JOC The Journal of Organic Chemistry

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Kelu Yan, Daoshan Yang, Wei Wei, Fen Wang, Yuanyuan Shuai, Qiannan Li, and Hua Wang J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/jo502474z • Publication Date (Web): 06 Jan 2015
 Downloaded from http://pubs.acs.org on January 12, 2015

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Silver-Mediated Radical Cyclization of Alkynoates and α-Keto Acids Leading to Coumarins via Cascade Double C-C Bond Formation

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ABSTRACT: A novel and convenient silver-mediated radical cyclization method for the synthesis of coumarin derivatives via the direct difunctionalization of alkynoates with α -keto acids through double C-C bond formation under mild conditions has been developed. This new method is highly efficient and practical, and the starting materials are readily prepared. The present method should provide a useful strategy for the construction of coumarin motifs.

INTRODUCTION:

The coumarin nucleus is a key core structure that widely occurs in natural products, biological molecules and they are also widely used in material chemistry.¹ Importantly,

coumarin derivatives are well documented as therapeutic agents and possess a variety of pharmacological properties, such as antitumour,² antimalarial,³ anticoagulant,⁴ antimicrobial,⁵ and anti-HIV properties⁶ (Scheme 1). Thus, development of novel and efficient methods for construction of these compounds will be great value for the screening of novel biologically active molecules. The conventional methods for the preparation of coumarins typically involve three approaches, including the Pechmann reaction,⁷ the Wittig reaction,⁸ and the Knoevenagel condensation.⁹ In 2008, Gabriele and co-workers developed a palladium-catalyzed dicarbonylation process to construct coumarins using 2-(1-hydroxyprop-2-ynyl)phenols as substrates.¹⁰ Despite these methods have made various successes, the harshness of strong acid conditions and the uneasily available precursors could limit their wide applications. Therefore, more effective processes are needed. Transition-metal-catalyzed transformations are useful Recently, Heck cross-couplings,¹¹ chemistry. tools Suzuki organic in cross-couplings,¹² and Pd-catalyzed site-selective cross-coupling reactions¹³ have emerged as attractive methods for the synthesis of coumarin derivatives. However, challenges still remain, it is still highly desirable to develop new strategies to prepare functionalized coumarins that are utilizing inexpensive substrates and proceeding under mild conditions.

As one of the promising synthesis strategies, direct difunctionalization of alkynes has attracted considerable attention, due to its high efficiency in the cascade formation of carbon-carbon or carbon-heteroatom bonds. In this field, some excellent difunctionalization reactions such as halosulfonylation,¹⁴ *ipso*-Carboacylation,¹⁵

arylphosphorylation,¹⁶ and oxyvinylcyclization¹⁷ have been significantly disclosed. Also, as a valuable functional group, carbonyl functionality is widely used in organic chemistry. Consequently, the introduction of carbonyl group into organic framework strongly attracts synthetic pursuit of chemists.¹⁸ Nevertheless, up to date, very few strategies for the fabrication of carbonyl compounds have been developed via the difunctionalization of alkynes.^{15a, 15c, 15d} In addition, recent years have witnessed significant efforts devoted to the development of decarboxylative reactions using carboxylic acids as the coupling partners, owing to that those substrates are readily available and stable, and besides that, CO₂ is the sole waste product from the transformation.¹⁹ For example, Jafarpour and co-workers developed an elegant work for the synthesis of coumarins via palladium-catalyzed decarboxylative arylation and alkenylation of coumarin-3-carboxylic acids.²⁰ Among all the carboxylic acids, α -keto acids have been emerging as appealing coupling partners in decarboxylative reactions. In 2008, Gooßen and co-workers firstly reported a Cu/Pd-catalyzed decarboxylative cross-coupling of α -keto carboxylate salts with any bromides to afford diary ketones.²¹ Since then, about the α -keto acids decarboxylative reaction has been extensively studied.²² Meanwhile, about the α -keto acids decarboxylative reactions via radical pathways have also been widely explored, such as difunctionalization of activated alkenes,²³ acylfluorination of styrenes,²⁴ and acyloxylation of sp^{3} C–H Bond.²⁵ Inspired and encouraged by these excellent works and with our interest in heterocycles synthesis via radical pathways,²⁶ we herein describe a new silver-mediated direct carbonylation of alkynes with α -keto acids towards

3-carbonylated coumarins under mild conditions.

Scheme 1. Some representative compounds containing the coumarin motif



RESULTS AND DISCUSSION

Initially, phenyl 3-phenylpropiolate (**1a**) and 2-oxo-2-phenylacetic acid (**2a**) were chosen as the model substrates to optimize reaction conditions including the catalysts, oxidants and solvents under nitrogen atmosphere. As shown in Table 1, five oxidants such as Na₂S₂O₈, K₂S₂O₈, (NH₄)₂S₂O₈, TBHP and O₂ were investigated at 60 °C by using 1.0 equiv of AgNO₃ (relative to amount of 2a) in 2 mL CH₃CN/H₂O (v_1/v_2 =1:1), and K₂S₂O₈ gave the highest yield (75%) (entries 1-5, Table 1). Furthermore, the silver salts, including AgNO₃, Ag₂O, Ag₂CO₃ and AgOAc were tested in CH₃CN/H₂O (entries 5-8, Table 1) using K₂S₂O₈ as the oxidant at 60 °C, and AgNO₃ was found to be the most effective catalyst (entries 5-9, Table 1). We attempted to use different solvents, and CH₃CN/H₂O was superior to the others (compare entries 5, 10-12, Table 1). Various reaction temperatures were attempted (entries 5, 13 and 14, Table 1), and 60 °C was found to be suitable for this reaction (entry 5, Table 1). Notably, elevated

temperature didn't obviously enahance the yield (entry 15, Table 1). Additionally,

Table 1. Silver-mediated synthesis of 3-benzoyl-4-phenyl-2*H*-chromen-2-one via cascade reaction of phenyl 3-phenylpropiolate with 2-oxo-2-phenylacetic acid: optimization of the catalysis conditions^a

		HOOC	xidant t, temp.	
	✓ O O 1a	2a	3a	, , ,
entry	catalyst	oxidant	solvent	yield ^b (%)
1	AgNO ₃	$Na_2S_2O_8$	CH ₃ CN:H ₂ O	57
2	AgNO ₃	$(NH_4)_2S_2O_8$	CH ₃ CN:H ₂ O	40
3	AgNO ₃	TBHP	CH ₃ CN:H ₂ O	20
4	AgNO ₃	O_2	CH ₃ CN:H ₂ O	trace
5	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	75
6	Ag ₂ O	$K_2S_2O_8$	CH ₃ CN:H ₂ O	44
7	Ag ₂ CO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	46
8	AgOAc	$K_2S_2O_8$	CH ₃ CN:H ₂ O	49
9	None	$K_2S_2O_8$	CH ₃ CN:H ₂ O	16
10	AgNO ₃	$K_2S_2O_8$	DMSO :H ₂ O	31
11	AgNO ₃	$K_2S_2O_8$	H_2O	trace
12	AgNO ₃	$K_2S_2O_8$	DMF: H ₂ O	32
13	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	38 ^c
14	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	58 ^d
15	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	76 ^e
17	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	39 ^f
18	AgNO ₃	$K_2S_2O_8$	CH ₃ CN:H ₂ O	56 ^g

^a Reaction conditions: under nitrogen atmosphere, **1a** (0.3mmol), **2a** (0.6 mmol), catalyst (0.3 mmol), oxidant (4.0 equiv.), solvent 2 mL CH₃CN/H₂O ($v_1/v_2=1:1$), 60°C and reaction time (24 h). TBHP= te*rt*-butyl hydroperoxide solution 5.5M in decane. ^b Isolated yield. ^c Reaction temperature (30°C). ^d Reaction temperature (50°C). ^d Reaction temperature (50°C). ^e Reaction temperature (70°C). ^f AgNO₃ (0.06mmol). ^gAgNO₃ (0.18 mmol).

the amount of AgNO₃ was rationally changed (compare entries 5, 17 and 18, Table 1), and 1.0 equiv of AgNO₃ provided the highest yield. After the optimization process for catalysts, oxidants, solvents and temperature, the various coumarin derivatives were synthesized under our standard conditions: 1.0 equiv of AgNO₃ as the promoter, 4.0 equiv of K₂S₂O₈ as the oxidant, and 2 mL CH₃CN/H₂O(v₁/v₂=1:1) as the solvent at 60° C under nitrogen atmosphere.



Table 2. Sliver-mediated synthesis of coumarin derivatives *via* radical cyclization of alkynoates with α -keto acids ^{*a,b,c*}

^{*a*} Reaction conditions: under nitrogen atmosphere, substituted alkynoates (0.3 mmol), α-keto acids (0.6 mmol), AgNO₃(0.3 mmol), K₂S₂O₈ (1.2 mmol), CH₃CN/H₂O(v₁/v₂=1:1) (2.0 mL), 60°C. ^{*b*} Isolated yield. ^{*c*} Reaction time (24 h).

With the optimum reaction conditions in hand, we investigated the scope of substrates for the silver-mediated radical cyclization of substituted alkynoates (1) with α -keto acids (2) leading to coumarin derivatives (3). As shown in Table 2, the tested substrates afforded moderate to good yields. For the substituted α -keto acids which bearing electron withdrawing group, such as -Cl and -Br (Table 2, 3d, 3h, 3o and 3t) could give slight good yields as compared to the α -keto acids with the electron donating substituents (Table 2, 3g, 3n and 3r). For the substituted alkynoates, the electron-withdrawing as well as electron-donating substituents did not significantly affect the catalytic activity. With a strong electron-withdrawing substituent (CF_3) on the phenoxy ring, the corresponding product (3q-3t) were obtained in good yield. However, alkynoates containing NO₂ group did not work in the reaction. The steric hindrance in the α -keto acids did not significantly affect the catalytic efficiency (Table 2, **3b** and **3r**). Although aromatic α -keto acids showed high reactivity, unfortunately, aliphatic ones were poor substrates. If aliphatic α -keto acids such as 2-oxopropanoic acid and 3,3-dimethyl-2-oxobutanoic acid were used as the substrates under the optimal reaction conditions, only a trace of product was obtained (Table 2, 3u and 3v). As expected, meta-substituent group of the phenoxy ring gave two regioselective products (3aa/3aa'). Unfortunately, alkylpropiolate such as methylpropiolate was not tolerated in the transformation (3ab). The silver-mediated domino reactions could tolerate some functional groups such as alkyl group, C-Cl bonds, C-Br bonds and C-CF₃ bonds which could be used for further modifications at the substituted positions. The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis

(Figure 1, see Supporting Information).

Scheme 2. Control experiments



According to the previous report that acyl radicals were easily generated from the $Ag(I)/K_2S_2O_8$ system,²⁶ which implies that the transformation should proceed through a free-radical mechanism. As shown in Scheme 2, when 2.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxy, a well-known radical inhibitor) was added in the standard reaction conditions, the formation of **2a** was completely inhibited as expected. In addition, another radical scavenger such as BHT (butylated hydroxytoluene) was also proven to inhibit the transformation. Furthermore, the cyclization product **4a** was not obtained when **1a** was performed only under the standard conditions.

4 5

6 7

8

9

51

52 53 54

55 56 57

58 59

60



Scheme 3. A proposed mechanism for the direct transformation



On the basis of these preliminary results above, a possible mechanism for the silver-mediated radical cyclization reactions for the synthesis of coumarin derivatives is suggested in Scheme 3. Firstly, a acyl radical (A) is generated from α -keto acids (2) by $Ag(I)/K_2S_2O_8$ with releasing one molecular CO_2 .²⁷ Selective addition of the acyl radical (A) to the alkynoates (1) gives the vinyl radical (B) stabilized by the phenyl group. Subsequently, the vinyl radical (B) undergoes an intramolecular cyclization to generate radical intermediate C. Finally, an Ag(II)-mediated hydrogen abstraction of radical intermediate C take place, releasing the product 3, H^+ and Ag(I).

In summary, a novel and useful protocol has been developed for the synthesis of coumarin derivatives via silver-mediated tandem radical cyclization of readily prepared alkynoates and α -keto acids. A series of potentially biological coumarin frameworks could be conveniently and efficiently obtained in moderate to good yields with excellent functional group tolerance. The easy and efficient method for the synthesis of coumarin compounds should attract much attention in synthetic and

pharmaceutical chemistry.

EXPERIMENTAL SECTION

General.

All commercially available reagent grade chemicals were purchased from chemical suppliers and used as received without further purification unless otherwise stated. Alkynoates were prepared according to previous literatures.²⁸ All solvents were dried according to standard procedures. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on a 400 MHz spectrometer with TMS as internal standard (400 MHz ¹H, 100 MHz ¹³C) at room temperature, the chemical shifts (δ) were expressed in ppm and *J* values were given in Hz. The following abbreviations are used to indicate the multiplicity: singlet (s), doublet (d), triplet (t) and multiplet (m). All first order splitting patterns that could not be easily interpreted were designated as multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m). Mass analyses and HRMS were obtained by ESI on a TOF mass analyzer. Column chromatography was performed on silica gel (200-300 mesh).

General experimental procedures.

A 25 ml Schlenk tube equipped with a magnetic stirring bar was charged with AgNO₃ (51 mg, 0.3 mmol), potassium persulfate(324mg, 1.2 mmol), substituted various alkynoates (1) (0.3 mmol) and α -keto acids (2) (0.6 mmol). The tube was evacuated twice and backfilled with nitrogen, and 2 mL CH₃CN/H₂O(v₁/v₂=1:1) was added to the tube under nitrogen atmosphere. The tube was sealed with a balloon and then the

mixture was allowed to stir under nitrogen atmosphere at 60 °C for 24 h. After completion of the reaction, the resulting solution was cooled down to room temperature, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product (**3**).

3-benzoyl-4-phenyl-2*H***-chromen-2-one (3a):** Compound **3a** was obtained in 75% yield (74 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 100-101°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.66-7.62 (m, 1H), 7.50 (t, 2H, *J* = 8.0 Hz), 7.38-7.35 (m, 5H), 7.30-7.27 (m, 4H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 192.1, 158.8, 153.8, 153.0, 136.3, 133.8, 132.7, 132.3, 129.5, 129.3, 128.7, 128.6, 128.0, 126.0, 124.7, 119.5, 117.2. HRMS m/z calcd. for C₂₂H₁₄O₃ [M+Na]⁺: 349.0841, found: 349.0827.

3-(2-methylbenzoyl)-4-phenyl-2*H***-chromen-2-one (3b):** Compound **3b** was obtained in 67% yield (68 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 177-179°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.64-7.58 (m, 2H), 7.48 (d, 2H, J = 8.0 Hz), 7.36-7.32 (m, 4H), 7.26-7.23 (m, 4H), 7.17-7.12 (m, 2H), 2.41 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 193.8, 158.8, 153.7, 152.3, 140.2, 136.0, 132.6, 132.5, 132.4, 132.0, 131.1, 129.3, 128.6, 128.5, 127.9, 127.5, 125.5, 124.6, 119.6, 117.2, 21.3. HRMS m/z calcd. for C₂₃H₁₆O₃ [M+Na]⁺: 363.0997, found: 363.0996.

3-(3-methylbenzoyl)-4-phenyl-2*H***-chromen-2-one (3c):** Compound **3c** was obtained in 72% yield (73 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 154-156°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.72 (d, 2H, *J* = 8.0 Hz), 7.65-7.61 (m, 1H), 7.48 (d, 1H, *J* = 8.0 Hz), 7.37-7.35 (m, 3H), 7.18 (d, 1H, *J* = 8.0 Hz), 2.38 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.7, 158.6, 153.7, 152.7, 144.9, 133.8, 132.6, 132.4, 129.4, 129.3, 128.7, 128.6, 128.0, 126.2, 124.6, 119.5, 117.2, 21.8. HRMS m/z calcd. for C₂₃H₁₆O₃ [M+Na]⁺: 363.0997, found:

363.0996.

3-(3-bromobenzoyl)-4-phenyl-2*H***-chromen-2-one (3d):** Compound **3d** was obtained in 78% yield (95 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 150-152°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.91 (s, 1H), 7.43 (d, 1H, *J* = 8.0 Hz), 7.66-7.63 (m, 2H), 7.50 (d, 1H, *J* = 8.0 Hz), 7.40-7.36 (m, 3H), 7.34-7.24 (m, 5H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.6, 158.5, 153.8, 153.5, 138.0, 136.5, 132.9, 132.2, 132.0, 130.1, 129.7, 128.7, 128.1, 127.7, 125.3, 124.7, 122.9, 119.3, 117.3. HRMS m/z calcd. for C₂₂H₁₃BrO₃ [M+Na]⁺: 426.9946, 428.9925 found: 426.9947, 428.9925.

3-benzoyl-6-methyl-4-phenyl-2*H***-chromen-2-one (3e):** Compound **3e** was obtained in 57% yield (58 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 167-169°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.51 (t, 1H, *J* = 8.0 Hz), 7.40-7.33 (m, 5H), 7.29-7.26 (m, 3H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.08 (d, 1H, *J* = 8.0 Hz), 7.51 (t, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 192.4, 159.1, 153.9, 153.1, 144.3, 133.7, 132.6, 129.4, 129.3, 128.7, 128.6, 128.5, 127.7, 125.9, 117.3, 117.0, 21.7. HRMS m/z calcd. for C₂₃H₁₆O₃ [M+Na]⁺: 363.0997 found: 363.0992.

3-benzoyl-6-methyl-4-phenyl-2*H***-chromen-2-one (3f):** Compound **3f** was obtained in 69% yield (73 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 131-132°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.57 (d, 1H, *J* = 8.0 Hz), 7.34-7.28 (m, 5H), 7.23-7.20 (m, 2H), 7.16-7.11 (m, 3H), 7.05 (d, 1H, *J* = 8.0 Hz), 2.50 (s, 3H) , 2.40 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 194.0, 159.0, 153.8, 152.5, 144.1, 140.1, 132.7, 132.3, 131.9, 131.0, 129.2, 128.5, 128.4, 127.7, 125.8, 125.5, 117.3, 117.2, 21.7, 21.2. HRMS m/z calcd. for C₂₄H₁₈O₃ [M+Na]⁺: 377.1154 found: 377.1149.

6-methyl-3-(2-methylbenzoyl)-4-phenyl-2*H***-chromen-2-one (3g):** Compound **3g** was obtained in 61% yield (65 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 124-126°C. ¹H NMR (CDCl₃, 400 MHz, ppm)

δ 7.63-7.60 (m, 2H), 7.36-7.32 (m, 4H), 7.29-7.24 (m, 4H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.08 (d, 1H, *J* = 8.0 Hz), 2.51 (s, 3H) , 2.34 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 192.5, 159.1, 153.9, 153.0, 144.2, 134.6, 129.6, 129.4, 128.7, 128.5, 128.4, 127.7, 126.7, 125.9, 117.3, 117.1, 21.7, 21.3. HRMS m/z calcd. for C₂₄H₁₈O₃ [M+Na]⁺: 377.1154 found: 377.1149.

3-(4-chlorobenzoyl)-6-methyl-4-phenyl-2*H***-chromen-2-one (3h):** Compound **3h** was obtained in 73% yield (82 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 155-156°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.66 (t, 1H, *J* = 4.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.38-7.35 (m, 3H), 7.34-7.25 (m, 4H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.0 Hz), 2.52 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.1, 158.9, 153.9, 153.7, 144.6, 134.9, 133.6, 129.9, 129.6, 129.1, 128.6, 127.8, 127.3, 126.0, 117.4, 116.9, 21.7. HRMS m/z calcd. for C₂₃H₁₅ClO₃ [M+Na]⁺: 397.0607 found: 397.0612.

3-(3-bromobenzoyl)-6-methyl-4-phenyl-2*H***-chromen-2-one (3i):** Compound **3i** was obtained in 73% yield (89 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 147-149°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.91 (t, 1H, *J* = 4.0 Hz), 7.72 (d, 1H, *J* = 8.0 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.38-7.35 (m, 3H), 7.30-7.25 (m, 4H), 7.22 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.0 Hz), 2.52 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.1, 158.9, 153.9, 153.8, 144.7, 136.5, 132.0, 130.1, 129.6, 128.6, 127.8, 126.0, 117.4, 116.9, 21.9. HRMS m/z calcd. for C₂₃H₁₅BrO₃ [M+Na]⁺: 441.0102, 443.0082 found: 441.0111, 443.0076.

3-benzoyl-6-chloro-4-phenyl-2*H***-chromen-2-one (3j):** Compound **3i** was obtained in 72% yield (67 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 148-150°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.54-7.49 (m, 2H), 7.40-7.34 (m, 5H), 7.27-7.24 (m, 4H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.7, 158.2, 154.0, 152.4, 138.8, 136.1, 134.0, 132.0, 129.7, 129.3, 128.9, 128.7, 128.6, 125.9, 125.3, 118.1, 117.4. HRMS m/z calcd. for C₂₂H₁₃ClO₃ [M+Na]⁺: 383.0451 found: 383.0449. **3-benzoyl-6-chloro-4-phenyl-2***H***-chromen-2-one (3k):** Compound **3k** was obtained in 65% yield (73 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 142-144°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.56 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 4.0 Hz), 7.37-7.30 (m, 4H), 7.22-7.19 (m, 4H), 7.15 (d, 2H, *J* = 8.0 Hz), 2.40 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 193.3, 158.2, 153.9, 151.7, 140.2, 138.7, 132.6, 132.0, 131.0, 129.5, 128.9, 128.6, 128.5, 125.6, 125.2, 118.3, 117.4, 21.3. HRMS m/z calcd. for C₂₃H₁₅ClO₃ [M+Na]⁺: 397.0607 found: 397.0603.

3-benzoyl-6-bromo-4-phenyl-2*H***-chromen-2-one (3l):** Compound **3l** was obtained in 52% yield (63 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 185-187°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.80 (d, 2H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 4.0 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.40-7.35 (m, 6H), 7.27-7.25 (m, 2H), 7.17 (d, 2H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.7, 158.1, 153.9, 152.4, 136.1, 134.0, 131.9, 129.7, 129.2, 129.0, 128.7, 128.1, 126.9, 126.1, 120.4, 118.5. HRMS m/z calcd. for C₂₂H₁₃BrO₃ [M+Na]⁺: 426.9946, 428.9925 found: 426.9941, 428.9927.

6-bromo-3-(3-methylbenzoyl)-4-phenyl-2*H*-chromen-2-one (3m): Compound 3m was obtained in 58% yield (73 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 145-146°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.66 (d, 1H, *J* = 4.0 Hz), 7.61-7.58 (m, 2H), 7.41-7.34 (m, 5H), 7.29-7.25 (m, 3H), 7.17 (d, 2H, *J* = 8.0 Hz), 2.35 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.9, 158.1, 153.8, 152.3, 138.5, 134.8, 132.0, 129.7, 129.5, 129.0, 128.7, 128.5, 128.1, 126.7, 120.4, 118.5, 21.2. HRMS m/z calcd. for C₂₃H₁₅BrO₃ [M+Na]⁺: 441.0102, 443.0082 found: 441.0113, 443.0081.

6-bromo-3-(4-methylbenzoyl)-4-phenyl-2*H*-chromen-2-one (3n): Compound 3n was obtained in 61% yield (76 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 203-204°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.70 (d, 2H, J = 8.0 Hz), 7.65 (s, 1H), 7.40-7.36 (m, 4H), 7.29-7.25 (m, 2H),

 7.19-7.15 (m, 3H), 2.38 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 191.3, 158.2, 153.8, 152.1, 145.1, 133.7, 132.0, 129.7, 129.4, 128.9, 128.7, 128.6, 128.1, 126.7, 126.3, 120.4, 118.6, 21.8. HRMS m/z calcd. for C₂₃H₁₅BrO₃ [M+Na]⁺: 441.0102, 443.0082 found: 441.0112, 443.0081.

6-bromo-3-(3-bromobenzoyl)-4-phenyl-2*H***-chromen-2-one (30):** Compound **30** was obtained in 66% yield (95 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 138-140°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.89 (t, 1H, *J* = 2.0 Hz), 7.70 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 4.0 Hz), 7.62 (d, 1H, *J* = 8.0 Hz), 7.42-7.36 (m, 4H), 7.26-7.22 (m, 3H), 7.18 (d, 1H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.4, 157.9, 153.9, 153.0, 137.8, 136.7, 131.9, 131.7, 130.2, 129.9, 129.4, 129.1, 128.8, 128.6, 128.3, 127.7, 127.2, 122.9, 120.5, 118.3. HRMS m/z calcd. for C₂₂H₁₂Br₂O₃ [M+Na]⁺: 504.9051, 506.9030 found: 504.9049, 506.9033.

6-bromo-3-(4-chlorobenzoyl)-4-phenyl-2*H***-chromen-2-one (3p):** Compound **3p** was obtained in 55% yield (72 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 164-166°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.74 (d, 2H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 4.0 Hz), 7.43-7.35 (m, 6H), 7.26-7.23 (m, 2H), 7.17 (d, 1H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.5, 158.0, 153.9, 152.8, 140.5, 130.5, 129.9, 129.1, 129.0, 128.8, 128.6, 120.5, 118.4. HRMS m/z calcd. for C₂₂H₁₂BrClO₃ [M+Na]⁺: 460.9556, 462.9536 found: 504.9049, 506.9033.

3-benzoyl-4-phenyl-6-(trifluoromethyl)-2*H***-chromen-2-one (3q): Compound 3q was obtained in 71% yield (84 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 206-208°C. ¹H NMR (CDCl₃, 400 MHz, ppm) \delta 7.80 (d, 2H,** *J* **= 8.0 Hz), 7.74 (s, 1H), 7.52 (t, 2H,** *J* **= 8.0 Hz), 7.46-7.44 (m, 1H), 7.41-7.36 (m, 5H), 7.29-7.25 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz, ppm) \delta 191.4, 157.9, 153.4, 151.7, 135.8, 134.1(q, ²***J* **= 32.3 Hz), 131.6, 129.9, 129.2 (q, ¹***J* **= 271.2 Hz), 128.9, 128.8, 128.7, 128.6, 127.9, 121.1, 121.0, 114.6, 114.5, 114.4. HRMS m/z**

calcd. for $C_{23}H_{13}F_{3}O_{3}$ [M+Na]⁺: 417.0714 found: 417.0716.

3-(2-methylbenzoyl)-4-phenyl-6-(trifluoromethyl)-2*H***-chromen-2-one (3r): Compound 3r** was obtained in 62% yield (76 mg). according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 111-113°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.73-7.30 (m, 3H), 7.52-7.44 (m, 2H), 7.40-7.37 (m, 3H), 7.30-7.26 (m, 2H), 7.19 (d, 2H, *J* = 8.0 Hz), 2.38 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.9, 158.0, 153.3, 151.4, 145.3, 133.4 (q, ²*J* = 33.0 Hz), 131.7, 129.5 (q, ¹*J* = 270.2 Hz), 128.8, 128.6, 127.9, 121.0, 114.6, 114.5, 21.8. HRMS m/z calcd. for C₂₄H₁₅F₃O₃ [M+Na]⁺: 431.0871 found: 431.0874.

3-(3-bromobenzoyl)-4-phenyl-6-(trifluoromethyl)-2*H***-chromen-2-one (3s): Compound 3r** was obtained in 75% yield (106 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (30:1). mp 176-178°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.90 (t, 1H, *J* = 2.0 Hz), 7.74 (s, 1H), 7.71 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 7.51-7.46 (m, 2H), 7.42-7.39 (m, 3H), 7.30-7.26 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.1, 157.7, 153.4, 152.3, 137.5, 136.9, 131.9, 131.4, 130.2, 130.1, 128.9 (q, ¹*J* = 270.0 Hz), 127.3, 123.0, 121.2, 114.7, 114.6. HRMS m/z calcd. for C₂₄H₁₅F₃O₃ [M+Na]⁺: 431.0871 found: 431.0874.

3-(3-bromobenzoyl)-4-phenyl-6-(trifluoromethyl)-2*H***-chromen-2-one (3t): Compound 3t** was obtained in 76% yield (98 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 162-164°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.75-7.72 (m, 3H), 7.51-7.45 (m, 2H), 7.41-7.35 (m, 5H), 7.29-7.25 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.2, 157.8, 153.4, 152.0, 140.7, 134.2, 131.5, 130.5, 130.1, 129.1(q, ¹*J* = 270.0 Hz), 128.9, 128.6, 114.7, 114.6. HRMS m/z calcd. for C₂₃H₁₂ClF₃O₃ [M+Na]⁺: 451.0325 found: 451.0320.

3-(3-bromobenzoyl)-4-(4-bromophenyl)-2H-chromen-2-one (3x): Compound **3w** was obtained in 72% yield (104 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 121-123°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.92 (s, 1H), 7.74 (d, 1H, J = 8.0 Hz), 7.69-7.64 (m, 2H), 7.52-7.48 (m, 3H),

 7.32-7.25 (m, 3H), 7.17 (d, 2H, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.5, 158.4, 153.8, 152.5, 137.8, 136.9, 133.3, 132.1, 132.0, 131.0, 130.4, 130.3, 127.8, 125.5, 125.0, 124.3, 123.1, 119.0, 117.4. HRMS m/z calcd. for C₂₂H₁₂Br₂O₃ [M+Na]⁺: 504.9051, 506.9030 found: 504.9049, 506.9033.

3-(3-bromobenzoyl)-4-(4-chlorophenyl)-2*H***-chromen-2-one (3y):** Compound 3x was obtained in 70% yield (92 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 103-104°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.93 (s, 1H), 7.74 (d, 1H, *J* = 8.0 Hz), 7.69-7.64 (m, 2H), 7.49 (d, 1H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 7.31-7.26 (m, 3H), 7.23 (d, 2H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.6, 158.4, 153.8, 152.5, 137.8, 136.9, 136.1, 133.2, 132.0, 130.5, 130.4, 130.1, 128.1, 127.8, 125.6, 125.0, 123.1, 119.1, 117.4. HRMS m/z calcd. for C₂₂H₁₂BrClO₃ [M+Na]⁺: 460.9556, 462.9536 found: 460.9551, 462.9532.

3-(3-bromobenzoyl)-4-(4-bromophenyl)-6-methyl-2H-chromen-2-one (3z): Compound **3y** was obtained in 68% yield (101 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (20:1). mp 126-127°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.92 (s, 1H), 7.73 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.53 (d, 2H, *J* = 8.0 Hz), 7.30-7.26 (m, 2H), 7.16-7.11 (m, 4H), 2.52 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 190.7, 158.7, 153.9, 152.7, 144.9, 136.8, 136.7, 132.0, 131.2, 130.3, 130.2, 130.1, 127.7, 127.5, 126.2, 124.1, 123.0, 111.5, 116.5, 21.8. HRMS m/z calcd. for C₂₃H₁₄Br₂O₃ [M+Na]⁺: 518.9207, 520.9187 found: 518.9201, 520.9185.

7-methyl-3-(2-methylbenzoyl)-4-phenyl-2*H***-chromen-2-one (3aa):** Compound 3aa was obtained in 44% yield (47 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (50:1). mp 139-141°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.59 (d, 1H, *J* = 8.0 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 7.37-7.29 (m, 4H), 7.22-7.20 (m, 2H), 7.16-7.10 (m, 2H), 7.00 (s, 1H), 2.39 (s, 3H), 2.32 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 194.0, 159.1, 152.4, 151.8, 141.1, 136.1, 134.5, 133.7, 132.5, 132.4,

131.9, 131.1, 129.3, 128.5, 128.4, 127.9, 127.3, 125.5, 119.2, 116.9. HRMS m/z calcd. for C₂₄H₁₈O₃ [M+Na]⁺: 377.1154 found: 377.1150.

5-methyl-3-(2-methylbenzoyl)-4-phenyl-2H-chromen-2-one (3aa'): Compound 3aa was obtained in 40% yield (43 mg) according to the general procedure. Eluent petroleum ether/ethyl acetate (50:1). mp 131-133°C. ¹H NMR (CDCl₃, 400 MHz, ppm) δ 7.59 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.34-7.28 (m, 4H), 7.22-7.20 (m, 2H), 7.16-7.07 (m, 4H), 2.39 (s, 3H), 2.32 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz, ppm) δ 194.0, 159.0, 152.0, 140.0, 136.1, 133.9, 132.8, 132.4, 132.0, 131.1, 129.2, 128.6, 128.4, 126.6, 125.7, 125.5, 124.0, 119.4, 21.3. HRMS m/z calcd. for C₂₄H₁₈O₃ [M+Na]⁺: 377.1154 found: 377.1150.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra for all compounds and ORTEP structures of compound **3a**, and CIF files giving spectroscopic data for **3a**; X-ray results. This information 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.

ACKNOWLEGEMENTS

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21302110, 21302109 and21375075), the Taishan Scholar Foundation of Shandong Province, the Natural Science Foundation of Shandong Province (ZR2013BQ017), the Project of Shandong Province Higher Educational Science and Technology Program (J13LD14).

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