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Tandem Reactions Leading to Benzo[*c*]chromen-6-ones and 3-Substituted Isocoumarins

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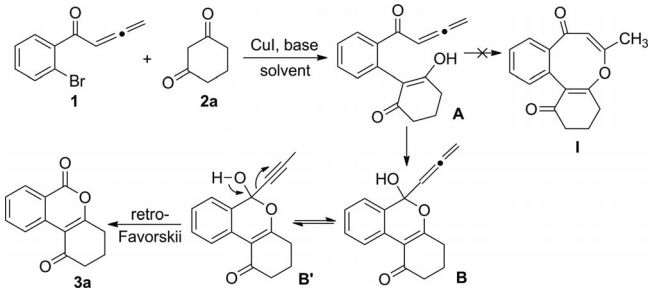
A simple and convenient protocol for the synthesis of benzo[*c*]chromen-6-ones and 3-substituted isocoumarins through a Cu^{I}-catalyzed tandem reaction of 2-bromobenzoates with cyclohexane-1,3-diones or acyclic 1,3-diones is developed. This strategy can also be extended to the one-pot synthesis of isoquinolin-1(2*H*)-one and 3,4-dihydrophenanthridine-1,6(2*H*,5*H*)-dione.

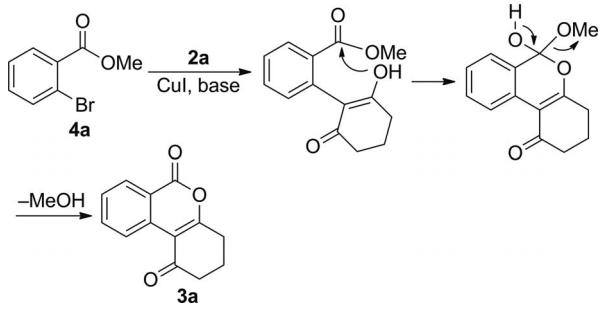
Introduction

Recently, we sought to develop new synthetic strategies by exploring the Michael addition of 1,2-allenic ketones.[1] In this regard, we envisioned a synthetic pathway to benzoxocinone[2] through the copper-catalyzed tandem reaction of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1**) with cyclohexane-1,3-dione (**2a**). Unexpectedly, the reaction did not give the envisioned benzoxocinone (**I**); instead, 3,4-dihydro-2*H*-benzo[*c*]chromene-1,6-dione (**3a**) was obtained (Scheme 1). This result might be explained by the following mechanistic rationale: the Cu^{I}-catalyzed C–C coupling of **1** with **2a** affords intermediate **A**.[3] Subsequent intramolecular nucleophilic 1,2-addition of the enol onto the carbonyl group, instead of 1,4-addition onto the allene moiety, yields intermediate **B**. Intermediate **B** isomerizes to **B′**, which then undergoes a retro-Favorskii reaction to afford **3a** as the final product.



Scheme 1. Unexpected formation of **3a** from **1** and **2a**.

Even though the reaction of **1** with **2a** failed to give the proposed benzoxocinone, it still attracted our interest, as it offered a potential pathway towards benzo[*c*]chromen-6-ones. Benzo[*c*]chromen-6-ones constitute one of the major classes of pharmacologically relevant natural products[4] that display a wide range of biological activities.[5] The development of general and practical synthetic methods for the preparation of benzo[*c*]chromen-6-ones has thus been strongly pursued.[6] On the basis of the pathway described in Scheme 1, we speculated that commercially available methyl 2-bromobenzoate (**4a**) might be a more direct and economical substrate than **1** for the preparation of **3a** (Scheme 2).



Scheme 2. Proposed synthesis of **3a** from **4a** and **2a**.

A literature search revealed that the Cu^{I}-catalyzed coupling of *o*-bromobenzoic acid with 1,3-diketones has been sporadically described,[7] but those few cases were limited to carboxylic acid. It is believed that under basic conditions, carboxylic acid could form a chelate with copper to activate the bromine towards nucleophilic displacement (Scheme 3).

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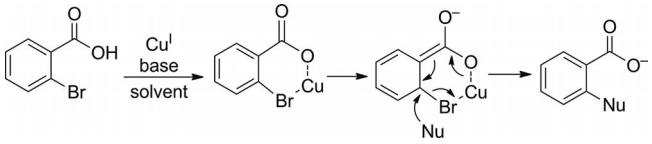
On the other hand, the reaction of 2-bromobenzoate with 1,3-diketones under Cu^I catalysis still remains to be explored.



Scheme 3. Cu^I-catalyzed reaction of *o*-bromobenzoic acid.

Results and Discussion

Initially, a mixture of **4a** (0.5 mmol) and **2a** (1.0 mmol) was treated with CuI (0.05 mmol) and K_2CO_3 (2 mmol) in DMF at 80 °C for 12 h. To our delight, it gave **3a** in 41% yield. Optimization of the reaction conditions with regard to Cu source, base, solvent, temperature, and molar ratio of substrates revealed that 66% yield of **3a** was obtained when **4a** (0.5 mmol) and **2a** (1.5 mmol) were treated with CuI (0.05 mmol) and K_2CO_3 (1.5 mmol) in DMF at 90 °C for 20 h. Several ligands such as pipecolinic acid, *N*,*N*-dimethylglycine, and L-proline were also examined, but no improvement in the yield of **3a** was observed, indicating that the ligand may be unnecessary for this process.

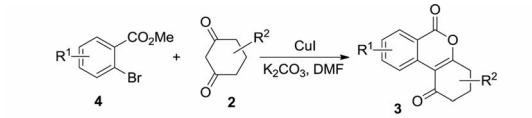
With the optimized reaction conditions, the scope and generality of this reaction were studied. For this purpose, several alkyl-substituted cyclohexane-1,3-diones were firstly treated with different 2-bromobenzoates. The results in Table 1 show that the reaction is compatible with 5-methyl-, 5-isopropyl-, and 5,5-dimethylcyclohexane-1,3-diones. With 4-methyl- or 4,4-dimethylcyclohexane-1,3-dione, two isomeric products were observed, whereas the 2-substituted isomer was found to be dominant (Table 1, Entries 5, 6 and 11). Identification of the isomers was established on the basis of heteronuclear multiple bond correlation (HMBC) studies.

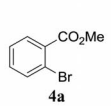
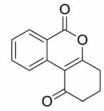
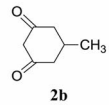
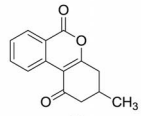
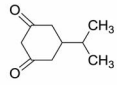
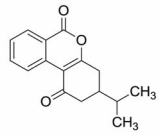
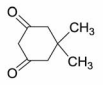
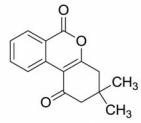
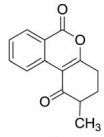
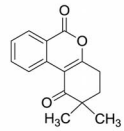
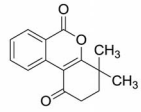
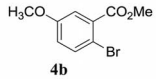
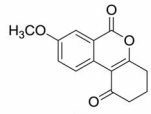
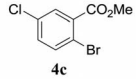
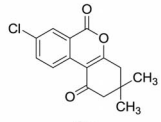
The reaction was then studied with 5-phenylcyclohexane-1,3-dione (**5a**). Surprisingly, instead of the expected 3,4-dihydro-3-phenyl-2*H*-benzo[*c*]chromene-1,6-dione (**II**), 1-hydroxy-3-phenyl-6*H*-benzo[*c*]chromen-6-one (**6a**) was obtained (Scheme 4). A plausible pathway including copper-catalyzed C–C coupling, intramolecular transesterification, and subsequent in situ oxidative aromatization of **II** to account for the formation of **6a** is outlined in Scheme 4.

To further investigate the unexpected formation of **6a**, several 5-arylcyclohexane-1,3-diones **5** were employed as substrates. The results in Table 2 show that substrates with either electron-withdrawing or electron-donating groups on the aryl rings of **4** or **5** were tolerated. Functional groups such as methyl, methoxy, and halides were well tolerated under these conditions.

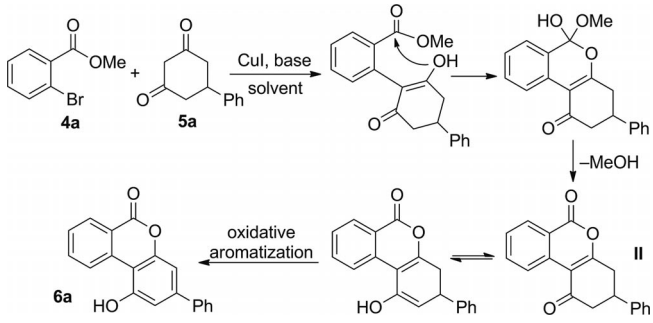
From the results listed in Tables 1 and 2, it was concluded that unsubstituted or alkyl-substituted 3,4-dihydro-2*H*-benzo[*c*]chromene-1,6-diones **3** are less prone to undergo oxidative aromatization than their aryl-substituted

Table 1. Scope of the reaction leading to **3** from **4** and **2**.[a]



Entry	4	2	3	Yield [%][b]
1	 **4a**	 **2a**	 **3a**	66
2	**4a**	 **2b**	 **3b**	63
3	**4a**	 **2c**	 **3c**	59
4	**4a**	 **2d**	 **3d**	73
5	**4a**	 **2e**	 **3e**	50
6	**4a**	 **2f**	 **3f**	60
			 **3g**	10
7	 **4b**	**2a**	 **3h**	55
8	**4b**	**2b**	**3i**	57
9	**4b**	**2c**	**3j**	61
10	**4b**	**2d**	**3k**	65
11	**4b**	**2f**	**3l**	70
12	 **4c**	**2d**	 **3m**	68

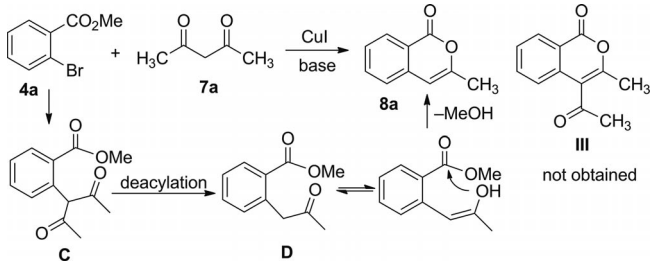
[a] Reaction conditions: **4** (0.5 mmol), **2** (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), DMF (3 mL), 90 °C, 20 h. [b] Isolated yield.



Scheme 4. Plausible pathway for the formation of **6a**.

counterparts (i.e., **II**) and thus fail to give the corresponding 6*H*-benzo[*c*]chromen-6-ones **6** under the same conditions. To assist the oxidative aromatization of **3**, $FeCl_3$, $FeCl_3{\cdot}6H_2O$, $RuCl_3$, DDQ, and I_2 were investigated as possible oxidants. Among them, I_2 was found to be the most efficient. With the promotion of I_2, several alkyl-substituted benzo[*c*]chromene-6-ones **6** were successfully obtained (Table 3).

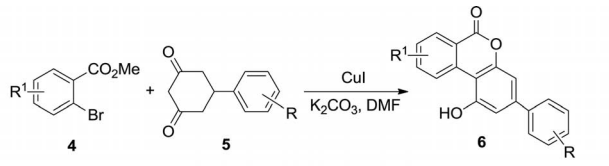
To further extend the scope of the above reactions and considering that isocoumarins are ubiquitous structural units in a plethora of natural products with biological interests,[8–10] we set out to study the reaction between **4** and acyclic 1,3-diketones **7** with the aim to develop a new method for the synthesis of 3,4-disubstituted isocoumarins. To our surprise, the reaction of **4a** and pentane-2,4-dione (**7a**) under the promotion of CuI/K_2CO_3 in DMF afforded 3-methyl-1*H*-isochromen-1-one (**8a**) exclusively, rather than the expected 4-acetyl-3-methyl-1*H*-isochromen-1-one (**III**, Scheme 5). This result may be explained by the following pathway: initially formed C–C coupling product **C** undergoes retro-Claisen deacylation to give intermediate **D**,[11] which then undergoes intramolecular transesterification to give **8a** as the final product.

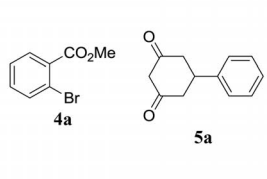
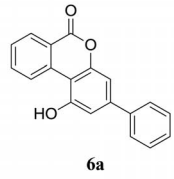
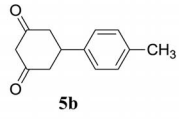
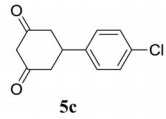
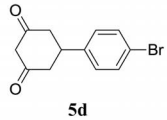
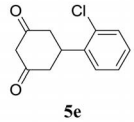
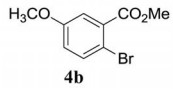
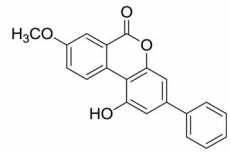
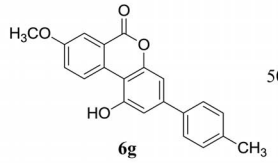
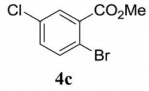
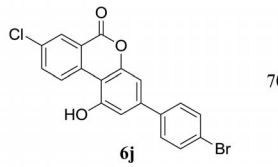


Scheme 5. Unexpected formation of **8a** from **4a** and **7a**.

The formation of **8a** turns out to be very interesting, because the majority of the naturally occurring isocoumarins that are of polyketide origin possess a C-3 substituent and the development of practical and convenient synthetic protocols for 3-substituted isocoumarins has been a challenge in the synthetic community.[8,12] On the basis of the above facts, we set out to develop the reaction of **4** with **7** into a general method for the synthesis of 3-substituted isocoumarins. A range of acyclic 1,3-diketones was thus studied as

Table 2. Scope of the reaction leading to **6**.[a]

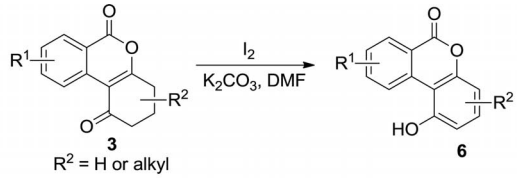


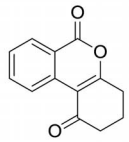
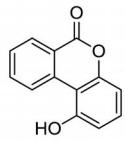
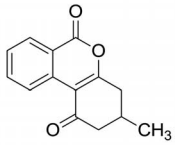
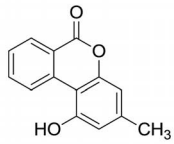
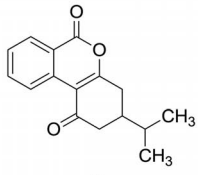
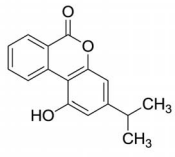
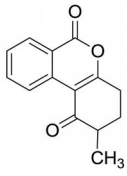
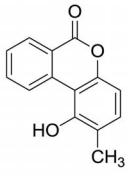
Entry	4	5	6	Yield [%][b]
1				69
2	**4a**		**6b**	63
3	**4a**		**6c**	67
4	**4a**		**6d**	73
5	**4a**		**6e**	65
6		**5a**		47
7	**4b**	**5b**		50
8	**4b**	**5c**	**6h**	40
9	**4b**	**5d**	**6i**	43
10		**5d**		70

[a] Reaction conditions: **4** (0.5 mmol), **5** (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), DMF (3 mL), 90 °C, 20 h. [b] Isolated yield.

substrates and all the reactions proceeded smoothly with moderate efficiency (Table 4). It is noted that in the formation of **8**, the retro-Claisen deacylation is highly regioselec-

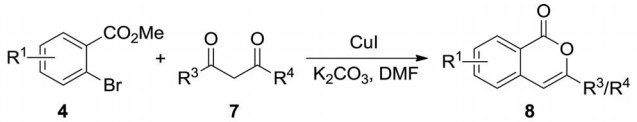
Table 3. Oxidative aromatization of **3** toward **6**.[a]

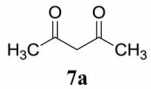
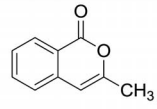
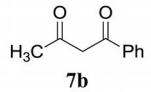
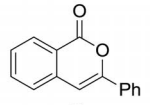
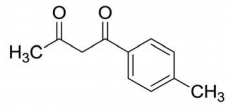
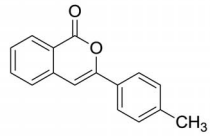
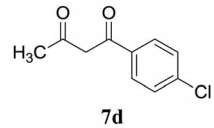
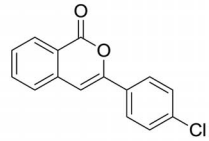
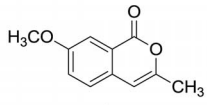
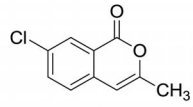
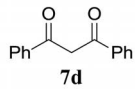


Entry	3	6	Yield [%][b]
1	 **3a**	 **6k**	86
2	 **3b**	 **6l**	79
3	 **3c**	 **6m**	88
4	 **3e**	 **6n**	85

[a] Reaction conditions: **3** (0.5 mmol), K_2CO_3 (0.5 mmol), I_2 (0.5 mmol), DMF (5 mL), 90 °C, 16 h. [b] Isolated yield.

Table 4. Synthesis of 3-substituted isocoumarins.[a]

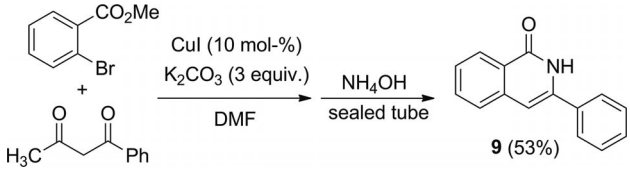


Entry	4	7	8	Yield [%][b]
1	**4a**	 **7a**	 **8a**	61
2	**4a**	 **7b**	 **8b**	65
3	**4a**	 **7c**	 **8c**	55
4	**4a**	 **7d**	 **8d**	63
5	**4b**	**7a**	 **8e**	62
6	**4b**	**7b**	**8f**	67
7	**4c**	**7a**	 **8g**	53
8	**4c**	**7b**	**8h**	57
9	**4a**	 **7d**	**8b**	72

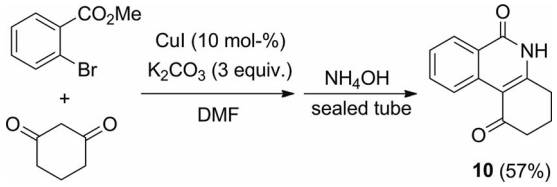
[a] Reaction conditions: **4** (0.5 mmol), **7** (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), DMF (3 mL), 90 °C, 20 h. [b] Isolated yield.

tive with the unsymmetrical 1-arylbutane-1,3-dione, and only the deacetylated product, 3-arylisocoumarin, was obtained. The debenzoylation product, 3-methylisocoumarin, was not observed. Interestingly, with 1,3-diphenylpropane-1,3-dione (**7d**), debenzoylation did occur smoothly to give 3-phenylisocoumarin with good efficiency (Table 4, Entry 9).

Finally, we noticed that isoquinolin-1(2*H*)-ones are important structural moieties in both synthetic and medicinal chemistry and several procedures for their synthesis from isocoumarins have been reported.[13] Having successfully developed an efficient procedure for the preparation of 3-substituted isocoumarins, we turned our attention to study the feasibility of developing a one-pot synthesis of isoquinolin-1(2*H*)-one directly from 2-bromobenzoate and 1,3-diketones. It turned out that treatment of 2-bromobenzoate with 1-phenylbutane-1,3-dione in the presence of CuI and K_2CO_3 in DMF followed by reaction with NH_4OH allowed the isolation of 3-phenylisoquinolin-1(2*H*)-one (**9**) in 53% yield (Scheme 6). This methods offers a straightforward one-pot route towards isoquinolin-1(2*H*)-one from readily available starting materials. As an extension of this procedure, 3,4-dihydrophenanthridine-1,6-(2*H*,5*H*)-dione (**10**) was also obtained directly and conveniently from 2-bromobenzoate and cyclohexane-1,3-dione as shown in Scheme 7.



Scheme 6. One-pot synthesis of isoquinolin-1(2*H*)-one (**9**).



Scheme 7. One-pot synthesis of 3,4-dihydrophenanthridine-1,6-(2*H*,5*H*)-dione (**10**).

Conclusions

In conclusion, we have developed a copper-catalyzed tandem process for the assembly of benzo[*c*]chromen-6-ones and 3-substituted isocoumarins from 2-bromobenzoates and 1,3-diketones. In addition, this new process was successfully extended to the one-pot synthesis of isoquinolin-1(2*H*)-one and 3,4-dihydrophenanthridine-1,6-(2*H*,5*H*)-dione. With advantages such as readily available starting materials, mild reaction conditions, and simple synthetic procedures, the methods developed herein are expected to serve as promising protocols for the construction of relevant oxygen- and nitrogen-containing heterocycles.

Experimental Section

Typical Procedure for the Preparation of Benzo[*c*]chromene-6-ones 3a–m and 6a–j and Isochromen-1-ones 8a–h: To a flask containing the 2-bromobenzoate (0.5 mmol) and the dione (1.5 mmol) was added DMF (3 mL), CuI (0.05 mmol), and K_2CO_3 (1.5 mmol). The mixture was stirred at 90 °C. Upon completion of the reaction as monitored by TLC, the reaction was quenched with aqueous NH_4Cl. Then, the mixture was filtered through Celite, and the filtrate was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

Supporting Information (see footnote on the first page of this article): Full experimental details, characterization data, ^1H NMR and ^{13}C NMR spectra of all products, and HMBC spectra of **3g** and **3l**.

Acknowledgments

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