ORGANIC LETTERS

2012
Vol. 14, No. 24
6122–6125

An Organic Molecule Modulated Chemoselective Cyclization of Alkynyl Nitriles Tethered to 2-Alkyl Substituted Chromones with Multireactive Sites

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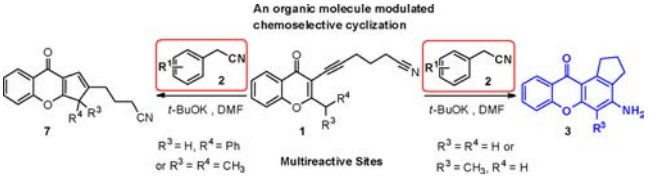
Received August 21, 2012

ABSTRACT



A small organic molecule phenylacetonitrile promoted chemoselective cyclization of (chromen-3-yl)alkynylnitriles to generate a novel tetracyclic or tricyclic chromone scaffold has been discovered. Importantly, the phenylacetonitrile serves as an anion transfer reagent changing the normal reaction of the substrate.

Intramolecular carbocyclizations of alkynes serve as direct and efficient methods for the preparation of five- or six-membered cyclic compounds.[1] A number of transition metal (Pd,[2] Au,[3] or other transition metal[4]) catalyzed, electrophile induced[5] or base promoted[6] cyclizations of alkynes and stabilized carbanions derived from malonate derivatives or enolates have been explored. These cyclizations usually proceed *via* a 5- or 6-*exo*-dig mode; however, 5- or 6-*endo*-dig cyclizations of nonterminal alkynes are relatively rare,[2n,3a,3c,4d,5a] and few examples exist of an 6-*endo*-dig cyclization of a stabilized lithio carbanion with an alkoxyacetylene under basic conditions.[7] In the investigation described below, we have developed chemoselective

(1) For reviews of intramolecular carbocyclizations of alkynes, see: (a) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366. (b) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2010**, *44*, 111.

(2) For papers of Pd-catalyzed intramolecular cyclizations of alkynes, see: (a) Bouyssi, D.; Balme, G.; Fournet, G.; Monteiro, N.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 1641. (b) Monteiro, N.; Balme, G.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 1645. (c) Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103. (d) Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2477. (e) Duan, X.-H.; Guo, L. N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 3053. (f) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (g) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325. (h) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2006**, *72*, 251. (i) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538. (j) Guo, L.-N.; Duan, X.-H.; Liu, X.-Y.; Hu, J.; Bi, H.-P.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 5425. (k) Guan, Z.-H.; Ren, Z.-H.; Zhao, L.-B.; Liang, Y.-M. *Org. Biomol. Chem.* **2008**, *6*, 1040. (l) Hess, W.; Burton, J. W. *Chem.—Eur. J.* **2010**, *16*, 12303. (m) Chernyak, N.; Gorelsky, S. I.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2342. (n) Fujino, D.; Yorimitsu, H.; Osuka, A. *Org. Lett.* **2012**, *134*, 2914.

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(4) For papers of other transition-metal-catalyzed intramolecular cyclizations of alkynes, see: (a) Gou, F.-R.; Bi, H.-P.; Guo, L.-N.; Guan, Z.-H.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 3837. (b) Montaignac, B.; Vitale, M. R.; Ratovelomanana-Vidal, V.; Michelet, V. R. *J. Org. Chem.* **2010**, *75*, 8322. (c) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Wang, Z.-Q.; Liu, Y.; Huang, X.-C.; Xie, Y.-X.; Li, J.-H. *Chem. Sci.* **2011**, *2*, 2131. (d) Suzuki, S.; Tokunaga, E.; Reddy, D. S.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4131.

(5) For papers of electrophile induced cyclizations of alkynes, see: (a) Barluenga, J.; Palomas, D.; Rubio, E.; González, J. M. *Org. Lett.* **2007**, *9*, 2823. (b) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397. (c) Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

(6) For papers of base promoted cyclizations of alkynes, see: (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, *1998*, 446. (b) Koradin, C.; Rodriguez, A.; Knochel, P. *Synlett* **2000**, *2000*, 1452. (c) Arcadi, A.; Marinelli, F.; Rossi, L.; Verdecchia, M. *Synthesis* **2006**, *2006*, 2019.

(7) For a related example of a 6-*endo-dig* carbocyclization process of a stabilized lithio carbanion with an alkoxyacetylene, see: Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023.

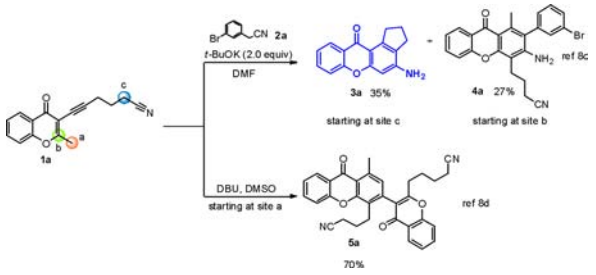
10.1021/ol302964x © 2012 American Chemical Society
Published on Web 12/04/2012

5- or 6-*endo* carbocyclization of biscarbanions arising from alkynyl nitriles tethered to chromones. These processes, which utilize 4-*N,N*-diethylaminophenylacetonitrile as an anion transfer reagent along with *n*-Bu_4NCl as a phase-transfer reagent, take place under transition-metal-free conditions to form polycyclic chromones.

In our earlier studies with 3-(1-alkynyl)chromones, we have devised routes for the preparation of functionalized xanthones.[8] When (chromen-3-yl)alkynylnitrile **1a** was treated with 2-(3-bromophenyl)acetonitrile **2a** in the presence of *t*-BuOK at 150 °C under microwave irradiation (MW), a surprising new product **3a** was isolated rather than the anticipated product **4a**[8c] (Scheme 1). The structure of **3a** was unambiguously established by X-ray crystal structure analysis (Figure 1). Significantly, the control experiments showed that a reaction without **2a** was complicated and only a trace of **3a** (< 5%) was obtained.

There are three potential reactive sites of **1a** under basic conditions (Scheme 1). The methyl group (site a) of **1a** can be deprotonated by a strong base to form a carbanion that then undergoes the cascade dimeric reaction involving double Michael additions and cyclizations to afford **5a**.[8d] Alternatively, **1a** could serve as a Michael acceptor (site b), which is attacked by the nucleophile **2a** to eventually generate amino-substituted xanthone **4a**.[8c]

Scheme 1. Regio- and Chemoselective Reactions of **1a** under Basic Conditions



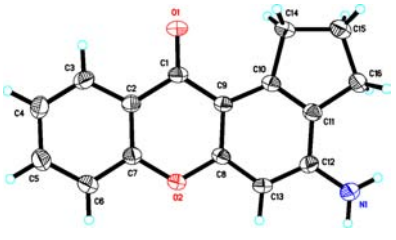
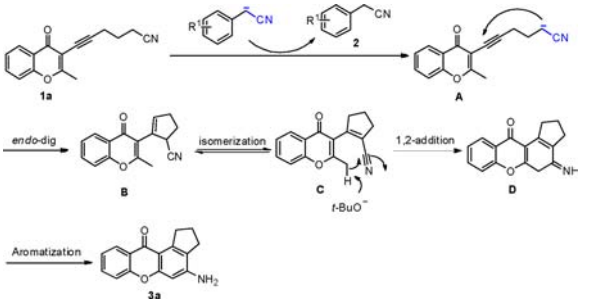


Figure 1. X-ray structure of **3a**.[9]

We envisioned that the novel transformation of **1a** to **3a** might occur involving double cyclizations as depicted in Scheme 2. Initially, the anion was selectively transferred from compound **2** to the α-carbon of the cyano in **1a** (Scheme 1, site c). The triple bond of **A** was attacked by the α-cyano anion to give the first cyclized product **B** *via* a 5-*endo*-dig mode. Subsequently, the intermediate **B** was isomerized to the conjugate **C**. Under the basic conditions, the resulting methyl anion of **C** could further add to the cyano group by intramolecular 1,2-addition to provide the second cyclized product **D**, which upon aromatization gave product **3a**.

To gain support for this mechanistic proposal, the reaction was performed at 90 °C instead of 150 °C. Under these conditions, intermediate **C** was isolated, which was completely converted to **3a** in excellent yields in either the presence or absence of **2a** (Scheme 3). When the methyl of **1a** was replaced with nondeprotonatable phenyl (**1a′**), the anticipated product **C′** could be obtained only in the presence of **2a**. When the methyl was replaced by hydrogen, only amino-substituted xanthone[8c] was isolated.

Scheme 2. Plausible Mechanism for the Formation of **1a**

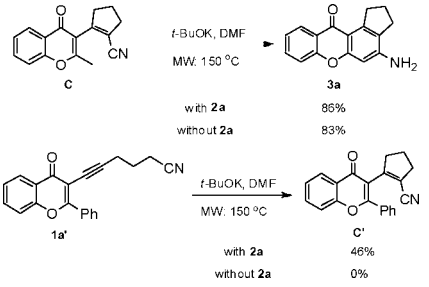


To further investigate the particular role of **2a** played in the conversion of **1a** to **B**, we first carried out the reactions without **2a** in the presence of common bases (*t*-BuOK, NaH, LDA, or NaHDMS). The reactions were complicated, and only a trace of **3a** was obtained (Table 1, entry 1). These strong bases could deprotonate both the methyl[8d] (site a) and α-methylene of cyano[1a] (site c) of **1a** and rendered the reaction less selective and more complicated. Other carbanion transferring reagents similar to **2a** were then screened (Table 1, entries 2−11). The results showed that when *ortho*- and *para*-position substituted electron-donating groups were used for R^1, the formation of **3a** was favored (Table 1, entries 2−11). Phenylacetate **2k** and phenylacetamide **2l** resulted in inferior efficiency, and only **5a** was afforded (Table 1, entries 12−13). Notably, when **2m** 9*H*-fluorene was empolyed, **3a** was also formed in 45% yield (Table 1, entry 14), which further confirmed that these small molecules acted as anion donors. Finally, the effect of the strength of anion donors was investigated. The reaction gave complicated products when the weak anion donor MeCN was used (Table 1, entry 15). Surprisingly, when the strong anion donor ethyl 2-cyanoacetate **2o** or

(8) (a) Zhao, L.; Xie, F.; Cheng, G.; Hu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6520. (b) Gong, J.; Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3848. (c) Liu, Y.; Huang, L.; Xie, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 6304. (d) Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3086. (e) Xie, F.; Pan, X.; Lin, S.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1378. (f) Liu, Y.; Huang, L.; Xie, F.; Chen, X.; Hu, Y. *Org. Biomol. Chem.* **2011**, *9*, 2680.

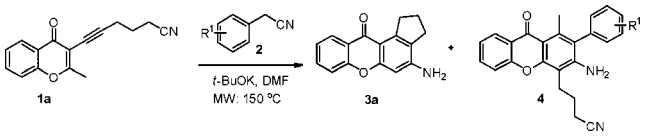
diethyl malonate **2p** was employed (Table 1, entries 16–17), **5a** and **6a** (X-ray structure in Supporting Information) was isolated instead of **3a**. The corresponding anion of **2o** or **2p** selectively transferred to the methyl to form the dimeric product **5a**,[8d] which gave **6a** by further cyclization, isomerization, and desalicyloylation (Scheme 4).

Scheme 3. Support for the Proposed Mechanism



With **2h** as the best anion transfer reagent, the examination of the effect of temperature and base to the reaction was carried out (Table 2). When the temperature was decreased from 150 to 110 °C, the yield increased to 62% (Table 2, entries 1–2). Among a variety of bases tested, *t*-BuOK was found to be superior to MeONa, EtONa (Table 2, entries 2–4). In addition, this process did not occur efficiently when common solvents, such as THF, DMSO, MeCN, and toluene, were used. Moreover, the addition of transition metals to the reaction mixture did not lead to improved yields but gave **4a** and intermediate **C** as byproducts, confirming that this unique process would not be promoted by metal impurities (Table 2, entries 5–10).

Table 1. Screening of Anion Transfer Reagents[a]



entry	anion transfer reagent	**3a** (%)[b]	**4** (%)[b]
1[c]	–	<5	–
2	**2a** R^1 = 3-Br	35	27
3	**2b** R^1 = 4-Br	35	30
4	**2c** R^1 = H	40	20
5	**2d** R^1 = 2-OMe	42	15
6	**2e** R^1 = 3-OMe	37	20
7	**2f** R^1 = 4-OMe	50	8
8	**2g** R^1 = 3,4,5-OMe	42	18
9	**2h** R^1 = 4-NEt_2	55	0
10	**2i** R^1 = 4-$N(CH_2)_4$	52	0
11	**2j** R^1 = 2-$N(CH_2)_4$	48	5
12	**2k** ethyl 2-phenylacetate	<5	–
13	**2l** 2-phenylacetamide	<5	–
14	**2m** 9H-fluorene	45	–
15	**2n** MeCN	<5	–
16[d]	**2o** EtOOC–CH_2CN	0	–
17[d]	**2p** $CH_2(COOEt)_2$	0	–

[a] General conditions: **1a** (0.4 mmol), *t*-BuOK (0.8 mmol), and **2** (0.4 mmol) in DMF (2 mL). [b] Isolated yield. [c] The reaction was carried out in the presence of bases (*t*-BuOK, NaH, LDA, or NaHDMS) without **2**. [d] **3a** was not isolated (see Scheme 4).

Scheme 4. Formation of **5a** and **6a** Modulated by **2p** and the Plausible Mechanism of **6a**

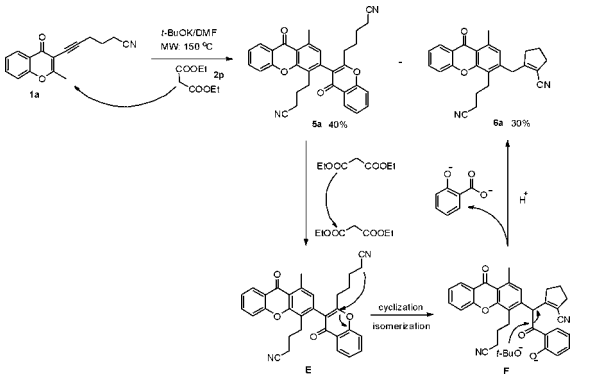
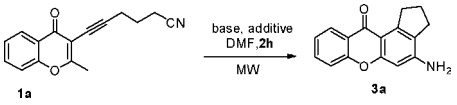


Table 2. Optimization of Reaction Conditions[a]

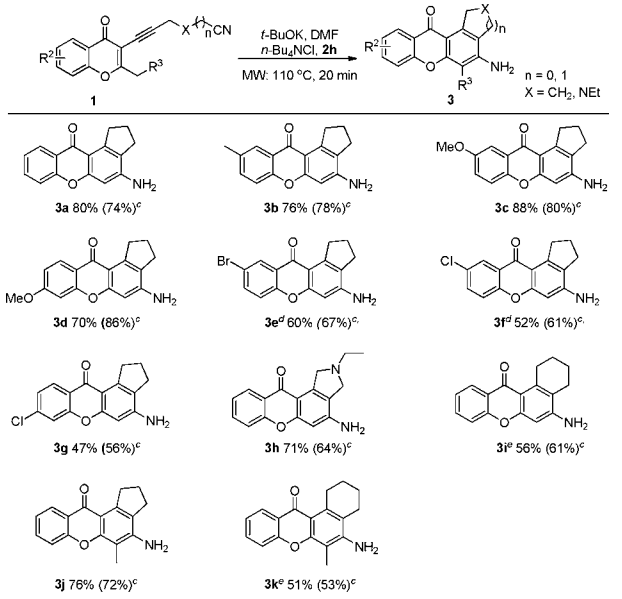


entry	base	additive (equiv)	temp, time	yield(%)[b]
1	*t*-BuOK	none	150 °C, 10 min	55
2	*t*-BuOK	none	110 °C, 10 min	62
3	MeONa	none	110 °C, 10 min	52
4	EtONa	none	110 °C, 10 min	27
5[c]	*t*-BuOK	Ag_2SO_4	110 °C, 10 min	34
6[c]	*t*-BuOK	CuCl	110 °C, 10 min	31
7[c]	*t*-BuOK	$CuCl_2$	110 °C, 10 min	20
8[c]	*t*-BuOK	$PdCl_2(PPh_3)_2$	110 °C, 10 min	33
9[c]	*t*-BuOK	$Pd(PPh_3)_4$	110 °C, 10 min	30
10[c]	*t*-BuOK	$PtCl_2$	110 °C, 10 min	60
11	*t*-BuOK	*n*-Bu_4NCl (2)	110 °C, 20 min	80
12	*t*-BuOK	*n*-Bu_4NF (2)	110 °C, 20 min	70
13	*t*-BuOK	*n*-Bu_4NBr (2)	110 °C, 20 min	64
14	*t*-BuOK	*n*-Bu_4NI (2)	110 °C, 20 min	60
15[d]	*t*-BuOK	*n*-Bu_4NCl (2)	110 °C, 20 min	71
16[e]	*t*-BuOK	*n*-Bu_4NCl (2)	110 °C, 20 min	74
17	*t*-BuOK	*n*-Bu_4NCl (0.2)	110 °C, 20 min	65
18	*t*-BuOK	*n*-Bu_4NCl (0.5)	110 °C, 20 min	67
19	*t*-BuOK	*n*-Bu_4NCl (1)	110 °C, 20 min	70

[a] General conditions: **1a** (0.4 mmol), base (0.8 mmol), and **2h** (0.4 mmol) in DMF (2 mL). [b] Isolated yield. [c] 5 mol % of metal was added. [d] 0.2 equiv of **2h** was added. [e] 0.5 equiv of **2h** was added.

(9) CCDC 883517 (**3a**) 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.

Scheme 5. Formation of the Tetracyclic Chromone Derivatives **3**[a,b]

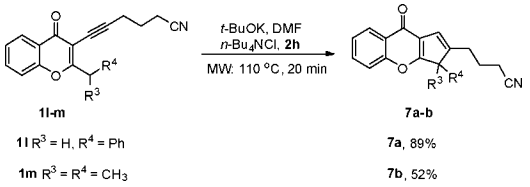


[a] Unless otherwise noted, reactions were carried out under the optimized reaction conditions. [b] Isolated yields given. [c] 0.5 equiv of **2h** was employed. [d] Reactions were carried out for 30 min. [e] Reactions were carried out at 150 °C.

Importantly, when *n*- Bu_4NCl (2.0 equiv) was used as a phase transfer reagent, the yield increased to 80%. Other additives such as *n*-Bu_4NF, *n*-Bu_4NBr, and *n*-Bu_4NI resulted in inferior efficiency (Table 2, entries 11−14). Finally, the reaction of **1a** to generate **3a** also took place smoothly in a slightly lower yield when a a catalytic amount of **2h** or *n*-Bu_4NCl was employed (Table 2, entries 15−19). The observations described above showed that the optimized coditions for the production of **3a** involve *t*-BuOK (2.0 equiv), *n*-Bu_4NCl (2.0 equiv), and **2h** (1.0 equiv) in DMF at 110 °C for 20 min under microwave irradiation.

The scope of this process, utilizing the optimized conditions, was explored (Scheme 5). The results showed that electron-donating groups in contrast to electron-withdrawing groups on the arene ring of chromone **1** (R^2) facilitate the cascade reaction (*e.g.*, **3b**−**3d** and **3e**−**3g**). When the central atom X in **1a** was replaced by nitrogen,the fused pyrrolidine product **3h** was generated in 71% yield. When a four carbon tether was present in the reactant, the reaction occurred at the higher temperature 150 °C to form the fused cyclohexane product **3i**. It should be noted that the first cyclization step in the transformation

Scheme 6. Cyclization of **1l** and **1m** To Form **7a** and **7b**



of **1i** took place exclusively *via* a 6-*endo*-dig rather than 5-*exo*-dig mode. When the nitrile was replaced by the ester or amide, the desired product was not observed and only amino-substituted xanthone[8c] was obtained. Finally, this process occurred in a reasonable yield when the R^3 substituent was methyl (*e.g.*, **3j**−**3k**).

Remarkably, this cascade reaction displayed a different chemoselectivity when the 2-substituent of chromone was either benzyl or isopropyl (**1l**−**1m**). The respective substituted cyclopenta[*b*]chromen-9(3*H*)-ones **7a** and **7b** were produced in high yields by chemoselective cyclization through deprotonation at the α-hydrogen of the 2-substituent (Scheme 6). The benzyl group in **1l** might be more acidic than the α-methylene of the cyano, and the bulky isopropyl group in **1m** might sterically hinder the 5-*endo*-dig cyclization.

In the study described above, we discovered a novel, small organic molecule-modulated, intramolecular carbocyclization of alkynyl nitriles tethered to chromones that chemoselectively afford a new class of polycyclic chromone derivatives. The cascade process, which does not require transition metal catalysts, involves multiple reactions including an *endo*-dig cyclization, an isomerization, and a 1,2-addition. Importantly, the results of this effort show that a small organic molecule can serve as an anion transfer reagent and change the course of the normal reaction of the substrate with three reactive sites.

Acknowledgment. This work was supported by a grant from the National Natural Science Foundation of China (21172232) and Ministry of Science and Technology of China (2009CB940903).

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.