Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2680

www.rsc.org/obc

PAPER

Synthesis of novel functional polycyclic chromones through Michael addition and double cyclizations†

Yang Liu, Liping Huang, Fuchun Xie, Xuxing Chen and Youhong Hu*

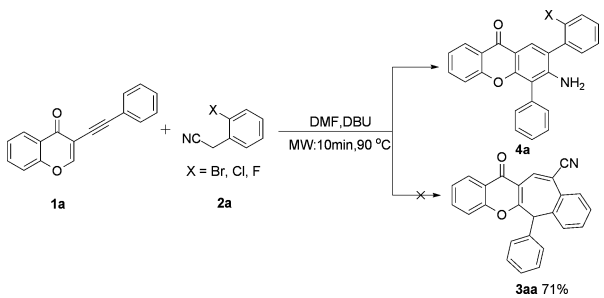
Received 9th November 2010, Accepted 1st February 2011
DOI: 10.1039/c0ob01000f

A base-promoted, microwave-assisted one-pot tandem reaction from simple 3-(1-alkynyl)chromones with 2-halobenzylic nitriles (esters or amides) for the synthesis of novel functional polycyclic chromenones has been developed. This tandem process involves multiple reactions, such as Michael addition and double cyclizations without a transition metal catalyst.

Introduction

Tandem reactions provide an efficient way to generate molecular complexity from readily accessible intermediates.[1] 2-(1-Alkynyl)-2-alken-1-one was applied as a special unit in a tandem reaction catalyzed by transition metals or acids, involving an electrophile-induced cascade process to form highly substituted furans.[2] Under basic conditions, the cascade reaction of this unit with nucleophilic substrates proceeded in a different cascade way to generate a different product.[3]

Our research group has focused on functionalized 3-(1-alkynyl)chromones to generate diversified natural-product-like scaffolds through cascade reactions.[3d–g] Recently, we described a base-promoted one-pot tandem reaction of 3-(1-alkynyl)chromones under microwave irradiation to generate functionalized amino-substituted xanthones.[3h] Continuing our efforts in this area, various substituted acetonitriles were treated with functionalized 3-(1-alkynyl)chromones to generate the diversified amino-substituted xanthones library for high throughput screening. Surprisingly, the reaction of 3-(1-phenylethynyl)chromone **1a** with 2-(2-bromophenyl)acetonitrile **2a** afforded the unexpected novel compound **3aa** containing a benzo seven-membered ring as the sole product in 71% yield in contrast to the formation of an aromatic ring for amino-substituted xanthone **4a** (Scheme 1). The structure was unambiguously established by X-ray crystal structure analysis (Fig. 1).[4] This natural-product-like structural skeleton is reported here for the first time. When Br was changed to Cl or F for the substrate **2a**, the product **3aa** was observed in a similar yield.



Scheme 1 Base-promoted tandem reaction to form the functional polycyclic chromenone **3aa**.

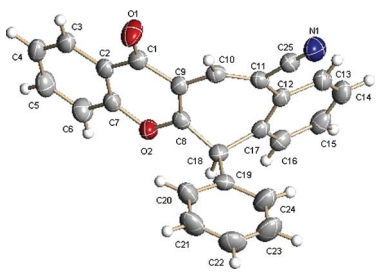


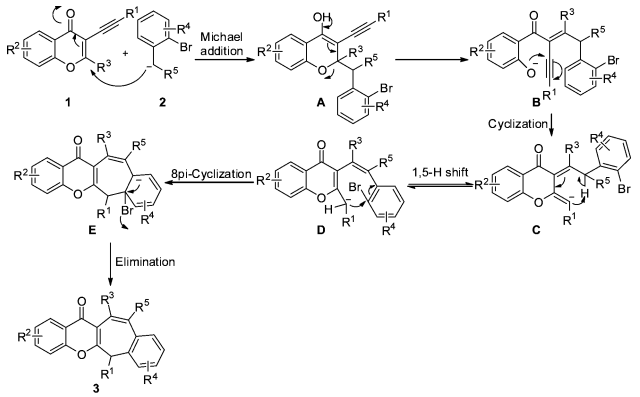
Fig. 1 ORTEP plot of **3aa** shown with ellipsoids at the 50% level.

Results and discussion

We envisioned that this novel transformation involves a domino process of a Michael addition-elimination and double cyclizations. (Scheme 2). Firstly, in the presence of a base and under microwave irradiation, the 3-(1-alkynyl)chromone **1** as a Michael acceptor could be attacked by **2** to generate **A**, along with the opening of the pyrone ring to form **B**.[5] Subsequently, the phenol group of **B** could recyclize with the alkynyl bond to produce the intermediate **C**, which could rearrange to **D** *via* a 1,5-H shift.[3d] Then an 8π-electrocyclization of **D**[6] was possible to form **E** and followed by the elimination of bromide to generate the stable seven-membered polycyclic chromone **3**.

State Key Laboratory of Drug Research, 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**, **3** and **4**. CCDC reference numbers 755402 and 792937. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01000f

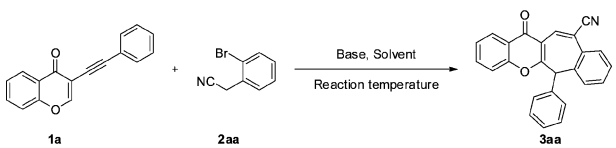


Scheme 2 A proposed mechanism of the tandem reaction.

Based on the above results, different bases such as DBU, *t*-BuOK, MeONa and K_2CO_3 were tested (Table 1, entries 1–4). DBU and *t*-BuOK generally performed better. Since the 8π-electrocyclization might need more energy, the reaction temperature was increased to 130 °C to improve the yields a little (Table 1, entries 5 and 6). By decreasing the amount of *t*-BuOK from 3 equiv to 1 equiv, the reaction proceeded well and gave 82% yield (Table 1, entry 8). Among the different solvents (Table 1, entries 8–10), DMF was best. In the absence of microwave irradiation, the reaction at 130 °C in an oil bath took longer to give **3aa** in 70% yield (Table 1, entry 11). There was no big difference whether the reaction was catalyzed by palladium or copper for the activation of aryl bromide (Table 1, entries 12 and 13). The optimized conditions were defined as carrying out the reaction in DMF at 130 °C for 10 min in the presence of 1 equiv *t*-BuOK under microwave irradiation.

By using the optimized reaction conditions, various substituted 3-(1-alkynyl)chromones **1** were treated with **2aa** for generating more functional polycylic chromones (Table 2). When R^1 is an aromatic or heteroaryl group on the acetylene moiety and R^3 is a hydrogen, good to excellent yields were obtained (Table 2, entries 1–7). It is noted that an electron-donating group on the aromatic ring of 3-(1-alkynyl)chromone is beneficial to this domino process (Table 2, entries 2 and 7). When R^3 is a methyl group, the desired product was formed in low yield (Table 2, entry 8) along with a dimeric byproduct.[3f] When R^1 is a trimethyl-silyl group, the desilylated product **3ja** was observed in a reasonable yield since desilylation of **1j** easily occurred under basic conditions[7] (Table 2, entry 9). In addition, the desired products were produced in reasonable yields when R^1 was an aliphatic group on the acetylene moiety (Table 2, entries 10–12). Interestingly, ^{1}H NMRs of **3ka** and **3la** show the existence of two conformational isomers at room temperature in d_6-DMSO. It is clear from the X-ray structure that the phenyl substituent on C_{18} of **3aa** is in an axial position (Fig. 1), which places the phenyl group below and away from the cyclic units on either side of the seven-membered ring. This axial orientation of a bulky substituent is evidently the most stable conformation for this type of polycyclic chromone. Furthermore, the X-ray crystal study [8] of **3ka** (see supporting information†) shows the substitution is in the axial position too. We speculate that the seven-membered ring should have a degree of conformational flexibility, which could orientate an axial group into an equatorial position for substituents of certain size in solution. Insertion of a methylene unit between C_{18} and the phenyl ring, as in **3ka** or **3la**, may achieve that, and the interconversion of the two conformational isomers on the NMR timescale at room temperature may occur. Further study of the NMR of **3ka** at variant temperature was carried out in d_6-DMSO over a range of 20–70 °C (Fig. 2). At 70 °C, the broadening of peaks indicates the conformational flexing of the seven-membered ring system at higher temperature. At various temperatures, no difference of NMR spectra of **3aa** was found. This means that substituents of a certain size on the C_{18} position is critical to the conformational flexibility of the seven-membered ring system.

Table 1 Optimization of the one-pot tandem reaction of **1a**[a]

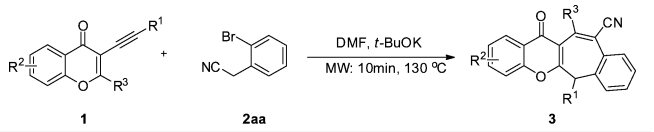


1a **2aa** **3aa**

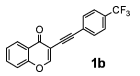
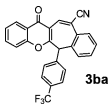
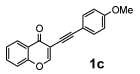
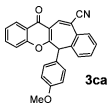
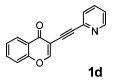
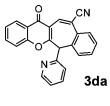
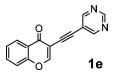
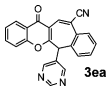
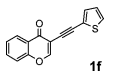
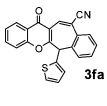
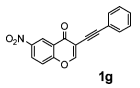
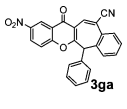
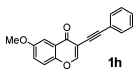
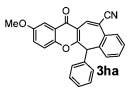
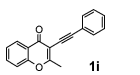
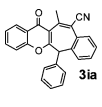
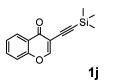
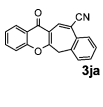
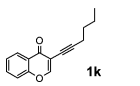
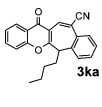
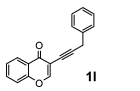
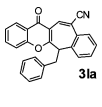
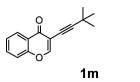
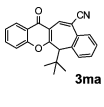
Entry	Solvent	Base	Temp/time	Yield (%)[c]
1	DMF	3 equiv DBU	90 °C, 10 min	71
2	DMF	3 equiv *t*-BuOK	90 °C, 10 min	68
3	DMF	3 equiv MeONa	90 °C, 10 min	57
4	DMF	3 equiv K_2CO_3	90 °C, 10 min	33
5	DMF	3 equiv DBU	130 °C, 10 min	72
6	DMF	3 equiv *t*-BuOK	130 °C, 10 min	75
7	DMF	1 equiv DBU	130 °C, 10 min	77
8	DMF	1 equiv *t*-BuOK	130 °C, 10 min	82
9	Toluene	1 equiv *t*-BuOK	130 °C, 10 min	66
10	DMSO	1 equiv *t*-BuOK	130 °C, 10 min	73
11[b]	DMF	1 equiv *t*-BuOK	130 °C, 3 h	70
12[d]	DMF	1 equiv *t*-BuOK	130 °C, 10 min	80
13[e]	DMF	1 equiv *t*-BuOK	130 °C, 10 min	64

[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**. [d] 5% equiv $PdCl_2(PPh_3)_2$ catalyst was added. [e] 5% equiv CuI catalyst was added.

Table 2 Tandem reaction of **2aa** with various 3-(1-alkynyl) chromones[a]



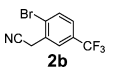
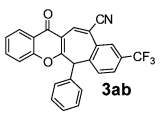
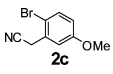
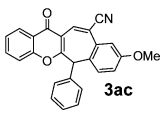
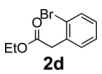
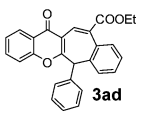
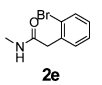
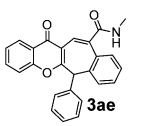
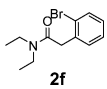
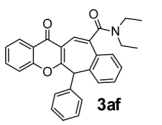
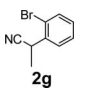
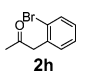
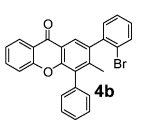
1 2aa 3

Entry	Substrate	Product	Yield(%)[b]
1	 1b	 3ba	51
2	 1c	 3ca	85
3	 1d	 3da	65
4	 1e	 3ea	62
5	 1f	 3fa	60
6	 1g	 3ga	45
7	 1h	 3ha	77
8	 1i	 3ia	28
9	 1j	 3ja	52
10	 1k	 3ka	63
11	 1l	 3la	57
12	 1m	 3ma	60

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

Table 3 Tandem reaction of **1a** with various substrates **2**[a]

1a 2 3

Entry	Substrate	Product	Yield(%)[b]
1	 2b	 3ab	88
2	 2c	 3ac	66
3	 2d	 3ad	62
4	 2e	 3ae	63
5	 2f	 3af	43
6	 2g	NA[c]	
7	 2h	NA[c]  4b	91

[a] Unless otherwise noted, the reactions were carried out under standard conditions. [b] Yields of isolated products based on **1a**. [c] No desired product.

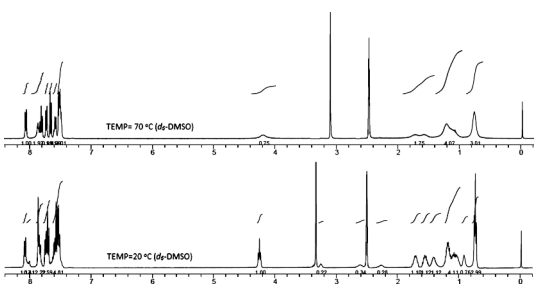


Fig. 2 Temperature dependent NMR spectra of **3ka**.

To extend the scope of this reaction, various substrates of **2** were used. Products **3ab–3af** were obtained in 43–88% yields (Table 3). It is noted that an electron-withdrawing group on the aromatic ring of **2** is beneficial to this domino process for easy removal of the leaving group, Br^-, from the *para*-position, according to the proposed mechanism (Table 3, entry 1). When R^5 was an ester

group or amide group, this tandem reaction proceeded smoothly to give the desired products (Table 3, entries 3–5). In the case where there was a methyl group adjacent to the cyano group (**2g**), no desired product was formed and only the desalicyloylative dimerization product[3e] of **1a** was obtained (Table 3, entry 6). In addition, when R^5 is a ketone group (**2h**), the aromatic compound **4b** was formed in 91% yield, since the 1,2-addition [3d] to the keto group is more active than the 8π-electrocyclization in this tandem process.

Conclusions

In conclusion, we have developed a novel base-promoted, microwave-assisted one-pot tandem reaction for the synthesis of functionalized polycyclic chromenones. Notably, we found that this tandem process involves the formation of a benzo seven-membered ring by 8π-electrocyclization. The process efficiently generates novel natural-product-like diversified polycyclic chromenone scaffolds. The library generation and biological evaluation of the novel polycyclic chromenones are under investigation.

Experimental

General information

All reactions were performed under a nitrogen atmosphere. Dry solvents were distilled prior to use; DMF was dried over microwave-dried molecular sieve; 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 $CDCl_3$ or d_6-DMSO 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 synthesis of the novel functional polycyclic chromenones 3

A typical procedure for the preparation of **3aa**: To a solution of 2-(2-bromophenyl)acetonitrile **2aa** (40 mg, 0.2 mmol) in dry DMF (1 mL) was added *t*-BuOK (24 mg, 0.2 mmol) at room temperature under a 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 130 °C (monitored by TLC). The mixture was extracted with ethyl acetate (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 by column chromatography (petroleum ether/ethyl acetate 6 : 1) to afford compound **3aa** as a white solid; m.p. 235–236 °C; IR (KBr) ν_{max} 3429, 3053, 2212, 1651, 1620, 1570, 1464, 1400, 1365, 1217, 1167, 764, 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.91 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.70–7.79 (m, 2H), 7.44–7.67 (m, 5H), 7.12–7.21 (m, 3H), 6.70–6.77 (m, 2H), 5.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.8, 166.0, 155.9, 136.2, 135.8, 134.3, 133.9, 131.2, 131.1, 128.9, 128.6, 128.3, 127.6, 126.4, 126.3, 126.1, 122.6, 118.8, 118.1, 116.1, 114.9, 55.0. HRMS [M]$^+$ Calculated for $C_{25}H_{15}NO_2$ 361.1103, found 361.1106.

General procedure for synthesis of xanthone 4b

To a solution of 1-(2-bromophenyl)propan-2-one **2g** (44 mg, 0.2 mmol) in dry DMF (1 mL) was added *t*-BuOK (24 mg, 0.2 mmol) at room temperature under a 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 130 °C (monitored by TLC). The mixture was extracted with ethyl acetate (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 by column chromatography (petroleum ether/ethyl acetate 10 : 1) to afford compound **4b** as a white solid; m.p. 185–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (dd, *J* = 1.7, 7.9 Hz, 1H), 8.15 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (td, *J* = 1.6, 7.7 Hz, 1H), 7.26–7.58 (m, 9H), 7.23 (d, *J* = 8.8 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 156.1, 153.0, 143.0, 141.5, 137.9, 135.5, 134.5, 132.6, 131.3, 131.1, 130.3, 130.0, 129.2, 128.4, 128.3, 127.6, 127.4, 126.4, 126.0, 124.0, 123.8, 121.5, 119.5, 118.2, 18.9. HRMS [M]$^+$ Calculated for $C_{26}H_{17}BrO_2Na$ 463.0310, found 463.0298

Acknowledgements

Financial supports of this project, provided by the NST Major Project "Key New Drug Creation and Manufacturing Program" (2009ZX09501-010) and SIMM0909KF-04, are gratefully acknowledged.

References

1 For recent reviews, see: (*a*) D. Enders, C. Grondal and M. R. Huttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*b*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*c*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*d*) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, 551; (*e*) P. Eilbracht, L. Barfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck and A. Schmidt, *Chem. Rev.*, 1999, **99**, 3329; (*f*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*g*) P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195.

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

3 (*a*) W. Li, Y. Xiao and J. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 617; (*b*) Y. Xiao and J. Zhang, *Chem. Commun.*, 2009, 3594; (*c*) X. Yu, H. Ren, Y. Xiao and J. Zhang, *Chem.–Eur. J.*, 2008, **14**, 8481; (*d*) L. Zhao, F. Xie, G. Cheng and Y. Hu, *Angew. Chem., Int. Ed.*, 2009, **48**, 6520; (*e*) F. Xie, X. Pan, S. Lin and Y. Hu, *Org. Biomol. Chem.*, 2010, **8**, 1378; (*f*) F. Xie, H. Chen and Y. Hu, *Org. Lett.*, 2010, **12**, 3086; (*g*) J. Gong, F. Xie, H. Chen and Y. Hu, *Org. Lett.*, 2010, **12**, 3848; (*h*) Y. Liu, L. Huang, F. Xie and Y. Hu, *J. Org. Chem.*, 2010, **75**, 6304.

4 CCDC 755402† (**3aa**) contains 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.
5 V. Y. Sosnovskikh, R. A. Irgashev and M. I. Kodess, *Tetrahedron*, 2008, **64**, 2997.
6 (*a*) Y. Matsuya, N. Ohsawa and H. Nemoto, *J. Am. Chem. Soc.*, 2006, **128**, 13072; (*b*) C. Hulot, G. Blond and J. Suffert, *J. Am. Chem. Soc.*, 2008, **130**, 5046.
7 Removal of TMS-alkynes under basic conditions, see: T. W. Greene and P. G. M Wuts In *Protective Groups in Organic Chemistry*, 3rd ed., Wiley-Interscience, New York, 2007, Chapter 8, pp. 928.
8 CCDC 792937† (**3ka**) contains 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.

