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

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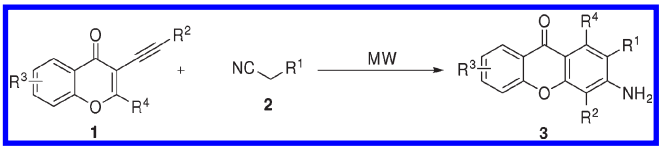
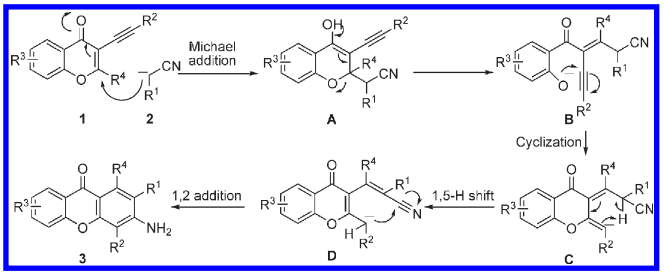



A base-promoted one-pot tandem reaction has been developed from 3-(1-alkynyl)chromones with various acetonitriles to afford functionalized amino-substituted xanthones **3** under microwave irradiation. This tandem process involves multiple reactions, such as Michael addition/cyclization/1,2-addition, 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.[1] 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.[2]

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

**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.[5] Consequently, there has been continued interest in the development of efficient methods for the synthesis of xanthones bearing multiple and diverse substitution patterns.[6] 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

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(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) Zelefack, 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.

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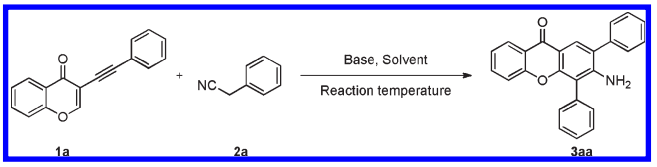
**TABLE 1. Optimization of the Tandem Reaction to Form Amino-Substituted Xanthone 3aa**




| entry | solvent | base | temp/time[a] | yield (%)[c] |
|---|---|---|---|---|
| 1[b] | DMF | 1 equiv DBU | 45 °C, 18 h | 42 |
| 2[b] | 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 *t*-BuOK | 90 °C, 10 min | 51 |
| 6 | DMF | 3 equiv *t*-BuOK | 90 °C, 10 min | 82 |
| 7[b] | DMF | 3 equiv *t*-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 $K_2CO_3$ | 90 °C, 10 min | 20 |
| 11 | DMF | 3 equiv $K_2CO_3$ | 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 |

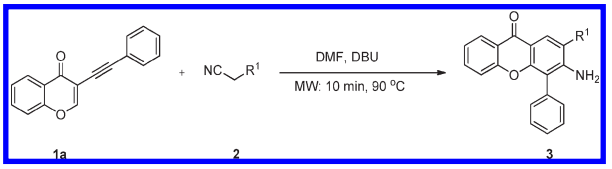
[a]Unless otherwise noted, the reactions were carried out under microwave irradiation. [b]Reactions were carried out in an oil bath. [c]Yield of isolated product based on **1a**.

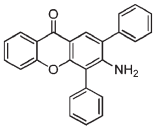
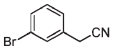
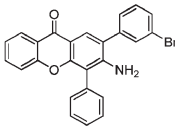
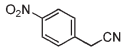
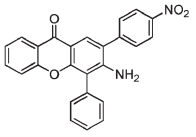
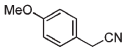
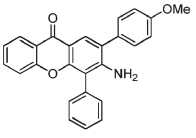
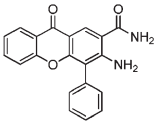
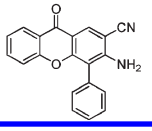
previously,[4d] in which 1 equiv of DBU was used as the base in DMF at 45 °C, the desired product **3aa** was observed in 42% yield with slow transformation. When the reaction temperature was increased to 100 °C, the reaction was completed in 2 h and **3aa** was obtained in 50% yield with a dimeric byproduct.[4e] Since 2-phenylacetonitrile is less nucleophlic 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 $K_2CO_3$, DBU generally performed the best (Table 1, entries 3−11). The optimized conditions to amino-substituted xanthones **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 $R_1$ 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 $R^1$ was an amide or cyano group, functional xanthones **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 xanthones **4** in good yields (Scheme 2), which can rapidly generate a structurally diverse and medicinally interesting new small-molecule library.

Furhermore, we applied **2b** with various 3-(1-alkynyl)chromones to extend the tandem reaction for generating functionalized amino-substituted xanthones. Products **3bb**−**3bj** were obtained in 65−96% yields (Table 3). It was noted that the electron effect of the $R^2$ group did not influence the reaction efficacy under microwave irradiation. When $R^2$ 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 2. Tandem Reaction of 1a with Various Acetonitriles 2 to Form Amino-Substituted Xanthones 3[a]**




| Entry | Substrate | | Product | | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | **2a** |  | **3aa** | 90 |
| 2 |  | **2b** |  | **3ab** | 95 |
| 3 |  | **2c** |  | **3ac** | 87 |
| 4 |  | **2d** |  | **3ad** | 69 |
| 5 |  | **2e** |  | **3ae** | 86 |
| 6 |  | **2f** |  | **3af** | 88 |

[a]Unless otherwise noted, the reactions were carried out under standard conditions. [b]Yield of isolated product based on **1a**.

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

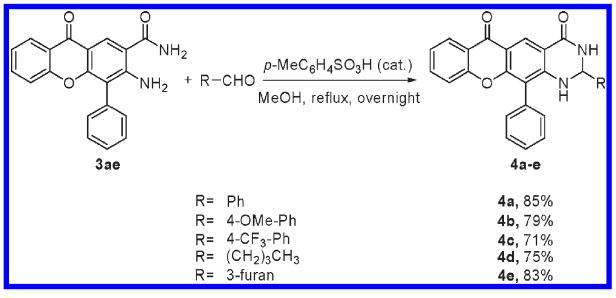
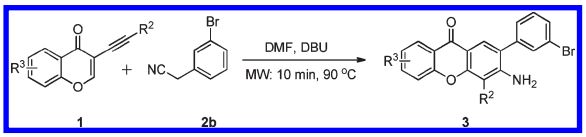
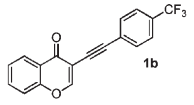
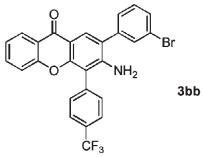
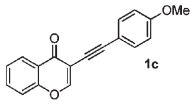
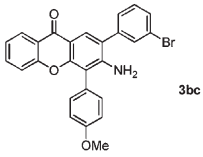
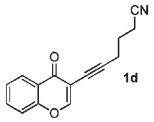
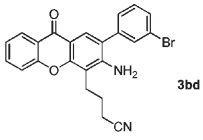
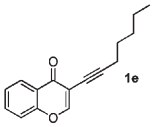
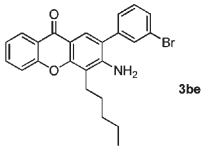
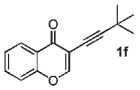
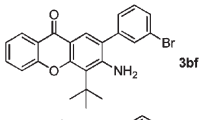
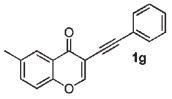
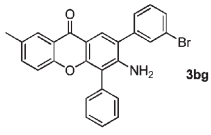
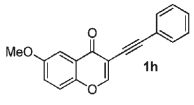
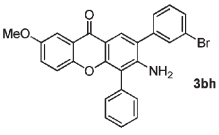
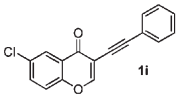
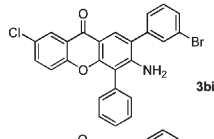
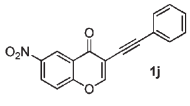
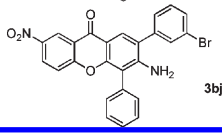


**TABLE 3. Tandem Reaction of 2b with Various 3-(1-Alkynyl) chromones.**[a]



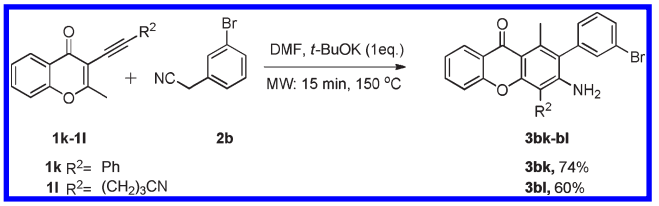

| Entry | Substrate | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  1b |  3bb | 90 |
| 2 |  1c |  3bc | 86 |
| 3 |  1d |  3bd | 83 |
| 4 |  1e |  3be | 92 |
| 5[c] |  1f |  3bf | 65 |
| 6 |  1g |  3bg | 96 |
| 7 |  1h |  3bh | 92 |
| 8 |  1i |  3bi | 94 |
| 9 |  1j |  3bj | 66 |

[a]Unless otherwise noted, the reactions were carried out under standard conditions. [b]Yield of isolated product based on **1**. [c]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.[7] 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-xanthones (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 xanthones. 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 xanthones. Further library generation and biological evaluation of the diversified xanthones are under investigation.

## Experimental Section

**General Procedure of the Tandem Reaction of 3-(1-Alkynyl) Chromones with Various Acetonitriles to Amino-Substituted Xanthones.** 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 $Na_2SO_4$, 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; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 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 $[M]^+$ calcd for $C_{25}H_{17}NO_2$ 363.1259, found 363.1264.

**General Procedure of the Tandem Reaction of 2-Methyl-3-(1-Alkynyl) Chromones with 2b to Amino-Substituted Xanthones.** 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 $Na_2SO_4$, 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; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 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 $[M]^+$ calcd for $C_{26}H_{18}BrNO_2$ 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; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}$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 $[M]^+$ calcd for $C_{27}H_{18}N_2O_3$ 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.