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Synthesis of Benzil-*o*-carboxylate Derivatives and Isocoumarins Through Neighboring Ester-Participated Bromocyclization of *o*-Alkynylbenzoates

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A bromide mediated neighboring ester-participated bromocyclization of *o*-alkynylbenzoates is described here for synthesis of benzil-*o*-carboxylate. 4-bromoisocoumarins are also reached when phenyl *o*-alkynylbenzoate is used as the substrate. Mechanism studies suggest that the whole process is comprised by electrophilic bromocyclization and dibromohydration-based ring-opening, and the neighboring ester group participates in the bromocyclization. Interestingly, the two oxygen atoms of keto carbonyl in benzil-*o*-carboxylate are both derived from water. Electrophilic bromo source is *in situ* generated from oxidation of bromide.

Alkyne chemistry has attracted profound interest of chemists due to its versatility in producing diverse useful synthons or biologically interesting architectures in organic synthesis.[1] To date, ever-growing efforts were made on exploiting new alkyne-based transformations from accessibility-simple yet powerfull dual-functionalized substrates with alkynyl and another reactive group at *ortho* position.[2] Among the dual-functionalized substrates, *o*-alkynylbenzoate was a versatile building block for the synthesis of diverse isocoumarins.[3-8] As an initial example, Oliver and Gandour found that liquid bromine (Br_2) enabled the formation of 4-bromoisocoumarin through 6-*endo* electrophilic bromocyclization.[3] However, the generality and scope have not been explored. Reported by Larock and others,[4] Iodine (I_2) and iodine chloride (ICl) were then highlighted by as a safe facilitator of 6-*endo* cyclization of *o*-alkynylbenzoate to provide 4-iodoisocoumarins (Scheme 1a). Additionally, 6-*endo* cyclization of *o*-alkynylbenzoate could be reached by means of Bronst acid[5] and Lewis acid[6] as well as transitional metal catalysis.[7]

Recently, our group developed a novel procedure for the synthesis of *N*-(2-(2,2-dibromo-2-arylacetyl)aryl)acetamide from *N*-(2-alkynylaryl)acetamide in absence of metal catalysis under mild conditions (Scheme 1b).[8] Mechanism studies suggested that an amide oxygen transfer reaction-based pathway was involved in the whole process, which was comprised by oxidative bromocyclization and dibromohydration-based ring-opening of the resulting benzoxazine intermediate. Inspired by this result, In this paper we would like to disclose a formal diketonization of *o*-alkynylbenzoate for the synthesis of benzil-*o*-carboxylate.

To the best of our knowledge, diketonization of *o*-alkynylbenzoate towards benzil-*o*-carboxylates was witnessed by Liu and co-workers.[10] Liu's work resorted to a gold (I)-based catalytic system with selectfluor as an oxidant. In the process, the *ortho* ester group served as a directing group to assist the formation of cyclic gold-enol species. The reaction scope investigation implied that the reaction was restricted to the use of *o*-arylacetylenylbenzoates as substrates. In this paper we envisioned that electrophilic 6-*endo* bromocyclization, oxidative ring-opening and hydrolysis of the resulting dibromoketone could give rise to benzil-*o*-carboxylate (Scheme 1c). Distinctively, our projected procedure avioded the use of gold metal as catalyst. More importantly, the reaction involved participation of the *ortho* ester group[11] for the formation of isocoumarin cation intermediate, thus representing a novel alternative of diketonization of triple bonds to deliver benzil-*o*-carboxylate.

According to the findings from Srinivasan and co-workers, a I_2 or ICl/water system enabled diketonization of alkynyl in *o*-alkynylbenzaldehyde and *o*-alkynylaroyl compounds by neighboring carbonyl-pariticipated 6-*endo*-*dig* cyclization.[12] However, a preliminary trial showed that the I_2 or ICl/water system was not compatible for the model reaction of methyl *o*-alkynylbenzoate **1a** in the presence of a co-solvent (1,2-dichloroethane:water, 1:1, v/v) at 80 °C. This discrepant result promoted us to develop another new reaction system for metal-free and neighboring ester-participated diketonization of *o*-alkynylbenzoate.

Recently, our group found that *tetra*-*n*-butylammonium bromide TBAB/$K_2S_2O_8$ was an efficient system to convert aryl propiolate to 3-bromocoumarins.[13] Control experiments and mechanism studies suggested that bromo radical derived from single-electron-oxidation of bromide was involved in the process. Considering our continuous interest in peroxydisulfate chemistry,[14] we attempted to expand the TBAB/$K_2S_2O_8$ system to this neighboring ester-participated diketonization of *o*-alkynylbenzoate for the synthesis of benzil-*o*-carboxylate, since peroxydisulfate could oxidise bromide to electrophilic bromo cation through two-electron-oxidation.[15]

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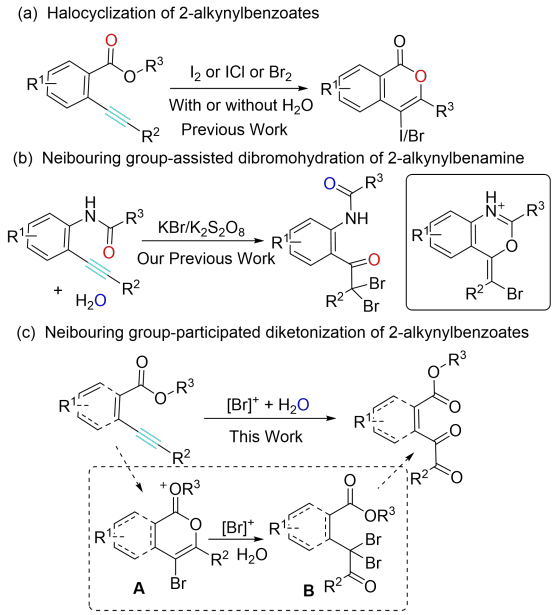
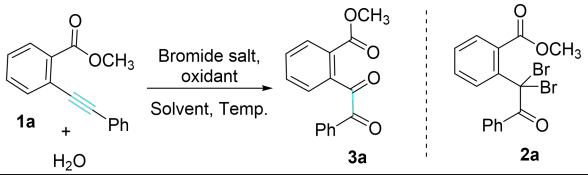


Scheme 1. Proposed route for the synthesis of benzil-*o*-carboxylate

To our delight, the TBAB/$K_2S_2O_8$ system made a sucess in diketonization of *o*-alkynylbenzoate **1a** to produce benzil-*o*-carboxylate 3**a** in 43% isolated yield after chromatography purification (entry 1, table 1). As expected, a crude NMR analysis of the model reaction indicated that benzil-*o*-carboxylate 3**a** came from hydrolysis of *o*-dibromoketobenzoate **2a** during chromatography purification. A control experiment treating **2a** with 10 equiv silica gel quantitatively offered the desired benzil-*o*-carboxylate 3**a** within 10 minutes, which supported the above assumption. To our surprise, 4-bromoisocoumarin, a well-known product derived from an electrophilic bromocyclization, was not observed at all. This promising result was supportive for our desiged project, thus encouraging us to evaluate various result-affecting factors in the reaction. The results were presented in table 1. From the results of bromide screening, it might draw a conclusion that bromide source would make great impact on the reaction. No better yields were observed when bromide was changed to KBr (entry 2, table 1). The reaction using $ZnBr_2$ as bromide source became complex, probably because lewis acidity of zinc salt rendered triple bond to be more open to various nucleophiles. Pleasingly, the reaction efficiency was drastically improved when oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) was employed as an oxidant (entry 4, table 1), leading to the desired **3a** in 80% isolated yield. Screening of other oxidants such as MnO_2, TBHP, and H_2O_2 showed the peroxydisulfate-type of oxidant was uniquely effective for this reaction (entries 5-6, table 1). The reactions using MnO_2, TBHP, and H_2O_2 gave a trace of the desired product **3a**. Subsequently, the solvent effect was also examined accordingly. From the results, it seemed that the co-solvent DCE (1,2-dichloroethane):water (v/v, 1:1) was the best choice. The use of either MeCN:H_2O or MeOH:H_2O would reduce the reaction efficiency. Interestingly, the reaction proceeded smoothly in pure water, providing the desired **3a** in 53% yield (entry 9, table 1). The blank reaction without water was totally retarded. A trace amount of **3a** was observed, and the starting material **1a** converted into 4-bromoisocoumarin in 47% yield. To reduce temperature was not favourable for the reaction (entries 14-15, table 1). A similar yield was detected when the loading of TBAB was increased from 2.1 equiv to 2.5 equiv (entry 16, table 1).

With the optimized conditions (see Entry 4 in table 1), we then explored the reaction generality. The results were illustrated in table 2. A series of benzil-*o*-carboxylates were achieved accordingly. As presented in table 2, the electronic effect of substituent R^1 made slight impact on the outcomes, producing the corresponding products **3a-3d** in good yields. Particularly, the phenylacetylenyl group attached on R^1 survived under standard conditions, releasing 5-phenylacetylenylbenzil-*o*-carboxylate **3e** in 76% yield. The reaction of 2-alkynylpyridine-o-carboxylate under standard conditions provided *N*-benzil-o-carboxylate **3f** in 75% yield. Interestingly, methyl 2-(phenylethynyl)cyclohex-1-ene-1-carboxylate were also compatible for the reaction, offering the desired product **3p** in 76% yield. It is noteworthy that this compound **3p** can not be achieved by Liu's procedure.[10]

Table 1 Initial studies for the reaction of neibouring group-participated dibromohydration of 2-alkynylbenzoate.



Entry	[Br] (2.1 eq.)	Oxidant (2.0 eq.)	T (°C)	Solvent	Yield (%)[a,b]
1	TBAB	$K_2S_2O_8$	80	DCE:H_2O (v/v, 1:1)	43
2	KBr	$K_2S_2O_8$	80	DCE:H_2O (v/v, 1:1)	18
3	$ZnBr_2$	$K_2S_2O_8$	80	DCE:H_2O (v/v, 1:1)	complex
4	TBAB	Oxone	80	DCE:H_2O (v/v, 1:1)	80
5	TBAB	MnO_2	80	DCE:H_2O (v/v, 1:1)	trace
6	TBAB	H_2O_2	80	DCE:H_2O (v/v, 1:1)	trace
7	TBAB	Oxone	80	MeCN:H_2O (v/v, 1:1)	71
8	TBAB	Oxone	80	MeOH:H_2O (v/v, 1:1)	complex
9	TBAB	Oxone	80	H_2O	53
10[c]	TBAB	Oxone	80	DCE	trace
11	TBAB	Oxone	80	DCE:H_2O (v/v, 5:1)	64
12	TBAB	Oxone	80	DCE:H_2O (v/v, 1:5)	65
13	TBAB	Oxone	80	DCE:H_2O (v/v, 1:1)	36
14	TBAB	Oxone	60	DCE:H_2O (v/v, 1:1)	66
15[d]	TBAB	Oxone	rt	DCE:H_2O (v/v, 1:1)	49
16[e]	TBAB	Oxone	80	DCE:H_2O	79

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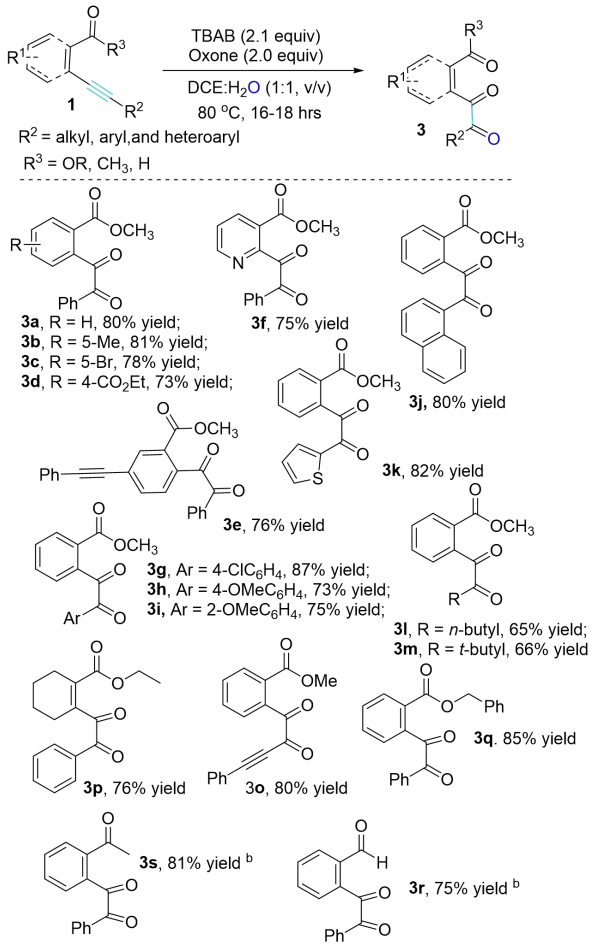
(v/v, 1:1)

[a] Isolated yield based on 2-alkynylbenzoate **1a**. [b] Standard conditions: 2-alknylbenzoate **1a** (0.2 mmol), TBAB (2.1 equiv), Oxone (2.0 equiv), solvent (2 mL), 18 hrs. [c] 4-bromoisocoumarin was achieved in 47% yield. [d] the reaction time was prolonged to 36 hrs. [e] The loading of TBAB was increased to 2.5 equiv.

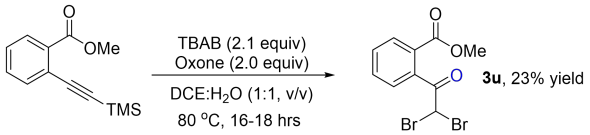
Table 2 Generation of benzil-o-carboxylate **3** through neighboring ester participated reaction of *o*-alkynylbenzoate **1**[a,b]



[a] Isolated yield based on aniline **1a**. [b] room temperature

Subsequently, we explored tolerance of R^2 substituents. To our delight, it seemed that R^2 substituents could be occupied with aryl, heteroaryl, and alkyl. The corresponding products **3g-3m** were obtained in good to excellent yields. Generally, the substrate with aryl connected on R^2 was more efficient for the above diketonization than that of alkyl attached on R^2 position. For example, alkyl-linked benzil-o-carboxylates **3l** and **3m** were afforded under standard conditions in good yields when the corresponding substrates were used. It was surprised to find that these two compounds **3l** and **3m** were also not reached by Liu's method.[9] Additionally, the substrate attaching phenylethynyl on R^2 position was compatible for the reaction, leading to ethyl-connected benzil-o-carboxylate **3o** in 80% yieldd. Interestingly, a distinctive compound was afforded efficiently when we expanded the reaction to the substrate with trimethylsilyl at R^2 position (Table 3). This distinctive compound was identified as methyl 2-(2,2-dibromoacetyl)benzoate **3u**. In the reaction, the dibrominative **3u** was not hydrolysed into benzil-*o*-carboxylate when treating with silica gel. Interestingly, the silyl group was removed under standard conditions. Water was installed in internal carbon of triple bond to 2-dibromoacetylbenzoate **3u**, which attributed to an electrophilic *5-exo-dig* cyclization of methyl 2-((trimethylsilyl)ethynyl)benzoate[4a,16] and subsequential oxidative ring-opening.

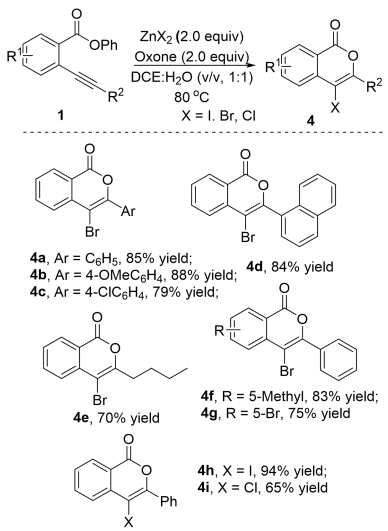
Table 3. The reaction of neibouring group-participated dibromohydration of 2-acetylenylbenzoate and 2-trimethylsilylbenzoate.[a]



[a] Isolated yield based on *o*-alkynylbenzoate **1**.

Various types of carbonyl including ester, ketone, and aldehyde were also examined. For instance, the reaction of benzyl 2-alkynylbenzoate gave desired product **3q** in 85% yield. Interestingly, the standard conditions were compatible for the reaction of *o*-alkynylbenzaldhyde and 1-(2-alkynylphenyl)ethanone for the synthesis of benzil-*o*-carbonyl compounds **3r** and **3s** with high efficiency, which were produced by Srinivasan and co-workers through a I_2 or ICl/water-mediated cyclization and oxidative ring-opening.[12]

Table 4. Generation of 4-haloisocoumarins through the $ZnBr_2$/oxone-mediated cyclization of phenyl *o*-alkynylbenzoate.[a]



[a] Isolated yield based on phenyl 2-alkynylbenzoate **1**.

Surprisingly, the reaction of phenyl 2-alkynylbenzoate did not produce benzil-*o*-carboxylate but offered 4-bromoisocoumarins through electrophilic 6-*endo* bromocyclization[3,4,17] (table 4). By altering bromide to zinc bromide,[18] the reaction of phenyl 2-phenylacetylenylbenzoate gave rise to 4-bromoisocoumarin **4a** in 85% yield. As we know, the traditional synthesis of 4-bromoisocoumarins needed the use of liquid bromine as electrophilic bromo source.[3] Our method reported here avoided the use of Br_2, representing a safe alternative. Consequently, we explored the reaction scope and generality. As shown in table 4,

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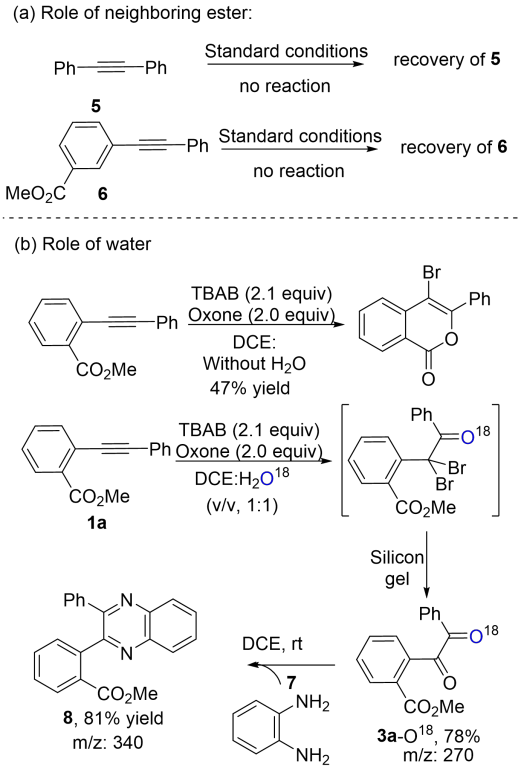
an array of 4-bromoisocoumarins were achieved in good yields. For example, the reaction of phenyl 2-(hex-1-yn-1-yl)benzoate under standard conditions provided 3-butyl-4-bromoisocoumarin **4e** in 70% yield. Iodocyclization and chlorocyclization were also realized when zinc iodide and zinc chloride were used, and 4-iodoisocoumarin **4h** and 4-chloroisocoumarin **4i** were obtained accordingly in 94% and 65% yield, respectively.

To get insight into the mechanism, several control experiments were carried out. Firstly, we would like to clarify the role of neighboring ester group by the reaction of the substrate without ester group **5** and the substrate with *meta*-ester **6**. As shown in table 5, the two control experiments did not provide the desired products, thus illustrating an important role of neighboring ester in diketonization of alkynes. What then came was that we should identify an exact role of water in the reaction. A reaction without water as co-solvent was ran. No benzil-o-carboxylate was formed but cyclic 4-bromoisocoumarin was uniquely observed. The reaction with DCE:H_2O^{18} as the solvent provided O^{18}-labelled benzil-*o*-carboxylate **3a** in 78% yield. GC-MS analysis showed a strong signal at m/z = 270 that was assigned to the final product **3a**-O^{18}. The result indicated that one equivalent of H_2O^{18} was incorporated into final molecule **3a**. Subsequently, a condensation reaction of **3a**-O^{18} and benzene-1,2-diamine was carried out with an aim to understand the exact site of oxygen-18. The expected quinoxaline **8** was achieved at 1,2-dichloroethane in 81% yield. The result from GC-MS analysis of compound **8** showed that oxygen-18 was installed into triple bond to form a carbonyl group since a strong m/z signal of compound **8** was equal to 340 (m/z of **8**-O^{18} should be 342).

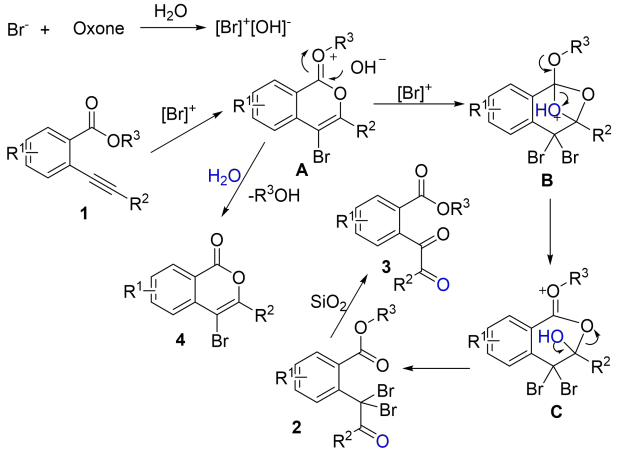
A plausible mechanism was proposed in Scheme 3. According to the previous findings,[15] Oxone could oxidize bromide to electrophilic bromo cation through two-electron-oxidation. This bromo cation-triggered bromocyclization offered 4-bromoisocoumarin cation species **A**. One of possibility happened to species **A** was a removal of R^3OH in the presence of water, leading to the final products **4**. Otherwise, species **A** would produce species **B** in the presence of another eletrophilic bromo cation and water, which finally converted into species **C**. Ring-opening of the intermediate **C** afforded dibromohydrative intermediate **2**. Treating with silica gel, dibromohydrative intermediate **2** was hydrolysed into benzil-*o*-carboxylate **3**. The two oxygen atoms in keto group of product **3** were both derived from water.

Very recently, a NBS-mediated diketonization of *o*-alkynylbenzoate was reported by our group for the synthesis of benzil-*o*-carboxylate.[17c] Interestingly, an oxygen of ester transfer reaction happened to this diketonization, and thus one of two oxygen atoms in keto groups of benzil-*o*-carboxylate came from ester of *o*-alkynylbenzoate.

Table 5. Control experiments



[a] Isolated yield based on phenyl 2-alkynylbenzoate **1**.



Scheme 3. Proposed pathway for the designed reaction

In conclusion, we have developed a novel and bromide/oxone-based electrophilic bromocyclization of *o*-alkynylbenzoates for switchable synthesis of benzil-*o*-carboxylate and 4-bromoisocoumarins. The selectivity was controlled by substrates. The reaction using *o*-alkynyl-linked phenol ester provided 4-bromoisocoumarins while the reaction using *o*-alkynyl-connected alcohol ester produced benzil-*o*-carboxylates. Mechanism studies showed that neighboring ester group played a pivotal role in the reaction. For benzil-*o*-carboxylates, the two oxygen atoms of keto carbonyl in benzil-*o*-carboxylate were derived from different sources. One of them came from water and other was introduced by silica gel-based hydrolysis of dibromohydrative products. In the reaction, neighboring ester group-participated electrophilic bromocyclization and substrate-controlled dibromohydration as

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well as hydrolysis of dibromohydrative product was involved for the formation of benzil-*o*-carboxylates.

Experimental Section

General procedure for the synthesis of compound 3: 2-alkynylbenzoate **1** (0.2 mmol), TBAB (2.1 equiv) and Oxone (2.0 equiv) was added to a test tube, and then co-solvent DCE:H_2O (v/v =1:1, 2.0 mL) was added. The mixture was stirred at 80 °C. After completion of reaction as indicated by TLC, the mixture was filtrated and the resulting filtrate was dried by Na_2SO_4. Then filtration, evaporation of the solvent and purification by flash column chromatograph provided the desired product **3**.

General procedure for the synthesis of compound 4: Phenyl 2-alkynylbenzoate **1** (0.2 mmol), $ZnBr_2$ (2.0 equiv) and Oxone (2.0 equiv) was added to a test tube, and then co-solvent DCE:H_2O (v/v =1:1, 2 mL) was added. The mixture was stirred at 80 °C. After completion of reaction as indicated by TLC, the mixture was filtrated and the resulting filtrate was dried by Na_2SO_4. Then filtration, evaporation of the solvent and purification by flash column chromatograph provided the desired product **4**.

Methyl 2-(1,1-dibromo-2-oxo-2-phenylethyl)benzoate (**2a**) (Crude spectrum)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.1 Hz, 1H), 7.85 – 7.60 (m, 4H), 7.50 – 7.34 (m, 2H), 7.25 – 7.18 (m, 2H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.86, 166.66, 140.99, 132.95, 132.51, 131.59, 131.46, 131.14, 130.52, 129.89, 127.79, 127.57, 70.40, 52.21.

Methyl 2-(2-oxo-2-phenylacetyl)benzoate (**3a**)[9a] (42.9 mg, 80%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.17 (m, 2H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.60 (m, 4H), 7.58 – 7.48 (m, 2H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.61, 188.97, 166.84, 138.70, 133.88, 133.04, 132.96, 131.59, 130.77, 130.06, 129.68, 129.51, 128.43, 52.70.

Methyl 5-methyl-2-(2-oxo-2-phenylacetyl)benzoate (**3b**) (45.7 mg, 81%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.10 (m, 2H), 7.80 (s, 1H), 7.66 – 7.57 (m, 2H), 7.55 – 7.40 (m, 3H), 3.63 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.68, 189.51, 167.19, 142.83, 135.48, 134.00, 133.65, 133.21, 130.85, 130.38, 130.32, 130.03, 128.59, 52.75, 21.60. HRMS (ESI) calcd for $C_{17}H_{15}O_4^+$: 283.0965 (M^++H), found: 283.0973

Methyl 5-bromo-2-(2-oxo-2-phenylacetyl)benzoate (**3c**) (54.1 mg, 78%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.06 (m, 3H), 7.89 – 7.80 (m, 1H), 7.72– 7.60 (m, 1H), 7.58 – 7.49 (m, 3H), 3.68 (s, 3H). ^{13}C NMR (100 MHz,$CDCl_3$) δ 192.57, 188.68, 165.63, 137.35, 136.04, 134.05, 132.73, 132.68, 131.55, 131.13, 130.76, 128.47, 126.17, 53.01. HRMS (ESI) calcd for $C_{16}H_{12}BrO_4^+$: 346.9913 (M^++H), found: 346.9914

Dimethyl 2-(2-oxo-2-phenylacetyl)terephthalate (**3d**) (47.6 mg, 73%)
^{1}H NMR (400 MHz,$CDCl_3$) δ 8.31 (d, *J* = 1.5 Hz, 1H), 8.27 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.23 – 8.15 (m, 2H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.71 –7.62 (m, 1H), 7.57 – 7.50 (m, 2H), 3.96 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.49, 188.61, 166.16, 165.28, 139.02, 134.26, 134.08, 132.96, 132.73, 132.40, 131.04, 130.80, 129.82, 128.49, 53.03, 52.71. HRMS (ESI) calcd for $C_{18}H_{15}O_6^+$: 327.0863 (M^++H), found: 327.0863

Methyl 2-(2-oxo-2-phenylacetyl)-5-(phenylethynyl)benzoate (**3e**) (56.0 mg, 76%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.3, 1.3 Hz, 2H), 8.15 (d, *J* = 1.3 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.52-7.59 (m, 4H), 7.45 – 7.30 (m, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.89, 188.90, 166.35, 137.52, 135.47, 133.98, 132.88, 132.67, 131.80, 130.76, 130.33, 130.01, 129.02, 128.47, 127.30, 122.30, 93.01, 87.56, 52.87. HRMS (ESI) calcd for $C_{24}H_{17}O_4^+$: 369.1121 (M^++H), found: 369.1126

Ethyl 2-(2-oxo-2-phenylacetyl)nicotinate (**3f**) (42.5 mg, 75%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.4, 1.2 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.44 – 7.33 (m, 2H), 7.28 – 7.21 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 – 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.28, 165.19, 155.88, 150.90, 139.55, 132.51, 132.02, 130.59, 127.88, 124.71, 124.23, 62.25, 13.96. HRMS (ESI) calcd for $C_{16}H_{14}NO_4^+$: 284.0917 (M^++H), found: 284.0921

Methyl 2-(2-(4-chlorophenyl)-2-oxoacetyl)benzoate (**3g**) (52.7 mg, 87%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.60 (m, 3H), 7.58 – 7.48 (d, *J* = 8.6 Hz, 2H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.48, 187.71, 166.89, 140.35, 138.81, 133.18, 132.16, 131.61, 131.42, 129.97, 129.66, 129.32, 128.79, 52.80. HRMS (ESI) calcd for $C_{16}H_{12}ClO_4^+$: 303.0419 (M^++H), found: 303.0420

Methyl 2-(2-(4-methoxyphenyl)-2-oxoacetyl)benzoate (**3h**) (43.5 mg, 73%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29– 8.12 (m, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.73– 7.64 (m, 2H), 7.65 – 7.57 (m, 1H), 7.06– 6.88 (m, 2H), 3.91 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.05, 187.69, 166.82, 164.23, 138.85, 133.19, 132.87, 131.45, 130.02, 129.60, 125.93, 113.82, 55.52, 52.62. HRMS (ESI) calcd for $C_{17}H_{15}O_5^+$: 299.0914 (M^++H), found: 299.0916

Methyl 2-(2-(2-methoxyphenyl)-2-oxoacetyl)benzoate (**3i**) (44.7 mg, 75%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.67 – 7.50 (m, 3H), 7.18 – 7.04 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.83, 191.25, 168.29, 160.05, 135.68, 134.02, 132.39, 132.35, 131.44, 131.26, 130.76, 129.09, 123.53, 121.00, 112.17, 55.81, 52.60. HRMS (ESI) calcd for $C_{17}H_{15}O_5^+$: 299.0914 (M^++H), found: 299.0916

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Methyl 2-(2-(naphthalen-1-yl)-2-oxoacetyl)benzoate (**3j**) (50.9 mg, 80%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 7.3 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.46 (m, 6H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.74, 190.99, 167.10, 138.72, 134.53, 134.35, 133.92, 132.89, 131.57, 131.46, 130.22, 130.09, 129.54, 128.73, 128.62, 128.41, 126.39, 125.37, 124.42, 52.78. HRMS (ESI) calcd for $C_{20}H_{15}O_4^+$: 319.0965 (M^++H), found: 319.0966

Methyl 2-(2-oxo-2-(thiophen-2-yl)acetyl)benzoate (**3k**) (45.0 mg, 82%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 3.0 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 4.1 Hz, 1H), 7.74 – 7.58 (m, 3H), 7.30 – 7.21 (m, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.30, 180.35, 166.60, 138.48, 138.12, 136.76, 136.33, 133.00, 131.36, 129.66, 129.55, 129.38, 128.47, 52.63. HRMS (ESI) calcd for $C_{14}H_{11}O_4S^+$: 275.0373 (M^++H), found: 275.0374

Methyl 2-(2-oxohexanoyl)benzoate (**3l**) (32.3 mg, 65%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.7, 0.6 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.70 – 7.62 (m, 1H), 7.49 (dd, *J* = 7.5, 0.8 Hz, 1H), 3.86 (s, 3H), 3.01 (t, *J* = 7.4 Hz, 2H), 1.69 – 1.58 (m, 2H), 1.47 – 1.36 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.18, 194.08, 167.07, 138.74, 133.12, 131.01, 129.39, 129.29, 128.91, 52.77, 36.09, 24.99, 22.25, 13.87. HRMS (ESI) calcd for $C_{14}H_{17}O_4^+$: 249.1121 (M^++H), found: 249.1126

Methyl 2-(3,3-dimethyl-2-oxobutanoyl)benzoate (**3m**) (32.8 mg, 66%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 1H), 7.71 – 7.61 (m, 1H), 7.60 – 7.53 (m, 2H), 3.87 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.37, 192.42, 167.31, 138.69, 132.78, 131.21, 129.86, 129.68, 129.14, 52.71, 42.54, 26.71. HRMS (ESI) calcd for $C_{14}H_{17}O_4^+$: 249.1121 (M^++H), found: 249.1121

Methyl 2-(2-oxo-4-phenylbut-3-ynoyl)benzoate (**3o**) (46.8 mg, 80%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.59 (m, 4H), 7.58 – 7.47 (m, 2H), 7.45 – 7.38 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.34, 174.85 166.55, 137.68, 133.79, 133.29, 131.46, 129.62, 129.13, 128.67, 119.54, 98.21, 86.30, 52.96.

Ethyl 2-(2-oxo-2-phenylacetyl)cyclohex-1-enecarboxylate (**3p**) (43.5 mg, 76%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.52 – 7.46 (m, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 2.51 – 2.36 (m, 4H), 1.80– 1.71 (m, 4H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.60, 188.79, 167.34, 149.44, 133.66, 132.97, 131.21, 130.81, 128.27, 61.40, 28.74, 24.58, 21.40, 21.26, 14.00.

Benzyl 2-(2-oxo-2-phenylacetyl)benzoate (**3q**) (58.5 mg, 85%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 2H), 8.07 – 7.97 (m, 1H), 7.74 – 7.68 (m, 2H), 7.68 – 7.57 (m, 2H), 7.57 – 7.48 (m, 2H), 7.35 – 7.30 (m, 3H), 7.30 – 7.27 (m, 2H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.69, 189.03, 166.46, 139.03, 135.06, 133.80, 133.09, 133.07, 131.52, 130.82, 130.05, 129.66, 129.62, 128.55, 128.41, 128.36, 128.25, 67.55. HRMS (ESI) calcd for $C_{22}H_{17}O_4^+$: 345.1121 (M^++H), found: 345.1128

2-(2-oxo-2-phenylacetyl)benzaldehyde (**3r**)[11a] (35.7 mg, 75%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.19 (dd, *J* = 8.4, 1.3 Hz, 2H), 8.00 – 7.90 (m, 1H), 7.81 – 7.72 (m, 3H), 7.71 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.43, 192.47, 189.46, 137.05, 135.81, 134.40, 134.23, 132.94, 132.42, 132.41, 130.82, 130.65, 128.58.

1-(2-acetylphenyl)-2-phenylethane-1,2-dione (**3s**)[11b] (40.9 mg, 81%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.20 (m, 2H), 7.94-7.89 (m, 1H), 7.77 – 7.70 (m, 1H), 7.69 – 7.61 (m, 3H), 7.60– 7.49 (m, 2H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.97, 194.03, 189.27, 138.55, 137.04, 133.89, 133.48, 133.22, 131.43, 130.84, 130.33, 129.30, 128.41, 26.60.

Methyl 2-(2,2-dibromoacetyl)benzoate (**3u**)[4g]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.45 (m, 3H), 6.37 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.77, 166.13, 137.83, 133.04, 130.66, 130.36, 130.23, 53.17, 44.17.

4-Bromo-3-phenyl-1H-isochromen-1-one (**4a**)[4d] (51.2 mg, 85%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.89 – 7.84 (m, 2H), 7.64 – 7.58 (m, 1H), 7.51 – 7.46 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.14, 151.81, 136.60, 135.46, 132.76, 130.18, 129.79, 129.66, 129.16, 128.10, 126.65, 120.57, 101.37.

4-Bromo-3-(4-methoxyphenyl)-1H-isochromen-1-one (**4b**)[16a] (58.3 mg, 88%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.89 – 7.79 (m, 1H), 7.79 – 7.73 (m, 2H), 7.62 – 7.50 (m, 1H), 7.03 – 6.91 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.32, 160.88, 151.71, 136.86, 135.41, 131.30, 129.73, 128.85, 126.52, 125.00, 120.38, 113.46, 100.57, 55.38.

4-Bromo-3-(4-chlorophenyl)-1H-isochromen-1-one (**4c**)[16b] (53.0 mg, 79%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.79 – 7.73 (m, 2H), 7.66 – 7.58 (m, 1H), 7.51 – 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.90, 150.61, 136.39, 136.30, 135.56, 131.11, 131.03, 129.85, 129.38, 128.45, 126.72, 120.57, 101.68.

4-Bromo-3-(naphthalen-1-yl)-1H-isochromen-1-one (**4d**) (59.0 mg, 84%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.9 Hz, 1H), 8.03 – 7.85 (m, 4H), 7.83 – 7.77 (m, 1H), 7.72 – 7.62 (m, 2H), 7.62 – 7.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.27, 151.76, 136.21, 135.57, 133.43, 130.71, 130.65, 130.59, 129.99, 129.45, 128.68, 128.55, 127.10, 126.51, 126.40, 124.98, 124.93, 120.89, 104.26. HRMS (ESI) calcd for $C_{19}H_{12}BrO_2^+$: 351.0015 (M^++H), found: 351.0013

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4-Bromo-3-butyl-1H-isochromen-1-one (**4e**)[4d] (39.4 mg, 70%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 7.91 – 7.71 (m, 2H), 7.64 – 7.39 (m, 1H), 2.82 (t, J = 7.7 Hz, 2H), 1.80 – 1.68 (m, 2H), 1.50 – 1.38 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.55, 155.76, 136.33, 135.33, 129.71, 128.44, 125.67, 120.22, 101.14, 33.19, 28.95, 22.23, 13.78.

4-Bromo-7-methyl-3-phenyl-1H-isochromen-1-one (**4f**) (52.3 mg, 83%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.68 – 7.62 (m, 1H), 7.50 – 7.41 (m, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.39, 150.90, 139.72, 136.66, 134.21, 132.80, 130.04, 129.65, 129.55, 128.06, 126.63, 120.37, 101.42, 21.23. HRMS (ESI) calcd for $C_{16}H_{12}BrO_2^+$: 315.0015 (M^++H), found: 315.0018

4,7-Dibromo-3-phenyl-1H-isochromen-1-one (**4g**) (57.0 mg, 75%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.6, 2.2 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.56 – 7.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.85, 152.19, 138.50, 135.50, 132.39, 132.21, 130.41, 129.60, 128.49, 128.16, 123.04, 121.80, 100.57. HRMS (ESI) calcd for $C_{15}H_9Br_2O_2^+$: 378.8964 (M^++H), found: 378.8969

4-Iodo-3-phenyl-1H-isochromen-1-one (**4h**)[4a] (65.4 mg, 94%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.9 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.85 – 7.76 (m, 1H), 7.73 – 7.64 (m, 2H), 7.61 – 7.52 (m, 1H), 7.51 – 7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.54, 154.76, 146.33, 138.14, 135.71, 135.20, 131.51, 130.18, 129.97, 129.72, 129.25, 128.08, 120.23.

4-Chloro-3-phenyl-1H-isochromen-1-one (**4i**)[7b] (33.4 mg, 65%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 8.1Hz, 1H), 7.90 – 7.81 (m, 3H), 7.66– 7.58 (m, 1H), 7.56 – 7.43 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.91, 150.40, 135.93, 135.33, 131.40, 130.19, 129.83, 129.32, 129.11, 128.20, 124.03, 120.49, 111.29.

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Synthesis of Benzil-*o*-carboxylate Derivatives and Isocoumarins Through Neighboring Ester-Participated Bromocyclization of *o*-Alkynylbenzoates

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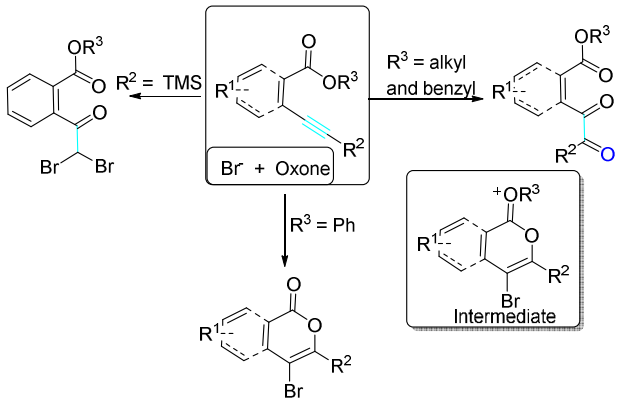
Graphical Abstract



Neighboring ester-participated bromocyclization of *o*-alkynylbenzoates is developed for switchable synthesis of benzil-o-carboxylate derivatives and isocoumarins.