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Synthesis of Isocoumarin Derivatives via the Copper-Catalyzed Tandem Sequential Cyclization of 2- Halo-*N*-phenyl Benzamides and Acyclic 1,3-Diketones

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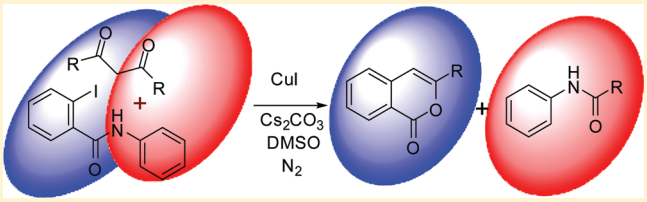
Supporting Information

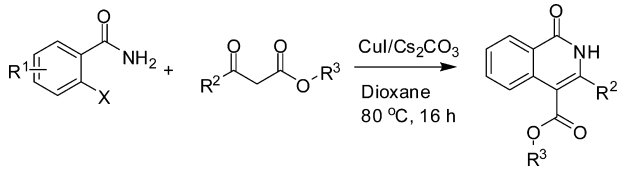
ABSTRACT: A facile and rapid synthesis of isocoumarin derivatives using a copper-catalyzed tandem C−C/C−O coupling strategy from readily available substrates is described. The reactions of a wide range of 2-iodo-*N*-phenyl benzamides and acyclic diketones as starting materials were investigated.



INTRODUCTION

Copper-catalyzed tandem sequential cyclization reactions are powerful tools for the construction of a wide variety of heterocyclic frame works.[1] A wide range of heterocycles including indoles, benzofurans, quinolines, isoqunolines, quinazalines, quinazolones, and many more heterocycles have been synthesized using this approach.[2] We also recently reported on a copper-catalyzed tandem cyclization leading to the synthesis of triazole fused sultum derivatives[3] In a continuation to our interest in copper-catalyzed tandem cyclization reactions, we wish to investigate the synthesis of isoquinolinone[4] derivatives using 2-halo-*N*-alkyl/aryl-benzamides and 1,3-dicarbonyl as the starting compounds. In fact, Wang et al. reported on the synthesis of isoquinolinone derivatives from the 2-halobenzamides and with various ketoesters (Scheme 1).[5] They did not, however, investigate the possibility of using 1,3-diketones as coupling partners with *N*-substituted-2-halobenzamides.

Scheme 1. Approach by Wang et al. to the Synthesis of Isoquinolin-1(2*H*)-one Derivatives



RESULTS AND DISCUSSION

To pursue our objective, we used 2-iodo- *N*-phenyl-benzamide and acetylacetone as model substrates. The reaction of 2-iodo-*N*-phenyl-benzamide and acetylacetone was conducted in the presence copper(I) iodide (10 mol %) and cesium carbonate in DMSO at 100 °C. After a 10 min reaction, the starting amide was completely consumed, and two products were produced. Both products were isolated and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. From the analytical data, the first product was determined to be 3-methylisocoumarin, and the second was acetanilide. The structure of the 3-methylisocoumarin product was further confirmed by single crystal X-ray analysis (Supporting Information). No trace of isoquinolinone derivative was observed in this reaction. This interesting result prompted us to investigate the reaction in more detail. Isocoumarins are an important class of heterocyclic scaffolds that exhibit a wide range of biological activities.[6] In addition, isocoumarin derivatives are useful precursors for the synthesis of various natural products and isoquinoline derivatives.[7] A plethora of methods are available for the construction of isocoumarin rings from various sources.[8] However, most of the reported procedures have drawbacks, which include the use of expensive catalysts such as palladium or rhodium, the need for complex starting materials, and drastic conditions. Therefore, an easy and handy method for the synthesis of isocoumarin derivatives would be highly desirable, considering the above drawbacks. Given this situation, we now report a new methodology for the rapid synthesis of isocoumarin derivatives by a copper-catalyzed one-pot sequential cyclization. While our manuscript was being prepared, we found two papers based on a similar concept for the synthesis of isocoumarin derivatives using 2-iodobenzoic acids[9] and methyl-2-iodobenzoates[10] as starting compounds. However, the conditions described in these protocols required quite long reaction times, and when substrates containing electron-withdrawing groups were used, the product yields were low.

The reaction is presumably initiated with the reaction of copper iodide and acetylacetone to produce a copper(I) complex, and the oxidative addition of 2-iodo-*N*-phenyl-

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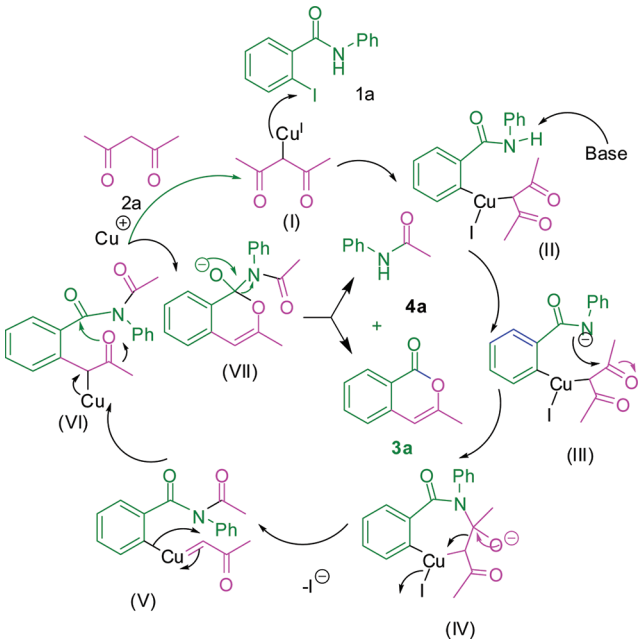
benzamide to this copper(I) complex results in the formation the Cu(III) intermediate (II). The base-mediated abstraction of the amidic proton from the intermediate (II) followed by the intramolecular nucleophilic addition of the amide nitrogen to one of the carbonyl groups of intermediate (III) produces the intermediate (IV). Since this intermediate (IV) is a charged species, it is unstable. Hence, it undergoes a C−C bond cleavage to furnish intermediate (V), which is further converted to intermediate (VI) via reductive elimination. The attack of acetylacetone on intermediate (VI) results in the regeneration of the copper catalyst and the formation of intermediate (VII). Intermediate (VII) then loses an acetanilide (**4a**) molecule to produce the isocoumarin derivative **3a** (Scheme 2). This

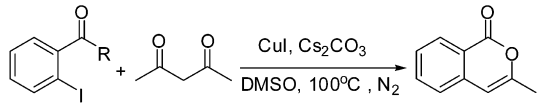
Scheme 2. Plausible Mechanistic Pathway



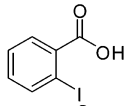
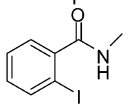
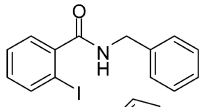
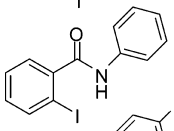
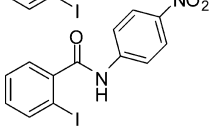
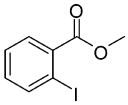
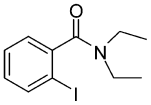
reaction mechanism is very similar to the mechanism proposed by Lei and co-workers for the reaction of aryl halides with acetyl acetone.[11] The difference here is the internal nucleophile (amidic nitrogen) attack on one of the carbonyl carbons of the Cu(III) complex, whereas in Lei's proposed mechanism the attack involves an external nucleophile (H_2O).

To determine if other 2-iodobenzoic acid derivatives, such as 2-iodobenzoic acid, methyl-2-iodobenzoate, and *N*-alkyl-2-iodobenzamide, could be used in this reaction, we examined the reaction of all of these derivatives with acetylacetone in the presence of the copper catalyst (CuI) and cesium carbonate in DMSO at 100 °C. The results were summarized in Table 1. As can be seen from the Table 1, when 2-iodo-benzoic acid was used in the reaction, the desired product was produced in moderate yield. In this case, however, the reaction time needed to be extended, compared with the use of amide derivatives such as 2-iodo-*N*-methyl-benzamide and *N*-benzyl-2-iodobenzamide. It should also be noted that the reaction of 2-iodo-*N*-phenyl-benzamide resulted in the production of high yields of the expected isocoumarin derivative within 10 min. When the reaction was performed with 2-iodo-*N*-(4-nitrophenyl)-benzamide under the present reaction conditions, the reaction completed in 10 min but yield of the product was 85%. The higher reactivity of 2-iodo-*N*-phenylbenzamides may be

Table 1. Reactions of Various 2-Benzoic Acid Derivatives with Acetylacetone



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

Entry[a]	1	Time (h)	Yield(%)[b]
1		2.5	58
2		0.5	67
3		0.5	75
4		0.16	98
4		0.16	85
5		24	Trace
6		24	N.R

[a]Reaction conditions: nitrogen atmosphere, **1** (0.5 mmol), **2a** (1 mmol), Cs_2CO_3 (1 mmol), CuI (0.05 mmol), DMSO (3 mL). [b]NMR yield with CH_2Br_2 as internal standard.

attributed to the stronger *ortho* effect of *N*-phenylamides.[12] It is interesting to note that the reactions of methyl-2-iodobenzoate and *N*,*N*-diethyl-2-iodobenzamide failed to give the expected products. However, Fan et al.[10] have obtained moderate yield of the product with methyl-2-bromobenzoate with the same catalyst in the presence of K_2CO_3 as base and DMF as solvent. The reason for this failure may be due to the absence of the nucleophilic oxygen or a nitrogen site in both entry 5 and entry 6. From all of the experiments described in Table 1, it is quite clear that 2-iodo-*N*-phenyl-benzamide derivatives are superior for the generation of isocoumarin derivatives. Hence, we then used a variety of substituted 2-iodo-*N*-phenyl-benzamide derivatives for the synthesis of a structurally diverse series of isocoumarin derivatives.

Encouraged by these initial observations, we first focused our attention on optimizing the reaction conditions. In this regard, we examined various solvents. The findings indicated that the reaction proceeded well in polar aprotic solvents such as DMF and DMSO, and moderate yields were obtained when acetonitrile was used. The poor yields were obtained when a nonpolar solvent, such as toluene, was used. The next screened various copper sources. The reaction was equally efficient when copper salts such as CuCl, CuBr, and CuI were used. We also tested various inorganic bases in the reaction. Both cesium

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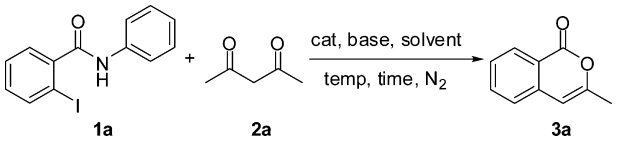
carbonate and potassium carbonate were found to be more efficient for this reaction (Table 2).

Table 2. Screening for Reaction Conditions



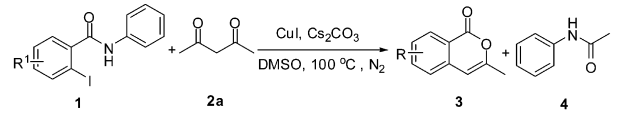
entry[a]	catalyst	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	CuI	Cs_2CO_3	toluene	90	40	50
2	CuI	Cs_2CO_3	dioxane	100	12	26
3	CuI	Cs_2CO_3	MeCN	60	19	95
4	CuI	Cs_2CO_3	DMF	100	0.5	81
5	CuI	Cs_2CO_3	DMSO	60	7	85
6	CuI	Cs_2CO_3	DMSO	80	2.5	93
7	**CuI**	**Cs_2CO_3**	**DMSO**	100	**0.16**	**98**
8	CuI	Cs_2CO_3	DMSO	100	0.5	85
9	CuI	K_2CO_3	DMSO	100	1.5	92
10	CuI	Na_2CO_3	DMSO	100	3	79
11	CuI	K_3PO_4	DMSO	100	49	16
12	CuCl	Cs_2CO_3	DMSO	100	0.5	90
13	CuBr	Cs_2CO_3	DMSO	100	0.5	87

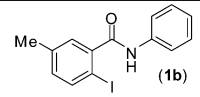
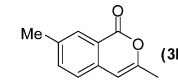
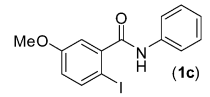
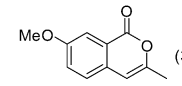
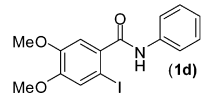
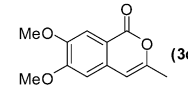
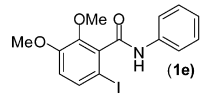
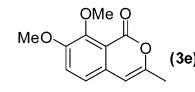
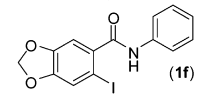
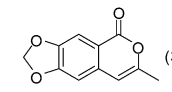
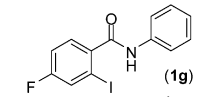
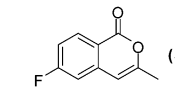
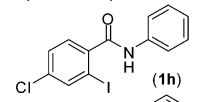
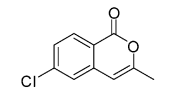
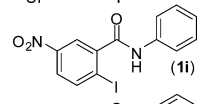
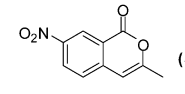
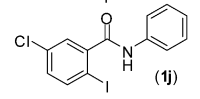
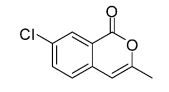
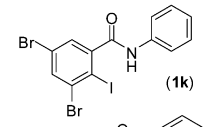
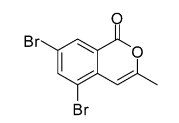
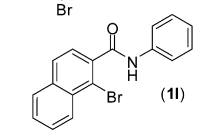
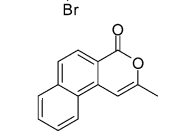
[a]Reaction conditions:nitrogen atmosphere, **1a** (0.5 mmol), **2a** (1 mmol), Cs_2CO_3 (1 mmol), CuI (0.05 mmol), solvent (3 mL). [b]NMR yields with CH_2Br_2 as internal standard.

With the optimal conditions in hand, the scope of the tandem sequential cyclization was then explored. The reaction of a variety of 2-iodo-*N*-phenyl-substituted benzamide derivatives with acetylacetone was initially examined, and the results are summarized in Table 3. Reactions of 2-iodo-*N*-phenyl-substituted benzamide derivatives containing electron-withdrawing or electron-donating groups with acetylacetone were performed under the optimized reaction conditions, and the corresponding isocoumarin derivatives were produced in good to excellent yields. It is noteworthy that when substrates that contained electron-releasing groups were used, the reaction required a longer time compared to reactions of substrates possessing electron-withdrawing groups. The reaction is very fast in the case of substrates with electron-withdrawing groups. In particular, substrates containing nitro and dibromo functional groups react rapidly to produce the corresponding product. It is important to note that products containing electron-withdrawing groups were very unstable under the reaction conditions used, and it was necessary to quench the reaction immediately after completion of the reaction. In the case of substrates having nitro and fluoro groups, the reaction was very rapid and the product also decomposed rapidly in the reaction medium.

Next, the scope of this reaction was extended to various 1,3-dicarbonyl compounds. When an unsymmetrical diketone such as 1-phenylbutane-1,3-dione was used as the coupling partner in the reaction with **1a**, we observed the formation of two isomeric products in which 3-phenylisocoumarin (56%) was the major product and 3-methylisocoumarin the minor product (10%). Reactions with symmetrical substituted diphenylpropane-1,3-dione derivatives gave a single product in moderate yields. Under the present reaction conditions, several unidentified products were produced when 3-methylpentane-2,4-dione and ethylacetoacetate were employed as substrates (Table 4).

Table 3. Scope of the Reaction with Respect to Various 2-Iodo-*N*-phenyl-benzamides



Entry[a]	Amide	Product	Time (min)	Yield (%)[b]
1	 (1b)	 (3b)	15	74
2	 (1c)	 (3c)	15	87
3	 (1d)	 (3d)	30	85
4	 (1e)	 (3e)	60	70
5	 (1f)	 (3f)	30	72
6	 (1g)	 (3g)	10	69
7	 (1h)	 (3h)	15	70
8[c]	 (1i)	 (3i)	5	76
9	 (1j)	 (3j)	15	83
10	 (1k)	 (3k)	5	85
11	 (1l)	 (3l)	60	94

[a]Reaction conditions: nitrogen atmosphere, **1** (1 mmol), **2a** (2 mmol), Cs_2CO_3 (2 mmol), CuI (0.1 mmol), DMSO (3 mL). [b]Isolated yields. [c]Reaction performed at 80 °C.

To further demonstrate the generality of our methodology, we utilized 2-bromo-*N*-phenyl-benzamide and 2-chloro-*N*-phenyl-benzamide as substrates. To our delight, both substrates gave the corresponding product within very short time (Scheme 3). This reaction trend is also consistent with the stronger *ortho* effect of *N*-phenylamides.[13]

Pyranoquinoline is one of the prominent structural motifs found in alkaloids extracted from rutaceae plants.[14] Derivatives of pyranoquinoline compounds are known to exhibit a wide range of pharmacological and biological activities and can have antiallergic, anticoagulant, coronary constricting, and antihistamic effects.[15] Considering the importance of the pyranoquino-

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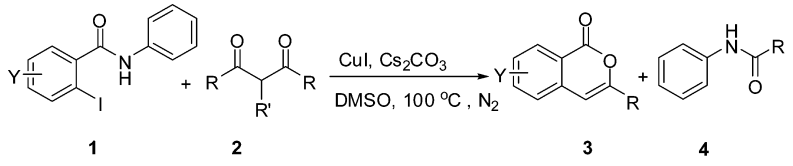
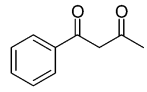
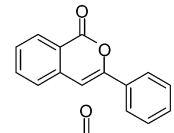
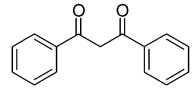
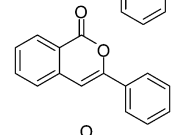
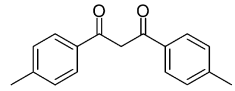
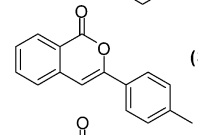
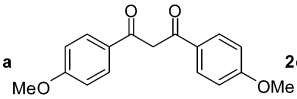
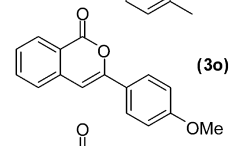
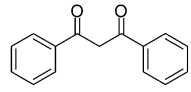
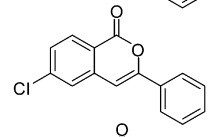
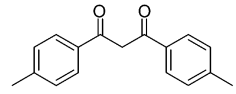
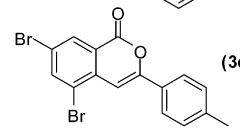
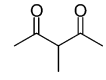
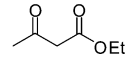
Table 4. Scope of the Reaction with Respect to Various 1,3-Diketones

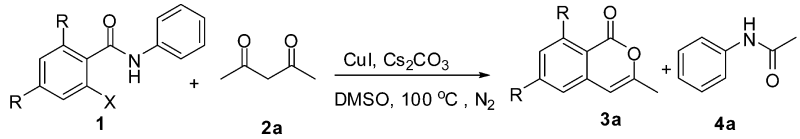


1 2 3 4

Entry[a]	Amide	Diketone	Product		Time (min)	Yield (%)[b]
1	1a		2b	 (3m)	30	56
2	1a		2c	 (3m)	30	64
3	1a		2d	 (3n)	10	65
4	1a		2e	 (3o)	15	80
7	1h		2c	 (3p)	30	68
8	1k		2d	 (3q)	15	70
5	1a		2f	Complex mixture	30	-
6	1a		2g	Complex mixture	30	-

[a]Reaction conditions: nitrogen atmosphere, **1** (1 mmol), **2** (1.2 mmol), Cs_2CO_3 (2 mmol), CuI (0.1 mmol), DMSO (3 mL). [b]Isolated yields.

Scheme 3. Reaction of Chloro and Bromo Benzamides with Acetylacetone



1 2a 3a 4a

	R	X	Product	Reaction time (min)	Yield (%)
1m	H	Br	(3a)	10	83
1n	H	Cl	(3a)	15	81
1o	Cl	Cl	(3r)	25	67

line derivatives, we attempted to synthesize these derivatives using the present method. Starting materials such as 2-chloro-*N*-phenylquinoline-3-carboxamide derivatives were synthesized in four steps, starting from aniline, by following established procedures.[16] These 2-chloro-*N*-phenylquinoline-3-carboxamide derivatives were treated with acetylacetone under the optimized reaction conditions, and pyarnoquinolinone derivatives were produced in good yields (Table 5). As can be seen in Table 5, it is important to note that all of the 2-chloro-*N*-phenylquinoline-3-carboxamide derivatives participated in the reaction with equal ease to produce the corresponding pyranoquinolinone derivatives. It should also be noted that the present methodology can also be used in the synthesis of benzopyranoquinolinone derivatives. The structure of the newly synthesized pyranoquinolinone derivatives were con-

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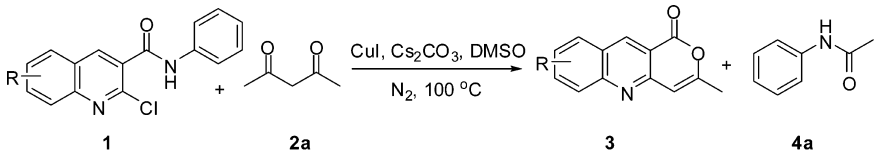
Table 5. Synthesis of Pyranoquinolinone Derivatives



Entry[a]	Starting Material	Product	Time (min)	Yield(%)[b]
1	1p	3s	15	68
2	1q	3t	25	67
3	1r	3u	25	75
4	1s	3v	20	60

[a]Reaction conditions: nitrogen atmosphere, **1** (1 mmol), **2a** (2 mmol), Cs_2CO_3 (2 mmol), CuI (0.1 mmol), DMSO (3 mL). [b]Isolated yield.

firmed by the single crystal X-ray analysis of a representative sample, namely, compound **3s** (Figure 1).

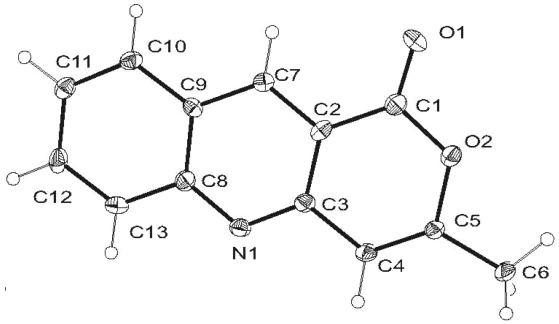
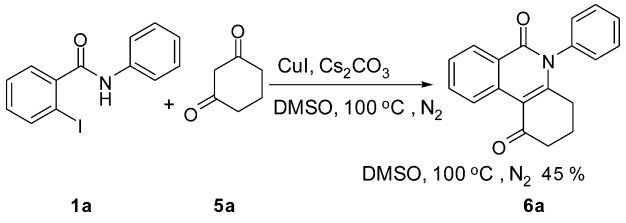


Figure 1. Single crystal structure of compound **3s**.

Finally, we carried out the reaction of 2-iodo-*N*-phenyl-benzamide with a cyclic diketone 1,3-cyclohexadione using the present reaction conditions (Scheme 4). To our delight, an isoquinolinone derivative was produced (Figure 2). This outcome is very different from reactions involving acyclic ketones.

In summary we report herein on the efficient rapid synthesis of isocoumarin derivatives by employing copper-catalyzed tandem C−C/C−O coupling transformation as the key step. A remarkable number of 2-iodo-*N*-phenyl-benzamides with a

Scheme 4. Reaction of 2-Iodo-*N*-phenyl-benzamide with 1,3-Cyclohexadione



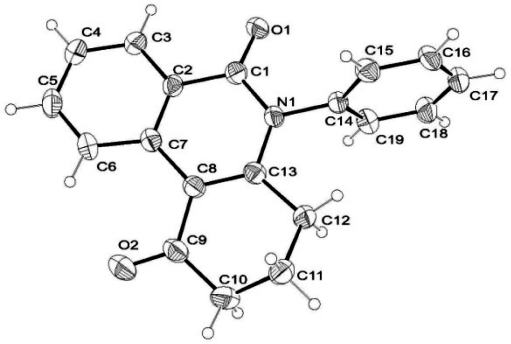


Figure 2. Single crystal structure of compound **6a**.

variety of different electronic properties and various 1,3-diketones could be successfully used to access structurally diverse isocoumarin derivatives in good to excellent yields. In addition, this methodology can also be utilized for the synthesis of various pyranoquinolinone derivatives, which are important constituents in many pharmaceutically active substances. Interestingly, the reaction involving 1,3-cyclohexadione gave an isoquinolinone derivative. Further investigations of the scope of this reaction are currently underway in our laboratory.

EXPERIMENTAL SECTION

All chemicals were purchased from various sources and used directly without further purification. Analytical thin-layer chromatography was performed using silica gel 60F glass plates and gel 60 (230−400 mesh) was used in flash chromatography separations. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz), and coupling constants are expressed in hertz. HRMS spectra were recorded using ESI-TOF or EI^+ mode. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

General Procedure. A 25 mL round-bottom flask was charged with a magnetic stirrer and 3 mL of DMSO. Substituted *N*-pheny-2-halobenzamide (1 mmol), 1,3-diketone (1.2 mmol), copper(I) iodide (10 mol %), and cesium carbonate (2 mmol) were then added to the

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flask. The reaction solution was stirred at 100 °C under N_2 until the reaction was complete as evidenced by TLC. After completion of the reaction, the resulting solution was transferred to a beaker containing crushed ice, and the resulting solid was isolated on a filter. In most cases, the isolated solid contained only the isocoumarin derivative (**3**) and the amide remained in the solution (**4**). In a very few cases the solid was a mixture of the products. In such cases, the crude product was purified by column chromatography (ethylacetate/hexane) on silica gel.

Spectral Data. 3-Methyl-1*H*-isochromen-1-one (3a). Pale yellow solid; 144.2 mg (90%); mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.96 Hz, 1H), 7.66 (td, J = 7.60, 1.13 Hz, 1H), 7.46−7.42 (m, 1H), 7.33 (d, J = 7.84 Hz, 1H), 6.25 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 154.7, 137.8, 134.8, 129.6, 127.6, 125.0, 120.0, 103.6, 19.7; MS (ESI) m/z (relative intensity) 161 (M + H, 100), 143 (18). HRMS (ESI) m/z calcd for $C_{10}H_8O_2$ (M + H) 161.0603, found 161.0603.

3,7-Dimethyl-1*H*-isochromen-1-one (3b). White solid; 128.9 mg (74%); mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.48 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 6.22 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 153.8, 137.8, 136.2, 135.3, 129.3, 124.9, 119.9, 103.5, 21.4, 19.7; MS (ESI) m/z (relative intensity) 175 (M + H, 100), 147 (2). HRMS (ESI) m/z calcd for $C_{11}H_{10}O_2$ (M + H) 175.0759, found 175.0747.

7-Methoxy-3-methyl-1*H*-isochromen-1-one (3c). White solid; 165.5 mg (87%); mp 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.27 (d, J = 1.08 Hz, 2H), 6.22 (s, 1H), 3.89 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 159.1, 152.4, 131.4, 126.5, 124.5, 121.0, 109.9, 103.2, 55.7, 19.5; MS (ESI) m/z (relative intensity) 191 (M + H, 100), 173 (4), 145 (2). HRMS (ESI) m/z calcd for $C_{11}H_{10}O_3$ (M + H) 191.0708, found 191.0705.

6,7-Dimethoxy-3-methyl-1*H*-isochromen-1-one (3d). Blue solid; 187.3 mg (85%); mp 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 6.70 (s, 1H), 6.18 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 155.3, 153.6, 149.4, 133.5, 113.1, 109.6, 105.7, 103.3, 56.4, 56.3, 19.7; MS (EI) m/z (relative intensity) 220 (M^+, 100), 171 (68), 170 (64), 149 (16), 115 (6). HRMS (EI) m/z calcd for $C_{12}H_{12}O_4$ (M^+) 220.0736, found 220.0739.

7,8-Dimethoxy-3-methyl-1H-isochromen-1-one (3e). Pale yellow solid; 154.2 mg (72%); mp 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d,, J = 9.2 Hz, 1H), 7. 02 (d,, J = 9.2 Hz, 1H), 6.11(s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 152.6, 152.3, 151.2, 132.5, 120.7, 120.4, 114.6, 103.2, 61.7, 56.8, 19.5; MS (EI) m/z (relative intensity) 220 (M^+, 100), 205(74), 191 (46), 147 (16). HRMS (EI) m/z calcd for $C_{12}H_{12}O_4$ (M^+) 220.0736, found 220.0740.

7-Methyl-5*H*-[1,3]dioxolo[4,5-*g*]isochromen-5-one (3f). Pale pink solid; 147.4 mg (72%); mp 187−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.70 (s, 1H), 6.14 (s, 1H), 6.07 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 153.8, 153.7, 148.0, 135.5, 114.6, 107.5, 103.7, 103.6, 102.2, 19.6; MS (EI) m/z (relative intensity) 204 (M^+, 44), 162 (27), 133 (32). HRMS (EI) m/z calcd for $C_{11}H_8O_4$ (M^+) 204.0423, found 204.0422.

6-Fluoro-3-methyl-1*H*-isochromen-1-one (3g). Colorless solid; 123.2 mg (69%); mp 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.22 (m, 1H), 7.11 (td, J = 8.62, 2.33 Hz, 1H), 6.96 (dd, J = 8.92, 2.30 Hz, 1H), 6.20 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (d, J_{C-F} = 255 Hz), 162.1, 156.2, 140.5 (d, J_{C-F} = 10 Hz), 133.0 (d, J_{C-F} = 11 Hz), 116.6, 115.9 (d, J_{C-F} = 23 Hz), 110.6 (d, J_{C-F} = 22 Hz), 103.2 (d, J_{C-F} = 3 Hz), 19.8; MS (EI) m/z (relative intensity) 178 (M^+, 100), 136 (23), 107 (23). HRMS (EI) m/z calcd for $C_{10}H_7FO_2$ (M^+) 178.0430, found 178.0435.

6-Chloro-3-methyl-1*H*-isochromen-1-one (3h). White solid; 134.3 mg (70%); mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.44 Hz, 1H), 7.39 (dd, J = 8.52, 1.98 Hz, 1H), 7.32 (d, J = 1.88 Hz, 1H), 6.18 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 156.2, 141.5, 139.1, 131.3, 128.2, 124.5, 118.4, 102.8, 19.9; MS (ESI) m/z (relative intensity) 195 (M + H, 26), 172 (21), 150 (100), 161 (12), 136 (6). HRMS (ESI) m/z calcd for $C_{10}H_7ClO_2$ (M + H) 195.0213, found 195.0199.

3-Methyl-7-nitro-1*H*-isochromen-1-one (3i). Yellow solid; 156.6 mg (76%); mp 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 2.12 Hz, 1H), 8.47 (dd, J = 8.72, 2.36 Hz, 1H), 7.49 (d, J = 8.64 Hz, 1H), 6.38 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.0, 146.8, 142.7, 129.1, 126.4, 125.8, 120.4, 103.1, 20.1; MS (EI) m/z (relative intensity) 205 (M^+, 100), 175 (26), 159 (16), 103 (13). HRMS (EI) m/z calcd for $C_{10}H_7NO_4$ (M^+) 205.0375, found 205.0373.

7-Chloro-3-methyl-1*H*-isochromen-1-one (3j). Colorless solid; 161.8 mg (83%); mp 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 1.88 Hz, 1H), 7.61 (dd, J = 8.40, 2.14 Hz, 1H), 7.28 (d, J = 8.40 Hz, 1H), 6.23 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 155.1, 136.1, 135.2, 133.3, 129.0, 126.6, 121.2, 103.0, 19.8; MS (EI) m/z (relative intensity) 194 (M^+, 100), 152 (22), 123 (17), 102 (3). HRMS (EI) m/z calcd for $C_{10}H_7ClO_2$ (M^+) 194.0135, found 194.0133.

5,7-Dibromo-3-methyl-1*H*-isochromen-1-one (3k). Pale yellow solid; 270.7 mg (85%); mp 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 1.68 Hz, 1H), 8.02 (d, J = 2.00 Hz, 1H), 6.57 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 156.5, 140.7, 136.0, 131.6, 122.4, 120.7, 120.3, 102.0, 20.2; MS (EI) m/z (relative intensity) 320 (M^+ + 4, 54), 318 (M^+ + 2, 100), 315 (M^+, 44), 275 (11), 239 (13), 237 (12), 170 (34), 102 (7). HRMS (EI) m/z calcd for $C_{10}H_6Br_2O_2$ (M^+) 315.8735, found 315.8737.

2-Methyl-4*H*-benzo[*f*]isochromen-4-one (3l). Colorless solid; 197.8 mg (94%); mp 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.36 Hz, 1H), 8.20 (d, J = 8.72 Hz, 1H), 7.92 (d, J = 8.44 Hz, 1H), 7.83 (d, J = 8.72 Hz, 1H), 7.72−7.64 (m, 2H), 7.04 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 156.3, 137.0, 136.1, 129.4, 128.9, 127.9, 127.4, 127.2, 124.2, 124.1, 116.8, 99.5, 20.3; MS (ESI) m/z (relative intensity) 211 (M + H, 100), 195 (7), 122 (3). HRMS (ESI) m/z calcd for $C_{14}H_{10}O_2$ (M + H) 211.0759, found 211.0754.

3-Phenyl-1*H*-isochromen-1-one (3m). Pale yellow solid; 142.5 mg (64%); mp 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.20 Hz, 1H), 7.90−7.88 (m, 2H), 7.72 (td, J = 7.60, 0.96 Hz, 1H), 7.52−7.43 (m, 5H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 153.7, 137.6, 134.9, 132.0, 130.0, 129.7, 128.9, 128.2, 126.1, 125.3, 120.6, 101.9; MS (ESI) m/z (relative intensity) 223 (M + H, 100), 201 (10), 195 (5). HRMS (ESI) m/z calcd for $C_{15}H_{10}O_2$ (M + H) 223.0759, found 223.0734.

3-(*p*-Tolyl)-1*H*-isochromen-1-one (3n). White solid; 153.9 mg (65%); mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.04 Hz, 1H), 7.78 (d, J = 8.08 Hz, 2H), 7.70 (t, J = 7.62 Hz, 1H), 7.50−7.46 (m, 2H), 7.27 (d, J = 8.08 Hz, 2H), 6.91 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 154.0, 140.4, 137.9, 134.9, 129.8, 129.7, 129.4, 128.0, 126.0, 125.3, 120.6, 101.2, 21.5; MS (EI) m/z (relative intensity) 236 (M^+, 100), 208 (74), 165 (22), 152 (3), 119 (4). HRMS (EI) m/z calcd for $C_{16}H_{12}O_2$ (M^+) 236.0837, found 236.0838.

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (3o). White solid; 201.8 mg (80%); mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.36 Hz, 1H), 7.83 (d, J = 9.00 Hz, 2H), 7.72−7.67 (m, 1H), 7.48−7.44 (m, 2H), 6.98 (d, J = 8.88 Hz, 2H), 6.84 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.3, 153.9, 138.1, 135.0, 129.8, 127.8, 127.0, 125.9, 124.7, 120.3, 114.4, 100.4, 55.6; MS (EI) m/z (relative intensity) 252 (M^+, 100), 224 (60), 181 (17), 152 (9), 112 (5). HRMS (EI) m/z calcd for $C_{16}H_{12}O_3$ (M^+) 252.0786, found 252.0780.

6-Chloro-3-phenyl-1*H*-isochromen-1-one (3p). White solid; 175.2 mg (68%); mp 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.44 Hz, 1H), 7.88−7.86 (m, 2H), 7.48−7.43 (m, 5H), 6.88(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 155.2, 141.7, 139.1, 131.8, 131.5, 130.6, 129.1, 128.8, 125.6, 119.0, 101.0; MS (EI) m/z (relative intensity) 256 (M^+, 60), 211 (84), 193 (15), 165 (21), 119 (100). HRMS (EI) m/z calcd for $C_{15}H_9ClO_2$ (M^+) 256.0291, found 256.0297.

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5,7-Dibromo-3-(*p*-tolyl)-1*H*-isochromen-1-one (3q). Greenish yellow solid; 275.8 mg (70%); mp 216−218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.06 (d, J = 1.84 Hz, 1H), 7.80 (d, J = 8.28 Hz, 2H), 7.29 (d, J = 8.24 Hz, 2H), 7.19 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 155.5, 141.4, 141.0, 136.3, 131.9, 129.9, 128.8, 125.7, 122.9, 121.3, 121.0, 99.4, 21.7; MS (EI) m/z (relative intensity) 396 (M^+ + 4, 58), 394 (M^+ + 2, 100), 391 (M^+, 58), 366 (55), 178 (10), 119 (12). HRMS (EI) m/z calcd for $C_{16}H_{10}Br_2O_2$ (M^+) 391.9048, found 391.9054.

6,8-Dichloro-3-methyl-1*H*-isochromen-1-one (3r). Colorless solid; 158.7 mg (70%); mp 163−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 1.72 Hz, 1H), 7.20 (d, J = 1.68 Hz, 1H), 6.14 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.0, 141.6, 138.4, 130.4, 123.6, 115.6, 102.9, 19.7; MS (EI) m/z (relative intensity) 228 (M^+, 100), 213 (38), 157 (30). HRMS (EI) m/z calcd for $C_{10}H_6Cl_2O_2$ (M^+) 227.9745, found 227.9743.

3-Methyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3s). Yellow solid; 143.9 mg (68%); mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.09 (d, J = 8.96 Hz, 1H), 7.98 (d, J = 8.20 Hz, 1H), 7.90−7.85 (m, 1H), 7.61−7.57 (m, 1H), 6.61 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 158.6, 152.7, 151.6, 140.5, 133.4, 129.6, 129.1, 127.0, 126.9, 115.1, 106.0, 20.2; HRMS (ESI) m/z calcd for $C_{13}H_9NO_2$ (M + H) 212.0711, found 212.0703; MS (ESI) m/z (relative intensity) 212 (M + H, 100), 202 (20), 184 (55), 156 (15).

8-Methoxy-3-methyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3t). Yellow solid; 161.6 mg (67%); mp 232−234 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.98 (d, J = 9.32 Hz, 1H), 7.52 (dd, J = 9.28, 2.66 Hz, 1H), 7.17 (d, J = 2.56 Hz, 1H), 6.57 (s, 1H), 3.96 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.1, 157.5, 150.8, 148.2, 138.5, 130.5, 128.1, 127.2, 115.3, 106.0, 105.8, 55.9, 20.2; HRMS (EI) m/z calcd for $C_{14}H_{11}NO_3$ (M^+) 241.0739, found 241.0744; MS (EI) m/z (relative intensity) 241 (M^+, 100), 226 (35), 198 (22), 170 (12), 119 (22).

3,6-Dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3u). Pale brown solid; 168.6 mg (75%); mp 188−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.80 (d, J = 8.24 Hz, 1H), 7.70 (d, J = 6.6 Hz, 1H), 7.46 (t, J = 7.50 Hz, 1H), 6.66 (s, 1H), 2.81 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.0, 151.7, 150.8, 140.5, 137.3, 133.2, 127.5, 126.9, 126.6, 114.8, 106.6, 20.2, 18.2; HRMS (EI) m/z calcd for $C_{14}H_{11}NO_2$ (M^+) 225.0790, found 225.0793; MS (EI) m/z (relative intensity) 225 (M^+, 100), 182 (11), 154 (13), 127 (3).

10-Methyl-8*H*-benzo[*h*]pyrano[4,3-*b*]quinolin-8-one (3v). Yellow solid; 156.7 mg (60%); mp 262−264 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34−9.32 (m, 1H), 9.00 (s, 1H), 7.92−7.90 (m, 1H), 7.81−7.73 (m, 4H), 6.76 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 158.4, 152.4, 151.3, 138.7, 135.3, 130.9, 130.2, 128.4, 128.2, 127.6, 125.9, 125.7, 125.5, 115.1, 106.6, 20.2; HRMS (EI) m/z calcd for $C_{17}H_{11}NO_2$ (M^+) 261.0790, found 261.0795; MS (EI) m/z (relative intensity) 261 (M^+, 100), 246 (10), 219 (7), 190 (17), 171 (7), 163 (3), 127(3), 111 (3).

5-Phenyl-3,4-dihydrophenanthridine-1,6(2*H*,5*H*)-dione (6a). Pale yellow solid; 130.3 mg (45%); mp 187−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, J = 8.52 Hz, 1H), 8.40 (dd, J = 7.96, 1.34 Hz, 1H), 7.79−7.74 (m, 1H), 7.59−7.49 (m, 4H), 2.62 (t, J = 6.66 Hz, 2H), 2.51 (t, J = 6.18 Hz, 2H), 2.05−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 162.9, 154.3, 138.3, 134.4, 133.9, 130.1, 129.3, 128.4, 127.9, 127.2, 126.5, 124.8, 111.6, 39.8, 30.5, 21.2; HRMS (ESI) m/z calcd for $C_{19}H_{15}NO_2$ (M + H) 290.1181, found 290.1184; MS (ESI) m/z (relative intensity) 290 (M + H, 100), 288 (4).

***N*-Phenylacetamide(4a).** Pale yellow solid; mp 114−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.96 Hz, 2H), 7.31 (t, J = 7.66 Hz, 3H), 7.10 (t, J = 7.34 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 138.1, 129.1, 124.4, 120.2, 24.6; HRMS (ESI) m/z calcd for C_8H_9NO (M + H) 136.0762, found 136.0746; MS (ESI) m/z (relative intensity) 136 (M + H, 100).

4-Methyl-*N*-phenylbenzamide(4b). Greenish yellow solid; mp 142−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.12 Hz, 3H), 7.63 (d, J = 7.64 Hz, 2H), 7.37 (t, J = 7.94 Hz, 2H), 7.28 (d, J = 7.84 Hz, 2H), 7.16−7.12 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 142.5, 138.2, 132.3, 129.5, 129.2, 127.2, 124.6, 120.4, 21.6; MS (EI) m/z (relative intensity) 211 (M^+, 65), 167 (1), 119 (100); HRMS (EI) m/z calcd for $C_{14}H_{13}NO$ (M^+) 211.0997, found 211.0994.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data of compound **3a**, **3l**, **3q**, and **6a** in CIF format and copies of ^{1}H and ^{13}C NMR spectra of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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