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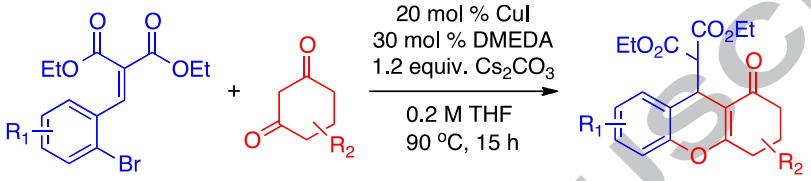

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ABSTRACT

4*H*-Chromenes were synthesized from 2-bromobenzylidenemalonates and 1,3-dicarbonyls under mild and simple reaction conditions *via* copper-catalysed domino reactions involving Michael addition and intramolecular Ullmann-type C(aryl)-O bond formation. Although a competitive elimination affected these reactions, this catalytic system readily provided chromenes with functionality at the C-4 position.

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Introduction

Metal-catalysed domino reactions have drawn significant attention from synthetic chemists for more than a century, especially reactions catalysed by copper due to its low toxicity and high natural abundance. Therefore, copper-catalysed domino reactions have been developed for the formation of C(aryl)-N, C(aryl)-C and C(aryl)-O bonds.[1] Unlike C(aryl)-N bond formation, tandem reactions for C(aryl)-O formation offer considerably less reaction diversity due to the lower valence of the oxygen atom.[2] In continuation of our research interest in copper-catalysed domino reactions for the synthesis of heterocyclic molecules, we were inspired by the work of Li and Fang for the formation of 4*H*-chromenes *via* copper-catalysed intramolecular coupling of aryl bromides and 1,3-dicarbonyls.[3] Their results suggested that C(aryl)-O Ullmann-type coupling occurred smoothly in an intramolecular fashion. Furthermore, Beifuss and co-workers recently took advantage of intramolecular C(aryl)-O coupling to furnish 4*H*-chromene derivatives *via* tandem process from 2-bromobenzyl bromides and 1,3-ketoesters.[4] These domino reactions involved substitution of a stabilised carbanion, generated from a 1,3-ketoester, with a bromine atom at the benzylic position, followed by tautomerization and intramolecular Ullmann-type C-O bond formation. In order to introduce functionality at the C-4 position of 4*H*-chromenes, we alternatively envisioned that the 2-bromobenzylidenemalonates would undergo C-C bond formation *via* Michael addition with 1,3-dicarbonyls, followed by intramolecular copper-catalysed C(aryl)-O bond formation to afford the desired 4*H*-chromenes (Fig. 1).

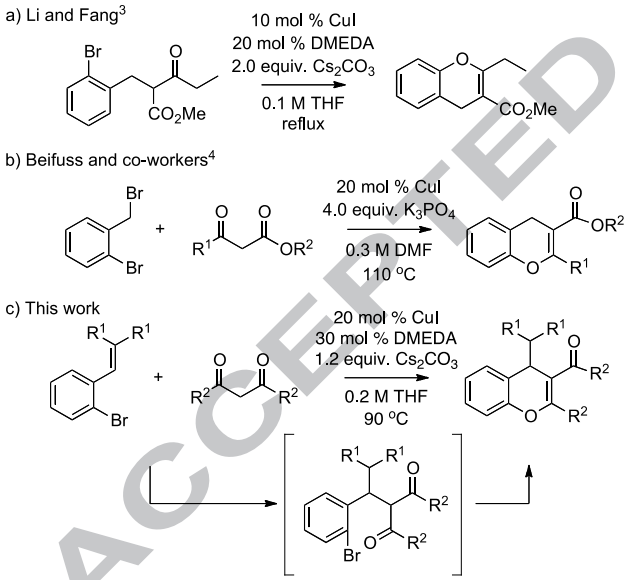


Figure 1. Copper-catalysed reactions for the synthesis of 4*H*-chromenes

Chromenes are one of the most important *O*-containing heterocyclic systems due to their common occurrence as a structural motif in natural products[5] as well as their biological activities which include antitumor, antimicrobial, antioxidant, anticancer and estrogenic properties[6] (Fig. 2). Chromene derivatives also play important roles in material science, for example as fluorescent dyes, synthetic fibers, daylight fluorescent pigments and electroluminescent devices.[7] Due to their wide range of utilities, the syntheses of chromene have been consistently developed; most reported methods involve phenol derivatives.[8] Herein, we reported a synthesis of 4*H*-chromenes containing a functionality pendent at the C-4 position *via* domino, Michael addition and C-O Ullmann type coupling reactions.

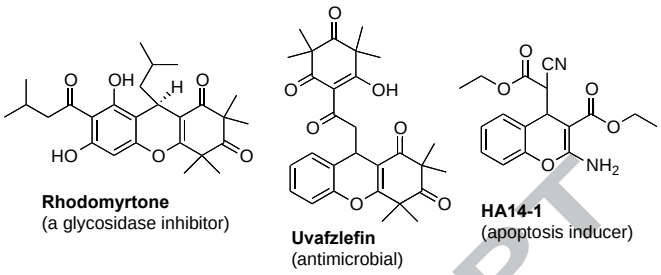


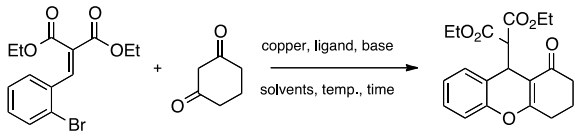
Figure 2. Representative biologically active molecules containing the chromene moiety

Our investigation initially began with optimization of the reaction conditions. The reaction of diethyl 2-(2-bromobenzylidene) malonate (**1a**) and cyclohexane-1,3-dione (**2a**) was selected as a model (Table 1).

Various ligands were examined using CuI as the copper source, K_2CO_3 as a base and ACN as a solvent. The reactions were heated at 90 ^oC for 15 hours (Entries 1–7). The reaction with DMEDA as ligand gave the best yield (Entry 3), while PPh_3 afforded none of the desired product (Entry 5). On the other hand, proline and ethylenediamine were not effective in this reaction (Entries 1 and 6) and only trace amounts of the product were observed from the ^1H NMR spectrum of the crude reaction mixture. Next, various copper salts were explored. With $Cu(OAc)_2$, chromene **3a** was obtained in 32% yield (Entry 10) while CuBr and CuCl were not applicable to this system, resulting in low yield and no reaction, respectively (Entries 8 and 9). Without copper there was no reaction (Entry 11). Accordingly, the choice of copper was CuI. A variety of bases were then examined. NEt_3, an organic base, was not effective and no reaction was observed according to the ^1H NMR spectrum of the crude reaction mixture (Entry 14). The reactions with weak inorganic bases, K_3PO_4 or Cs_2CO_3 (Entries 12 and 13), gave comparable yields to the reaction with K_2CO_3 (Entry 3). The yield was slightly decreased when the stronger base ^{t}BuOK was used (Entry 15). We then conducted an exploration of solvents. The yield of reaction in THF with K_3PO_4 as a base was 50% (Entry 16), slightly lower than that of ACN (Entry 12). However, upon changing the base to Cs_2CO_3, the yield increased to 68% (Entry 17). These results suggested that the combination of base and solvent affected this catalytic reaction. Upon using the less polar solvent, toluene, or the more polar solvent, DMSO, the yield dropped dramatically to 30% and 15%, respectively (Entries 18 and 20). Finally, the higher boiling point solvent dioxane was used, resulting in a much lower yield (Entry 19). Subsequently, the optimal reaction conditions were DMEDA as a ligand, CuI as a copper source, Cs_2CO_3 as a base and THF as a solvent. Notably, the use of 20 mol% of copper and 30 mol% of ligand was required to complete the reaction.

Interestingly, the diester moiety of benzylidene was required. Upon subjecting ethyl-3-(2-bromophenyl)acrylate, an α,β-unsaturated monoester, to the optimal conditions (Scheme 1), we only observed both starting materials from the ^1H NMR spectrum of the crude reaction mixture.

Table 1. Reaction optimization[a]



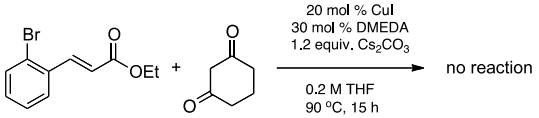
1a 2a 3a

Entry	Cu	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	proline	K_2CO_3	ACN	Trace[c]
2	CuI	1,10-phenanthroline	K_2CO_3	ACN	10
3	CuI	DMEDA	K_2CO_3	ACN	52
4	CuI	picolinic acid	K_2CO_3	ACN	42
5	CuI	PPh_3	K_2CO_3	ACN	0
6	CuI	ethylene diamine	K_2CO_3	ACN	Trace
7	CuI	2,2'-bipyridine	K_2CO_3	ACN	12
8	CuBr	DMEDA	K_2CO_3	ACN	15
9	CuCl	DMEDA	K_2CO_3	ACN	0
10	$Cu(OAc)_2$	DMEDA	K_2CO_3	ACN	32
11	-	DMEDA	K_2CO_3	ACN	0
12	CuI	DMEDA	K_3PO_4	ACN	58
13	CuI	DMEDA	Cs_2CO_3	ACN	56
14	CuI	DMEDA	NEt_3	ACN	0
15	CuI	DMEDA	^tBuOK	ACN	43
16	CuI	DMEDA	K_3PO_4	THF	50
17	CuI	DMEDA	Cs_2CO_3	THF	68
18	CuI	DMEDA	Cs_2CO_3	toluene	30
19	CuI	DMEDA	Cs_2CO_3	dioxane	15
20	CuI	DMEDA	Cs_2CO_3	DMSO	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (20 mol %), ligand (30 mol %), solvent (0.1 M), 90 °C, 15 h. [b]Isolated yield. [c]Trace amount of product observed from the ^1H NMR spectrum of the crude reaction mixture.

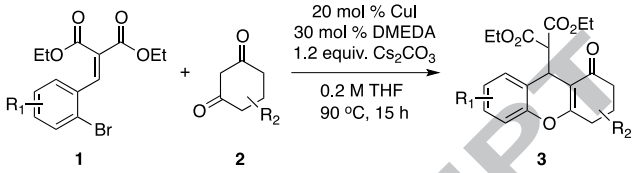
Based on this result, the electrophilicity of the Michael acceptor was deemed crucial in this system. Having established the optimal reaction conditions, we explored the substrate scope in the copper-catalysed domino reaction (Table 2).

Scheme 1. Reaction of ethyl-3-(2-bromophenyl)acrylate and 1,3-cyclicdiketone



Cyclohexane-1,3-diones, with and without the geminal-dimethyl substituent, gave the desired chromenes in moderate yield (Entries 1–3). The results showed that the presence of the active geminal-dimethyl substituent had no effect on the reaction. Additionally, we confirmed the location of the geminal-dimethyl unit of chromene **3c** using heteronuclear multiple bond correlation (HMBC) spectroscopy (see ESI). Based on the structure of **3c**, the less sterically hindered oxygen nucleophile was postulated to undergo C(aryl)-O bond formation faster than the more sterically hindered one. This indicated that in the catalytic cycle, the rate determining step was possibly the Ullmann-type coupling.

Table 2. Formation of chromenes **3a-g** from 1,3-dicarbonyls[a]



1 2 3

Entry	Benzylidene malonate	Chromene	Yield (%)[b]
1	**1a**	**3a**	68
2	**1a**	**3b**	66
3	**1a**	**3c**	62
4	**1b**	**3d**	48
5	**1c**	**3e**	65
6	**1d**	**3f**	56
7	**1a**	**3g**	50

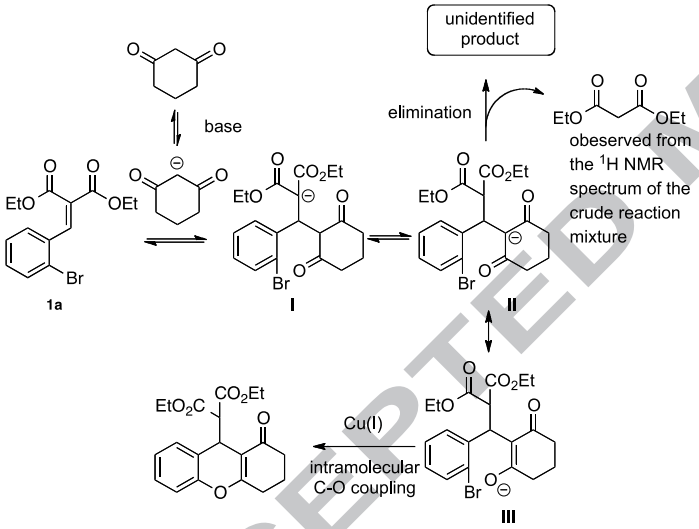
[a]Reaction conditions: **1a-d** (0.5 mmol), **2** (0.75 mmol). [b]Isolated yield.

We then explored the effect of electron density on the aromatic ring of the benzylidenemalonates. Benzylidenemalonates bearing both electron-donating and electron-withdrawing groups on the benzene ring were applicable to the reaction. However, dimethoxy substituents gave the desired chromene in only 48% yield (Entry 4). On the other hand, the reaction of benzylidenemalonates with a nitro group at the *para*-position to the bromine on the benzene ring gave a slightly better yield than that at the *ortho*-position (Entries 5 and 6), resulting from a steric effect. Next, acyclic dicarbonyls were subjected to

the reaction. Unfortunately, acetylacetone and 1,3-diphenyl-1,3-propanedione were unreactive in this system. However, the reaction of methyl acetoacetate gave a moderate yield (Entry 7). These results suggested that the nucleophilicity of the dicarbonyls was crucial.

We hypothesized that the first transformation was intermolecular Michael addition, followed by intramolecular C-O bond formation since an isochromene had not been observed. Furthermore, we observed the loss of diethylmalonate from the ^{1}H NMR spectrum of the crude reaction, resulting in the low to moderate product yield obtained for the domino reaction. Our findings were consistent with a report from Mayr and co-workers regarding the reactivity of benzylidenemalonates in the Michael addition of carbanion nucleophiles.[9] We postulated that the stabilized carbanion added to the benzylidenemalonate to form the carbanion intermediate **I** which further underwent proton transfer to generate carbanion intermediate **II**. Based on the loss of diethylmalonate and reports from Mayr[10] and Li[4], we rationalized that **II** could alternatively undergo elimination, resulting in the elimination of diethylmalonate to give an unidentified product or tautomerization to form the enolate **III**. Subsequently, Ullmann-type C-O bond formation takes place to give desired chromene (Scheme 2).

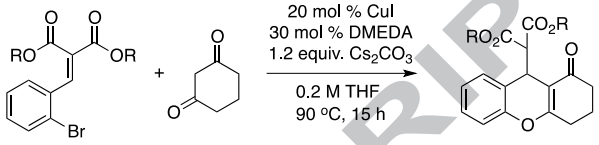
Scheme 2. Possible reaction mechanism

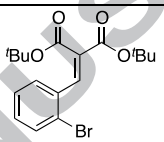
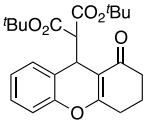
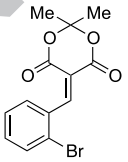
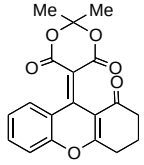
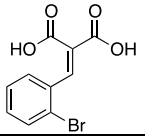
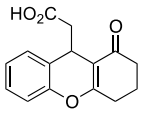


In this catalytic system, the product yields were limited by the nature of benzylidenemalonates in the Michael addition. Alternatively, Beifuss and co-workers elegantly designed a domino process[4] utilizing the nucleophilic substitution reactions of benzylbromide and 1,3-ketoesters, followed by C-O Ullmann-type coupling yielding 4*H*-chromene derivatives in moderate to high yields. Based on our proposed mechanism, the yields were diminished *via* an elimination step. Next, we explored the ester substituents of benzylidenemalonates in order to possibly avoid undesired elimination (Table 3).

Increasing the size of the ester group was initially examined. Unfortunately, the reaction of di-*tert*-butyl benzylidenemalonate (**1e**) gave a low yield of the desired chromene (Entry 1). Additionally, the ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of **1e** and **3h** was 10:1. The result suggested that the bulky ester group resulted in low reactivity. We next considered the geometry of benzylidenemalonate. 5-(2-Bromobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1f**), derived from Meldrum's acid, was selected, however, the expected chromene **3i** was not observed (Entry 2). Moreover, **1f** decomposed throughout the reaction course. In order to overcome the undesired elimination, we speculated that benzylidenemalonic acid (**1g**) would undergo decarboxylation after the addition of **2a**, instead of elimination to give the mono acid substituent on the chromene. Based on our proposal, the yield of chromene would be improved. However, the reaction of diacid **1g** and **2a** gave chromene **3j** in comparable yield to the reaction of diethyl ester **1a** (Entry 3). Furthermore, the ^{1}H NMR spectrum of the crude reaction mixture prior to being quenched with acid showed a mixture of mono- and di-acid chromenes (see ESI).

Table 3. 4*H*-Chromene formation from a variety of ester substituted benzylidenemalonates[a]



Entry	Benzylidene malonate		Chromene		Yield (%)[b]
1	**1e**		**3h**		10
2	**1f**		**3i**		0
3	**1g**		**3j**		65

[a]Reaction conditions: benzylidenemalonate (0.5 mmol), cyclohexane-1,3-dione (0.75 mmol). [b]Isolated yield.

Conclusion

We have demonstrated the domino synthesis of 4*H*-chromene derivatives *via* a copper-catalysed Michael addition and C-O Ullmann-type coupling reaction under mild and simple reaction conditions. The 1,3-cyclic diketones were shown to be a better reaction partner than 1,3-acyclic diketones which were not suitable in this domino system. Nonetheless, the reaction with 1,3-diketo ester gave satisfactory yields.

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Supplementary Material

Supplementary data (experimental procedures and characterization data) for new compounds associated with this article can be found, in the online version, at

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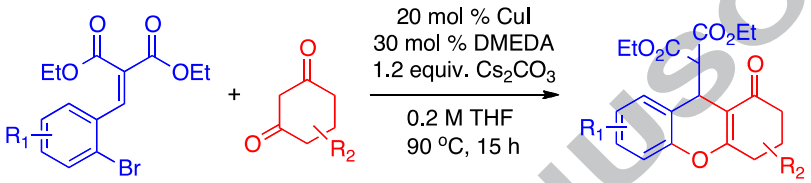

Highlights

- 4*H*-Chromenes were synthesized from benzylidenemalonates and 1,3-dicarbonyls.
- The reactions proceed under simple reaction conditions.
- Michael addition and Ullmann-type coupling are two key features in the domino process.
- The elimination of stabilized carbanion is rationalized as the competitive reaction.