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Copper-Catalyzed Selective Oxidative Acylation of Secondary Anilines with Ethyl Glyoxalate: Domino Synthesis of Indoline-2,3-diones

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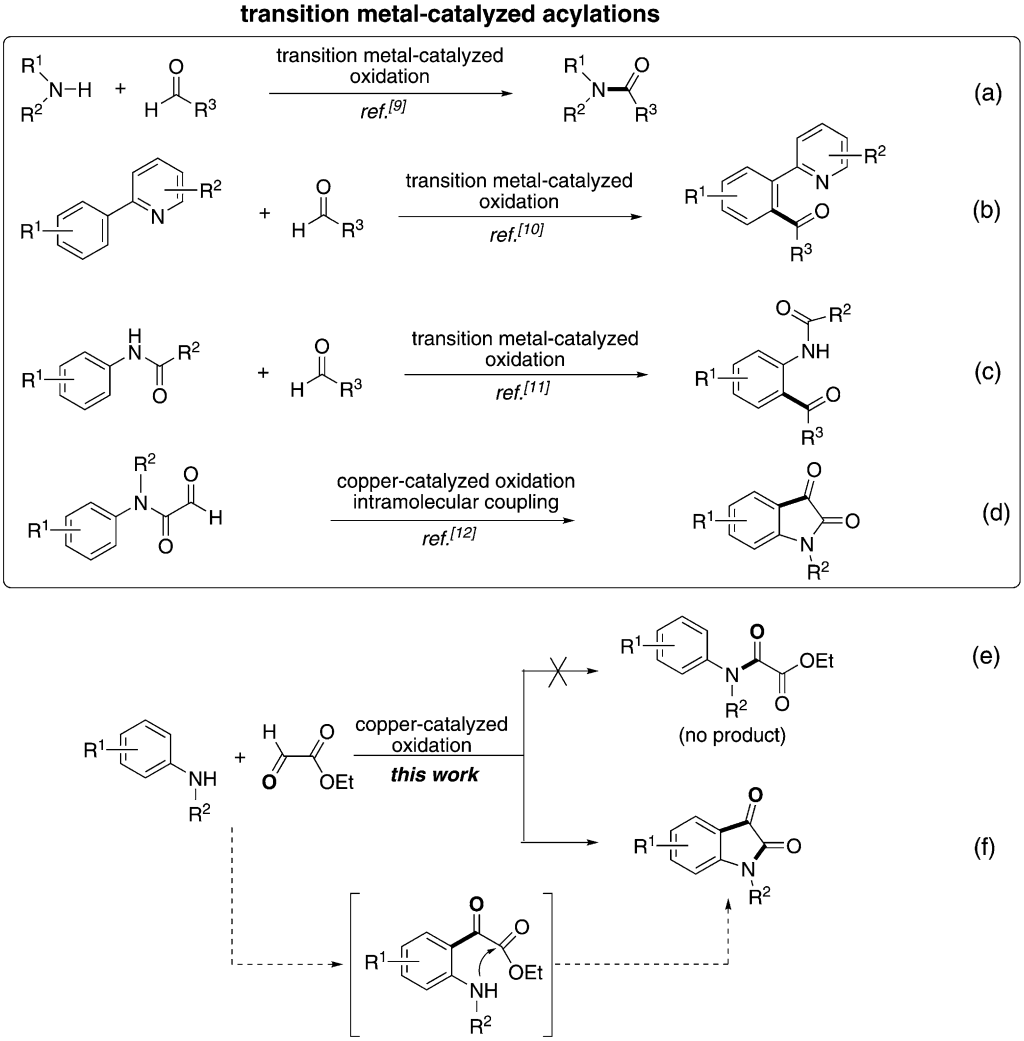
Abstract: A novel, easy and useful copper-catalyzed selective acylation of secondary anilines with ethyl glyoxalate has been developed, and the corresponding indoline-2,3-dione derivatives were prepared. The procedure comprises the sequential intermolecular copper-catalyzed selective oxidative *ortho*-site aromatic acylation of the NH group in secondary anilines and intramolecular nucleophilic attack of the NH group to the ester. The inexpensive, easy and efficient method should provide a new strategy for synthesis of dicarbonyl compounds.

Keywords: acylation; C–H functionalization; copper; indoline-2,3-diones; selectivity

Introduction

Nitrogen-containing heterocycles are ubiquitous subunits of a variety of biologically active substances,[1] and they have been assigned as privileged structures in drug development.[2] The indoline-2,3-dione derivatives found in natural products[3] show various biological activities such as anticonvulsant,[4a] antimicrobial,[4b] antitumor,[4c] antiviral,[4d] anti-HIV,[4e] and antitubercular,[4f] and they are used as important intermediates in organic synthesis.[5] The traditional synthesis of indoline-2,3-diones usually uses coupling of anilines with oxalyl chloride in the presence of excess $AlCl_3$.[6] However, the method is environmentally unfriendly, and it does not meet the requirements of modern green chemistry. Therefore, it is highly desirable to develop a convenient and practical approach to this kind of compound.

Recently, transition metal-catalyzed C–H functionalization has emerged as a sustainable and intriguing protocol because it does not need one to preinstall functional groups which can minimize the requisite reagents, separation processes, waste, energy, time and cost,[7] and some valuable products including N-heterocycles[8] have been synthesized *via* this strategy. However, it is still a challenge to develop an efficient and highly selective approach. Aldehydes are attractive substrates for various acylation reactions in the transition metal-catalyzed C–H activation. For example, amines could efficiently be transformed into amides by using aldehydes as the partners (Scheme 1a).[9] Aromatic C–H bond acylations performed well in the presence of *ortho*-site directing groups. Recently, the acylation of 2-arylpyridines with aldehydes has been developed by using the pyridine moiety as the directing group (Scheme 1b).[10] Acetanilides are also common substrates for *ortho*-acylation of aromatic C–H bonds (Scheme 1c).[11] Recently, Li and co-workers have developed an efficient copper-catalyzed oxidative intramolecular acylation of *N*-alkyl-2-oxo-*N*-phenylacetamides leading to indoline-2,3-diones (Scheme 1d).[12] However, to the best of our knowledge, the direct *ortho*-site aromatic C–H functionalization of anilines did not work in the absence of directing groups in the previous research works.[13] Considering the low-cost and low toxicity of copper catalysts, the good functional tolerance of copper-catalyzed reactions,[14] and the efficacy in the copper-catalyzed synthesis of N-heterocycles *via* the C–H functionalization strategy,[15,16] we investigated the copper-catalyzed oxidative reactions of secondary anilines with ethyl glyoxalate. Surprisingly, indoline-2,3-diones were obtained *via* sequential intermolecular selective oxidative *ortho*-site aromatic C–H acyla-



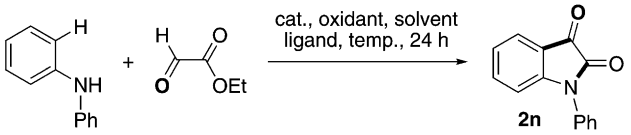
Scheme 1. (a) Transition metal-catalyzed acylation of amines with aldehydes. (b–d) Transition metal-catalyzed *ortho*-acylation of aromatic C–H bonds in the presence of directing groups. (e) No acylation of NH group in secondary anilines under copper catalysis. (f) Copper-catalyzed selectively oxidative acylation and amidation of secondary anilines with ethyl glyoxalate leading to indoline-2,3-diones (***our strategy***).

tion of NH group and intramolecular formation of the amide bond (Scheme 1f). However, acylation products of the NH group in secondary anilines were not observed (Scheme 1e). In addition, no decarbonylation occurred in the copper-catalyzed oxidative acylation reactions. In fact, the decarbonylation had often been observed in the previous transition metal-catalyzed acylation of aromatic C–H bonds by using the dicarbonyl compounds as the acylating agents.[11b,17] Herein, we report this novel copper-catalyzed selective acylation of secondary anilines with ethyl glyoxalate leading to indoline-2,3-diones.

Results and Discussion

At first, diphenylamine was chosen as the partner of ethyl glyoxalate to optimize the reaction conditions including the catalysts, oxidants, solvents, ligands and temperature. As shown in Table 1, various copper salts were screened (entries 1–8) using 1.5 equivalents of *tert*-butyl hydroperoxide (TBHP) in decane as the oxidant, dichloroethane as the solvent at 100 °C for 24 h, and $Cu(OAc)_2$ exhibited the highest activity (entry 4). No target product was observed in the absence of a copper catalyst (entry 9). Other solvents were attempted (entries 10–13), and toluene provided the highest yield (entry 10). Various ligands were added to the reaction systems (entries 14–17), and the yield was greatly increased in the presence of 0.2 equiv. of nicotinic acid (entry 16). The results

Table 1. Copper-catalyzed reaction of diphenylamine with ethyl glyoxalate leading to 1-phenylindoline-2,3-dione (**2n**): optimization of conditions.[a]



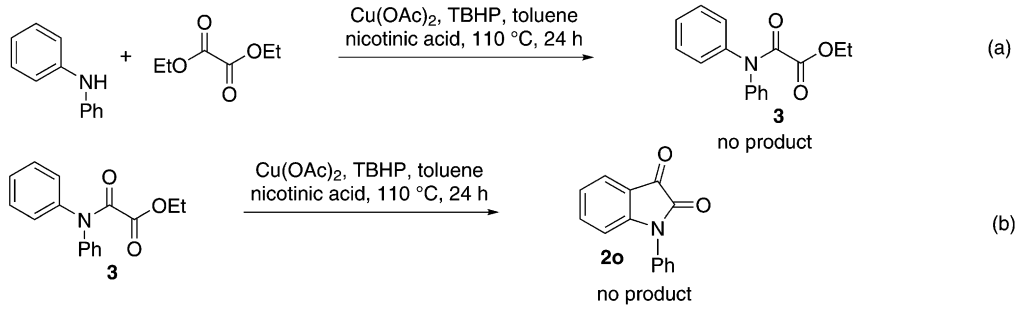
Entry	Cat.	Oxidant	Solvent	Ligand	Yield [%][b]
1	CuI	TBHP	DCE		30
2	CuBr	TBHP	DCE		23
3	CuCl	TBHP	DCE		24
4	$Cu(OAc)_2$	TBHP	DCE		33
5	$Cu(TFA)_2$	TBHP	DCE		27
6	$Cu(OTf)_2$	TBHP	DCE		29
7	$CuCl_2$	TBHP	DCE		26
8	CuO	TBHP	DCE		21
9	–	TBHP	DCE		0
10	$Cu(OAc)_2$	TBHP	toluene		44
11	$Cu(OAc)_2$	TBHP	*o*-xylene		39
12	$Cu(OAc)_2$	TBHP	DMF		0
13	$Cu(OAc)_2$	TBHP	DMSO		trace
14	$Cu(OAc)_2$	TBHP	toluene	pyridine	20
15	$Cu(OAc)_2$	TBHP	toluene	PA	34
16	**$Cu(OAc)_2$**	**TBHP**	**toluene**	**NA**	**65**
17	$Cu(OAc)_2$	TBHP	toluene	EN	44
18	$Cu(OAc)_2$	TBHP[c]	toluene	NA	12
19	$Cu(OAc)_2$	O_2	toluene	NA	trace
20	$Cu(OAc)_2$	$K_2S_2O_8$	toluene	NA	0
21	$Cu(OAc)_2$	TBHP	toluene	NA	55[d]
22	$Cu(OAc)_2$	TBHP	toluene	NA	58[e]

[a] *Reaction conditions:* diphenylamine (**1a**) (0.25 mmol), ethyl glyoxalate in toluene (50%, 0.5 mmol), catalyst (0.025 mmol), TBHP in decane (5.5 M, 0.375 mmol), ligand (0.05 mmol), solvent (1 mL), reaction temperature (100 °C), reaction time (24 h).
[b] Isolated yield.
[c] TBHP in water (70%, 0.375 mmol).
[d] Reaction temperature (90 °C).
[e] Reaction temperature (110 °C). Tf = $CF_3SO_2^-$; TFA = CF_3COO^-; TBHP = *tert*-butyl hydroperoxide; DCE = 1,2-dichloroethane; PA = picolinic acid; NA = nicotinic acid; EN = ethyl nicotinate.

showed that the electronic nature of the ligands (i.e., pK_a) also was a key factor for the formation of the target product. A similar result was found by Stoltz's group.[18] The reactivity obviously decreased upon using aqueous TBHP as the oxidant (entry 18). Oxygen (entry 19) and $K_2S_2O_8$ (entry 20) were used as oxidants, and they gave poor results. We attempted different temperature (entries 21 and 22), and 100 °C was suitable (compare entries 16, 21 and 22). Therefore, the optimum conditions for the copper-catalyzed protocol are as follows: 10 mol% $Cu(OAc)_2$ as the catalyst, 1.5 equiv. of TBHP in decane as the oxidant, 20 mol% nicotinic acid as the ligand, and toluene as the solvent at 100 °C.

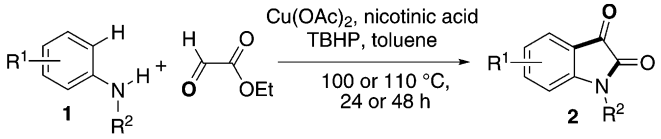
With the optimum reaction conditions in hand, we investigated the scope of substrates for the copper-catalyzed oxidative acylation and amidation of secondary anilines (**1**) with ethyl glyoxalate leading to indoline-2,3-dione derivatives (**2**). As shown in Table 2, the tested substrates afforded moderate to good yields. For substituted *N*-alkylanlines, the acylation undisputably occurred on the aromatic ring (entries 1–14). For the *N*-alkylanline with a *meta*-substituent, *N*-cyclohexyl-3-methylbenzenamine, two acylation products (**2k** and **2k′**) were obtained (entry 11). When the substrates were diarylamines, the site of acylation highly depended on the electronic effect of the two aromatic rings, and the phenyl rings containing rich-electron groups were favored (entries 15–21). The copper-catalyzed domino reactions could tolerate some functional groups including C–Cl bonds (entries 4, 12, and 16-18), and CF_3 groups (entries 19 and 20) in the substrates. Interestingly, the copper-catalyzed acylation selectively occurred on the *ortho*-site of the NH group in the secondary anilines, and the dicarbonyl group was retained in the target products. Therefore, the present method provides a novel and useful strategy for synthesis of dicarbonyl compounds.

In order to explore the mechanism for copper-catalyzed oxidative coupling of secondary anilines with ethyl glyoxalate leading to indoline-2,3-diones, two control experiments were performed under the standard conditions. Treatment of diphenylamine with diethyl oxalate did not provided amidation product **3** (Scheme 2a), and the result showed that the domino reactions of secondary anilines with ethyl glyoxalate did not start from nucleophilic attack of NH to ester. Treatment of **3** under the standard conditions did not lead to **2o** (Scheme 2b), and this result showed that the formation of the target product (**2**) was not from intermediate **3**. Control experiments were performed for the treatment of ethyl glyoxalate with *tert*-butyl hydroperoxide under catalysis of $Cu(OAc)_2$, and the *in situ* ESR showed the corresponding free radical signal (see the Supporting Information for the details). Therefore, a possible mechanism for the copper-catalyzed synthesis of indoline-2,3-dione derivatives (**2**) is proposed as shown in Scheme 3. First, coordination of copper catalyst Cu(II) with ligand NH in secondary aniline and two oxygens in ethyl glyoxalate provides **I**, and reaction of **I** with *tert*-butyl hydroperoxide gives free radicals **II**[11b] and *t*-BuO•. *ortho*-Aromatic acylation of the NH group in **II** gives **III** freeing the copper catalyst and ligand, and dissociation of the hydrogen free radical in **III** in the presence of *t*-BuO• yields **IV**. Finally, intramolecular nucleophilic attack of the NH group to the ester in **IV** affords the target product (**2**). The structure of complex **II** makes acylation of the aryl group more favorable



Scheme 2. Under the standard conditions: (a) Treatment of diphenylamine with diethyl oxalate. (b) Treatment of ethyl (diphenylcarbamoyl)formate.

Table 2. Copper-catalyzed synthesis of indoline-2,3-dione derivatives (**2**).[a]



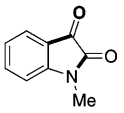
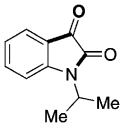
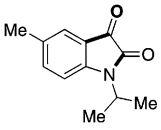
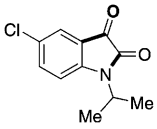
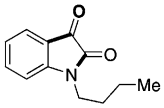
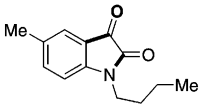
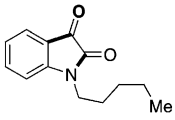
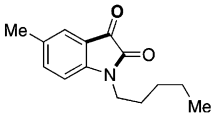
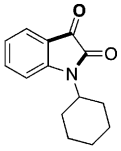
Entry	Temp./Time	**2**		Yield [%][b]
1	100 °C/24 h		**2a**	36
2	100 °C/24 h		**2b**	55
3	100 °C/24 h		**2c**	58
4	110 °C/48 h		**2d**	45
5	100 °C/24 h		**2e**	46
6	110 °C/24 h		**2f**	51
7	110 °C/48 h		**2g**	54
8	110 °C/24 h		**2h**	53
9	100 °C/24 h		**2i**	59

Table 2. (Continued)

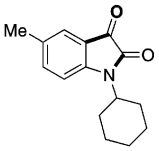
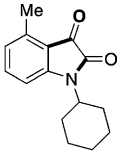
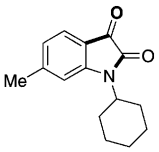
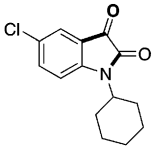
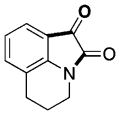
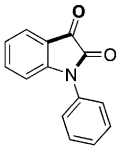
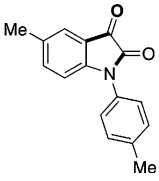
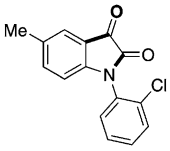
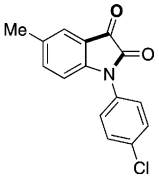
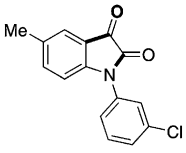
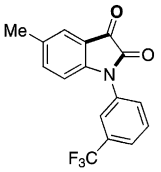
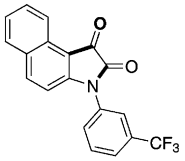
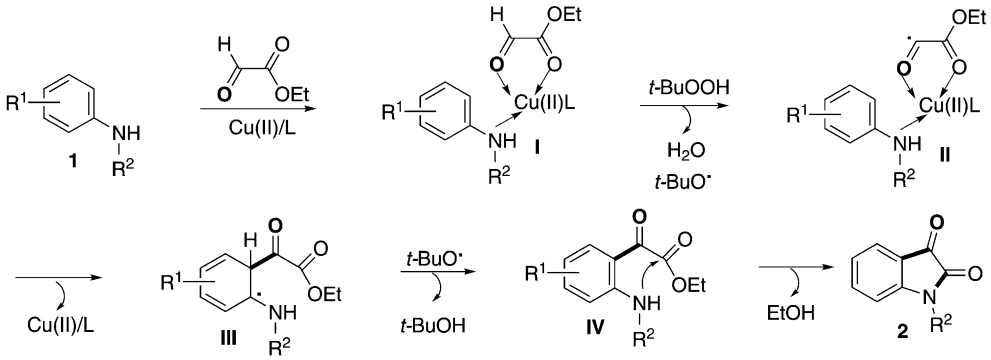
Entry	Temp./Time	**2**	Yield [%][b]
10	100 °C/24 h	 **2j**	64
11	100 °C/24 h	 **2k**  **2k′**	52: **2k**/**2k′** (2:1)
12	110 °C/48 h	 **2l**	49
13	110 °C/48 h	 **2m**	47
14	100 °C/24 h	 **2n**	65
15	100 °C/24 h	 **2o**	60
16	100 °C/24 h	 **2p**	52
17	110 °C/24 h	 **2q**	58
18	100 °C/24 h	 **2r**	42

Table 2. (Continued)

Entry	Temp./Time	2		Yield [%][b]
19	110 °C/24 h		**2s**	60
20	100 °C/24 h		**2t**	53

[a] Reaction conditions: secondary aniline (**1**) (0.25 mmol), ethyl glyoxalate in toluene (50%, 0.5 mmol), $Cu(OAc)_2$ (0.025 mmol), TBHP in decane (5.5 M, 0.375 mmol), nicotinic acid (0.05 mmol), toluene (1 mL), reaction temperature (100 or 110 °C), reaction time (24 or 48 h).
[b] Isolated yield.



Scheme 3. Possible mechanism for the copper-catalyzed oxidative synthesis of indoline-2,3-dione derivatives (**2**).

than acylation of the NH group. In addition, the decarbonylation of ethyl glyoxalate is suppressed because of efficient coordination of Cu(II) with the ethyl glyoxalate unit in **I** and **II**.

Conclusions

We have developed a novel and useful copper-catalyzed method for the synthesis of indoline-2,3-dione derivatives. The protocol uses inexpensive $Cu(OAc)_2$ as the catalyst, picolinic acid as the ligand, and *tert*-butyl hydroperoxide as the oxidant, readily available secondary anilines and ethyl glyoxalate as the starting materials, and the corresponding indoline-2,3-dione derivatives were prepared in moderate to good yields. The procedure involves intermolecular copper-catalyzed selective oxidative *ortho*-site aromatic acylation of the NH group in secondary anilines and intramolecular nucleophilic attack of the NH group to the ester. This is the first copper-catalyzed example for the synthesis of dicarbonyl compounds using ethyl glyoxalate as the dicarbonylating agent. Therefore, the inexpensive, easy and efficient method for the synthesis of dicarbonyl compounds should attract much attention in academic and industrial researches. Investigations on further application of this reaction are in progress.

Experimental Section

General Procedure for Synthesis of Compounds 2a–t

A 25-mL Schlenk tube was charged with a magnetic stirrer and toluene (1.0 mL). Secondary aniline (**1**) (0.25 mmol), ethyl glyoxalate in toluene (50%, 100 μL, 0.5 mmol), $Cu(OAc)_2$ (0.025 mmol, 5 mg), TBHP in decane (5.5 M, 70 μL, 0.375 mmol) and nicotinic acid (0.05 mmol, 6 mg) were added to the tube. The mixture was stirred at 100 or 110 °C for 24 or 48 h (see Table 2 for details). The resulting mixture was cooled to room temperature, the solvent was removed on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired target product (**2**). Three representative examples are shown below.

1-Isopropyl-5-methylindoline-2,3-dione (2c): Eluent: petroleum ether/ethyl acetate (10:1); yield: 29 mg (58%); red solid; mp 84–86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.41 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 4.52 (m, 1H), 2.32 (s, 3H), 1.51 (d, J = 8.0 Hz, 3H), 1.48 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 184.2, 158.0, 148.3, 138.6, 133.1, 126.0, 118.1, 111.3, 44.7, 20.6, 19.5; HR-MS (ESI): m/z = 226.0843, calcd. for $(C_{12}H_{13}NO_2+Na)^+$: 226.0844.

5-Methyl-1-*p*-tolylindoline-2,3-dione (2o): Eluent: petroleum ether/ethyl acetate (10:1); yield: 38 mg (60%); red solid; mp 157–159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.35 (m, 3H), 7.26 (d, J = 8.8 Hz, 3H), 7.72 (d, J = 8.1 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 183.4, 157.6, 149.8, 138.9, 138.8, 134.2, 130.6, 127.8, 125.8, 125.8, 117.6, 111.2, 21.3, 20.8; HR-MS (ESI): m/z = 274.0845, calcd. for $(C_{16}H_{13}NO_2+Na)^+$: 274.0844.

1-[3-(Trifluoromethyl)phenyl]-5-methylindoline-2,3-dione (2s): Eluent: petroleum ether/ethyl acetate (10:1); yield: 46 mg (60%); red solid; mp 192–194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.70–7.66 (m, 3H), 7.64–7.70 (m, 1H), 7.52 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H) 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 182.4, 157.3, 148.7, 139.1, 134.9, 133.9, 132.3 (J = 33.1 Hz), 130.7, 129.4, 126.2, 125.4 (J = 4.1 Hz), 121.7 (J = 290.0 Hz), 122.7 (J = 4.1 Hz), 117.7, 111.0, 20.8; HR-MS (ESI): m/z = 328.0558, calcd. for $(C_{16}H_{10}F_3NO_2+Na)^+$: 328.0561.

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