ORGANIC LETTERS

2010
Vol. 12, No. 13
3086−3089

Efficient Construction of a 3*C*-Xanthone-Linked 3*C*-Chromone Scaffold by Novel Double Michael Additions and Cyclizations

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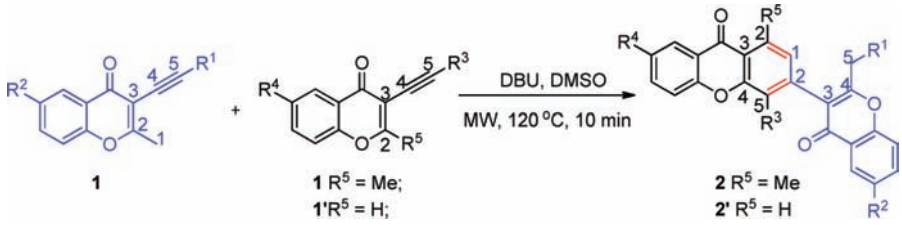
Received May 13, 2010

ABSTRACT



A novel base-promoted cascade reaction of 2-methyl-3-(1-alkynyl)chromones to produce a 3*C*-xanthone-linked 3*C*-chromone scaffold has been developed. This tandem process involves multiple reactions such as Michael additions/cyclizations under mild conditions without a transition metal catalyst and inert atmosphere.

Tandem reactions that involve the production of multiple C−C bonds in a single manipulation provide an efficient way to construct complex molecules from readily available materials.[1] The design of a tandem reaction from an easily prepared ingenious intermediate with multiple reactive sites to generate complex molecular architectures is significant and attractive, especially for the synthesis of natural product skeletons.[2] Our group has been pursuing the diversified synthesis of natural-product-like scaffolds through cascade reactions based on 3-(1-alkynyl)chromone intermediates.[3] The chromone moiety is well-known as a Michael receptor.[4] However, the reactivity of the methyl group of chromone at the 2-position has rarely been investigated. Only a few reports have mentioned that the methyl group of 2-methyl chromone could be used in aldol condensations with electrophiles (such as aromatic aldehydes, dimethylformamide dimethyl acetal, diethyl oxalate, and 4-nitrosodimethylanilines) under basic conditions.[5] We envisioned that the

(1) For recent reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (c) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (d) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (e) Enders, D.; Grondal, C.; Huttl, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (f) Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (g) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (h) Gorobets, E. V. M.; Mansur, S.; Valeev, F. A. *Russ. Chem. Rev.* **2000**, *69*, 1001.

(2) 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.

(3) (a) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285. (b) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732. (c) Zhao, L.; Cheng, G.; Hu, Y. *Tetrahedron Lett.* **2008**, *49*, 7364. (d) Zhao, L.; Xie, F.; Cheng, G.; Hu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6520. (e) Xie, F.; Pan, X.; Lin, S.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1378.

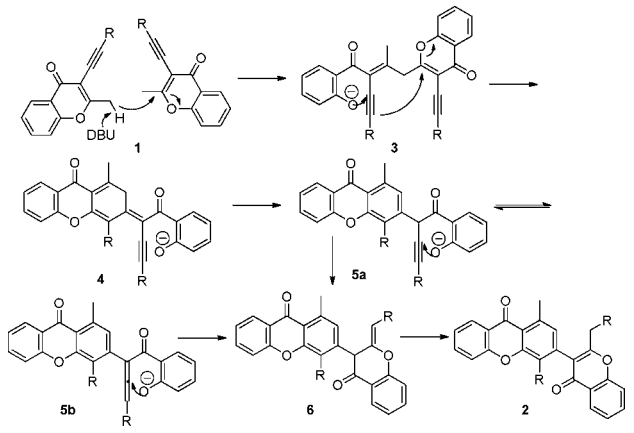
(4) For recent examples, see: (a) Ibrahim, M. A. *Arkivoc* **2008**, 192. (b) Sosnovskikh, V.; Irgashev, R.; Moshkin, V.; Kodess, M. *Russ. Chem. Bull.* **2008**, *57*, 2146. (c) Sosnovskikh, V. Y.; Irgashev, R. A.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 2997. (d) Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 7877. (e) Sosnovskikh, V. Y.; Moshkin, V. S.; Irgashev, R. A. *Tetrahedron Lett.* **2006**, *47*, 8543. (f) Lin, Y. D.; Kao, J. Q.; Chen, C. T. *Org. Lett.* **2007**, *9*, 5195. (g) Shokol, T.; Turov, V.; Semeniuchenko, V.; Krivokhizha, N.; Khilya, V. *Chem. Heterocycl. Compd.* **2006**, *42*, 500. (h) Gasparova, R.; Lacova, M. *Molecules* **2005**, *10*, 937.

10.1021/ol101100d
Published on Web 06/10/2010

employment of the nucleophilic methyl group and the α,β-unsaturated system of 2-methylchromones with a triple bond under basic conditions could initiate a new cascade reaction to produce a 3*C*-xanthone-linked 3*C*-chromone skeleton.

The proposed reaction is shown in Scheme 1. First, the methyl group of **1** could be deprotonated by a base, such as DBU, to generate the corresponding carbanion, which attacks at the 2-position of a second molecule with pyrone ring opening to give intermediate **3**. Subsequently, phenol ion **3** undergoes a cyclization with the adjacent alkynyl bond, which is followed by a second Michael addition with pyrone ring opening to produce intermediate **4**, which can be isomerized to intermediate **5a** or **5b**.The phenol ion **5a** or **5b** could also undergo a second cyclization with the adjacent alkynyl bond or allene and isomerize to afford product **2**. Significantly, from the easily prepared 2-methyl-3-(1-alkynyl)chromones, the formation of two new C−C bonds and C−O bonds could be efficiently created accompanying double ring openings and closings.

Scheme 1. Plausible Reaction Mechanism



3*C*-Xanthone-linked 3*C*-chromone with an axial chirality as a core structure was found in the fascinating unique natural products vinaxanthone, (α*R*)-2′-methoxyvinaxanthone, and chaetocyclinone C (Figure 1) from penicillium,[6] which exhibited important biological activity.[7] Only the Tatsuta group has reported a biomimetic synthesis of vinaxanthone through an intermolecular Diels−Alder cycloaddition between two molecules of the precursor.[8] Herein, we report an efficient, novel cascade reaction for constructing this interesting framework rapidly under microwave irradiation in good to excellent yields.

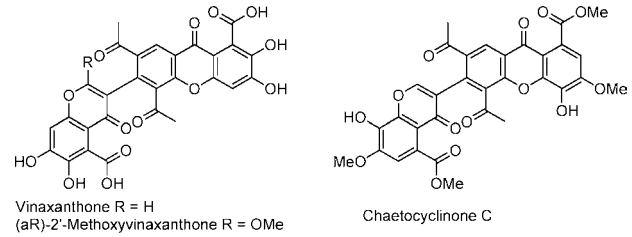
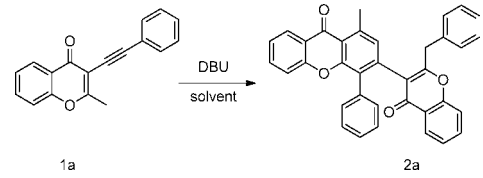


Figure 1. Unique bioactive natural products with a 3*C*-xanthone-linked 3*C*-chromone substructure.

Table 1. Optimization of Reaction Conditions[a]



entry	base (equiv)	solvent	temp (°C)	*t* (min)	yield[b] (%)
1[c]	DBU (2.0)	THF	120	10	<30
2[c]	DBU (2.0)	acetonitrile	120	10	<30
3[c]	DBU (2.0)	DME	120	10	<30
4[c]	DBU (2.0)	dioxane	120	10	<30
5[c]	DBU (2.0)	toluene	120	10	<30
6[c]	DBU (2.0)	DMF	120	10	<30
7	DBU (2.0)	DMSO	120	10	50[d]
8	DBU (1.0)	DMSO	120	10	90[d]
9[c]	DBU (0.5)	DMSO	120	10	85[d]

[a] General conditions: **1a** (0.4 mmol) and DBU in solvent (1.5 mL) heated in a microwave reactor at 120 °C for 10 min. [b] Yield was evaluated by TLC. [c] With **1a** recovered. [d] Isolated yield.

Initially, we investigated the cascade dimeric reaction of **1a** with DBU (2 equiv) as base in THF at 50 °C for 24 h under oil-bath heating conditions. The desired product **2a** was obtained with slow transformation. Therefore, we decided to apply this tandem process under microwave irradiation (Table 1). The reaction did not proceed well in most common solvents such as THF, DME, toluene, DMF, etc., giving less than 30% yield of **2a** with abundant **1a** recovered (Table 1, entries 1−6). To our delight, when the solvent was changed to DMSO, **1a** was consumed completely to afford **2a** in 50% yield (Table 1, entry 7). Employing DBU as 1.0 equiv, the reaction proceeded smoothly in 10 min and the yield increased significantly to 90% (Table 1, entry 8).

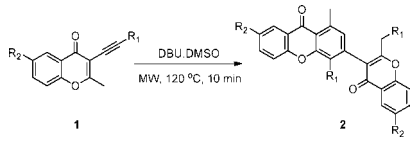
(5) (a) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2009**, 2642. (b) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett* **2005**, 3095. (c) Venkateswara Rao, K. *Ind. Eng. Chem. Res.* **2002**, *41*, 3333. (d) Alonso, R.; Brossi, A. *Tetrahedron Lett.* **1988**, *29*, 735. (e) Ghosh, C. K.; Bhattacharyya, S.; Patra, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3005. (f) Sami, S. M.; Sayed, A. A.; Ibrahim, S. S. *Egypt. J. Chem.* **1981**, *23*, 337. (g) El-Shaaer, M. H.; Lacova, P. Z. M.; Matulova, M. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1673.

(6) (a) Aoki, M.; Itezono, Y.; Shirai, H.; Nakayama, N.; Sakai, A.; Tanaka, Y.; Yamaguchi, A.; Shimma, N.; Yokose, K.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 4737. (b) Wrigley, S. K.; Latif, M. A.; Gibson, T. M.; Chicarelli-Robinson, M.; Williams, D. H. *Pure Appl. Chem.* **1994**, *66*, 2383. (c) Lösgen, S.; Schlörke, O.; Meindl, K.; Herbst-Irmer, R.; Zeeck, A. *Eur. J. Org. Chem.* **2007**, 2191. (d) Rezanka, T.; Rezanka, P.; Sigler, K. *J. Nat. Prod.* **2008**, *71*, 820.

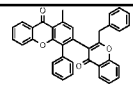
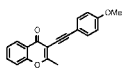
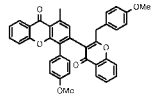
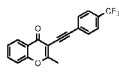
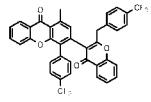
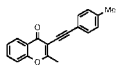
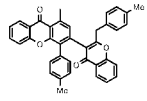
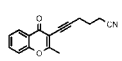
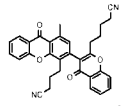
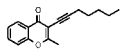
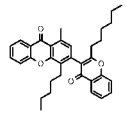
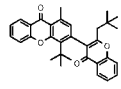
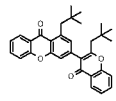
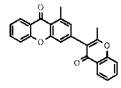
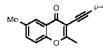
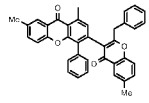
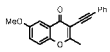
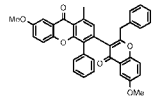
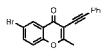
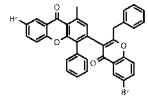
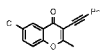
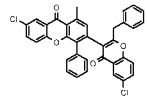
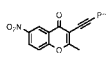
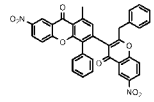
(7) (a) Kumagai, K.; Hosotani, N.; Kikuchi, K.; Kimura, T.; Saji, I. *J. Antibiot.* **2003**, *56*, 610. (b) Zheng, C. J.; Sohn, M. J.; Kim, W. G. *J. Antimicrob. Chemother.* **2009**, *63*, 949.

(8) Tatsuta, K.; Kasai, S.; Amano, Y.; Yamaguchi, T.; Seki, M.; Hosokawa, S. *Chem. Lett.* **2007**, *36*, 10.

Table 2. Scope of the Reaction[a]

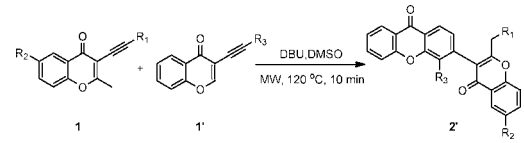


1 2

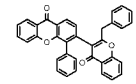
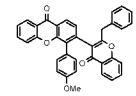
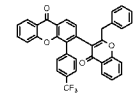
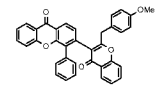
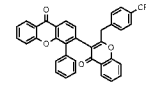
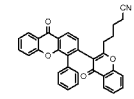
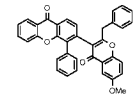
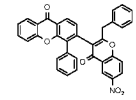
entry	substrate **1**		product		yield[b] (%)
1		**1a**		**2a**	90
2		**1b**		**2b**	85
3		**1c**		**2c**	79
4		**1d**		**2d**	82
5		**1e**		**2e**	70
6		**1f**		**2f**	65
7[c]		**1g**		**2g$_1$**	14
				**2g$_2$**	57
8		**1h**		**2h**	63
9		**1i**		**2i**	78
10		**1j**		**2j**	80
11		**1k**		**2k**	74
12		**1l**		**2l**	77
13		**1m**		**2m**	75

[a] Reaction conditions: **1** (0.4 mmol), DBU (1.0 equiv), DMSO (1.5 mL), 120 °C, 10 min. [b] Isolated yields. [c] The reaction was carried out on a 0.6 mmol scale at 140 °C.

Table 3. Scope of the Reaction[a]



1 1′ 2′

entry	substrate		product		yield[b] (%)
1	**1a**	**1′a** R_3 = Ph		**2′a**	71
2	**1a**	**1′b** R_3 = 4-OMePh		**2′b**	68
3	**1a**	**1′c** R_3 = 4-CF_3Ph		**2′c**	75
4	**1b**	**1′a**		**2′d**	65
5	**1c**	**1′a**		**2′e**	63
6[c]	**1e**	**1′a**		**2′f**	76
7	**1j**	**1′a**		**2′g**	75
8	**1m**	**1′a**		**2′h**	78

[a] Reaction conditions: **1** (0.2 mmol), **1′** (0.2 mmol), DBU (1.0 equiv), DMSO (1.5 mL), 120 °C, 10 min. [b] Isolated yields. [c] The reaction was carried out at 130 °C.

Lowering the amount of DBU (0.5 equiv), the yield decreased slightly to 85% with less **1a** recovered (Table 1, entry 9). These results show that this tandem process can be catalyzed by the base and transformed completely only in DMSO.

Various 2-methyl-3-(1-alkynyl)chromones **1** were used to extend the scope of this reaction under the optimized conditions. Good to excellent yields were obtained when R^1 was an aromatic group on the acetylene moiety (Table 2, entries 1−4). When R^1 was an aliphatic chain, the reaction also gave good yields (Table 2, entries 5 and 6). Substitution with a sterically hindering group (*tert*-butyl) afforded the desired product **2g$_1$** in a 14% yield, along with **2g$_2$** in a 57% yield (Table 2, entry 7).[9] When R^1 was a trimethylsilyl group, the desilylated product **2h** was obtained in a 63% yield (Table 2, entry 8). In addition, reactions with various substituents on the aryl ring of the 2-methyl-3-(1-alkynyl)chromones

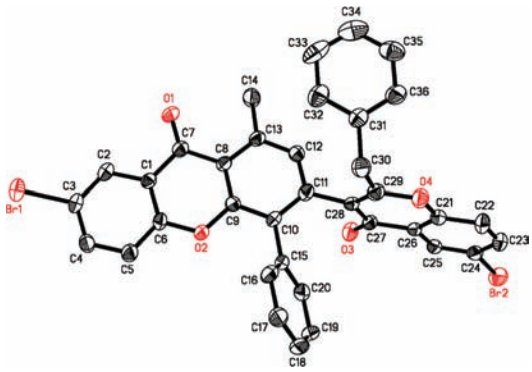
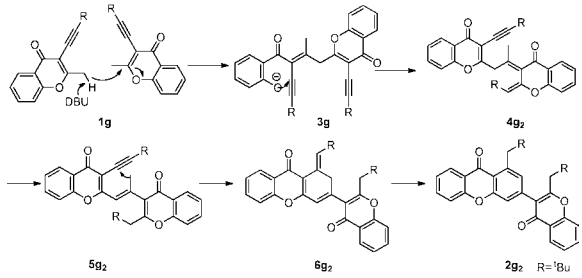


Figure 2. X-ray structure of **2k**.[10]

proceeded smoothly in good yields (Table 2, entries 9−13). The structures of **2h** and **2k** were further confirmed by X-ray crystal structure analysis (Figure 2).[10]

According to the proposed mechanism, we expected that 3-(1-alkynyl)chromones without a sterically hindering methyl group could be better Michael acceptors than 2-methyl-3-(1-alkynyl)chromones and preferred to undergo the cross-cascade process. To our delight, the cross dimerization of **1a** and **1′a** did afford the desired product **2′a** in 71% yield along with two self-dimeric byproducts of **1a** and **1′a** (Table 3, entry 1).[3e] The cross reaction of **1** and **1′** gave good yields when R^1 or R^3 were aromatic groups (Table 3, entries 2−5).

(9) The formation of $\mathbf{2g_2}$ can be explained as follows. The phenol ion **3g** firstly undergoes a cyclization; however, the further Michael addition is unfavorable because of the steric effect of the *tert*-butyl group. The major intermediate $\mathbf{4g_2}$ isomerizes into $\mathbf{5g_2}$, the methyl group of which is then deprotonated by base and undergoes a cyclization and isomerization to give product $\mathbf{2g_2}$.



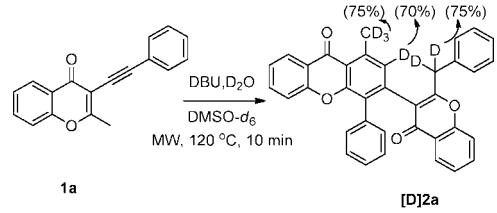
(10) CCDC 764693 (**2h**) and 768701 (**2k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Interestingly, the reaction of **1e** with an aliphatic chain and **1′a** gave the desired product **2′f** (Table 3, entry 6). When the R^3 groups of **1′** were an aliphatic chain, the cross-dimeric reaction failed to give just the self-dimeric product. In addition, substituents on the aryl ring of **1** had no effect on the cross-dimerization reaction (Table 3, entries 7 and 8).

The deuterium labeling experiment of **1a** with D_2O produced **[D]2a** with 70% deuterium incorporation on the aryl ring and 75% at the methyl and methylene moieties, respectively. Those 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.

In conclusion, we have discovered a novel base-promoted cascade reaction to produce the 3*C*-xanthone-linked 3*C*-chromone scaffold. The products were unambiguously established using X-ray crystal structure analysis. This unusual tandem process involves multiple reactions without the necessity for a transition metal and inert atmosphere. Further application of **1** and **1′** to generate novel natural-product-like compounds and biological evaluation of the novel compounds is ongoing in our laboratory.

Scheme 2. Deuterium Labeling Experiment of **1a**



Acknowledgment. This work was supported by grants from Major Projects in National Science and Technology, "Creation of major new drugs" (No.2009ZX09301-001) and National Natural Science Foundation of China (30873142).

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for compounds in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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