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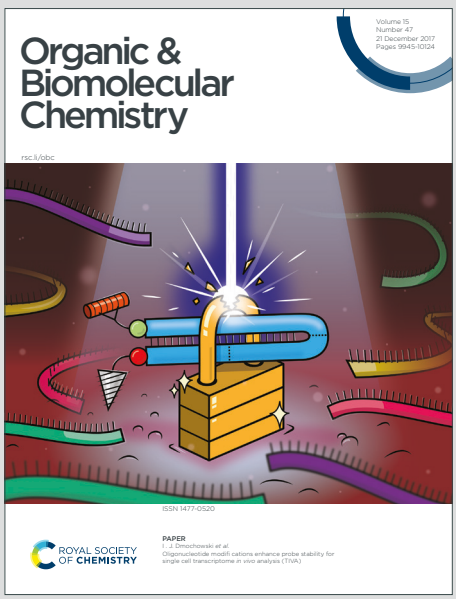

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ARTICLE

Visible-Light-Promoted Acyl Radical Cascade Reaction for Accessing Acylated Isoquinoline-1,3(2*H*,4*H*)-dione Derivatives

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Yingpeng Su,* Rong Zhang, Wenxuan Xue, Xuan Liu, Yanan Zhao, Ke-Hu Wang, Danfeng Huang, Congde Huo,* Yulai Hu*

A visible-light-promoted decarboxylative acyl radical acylation/cyclization cascade reaction of *N*-methacryloylbenzamides for accessing acylated isoquinoline-1,3(2*H*,4*H*)-dione derivatives was described. In this report, α-keto acids were resorted to generating acyl radicals and inducing the radical acylations. This protocol features mild reaction conditions, operational practicality and a broad substrate scope.

Introduction

The isoquinoline-1,3(2*H*,4*H*)-dione skeleton is frequently found in natural products and also serves as significant structural unit for many potentially physiologically active compounds, which shows obvious biological activities.[1] In Figure 1, several representative bioactive molecules possessing isoquinoline-1,3(2*H*,4*H*)-dione moiety are listed.[2] All of them exhibit distinctive biological activities. Consequently, many efforts from medicinal and synthetic chemists have been devoted to develop convenient and versatile methods for the synthesis of such molecules.[3] In this scenario, various free-radical additions/tandem cyclizations of *N*-methacryloylbenzamides have emerged as effective approachs to access functionalized isoquinoline-1,3(2*H*,4*H*)-dione derivatives.[4] Specifically, several radical species, such as carbon-,[4a-h] acyl-,[4i] fluoro-alkyl-,[4j-o] nitrogen-,[4p, 4q] sulfur- and phosphorus-containing radicals[4r-x] have been used to initiate this intriguing reaction. Among these cascade radical addition/cyclization strategies for rendering potentially bioactive functionalized isoquinoline-1,3(2*H*,4*H*)-dione derivatives, few reports on the synthesis of acylated isoquinoline relying on the acyl radical have been disclosed. In 2014, Zhou and co-workers have reported the method to obtain acylated isoquinoline-1,3(2*H*,4*H*)-dione derivatives from *N*-alkyl-*N*-acylbenzamide resorting aromatic aldehyde to forming acyl radical in high temperature[4i] (Scheme 1). Given the potential importance of acylated isoquinoline-1,3(2*H*,4*H*)-dione derivatives in drug discovery, the more mild and efficient methods to obtain acyl-containing isoquinoline-1,3(2*H*,4*H*)-dione derivatives are still desirable and valuable.

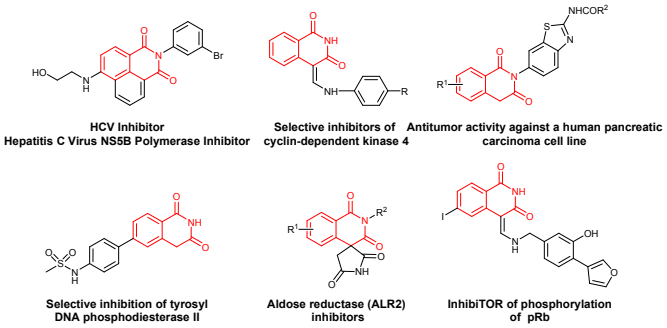

Figure 1. Biologically active isoquinoline-1,3(2*H*,4*H*)-dione derivatives.

In the past two decades, visible-light photo-redox catalysis has been regard as an ecofriendly and effective strategy for the advantages of convenience, availability and safety.[5] In this context, photo-redox catalysis has also been used to access various functionalized isoquinoline-1,3(2*H*,4*H*)-dione derivatives via the light-induced radical strategies.[4k-n, 4r, 4u, 4x] On the other hand, α-keto acids were regarded as highly reactivity acylation reagents[6] not only in transition-metal catalyzed decarboxylative coupling reaction, but also in the light-induced acyl radical-mediated transformations.[7] For instances, in 2014 Lei's research group first revealed the decarboxylative coupling of α-keto acids with amine by visible light irradiation.[7a] Afterwards, various visible light-induced acylated processes dealing with the functionalized compounds *via* a decarboxylative radical acylation with α-keto acids were reported.[7b-t] Inspired by these mild, efficient and good functional tolerant decarboxylative acylation reactions with α-keto acids, we herein report a visible-light-promoted decarboxylative acylation/cyclization cascade of *N*-aryl-*N*-acryl benzamides **1** with α-keto acids to obtain acyl-containing isoquinoline-1,3(2*H*,4*H*)-dione derivatives.

Results and discussion

College of Chemistry and Chemical Engineering, Northwest Normal University, 967 Anning East Road, Lanzhou 730070, P. R. China. E-mail: suyp51@nwnu.edu.cn; huocongde1978@hotmail.com; huyl@nwnu.edu.cn

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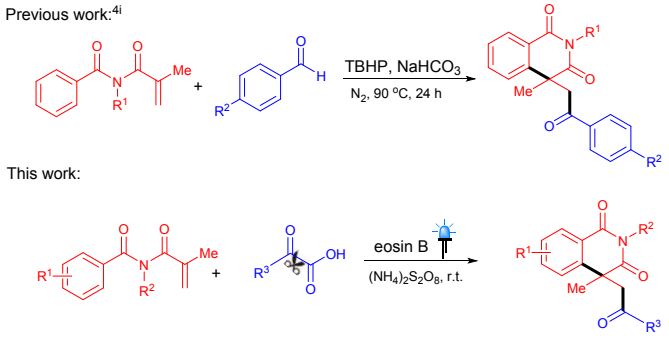
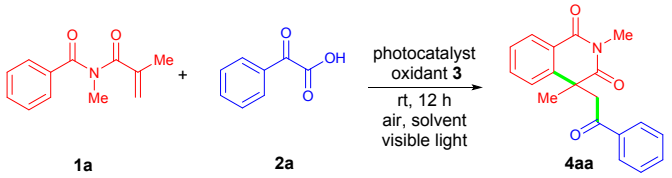
To investigate the feasibility of our design, the *N*-methacryloyl-*N*-methylbenzamide (**1a**) and 2-oxo-2-phenylaceticd acid (**2a**) were chosen as the model substrates (Table 1). Initially, the reaction was performed by using eosin B as a photoredox catalyst and $(NH_4)_2S_2O_8$ as an oxidant in DMSO upon irradiation of 2 × 3 W blue LED lights under an air atmosphere. To our delight, the desired product 2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione **4aa** was obtained in 56% yield, composing a reaction mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), 2 mol% eosin B and $(NH_4)_2S_2O_8$ (0.4 mmol) in DMSO (3 mL) at room temperature by irradiation for 12 h (Table 1, entry 1). The structure of **4aa** was determined unambiguously by X-ray (Table 2, CCDC: 1937084).[8] As anticipated, the formation of the desired product **4aa** was completely impeded without the light irradiation (Table 1, entry 2). Furthermore, running the reaction in the absence of photocatalyst, or oxidant, the reactions gave significant decrease in yield (29% and 36%; Table 1, entries 3 and 4). These results indicated that the photocatalyst and oxidant simultaneously promoted the decarboxylative acylation (Table 1, entries 2 and 3). In order to improve the yield, different mole ratios of **2a** and oxidant were screened (Table 1, entries 5–8). Gratifyingly, treatment of **1a** with 3.0 equivalents of **2a** and 2.5 equivalents $(NH_4)_2S_2O_8$ led to acylated product **4aa** in good yield of 90% (Table 1, entry 7). Among the various photoredox catalysts (Table 1, entries 9 and 10), eosin B was found to be the best choice for this cascade reaction. Subsequently, other common oxidants, such as $K_2S_2O_8$, TBHP, and O_2, were also investigated but found to be less effective than $(NH_4)_2S_2O_8$ for this transformation (Table 1, entries 7, 11–13). When other solvents, such as DMF, CH_3CN and THF, were used to instead of DMSO, the yield of the desired product dramatically dropped (Table 1, entries 7, 14–16). Finally, different irradiation sources were also tested in the reaction, affording the desired product **4aa** in lower yields (Table 1, entries 17 and 18). Therefore, we identified eosin B (2 mol%)/$(NH_4)_2S_2O_8$ (2.5 equiv)/DMSO/2 × 3 W blue LEDs/**2a** (3.0 equiv)/room temperature as optimal reaction conditions for the cascade radical acylation/cyclization of *N*-methacryloylbenzamides **1a**; the desired product **4aa** was synthesized in 12 h and in 90% yield (Table 1, entry 7).



Scheme 1. Synthesis of acyl-containing isoquinoline-1,3(2*H*,4*H*)-dione derivatives

Table 1. Optimization of Reaction Conditions[a]



1a 2a 4aa

Entry	Mole ratio of **1a**/**2a**/**3**	Photocatalyst	Oxidant	Solvent	Yield[b] (%)
1	1.0/2.0/2.0	eosin B	$(NH_4)_2S_2O_8$	DMSO	56
2[c]	1.0/2.0/2.0	eosin B	$(NH_4)_2S_2O_8$	DMSO	0
3	1.0/2.0/2.0	—	$(NH_4)_2S_2O_8$	DMSO	29
4	1.0/2.0/2.0	eosin B	—	DMSO	36
5	1.0/2.5/2.0	eosin B	$(NH_4)_2S_2O_8$	DMSO	71
6	1.0/3.0/2.0	eosin B	$(NH_4)_2S_2O_8$	DMSO.	84
7	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	DMSO	90
8	1.0/3.0/3.0	eosin B	$(NH_4)_2S_2O_8$	DMSO	89
9	1.0/3.0/2.5	eosin Y	$(NH_4)_2S_2O_8$	DMSO.	87
10	1.0/3.0/2.5	$Ru(bpy)_3Cl_2•6H_2O$	$(NH_4)_2S_2O_8$	DMSO	85
11	1.0/3.0/2.5	eosin B	$K_2S_2O_8$	DMSO	26
12	1.0/3.0/2.5	eosin B	TBHP	DMSO	58
13	1.0/3.0/2.5	eosin B	O_2	DMSO	70
14	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	DMF	18
15	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	CH_3CN	0
16	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	THF	0
17[d]	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	DMSO	63
18[e]	1.0/3.0/2.5	eosin B	$(NH_4)_2S_2O_8$	DMSO	45

[a] General reaction conditions: amide **1a** (0.3 mmol), photocatalyst (2 mol %), solvent(3 mL) in a sealed tube, air atmosphere, ambient temperature, irradiation with 2 × 3 W blue LED lights, 12 h. [b]Isolated yield. [c] Dark condition. [d] Irradiation with 2 × 3 W green LEDs. [e] Irradiation with 2 × 3 W white LEDs.

With the optimized reaction conditions established (Table 1, entry 7), the scope of the decarboxylative acylation/cyclization cascade reaction was explored by first varying the *N*-arylacrylbenzamides **1** with the 2-oxo-2-phenylacetic acid **2a** (Table 2). The effect of various groups on the aromatic ring of amides was examined firstly. A variety of substituents such as methyl, methoxyl, ethoxyl, fluorine, chlorine, bromine and acetyl on different positions of the aromatic ring of amide **1** were all compatible, leading the respective desired products (**4ba-4ka**) in reasonable to good yields (52%-82%). The presence of electron-donating substituents at the aryl rings had positive effect on chemical yields. Exposing the amides (**1b-1f**) to the standard conditions, the corresponding products (**4ba-4fa**) were obtained in moderate to good yields (67%-81%). As anticipated, *meta*-methyl-substituted substrate **1d** furnished two region-isomers **4da** and **4da'** in 77% total yield with 4:1 isomeric ratio (determined by ^{1}H NMR). Comparing the ratio of two isomers, and the yields of **4ba** with **4ca**, it indicated that a steric effect is negative influence for formation of the bulky products. Hence, the steric effect may lead to the moderate yield of the *para*-phenyl-substituted **4ga** (64%). On the other hand, amides (**1ha-1ka**) with electron-withdrawing groups (fluorine, chlorine, bromine and acetyl) on the *para*- or *meta*-position of the aromatic rings just provided the relative isoquinoline diones in reasonable yields (**4ha-4ka**, in 52%-60% yields), on which a slight erosion occurred in

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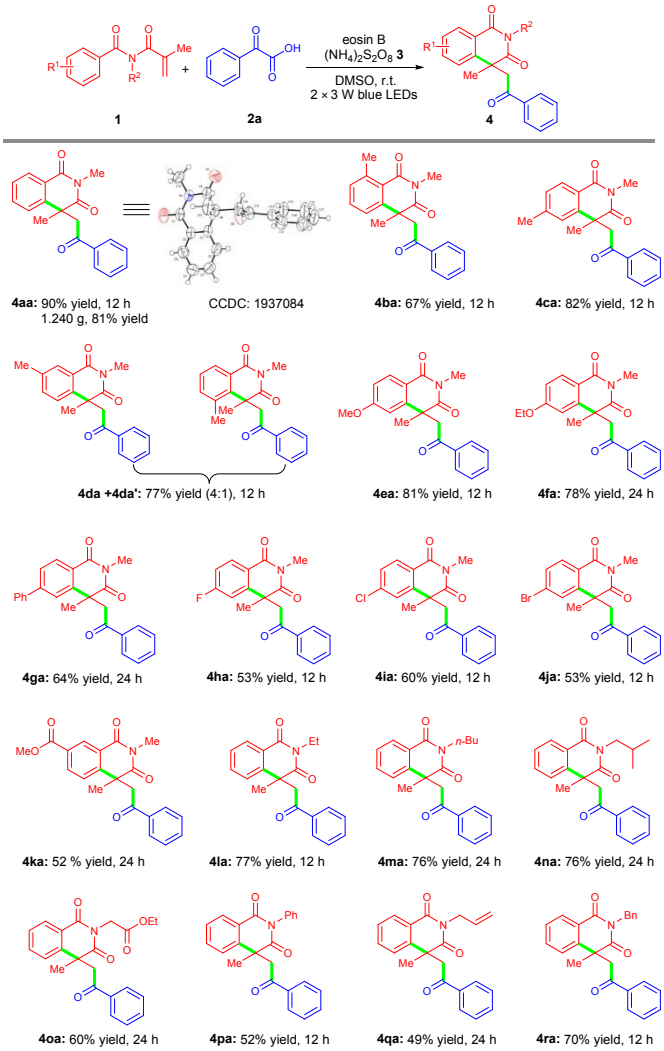
Table 2. Scope of methacryloyl benzamide derivatives.[a, b]

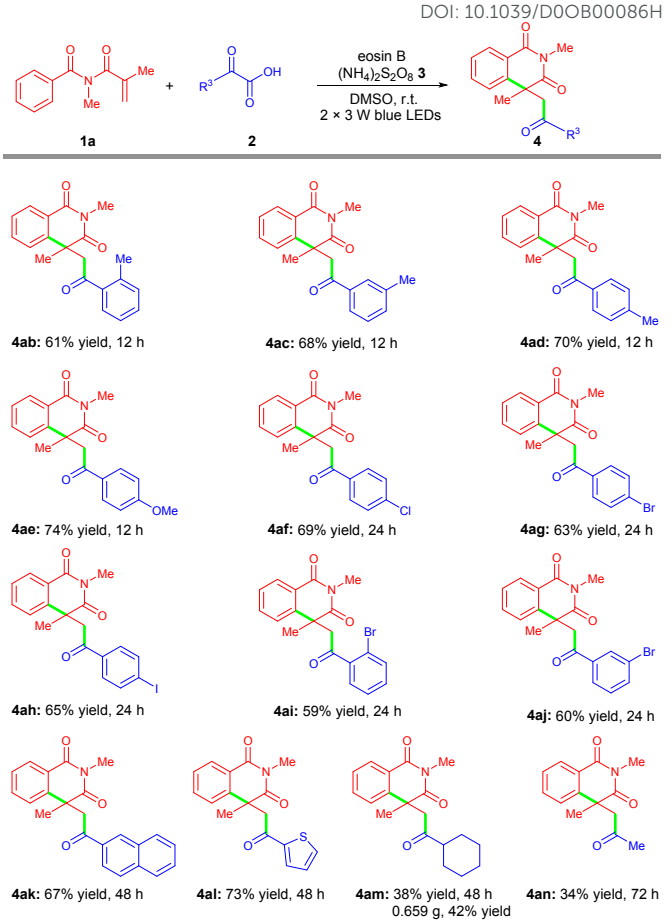


[a] Reaction conditions: Amide **1** (0.3 mmol), **2a** (0.9 mmol, 3.0 equiv.), $(NH_4)_2S_2O_8$ (0.75 mmol, 2.5 equiv.), eosin B (2 mol%), DMSO (3 mL) in a sealed tube, air atmosphere, ambient temperature, irradiation with 2 × 3 W blue LEDs. [b] Isolated yield.

comparison to the electron-donating substituents. Notably, *para*-NO_2 substituted amide (not shown) generated the corresponding product in very lower yield, which is prone to decomposition. Subsequently, the *N*-substituents of methacryloyl benzamides were also investigated. The ethyl, n-butyl, isobutyl, ester, phenyl, allyl and benzyl substituted on the N atom were compatible with this transformation (**4la–4ra**). To explore the synthetic potential, a gram-scale reaction was conducted for amide **1a** (5 mmol) with **2a** and furnished **4aa** in 81% yield (1.240 g).

Following these encouraging results for different *N*-methacryloylbenzamides, the scope of the reaction with respect to the α-keto acid unit was investigated (Table 3, **4ab–4an**). A variety of aromatic α-keto acids bearing different electron property substituents at the phenyl rings were employed to this reaction and smoothly afforded the respective products in moderate to good yields (59-74%).

Table 3. Scope of α-keto acids.[a, b]



[a] Reaction conditions: Amide **1a** (0.3 mmol), **2** (0.9 mmol, 3.0 equiv.), $(NH_4)_2S_2O_8$ (0.75 mmol, 2.5 equiv.), eosin B (2 mol%), DMSO (3 mL) in a sealed tube, air atmosphere, ambient temperature, irradiation with 2 × 3 W blue LEDs. [b] Isolated yield.

Variation of the substituents and positions at the phenyl rings of α-keto acids had a minor influence on the yield of corresponding isoquinoline-1,3-diones **4ab-4aj**. However, α-keto acids **2f-2j** bearing electron-withdrawing substituents had lower reactivity than α-keto acids **2b-2e** containing electron-donating groups at phenyl rings. To obtain the comparable yields to **4ab-4ae**, reactions with α-keto acids **2f-2j** had to be extended to 24 h. Moreover, the steric hindrance effect of α-keto acids has negative influence on this coupling reaction, comparing **4ab** to **4ac** and **4ad**, **4ag** to **4ai** and **4aj**. α-Keto acids containing naphthyl and thienyl groups (**2k** and **2l**) underwent the reactions smoothly to provide the corresponding products **4ak** in yield of 67% and **4al** in yield of 73% for 48 h. Noteworthily, aliphatic α-keto acids **2m** and **2n** were also compatible with this coupling, although acylated isoquinoline-1,3(2*H*,4*H*)-dione derivatives **4am** and **4an** were delivered in merely around 35% yields. Finally, a gram-scale reaction of **1a** (5 mmol) with **2m** was conducted under the standard conditions and yielded the acylated product **4am** in 42% yield (0.659 g).

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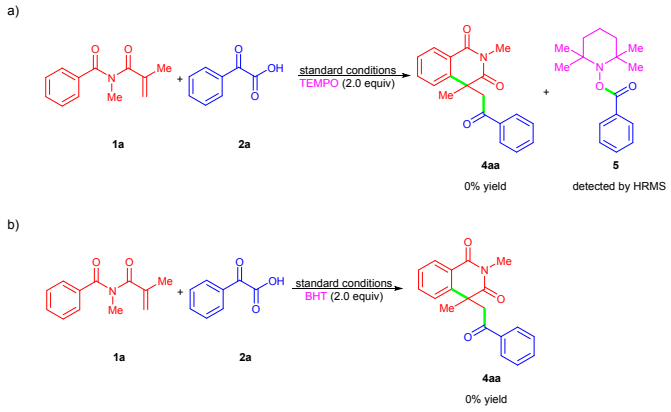
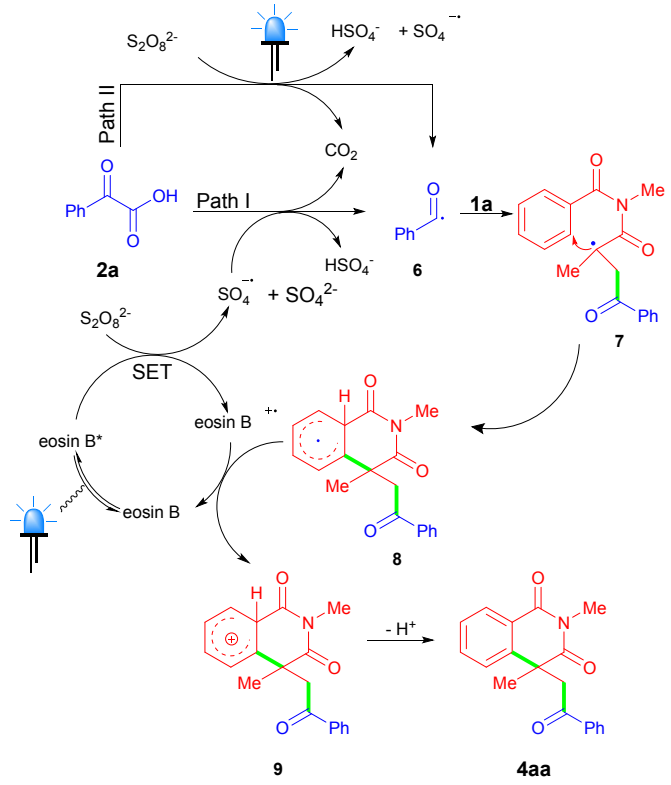


Scheme 2. Control Experiments for Mechanism

In order to probe the reaction mechanism, common control experiments were performed in the presence of the radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard reaction conditions. As shown in scheme 2, when 2 equiv. of radical inhibitors TEMPO or BHT were loaded, the reactions were completely restricted. Furthermore, the addition of TEMPO as the radical scavengers led to formation of the TEMPO-benzoyl adduct **5**, detecting by HRMS, and the recovery of the starting material **1a** (Scheme 2, equation a). These results indicated that this visible-light-promoted decarboxylative acylation/cyclization cascade likely occurred *via* a radical pathway.

On the basis of the above experimental results and previous literature reports,[6, 9] a possible reaction mechanism was proposed in Scheme 3. Initially, the photo excitation of the eosin B with blue LED generated the excited-state species eosin B*, which underwent a single-electron transfer (SET) with the persulfate anion to produce the eosin B radical cation, sulfate dianion, and sulfate radical anion.[10] The hydrogen atom transfer (HAT) and the SET between the 2-oxo-2-phenylacetic acid **2a** and the sulfate radical anion led decarboxylation to yield a benzoyl radical **6** *via* the path I. Then, benzoyl radical **6** added to the carbon-carbon double bond of *N*-methacryloyl-*N*-methylbenzamide **1a** to generate the radical intermediate **7**, which underwent an intramolecular cyclization to give the radical intermediate **8**. The carbocation intermediate **9** was then produced through the single-electron oxidation of the radical **8** by the eosin B radical cation. Finally, the deprotonation of the carbocation **9** regenerated the aromatic system and formed the desired isoquinoline-1,3-diones **4aa**. Additionally, formation of the benzoyl radical **6** *via* the path II, promoted by $(NH_4)_2S_2O_8$ through the decarboxylation of *α*-keto acid **2a** with visible light irradiation, could not be excluded (Table 1, entries 2 *vs* 3).[7f]



Scheme 3. Proposed Mechanism

Conclusions

In summary, we developed a mild visible-light-promoted decarboxylative acylation/radical addition/cyclization cascade reaction to access acyl-containing isoquinoline-1,3(2*H*,4*H*)-dione derivatives under transition-metal-free conditions. The $(NH_4)_2S_2O_8$/eosin B system is valid for the decarboxylation of *α*-keto acids through a radical pathway with blue light irradiation. This method features mild reaction conditions, operational practicality and a broad substrate scope. The introduction of acyl groups and the construction of fused heterocycles take place in one efficient step.

Experimental section

General Methods

All solvents were treated according to standard procedures. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Silica gel column chromatography was carried out using 250–400 mesh silica gel. The progress of reactions was monitored by TLC. TLC plates were analyzed by an exposure to ultraviolet (UV) light. NMR experiments were carried out in deuteron chloroform ($CDCl_3$). ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz or 600 MHz and 100 MHz or 150 MHz spectrometers, respectively. Chemical shifts are reported as δ values relative to internal TMS (*δ* = 0.00 ppm for 1H NMR), chloroform (*δ* = 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) in parts permillion (ppm). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quartet, m: multiplet. Coupling constants (*J*) are reported in Hertz (Hz). Melting points were uncorrected. High resolution mass spectra (HRMS) were recorded on Micro TOF-QII mass instrument (ESI).

General procedures for synthesis of the isoquinoline-1,3(2*H*,4*H*)-dione 4

N-arylacrylbenzamides **1** (0.30 mmol), *α*-keto acids **2** (0.90 mmol), eosin B (0.006 mmol, 2.0 mol%) and $(NH_4)_2S_2O_8$ (0.75 mmol) were dissolved in DMSO (3.0 mL). Then, the solution was stirred at room temperature under 2 × 3 W blue LEDs irradiation for 24 hrs- 72 hrs. After the reaction was completed by TLC monitoring, the reaction mixture was diluted by adding $NaHCO_3$ and brine. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate 5:1 as the eluant) on silica gel to give the desired isoquinoline-1,3(2*H*,4*H*)-diones **4**.

2,4-Dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4aa). 58 mg, 90% yield, white solid, mp 143–145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.31 (d, *J* = 7.8 Hz, 1H), 7.86 (d, 2H), 7.56–7.49 (m, 2H), 7.44–7.37 (m, 3H), 7.27 (d, *J* = 7.2 Hz, 1H), 4.22 (d, *J* = 18.6 Hz, 1H), 3.97 (d, *J* = 18.0 Hz, 1H), 3.45 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.2, 176.7, 164.6, 143.7, 135.9, 133.7, 133.5, 129.3, 128.6, 128.0, 127.1, 125.0, 123.5, 49.1, 44.5, 30.9, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}NO_3Na$ $[M + Na]^+$ 330.11006; found 330.11004.

2,4,8-Trimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ba). 64 mg, 67% yield, white solid, mp 156–157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.87 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 6.6 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 4.22 (d, *J* = 18.0 Hz, 1H), 3.98 (d, *J* = 18.0 Hz, 1H), 3.41 (s, 3H), 2.82 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.4, 176.4, 165.2, 145.0, 142.9, 136.0, 133.4, 132.5, 131.2, 128.6, 127.9, 123.2, 121.6, 49.1, 44.6, 31.4, 27.3, 24.1; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14379.

2,4,6-Trimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ca). 79 mg, 82% yield, white solid, mp 121–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.04 (s, 1H), 4.21 (d, *J* = 18.0 Hz, 1H), 3.95 (d, *J* = 18.0 Hz, 1H), 3.43 (s, 3H), 2.34 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 176.9, 164.6, 144.4, 143.7, 135.9, 133.4, 129.3, 128.6, 128.2, 128.0, 124.0, 122.5, 49.1, 44.4, 30.9, 27.2, 21.9; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14373.

2,4,7-Trimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4da) and **2,4,5-Trimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4da')(asterisk denotes minor isomer 4da' peaks).** 74 mg, 77% yield, yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.31 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 4.45* (d, *J* = 18.6 Hz, 1H), 4.27* (d, *J* = 18.6 Hz, 1H), 4.18 (d, *J* = 18.0 Hz, 1H), 3.95 (d, *J* = 18.0 Hz, 1H), 3.43 (s, 3H), 2.50* (s, 3H), 2.37 (s, 3H), 1.71* (s, 3H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.5*, 196.2, 177.5*, 176.9, 164.9*, 164.8, 140.8, 140.6*, 138.3*, 137.0, 135.9*, 134.7, 133.4, 129.4, 128.6*, 128.6, 128.3*, 127.9, 127.9*, 127.1*, 126.3*, 124.7, 123.5, 49.1, 47.3*, 46.0*, 44.2, 30.9, 27.6*, 27.3, 27.0*, 22.9*, 20.9; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14375.

6-Methoxy-2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ea). 82 mg, 81% yield, white solid, mp 164–165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.26 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 6.89 (dd, *J* = 9.0, 1.8 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.91 (d, *J* = 18.0 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.1, 176.8, 164.2, 163.8, 145.8, 135.8, 133.5, 131.7, 128.6, 127.9, 118.0, 112.0, 109.7, 55.4, 49.0, 44.7, 30.9, 27.1; HRMS (ESI): calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$ 338.13868; found 338.13865.

6-Ethoxy-2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4fa). 82 mg, 78% yield, white solid, mp 103–105 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 6.87 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 4.20 (d, *J* = 18.0 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.90 (d, *J* = 18.0 Hz, 1H), 3.42 (s, 3H), 1.59 (s, 3H), 1.37 (t, *J* = 6.6. Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.1, 176.8, 164.3, 163.3, 145.9, 135.9, 133.4, 131.7, 128.6, 128.0, 117.9, 112.4, 110.1, 63.8, 49.1, 44.7, 31.0, 27.1, 14.6; HRMS (ESI): calcd for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.15433; found 352.15430.

2,4-Dimethyl-4-(2-oxo-2-phenylethyl)-6-phenylisoquinoline-1,3(2*H*,4*H*)-dione (4ga). 74 mg, 64% yield, white solid, mp 178–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.37 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.60 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 5H), 7.37 (t, *J* = 7.2 Hz, 1H), 4.27 (d, *J* = 18.0 Hz, 1H), 4.03 (d, *J* = 18.0 Hz, 1H), 3.47 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.2, 176.7, 164.5,146.6, 144.2, 139.8, 135.9, 133.5, 129.9, 128.9, 128.6, 128.4, 128.0, 127.3, 126.2, 123.9, 122.2, 49.3, 44.7, 31.0, 27.3; HRMS (ESI): calcd for $C_{25}H_{22}NO_3$ $[M + H]^+$ 384.15942; found 384.15910.

6-Fluoro-2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ha). 52 mg, 53% yield, white solid, mp 127–128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.33 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.87–7.85 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.25 (d, *J* = 18.0 Hz, 1H), 3.87 (d, *J* = 18.0 Hz, 1H), 3.43 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.0, 176.2, 166.1 (d, *J* = 253.5 Hz), 163.7, 146.7 (d, *J* = 9.0 Hz), 135.7, 133.7, 132.4 (d, *J* = 9.0 Hz), 128.7, 128.0, 121.5 (d, *J* = 3.0 Hz), 114.9 (d, *J* = 22.5 Hz), 110.6 (d, *J* = 22.5 Hz), 49.2, 44.8, 30.7, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}FNO_3$ $[M + H]^+$ 326.11870; found 326.11872.

6-Chloro-2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ia). 62 mg, 60% yield, white solid, mp 73–74 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 4.25 (d, *J* = 18.0 Hz, 1H), 3.88 (d, *J* = 18.0 Hz, 1H), 3.43 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 196.0, 176.1, 163.8, 145.5, 140.2, 135.7, 133.7, 131.0, 128.7, 128.0, 127.8, 123.9, 123.6, 49.2, 44.6, 30.7, 27.4; HRMS (ESI): calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.08915; found 342.08911.

6-Bromo-2,4-dimethyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ja). 61 mg, 53% yield, white solid, mp 155–156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.17 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 1.2 Hz, 1H), 4.25 (d,

J = 18.0 Hz, 1H), 3.88 (d, *J* = 18.0 Hz, 1H), 3.42 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.0, 163.9, 145.5, 135.6, 133.7, 131.0, 130.7, 128.9, 128.7, 128.0, 126.9, 124.0, 49.2, 44.5, 30.7, 27.4; HRMS (ESI): calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.03863; found 386.03865.

Methyl 2,4-dimethyl-1,3-dioxo-4-(2-oxo-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (4ka). 57 mg, 52% yield, white solid, mp 154–155 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.96 (d, *J* = 1.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.27 (d, *J* = 18.0 Hz, 1H), 4.02 (d, *J* = 18.0 Hz, 1H), 3.90 (s, 3H), 3.45 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 176.3, 166.0, 163.9, 143.9, 135.7, 134.6, 133.7, 129.6, 128.6, 128.5, 128.1, 127.9, 125.1, 52.6, 49.4, 44.6, 30.6, 27.5; HRMS (ESI): calcd for $C_{21}H_{20}NO_5$ $[M + H]^+$ 366.13360; found 366.13374.

2-Ethyl-4-methyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4la). 74 mg, 77% yield, yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 4.21 (d, *J* = 18.6 Hz, 1H), 4.17–4.06 (m, 2H), 3.97 (d, *J* = 18.0 Hz, 1H), 1.61 (s, 3H), 1.27 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 176.1, 164.1, 143.7, 136.0, 133.6, 133.4, 129.3, 128.6, 127.9, 127.1, 125.2, 123.5, 49.1, 44.4, 35.6, 30.8, 12.9; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14374.

2-Butyl-4-methyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ma). 80 mg, 76% yield, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.56–7.47 (m, 2H), 7.43–7.34 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 4.21 (d, *J* = 18.0 Hz, 1H), 4.13–4.01 (m, 2H), 3.97 (d, *J* = 18.0 Hz, 1H), 1.73–1.62 (m, 2H), 1.60 (s, 3H), 1.46–1.36 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.3, 164.3, 143.7, 136.0, 133.6, 133.4, 129.3, 128.5, 127.9, 127.0, 125.1, 123.4, 48.9, 44.5, 40.3, 30.9, 29.8, 20.2, 13.8; HRMS (ESI): calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.17507; found 350.17503.

2-Isobutyl-4-methyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4na). 79 mg, 76% yield, white liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 4.23 (d, *J* = 18.0 Hz, 1H), 3.98–3.93 (m, 2H), 3.92–3.87 (m, 1H), 2.22–2.14 (m, 1H), 1.61 (s, 3H), 0.96 (q, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.7, 164.6, 143.8, 136.0, 133.6, 133.4, 129.5, 128.6, 127.9, 127.1, 125.1, 123.3, 48.8, 47.3, 44.6, 31.2, 27.3, 20.2; HRMS (ESI): calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.17507; found 350.17502.

Ethyl 2-(4-methyl-1,3-dioxo-4-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (4oa). 68 mg, 60% yield, white liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.56–7.51 (m, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 4.89 (d, *J* = 16.8 Hz, 1H), 4.78 (d, *J* = 16.8 Hz, 1H), 4.26–4.17 (m, 3H), 4.03 (d, *J* = 18.0 Hz, 1H), 1.67 (s, 3H), 1.27 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.1, 168.1, 163.8, 143.9, 135.8, 134.1, 133.5, 129.6, 128.6, 128.0, 127.2, 124.5, 123.4, 61.4, 48.5, 44.8, 41.4, 30.9, 14.1; HRMS (ESI): calcd for $C_{22}H_{22}NO_5$ $[M + H]^+$ 380.14925; found 380.14923.

4-Methyl-4-(2-oxo-2-phenylethyl)-2-phenylisoquinoline-1,3(2*H*,4*H*)-dione (4pa). 58 mg, 52% yield, white liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.59–7.53 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.45–7.40 (m, 4H), 7.36–7.32 (m, 3H), 4.21 (d, *J* = 18.0 Hz, 1H), 4.05 (d, *J* = 18.0 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 176.6, 164.6, 143.8, 135.9, 135.9, 134.0, 133.5, 129.6, 129.2, 128.6, 128.5, 128.4, 128.0, 127.3, 125.2, 123.8, 49.7, 45.0, 30.7; HRMS (ESI): calcd for $C_{24}H_{20}NO^3$ $[M + H]^+$ 370.14377; found 370.14376.

2-Allyl-4-methyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4qa). 49 mg, 49% yield, white solid, mp 100–101 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 3.6 Hz, 1H), 5.97–5.90 (m, 1H), 5.34 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.18 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.72–4.64 (m, 2H), 4.22 (d, *J* = 18.6 Hz, 1H), 3.98 (d, *J* = 18.0 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.1, 164.0, 143.8, 136.0, 133.8, 133.5, 132.1, 129.5, 128.6, 128.0, 127.2, 125.0, 123.4, 116.8, 48.9, 44.6, 42.5, 31.0; HRMS (ESI): calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 334.14377; found 334.14378.

2-Benzyl-4-methyl-4-(2-oxo-2-phenylethyl)isoquinoline-1,3(2H,4H)-dione (4ra). 80 mg, 70% yield, white solid, mp 165–166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.44–7.40 (m, 4H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 14.4 Hz, 1H), 5.23 (d, *J* = 14.4 Hz, 1H), 4.23 (d, *J* = 18.0 Hz, 1H), 3.99 (d, *J* = 18.6 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 176.4, 164.3, 143.8, 137.3, 136.0, 133.8, 133.5, 129.6, 128.6, 128.3, 128.1, 128.0, 127.2, 127.1, 125.0, 123.4, 48.8, 44.8, 43.7, 30.9; HRMS (ESI): calcd for $C_{25}H_{22}NO_3$ $[M + H]^+$ 384.15942; found 384.15939.

2,4-Dimethyl-4-(2-oxo-2-(o-tolyl)ethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ab). 59 mg, 61% yield, white solid, mp 140–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 4.19 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 3.44 (s, 3H), 2.13 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.1, 176.7, 164.6, 143.7, 138.3, 136.8, 133.6, 131.9, 131.6, 129.3, 128.3, 127.1, 125.6, 125.1, 123.5, 51.9, 44.9, 30.8, 27.3, 20.9; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14378.

2,4-Dimethyl-4-(2-oxo-2-(m-tolyl)ethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ac). 65 mg, 68% yield, white solid, mp 155–156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.39–7.34 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 4.20 (d, *J* = 18.6 Hz, 1H), 3.97 (d, *J* = 18.0 Hz, 1H), 3.45 (s, 3H), 2.36 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.4, 176.7, 164.6, 143.7, 138.4, 135.9, 134.2, 133.7, 129.3, 128.5, 128.4, 127.1, 125.2, 125.0, 123.5, 49.2, 44.5, 30.8, 27.3, 21.2; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14375.

2,4-Dimethyl-4-(2-oxo-2-(p-tolyl)ethyl)isoquinoline-

1,3(2*H*,4*H*)-dione (4ad). 67 mg, 70% yield, white solid, mp 161–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (dd, J = 7.8, 1.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 7.8 Hz, 2H), 4.18 (d, J = 18.0 Hz, 1H), 3.96 (d, J = 18.0 Hz, 1H), 3.44 (s, 3H), 2.38 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 176.7, 164.6, 144.4, 143.8, 133.6, 133.5, 129.3, 129.2, 128.0, 127.1, 125.0, 123.5, 49.0, 44.5, 30.8, 27.3, 21.6; HRMS (ESI): calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.14377; found 322.14379.

4-(2-(4-Methoxyphenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4ae). 75 mg, 74% yield, white solid, mp 141–143 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (dd, J = 7.8, 1.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 4.16 (d, J = 18.0 Hz, 1H), 3.93 (d, J = 18.0 Hz, 1H), 3.84 (s, 3H), 3.44 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.6, 176.8, 164.6, 163.7, 143.8, 133.6, 130.2, 129.3, 129.0, 127.0, 125.0, 123.5, 113.7, 55.5, 48.8, 44.5, 30.8, 27.23; HRMS (ESI): calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$ 338.13868; found 338.13866.

4-(2-(4-Chlorophenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4af). 70 mg, 69% yield, white solid, mp 171–172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 8.4, 1.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.41–7.38 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 18.0 Hz, 1H), 3.91 (d, J = 18.0 Hz, 1H), 3.44 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.0, 176.6, 164.5, 143.5, 140.0, 134.2, 133.7, 129.4, 129.4, 129.0, 127.2, 125.0, 123.4, 49.1, 44.5, 30.9, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.08915; found 342.08910.

4-(2-(4-Bromophenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4ag). 73 mg, 63% yield, white solid, mp 176–177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.2 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 4.18 (d, J = 18.0 Hz, 1H), 3.90 (d, J = 18.0 Hz, 1H), 3.44 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.0, 176.6, 164.5, 143.5, 140.0, 134.2, 133.7, 129.4, 129.4, 128.9, 127.2, 125.0, 123.4, 49.0, 44.5, 30.9, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.03863; found 386.03866.

***4-(2-(4-Iodophenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione* (4ah).** 84 mg, 65% yield, white solid, mp 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 4.16 (d, J = 18.0 Hz, 1H), 3.89 (d, J = 18.0 Hz, 1H), 3.44 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 176.6, 164.5, 143.5, 137.9, 135.1, 133.7, 129.4, 129.3, 127.2, 125.0, 123.4, 101.6, 49.0, 44.5, 30.9, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}INO_3$ $[M + H]^+$ 434.02476; found 434.02472.

4-(2-(2-Bromophenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4ai) 69 mg, 59% yield, white liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.2 Hz, 1H), 7.59–7.54 (m, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.28–7.25 (m, 1H), 7.22 (dd, J = 7.2, 1.8 Hz, 1H), 4.19 (d, J = 18.6 Hz, 1H), 3.91 (d, J = 18.6 Hz, 1H), 3.45 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.1, 176.4, 164.5, 143.0, 140.3, 133.7, 133.6, 131.9, 129.3, 128.7, 127.4, 127.3, 125.1, 124.0, 118.6, 52.9, 44.9, 30.8, 27.4; HRMS (ESI): calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.03863; found 386.03864.

4-(2-(3-Bromophenyl)-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4aj). 70 mg, 60% yield, white solid, mp 123–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.2 Hz, 1H), 7.97 (t, J = 1.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.25 (s, 1H), 4.18 (d, J = 18.6 Hz, 1H), 3.91 (d, J = 18.0 Hz, 1H), 3.44 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.9, 176.5, 164.5, 143.4, 137.5, 136.3, 133.8, 131.1, 130.2, 129.4, 127.3, 126.5, 125.0, 123.4, 123.0, 49.1, 44.5, 30.8, 27.3; HRMS (ESI): calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.03863; found 386.03866.

2,4-Dimethyl-4-(2-(naphthalen-2-yl)-2-oxoethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4ak). 72 mg, 67% yield, white solid, mp 171–172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.33 (dd, J = 7.8, 1.2 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.87–7.82 (m, 3H), 7.60 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 4.36 (d, J = 18.0 Hz, 1H), 4.13 (d, J = 18.0 Hz, 1H), 3.47 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 176.8, 164.7, 143.7, 135.7, 133.7, 133.3, 132.4, 129.8, 129.5, 129.4, 128.7, 128.5, 127.8, 127.2, 126.9, 125.1, 123.5, 123.5, 49.2, 44.6, 30.9, 27.4; HRMS (ESI): calcd for $C_{23}H_{20}NO_3$ $[M + H]^+$ 358.14377; found 358.14377.

2,4-Dimethyl-4-(2-oxo-2-(thiophen-2-yl)ethyl)isoquinoline-1,3(2*H*,4*H*)-dione (4al). 69 mg, 73% yield, white solid, mp 107–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.8, 1.2 Hz, 1H), 7.72 (dd, J = 4.2, 1.2 Hz, 1H), 7.59 (dd, J = 4.8, 1.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 8.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.10 (t, J = 4.2, 1H), 4.16 (d, J = 18.0 Hz, 1H), 3.88 (d, J = 18.0 Hz, 1H), 3.43 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.0, 176.5, 164.5, 143.3, 142.9, 134.0, 133.7, 132.1, 129.3, 128.1, 127.2, 124.9, 123.6, 49.5, 44.5, 30.8, 27.3; HRMS (ESI): calcd for $C_{17}H_{16}NO_3S$ $[M + H]^+$ 314.08454; found 314.08454.

4-(2-Cyclohexyl-2-oxoethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (4am). 36 mg, 38% yield, yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (dd, J = 7.8, 1.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 3.67 (d, J = 18.0 Hz, 1H), 3.40 (d, J = 18.6 Hz, 1H), 3.40 (s, 3H), 2.24–2.18 (m, 1H), 1.77–1.67 (m, 4H), 1.62–1.57 (m, 1H), 1.49 (s, 3H), 1.26–1.17 (m, 3H), 1.14–1.03 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.1, 176.7, 164.5, 143.6, 133.5, 129.3, 127.1, 125.0, 123.4, 51.0, 50.1, 44.2, 30.6, 28.1, 28.0, 27.3, 25.7, 25.5, 25.4; HRMS (ESI): calcd for $C_{19}H_{24}NO_3$ $[M + H]^+$ 314.17507; found 314.17507.

2,4-Dimethyl-4-(2-oxopropyl)isoquinoline-1,3(2*H*,4*H*)-dione (4an). 25 mg, 34% yield, white liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.8, 1.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 3.70 (d, J = 18.6 Hz, 1H), 3.40 (s, 3H), 3.35 (d, J = 18.6 Hz, 1H), 2.01 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.7, 176.6, 164.5, 143.4, 133.7, 129.3, 127.2, 125.0, 123.5, 53.8, 44.3, 30.5, 29.5, 27.2; HRMS (ESI): calcd for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.11247; found 246.11245.

Conflicts of interest

There are no conflicts to declare.

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