

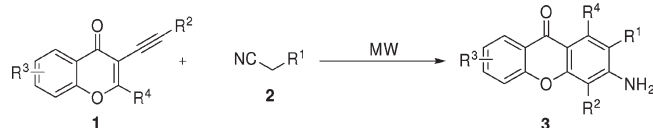
Base-Promoted One-Pot Tandem Reaction of  
3-(1-Alkynyl)chromones under Microwave  
Irradiation to Functionalized  
Amino-Substituted Xanthenes

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A base-promoted one-pot tandem reaction has been developed from 3-(1-alkynyl)chromones with various acetonitriles to afford functionalized amino-substituted xanthenes **3** under microwave irradiation. This tandem process involves multiple reactions, such as Michael addition/cyclization/1,2-addition, without a transition metal catalyst. This method provides an efficient approach to build up natural product-like diversified amino-substituted xanthone scaffolds rapidly.

Tandem reactions provide an efficient way to generate molecular complexity from readily accessible intermediates.<sup>1</sup> The combination of very efficient cascade or one-pot processes with microwave-assisted organic synthesis should provide a powerful tool for saving both energy and resources and rapidly generating a diversified new target molecules library to help speed up drug discovery projects in industry and academia.<sup>2</sup>

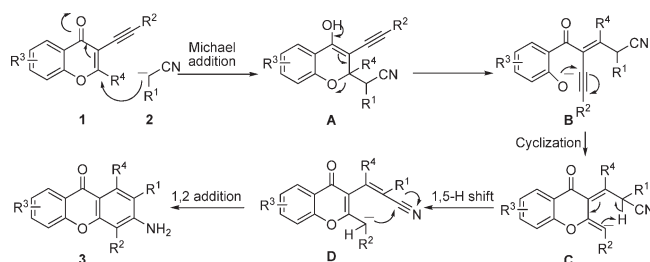
2-(1-Alkynyl)-2-alken-1-ones as special units were applied in tandem reactions through a transition metal, an acid-catalyzed or an electrophile-induced cascade process to form

(1) For recent reviews, see: (a) Enders, D.; Grondal, C.; Huttel, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem Commun. (Cambridge, U. K.)* **2003**, 551. (e) 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. (f) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (g) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.

(2) For recent review: (a) Kreamer, J. M.; Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 285. (b) Mavandadi, F.; Pilotti, A. *Drug Discovery Today* **2006**, *11*, 165. (c) Tierney, J. P.; Lidstrom, P. *Microwave Assisted Organic Synthesis*, Blackwell: Oxford, 2005. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (e) NMcHter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128. (f) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron.* **2001**, *57*, 9225.

highly substituted furans.<sup>3</sup> Under basic conditions, the cascade reaction of these units with nucleophilic substrates proceeded in different ways.<sup>4</sup> Recently, we described a novel base-promoted tandem reaction of 3-(1-alkynyl)chromones with 1,3-dicarbonyl compounds to afford functionalized xanthenes.<sup>4d</sup>

SCHEME 1. Proposed Mechanism



The xanthone framework is a ubiquitous structure that occurs in a wide variety of naturally occurring and synthetic compounds exhibiting important biological activity.<sup>5</sup> Consequently, there has been continued interest in the development of efficient methods for the synthesis of xanthenes bearing multiple and diverse substitution patterns.<sup>6</sup> Herein, we report our recent achievement to build up diversified amino-substituted xanthone scaffolds rapidly by a tandem reaction of 3-(1-alkynyl)chromones with various acetonitriles under microwave irradiation through Michael addition/cyclization/1,2-addition reaction without a transition metal catalyst (Scheme 1).

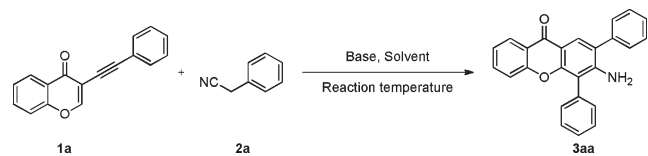
We investigated the reaction of **1a** with 2-phenylacetonitrile **2a** under different reaction conditions (Table 1). When the reaction was carried out under the conditions used

(3) (a) Gao, H.; Zhao, X.; Yu, Y.; Zhang, J. *Chem.—Eur. J.* **2010**, *16*, 456. (b) Liu, R.; Zhang, J. *Chem.—Eur. J.* **2009**, *15*, 9303. (c) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505. (d) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (e) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732. (f) Cheng, G.; Hu, Y. *Chem Commun. (Cambridge, U. K.)* **2007**, 3285. (g) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307. (h) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609. (i) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (j) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (k) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164.

(4) (a) Li, W.; Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 617. (b) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594. (c) Yu, X.; Ren, H.; Xiao, Y.; Zhang, J. *Chem.—Eur. J.* **2008**, *14*, 8481. (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.

(5) For recent studies, see: (a) Sousa, E.; Paiva, A.; Nazareth, N.; Gales, L.; Damas, A. M.; Nascimento, M. S. *J. Eur. J. Med. Chem.* **2009**, *44*, 3830. (b) Kondo, M.; Zhang, L.; Ji, H.; Kou, Y.; Ou, B. *J. Agric. Food Chem.* **2009**, *57*, 8788. (c) Zelefsack, F.; Guilet, D.; Fabre, N. *J. Nat. Prod.* **2009**, *72*, 954. (d) Ngoupayo, J.; Tabopda, T. K.; Ali, M. S. *Bioorg. Med. Chem.* **2009**, *17*, 5688. (e) Ryu, Y. B.; Curtis-Long, M. J.; Lee, J. W. *Bioorg. Med. Chem.* **2009**, *17*, 2744. (f) Pouli, N.; Marakos, P. *Anticancer Agents Med. Chem.* **2009**, *9*, 77.

(6) For selected examples, see: (a) Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462. (b) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169. (c) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2009**, *16*, 2642. (d) Barbero, N.; SanMartin, R.; Dominguez, E. *Tetrahedron* **2009**, *65*, 5729. (e) Mross, G.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2009**, *65*, 3910. (f) Xu, W. Z.; Huang, Z. T.; Zheng, Q. Y. *J. Org. Chem.* **2008**, *73*, 5606. (g) Dang, A. T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233. (h) Swamy, N. K.; Tatini, L. K.; Babu, J. M.; Annamalai, P.; Oal, M. *Chem. Commun.* **2007**, 1035.

**TABLE 1. Optimization of the Tandem Reaction to Form Amino-Substituted Xanthone 3aa**

entry	solvent	base	temp/time <sup>a</sup>	yield (%) <sup>c</sup>
1 <sup>b</sup>	DMF	1 equiv DBU	45 °C, 18 h	42
2 <sup>b</sup>	DMF	1 equiv DBU	100 °C, 2 h	50
3	DMF	1 equiv DBU	90 °C, 10 min	60
4	DMF	3 equiv DBU	90 °C, 10 min	90
5	DMF	1 equiv <i>t</i> -BuOK	90 °C, 10 min	51
6	DMF	3 equiv <i>t</i> -BuOK	90 °C, 10 min	82
7 <sup>b</sup>	DMF	3 equiv <i>t</i> -BuOK	90 °C, 8 h	69
8	DMF	1 equiv MeONa	90 °C, 10 min	46
9	DMF	3 equiv MeONa	90 °C, 10 min	68
10	DMF	1 equiv K <sub>2</sub> CO <sub>3</sub>	90 °C, 10 min	20
11	DMF	3 equiv K <sub>2</sub> CO <sub>3</sub>	90 °C, 10 min	35
12	THF	3 equiv DBU	90 °C, 10 min	73
13	toluene	3 equiv DBU	90 °C, 10 min	76
14	MeCN	3 equiv DBU	90 °C, 10 min	69

<sup>a</sup>Unless otherwise noted, the reactions were carried out under microwave irradiation. <sup>b</sup>Reactions were carried out in an oil bath. <sup>c</sup>Yield of isolated product based on **1a**.

previously,<sup>4d</sup> in which 1 equiv of DBU was used as the base in DMF at 45 °C, the desired product **3aa** was observed in 42% yield with slow transformation. When the reaction temperature was increased to 100 °C, the reaction was completed in 2 h and **3aa** was obtained in 50% yield with a dimeric byproduct.<sup>4c</sup> Since 2-phenylacetonitrile is less nucleophilic than a 1,3-dicarbonyl compound, and 1,2-addition to a cyano group is harder than to a carbonyl group in the last step, the cascade process should need more energy. Under microwave irradiation at 90 °C, the reaction was rapidly completed in 10 min and gave **3aa** in 60% yield. By increasing the amount of DBU from 1 equiv to 3 equiv, the yield was improved significantly, to 90%. The reaction heating at 90 °C under an oil bath and using 3 equiv of *t*-BuOK gave the desired product **3aa** in 69% yield. Among the different bases such as DBU, *t*-BuOK, NaOMe, and K<sub>2</sub>CO<sub>3</sub>, DBU generally performed the best (Table 1, entries 3–11). The optimized conditions to amino-substituted xanthenes **3** were defined as carrying out the reaction in DMF at 90 °C for 10 min with 3 equiv of DBU under microwave irradiation.

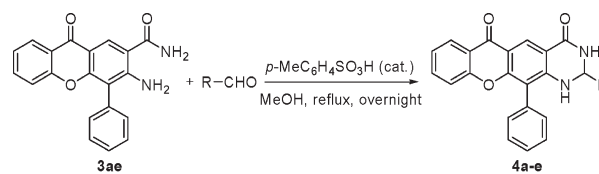
Using the optimized reaction conditions, various substituted acetonitriles **2** were treated with **1a** to extend the scope of this tandem reaction (Table 2). Good to excellent yields were obtained when R<sup>1</sup> was an aromatic group (Table 2, entries 1–4). Obviously, substrate **2d**, with an electron-donating group at the *para* position of the aryl ring, decreased the nucleophilicity to give a lower yield than the others. Especially when R<sup>1</sup> was an amide or cyano group, functional xanthenes **3ae** and **3af** were obtained in 86% and 88% yield, respectively (Table 2, entries 5, 6). Compound **3ae** was further condensed with various aldehydes to form the linear heterocyclic xanthenes **4** in good yields (Scheme 2), which can rapidly generate a structurally diverse and medicinally interesting new small-molecule library.

Furthermore, we applied **2b** with various 3-(1-alkynyl)chromones to extend the tandem reaction for generating functionalized amino-substituted xanthenes. Products **3bb**–**3bj**

**TABLE 2. Tandem Reaction of 1a with Various Acetonitriles 2 to Form Amino-Substituted Xanthenes 3<sup>a</sup>**

Entry	Substrate	Product	Yield (%) <sup>b</sup>
1			90
2			95
3			87
4			69
5			86
6			88

<sup>a</sup>Unless otherwise noted, the reactions were carried out under standard conditions. <sup>b</sup>Yield of isolated product based on **1a**.

**SCHEME 2. Synthetic Application for 3ae**

R= Ph	<b>4a</b> , 85%
R= 4-OMe-Ph	<b>4b</b> , 79%
R= 4-CF <sub>3</sub> -Ph	<b>4c</b> , 71%
R= (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	<b>4d</b> , 75%
R= 3-furan	<b>4e</b> , 83%

were obtained in 65–96% yields (Table 3). It was noted that the electron effect of the R<sup>2</sup> group did not influence the reaction efficacy under microwave irradiation. When R<sup>2</sup> was a sterically hindering *tert*-butyl group, the uncyclized intermediate **D** was obtained at 90 °C under microwave irradiation. By increasing the reaction temperature to 130 °C and prolonging the irradiation time to 15 min, the desired product **3bf** was obtained in 65% yield (Table 3, entry 5). In addition, reactions with various substituents on the aryl

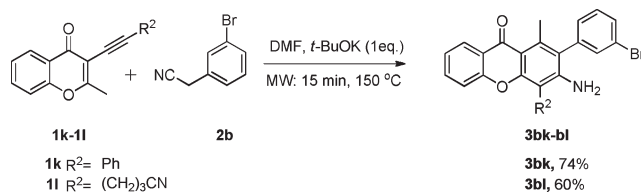
TABLE 3. Tandem Reaction of **2b** with Various 3-(1-Alkynyl)chromones.<sup>a</sup>

Entry	Substrate	Product	Yield (%) <sup>b</sup>
1			90
2			86
3			83
4			92
5 <sup>c</sup>			65
6			96
7			92
8			94
9			66

<sup>a</sup>Unless otherwise noted, the reactions were carried out under standard conditions. <sup>b</sup>Yield of isolated product based on **1**. <sup>c</sup>The reaction was irradiated for 15 min at 130 °C.

ring of the 3-(1-alkynyl)chromones also proceeded smoothly in good to excellent yields (Table 3, entries 6–9). When the reaction was applied to 2-methyl-3-(2-phenylethynyl)-4*H*-chromen-4-one (**1k**), the intermediate **D** was formed along with the dimeric product.<sup>7</sup> By increasing the reaction temperature to 130 °C, no desired product **3bk** was afforded.

(7) Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3086.

SCHEME 3. Tandem Reaction of **2b** with 2-Methyl-3-(1-alkynyl)chromones

When the base was changed to *t*-BuOK (1 equiv), the reaction at 150 °C under microwave irradiation proceeded smoothly to give the desired product **3bk** only in 74% yield. Also, the substrate **1l**, with an aliphatic chain, gave the product **3bl** in 60% yield. These conditions could extend the tandem reaction to the sterically hindering 2-methyl-3-(1-alkynyl)chromones to afford polysubstituted amino-xanthenes (Scheme 3).

In conclusion, we have developed a novel base-promoted tandem reaction from 3-(1-alkynyl)chromones with various acetonitriles under microwave irradiation to afford functionalized amino-substituted xanthenes. Notably, this tandem process involves multiple reactions, such as a Michael addition/cyclization/1,2-addition without a transition metal catalyst. This method provides an efficient approach to build up natural product-like diversified polysubstituted amino-xanthone scaffolds rapidly. The functionalized amino-substituted xanthone **3ae** can be easily condensed with various aldehydes to generate the linear heterocyclic xanthenes. Further library generation and biological evaluation of the diversified xanthenes are under investigation.

## Experimental Section

**General Procedure of the Tandem Reaction of 3-(1-Alkynyl) Chromones with Various Acetonitriles to Amino-Substituted Xanthenes.** Typical procedure for the preparation of **3aa**: To a solution of 2-phenylacetonitrile **2a** (24 mg, 0.2 mmol) in dry DMF (1 mL) was added DBU (0.1 mL, 0.6 mmol) at room temperature under nitrogen atmosphere. After stirring for 5 min, compound **1a** (50 mg, 0.2 mmol) was added, and the resulting dark red solution was irradiated for 10 min at 90 °C (monitored by TLC). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product, which was further purified by column chromatography (petroleum ether/ethyl acetate, 8:1) to afford compound **3aa** as a white solid (66 mg, 90%): mp 157–158 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.31 (dd, *J* = 1.7, 8.0 Hz, 1H), 8.15 (s, 1H), 7.4–7.6 (m, 11H), 7.31 (t, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 4.40 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.3, 156.0, 154.2, 148.0, 137.9, 133.6, 133.1, 130.7, 129.3, 129.2, 129.1, 128.1, 127.9, 127.6, 126.4, 125.1, 123.5, 121.8, 117.7, 113.3, 112.9; HRMS [M]<sup>+</sup> calcd for C<sub>25</sub>H<sub>17</sub>NO<sub>2</sub> 363.1259, found 363.1264.

**General Procedure of the Tandem Reaction of 2-Methyl-3-(1-Alkynyl) Chromones with **2b** to Amino-Substituted Xanthenes.** Typical procedure for the preparation of **3bk**: To a solution of 2-(3-bromophenyl)acetonitrile (**2b**) (40 mg, 0.2 mmol) in dry DMF (1 mL) was added *t*-BuOK (23 mg, 0.2 mmol) at room temperature under nitrogen atmosphere. After stirring for 5 min, compound **1k** (52 mg, 0.2 mmol) was added, and the resulting dark red solution was irradiated for 15 min at 150 °C (monitored by TLC). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product, which was further purified by column

chromatography (petroleum ether/ethyl acetate, 6:1) to afford compound **3bk** as a yellow solid (67 mg, 74%): mp 165–166 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (dd,  $J = 1.4, 8.0$  Hz, 1H), 7.4–7.6 (m, 9H), 7.29 (d,  $J = 8.0$  Hz, 1H), 7.24 (d,  $J = 7.8$  Hz, 1H), 7.09 (d,  $J = 7.8$  Hz, 1H), 3.97 (s, 2H), 2.64 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.0, 155.5, 154.9, 147.4, 140.3, 139.6, 133.4, 133.3, 131.1, 130.8, 130.4, 129.5, 129.2, 129.1, 128.0, 127.9, 126.5, 123.8, 123.5, 123.4, 122.9, 117.1, 20.4; HRMS  $[\text{M}]^+$  calcd for  $\text{C}_{26}\text{H}_{18}\text{BrNO}_2$  455.0521, found 455.0511.

**General Procedure of the Synthetic Application of 3ae.** Typical procedure for the preparation of **4a**: **3ae** (66 mg, 0.2 mmol) and benzaldehyde (22 mg, 0.2 mmol) were suspended in methanol (10 mL) and refluxed in the presence of catalytic amounts of *p*-toluenesulfonic acid (4 mg, 10%) overnight. After the reaction mixture was filtered and washed with cold methanol, **4a** was obtained as a light brown solid (72 mg, 85%): mp 257–258 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.02 (s, 1H), 8.29 (d,  $J = 8.0$  Hz,

1H), 7.3–7.7 (m, 12H), 7.15 (d,  $J = 8.3$  Hz, 1H), 6.24 (s, 1H), 5.93 (s, 1H) 4.89 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $d_6$ -DMSO)  $\delta$  174.7, 161.7, 155.9, 155.3, 149.0, 142.7, 134.8, 131.1, 130.9, 130.2, 129.2, 128.5, 128.3, 128.1, 126.7, 125.8, 125.7, 124.3, 120.9, 117.7, 112.9, 112.6, 112.4, 65.2; HRMS  $[\text{M}]^+$  calcd for  $\text{C}_{27}\text{H}_{18}\text{N}_2\text{O}_3$  418.1317, found 418.1324.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.