Tandem Reactions

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A Base-Promoted Tandem Reaction of 3-(1-Alkynyl)chromones with 1,3-Dicarbonyl Compounds: An Efficient Approach to Functional Xanthones**

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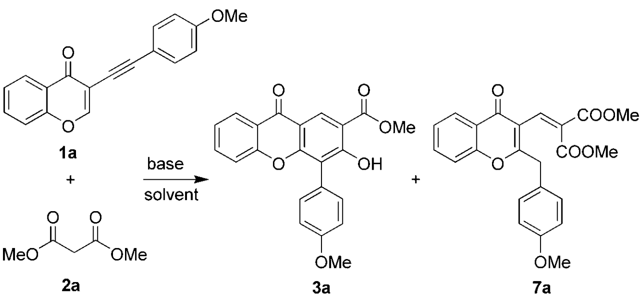
Tandem reactions provide an efficient way to generate molecular complexity from readily accessible intermediates.[1] 2-(1-Alkynyl)-2-alken-1-ones, which have a special α,β-unsaturated ketone skeleton with a triple bond, are very attractive units because a C−O bond and a remote carbon–nucleophile bond can be formed simultaneously. Based on these intermediates, the tandem synthesis of highly substituted furans through a transition metal, an acid catalyzed,[2] or an electrophile-induced cascade process[3] has been reported recently.

Our research group has focused on functionalized 3-(1-alkynyl)chromones to generate natural-product-like scaffolds through cascade reactions. The synthesis of substituted furo[3,2-c]coumarins and furo[3,2-c]chromenes[4] was explored by using a tandem process. We are continuing our efforts in this area, and have became interested in the replacement of alcohols with 1,3-dicarbonyl compounds to act as the carbon nucleophiles to construct more stable C−C bonds instead of C−O bonds. A preliminary study (Scheme 1) showed that the reaction failed to afford furo[3,2-c]chromenes under palladium-catalyzed conditions (alkynyl compound **1a**, dimethyl malonate **2a**, and aryl iodide in the presence of NaH and [$Pd_2(dba)_3$] (dba = *trans,trans*-dibenzylideneacetone) in DMF at 45 °C for 5 h).[4] However, an interesting and unexpected novel product **3a** was detected and isolated, and it was unambiguously established as a xanthone by X-ray crystal structure analysis (Figure 1). A control experiment showed that a reaction without the Pd catalyst occurred under basic conditions to afford **3a** in 70% yield.



Scheme 1. A base-promoted tandem reaction to form the functional xanthone **3a**.

We envisioned that this novel transformation involves a domino process of a Michael addition-elimination/cyclization/1,2-addition/elimination reaction (Scheme 2). First, in the presence of a base the 3-(1-alkynyl)chromone **1**, which acts as a Michael acceptor, could be attacked by a 1,3-dicarbonyl compound **2** to generate **4**, along with the opening of the pyrone ring to form **5**.[5] Subsequently, the OH group of **5** can recyclize with the alkynyl bond to produce the intermediate **6** regioselectively. Compound **6** can be rearranged to **7** through a 1, 5-hydrogen shift, and then the resulting carbanion of **7** can further add a to carbonyl group under basic conditions by intramolecular 1,2-addition to accomplish a second cyclization. The subsequent elimination and isomerization of **8** leads to the formation of xanthone **3**. In this process, the reaction does not afford a furan, as in the reported process.[2] To the best of our knowledge, this is the only example involving the generation of xanthones instead of furans by a tandem reaction from 3-(1-alkynyl)chromones. Xanthone frameworks are a ubiquitous structure in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activity.[6] Consequently, there has been continued interest in the development of efficient methods for the synthesis of xanthones bearing multiple and diverse substitution patterns.[7] Herein, we report an efficient, novel method for constructing functionalized xanthones with a broad scope under mild reaction conditions and in good to excellent yields.

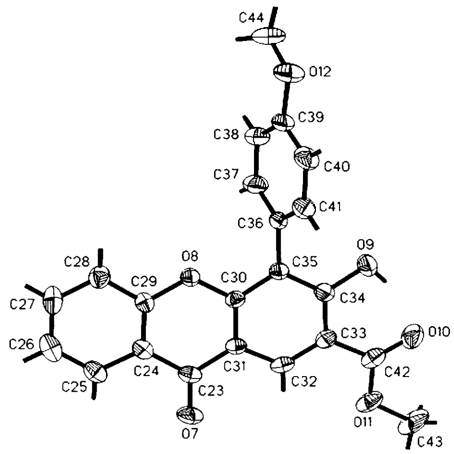


Figure 1. ORTEP plot of **3a** shown with ellipsoids at the 50% level.[8]

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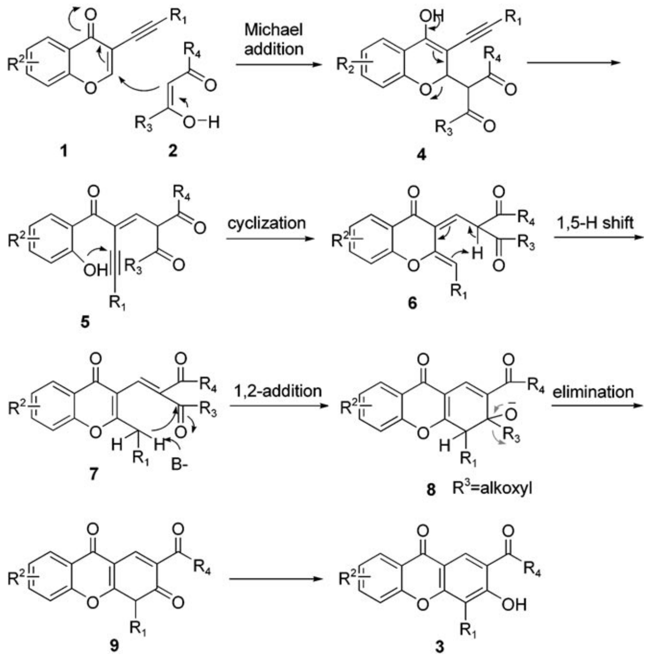


Scheme 2. A proposed mechanism.

We examined the reaction of **1a** with dimethyl malonate **2a** under different reaction conditions (Table S1 in the Supporting Information). When the reaction was carried out in DMF, using NaH as the base at 45 °C, the product was obtained in 70 % yield. On carrying out the reaction at room temperature for 10 hours, only a 30 % yield of the product was generated along with the intermediate **7a** in 35 % yield. By increasing the reaction temperature to 45 °C, **7a** can be converted into the desired product **3a**. These results support our proposed mechanism that **7a** has difficulty in undergoing a 1,2-addition at room temperature. The yield was increased to 82 % when NaH and DIPEA were used in combination. However, when only DIPEA (*N*,*N*-diisopropylethylamine) was used as the base, a trace amount of the desired product was observed along with recovered **1a**. This outcome means that a weak base cannot promote the initial Michael addition. Also, when using the inorganic base K_2CO_3, the desired product was obtained in 63 % yield. Interestingly, when DBU was employed, the yield increased significantly to 90 %. A modest decrease in the yield was observed on lowering the amount of DBU from 3 equivalents to 1 equivalents, or on changing the solvent to THF (tetrahydrofuran). The optimized reaction conditions were defined with the reaction carried out in DMF in the presence of DBU (3 equiv) at 45 °C for 5 hours.

By using the optimized reaction conditions, various 3-(1-alkynyl)chromones **1** were treated with **2a** to extend the scope of this tandem reaction. Good to excellent yields were obtained when R^1 was an aromatic group on the acetylene moiety (Table 1, entries 1–3). It was noted that an electron-donating group was beneficial to the domino process. When R^1 was an aliphatic chain, the reactions gave a modest yield (Table 1, entries 4 and 5). Substitution with a sterically hindering group (*tert*-butyl) afforded the intermediate **7f**, which did not readily transfer to the final product (Table 1, entry 6). For **1f**, the reaction became complicated upon raising the reaction temperature. When R^1 was a trimethylsilyl group, the desilylated product **3g** was obtained in a reasonable yield in which desilylation of **1g** easily occurred under basic condition[9] (Table 1, entry 7). In addition, reactions with various substituents on the aryl ring of the 3-(1-alkynyl)chromones proceeded smoothly (Table 1, entries 8–11). However, the transformations of **1h** and **1i**, which has an electron-withdrawing substituent, were carried out over a prolonged reaction time of 10 hours.

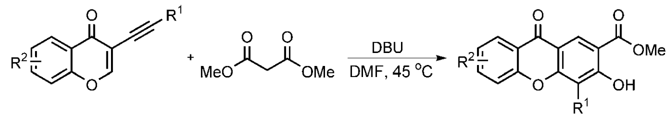
Besides **2a**, this tandem transformation can be successfully extended to various 1,3-dicarbonyl compounds, including β-ketone esters and 1,3-diketones, thus leading to the generation of the corresponding functionalized xanthones **4** in 60–82 % yield (Table 2). Notably, the reactions proceed to completion at room temperature over 3–6 hours. Clearly, in this tandem reaction the ketone moiety can more easily undergo 1,2-addition compared with the ester group. Interestingly, the asymmetric 1-phenylbutane-1,3-dione can undergo the tandem reaction to afford **4f** in 69 % yield with a high regioselectivity (Table 2, entry 6). The product **4f** was confirmed by using X-ray crystal structure analysis (see the Supporting Information).[8] A cyclic diketone was also amenable to the tandem reaction and gave a polycyclic product **4g** in 75 % yield (Table 2, entry 7). The results in Table 1 and 2 clearly show that this novel tandem process allows the generation of more complex xanthone-like natural products under mild reaction conditions with various functionalized groups, such as carbonyl, hydroxy, alkyl, and aryl groups.

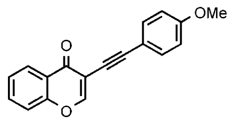
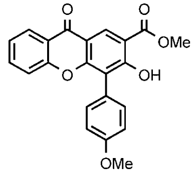
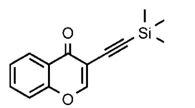
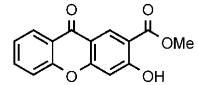
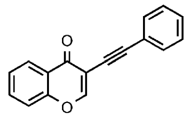
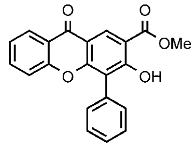
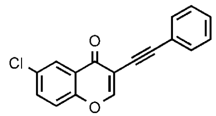
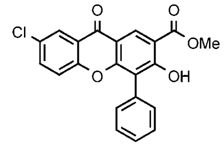
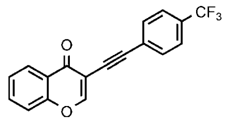
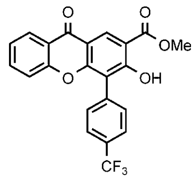
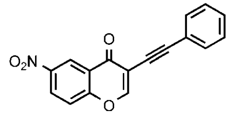
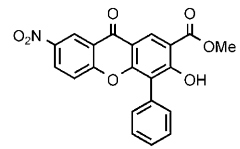
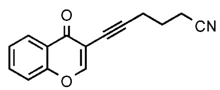
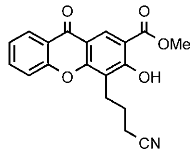
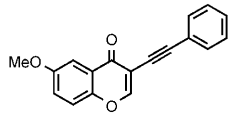
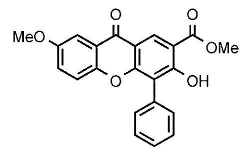
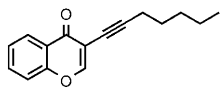
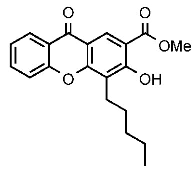
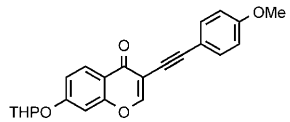
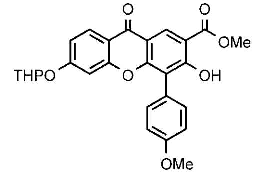
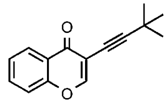
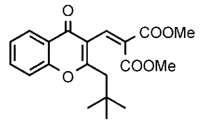
In conclusion, we have developed a novel base-promoted tandem reaction to afford functionalized xanthones from 3-(1-alkynyl)chromones with 1,3-dicarbonyl compounds under mild reaction conditions. Notably, we found that this tandem process involves multiple reactions, such as a Michael addition-elimination/cyclization/1,2-addition/elimination reactions, without the need for a transition metal catalyst. This approach differs from previous reports that claimed a furan is formed instead of a xanthone scaffold. Further library generation and biological evaluation of the diversified xanthones is under investigation.

Experimental Section

A typical procedure for the preparation of **3a**: A solution of dimethyl malonate **2a** (0.43 mmol) in dry DMF (3 mL) was added to DBU (0.16 mL, 1.08 mmol) at room temperature under a nitrogen atmosphere. After stirring for 5 min, **1a** (100 mg, 0.36 mmol) was added and the resulting yellow solution was stirred at 45 °C for 5 h. The reaction was quenched using water (20 mL) and the pH was adjusted to pH 5 using 1N HCl. The mixture was extracted using dichloromethane (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified using column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3a** as a white solid (m.p. 265–267 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.73 (s, 1H), 8.96 (s, 1H), 8.30 (dd, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.68–7.62 (m, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 4.03 (s, 3H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.27, 170.37, 163.15, 159.30, 157.48, 156.08, 134.80, 131.94, 129.80, 126.62,

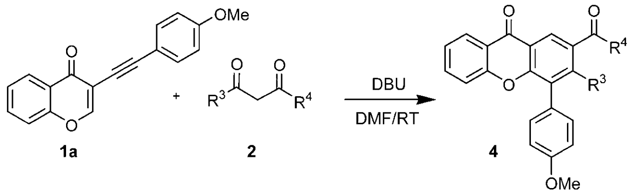
Table 1: Scope of the tandem reaction of **2a** and various 3-(1-alkynyl)chromones.[a]

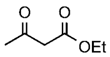
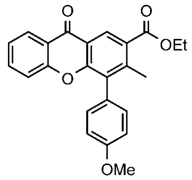
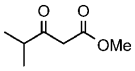
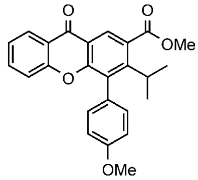
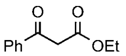
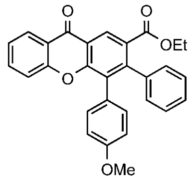
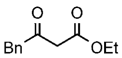
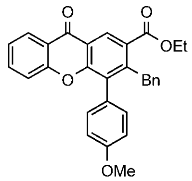
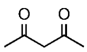
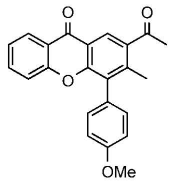
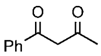
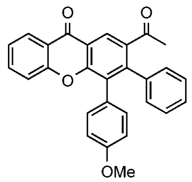
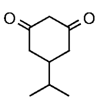
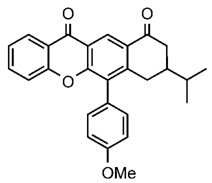


Entry	Substrate		Product		Yield [%][b]	Entry	Substrate		Product		Yield [%][b]
1	**1a**		**3a**		90	7	**1g**		**3g**		65
2	**1b**		**3b**		76	8[c]	**1h**		**3h**		80
3	**1c**		**3c**		68	9[c]	**1i**		**3i**		81
4	**1d**		**3d**		60	10	**1j**		**3j**		80
5	**1e**		**3e**		55	11	**1k**		**3k**		84
6	**1f**		**7f**		68						

[a] Unless otherwise noted, the reactions were carried out under the standard reaction conditions. [b] Yield of isolated product based on **1**. [c] The reaction was carried out over 10 hours. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, THP = tetrahydropyranyl.

Table 2: The tandem reaction of **1a** with various 1, 3-dicarbonyl compounds.[a]



Entry	Substrate		Product		Yield [%][b]
1	**2b**		**4a**		82
2	**2c**		**4b**		80
3	**2d**		**4c**		65
4	**2e**		**4d**		60
5	**2f**		**4e**		75
6	**2g**		**4f**		69
7	**2h**		**4g**		75

[a] Reaction conditions: **1a** (0.36 mmol), **2** (0.43 mmol), and DBU (1.08 mmol) in DMF (3 mL) at room temperature for 3–6 hours. [b] Yield of isolated product. Bn = benzyl.

124.34, 122.80, 121.29, 118.09, 117.67, 115.01, 113.69, 110.24, 55.27, 50.81 ppm; HRMS calcd for $C_{22}H_{16}O_6$ ($[M]^+$): 376.0947; found: 376.0936.

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Keywords: 1,3-dicarbonyl compounds · Michael addition · synthetic methods · tandem reactions · xanthones

[1] For recent reviews, see: a) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) P. Eilbracht, L. Barfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3366; d) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551–564; e) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760; f) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; g) D. Enders, C. Grondal, M. R. Huttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; h) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[2] a) G. Cheng, Y. Hu, *Chem. Commun.* **2007**, 3285–3287; b) G. Cheng, Y. Hu, *J. Org. Chem.* **2008**, *73*, 4732–4735; c) C. H. Oh, V. R. Reddy, A. Kim, C. Y. Rhim, *Tetrahedron Lett.* **2006**, *47*, 5307–5310; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531–4534; e) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; f) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929–1932; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903–1906; g) A. S. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288; h) A. S. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769–3771; i) X. Liu, Z. Pan, X. Shu, X. Duan, Y. Liang, *Synlett* **2006**, 1962–1964.

[3] a) Y. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609–4611; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679–7685.

[4] L. Zhao, G. Cheng, Y. Hu, *Tetrahedron Lett.* **2008**, *49*, 7364–7367.

[5] V. Y. Sosnovskikh, R. A. Irgashev, M. I. Kodess, *Tetrahedron* **2008**, *64*, 2997–3004.

[6] a) M. E. Sousa, M. M. Pinto, *Curr. Med. Chem.* **2005**, *12*, 2447–2479, and references therein; b) B. D. Palmer, K. Henare, S. T. Woon, R. Sutherland, C. Reddy, L. C. Wang, C. Kieda, L. M. Ching, *J. Med. Chem.* **2007**, *50*, 3757–3764.

[7] For recent studies, see: a) C. M. M. Santos, A. M. S. Silva, J. A. S. Cavaleiro, *Eur. J. Org. Chem.* **2009**, 2642–2660; b) W. Z. Xu, Z. T. Huang, Q. Y. Zheng, *J. Org. Chem.* **2008**, *73*, 5606–5608; c) A. T. Dang, D. O. Miller, L. N. Dawe, G. J. Bodwell, *Org. Lett.* **2008**, *10*, 233–236; d) N. K. Swamy, L. K. Tatini, J. M. Babu, P. Annamalai, M. Oal, *Chem. Commun.* **2007**, 1035–1037; e) J. Zhao, D. Yue, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2007**, *129*, 5288–5295; f) J. Zhao, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 583–588; g) M. Mondal, V. G. Puranik, N. P. Argade, *J. Org. Chem.* **2006**, *71*, 4992–4995; h) J. Zhao, R. C. Larock, *Org. Lett.* **2005**, *7*, 4273–4275; i) F. M. Hauser, W. A. Dorsch, *Org. Lett.* **2003**, *5*, 3753–3754.

[8] CCDC 730122 (**3a**), and 730123(**4f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Removal of TMS-alkynes under basic condition, see: T. W. Greene, P. G. M Wuts in *Protective Groups in Organic Chemistry*, *3rd ed.*, Wiley-Interscience, New York, **2007**, Chapter 8, pp. 928–930.