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ARTICLE

Visible-light-mediated radical cascade reaction: synthesis of 3-bromocoumarins from alkynoates

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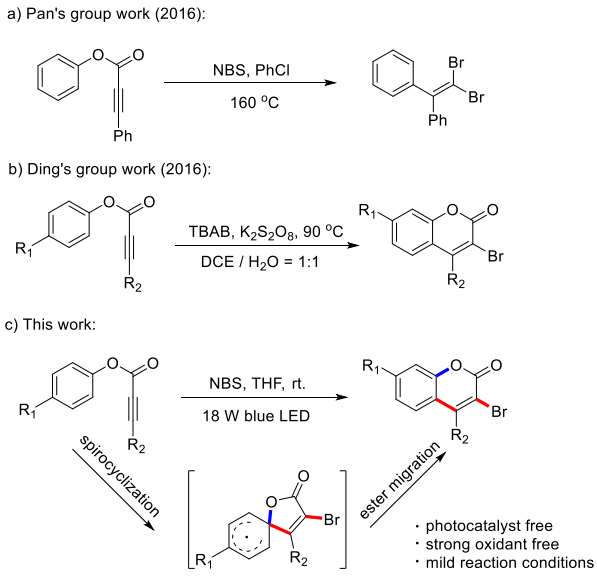
A visible-light-mediated radical addition of alkynoates to generate 3-bromocoumarins by using of N-bromosuccinimide as the bromo source has been accomplished. This procedure provides a bromo radical addition/spirocyclization/ester migration cascade reaction under very mild reaction conditions without using of any catalyst or strong oxidant and does not need high reaction temperature. Furthermore, the reaction can also be enlarged to gram scale, and the product 3-bromocoumarins can be further applied in the synthesis of complex compounds. .

Introduction

The bromo group has undoubtedly occupied a unique position in organic chemistry, as shown by its wide applications in elaborating into other versatile building blocks through transitional metal catalyzed coupling reactions, like Heck,[1] Suzuki[2] and Negishi,[3] and it also presents in many natural products.[4] Therefore, extensive efforts for constructing carbon-bromo bond have been pursued by chemists.[5] The direct bromination using bromine has a rich history, however, it's toxic, hazardous and less selective.[6] Transition metal catalyzed carbon–bromo bond formation is one of the most research in this field. Nevertheless, an initial organic halide[7] or sterically hindered ligands[8] are required in such transformations. Thus, it is still in great demand to develop an environmentally friendly, maneuverable strategy to construct carbon-bromo bond.

Over the past few years, visible-light mediated photoredox catalysis has emerged as a powerful synthetic tool in organic synthesis.[9] For its intrinsic characteristics of sustainability and green chemistry, the direct bromination via photoredox catalysis ever-grow interest from chemists.[10] On the other hand, readily available alkynoates have become fascinating and powerful intermediates in organic synthesis for they are good radical receptors and often along with a cascade cyclization reaction to construct 3-functionalized coumarins,[11] which have many pharmacological activities and widely found in the structures of natural or unnatural products.[12] For these reasons, some groups have tried bromination to alkynoates. In 2016, Pan's group demonstrated a novel bromination initiated decarboxylation and trifunctioalization of alkynoate (Scheme 1a).[13] Ding's group also reported an elegant work on a radical brominative addition of alkynoates, oxidative spirocyclization and 1,2-migration of esters for the synthesis of 3-bromocoumarins (Scheme 1b).[14] However, these reported reactions needed high reaction temperatures (160 or 90°C) or strong oxidant to generate the bromo radical which highly limited their applications in complex molecule synthesis and large scale preparation. Enlightened and encouraged by these brilliant works and aiming to synthesize coumarins under mild reaction conditions, herein we report a visible-light-mediated



Scheme 1 Functionalization of alkynoates with bromo radical.

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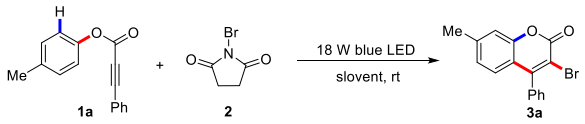
bromo radical addition / spirocyclization / ester migration cascade reaction to generate 3-bromocoumarins by using of N-bromosuccinimide as the bromo source under very mild reaction conditions without using photocatalyst or strong oxidant and the reaction can also be enlarged to gram scale.

Results and discussion

Initially, the reaction between tolyl alkynoate **1a** and NBS **2** was investigated. Using an 18 W blue LED strip as the visible light source, MeCN as solvent, this reaction was performed at room temperature in the air for 18 h. We were gratified to find that the desired 3-bromocoumarin **3a** was produced without using photocatalyst , although only in 11% isolated yield (Table 1, entry 1). After screening of solvents, we were delight to find that the reaction was implemented well in ethers solvent, and THF proved to be optimal (Table 1, entries 2–7). Changing light source into an 18 W fluorescent lamp, gave no better result (Table 1, entry 8). Furthermore, when the reaction was performed under argon atmosphere, it could give a better yield than in the air (Table 1, entry 9). Subsequently, the yield of **3a** could be further increased to 72% when we increased the amount of **2** to 3.0 equiv (Table 1, entry 10) and reduced **2** to 1.5 equiv led a lower yield (Table 1, entry 11). Finally, the control experiment proved that the yield of **3a** decreased significantly and had low conversion even prolonged reaction time to 48 h in the absence of light (Table 1, entry 12).

Table 1 Optimization of the reaction conditions[a]

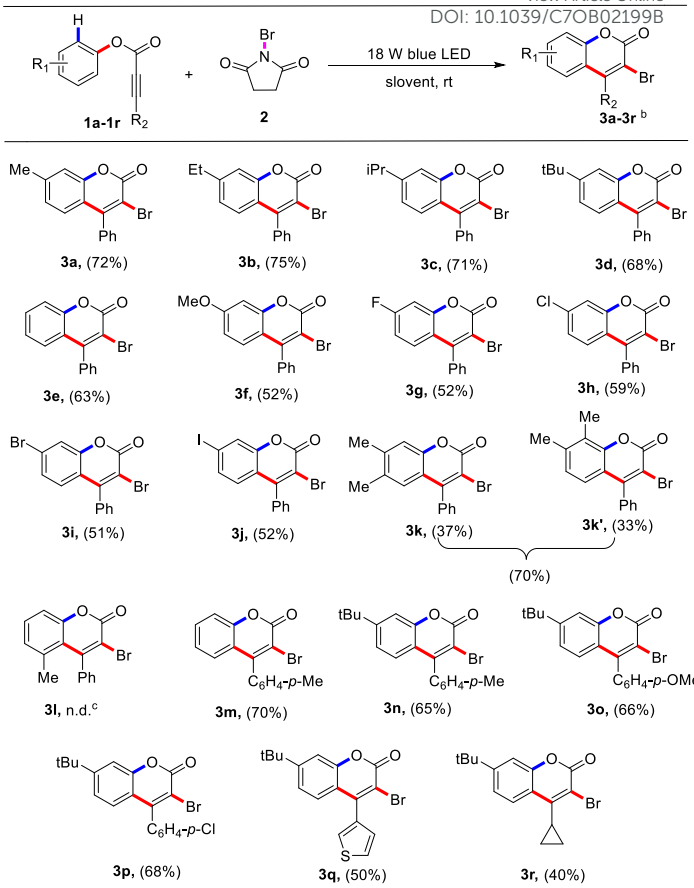


Entry	NBS (equiv)	Solvent	Yield [b](%)
1	2.0	CH_3CN	11
2	2.0	DCM	9
3	2.0	DMSO	n.r.
4	2.0	DMF	trace
5	2.0	1,4-dioxane	51
6	2.0	DME	43
7	2.0	THF	63
8[c]	2.0	THF	41
9[d]	2.0	THF	68
10[d]	**3.0**	**THF**	**72**
11[d]	1.5	THF	44
12[d,e]	3.0	THF	< 5

[a] Reaction conditions: tolyl alkynoate (**1a**, 0.2 mmol), solvent (2.0 mL) at room temperature in the air for 18 h. [b] Isolated yield. [c] A 18 W Fluorescent lamp was used. [d] Under argon atmosphere. [e] Without visible light irradiation.

To examine the substrate scope and limitations of this approach, various alkynoates were prepared and reacted with **2** under the optimized reaction conditions (Table 2). Some representative R^1-substituted alkynoates were first evaluated under the standard reaction conditions. When electron-donating groups, such as Me, Et, *i*-Pr, and *t*-Bu on the *para*-position of phenyl rings reacted with N-bromosuccinimide **2** generating the corresponding 3-bromocoumarins (**3a–e**) in moderate yields (63–75%). If there was a strong electron-donating substituent (MeO), the yield would decrease to 52%. The electron-withdrawing groups (F, Cl, Br and I) could also be well tolerated, giving the desired coumarins (**3g–j**) in 51–59% yields. To investigate the regioselectivity of the cyclization, a *meta*-substituted substrate **1k** was investigated and a mixture of two regioisomers **3k** and **3k'** were obtained in 70% total yield with a ratio of 1.12 : 1, respectively. However, the reaction became complex when **1l** was evaluated and the desired product **3l** was not detected, which could be attributed to the steric hindrance of the *ortho*-substituent. On the other hand, some R^2-substituted alkynoates were also evaluated. All of them (**1m**–**p**) underwent the desired reaction reposefully and gave the corresponding products (**3m**–**p**) in 65–70% yields regardless of electron-donating or -withdrawing groups. Moreover, when R^2 was a 3-thienyl group **1q**, it was also found to be suitable for the transformation with a moderate yield (**3q**, 50%). Furthermore, aliphatic substrate, with a cyclopropane group at the alkyne site **1r** was tested under the standard conditions. We were gratified to get the desired product **3r** in acceptable yield.

Table 2 Reaction scope of alkynoates[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv), THF (2.0 mL), 18 W blue LED strip, at room temperature under argon for 18-20 h. [b] Isolated yields. [c] The desired **3l** was not detected.

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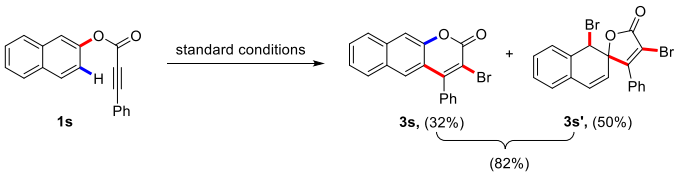
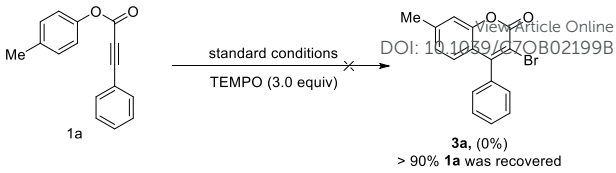


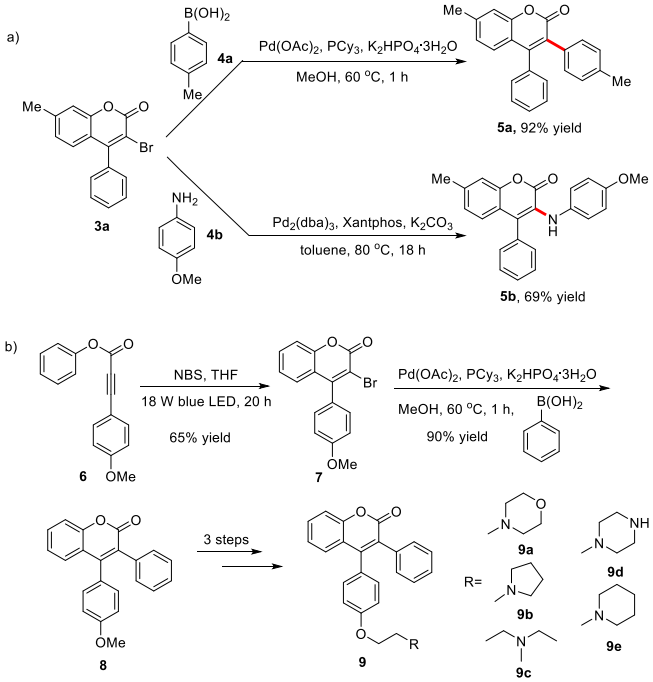
Scheme 2 Distinctive reaction of substrate **1s**.



Scheme 4 Mechanism study.

An interesting discovery should be noted that substrate **1s** with a naphthyl group was also evaluated under the standard reaction conditions. The desired product **3s** was obtained in 32% yield and a distinctive spirocyclization product **3s'** was also observed in moderate yield (scheme 2). This result was caused by the bromo radical captured spirocyclization intermediate again and it also provided us with a glimpse into the reaction mechanism.

To demonstrate the synthetic potential of this reaction, we enlarged **1a** to 1.058 g scale. To our delight, decreasing the amount of NBS to 2.0 equiv did not affect this transformation and **3a** was obtained in 70% isolated yield. We also wanted to demonstrate further applications of these derivatives **3** in the synthesis. Suzuki coupling reaction of **3a** with 4-Methylphenylboronic acid **4a** catalyzed by $Pd(OAc)_2$ and PCy_3 afforded the corresponding 3-tolylcoumarin **5a** in 92% yield (Scheme 3a).[15] For the 3-aminocoumarin core is a ubiquitous subunit in many natural products with great biological activities,[17] Buchwald-Hartwig amination of **3a** with *p*-anisidine in the presence of $Pd_2(dba)_3$ and Xantphos provided the 3-aminocoumarin **5b** in 69% yield (Scheme 3a).[15] we next sought to demonstrate the utility of this method in rapid syntheses of the 3,4-biphenyl coumarin derivatives **9a**-**9e**, which had

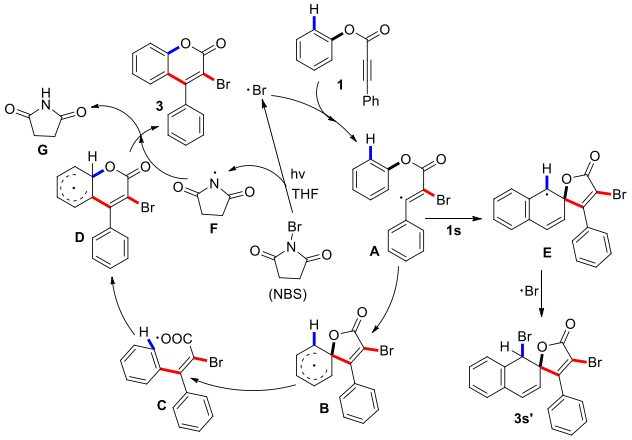


Scheme 3 Applications of this method in synthesis.

significant promoting effects of natural killer cell (a class of lymphocytes which have spontaneous cytotoxic activity) activity, and hold potential as immunomodulating agents (Scheme 3b).[16] Our strategy began with visible-light-mediated bromination and cyclization of **6** followed by Suzuki coupling reaction, to give 3,4-biphenyl coumarin derivative **8** and the synthesis of compounds **9a**-**9e** should be possible followed by three steps as published in the literature.[17]

In order to gain an insight into this transformation, we conducted radical inhibition experiment for the mechanistic study. When 3.0 equiv well-known radical scavenger 2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added under the standard conditions, the reaction was obviously inhibited (Scheme 4), and this result indicates that the transformation may proceed via a radical pathway.

On the basis of the above-mentioned experimental observations and previous literatures,[11] a plausible mechanism for this cascade reaction is depicted in Scheme 5. First, the bromo radical is generated from NBS through irradiation by the blue LED. In this process, THF may form halogen bonding adduct with NBS and facilitate the N-Br bond cleavage.[18] Then this bromo radical undergoes intermolecular selective addition to the α-position of the C=O bond in alkynoate **1** leads to vinyl intermediate **A**, which goes through intramolecular spirocyclization to provide intermediate **B**. Subsequently, it undergoes cleavage of the C–O bond to generate the carboxyl radical **C**, which can cyclize to form compound **D**. The abstraction a H-atom of **D** by succinimide radical **F** would give the product **3**. If **1s** is employed to this transformation, for the benzyl radical is stable, intermediate **A** can provide **E** by spirocyclization, and intermediate **E** is captured by another bromo radical to form **3s'**.



Scheme 5 Possible reaction mechanism.

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Conclusions

In summary, we have demonstrated a new approach for the synthesis of the pharmacological activity attractive coumarins core structure in moderate to good yields under catalyst and strong oxidant free conditions. And it can also be enlarged to gram scale, the product 3-bromocoumarins can be further applied in the synthesis.

Experimental section

General information.

Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. All syntheses of complex were carried out under argon atmosphere on Wattecs Parallel Reactor. Column chromatography was generally performed on silica gel (200-300 mesh) and reactions were monitored by thin layer chromatography (TLC) using silica gel GF254 plates with UV light to visualize the course of reaction. Melting points were determined with a digital Koffer apparatus and were uncorrected after recrystallized with petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR data were recorded on a 400 MHz or 300 MHz spectrometer using $CDCl_3$ as solvent at room temperature. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. High-resolution mass spectra (HRMS) were obtained on a FT-ICR spectrometer.

General procedure for the visible-light-promoted cascade reaction.

To a reaction tube equipped with a magnetic stir bar was added phenyl 3-phenylpropiolate **1** (0.2 mmol, 1.0 equiv), NBS **2** (N-bromosuccinimide, 0.6 mmol, 3.0 equiv). The reaction tube was then filled with dry argon. After that, THF (2.0 mL) was injected into the tube via a syringe. Then the reaction was irradiated with an 18 W blue LED strip and stirred at room temperature from 18-20 h. The reaction was monitored by TLC to establish the consumption of starting material. After it was complete, the reaction mixture was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography to afford the desired coumarin product.

Gram Scale Preparation of 3a.

To a reaction tube equipped with a magnetic stir bar was added tolyl alkynoate **1a** (1.058 g, 4.483 mmol, 1.0 equiv), NBS **2** (N-bromosuccinimide, 1.596 g, 8.966 mmol, 2.0 equiv). The reaction tube was then filled with dry argon. After that, THF (15.0 mL) was injected into the tube via a syringe. Then the reaction was irradiated with an 18 W blue LED strip and stirred at room temperature for 24 h. After it was complete, the reaction mixture was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50:1 to 20:1) to afford the desired **3a** in 70% yield (0.933 g).

3-bromo-7-methyl-4-phenyl-2*H*-chromen-2-one (3a).

Compound **3a** was obtained as a white solid in 72% yield according to the general procedure. Mp: 191–193°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 3H), 7.32 – 7.27 (m, 2H), 7.20 (s, 1H), 6.98 (dt, J = 18.7, 4.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.6, 152.5, 143.5, 135.4, 129.2, 128.8, 128.0, 127.3, 125.9, 117.9, 116.9, 111.2, 21.6. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{16}H_{12}BrO_2$: 315.0015, found: 315.0014.

3-bromo-7-ethyl-4-phenyl-2*H*-chromen-2-one (3b).

Compound **3b** was obtained as a white solid in 75% yield according to the general procedure. Mp: 157–158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 3H), 7.32 – 7.27 (m, 2H), 7.23 (s, 1H), 7.01 (dt, J = 19.1, 4.8 Hz, 2H), 2.73 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.6, 152.6, 149.7, 135.4, 129.2, 128.8, 128.1, 127.4, 124.7, 118.1, 115.7, 111.3, 28.8, 15.0. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{17}H_{14}BrO_2$: 329.0172, found: 329.0171.

3-bromo-7-isopropyl-4-phenyl-2*H*-chromen-2-one (3c).

Compound **3c** was obtained as a white solid in 71% yield according to the general procedure. Mp: 118–120°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 3H), 7.33 – 7.27 (m, 2H), 7.26 (s, 1H), 7.06 (dd, J = 8.3, 1.5 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 2.99 (hept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.6, 154.4, 152.7, 135.5, 129.2, 128.8, 128.1, 127.5, 123.4, 118.3, 114.4, 111.3, 34.2, 23.5. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{18}H_{16}BrO_2$: 343.0328, found: 343.0326.

3-bromo-7-(tert-butyl)-4-phenyl-2*H*-chromen-2-one (3d).

Compound **3d** was obtained as ropy oil in 68% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 3H), 7.41 (d, J = 1.8 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.22 (dd, J = 8.5, 1.9 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.7, 154.5, 152.5, 135.4, 129.3, 128.8, 128.1, 127.1, 122.2, 117.9, 113.6, 111.5, 35.3, 31.0. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{19}H_{18}BrO_2$: 357.0485, found: 357.0484.

3-bromo-4-phenyl-2*H*-chromen-2-one (3e).

Compound **3e** was obtained as a white solid in 63% yield according to the general procedure. Mp: 154–155°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 4H), 7.41 (dd, J = 8.3, 0.8 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.22 – 7.16 (m, 1H), 7.08 (dd, J = 8.0, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.34, 154.62, 152.48, 135.29, 132.02, 129.34, 128.85, 128.07, 127.60, 124.69, 120.35, 116.82, 112.65. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_{10}BrO_2$: 300.9859, found: 300.9863.

3-bromo-7-methoxy-4-phenyl-2*H*-chromen-2-one (3f).

Compound **3f** was obtained as a white solid in 52% yield according to the general procedure. Mp: 153–155°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 3H), 7.31 – 7.27 (m, 2H), 6.97 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.74 (dd, J = 8.9, 2.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 157.8, 154.8, 154.3, 135.6, 129.3, 128.8, 128.6, 128.1, 114.0, 112.9, 108.8, 100.6, 55.9. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{16}H_{12}BrO_3$: 330.9964, found: 330.9963.

3-bromo-7-fluoro-4-phenyl-2*H*-chromen-2-one (3g).

Compound **3g** was obtained as a white solid in 52% yield according to the general procedure. Mp: 206–207°C. ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 3H), 7.32 – 7.27 (m, 2H), 7.10 (ddd, *J* = 14.9, 8.8, 4.2 Hz, 2H), 6.92 (ddd, *J* = 8.9, 8.1, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (165.67, 163.13, d, *J* = 254 Hz), 157.01, 154.15, (153.55, 153.42, d, *J* = 13 Hz), 135.10, 129.52, (129.43, 129.33, d, *J* = 10 Hz), 128.96, 127.99, (117.15, 117.12, d, *J* = 3 Hz), (112.93, 112.70, d, *J* = 23 Hz), (111.42, 111.39, d, *J* = 3 Hz), (104.49, 104.23, d, *J* = 26 Hz). HRMS (ESI): m/z $[M+NH_4]^+$ calculated for $C_{15}H_{12}BrFNO_2$: 336.0030, found: 336.0031.

3-bromo-7-chloro-4-phenyl-2*H*-chromen-2-one (3h).

Compound **3h** was obtained as a white solid in 59% yield according to the general procedure. Mp: 204−205°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 3H), 7.42 (d, *J* = 1.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.16 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.0, 152.6, 138.0, 134.9, 129.6, 129.0, 128.5, 128.0, 125.3, 119.0, 117.1, 112.6. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_9BrClO_2$: 334.9469, found: 334.9468.

3,7-dibromo-4-phenyl-2*H*-chromen-2-one (3i).

Compound **3i** was obtained as a white solid in 51% yield according to the general procedure. Mp: 204−206°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 4H), 7.33 – 7.27 (m, 3H), 6.94 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.0, 152.5, 134.8, 129.6, 129.0, 128.6, 128.1, 128.0, 126.0, 120.0, 119.3, 112.8. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_9Br_2O_2$: 378.8964, found: 378.378.8962.

3-bromo-7-iodo-4-phenyl-2*H*-chromen-2-one (3j).

Compound **3j** was obtained as a white solid in 52% yield according to the general procedure. Mp: 204−206°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.30 – 7.26 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 154.1, 152.2, 134.8, 134.0, 129.6, 129.0, 128.5, 128.0, 125.9, 119.9, 113.1, 97.5. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{15}H_9BrIO_2$: 462.8825, found: 462.8837.

3-bromo-6,7-dimethyl-4-phenyl-2*H*-chromen-2-one (3k).

Compound **3k** was obtained as a white solid in 37% yield according to the general procedure. Mp: 181−183°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 3H), 7.31 – 7.27 (m, 2H), 7.18 (s, 1H), 6.77 (s, 1H), 2.33 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.6, 150.9, 142.3, 135.6, 133.6, 129.2, 128.8, 128.1, 127.5, 118.1, 117.3, 111.3, 20.2, 19.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{17}H_{14}BrO_2$: 329.0172, found: 329.0171.

3-bromo-7,8-dimethyl-4-phenyl-2*H*-chromen-2-one (3k').

Compound **3k'** was obtained as a white solid in 33% yield according to the general procedure. Mp: 186−189°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 3H), 7.30 – 7.26 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 2.43 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 155.1, 150.8, 142.0, 135.8, 129.1, 128.7, 128.1, 126.1, 124.7, 124.5, 118.3, 111.0, 20.4, 11.6. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{17}H_{14}BrO_2$: 329.0172, found: 329.0174.

3-bromo-4-(*p*-tolyl)-2*H*-chromen-2-one (3m).

Compound **3m** was obtained as a white solid in 70% yield according to the general procedure. Mp: 161−164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.22 –7.10 (m, 4H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 154.8, 152.5, 139.4, 132.3, 131.9, 129.5, 128.1, 127.7, 124.6, 120.5, 116.8, 112.6, 21.4. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{16}H_{12}BrO_2$: 315.0015, found: 315.0017.

3-bromo-7-(*tert*-butyl)-4-(*p*-tolyl)-2H-chromen-2-one (3n).

Compound **3n** was obtained as ropy oil in 65% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.8 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 – 7.16 (m, 3H), 7.04 (d, *J* = 8.5 Hz, 1H), 2.47 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.6, 154.7, 152.5, 139.3, 132.4, 129.4, 128.0, 127.2, 122.1, 118.0, 113.5, 111.4, 35.2, 30.9, 21.4. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{20}H_{20}BrO_2$:371.0641, found: 371.0651.

3-bromo-7-(*tert*-butyl)-4-(4-methoxyphenyl)-2*H*-chromen-2-one (3o).

Compound **3o** was obtained as ropy oil in 66% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.8 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.11 – 7.04 (m, 3H), 3.91 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.8, 156.6, 154.4, 152.5, 129.7, 127.5, 127.2, 122.2, 118.1, 114.1, 113.6, 111.6, 55.4, 35.2, 30.9. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{20}H_{20}BrO_3$: 387.0590, found: 387.0592.

3-bromo-7-(*tert*-butyl)-4-(4-chlorophenyl)-2*H*-chromen-2-one (3p).

Compound **3p** was obtained as a white solid in 68% yield according to the general procedure. Mp: 195−196°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.28 – 7.22 (m, 3H), 6.98 (d, *J* = 8.5 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 157.0, 153.3, 152.5, 135.5, 133.7, 129.6, 129.2, 126.8, 122.4, 117.6, 113.7, 111.7, 35.3, 30.9. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{19}H_{17}BrClO_2$: 391.0095, found: 391.0094.

3-bromo-7-(*tert*-butyl)-4-(thiophen-3-yl)-2*H*-chromen-2-one (3q).

Compound **3q** was obtained as a white solid in 50% yield according to the general procedure. Mp: 98−100°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.45 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.19 (s, 1H), 7.18 – 7.14 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 156.8, 152.4, 150.3, 134.8, 127.8, 126.9, 126.5, 126.0, 122.3, 117.8, 113.6, 111.8, 35.3, 31.0. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{17}H_{16}BrO_2S$: 363.0049, found: 363.0048.

3-bromo-7-(*tert*-butyl)-4-cyclopropyl-2*H*-chromen-2-one (3r).

Compound **3r** was obtained as ropy oil in 66% yield according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.31 (m, 2H), 1.89 (tt, *J* = 8.6, 5.9 Hz, 1H), 1.35 (s, 9H), 1.34 – 1.31 (m, 2H), 0.93 – 0.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 156.2, 153.5, 152.0, 125.1, 121.9, 118.2, 114.5, 113.6, 35.2, 31.0, 14.4, 9.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{16}H_{18}BrO_2$: 321.0485, found: 321.0487.

3-bromo-4-phenyl-2*H*-benzo[g]chromen-2-one (3s).

Compound **3s** was obtained as a white solid in 32% yield according to the general procedure. Mp: 183−186°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.60 (m, 1H), 7.89 – 7.81 (m, 1H), 7.71 – 7.64 (m, 2H), 7.61 – 7.55 (m, 4H), 7.40 – 7.31 (m, 2H),

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7.06 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.5, 149.7, 135.7, 134.8, 129.3, 129.1, 128.9, 128.1, 127.8, 127.5, 124.6, 122.9, 122.5, 115.6, 112.1, 100.0. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{19}H_{12}BrO_2$: 351.0015, found: 351.0017.

1',4-dibromo-3-phenyl-1'*H*,5*H*-spiro[furan-2,2'-naphthalen]-5-one (3s').

Compound **3s'** was obtained as a white solid in 50% yield according to the general procedure. Mp: 182−185°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.60 – 7.56 (m, 1H), 7.45 – 7.39 (m, 3H), 7.29 – 7.26 (m, 2H), 7.16 – 7.11 (m, 1H), 6.93 (d, *J* = 9.5 Hz, 1H), 6.09 (d, *J* = 9.5 Hz, 1H), 5.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 161.9, 134.1, 132.0, 130.7, 130.2, 129.5, 129.4, 129.2, 128.9, 128.8, 128.5, 127.7, 121.8, 112.1, 87.6, 53.4. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{19}H_{13}Br_2O_2$: 430.9277, found: 430.9270.

7-methyl-4-phenyl-3-(*p*-tolyl)-2*H*-chromen-2-one (5a).

$K_2HPO_4{\cdot}3H_2O$ (0.90 mmol, 3.0 equiv) was added to a mixture of compound **3a** (63.0 mg, 0.2 mmol, 1.0 equiv), 4-Methylphenylboronic acid **4** (41.0 mg, 0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5.0 mol %), and PCy_3 (5.6 mg, 10.0 mol %) in methanol (2.0 mL). The reaction mixture was stirred at 60°C for 1 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 to 5:1) to afford the product **5a** as a white solid in 92% yield (60.0 mg). Mp: 232−234°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.22 (s, 1H), 7.14 – 7.09 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.04 – 6.95 (m, 5H), 2.45 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 153.2, 151.3, 142.5, 137.2, 134.9, 131.0, 130.4, 129.4, 128.5, 128.2, 128.1, 127.4, 125.9, 125.2, 118.2, 116.9, 21.6, 21.2. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{23}H_{19}O_2$: 327.1380, found: 327.1381.

3-((4-methoxyphenyl)amino)-7-methyl-4-phenyl-2*H*-chromen-2-one (5b).

A mixture of compound **3a** (63.0 mg, 0.2 mmol, 1.0 equiv), *p*-anisidine **4b** (29.5 mg, 0.24 mmol, 1.2 equiv), $Pd_2(dba)_3$ (4.6 mg, 2.5 mol %), Xantphos (5.8 mg, 5 mol %), and K_2CO_3 (55.2 mg, 0.4 mmol, 2.0 equiv) in toluene (2.0 mL) was stirred at 80°C for 18 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1 to 10:1) to afford the product **5b** as a yellow solid in 69% yield (49.0 mg). Mp: 148−150°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 3H), 7.20 – 7.14 (m, 3H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.56 – 6.48 (m, 2H), 6.04 (s, 1H), 3.68 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 155.4, 149.6, 138.7, 134.7, 133.4, 129.4, 128.4, 128.1, 126.4, 125.5, 124.9, 122.7, 119.1, 116.6, 113.6, 55.5, 21.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{23}H_{20}NO_3$: 358.1438, found: 358.1439.

3-bromo-4-(4-methoxyphenyl)-2*H*-chromen-2-one (7).

Compound **7** was obtained as a white solid in 65% yield according to the general procedure. Mp: 154−156°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 1H), 7.43 – 7.36 (m, 1H), 7.29 – 7.14 (m, 4H), 7.12 – 7.05 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 157.4, 154.5, 152.4, 131.9, 129.7, 127.7, 127.2, 124.6, 120.5, 116.7, 114.1, 112.7, 55.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{16}H_{12}BrO_3$: 330.9964, found: 330.9966.

4-(4-methoxyphenyl)-3-phenyl-2*H*-chromen-2-one (8).

$K_2HPO_4{\cdot}3H_2O$ (0.90 mmol, 3.0 equiv) was added to a mixture of compound **7** (66.0 mg, 0.2 mmol, 1.0 equiv), phenylboronic acid (36.6 mg, 0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5.0 mol %), and PCy_3 (5.6 mg, 10.0 mol %) in methanol (2.0 mL). The reaction mixture was stirred at 60°C for 1 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1 to 5:1) to afford the product **8** as a faint yellow solid in 90% yield (59.0 mg). Mp: 226−228°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.24 – 7.11 (m, 6H), 7.08 – 7.00 (m, 2H), 6.87 – 6.79 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 159.4, 153.2, 151.4, 134.1, 131.3, 130.77, 130.5, 127.8, 127.7, 127.5, 126.8, 126.5, 124.0, 120.7, 116.7, 113.7, 55.1. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{22}H_{17}O_3$: 329.1172, found: 329.1173.

Conflicts of interest

There are no conflicts to declare.

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