ORGANIC LETTERS

2011
Vol. 13, No. 17
4526–4529

Synthesis of γ-Benzopyranone by TfOH-Promoted Regioselective Cyclization of *o*-Alkynoylphenols

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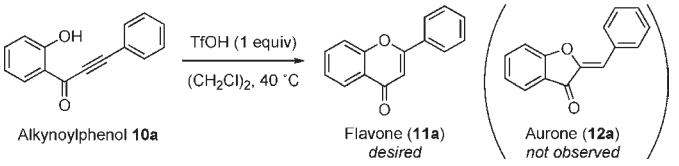
Received June 23, 2011

ABSTRACT



Regioselective cyclization of *o*-alkynoylphenols forming γ-benzopyranones has been demonstrated. Trifluoromethanesulfonic acid (TfOH) induced 6-*endo* cyclization of *o*-alkynoylphenols without forming 5-*exo* cyclized benzofuranone derivatives to provide the corresponding γ-benzopyranones in high yields.

γ-Benzopyranone-containing natural products such as nobiletin (**1**) and pluramycin A (**2**) exhibit a wide range of biological activities, especially, anti-inflammatory, antimicrobial, antitumoric, and cytotoxic (Figure 1).[1] Several approaches to the synthesis of a γ-benzopyranone skeleton have been reported, for example, acid-catalyzed cyclization of 1,3-dione derivatives prepared from 2-hydroxyacetophenones[2] and oxidative cyclization of 2-hydroxychalcones.[3] The γ-benzopyranone system with substituents at the C2 position can also be synthesized by 6-*endo*-*digonal* cyclization of *o*-alkynoylphenols **3**.[4] In general, cyclization of *o*-alkynoylphenols predominantly provides

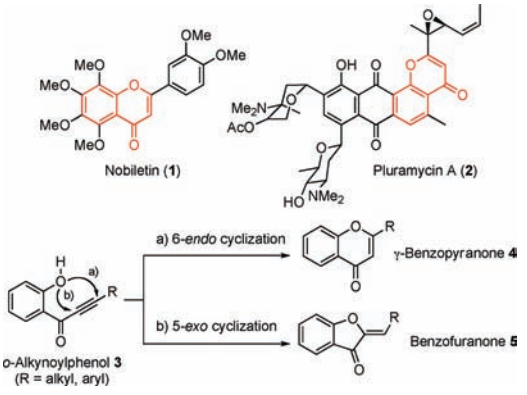


Figure 1. γ-Benzopyranone-containing natural products and possible mode of the cyclization of *o*-alkynoylphenol.

γ-benzopyranones **4** via 6-*endo*-*digonal* cyclization (path a), while a substantial amount of benzofuranone **5**, formed via 5-*exo*-*digonal* cyclization (path b), is also observed.[5] Several studies on cyclization of *o*-alkynoylphenols revealed that a mixture of γ-benzopyranones **4** and benzofuranones

(1) (a) Martens, S.; Mithofer, A. *Phytochemistry* **2005**, *66*, 2399–2407. (b) Veitch, N. C.; Grayer, R. J. *Nat. Prod. Rep.* **2008**, *25*, 555–611. (c) Crozier, A.; Jaganath, I. B.; Clifford, M. N. *Nat. Prod. Rep.* **2009**, *26*, 1001–1043. (d) Sequin, U. *Fortschr. Chem. Naturst.* **1986**, *50*, 57–122. (e) Hansen, M. R.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *29*, 249–258.

(2) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381–1389. (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767–1769. (c) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300–9305. (d) Asakawa, T.; Hiza, A.; Nakayama, M.; Inai, M.; Oyama, D.; Koide, H.; Shimizu, K.; Wakimoto, T.; Harada, N.; Tsukada, H.; Oku, N.; Kan, T. *Chem. Commun.* **2011**, *47*, 2868–2870.

(3) (a) Chen, F. C.; Chang, C. T.; Chen, C. Y.; Hung, M.; Lin, Y. C. *J. Org. Chem.* **1962**, *27*, 310–312. (b) Zhang, F.-J.; Lin, G.-Q.; Huang, Q.-C. *J. Org. Chem.* **1995**, *60*, 6427–6430. (c) Joo, Y. H.; Kim, J. K.; Kang, S. H.; Noh, M. S.; Ha, J. Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413–417.

(4) (a) Baldwin, J. K. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Baldwin, J. K.; Cutting, J.; Dupont, W.; Kruse, L.; Siberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.

(5) (a) García, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432–4436. (b) Brennan, C. M.; Johnson, C. D.; McDonnell, P. D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 957–961.

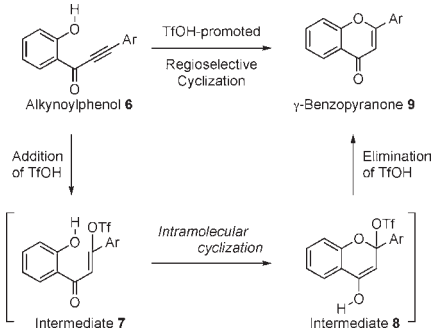
10.1021/ol2016934
Published on Web 08/03/2011

5 is obtained and their ratio is highly dependent on the reaction conditions as well as the substituents on the substrate.[6]

Therefore, we are interested in developing a versatile method for the synthesis of γ-benzopyranones from *o*-alkynoylphenols. We herein report that TfOH-promoted cyclization of *o*-alkynoylphenols exclusively produced γ-benzopyranones.

To achieve the regioselective cyclization of *o*-alkynoylphenol **6**, we postulated the production of α,β-unsaturated ketone **7** by 1,4-addition of triflic acid (TfOH) to *o*-alkynoylphenol **6** (Scheme 1). Vasilyev et al. reported that ynoates underwent 1,4-addition of TfOH to yield corresponding vinyl triflates **7**.[7] Vinyl triflate **7** should be a good Michael acceptor such that intramolecular 1, 4-addition of the phenolic hydroxy group, followed by the elimination of TfOH, would exclusively afford benzopyranone **9**. This integrated synthesis of a γ-benzopyranone skeleton would be useful because the above two reactions can be performed in a single one-pot operation.[8]

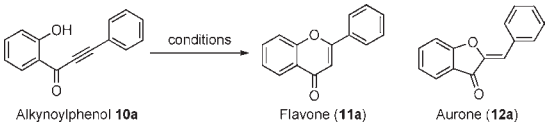
Scheme 1. TfOH-Promoted Regioselective Cyclization of *o*-Alkynoylphenols



We initially examined the regioselectivity of the cyclization of *o*-alkynoylphenol **10a**. Treatment of **10a** with 1 equiv of TfOH at 40 °C in 1,2-dichloroethane provided the 6-membered ring product flavone (**11a**) in 80% yield. The 5-membered ring product aurone (**12a**) was not observed under these reaction conditions (Table 1, entry 1, **11a**:**12a** = >99:1).[9] On the other hand, no reaction proceeded in the presence of other Brønsted acids. In addition, weaker acids such as trifluoroacetic acid, *p*-toluenesulfonic acid, camphor sulfonic acid, acetic acid, and formic acid gave no reaction (entries 3−7). Interestingly, bis(trifluoromethanesulfonyl)imide (Tf_2NH),[10] which is a stronger acid than TfOH, gave a trace amount of the product (entry 2).

When the reaction was conducted at rt, vinyl triflate **13** was isolated in 41% yield accompanied by **11a** (23%) (Scheme 2). Then, **13** was quantitatively converted to **11a** with heating at 40 °C without formation of **12a**. According to the above investigation, note that the TfOH-promoted cyclization of alkynoylphenol **10a** proceeded via an intermediate **13**; therefore the desired 6-*endo* cyclized product **11a** was regioselectively afforded.

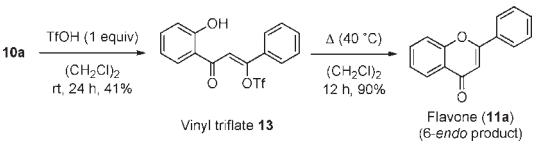
Table 1. Investigation of the Cyclization of *o*-Alkynoylphenol **10a** under Acidic Conditions



entry	reagent[a]	solvent	temp (°C)	time (h)	ratio of **11a**:**12a**[b]	yield of 6-*endo* **11a** (%)[c]
1	TfOH	$(CH_2Cl)_2$	40	10	>99:1	80
2	Tf_2NH	$(CH_2Cl)_2$	40	24	>99:1	5
3	TFA	$(CH_2Cl)_2$	40	24	–	0
4	*p*-TsOH	$(CH_2Cl)_2$	40	24	–	0
5	CSA	$(CH_2Cl)_2$	40	24	–	0
6	AcOH	$(CH_2Cl)_2$	40	24	–	0
7	HCOOH	$(CH_2Cl)_2$	40	24	–	0

[a] 100 mol % of Brønsted acid was used. [b] The ratio of **11a** and **12a** was determined by crude ^{1}H NMR. [c] Isolated yield.

Scheme 2. Reaction Pathway from **10a** to **11a** by TfOH-Promoted Cyclization



(6) (a) Alvaro, M.; Garcia, H.; Iborra, S.; Miranda, M. A.; Primo, J. *Tetrahedron* **1987**, *43*, 143–148. (b) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990**, *55*, 4349–4356. (c) Ciattini, P. G.; Morera, E.; Ortar, G.; Rossi, S. S. *Tetrahedron* **1991**, *47*, 6449–6456. (d) Torii, S.; Okumoto, H.; Xu, L. H.; Sadatake, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalini, V. N. *Tetrahedron* **1993**, *49*, 6773–6784. (e) Nakatani, K.; Okamoto, A.; Yamanuki, M.; Saito, I. *J. Org. Chem.* **1994**, *59*, 4360–4361. (f) Nakatani, K.; Okamoto, A.; Saito, I. *Tetrahedron* **1996**, *52*, 9427–9446. (g) Uno, H.; Sakamoto, K.; Honda, E.; Ono, N. *Chem. Commun.* **1999**, 1005–1006. (h) Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. *Tetrahedron Lett.* **1999**, *40*, 2469–2472. (i) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765–1768. (j) Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. *J. Comb. Chem.* **2000**, *2*, 597–599. (k) Huang, X.; Tang, E.; Xu, W.-M.; Cao, J. *J. Comb. Chem.* **2005**, *7*, 802–805. (l) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626–1632. (m) Likhar, P. R.; Subhas, M. S.; Roy, M.; Roy, S.; Kantam, M. L. *Helv. Chim. Acta* **2008**, *91*, 259–264. (n) Kraus, G. A.; Wie, J.; Thite, A. *Synthesis* **2008**, *15*, 2427–2431. (o) Yamaguchi, S.; Kobayashi, M.; Harada, S.; Miyazawa, M.; Hirai, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 863–868.

(7) Vasilyev, A. V.; Walspurger, S.; Chassaing, S.; Pale, P.; Sommer, J. *Eur. J. Org. Chem.* **2007**, 5740–5748.

(8) In classification of reaction integration, tandem reaction is categorized as a time and space integration by the Yoshida group; see: Suga., S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404–406.

(9) Aurone **12a** was prepared by treatment with a catalytic amount of AgCl; see: Jong, T.-T.; Leu, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 423–424.

(10) (a) Foropoulos, J.; DesMarteau, D. D. *Inorg. Chem.* **1984**, *23*, 3720–3723. (b) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.; Hu, L.; Sung, K.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, A. Y.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P. *J. Am. Chem. Soc.* **1994**, *116*, 3047–3057.

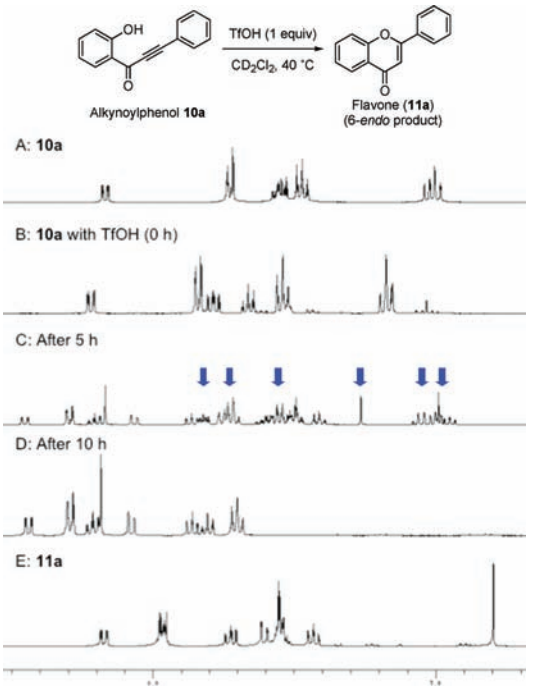
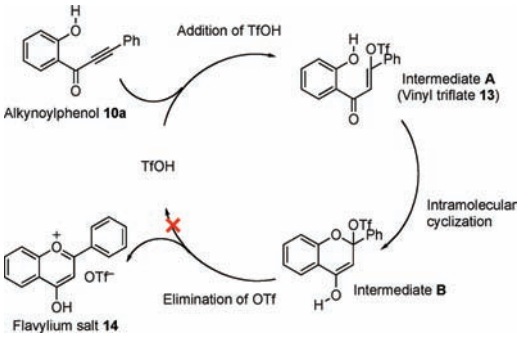


Figure 2. Selected ^{1}H NMR spectra (6.7−8.5 ppm) of the reaction of **10a** under the TfOH−CD_2Cl_2 conditions. (A) Substrate **10a**; (B) 0 h (**10a** with TfOH); (C) after 5 h, with blue arrows indicating the signal of intermediate **A** (vinyl triflate **13**); (D) after 10 h; (E) isolated **11a**.

When the regioselective cyclization of *o*-alkynoylphenol **10a** using 0.5 equiv of TfOH was performed, **11a** was produced in 41% yield with recovery of **10a** (47%). As it was speculated that the cyclization proceeded stoichiometrically, the time course of the cyclization of **10a** was monitored by ^{1}H NMR spectroscopy in CD_2Cl_2 (Figure 2). The substrate **10a** and the mixture of **10a** with 1 equiv of TfOH were initially measured. It was found that the ^{1}H NMR spectrum of the above mixture was completely distinguishable from that of substrate **10a** (Figure 2A and B). Therefore, we expected that **10a** was easily converted to the complex using TfOH by coordination with the carbonyl group. Substrate **10a** was consumed in 5 h; considerable amounts of intermediates **A**, **B** (see Scheme 3) and a cyclized product were observed (Figure 2C). After 10 h, the reaction was completed and a single product was detected by ^{1}H NMR (Figure 2D). The spectrum of the product in the reaction mixture was not identical to that of isolated **11a** (Figure 2D and E). Notably, when the product was generated, the color of the reaction mixture gradually turned from yellow to dark red.[11] It is suggested that flavylium salt **14** would be generated under the reaction conditions by coordination of TfOH (Scheme 3). According to the above observations, it should be noted that **14** was immediately formed by elimination of the TfO^- ion from the intermediate **B**. Therefore, addition of 1 equiv of TfOH is necessary to complete the reaction.

With the optimal reaction conditions for 6-*endo* cyclization of *o*-alkynoylphenol in hand, we evaluated the various substrates in TfOH-promoted regioselective cyclizaton. Cyclization of the substrates **10b**−**d** possessing methoxy groups on the right benzene ring (Table 2, entries 1−3) was easily completed within 4 h and yielded the corresponding 6-*endo* cyclized products **11b**−**d** in excellent yields; this was presumably because of the electron-donating effect of the methoxy group at the *para*-position on the right benzene ring. Except for **10e**, substrates **10f**−**h** bearing methoxy groups on the left benzene ring were also cyclized under the same reaction conditions to provide the corresponding products **11f**−**h** (entries 5−7). In the cyclization of **10e**, which has no methoxy group on the right benzene ring, a higher temperature (80 °C) was necessary because the electron-donating effect of the methoxy group strongly decreased the electrophilicity of the carbonyl group (entry 4). The cyclization of substrates **10i**−**l**, which contain a methoxy group at one of the *meta*-positions, was also selectively performed to yield **11i**−**l** in moderate yields (entries 8−11). Although TfOH also induced 6-*endo* cyclization in the case of substrates **10m** and **10n**, demethylation of the methoxy group was observed to provide 5-hydroxy derivatives **11m** (71%, entry 12) and **11n** (73%, entry 13), respectively.[12] In the cyclization of the substrates **10o**−**q** possessing alkyl groups instead of the aromatic ring, the reaction was not completed even at 80 °C. After extensive investigations, the reaction smoothly proceeded at 150 °C under microwave irradiation leading to the corresponding *6-endo* cyclized *γ*-benzopyranones **11o**−**q** in moderate yields (67−75%, entries 14−16).

Scheme 3. Plausible Mechanism of TfOH-Mediated Cyclization of *o*-Alkynoylphenol **10a**

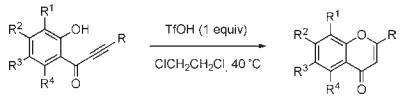


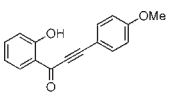
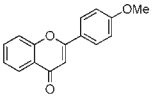
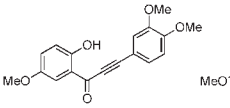
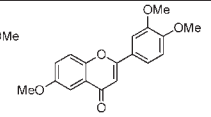
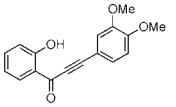
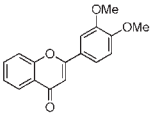
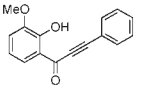
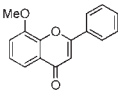
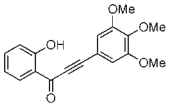
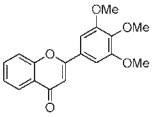
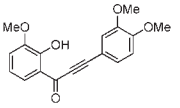
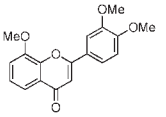
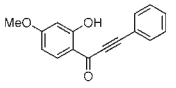
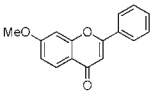
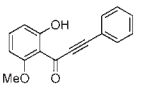
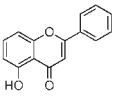
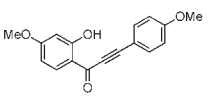
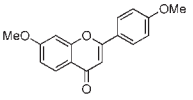
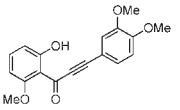
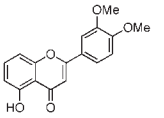
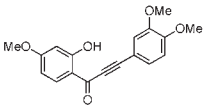
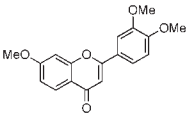
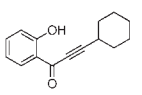
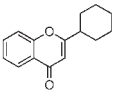
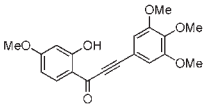
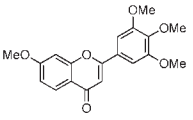
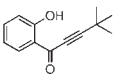
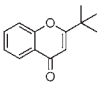
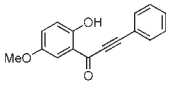
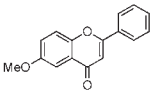
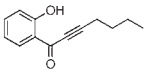
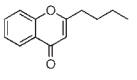
In summary, we have demonstrated the regioselective cyclization of *o*-alkynoylphenols in acidic media. It was found that the 6-*endo* cyclization was induced by TfOH to afford *γ*-benzopyranone derivatives in moderate to excellent yields without forming 5-*exo* cyclized benzofuranone

(11) Flipescu, N.; Chakrabarti, S. K.; Trassoff, P. G. *J. Phys. Chem.* **1973**, *77*, 2276–2282.

(12) Demethylation of the methoxy group under acidic conditions has been observed; see: Schönberg, A.; Badran, N. *J. Am. Chem. Soc.* **1951**, *73*, 2960–2961.

Table 2. TfOH-Promoted Regioselective Cyclization: Substrate Scope



entry	substrate	product	time (h)	yield (%)	entry	substrate	product	time (h)	yield (%)
1	 **10b**	 **11b**	4	90	9	 **10j**	 **11j**	13	92
2	 **10c**	 **11c**	1	90	10	 **10k**	 **11k**	14[a]	91
3	 **10d**	 **11d**	1	96	11	 **10l**	 **11l**	1.5	93
4	 **10e**	 **11e**	24[a]	40	12	 **10m**	 **11m**	24[a]	71[b]
5	 **10f**	 **11f**	17	61	13	 **10n**	 **11n**	3[a]	73[b]
6	 **10g**	 **11g**	2.5	82	14	 **10o**	 **11o**	24[a] 0.5[c]	trace 73
7	 **10h**	 **11h**	3	73	15	 **10p**	 **11p**	48[a] 0.5[c]	58 67
8	 **10i**	 **11i**	24[a]	91	16	 **10q**	 **11q**	48[a] 0.5[c]	53 75

[a] The reaction was conducted at 80 °C. [b] Demethylation of the methoxy group was observed. [c] The reaction was conducted at 150 °C under microwave irradiation.

derivatives. Using this methodology, the library synthesis of γ-benzopyranone-based natural product derivatives is currently underway in our laboratory.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Reaction Integration" (No. 2105, 22106503) from MEXT. We also thank the Circle for the Promotion of Science and Engineering for financial support.

Supporting Information Available. Experimental procedures and compound characterization data for **10a**–**q**, **11a**–**q**, **12a**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.