Synthesis of 4-Oxoindeno[1,2-*b*]pyrroles through Copper-Catalyzed Tandem Reactions of 1-(2-Haloaryl)enones with Isocyanides

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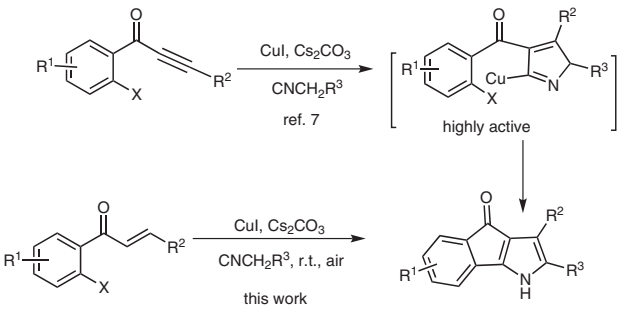
Abstract: Copper-catalyzed tandem reactions of 1-(2-haloaryl)-enones with isocyanides for the synthesis of 4-oxoindeno[1,2-*b*]pyrroles are described. Highly reactive cyclic organocopper intermediates are generated in the copper-catalyzed [3+2]-cycloaddition reactions of isocyanides to double or triple bonds. Successful intramolecular trapping of the organocopper intermediates led to the efficient formation of 4-oxoindeno[1,2-*b*]pyrroles.

Key words: copper-catalyzed, isocyanide, enones, pyrroles

The 4-oxoindeno[1,2-*b*]pyrroles and analogues are biologically important structures that have found extensive use in medicinal chemistry; such compounds have been used as $5HT_{2c}$ receptor agonists[1] and antiviral agents.[2] However, the synthesis of such compounds often takes several steps and is not efficient. General methods for preparing these compounds from simple starting materials are lacking, which has greatly hindered studies on their biological activities.[3]

Transition-metal-catalyzed cycloaddition reactions of isocyanides to double or triple bonds have been extensively explored in recent years, which has led to the development of a number of general ways to access a diverse range of heterocycles, such as pyrroles and oxazolines.[4–6] The mechanisms of such reactions were proposed to follow a formal [3+2] cycloaddition process, which produces a cyclic organometal intermediate that undergoes rapid protonation to form the stable products. We realized that the cyclized organometal intermediates may act as reactive intermediates for further aryl C–C coupling. Based on this hypothesis, we designed some novel tandem reactions to trap the organometal intermediates and thus open the way to new synthetic methods to access heterocycles.[7] In a previous communication,[7a] we reported our research on the intramolecular trapping of an organocopper intermediate produced in the copper-catalyzed cycloaddition reaction of isocyanides with 1-(2-iodoaryl)ynones, which led to the efficient formation of 4-oxoindeno[1,2-*b*]pyrrole compounds (Scheme 1). Further exploration revealed that the protocol was also applicable to the reaction of isocyanides with 1-(2-haloaryl)enones, which also furnished 4-oxoindeno[1,2-*b*]pyrrole products through an additional oxidation step. The new protocol could become practically useful for the synthesis of 4-oxoindeno[1,2-*b*]pyrroles because the 1-(2-haloaryl)enone substrates could be easily prepared through condensation of the corresponding ketones with aldehydes. Herein, we describe the copper-catalyzed tandem reactions of 1-(2-haloaryl)enones with isocyanides.



Scheme 1 Copper-catalyzed tandem reaction of isocyanides with 1-(2-haloaryl)unsaturated ketones for the synthesis of 4-oxoindeno[1,2-*b*]pyrroles

Based on the idea of intramolecular trapping of the organocopper intermediate, we speculated that the copper-catalyzed tandem reactions of 1-(2-haloaryl)enones with isocyanides would produce the corresponding 4-oxo-1,2,3,4-tetrahydroindeno[1,2-*b*]pyrrole products, which may be easily oxidized into the corresponding 4-oxoindeno[1,2-*b*]pyrroles (Scheme 1).

To test this idea, we first explored the conditions required for copper-catalyzed reaction of ethyl isocyanoacetate (**1a**) with (*E*)-1-(2-iodophenyl)-3-*p*-tolylprop-2-en-1-one (**2a**). Surprisingly, instead of producing the expected tandem product **3a**, or the protonolysis byproduct **4a**, this reaction generated 4-oxoindeno[1,2-*b*]pyrrole **5a** in approximately 68% yield [reaction performed under an N_2 atmosphere (balloon); Scheme 2]. We speculated that the formation of **5a** is likely the result of oxidation of initially formed **3a** by the small amount of air contained in the N_2. Since the reaction was thought to involve an oxidation process, we then tested it with oxygen as the oxidant. However, the yield of the reaction was reduced to only 31% (Table 1, entry 2). It was reasonable to assume that oxygen could oxidize the Cu(I) to Cu(II), which is unfavorable for the copper-catalyzed coupling step. We speculated that a small amount of O_2 may be better for the reaction, which was confirmed by the slightly improved

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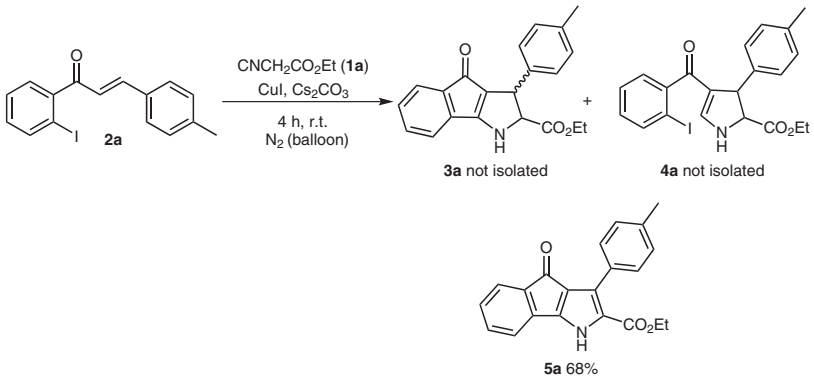


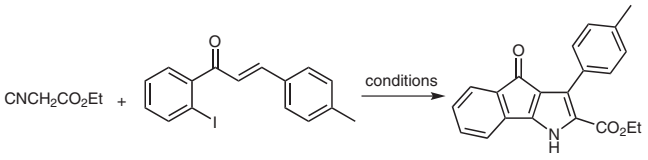
Scheme 2 Copper-catalyzed reaction of ethyl isocyanoacetate with 1-(2-iodophenyl)-3-*p*-tolylprop-2-en-1-one

yields (70%) when the reaction was performed in air (Table 1, entry 3). The important effect of the small amount of O_2 was further confirmed by conducting the reaction in Argon (balloon) with high purity; under these conditions, the product **5a** was obtained with only about 20% yield (Table 1, entry 4). Furthermore, we explored the model reaction with different solvents, bases and copper salts in air. The results revealed that the combination of CuI, Cs_2CO_3, and *N*,*N*-dimethylformamide (DMF) was the best choice for our reaction; other solvents, bases, and copper salts led to lower yields (Table 1, entries 5–14). No improvement was observed upon increasing the reaction temperature to 60 or 90 °C (Table 1, entries 15 and 16). In fact, some side products were produced and the reaction system became very complex at higher temperatures.

Under the optimized conditions, the new tandem protocol was applied to reactions of a series of 1-(2-iodoaryl)-enones with a range of isocyanides (Table 2). For the 1-(2-iodoaryl)enone substrates, the results revealed that the 1-(2-iodoaryl)enones bearing aryl groups at the terminal of a double bond were favored over those bearing alkyl groups (Table 2, entries 1–11). The low yields of the latter substrates were at least partially caused by dimerization or polymerization of the 3-alkyl enones.[8] For aryl substitutions at the double bond terminal, the results also showed that electron-rich aryl groups gave better results than electron-deficient aryl groups (Table 2, entries 1–6 and 7–9). The electronic effects of substituents on the 1-(2-idoaryl) ring were much clearer; compounds bearing electron-withdrawing groups on the 1-(2-idoaryl) ring provided the corresponding products in good yields (Table 2, entries 14–18), whereas compounds bearing electron-donating groups delivered the corresponding products only in low yields (Table 2, entries 12 and 13). The situation could be slightly improved by increasing the reaction temperature to 50 °C.

A second isocyanide, toluenesulfonylmethyl isocyanide (TOSMIC; **1b**) was also explored in the copper-catalyzed tandem reactions, and it was found that this substrate also furnished the corresponding products in acceptable yields (Table 2, entries 19 and 20). However, for the less reactive 1-(2-bromoaryl)enones, no desired products were detected when the reaction was performed at room tem-

Table 1 Reaction Conditions for the Copper-Catalyzed Tandem Reaction[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	CuI	Cs_2CO_3	DMF	r.t.	68[c]
2	CuI	Cs_2CO_3	DMF	r.t.	31[d]
3	CuI	Cs_2CO_3	DMF	r.t.	70
4	CuI	Cs_2CO_3	DMF	r.t.	20[e]
5	CuI	Cs_2CO_3	DMSO	r.t.	51
6	CuI	Cs_2CO_3	MeCN	r.t.	50
7	CuI	Cs_2CO_3	dioxane	r.t.	23
8	CuI	Cs_2CO_3	toluene	r.t.	n.d.[f]
9	CuI	NaOH	DMF	r.t	47
10	CuI	K_3PO_4	DMF	r.t	32
11	CuI	K_2CO_3	DMF	r.t	34
12	CuBr	Cs_2CO_3	DMF	r.t	33
13	CuOTf	Cs_2CO_3	DMF	r.t	41
14	$CuSO_4$	Cs_2CO_3	DMF	r.t	40
15	CuI	Cs_2CO_3	DMF	60	46
16	CuI	Cs_2CO_3	DMF	90	32

[a] Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), CuI (10 mg, 10 mol%), Cs_2CO_3 (1 mmol), r.t., 4 h, in air.
[b] Isolated yield.
[c] Under N_2 (balloon).
[d] Under O_2.
[e] Under Argon (balloon).
[f] No desired product was detected.

perature. When the reaction temperature was increased to 100 °C, lower yields were obtained in some cases (Table 2, entries 15 and 16). In the case of 1-(2-chloroaryl)enone substrates, no desired products were detected even under such harsh reaction conditions.

The structures of the indeno[1,2-*b*]pyrroles produced in these reactions were assigned by analogy to that of **5h**, the structure of which was unambiguously determined by X-ray crystallographic analysis (Figure 1).[9]

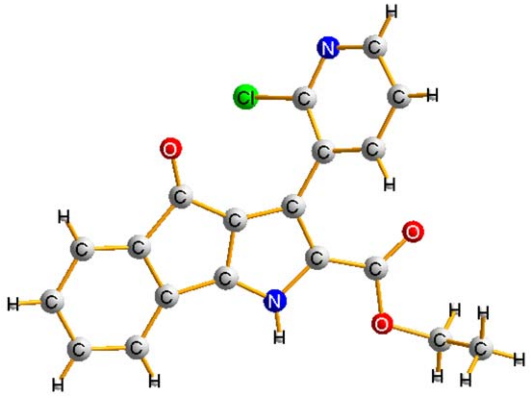
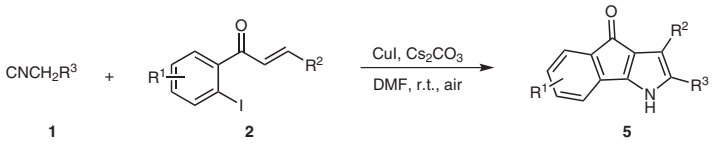


Figure 1 X-ray crystal structure of **5h**

Based on literature reports[6e,f] and on our experimental observations, a plausible reaction mechanism for the copper-catalyzed tandem reactions of isocyanides with 1-(2-haloaryl)enones was proposed as shown in Scheme 3. In this pathway, Cu-catalyst species **A** or **A′** was first formed through the reaction of the isocyanide with CuI in the presence of a base, which then generates the cyclic organocopper intermediate **B** through a [3+2] cycloaddition reaction with the 1-(2-haloaryl)enone. Intermediate **B** is transformed into intermediate **C** by intramolecular insertion of Cu into the aryl C–X bond and then the coupling product **D** is generated to end the catalytic cycle. Finally, 4-oxoindeno[1,2-*b*]pyrroles are produced by a tautomerization–oxidation process from **D**.

Table 2 Scope of the Copper-Catalyzed Tandem Reactions of 1-(2-Haloaryl)enones with Isocyanides[a]



1 2 5

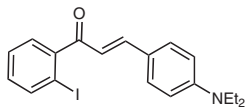
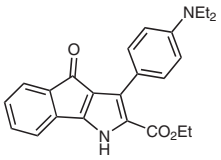
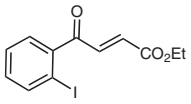
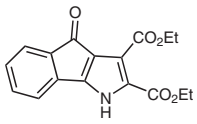
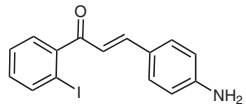
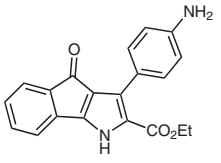
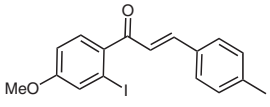
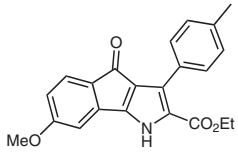
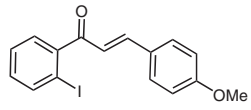
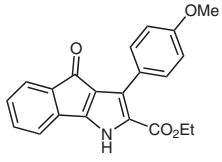
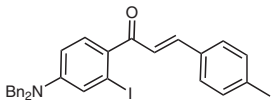
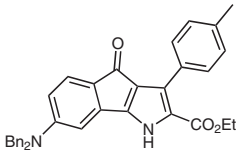
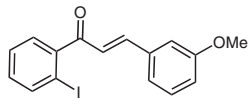
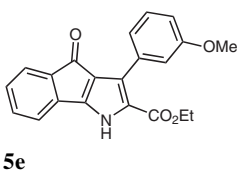
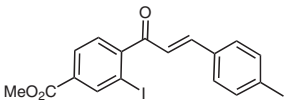
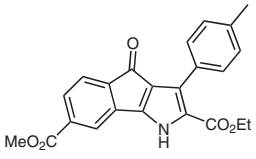
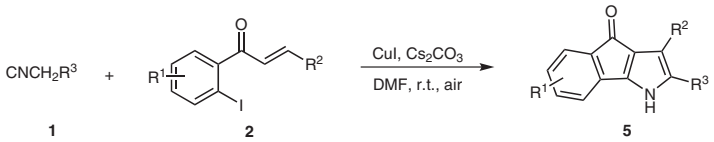
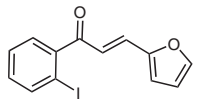
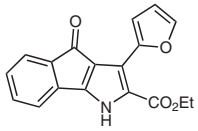
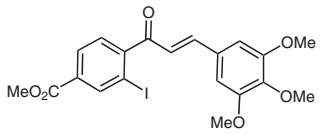
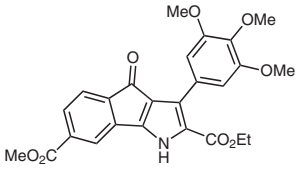
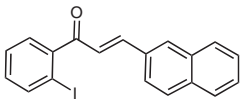
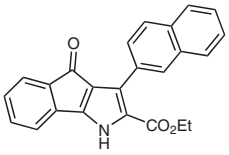
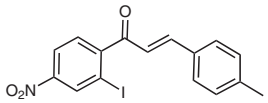
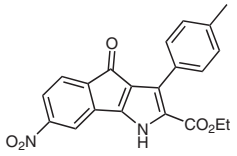
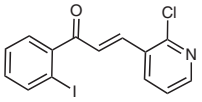
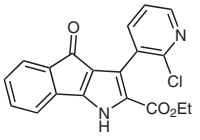
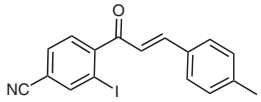
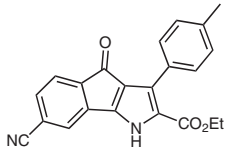
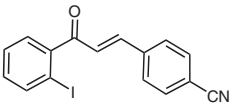
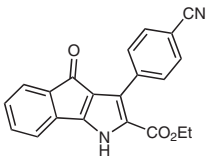
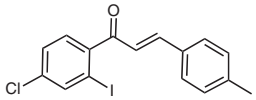
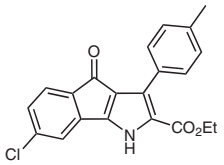
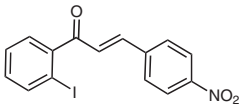
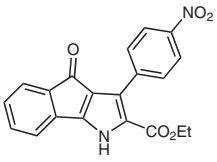
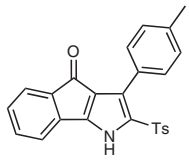
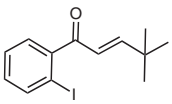
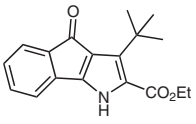
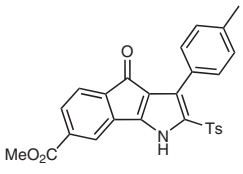
Entry	Aryl iodide	Product	Yield (%)[b]	Entry	Aryl iodide	Product	Yield (%)[b]
1	 **2b**	 **5b**	74	11	 **2l**	 **5l**	32
2	 **2c**	 **5c**	58	12	 **2m**	 **5m**	35[c]
3	 **2d**	 **5d**	61	13	 **2n**	 **5n**	33[c]
4	 **2e**	 **5e**	58	14	 **2o**	 **5o**	76

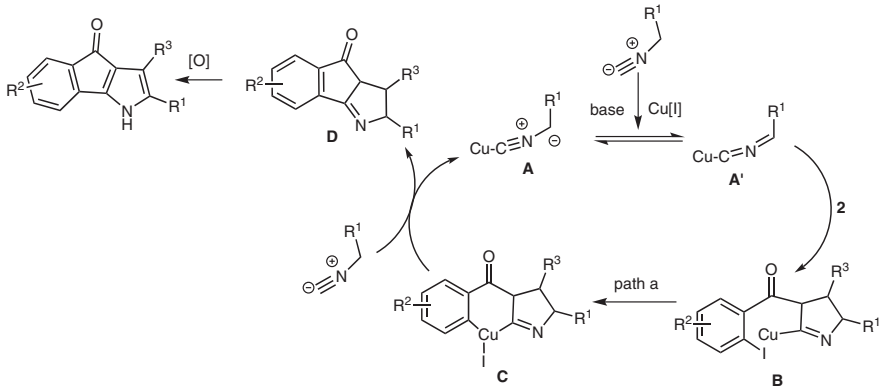
Table 2 Scope of the Copper-Catalyzed Tandem Reactions of 1-(2-Haloaryl)enones with Isocyanides[a] (continued)



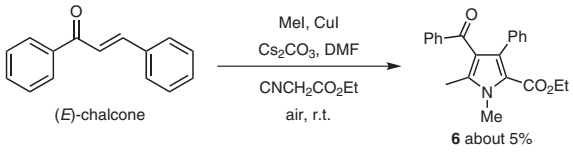
Entry	Aryl iodide	Product	Yield (%)[b]	Entry	Aryl iodide	Product	Yield (%)[b]
5	 **2f**	 **5f**	73	15	 **2p**	 **5p**	78 (38)[d]
6	 **2g**	 **5g**	60	16	 **2q**	 **5q**	78 (40)[d]
7	 **2h**	 **5h**	55	17	 **2r**	 **5r**	62
8	 **2i**	 **5i**	42[c]	18	 **2s**	 **5s**	58
9	 **2j**	 **5j**	41[c]	19	**2a**	 **5t**	43
10	 **2k**	 **5k**	30	20	**2o**	 **5u**	45

[a] Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), CuI (0.05 mmol), Cs_2CO_3 (1.0 mmol), r.t., 4–6 h. For entries 1–18, ethyl isocyanoacetate (**1a**) was used; for entries 19 and 20, TOSMIC (**1b**) was used.
[b] Isolated yield.
[c] Reaction conducted at 50 °C.
[d] X = Br, 100 °C.

Although the proposed organocopper intermediate was successfully trapped intramolecularly, our attempts to trap the intermediate in an intermolecular manner did not give satisfactory results. Previous attempts to achieve intermolecular trapping of the organocopper intermediate in the reaction of aryl ynone with isocyanide failed.[7a] However, when adding iodomethane to the copper-catalyzed reaction of (*E*)-chalcone and ethyl isocyanoacetate, the fully substituted pyrrole product **6** was isolated, albeit in low yield (Scheme 4),[10] which partially confirmed our as-



Scheme 3 Proposed mechanism



Scheme 4 Attempt at intermolecular trapping

sumption that the intermediate can also be trapped in an intermolecular fashion.

In summary, this investigation has led to the development of an efficient and practically useful method for the synthesis of 4-oxoindeno[1,2-*b*]pyrroles through copper-catalyzed tandem reaction of 1-(haloaryl)enones with isocyanides. The process takes place efficiently with a variety of 1-(2-iodoaryl)enone substrates and displays wide ranging functional-group compatibility. The method is a complementary alternative to our previously reported reactions of 1-(2-haloaryl)ynones and isocyanides because 1-(haloaryl)enones are much easier to prepare. Further applications of these methods are underway in our laboratory.

All products were characterized by their ^{1}H and ^{13}C NMR on a Bruker AV-400 or -500 MHz spectrometer, respectively. Mass spectrometric analyses were performed on an Agilent 1956B single quadrupole mass spectrometer. High resolution mass spectra (HRMS) were obtained on a Q-STAR Elite ESI-LC-MS/MS spectrometer. All reactions were carried out in 5 mL tubes. DMF was distilled from CaH_2 and stored over 4 Å activated molecular sieves. Cs_2CO_3 (Alfa Aesar), CuI (Aldrich) and all other solid materials were stored in the presence of P_2O_5 in a bench-top desiccator under vacuum at r.t. and weighed in air. Petroleum ether (PE) used was the fraction boiling in the temperature range 60–90 °C.

4-Oxoindeno[1,2-*b*]pyrroles; General Procedure

Isocyanide **1** (0.55 mmol) was added to a mixture of Cs_2CO_3 (325 mg, 1.0 mmol, 2.0 equiv), CuI (10 mg, 0.05 mmol, 10% equiv), and **2** (0.5 mmol, 1.0 equiv) in DMF (1 mL) at the stated temperature. The mixture was stirred under air for 4–6 h (until TLC showed that the reaction was complete), then H_2O (5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (3 × 5 mL), dried over Na_2SO_4, and concentrated in vacuum. The residue was loaded on a silica column and purified by column chromatography (SiO_2; PE–EtOAc, 8:1) to afford the final product **5a**–**u**.

Ethyl 4-Oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5a)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.82 (br s, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.42–7.48 (m, 2 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.23–7.27 (m, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 2.34 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.2, 160.3, 151.5, 139.7, 137.2, 134.0, 131.3, 133.4, 129.9, 129.3, 129.0, 128.5, 127.8, 123.0, 122.9, 121.6, 119.5, 60.1, 20.9, 14.1.

MS (ESI): *m*/*z* = 332.1 [M + H$^+$].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}NO_3$: 332.1281; found: 332.1282.

Ethyl 3-[4-(Diethylamino)]-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (br s, 1 H), 7.77 (d, *J* = 8.8 Hz, 2 H), 7.49 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.16–7.22 (m, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 3.38 (q, *J* = 7.2 Hz, 4 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 161.4, 151.2, 148.0, 140.7, 140.0, 132.6, 132.2, 131.7, 129.0, 123.6, 123.0, 120.0, 118.2, 117.8, 110.4, 60.7, 44.3, 14.3, 12.7.

MS (ESI): *m*/*z* = 389.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}N_2O_3$: 389.1860; found: 389.1862.

Ethyl 3-(4-Amino)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5c)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.64 (br s, 1 H), 7.43–7.47 (m, 4 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.23–7.27 (m, 1 H), 6.56 (d, *J* = 8.8 Hz, 2 H), 5.45 (br s, 2 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.6, 160.9, 151.8, 149.0, 140.4, 134.4, 133.7, 131.6, 131.5, 129.4, 123.3, 122.2, 121.6, 119.8, 119.0, 112.9, 60.3, 14.6.

MS (ESI): *m*/*z* = 333.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2O_3$: 333.1234; found: 333.1235.

Ethyl 3-(4-Methoxy)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5d)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.80 (br s, 1 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.42–7.47 (m, 2 H), 7.37 (d, *J* = 6.8 Hz, 1 H), 7.26 (t, *J* = 6.8 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 3.80 (s, 3 H), 1.23 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.7, 160.8, 159.5, 151.9, 140.2, 134.4, 133.9, 131.9, 129.8, 129.6, 124.1, 123.4, 123.0, 121.9, 119.9, 113.11, 60.1, 55.5, 14.6.

MS (ESI): *m*/*z* = 348.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}NO_3$: 348.1230; found: 348.1230.

Ethyl 3-(3-Methoxyphenyl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5e)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.88 (br s, 1 H), 7.43–7.48 (m, 2 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.23–7.31 (m, 4 H), 6.92 (d, *J* = 7.2 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.2, 160.3, 158.3, 151.6, 139.7, 134.0, 133.5, 132.7, 129.1, 128.2, 123.3, 123.0, 122.4, 121.7, 119.5, 115.2., 113.6, 60.1, 55.0, 14.0.

MS (ESI): *m*/*z* = 348.0 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}NO_4$: 348.1230; found: 348.1235.

Ethyl 3-(Furan-2-yl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5f)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.92 (br s, 1 H), 7.78 (s, 1 H), 7.41–7.50 (m, 3 H), 7.27–7.30 (m, 2 H), 6.62–6.63 (m, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.4, 160.3, 152.0, 146.9, 143.5, 140.0, 134.1, 133.9, 129.8, 123.6, 122.4, 120.6, 120.0, 117.9, 112.8, 112.1, 60.9, 14.7.

MS (ESI): *m*/*z* = 308.0 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}NO_4$: 308.0917; found: 308.0924.

Ethyl 3-(Naphthalen-1-yl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5g)

^{1}H NMR (400 MH, DMSO-d_6): δ = 13.08 (br s, 1 H), 7.95 (t, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 1 H), 7.40–7.55 (m, 6 H), 7.25–7.34 (m, 2 H), 3.92 (q, *J* = 6.4 Hz, 2 H), 0.71 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MH, DMSO-d_6): δ = 185.6, 160.6, 152.0, 140.0, 134.8, 134.0, 133.3, 131.9, 130.9, 129.6, 128.4, 128.3, 127.9, 126.3, 126.1, 126.0, 125.8, 125.4, 123.8, 123.5, 120.0, 60.2, 13.8.

MS (ESI): *m*/*z* = 368.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{19}NO_3$: 368.1281; found: 368.1282.

Ethyl 3-(2-Chloropyridin-3-yl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5h)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.16 (br s, 1 H), 8.42 (dd, *J* = 4.8, 2.0 Hz, 1 H), 7.79 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.44–7.48 (m, 3 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.25–7.29 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 1.03 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.4, 160.4, 151.9, 149.9, 149.2, 141.2, 139.8, 134.8, 134.2, 129.8, 125.6, 123.7, 123.1, 122.8, 120.1, 60.7, 14.3.

MS (ESI): *m*/*z* = 353.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}ClN_2O_3$: 353.0687; found: 353.0691.

Ethyl 3-(4-Cyanophenyl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5i)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.08 (br s, 1 H), 7.82–7.88 (m, 4 H), 7.46 (m, 2 H), 7.39 (m, 1 H), 7.28–7.30 (m, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.6, 160.5, 152.2, 139.9, 137.0, 134.4, 134.2, 131.7, 131.3, 129.8, 127.2, 124.2, 123.7, 122.1, 120.1, 119.3, 110.7, 60.9, 14.4.

MS (ESI): *m*/*z* = 343.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}ClN_2O_3$: 343.1077; found: 343.1078.

Ethyl 3-(4-Nitrophenyl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5j)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.11 (br s, 1 H), 8.24 (d, *J* = 8.8 Hz, 2 H), 7.91 (d, *J* = 8.8 Hz, 2 H), 7.47–7.48 (m, 2 H), 7.40 (d, *J* = 7.2 Hz, 1 H), 7.27–7.30 (m, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.6, 160.4, 152.2, 147.1, 139.8, 139.0, 134.4, 134.2, 131.7, 129.8, 126.6, 124.4, 123.7, 122.9, 122.2, 120.2, 61.0, 14.4.

MS (ESI): *m*/*z* = 363.0 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_2O_5$: 363.0975; found: 363.0972.

Ethyl 3-*tert*-Butyl-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5k)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (br s, 1 H), 7.46 (d, *J* = 7.2 Hz, 1 H), 7.30 (m, 1 H), 7.19 (m, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 1.52 (s, 9 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.4, 160.5, 150.3, 143.6, 140.2, 134.4, 133.4, 132.8, 129.1, 123.8, 123.6, 117.5, 60.9, 33.2, 31.1, 14.4.

MS (ESI): *m*/*z* = 298.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_3$: 298.1438; found: 298.1441.

Diethyl 4-Oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2,3-dicarboxylate (5l)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.12 (br s, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.32–7.36 (m, 1 H), 7.22–7.25 (m, 1 H), 7.19 (m, 1 H), 4.35–7.44 (m, 4 H), 1.13–1.43 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.3, 163.0, 160.3, 150.6, 139.4, 133.7, 133.2, 129.6, 126.3, 124.1, 123.5, 118.6, 118.3, 61.7, 61.7, 14.1, 14.1

MS (ESI): *m*/*z* = 314.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_5$: 314.1023; found: 314.1028.

Ethyl 7-Methoxy-4-oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5m)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.72 (br s, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 2.0 Hz, 1 H), 6.73 (dd, *J* = 8.0, 2.0 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.84 (s, 3 H), 2.34 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.1, 164.1, 160.7, 150.3, 137.6, 136.7, 132.5, 130.4, 129.6, 129.0, 128.3, 125.3, 123.2, 123.1, 111.9, 108.0, 60.5, 56.2, 21.3, 14.6.

MS (ESI): *m*/*z* = 362.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}NO_4$: 362.1387; found: 362.1388.

Ethyl 7-(Dibenzylamino)-4-oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5n)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.58 (br s, 1 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.37 (m, 4 H), 7.28 (m, 6 H), 7.14 (m, 3 H), 7.07 (m, 1 H), 6.35 (d, *J* = 8.0 Hz, 1 H), 4.78 (s, 4 H), 4.17 (q, *J* = 6.8 Hz, 2 H), 2.33 (s, 3 H), 1.18 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.2, 160.8, 153.1, 138.1, 137.3, 136.8, 130.5, 130.5, 129.3, 129.2, 128.2, 127.5, 127.0, 125.4, 123.6, 122.4, 109.6, 104.9, 60.3, 54.2, 21.3, 14.6.

MS (ESI): *m*/*z* = 527.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{31}N_2O_3$: 527.2329; found: 527.2329.

2-Ethyl 7-Methyl 4-Oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2,7-diarboxylate (5o)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.85 (br s, 1 H), 8.07 (s, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 2 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.89 (s, 3 H), 2.35 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.4, 165.7, 160.5, 151.0, 143.9, 137.8, 134.7, 134.1, 131.2, 130.4, 129.8, 128.7, 128.3, 123.8, 123.3, 122.6, 120.0, 60.6, 52.9, 21.3, 14.5.

MS (ESI): *m*/*z* = 390.0 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}NO_5$: 390.1336; found: 390.1337.

2-Ethyl 7-Methyl 4-Oxo-3-(3,4,5-trimethoxyphenyl)-1,4-dihydroindeno[1,2-*b*]pyrrole-2,7-dicarboxylate (5p)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.89 (br s, 1 H), 8.09 (s, 1 H), 7.88 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.15 (s, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.90 (s, 3 H), 3.81 (s, 6 H), 3.72 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.5, 165.8, 160.5, 152.1, 151.0, 143.8, 138.0, 134.6, 134.2, 131.3, 130.0, 126.8, 123.8, 123.5, 122.6, 120.1, 108.4, 60.8, 60.5, 56.3, 52.9, 14.6.

MS (ESI): *m*/*z* = 466.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_8$: 466.1496; found: 466.1500.

Ethyl 7-Nitro-4-oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5q)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.21 (d, *J* = 1.5 Hz, 1 H), 8.11 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.56 (m, 3 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 2.35 (s, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.1, 160.4, 151.0, 149.6, 144.9, 137.9, 135.6, 130.3, 129.8, 128.4, 125.5, 124.4, 123.9, 123.4, 123.3, 114.2, 60.8, 21.3, 14.4.

MS (ESI): *m*/*z* = 377.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O_5$: 377.1132; found: 377.1134.

Ethyl 7-Cyano-4-oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5r)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.97 (br s, 1 H), 7.78 (d, *J* = 7.5 Hz, 1 H), 7.70 (s, 1 H), 7.51–7.55 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 2.35 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.8, 160.7, 150.4, 143.7, 138.1, 135.2, 134.9, 130.5, 130.0, 129.8, 128.7, 128.5, 124.4, 124.0, 122.9, 122.1, 118.8, 115.8, 61.0, 21.5, 14.7.

MS (ESI): *m*/*z* = 357.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_3$: 357.1234; found: 357.1236.

Ethyl 7-Chloro-4-oxo-3-*p*-tolyl-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate (5s)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.5 (br s, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.19–7.24 (m, 4 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 2.39 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.3, 160.6, 150.0, 138.6, 138.3, 137.8, 136.4, 130.4, 129.8, 128.9, 128.7, 128.3, 124.9, 123.8, 122.7, 120.0, 60.7, 21.3, 14.5.

MS (ESI): *m*/*z* = 366.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}ClNO_3$: 366.0891; found: 366.0890.

3-*p*-Tolyl-2-tosylindeno[1,2-*b*]pyrrol-4(1*H*)-one (5t)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.41 (br s, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.48–7.75 (m, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.27–7.31 (m, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 2.35 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.4, 151.9, 144.6, 139.5, 139.4, 138.3, 134.1, 134.1, 130.4, 130.0, 129.4, 129.2, 128.8, 128.6, 128.4, 127.5, 126.6, 123.7, 122.2, 120.2, 21.4, 21.3.

MS (ESI): *m*/*z* = 414.1 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{20}NO_3S$: 414.1158; found: 414.1154.

Ethyl 4-Oxo-3-*p*-tolyl-2-tosyl-1,4-dihydroindeno[1,2-*b*]pyrrole-7-carboxylate (5u)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.46 (br s, 1 H), 8.10 (s, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 3.90 (s, 3 H), 2.36 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.6, 165.1, 150.5, 144.1, 142.7, 138.7, 137.9, 133.9, 133.8, 131.0, 130.0, 129.8, 129.5, 129.4, 128.2, 127.8, 126.8, 126.2, 123.1, 122.3, 119.7, 52.4, 20.8, 20.7.

MS (ESI): *m*/*z* = 472.0[M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{22}NO_5S$: 472.1213; found: 472.1209.

Ethyl 4-Benzoyl-1,5-dimethyl-3-phenyl-1*H*-pyrrole-2-carboxylate (6)

Ethyl isocyanoacetate (**1a**; 0.55 mmol) was added to a mixture of $CsCO_3$ (325 mg, 1.0 mmol, 2.0 equiv), CuI (10 mg, 0.05 mmol, 10% equiv), (*E*)-chalone (0.5 mmol, 1.0 equiv), and MeI (1.25 mmol, 2.5 equiv) in DMF (1 mL) at r.t. The mixture was stirred under air for 4–6 h, then H_2O (5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine (3 × 5 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was loaded on a silica column and purified by column chromatography (SiO_2; PE–EtOAc, 8:1) to afford **6**.

Yield: 8.5 mg (5%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.2 Hz, 2 H), 7.19–7.23 (m, 1 H), 7.08 (t, *J* = 8.0 Hz, 2 H), 7.01–7.03 (m, 2 H), 6.94–6.99 (m, 3 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 3.85 (s, 3 H), 2.31 (s, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.1, 161.9, 139.1, 138.6, 134.9, 132.9, 131.8, 129.5, 127.6, 126.9, 126.4, 122.3, 119.6, 60.0, 32.9, 13.5, 11.7.

MS (ESI): *m*/*z* = 347.1 [M + H]$^+$.

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(10) No fully substituted product **6** was detected without adding CuI as the catalyst.