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An Efficient Approach to Functionalized Benzo[*a*]xanthones through Reactions of 2-Methyl-3-(1-alkynyl)chromones with Electron-Deficient Chromone-Fused Dienes

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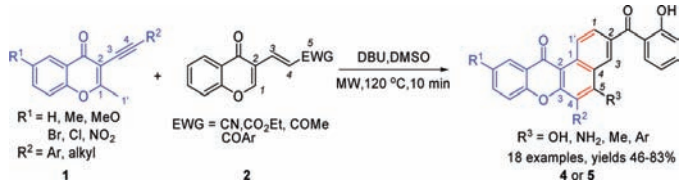
ABSTRACT



An efficient tandem process was developed to synthesize diversified benzo[*a*]xanthones from 2-methyl-3-(1-alkynyl)chromones with electron-deficient chromone-fused dienes. This unusual reaction, involving multiple steps and not requiring the use of transition metal catalysts or an inert atmosphere, results in the formation of three new C−C bonds and one C−O bond.

The xanthone framework is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activity.[1] Consequently, interest in the development of efficient methods for the synthesis of xanthones, bearing multiple and diverse substitution patterns, has continued.[2] Only a few synthetic routes for the preparation of benzo[*a*]xanthones have been described. One method, involving visible light induced photooxidative cyclization of (*E*)-2-styrylchromones,[3] requires long time periods and takes place in only modest yields. Other approaches employ harsh conditions or multistep sequences to obtain this target in low yields.[4] Below, we describe the results of an investigation that has led to the development of a facile and efficient method for the synthesis of functionalized benzo[*a*]xanthones that utilizes mild reaction conditions.

Tandem reactions, which employ easily prepared intermediates containing multiple reactive sites, serve as attractive methods to generate complex molecular architectures, especially those present in natural product skeletons.[5] Our earlier work in this area focused on the use of functionalized 3-(1-alkynyl)chromones to generate diversified natural product-

(1) (a) Sousa, M. E.; Pinto, M. M. *Curr. Med Chem.* **2005**, *12*, 2447, and references cited therein. (b) Palmer, B. D.; Henare, K.; Woon, S. T.; Sutherland, R.; Reddy, C.; Wang, L. C.; Kieda, C.; Ching, L. M. *J. Med. Chem.* **2007**, *50*, 3757.

(2) For recent studies, see: (a) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org.Chem.* **2009**, 2642. (b) Xu, W. Z.; Huang, Z. T.; Zheng, Q. Y. *J. Org. Chem.* **2008**, *73*, 5606. (c) Dang, A. T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233. (d) Swamy, N. K.; Tatini, L. K.; Babu, J. M.; Annamalai, P.; Pal, M. *Chem. Commun.* **2007**, 1035. (e) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288. (f) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (g) Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2006**, *71*, 4992. (h) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (i) Hauser, F. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753.

(3) Silva, A. M. S.; Pinto, D. C. G. A.; Tavares, H. R.; Cavaleiro, J. A. S.; Jimeno, M. L.; Elguero, J. *Eur. J. Org. Chem.* **1998**, 2031.

(4) (a) Brito, C. M.; Pinto, D. C. G. A.; Silva, A. M. S.; Silva, A. M. G.; Tome, A. C.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2006**, 2558. (b) Knight, D. W.; Little, P. B. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1771. (c) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, J. L. *Tetrahedron Lett.* **1998**, *39*, 881. (d) Horne, S. *J. Org. Chem.* **1990**, *55*, 4520. (e) Yokoe, I.; Higuchi, K.; Shirataki, Y.; Komatsu, M. *Chem. Pharm. Bull.* **1981**, *29*, 2670.

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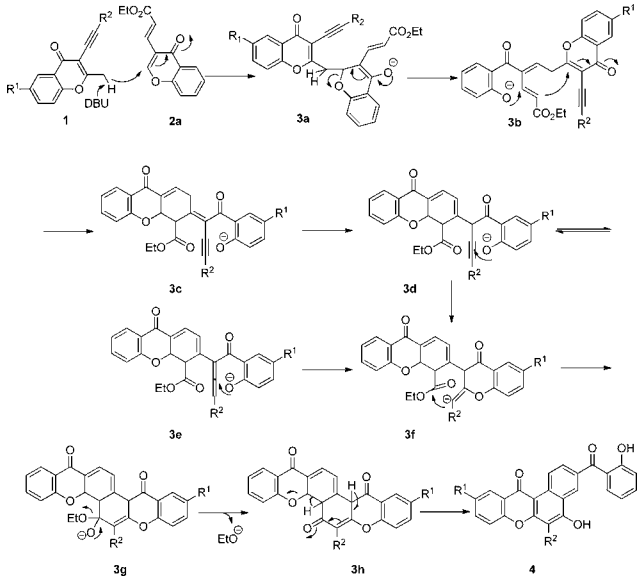
like scaffolds through employment of cascade reactions.[6] At the outset of the current effort, we envisaged that 2-methyl-3-(1-alkynyl)chromones **1**, possessing multiple reactive sites including latent nuclephilic (the methyl group at the 2-position) and electrophilic (the α,β-unsaturated system) centers, could participate in a tandem process for the generation of complex xanthones.[6c] In this process, electron-deficient chromone-fused dienes **2** would play the role of double Michael acceptors.[7] It should be noted that these substances are reported to participate in inverse-electron-demand Diels−Alder reactions with special dienophiles to afford xanthones.[8] Moreover, we reasoned that **2** would be a stronger electron acceptor than **1** and, as a result, it would react with **1** through a new cascade reaction sequence to form a novel complicated chromone-fused scaffold. The reaction mechanism used as the foundation of the design of the new tandem process is shown in Scheme 1. The pathway is

Scheme 1. Proposed Reaction Mechanism



initiated by deprotonation of the methyl group of **1** by a base to generate the corresponding carbanion, which would add to the 2-position of **2a** with concomitant pyrone ring-opening to give intermediate **3b**. Subsequently, the phenoxide center in **3b** undergoes tandem double Michael additions with pyrone ring-opening to produce intermediate **3c**, which could tautomerize to generate either **3d** or **3e**. The phenoxide

Scheme 2. Tandem Reaction of **1a** with **2a**

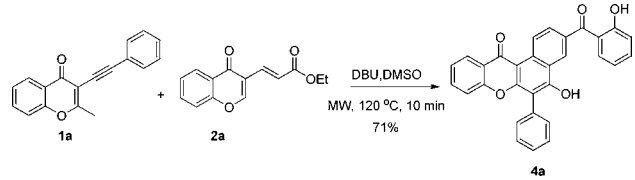
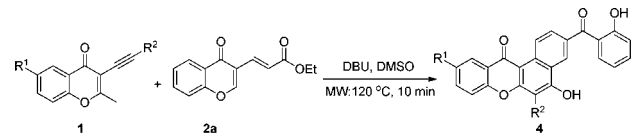
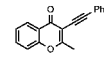
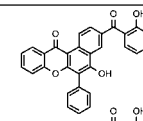
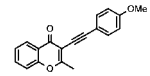
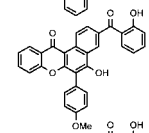
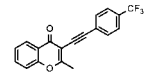
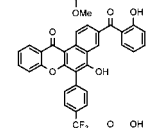
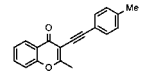
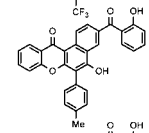
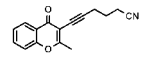
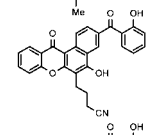
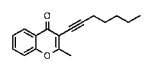
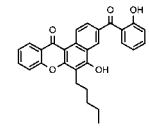
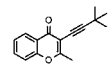
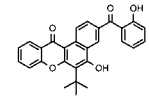
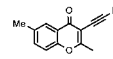
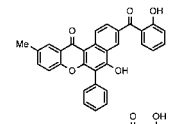
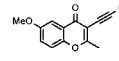
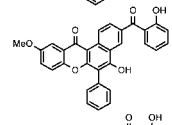
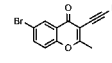
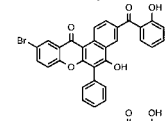
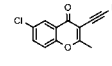
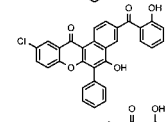
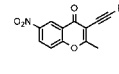
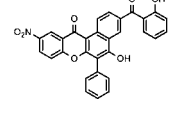


Table 1. Scope of Substrate **1**[a]



entry	substrate **1**		product		yield[b] (%)
1		**1a**		**4a**	71
2		**1b**		**4b**	61
3		**1c**		**4c**	70
4		**1d**		**4d**	55
5		**1e**		**4e**	54
6		**1f**		**4f**	61
7[c]		**1g**		**4g**	--
8		**1h**		**4h**	67
9		**1i**		**4i**	56
10		**1j**		**4j**	65
11		**1k**		**4k**	75
12		**1l**		**4l**	83

[a] Reaction condition: **1** (0.2 mmol), **2a** (0.2 mmol), DBU (0.2 mmol), DMSO (1.5 mL), 120 °C, 10 min. [b] Isolated yield. [c] The reaction was complicated and none of the desired product **4g** was produced.

centers in **3d** or **3e** then promote a cyclization process with the adjacent alkynyl or allene moiety, giving a carbanion of

3f, which could further undergo acyl substitution at the ester center to yield **3h**. The subsequent elimination and isomerization of **3h** leads to the formation of benzo[*a*]xanthone **4**. If successful, this cascade reaction would generate three new C−C bonds and one C−O bond.

To explore the feasibility of this process, we investigated the cascade reaction of **1a** with **2a** using DBU as the base and microwave irradiation conditions (Scheme 2). Importantly, this reaction yielded the desired product **4a** in 71% yield. Encouraged by this result, we probed the scope of this tandem reaction by using various 2-methyl-3-(1-alkynyl)-chromones **1** in reactions with **2a**. Moderate to good yields were obtained when the R^2 group in **1** was aromatic (Table 1, entries 1−4). In addition, the desired products were formed in reasonable yields (Table 1, entries 5 and 6) when R^2 was a nonsterically bulky alkyl group. However, when R^2 was sterically large (e.g., *tert*-butyl), the reaction was complicated and none of the desired product **4g** was produced (Table 1, entry 7). A study of the electronic effects of substituents on the aryl chromone ring showed that substrates containing electron-withdrawing groups (Br, Cl, NO_2) reacted to give products in higher yields in contrast to the subtrates that contained the electron-donating OMe group (Table 1, entries 9−12). It should be noted that the structure of **4h** was unambiguously assigned by using X-ray crystallographic analysis (Figure 1).[9]

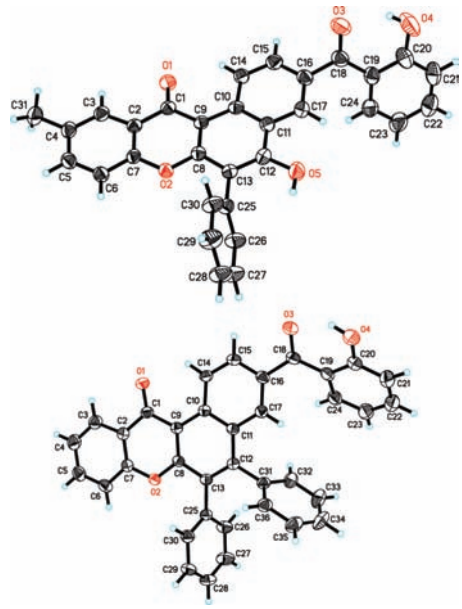
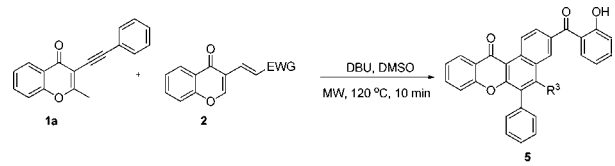
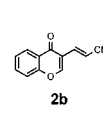
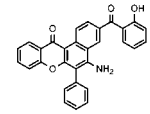
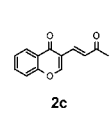
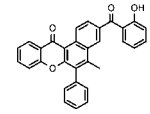
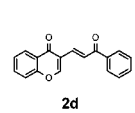
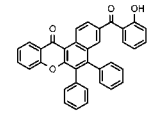
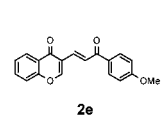
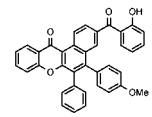
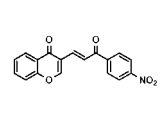
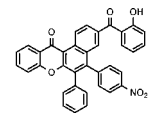
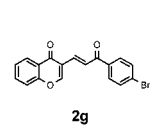
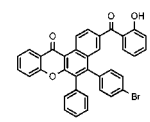


Figure 1. X-ray structures of **4h** and **5c**.[9]

Studies of the tandem reaction were extended to include various electron-deficient chromone-fused dienes (EWG = CN, COMe, and various aryl carbonyl). In these processes, the corresponding functionalized benzo[*a*]xanthones **5** were produced in 46−75% yields. Reactions involving chromone-fused dienes with less sterically hindered CN and COMe groups lead to higher product yields (Table 2, entries 1 and

Table 2. Scope of Substrate **2**[a]



entry	substrate **2**	product	yield[b] (%)
1	 **2b**	 **5a**	64
2	 **2c**	 **5b**	75
3	 **2d**	 **5c**	46
4	 **2e**	 **5d**	55
5[c]	 **2f**	 **5e**	20
6	 **2g**	 **5f**	50

[a] Reaction condition: **1a** (0.2 mmol), **2** (0.2 mmol) and DBU (0.2 mmol), DMSO (1.5 mL), 120 °C, 10 min. [b] Isolated yield. [c] **5e$_1$** was obtained as a major product.[10]

2) than those involving substrates with sterically more demanding substituents (Table 2, entries 3−6). Interestingly, when the substituent on the chromone-fused diene is the strong electron-withdrawing NO_2 group (**2f**), the unexpected product **5e$_1$** was generated in 60% yield along with the desired product **5e** in 20% yield (Table 2, entry 5).[10] The structure of **5c** was also assigned based on the results of X-ray crystallographic analysis (Figure 1).[9]

Reaction of **1a** with **2a**, carried out in DMSO-d_6 and D_2O leads to formation of **[D]4a**, which contains 76% deuterium

(5) For recent reviews, see: (a) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (e) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933.

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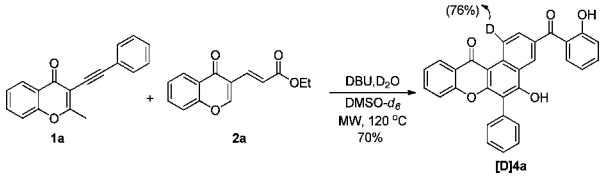
Scheme 3. Deuterium Labeling Experiment in the Reaction of **1a** with **2a**



incorporation at a single aryl ring position (Scheme 3). This result indicates that the methyl protons in **1a** exchange rapidly with D_2O through reversible formation of the corresponding carbanion under the basic conditions employed in this process.

In conclusion, this investigation has led to the development of a novel tandem process for the preparation of various benzo[*a*]xanthones starting with 2-methyl-3-(1-alkynyl)-chromones and electron-deficient chromone-fused dienes. The novel tandem process proceeds by way of a multistep pathway involving sequential Michael addition/cyclization/1,2-addition/elimination. Further applications of 2-methyl-3-(1-alkynyl)chromones in processes leading to the generation of interesting natural product-like and biologically active benzo[*a*]xanthones are under investigation.

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Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for compounds in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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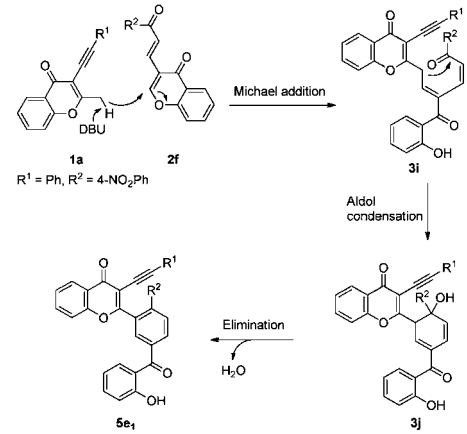
(9) CCDC 776163 (**4h**) and 776162 (**5c**) contain the supplementary crystallographic data for this paper. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 776163 and 776162. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/data_request/cif.

(10) Proposed mechanism for formation of $\mathbf{5e_1}$:



Reaction at the NO_2 group, which is a strong electron-withdrawing group activated methylene moiety in intermediate **3i**, which competes with that of the phenoxide ion through aldol condensation with the carbonyl group to give $\mathbf{5e_1}$.