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COMMUNICATION

Domino reactions of 2-methyl chromones containing an electron withdrawing group with chromone-fused dienes†

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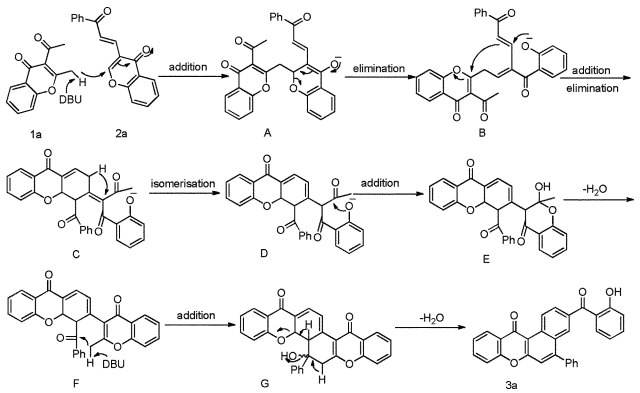
Domino reactions of 2-methyl substituted chromones containing an electron withdrawing group at the 3-position with chromone-fused dienes synthesized a diverse range of benzo[*a*]xanthones and complicated chromone derivatives. These multiple-step reactions result in either two or three new C–C bonds without a transition metal catalyst or an inert atmosphere.

Domino reactions that involve two or more bond-forming reactions under identical conditions, allow the synthesis of complex molecules from an easily prepared ingenious intermediate with multiple reactive sites. The design of these reactions has gained wide acceptance as an amazing modern synthetic strategy, due to an increase in synthetic efficiency by decreasing the number of laboratory operations required for satisfactory yields.[1] Our group has been pursuing the diversified synthesis of complicated natural-product-like scaffolds through cascade reactions based on 3-(1-alkynyl)chromone[2] and an electron-deficient chromone-fused diene[3] Significantly, we discovered that the methyl group of 2-methyl chromone could be changed from its usual role as a Michael acceptor[4] to a nucleophile[2c,3] to process different reactions. Herein, we designed the 3-acetyl-2-methyl-4*H*-chromen-4-one **1a** with multiple reactive sites, including latent nucleophilic (the methyl group at the 2-position) and electrophilic ($COCH_3$) centers, that could react with a Michael acceptor such as an electron-deficient–chromone-fused diene, **2a**,[5] to initiate a new cascade reaction for the efficient construction of substituted benzo[*a*]xanthones.

The proposed reaction mechanism for the new tandem process is shown in Scheme 1. The reaction is initiated by deprotonation of the 2-methyl group of **1a** by a base (*e.g.*, DBU) to generate the corresponding carbanion, which can attack the 2-position of **2a** generating intermediate **A** with concomitant pyrone ring-opening to give intermediate **B**. Subsequently, the phenoxide center in **B** undergoes tandem double Michael additions along with another pyrone ring-opening reaction to produce intermediate **C**, which could transform to **D** through an isomerisation. The phenoxide center in **D** then attacks the carbonyl group to give the intermediate **E**. The intermediate **F**, obtained from dehydration of **E**, can undergo further 1,2-addition at the carbonyl center to yield **G**. The subsequent elimination and pyrone ring opening of **G** leads to the formation of benzo[*a*]xanthone **3a**. This cascade reaction involves multiple additions/ring openings/eliminations and generates three new C–C bonds and one C–O bond.



Scheme 1 A proposed mechanism for the tandem reaction.

Initially, we investigated the cascade reaction of **1a** and **2a** using DBU (1.0 equiv) as the base in THF with microwave irradiation. To our delight, the target compound **3a** was obtained in 60% yield. Encouraged by this result, different solvents and various equivalents of DBU were tested to improve the reaction (Table 1). The reaction did not proceed well in common solvents such as MeCN, DME, 1,4-dioxane, toluene, *etc.*, giving poor yields. When DMSO was used, the yield increased to 68%. Interestingly, upon doubling the number of equivalents of DBU, the reaction proceeded efficiently in 10 min and the yield increased significantly to 98% in THF and 91% in DMSO, respectively.

This tandem reaction was extended to include various electron-deficient–chromone-fused dienes **2** with moderate to excellent yields. (Table 2). The yield was only 65% when the phenyl ring was replaced by a methyl group (Table 2, entry 1). It was noted that substitution on both the chromone ring and the aromatic ring

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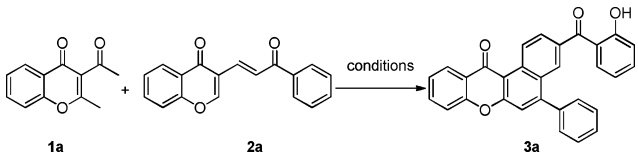
† Electronic supplementary information (ESI) available: Synthesis and ^1H and ^{13}C NMR spectra of compounds **3** and **4**. CCDC reference numbers 814417. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06613g

Table 1 Optimization of the tandem reaction of **1a** and **2a**[a]



Entry	Base (equiv)	Solvent	T (°C)	t (min)	Yield (%)[b]
1	DBU (1.0)	THF	100	10	60
2	DBU (1.0)	MeCN	100	10	43
3	DBU (1.0)	DME	100	10	0[c]
4	DBU (1.0)	1,4-dioxane	100	10	30
5	DBU (1.0)	toluene	100	10	34
6	DBU (2.0)	THF	100	10	98
7	DBU (1.0)	DMSO	100	10	68
8	DBU (2.0)	DMSO	100	10	91

[a] General conditions: **1a** (0.2 mmol), **2a** (0.2 mmol) and DBU in solvent (2 mL) heated in a microwave reactor at 100 °C for 10 min. [b] Isolated yield. [c] Reaction was complicated and no product was detected.

affected the yields. When substitution consisted of an electron-donating group (Table 2, entries 2 and 3), only moderate yields were given. However, when an electron-withdrawing group was used (Table 2, entries 5, 6 and 8), the reactions gave excellent yields. The structure of **3e** was unambiguously established by X-ray crystal structure analysis (Fig. 1).[6]

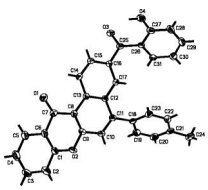
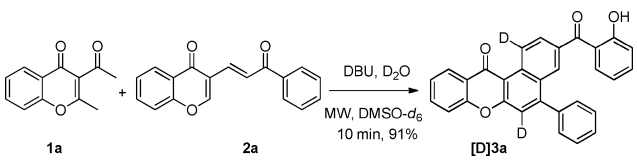


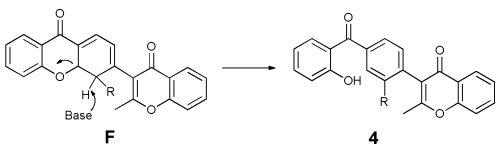
Fig. 1 X-ray crystal structure of **3e**. Ellipsoid probability: 50%.

In addition, reaction of **1a** with **2a**, carried out in DMSO-d_6 and D_2O leads to the formation of **[D]3a** with distinct deuterium incorporation at specific aryl ring positions (Scheme 2). These results indicate that the methylene and the methyl of intermediates could be exchanged with D_2O quickly because of the ready formation of the corresponding carbanion under basic conditions.



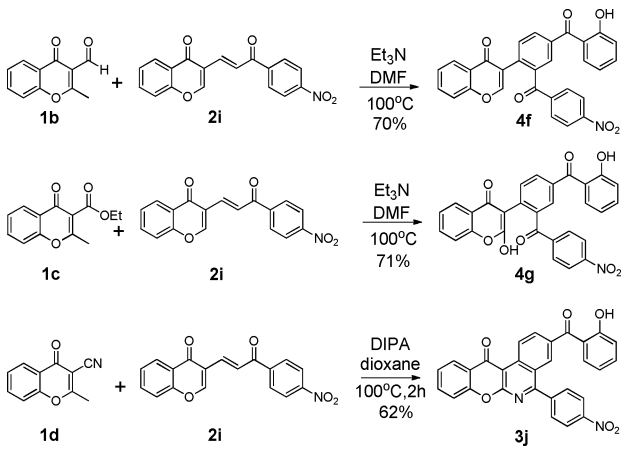
Scheme 2 Deuterium labeling experiment in the reaction of **1a** with **2a**.

When substrates **2** were changed from a ketone to an ester or nitrile under standard conditions, the reactions became complicated. After screening the reaction conditions by using different bases and solvents, the EtONa/EtOH system was chosen to obtain products **4a** and **4b** in 51 and 72% yield, respectively (Table 3, entries 1–2). The result shows that the reaction at the intermediate **F** stage did not proceed with further cyclization but directly eliminated the hydrogen in the presence of a base along with opening of the pyrone ring to generate the final product **4** (Scheme 3). To verify this hypothesis, substrates **2l**, **2m**, **2n** were investigated using this protocol. Products **4c**, **4d** and **4e** with the same core structure were obtained in reasonable yields (Table 3, entries 3–5).



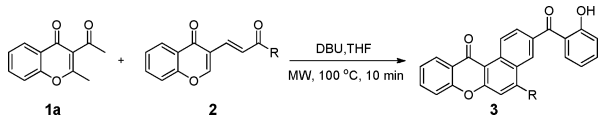
Scheme 3 A proposed mechanism for the products **4**.

When substrate **1a** was changed to **1b** or **1c**, the reactions in the presence of DBU or EtONa as the base gave complicated products. After changing to Et_3N as the base, the desired products **4f** and **4g** without further cyclization were separated in 70 and 71% yields, respectively (Scheme 4). When employing

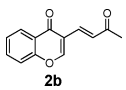
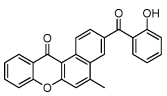
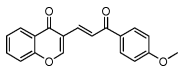
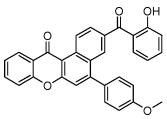
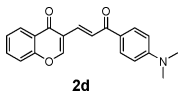
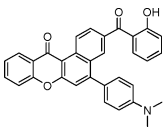
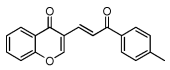
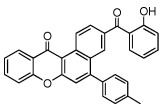
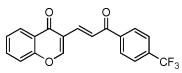
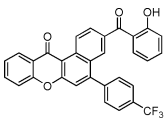
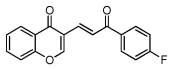
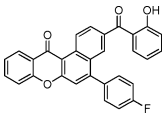
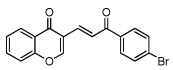
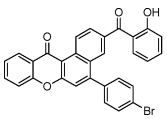
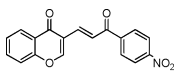
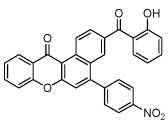


Scheme 4 Reaction of other 2-methyl chromones with EWGs at the 3 position with **2i**.

Table 2 Tandem reaction of **1a** with various electron-deficient–chromone-fused dienes **2**[a]



1a **2** **3**

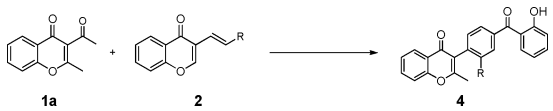
Entry	Substrate **2**	Product **3**	Yield (%)[b]
1	 **2b**	 **3b**	65
2	 **2c**	 **3c**	70
3	 **2d**	 **3d**	67
4	 **2e**	 **3e**	82
5	 **2f**	 **3f**	90
6	 **2g**	 **3g**	92
7	 **2h**	 **3h**	80
8	 **2i**	 **3i**	93[c]

[a] General conditions: **1a** (0.2 mmol), **2a** (0.2 mmol) and DBU (0.4 mmol) in THF (2 mL) heated in a microwave reactor at 100 °C for 10 min. [b] Isolated yield. [c] DBU, DMSO, 100 °C, 1 h. (THF is replaced by DMSO for good solubility of substrates **2i**.).

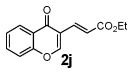
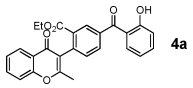
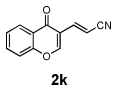
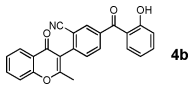
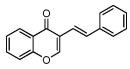
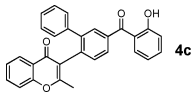
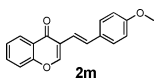
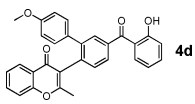
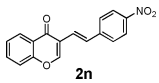
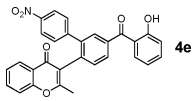
2-methyl-4-oxo-4*H*-chromene-3-carbonitrile **1d** in the reaction, the product **3j** was obtained in 62% yield after optimizing the conditions. This reaction is then followed by the reaction mechanism illustrated in Scheme 1 due to the NH_2 group being a stronger nucleophile.

In summary, we have developed efficient base-promoted domino reactions of 2-methyl chromones with electron withdrawing groups at the 3-position armed with latent nucleophilic and electrophilic centers. These mild tandem reactions provide efficient

Table 3 Extension of the tandem reaction[a]



1a **2** **4**

Entry	Substrate **2**	Product **3**	Yield (%)[b]
1	 **2j**	 **4a**	51
2	 **2k**	 **4b**	72
3	 **2l**	 **4c**	75
4	 **2m**	 **4d**	74
5	 **2n**	 **4e**	79

[a] General conditions: **1a** (0.2 mmol), **2a** (0.2 mmol) and EtONa (0.2 mmol) in EtOH (2 mL) heated in an oil bath at 80 °C for 1 h. [b] Isolated yield.

access to functionalized benzo[*a*]xanthones and novel chromone derivatives. Obviously, this study found unusual tandem processes that generate a diverse range of natural-like products from similar intermediates that involve multiple reactions, without the necessity for a transition metal and inert atmosphere. Further applications of these chromone substrates to construct interesting complicated molecules and their biological study are under investigation.

Acknowledgements

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Notes and references

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6 CCDC 814417 (**3e**) contains the supplementary crystallographic data for this paper (see the ESI†).