A base-promoted desalicyloylative dimerization of 3-(1-alkynyl)chromones: An unusual approach to 2-alkynyl xanthones†

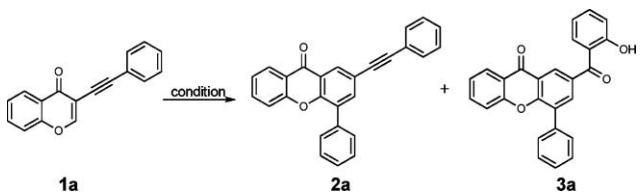
Fuchun Xie, Xuan Pan, Shijun Lin and Youhong Hu*

Received 13th October 2009, Accepted 3rd December 2009
First published as an Advance Article on the web 5th January 2010
DOI: 10.1039/b925234g

A novel base-promoted cascade desalicyloylative dimerization of 3-(1-alkynyl)chromones to produce 2-alkynyl xanthones has been developed. This tandem process involves multiple reactions, such as Michael additions/cyclizations/desalicyloylation without a transition metal catalyst and inert atmosphere.

Introduction

Xanthone frameworks are a ubiquitous structure in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activity.[1] Consequently, there has been continued interest in the development of efficient methods for the synthesis of xanthones bearing multiple and diverse substitution patterns.[2] Our group has focused on functionalized 3-(1-alkynyl)chromones to generate natural product-like scaffolds through cascade reactions.[3] Recently, we have reported a novel base-promoted tandem reaction to afford functionalized xanthones from 3-(1-alkynyl)chromones with 1,3-dicarbonyl compounds under mild reaction conditions.[4] We envisaged that an arylamine as a nucleophile could attack at the 2-position of the 3-(1-alkynyl)chromone with the opening of the pyrone ring, and then, substituted pyrrole may be formed by subsequent cyclization of the amine with the triple bond. Contrary to our expectation, the reaction (alkynyl compound **1a**, aniline, and DBU in DMF at 50% for 5 h, eqn (1)) failed to afford the desired pyrrole product. Instead, an interesting and unexpected novel product **2a** was obtained with **3a**.



(1)

Results and discussion

We examined the reaction under different conditions using 3-(1-alkynyl)chromone **1a** as a substrate (Table 1). The reaction proceeded slowly at room temperature (Table 1, entry 1). On increasing the reaction temperature, the desired product was obtained in a 50% yield (Table 1, entries 2 and 3). On changing the solvent to THF, the yield was significantly increased to 89% (Table 1, entry 5). The reaction did not proceed well using K_2CO_3 as a base, or carrying out the reaction without a base and water (Table 1, entries 4, 6 and 7), which indicated that water and base may play a crucial role in the reaction. When using KOH and KOBu^t as a base, the desired product **2a** was obtained in 68% and 63% yields, respectively (Table 1, entries 8 and 9). On lowering the amount of DBU (0.5 equiv.), the reaction did not go to completion within a period of 5 h, and **2a** was afforded in a 64% yield (Table 1, entry 10). Among these reaction conditions, a trace amount of one major by-product **3a** was isolated and identified by using X-ray crystal structure analysis (Fig. 1).

Table 1 Screening of the reaction conditions[a]

Entry	Base (equiv.)	Additive (equiv.)	Solvent	T/°C	T/h	Yield[b] (%)
1[c]	DBU(1.0)	H_2O(1.0)	DMF	rt	20	41
2	DBU(1.0)	H_2O(1.0)	DMF	50	3	50
3	DBU(1.0)	H_2O(1.0)	DMF	90	1	50
4[c]	—	H_2O(1.0)	DMF	90	20	0
5	DBU(1.0)	H_2O(1.0)	THF	50	5	89
6[c]	DBU(1.0)	4A MS	THF	50	5	<10
7	K_2CO_3(1.0)	H_2O(1.0)	THF	50	5	0
8	KOH(1.0)	H_2O(1.0)	THF	50	5	68
9	KOBu^t(1.0)	H_2O(1.0)	THF	50	5	63
10[c]	DBU(0.5)	H_2O(1.0)	THF	50	5	64

[a] General conditions: **1a** (0.6 mmol), H_2O (1.0 equiv.) and base (1.0 equiv.) in solvent (2 mL) at 50 °C. [b] Isolated yield. [c] With **1a** recovered.

Various 3-(1-alkynyl)chromones **1** were used to extend the scope of this reaction under the optimized conditions. Moderate to excellent yields were obtained when R^1 was an aromatic group on the acetylene moiety (Table 2, entries 1–3). The structure of **2b** was further confirmed by X-ray crystal structure analysis (Fig. 1). When R^1 was an aliphatic chain, the reaction could also give good yields (Table 2, entries 4 and 5). Substitution with a sterically hindering group, (*tert*-butyl), afforded the desired product **2f** in a 38% yield, along with **3f** in a 27% yield (Table 2, entry 6). When R^1 was a trimethylsilyl group, the desilylated product **2g** was obtained in a 48% yield with two desilylated by-products $\mathbf{3g}_1$ and $\mathbf{3g}_2$ in 16% and 26% yields, respectively. The structure of $\mathbf{3g}_1$[6] was determined using X-ray crystal structure analysis (Fig. 1). In addition, reactions with various substituents on the aryl ring of

Shanghai Institute of Materia Medica, Chinese Academy of Science, 555 Zu Chong Zhi Road, Shanghai, 201203, China. E-mail: yhhu@mail.shcnc.ac.cn; Fax: +86-21-5080-5896; Tel: +86-21-5080-5896

† Electronic supplementary information (ESI) available: Synthesis and ^{1}H and ^{13}C NMR spectra of compounds **2** and **3**. CCDC reference numbers 747501–747503. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b925234g

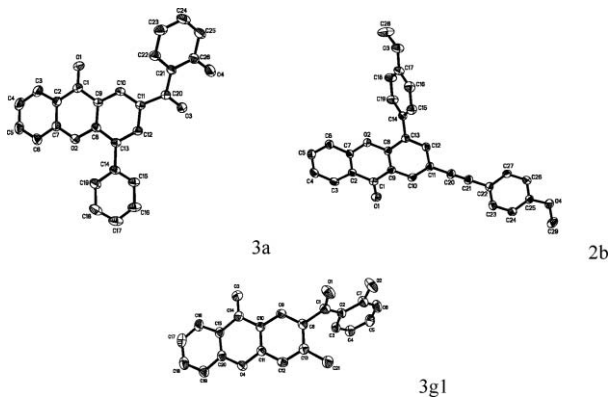
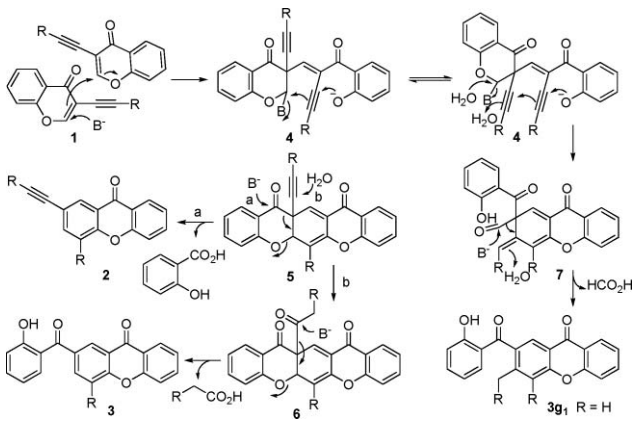


Fig. 1 X-Ray crystal structures of **3a**, **2b**, **3g**$_1$. Ellipsoid probability: 50%.

the 3-(1-alkynyl)chromones proceeded smoothly in good yields (Table 2, entries 8–12).

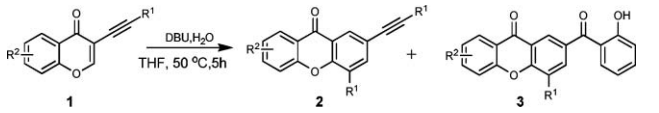
We envisioned that this dimerization reaction involves a domino process of Michael additions, cyclizations and desalicyloylation as shown in Scheme 1. First, the 3-(1-alkynyl)chromone **1** as a Michael acceptor could be attacked directly by a base to generate the corresponding carbanion, which subsequently attacks a second molecule at the 2-position through 1,4-addition and followed by the pyrone ring opening to afford **4**. Next, the phenol ion of **4** processes the cascade cyclizations with the alkynyl bond and intramolecular SN_2 by leaving the base to generate **5**. In the presence of a base and water, intermediate **5** undergoes desalicyloylation affording the product **2** and 2-hydroxybenzoic acid (Path a, Scheme 1).[5] In addition, the alkynyl bond of **5** can be added by water and then isomerized into **6**, which can be promoted by a base through deacylative pyrone ring opening to generate **3** (Path b, Scheme 1). Through Path b, **3f** and **3g**$_2$ that were obviously found in the reaction may be due to steric effects. In addition, the phenol ion **4g** (R = H) could also process double cyclization with alkynyl bonds, along with the hydrolysis opening of the pyrone ring to generate **7**, which undergoes deformylation in the presence of a base and water, forming **3g**$_1$. The deuterium labeling experiment of **1g** with D_2O also verified our proposed mechanism, as the methyl group of **3g**$_1$ was deuterized (see ESI for ^{1}H NMR spectra of the deuterated **2g** and **3g**$_1$†).

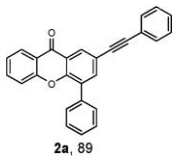
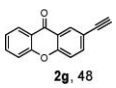
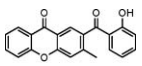
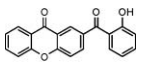
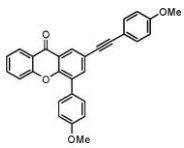
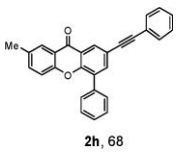
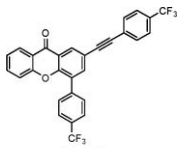
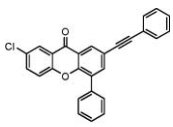
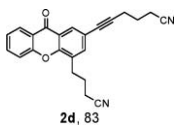
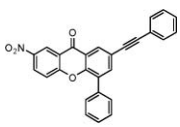
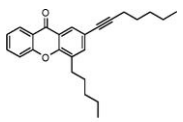
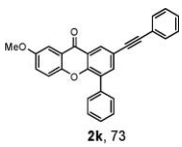
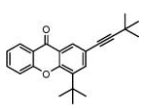
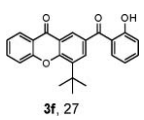
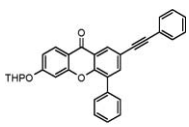


Scheme 1 Plausible reaction mechanism

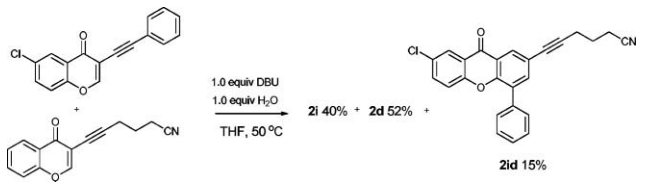
An experiment with a mixture of **1i** and **1d** was carried out under the standard reaction conditions (eqn (2)). Three products, **2i**, **2id** and **2d**, were obtained in 40%, 15% and 52% yields, respectively. The formation of **2id** was a heterodimerization of **1i** with **1d**.

Table 2 Scope of the reaction[a]



Entry	Product, yield[b] (%)	Entry	Product, yield[b] (%)
1	 **2a**, 89	7[c]	 **2g**, 48  **3g**$_1$, 16  **3g**$_2$, 26
2	 **2b**, 86	8	 **2h**, 68
3	 **2c**, 67	9	 **2i**, 76
4	 **2d**, 83	10	 **2j**, 60
5	 **2e**, 61	11	 **2k**, 73
6	 **2f**, 38  **3f**, 27	12	 **2l**, 80

[a] Reaction conditions: **1**, H_2O (1.0 equiv.), DBU (1.0 equiv.), THF (2 mL), 50 °C, 5 h. [b] Isolated yields. [c] The reaction was carried out on the 1.0 mmol scale at rt.



(2)

In conclusion, we have discovered a novel base-promoted cascade desalicyloylative dimerization of 3-(1-alkynyl)chromones to produce 2-alkynyl xanthones. 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** to generate novel natural product-like compounds by tandem reaction is ongoing in our laboratory.

Experimental

General information

All reactions were performed under nitrogen atmosphere. Dry solvents were distilled prior to use: DMF was dried over microwave-dried molecular sieve; THF was distilled from sodium-benzophenone; Petroleum ether refers to the fraction with boiling point in the range 60–90 °C. All ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. High resolution mass spectra were recorded on a Finnigan MAT 95 mass spectrometer (EI). Column chromatography was performed with 200–300 mesh silica gel using flash column techniques. Melting points are uncorrected.

General procedure for the desalicyloylative dimerization reaction

Synthesis of **2a** and **3a**: 3-(1-alkynyl)chromone **1a** (148 mg, 0.6 mmol), dry THF (3 mL), water (11 μL, 0.6 mmol) and DBU (90 μL, 0.6 mmol) were added sequentially to a 10 mL microwave vial containing a magnetic stir bar. The vial was sealed and then the resulting mixture was stirred at 50 °C for 5 h. When the reaction was complete (as monitored by TLC), it was quenched by water (20 mL). The resulting mixture was extracted with dichloromethane (15 mL×3) and 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 by column chromatography (petroleum ether/ethyl acetate 20 : 1 to petroleum ether/ethyl acetate 8 : 1) to afford 99 mg (89%) of compound **2a** as a white solid; m.p. 196–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 2.1 Hz, 1H), 8.36 (dd, J = 8.1, 1.8 Hz, 1H), 7.9 (d, J = 2.2 Hz, 1H), 7.74–7.64 (m, 3H), 7.60–7.44 (m, 5H), 7.43–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.44, 155.70, 152.375, 138.215, 135.44, 134.83, 131.76, 131.575, 129.53, 129.03, 128.44, 128.39, 128.32, 128.12, 126.58, 124.18, 122.75, 122.13, 121.26, 119.13, 118.08, 90.12, 87.87; HRMS calcd for $C_{27}H_{16}O_2$:372.1150, found: 372.1142; and trace **3a** as a light yellow solid; m.p. 185–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.90 (s, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 7.9, 1.1 Hz, 1H), 8.14 (d, J = 2.3 Hz, 1H), 7.75 (td, J = 7.8, 1.5 Hz, 1H), 7.72–7.68 (m, 3H), 7.59–7.41 (m, 6H), 7.11 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.37, 176.62, 163.19, 155.77, 154.90, 136.61, 135.82, 135.265, 135.20, 133.21, 133.16, 132.36, 129.57, 128.55, 128.43, 127.82, 126.68, 124.69, 121.51, 121.38, 119.04, 118.87, 118.53, 118.23; HRMS calcd for $C_{26}H_{16}O_4$:392.1049, found: 392.1045.

Synthesis of deuterated **[D]2g**, **[D]3g$_1$** and **[D]3g$_2$**: 3-(1-Alkynyl)chromone **1g** (242 mg, 1 mmol), dry THF (4 mL), D_2O (92 μL, 5 mmol) and DBU (300 μL, 2 mmol) were added sequentially to a 10 mL microwave vial containing a magnetic stir bar. The vial was sealed and then the resulting mixture was stirred at room temperature for 5 h. When the reaction was complete (as monitored by TLC), it was quenched by water (20 mL). The resulting mixture was extracted with dichloromethane (25 mL×3) and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which was further purified by column chromatography (petroleum ether/ethyl acetate 20 : 1 to petroleum ether/ethyl acetate 10 : 1) to afford 53 mg (48%) of compound **[D]2g** as a white solid; m.p. 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, J = 2.1 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.72 (td, J = 7.8, 0.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 3.13 (s, 0.2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.02, 155.79, 155.63, 137.60, 134.91, 130.60, 126.60, 124.12, 121.51, 121.48, 117.96, 117.95 (t, $^1J_{CD}$ = 25.1 Hz, 1C) 117.87, 82.04, 81.60, 77.895; HRMS calcd for $C_{15}H_8O_2$:220.0524, found: 220.0526, calcd for $C_{15}H_7DO_2$:221.0587, found: 221.0589, calcd for $C_{15}H_6D_2O_2$: 222.0650, found: 222.0649. 28 mg (17%) of compound **[D]3g$_1$** as a white solid; m.p. 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.12 (s, 1H), 8.33 (dd, J = 8.1, 1.8 Hz, 1H), 8.28 (s, 1H), 7.76 (td, J = 7.8, 1.6 Hz, 1H), 7.57–7.49 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.83 (t, J = 7.6 Hz), 2.50–2.45 (m, 0.1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.10, 176.34, 163.45, 156.63, 155.99, 144.13, 137.12, 135.06, 133.83, 133.45, 126.76, 126.68, 124.31, 121.79, 119.73 (t, $^1J_{CD}$ = 25.9 Hz, 1C), 119.67, 119.08, 119.00, 118.44, 118.01, 19.50 (h, J = 19.6 Hz, 1C); HRMS calcd for $C_{21}H_{12}D_2O_4$: 332.1018, found: 332.1010, calcd for $C_{21}H_{11}D_3O_4$: 333.1080, found: 333.1072, calcd for $C_{21}H_{10}D_4O_4$: 334.1143, found: 334.1136. 41 mg (26%) of compound **[D] 3g$_2$** as a white solid; m.p. 183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.87 (s, 1H), 8.67 (d, J = 1.7 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.13–8.08 (m, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.66–7.50 (m, 3H), 7.44 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.32, 176.44, 163.15, 157.99, 155.93, 136.59, 135.35, 135.13, 135.03, 133.30, 133.17, 128.82, 126.76, 124.61, 121.71, 120.975, 119.00, 118.83, 118.79, 118.52, 118.09; HRMS calcd for $C_{20}H_{12}O_4$:316.0736, found: 316.0734, calcd for $C_{20}H_{11}DO_4$: 317.0798, found: 317.0802.

Acknowledgements

We are grateful for financial supports from Major Projects in National Science and Technology, "Creation of major new drugs" (No.2009ZX09501-010).

References

1 (*a*) M. E. Sousa and M. M. Pinto, *Curr. Med. Chem.*, 2005, **12**, 2447 and references therein; (*b*) B. D. Palmer, K. Henare, S. T. Woon, R.

Sutherland, C. Reddy, L. C. Wang, C. Kieda and L. M. Ching, *J. Med. Chem.*, 2007, **50**, 3757.
2 For recent studies, see: (*a*) C. M. M. Santos, A. M. S. Silva and J. A. S. Cavaleiro, *Eur. J. Org. Chem.*, 2009, 2642; (*b*) W. Z. Xu, Z. T. Huang and Q. Y. Zheng, *J. Org. Chem.*, 2008, **73**, 5606; (*c*) A. T. Dang, D. O. Miller, L. N. Dawe and G. J. Bodwell, *Org. Lett.*, 2008, **10**, 233; (*d*) N. K. Swamy, L. K. Tatini, J. M. Babu, P. Annamalai and M. Pal, *Chem. Commun.*, 2007, 1035; (*e*) J. Zhao, D. Yue, M. A. Campo and R. C. Larock, *J. Am. Chem. Soc.*, 2007, **129**, 5288; (*f*) J. Zhao and R. C. Larock, *J. Org. Chem.*, 2007, **72**, 583; (*g*) M. Mondal, V. G. Puranik and N. P. Argade, *J. Org. Chem.*, 2006, **71**, 4992; (*h*) J. Zhao and R. C. Larock, *Org. Lett.*, 2005, **7**, 4273; (*i*) F. M. Hauser and W. A. Dorsch, *Org. Lett.*, 2003, **5**, 3753.
3 (*a*) G. Cheng and Y. Hu, *Chem. Commun.*, 2007, 3285; (*b*) G. Cheng and Y. Hu, *J. Org. Chem.*, 2008, **73**, 4732; (*c*) L. Zhao, G. Cheng and Y. Hu, *Tetrahedron Lett.*, 2008, **49**, 7364.
4 L. Zhao, F. Xie, G. Cheng and Y. Hu, *Angew. Chem., Int. Ed.*, 2009, **48**, 6520.
5 (*a*) C. K. Ghosh, S. Sahana and A. Patra, *Tetrahedron*, 1993, **49**, 4127; (*b*) C. K. Ghosh, S. Bhattacharyya and A. Patra, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3005.
6 CCDC 747503 (**3a**), 747502 (**2b**) and 747501 ($\mathbf{3g_1}$) 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.