1*H*-Indol-2-yl)(phenyl)methanone (3a)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2a** (109 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 78 mg (77%); yellow solid; mp 150–151 °C (Lit.[8a,b] 149–150 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (br s, 1 H), 8.01–7.98 (m, 2 H), 7.73 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.65–7.61 (m, 1 H), 7.56–7.47 (m, 2 H), 7.48 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.20–7.16 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 138.2, 137.8, 134.5, 132.3, 129.2, 128.4, 127.8, 126.5, 123.2, 121.0, 112.8, 112.3.

MS (ESI): *m*/*z* = 222 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NO$: 222.0913; found: 222.0915.

[5-(Benzyloxy)-1*H*-indol-2-yl](phenyl)methanone (3b)
Following the general procedure, the reaction was performed with **1b** (100 mg, 0.31 mmol) and **2a** (74 mg, 0.37 mmol). Eluent for chromatography: PE–EtOAc (10: 1).

Yield: 61 mg (60%); yellow solid; mp 190–191 °C (Lit.[8a] 190–191 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (br s, 1 H), 7.99–7.97 (m, 2 H), 7.64–7.60 (m, 1 H), 7.55–7.51 (m, 2 H), 7.47 (d, *J* = 7.2 Hz, 2 H), 7.41–7.38 (m, 3 H), 7.34–7.31 (m, 1 H), 7.16–7.13 (m, 2 H), 7.07 (d, *J* = 1.2 Hz, 1 H), 5.11 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.9, 154.0, 138.1, 137.2, 134.9, 133.2, 132.3, 129.2, 128.6, 128.4, 128.1, 127.9, 127.5, 119.0, 113.1, 112.3, 104.6, 70.7.

MS (ESI): *m*/*z* = 328 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}NO_2$: 328.1332; found: 328.1329.

(5*H*-[1,3]dioxolo[4,5-*f*]indo-6-yl)(phenyl)methanone (3c)
Following the general procedure, the reaction was performed with **1c** (100 mg, 0.38 mmol) and **2a** (91 mg, 0.46 mmol). Eluent for chromatography: PE–EtOAc (10:1).

Yield: 52 mg (52%); yellow solid; mp 198–200 °C (Lit.[8a] 200–201 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (br s, 1 H), 7.96–7.94 (m, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.53–7.50 (m, 2 H), 7.04 (d, *J* = 1.2 Hz, 1 H), 7.00 (s, 1 H), 6.89 (s, 1 H), 5.99 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.9, 149.0, 144.5, 138.3, 134.1, 133.8, 131.9, 129.0, 128.3, 122.2, 113.1, 101.1, 100.0, 91.8.

MS (ESI): *m*/*z* = 266 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}NO_3$: 266.0812; found: 266.0810.

(5,6-Dimethoxy-1*H*-indol-2-yl)(phenyl)methanone (3d)
Following the general procedure, the reaction was performed with **1d** (100 mg, 0.36 mmol) and **2a** (86 mg, 0.43 mmol). Eluent for chromatography: PE–EtOAc (10:1).

Yield: 72 mg (71%); yellow solid; mp 183–184 °C (Lit.[8a] 181–182 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (br s, 1 H), 8.00 (d, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 7.06–7.04 (m, 2 H), 6.91 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0, 151.4, 146.7, 138.5, 133.6, 133.4, 131.9, 129.0, 128.3, 121.0, 112.9, 103.3, 93.9, 56.3, 56.1.

MS (ESI): *m*/*z* = 282 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3$: 282.1125; found: 282.1121.

(6-Chloro-1*H*-indol-2-yl)(phenyl)methanone (3e)[7e]
Following the general procedure, the reaction was performed with **1e** (100 mg, 0.40 mmol) and **2a** (95 mg, 0.48 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 80 mg (79%); off-white solid; mp 205–206 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (br s, 1 H), 7.99 (d, *J* = 7.2 Hz, 2 H), 7.65 (d, *J* = 6.0 Hz, 1 H), 7.62 (s, 1 H), 7.54 (pseudo-t, *J* = 7.2 Hz, 2 H), 7.49 (s, 1 H), 7.15–7.14 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.0, 137.7, 135.0, 132.5, 132.4, 129.2, 128.5, 126.3, 124.2, 122.2, 112.5, 112.0.

MS (ESI): *m*/*z* = 256 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}ClNO$: 256.0524; found: 256.0521.

Methyl 2-(Phenylcarbonyl)-1*H*-indole-6-carboxylate (3f)
Following the general procedure, the reaction was performed with **1f** (100 mg, 0.36 mmol) and **2a** (87 mg, 0.44 mmol). Eluent for chromatography: PE–EtOAc (10:1).

Yield: 65 mg (64%); pale-yellow solid; mp 208–209 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (br s, 1 H), 8.26 (s, 1 H), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.85 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.55 (t, *J* = 7.6, 7.2 Hz, 2 H), 7.18 (d, *J* = 0.8 Hz, 1 H), 3.97 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.1, 167.4, 137.6, 136.6, 136.5, 132.7, 130.9, 129.3, 128.6, 127.8, 122.9, 121.6, 114.6, 111.9, 52.2.

MS (ESI): *m*/*z* = 280 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}NO_3$: 280.0968; found: 280.0968.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.92; H, 4.80; N, 5.07.

(1*H*-Indol-2-yl)(4-methyphenyl)methanone (3g)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2g** (117 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 62 mg (57%); off-white solid; mp 189–190 °C (Lit.[8a] 184–186 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (br s, 1 H), 7.92 (d, *J* = 8.0 Hz, 2 H), 7.72 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.48 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.39–7.33 (m, 3 H), 7.19–7.15 (m, 2 H), 2.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.7, 143.0, 137.4, 135.4, 134.6, 129.3, 129.1, 127.9, 126.3, 123.1, 121.0, 112.1, 112.0, 21.5.

MS (ESI): *m*/*z* = 236 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}NO$: 236.1070; found: 236.1069.

(1*H*-Indol-2-yl)(4-methoxyphenyl)methanone (3h)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2h** (126 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 80 mg (69%); off-white solid; mp 190–191 °C (Lit.[8a] 189–190 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (br s, 1 H), 8.04 (dt, *J* = 8.8, 1.9 Hz, 2 H), 7.73 (dd, *J* = 8.0, 0.3 Hz, 1 H), 7.48 (dd, *J* = 8.3, 0.6 Hz, 1 H), 7.37 (td, *J* = 7.0, 0.9 Hz, 1 H), 7.19–7.15 (m, 2 H), 7.03 (dt, *J* = 8.8, 1.9 Hz, 2 H), 3.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.8, 163.2, 137.3, 134.5, 131.5, 130.7, 127.8, 126.2, 123.1, 120.9, 113.8, 112.1, 111.8, 55.5.

MS (ESI): *m*/*z* = 252 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}NO_2$: 252.1019; found: 252.1022.

(4-Chlorophenyl)(1*H*-indol-2-yl)methanone (3i)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2i** (128 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 92 mg (78%); yellow solid; mp 196–198 °C (Lit.[8a] 196–197 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (br s, 1 H), 7.95 (dt, *J* = 8.8, 2.0 Hz, 2 H), 7.73 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.52 (dt, *J* = 8.8, 2.4 Hz, 2 H), 7.49 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.20–7.16 (m, 1 H), 7.14 (dd, *J* = 2.0, 0.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.8, 138.8, 137.6, 136.3, 134.0, 130.6, 128.8, 127.7, 126.8, 123.3, 121.2, 112.7, 112.2.

MS (ESI): *m*/*z* = 256 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}ClNO$: 256.0524; found: 256.0523.

(4-Fluorophenyl)(1*H*-indol-2-yl)methanone (3j)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2j** (119 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 70 mg (64%); white solid; mp 185–186 °C (Lit.[8b] 185.2–185.6 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (br s, 1 H), 8.08–8.03 (m, 2 H), 7.73 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.50 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.25–7.16 (m, 3 H), 7.15 (dd, *J* = 2.0, 0.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.7, 165.4 ($^1J_{C-F}$ = 253.6 Hz), 137.7, 134.2 ($^4J_{C-F}$ = 3.3 Hz), 134.1, 131.7 ($^3J_{C-F}$ = 8.9 Hz), 127.7, 126.6, 123.2, 121.1, 115.6 ($^2J_{C-F}$ = 22.0 Hz), 112.7, 112.2.

MS (ESI): *m*/*z* = 240 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}FNO$: 240.0819; found: 240.0815.

(1*H*-Indol-2-yl)(4-nitrophenyl)methanone (3k)[7c]
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2k** (134 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (10:1).

Yield: 61 mg (50%); yellow solid; mp 205–206 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (br s, 1 H), 8.39 (dt, *J* = 8.6, 2.0 Hz, 2 H), 8.12 (dt, *J* = 8.6, 2.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.2 (t, *J* = 7.4 Hz, 1 H), 7.14 (d, *J* = 1.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.0, 149.9, 143.2, 138.0, 133.6, 130.0, 127.6, 127.4, 123.7, 123.5, 121.5, 113.7, 112.3.

MS (ESI): *m*/*z* = 265 $[M - H]^-$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}N_2O_3$: 267.0764; found: 267.0766.

(1*H*-Indol-2-yl)(3-methoxyphenyl)methanone (3l)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2l** (126 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 81 mg (70%); yellow solid; mp 128–129 °C (Lit.[7e] 124–126 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (br s, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.55 (dd, *J* = 2.4, 1.6 Hz, 1 H), 7.52 (dd, *J* = 8.4, 0.4 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.21 (d, *J* = 1.2 Hz, 1 H), 7.20–7.16 (m, 2 H), 3.90 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.0, 159.6, 139.3, 137.7, 134.3, 129.4, 127.6, 126.5, 123.2, 121.8, 120.9, 118.6, 113.8, 112.9, 112.3, 55.4.

MS (ESI): *m*/*z* = 252 $[M + H]^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_2$: 252.1019; found: 252.1020.

(1*H*-Indol-2-yl)(2-methoxyphenyl)methanone (3m)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2m** (126 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 77 mg (67%); pale-yellow solid; mp 133–134 °C (Lit.[8a] 129–130 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (br s, 1 H), 7.66 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.55–7.47 (m, 3 H), 7.37–7.33 (m, 1 H), 7.16–7.12 (m, 1 H), 7.08–7.04 (m, 2 H), 6.93 (dd, *J* = 2.0, 0.8 Hz, 1 H), 3.84 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.2, 157.4, 137.8, 135.8, 132.0, 129.7, 128.2, 127.6, 126.4, 123.2, 120.8, 120.0, 113.2, 112.3, 111.6.

MS (ESI) *m*/*z* = 252 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_2$: 252.1019; found: 252.1017.

(2-Bromophenyl)(1*H*-indol-2-yl)methanone (3n)[15]
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2n** (152 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 99 mg (72%); yellow solid; mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (br s, 1 H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.66 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.57–7.54 (m, 2 H), 7.47–7.42 (m, 1 H), 7.41–7.37 (m, 2 H), 7.18–7.14 (m, 1 H), 6.90 (dd, *J* = 2.0, 0.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.1, 139.7, 138.4, 134.5, 133.5, 131.4, 129.3, 127.4, 127.1, 126.8, 123.3, 121.1, 120.0, 114.6, 112.6.

MS (ESI): *m*/*z* = 300 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}BrNO$: 300.0019; found: 300.0022.

(1*H*-Indol-2-yl)(naphthalene-2-yl)methanone (3o)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2o** (137 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 80 mg (64%); pale-yellow solid; mp 176–177 °C (Lit.[8a] 174–175 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (br s, 1 H), 8.56 (s, 1 H), 8.05 (dd, *J* = 8.4, 1.5 Hz, 1 H), 8.01 (t, *J* = 9.0 Hz, 2 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.66–7.58 (m, 2 H), 7.51 (d, *J* = 8.3 Hz, 1 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 7.25 (s, 1 H), 7.19 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.0, 137.5, 135.3, 134.5, 132.5, 130.6, 129.4, 128.4, 128.2, 127.9, 127.8, 126.9, 126.5, 125.3, 123.3, 121.1, 112.8, 112.2.

MS (ESI): *m*/*z* = 272 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}NO$: 272.1070; found: 272.1072.

(Furan-2-yl)(1*H*-indol-2-yl)methanone (3p)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2p** (113 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (20:1).

Yield: 75 mg (77%); pale-yellow solid; mp 130–132 °C (Lit.[8b] 128–131 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (br s, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.72 (s, 2 H), 7.50–7.48 (m, 2 H), 7.39–7.35 (m, 1 H), 7.19–7.15 (m, 1 H), 6.64 (dd, *J* = 3.6, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 152.9, 146.4, 137.4, 133.6, 128.1, 126.4, 123.3, 121.0, 118.4, 112.4, 112.1, 111.4.

MS (ESI): *m*/*z* = 212 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}NO_2$: 212.0706; found: 212.0703.

(1*H*-Indol-2-yl)(thiophen-2-yl)methanone (3q)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2q** (104 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (15:1).

Yield: 89 mg (85%); yellow solid; mp 162–163 °C (Lit.[8b] 161–163 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.85 (br s, 1 H), 8.07 (dd, *J* = 3.6, 0.9 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.73 (dd, *J* = 4.8, 0.8 Hz, 1 H), 7.53 (dd, *J* = 8.0, 0.3 Hz, 1 H), 7.46 (d, *J* = 1.2 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.23 (dd, *J* = 4.8, 3.9 Hz, 1 H), 7.20–7.17 (m, 1 H).

^{1}H NMR (400 MHz, DMSO-d_6 and D_2O): δ = 8.10 (d, *J* = 0.4 Hz, 1 H), 7.99 (d, *J* = 4.8 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 4.0 Hz, 2 H), 7.33–7.30 (m, 2 H), 7.12–7.09 (m, 1 H). The existence of active H-atom of indole was proved by the disappearance of H (no H shown from δ = 9 to 11 ppm) in the ^{1}H NMR spectra (the mixture of DMSO-d_6 and D_2O as the solvent).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9, 142.5, 137.5, 134.1, 133.2, 133.0, 128.1, 127.7, 126.4, 123.1, 121.0, 112.3, 110.7.

MS (ESI): *m*/*z* = 228 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}NOS$: 228.0478; found: 228.0482.

2-Acetylindole (3r)
Following the general procedure, the reaction was performed with **1a** (100 mg, 0.46 mmol) and **2r** (75 mg, 0.55 mmol). Eluent for chromatography: PE–EtOAc (10:1).

Yield: 60 mg (82%); white solid; mp 154–155 °C (Lit.[16] 157–158 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.45 (dd, *J* = 8.4, 0.4 Hz, 1 H), 7.38–7.36 (m, 1 H), 7.21 (d, *J* = 1.2 Hz, 1 H), 7.18–7.14 (m, 1 H), 2.61 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.4, 137.5, 135.5, 127.7, 126.3, 123.0, 120.9, 112.2, 109.8, 25.7.

MS (ESI): *m*/*z* = 160 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}NO$: 160.0757; found: 160.0756.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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