ORGANIC LETTERS

2012
Vol. 14, No. 13
3430–3433

A Silver(I)-Catalyzed Tandem Reaction of 2-Alkynylbenzaldoxime with Alkylidenecyclopropane

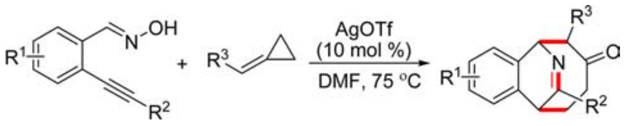
Qian Xiao,[†,‡] Shengqing Ye,[†] and Jie Wu*[,†,§]

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433,
China, Department of Chemistry, Nanchang University, 999 Xuefu Road, Nanchang,
Jiangxi 330031, China, and State Key Laboratory of Organometallic Chemistry,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
Shanghai 200032, China

jie_wu@fudan.edu.cn

Received May 20, 2012

ABSTRACT



A silver(I)-catalyzed tandem reaction of 2-alkynylbenzaldoxime with alkylidenecyclopropane gives rise to benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones in moderate to good yields. The complexity and diversity could be easily incorporated with the formation of three bonds during the process.

Continuous efforts to develop efficient approaches have been underway for the generation of nitrogen-containing heterocycles because of their remarkable biological and physical properties.[1] Recently, intense interest has been directed toward the strategy of diversity-oriented synthesis[2] for the concise assembly of structurally complex compounds. During studies of chemical genetics, we were interested in tandem reactions[3] for the preparation of natural product-like compounds with diversity and complexity using diversity-oriented synthesis. Recently, we and others identified that 2-alkynylbenzaldoxime was a useful building block for accessing *N*-heterocycles.[4,5] In the presence of a suitable metal salt or electrophile, isoquinoline *N*-oxide as the key intermediate could be easily formed from 2-alkynylbenzaldoxime, which would undergo subsequent nucleophilic addition or a [3 + 2] cycloaddition reaction. In the meantime, strained alkylidenecyclopropanes have been widely used for the synthesis of a variety of

---

[†] Fudan University.

[‡] Nanchang University.

[§] Shanghai Institute of Organic Chemistry.

(1) Recent reviews for the synthesis of heterocycles: (a) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (b) Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140. (d) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodrıguez-Garcıa, I. *Chem. Rev.* **2008**, *108*, 3174. (e) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (g) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

(2) (a) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476. (b) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339. (c) Schreiber, S. L. *Science* **2000**, *287*, 1964. (d) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (e) Schreiber, S. L. *Nature* **2009**, *457*, 153. (f) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (g) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep.* **2008**, *25*, 719.

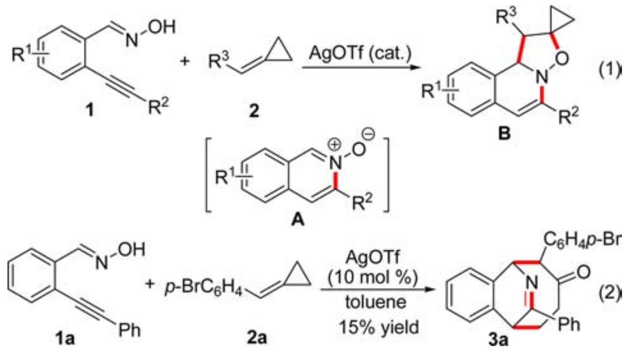
(3) For reviews, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) Negishi, E.; Coperet, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (e) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217. (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (g) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (h) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (i) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (j) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (k) Tietze, L. F.; Düfert, M. A.; Hungerland, T.; Oum, K.; Lenzer, T. *Chem.—Eur. J.* **2011**, *17*, 8452.

(4) (a) Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* **2011**, *13*, 2552. (b) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120. (c) Zheng, D.; Chen, Z.; Liu, J.; Wu, J. *Org. Biomol. Chem.* **2011**, *9*, 4763. (d) Ye, S.; Wang, H.; Wu, J. *Tetrahedron* **2011**, *67*, 4628. (e) Zheng, D.; Wang, Z.; Wu, J. *Synthesis* **2011**, 2810. (f) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746. (g) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem.* **2010**, 6436. (h) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702. (i) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921. (j) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850.

(5) (a) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924. (b) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.

10.1021/ol301393f

Scheme 1. Unexpected Silver(I)-Catalyzed Reaction of 2-Alkynylbenzaldoxime **1a** with 1-Bromo-4-(cyclopropylidenemethyl)benzene **2a**



carbocycles and heterocycles within complex molecules.[6−8] Encouraged by the chemistry of 2-alkynylbenzaldoxime and the advancement of alkylidenecyclopropanes, we envisioned that the fused 1,2-dihydroisoquinolines would be generated via a reaction of 2-alkynylbenzaldoxime with alkylidenecyclopropane. As outlined in Scheme 1, we anticipated that treatment of 2-alkynylbenzaldoxime **1** in the presence of a catalytic amount of silver triflate would lead to isoquinoline-*N*-oxide **A**. Then alkylidenecyclopropane would be involved through a [3 + 2] cycloaddition to provide access to 1,2-dihydroisoquinoline framework **B**.

In order to efficiently access the designed 1,2-dihydroisoquinoline scaffold, we first evaluated the proposed reaction using select 2-alkynylbenzaldoxime **1a** with 1-bromo-4-(cyclopropylidenemethyl)benzene **2a** in the presence of 10 mol % of silver triflate (Scheme 1, eq 2). Initially, the reaction was performed in 1,2-dichloroethane at room temperature. However, no reaction took place at all. A trace amount of product was detected when the reaction temperature was elevated to 60 °C. Interestingly, a product was isolated in 15% yield when the reaction occurred in toluene. However, structure elucidation revealed that the product was benzo-7-azabicyclo[4.2.2]dec-7-en-4-one **3a** instead of the expected one. The structure of compound **3a** was unambiguously demonstrated by X-ray diffraction analysis (Figure 1, also see the Supporting Information).

This unexpected result prompted us to investigate suitable conditions (Table 1). Solvent screening led to

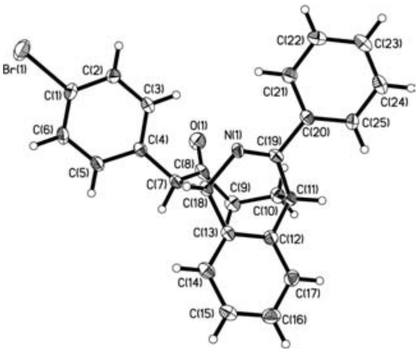
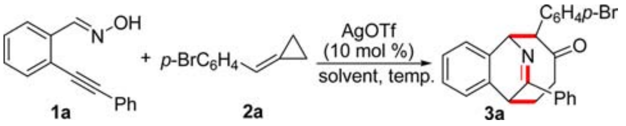


Figure 1. X-ray ORTEP illustration of benzo-7-azabicyclo[4.2.2]dec-7-en-4-one **3a** (30% probability ellipsoids).

Table 1. Initial Studies for the Silver Triflate-Catalyzed Reaction of 2-Alkynylbenzaldoxime **1a** with 1-Bromo-4-(cyclopropylidenemethyl)benzene **2a**



entry	additive	solvent	temp (°C)	yield[a] (%)
1		toluene	25	NR
2		toluene	60	15
3		DCE	25	NR
4		DCE	60	trace
5		MeCN	60	18
6		DMF	60	52
7		1,4-dioxane	60	23
8		THF	60	30
9	$Au(PPh_3)Cl$	DMF	60	25
10	$Sc(OTf)_3$	DMF	60	21
11	$Bi(OTf)_3$	DMF	60	30
12	$Zn(OTf)_2$	DMF	60	18
13	$Cu(OTf)_2$	DMF	60	22
14[b]		DMF	60	73
15[b]		DMF	45	49
16[b]		DMF	75	83
17[b]		DMF	90	82

[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**. [b] In the presence of 2.5 equiv of 1-bromo-4-(cyclopropylidenemethyl)benzene **2a**.

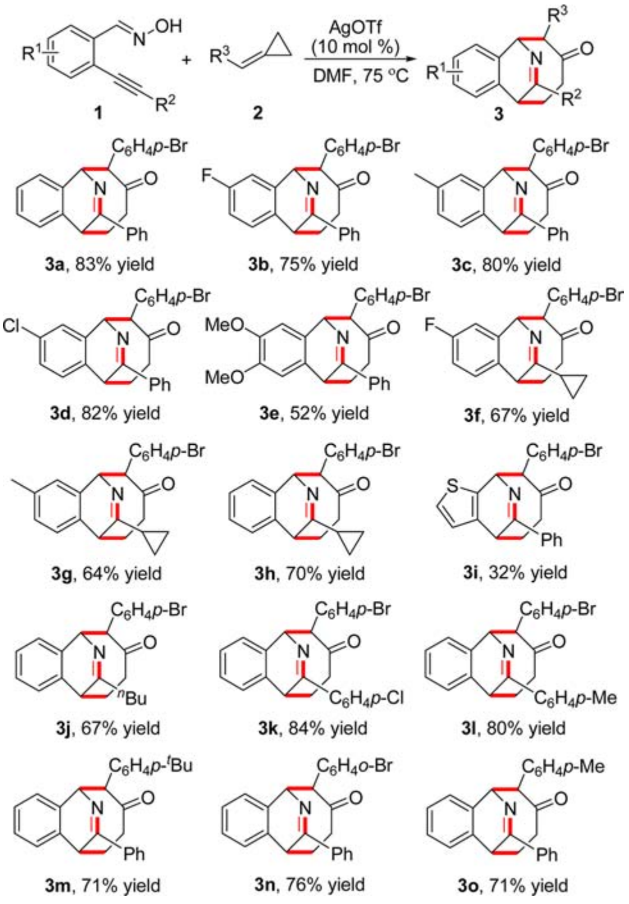
---

(6) For selected reviews on MCPs, see: (a) Nakamuran, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (d) Shao, L.-X.; Shi, M. *Curr. Org. Chem.* **2007**, *11*, 1135. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

(7) For examples of Lewis acid catalyzed ring-opening reactions of MCPs, see: (a) Hu, B.; Xing, S. Y.; Wang, Z. W. *Org. Lett.* **2008**, *10*, 5481. (b) Huang, X.; Yang, Y. *Org. Lett.* **2007**, *9*, 1667. (c) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (d) Lautens, M.; Han, W.; Liu, J. H. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (e) Scott, M. E.; Bethuel, Y.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 1482. (f) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521. (g) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (h) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (i) Yu, L.; Meng, J. D.; Xia, L.; Guo, R. *J. Org. Chem.* **2009**, *74*, 5087. (j) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (k) Scott, M. E.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8154. (l) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591. (m) Diev, V. V.; Tung, T. Q.; Molchanov, A. P. *Eur. J. Org. Chem.* **2009**, 525. (n) Hu, B.; Zhu, J. L.; Xing, S. Y.; Fang, J.; Du, D.; Wang, Z. W. *Chem.—Eur. J.* **2009**, *15*, 324. (o) Bagutski, V.; de Meijere, A. *Adv. Synth. Catal.* **2007**, *349*, 1247. (p) Hang, X.-C.; Chen, Q.-Y.; Xiao, J.-C. *Eur. J. Org. Chem.* **2008**, 1101.

(8) (a) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175. (b) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (c) Yao, L.-F.; Shi, M. *Eur. J. Org. Chem.* **2009**, 4971. (d) Jiang, M.; Liu, L.-P.; Shi, M.; Li, Y.-X. *Org. Lett.* **2010**, *12*, 116. (e) Jiang, M.; Shi, M. *Org. Lett.* **2010**, *12*, 2606. (f) Huang, X.; Miao, M.-Z. *J. Org. Chem.* **2008**, *73*, 6884. (g) Tang, X.-Y.; Wei, Y.; Shi, M. *Org. Lett.* **2010**, *12*, 5120. (h) Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.-P.; Renaud, J. L. *Adv. Synth. Catal.* **2008**, *350*, 40. (i) Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. *J. Org. Chem.* **2009**, *74*, 8963. (j) Ma, S.; Lu, L. *J. Org. Chem.* **2005**, *70*, 7629.

Scheme 2. Scope Investigation for the Silver Triflate-Catalyzed Tandem Reaction of 2-Alkynylbenzaldoxime **1** with Alkylidenecyclopropane **2**[a]

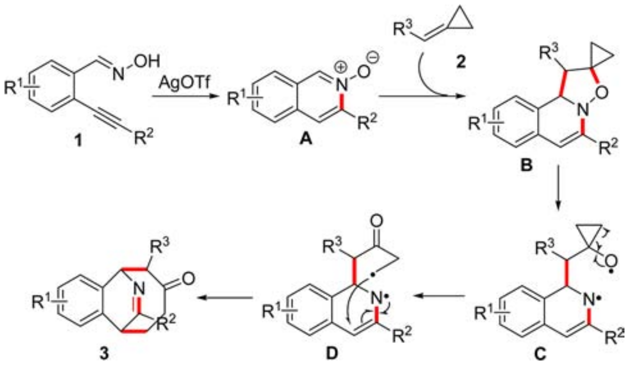


[a] Isolated yield based on 2-alkynylbenzaldoxime **1**.

identification of DMF as the best choice for the transformation (Table 1, entry 6). The addition of Lewis acids, usually found to be effective as additives for activation of alkylidenecyclopropanes, displayed inferior results in this reaction (Table 1, entries 9–13). A control experiment without the addition of silver triflate resulted in no reaction. The efficiency was retarded when the amount of silver triflate was reduced to 5 mol % (data not shown in Table 1). The yield was improved (73% yield) when 2.5 equiv of 1-bromo-4-(cyclopropylidenemethyl)-benzene **2a** was employed in the reaction (Table 1, entry 14). Further reaction optimization revealed that the conversion conducted at 75 °C in DMF afforded optimal result (83% yield, Table 1, entry 16).

The generality of this silver triflate-catalyzed tandem reaction of 2-alkynylbenzaldoximes **1** with alkylidenecyclopropanes **2** was then explored under the optimized conditions (10 mol % of AgOTf, DMF, 75 °C). The results are summarized in Scheme 2. This silver-mediated benzo-7-azabicyclo[4.2.2]dec-7-en-4-one formation was found to be workable with 2-alkynylbenzaldoximes **1** bearing electron-withdrawing and -donating substituents on the aromatic backbone. Methyl, methoxy, fluoro, and chloro functionalities were all tolerated, and the corresponding benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones **3** were obtained in moderate to good yields. For instance, 5-chloro-2-(2-phenylethynyl)benzaldehyde oxime reacted with 1-bromo-4-(cyclopropylidenemethyl)benzene leading to the product **3d** in 82% yield. Notably, the thiophenyl-incorporated oxime was a good partner as well in this tandem reaction, although the final outcome is not as good as expected (**3i**, 32% yield). Furthermore, the nature of the substituents at the R^2 position of 2-alkynylbenzaldoximes **1** could not affect the conversion. Reactions of 2-alkynylbenzaldoximes **1** with a cyclopropyl or *n*-butyl group attached to the triple bond also worked well to afford the desired products. Additionally, various alkylidenecyclopropanes **2** were examined in the reaction of 2-alkynylbenzaldoxime **1a**, which provided the expected products in good yields.

Scheme 3. Possible Mechanism for the Silver Triflate-Catalyzed Tandem Reaction of 2-Alkynylbenzaldoxime **1** with Alkylidenecyclopropane **2**



A possible mechanism for the formation of this unexpected benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones **3** was proposed in Scheme 3. Based on the previous reports,[4,5] we believed that isoquinoline-*N*-oxide **A** would be produced first via a silver triflate-catalyzed 6-*endo* cyclization of 2-alkynylbenzaldoxime **1**. Subsequently, [3 + 2] cycloaddition reaction of isoquinoline *N*-oxide **A** with alkylidenecyclopropanes **2** would occur, leading to a fused 1,2-dihydroisoquinoline compound **B**. The N–O bond of intermediate **B** would undergo a cleavage to produce radical **C**,[4a,9] which then would go through ring-opening of cyclopropane and intramolecular radical addition to provide the benzo-7-azabicyclo[4.2.2]dec-7-en-4-one **3**.

In summary, we have described an efficient and novel silver(I)-catalyzed tandem reaction of 2-alkynylbenzaldoxime with alkylidenecyclopropane, which gives rise to benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones in moderate to good yields. Diversity and complexity could be easily incorporated during the transformation, which proceeded through 6-*endo* cyclization, [3 + 2] cycloaddition, and

---

(9) (a) Coskun, N.; Tuncman, S. *Tetrahedron* **2006**, *62*, 1345. (b) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921.

intramolecular rearrangement. Further exploration using 2-alkynylbenzaldoximes for the construction of other *N*-heterocycles is in progress.

Acknowledgment. Financial support from National Natural Science Foundation of China (No. 21032007 and 21172038) is gratefully acknowledged.

Supporting Information Available. Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, and X-ray data for compound **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.