ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 4188

Received 26th January 2014, Accepted 28th February 2014

DOI: 10.1039/c4cc00691g

www.rsc.org/chemcomm

A silver(I) triflate-catalyzed reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)arene with 2-alkynylbenzaldoxime†

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A silver(I)-catalyzed reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)-arene with 2-alkynylbenzaldoxime leads to 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines in good to excellent yields. A radical process is believed to be involved in the transformation.

As we know, chemists are focusing on the pursuit of efficient and facile routes for the rapid generation of small molecules with molecular complexity and diversity, especially in the field of chemical biology and in the drug discovery process.[1] Among the strategies utilized, the tandem reaction has demonstrated its efficiency.[2] In the past few years, the attractiveness of tandem reactions has also prompted us to explore new pathways for the construction of natural product-like compounds.[3] For example, fused indolines could be synthesized *via* a tandem reaction of 2-ethynylaryl methylenecyclopropane with sulfonyl azide catalyzed by copper(I) iodide.[3a] From this transformation, we recognized that 2-alkynylaryl methylenecyclopropane[4] was a useful building block for the formation of polycyclic compounds. The two active sites (Fig. 1, alkynyl moiety and methylenecyclopropane) would be helpful in the rational design of complex small molecules. So far, the transformation of methylenecyclopropanes has been well documented due to their diverse reactivity driven by the relief of ring strain.[5] A variety of carbocycles and heterocycles could be formed *via* the ring-opening reactions of methylenecyclopropanes.[6] Encouraged by these results, we envisioned that 2-alkynylaryl methylenecyclopropane (Fig. 1) could be used in our approach for the construction of natural product-like compounds.

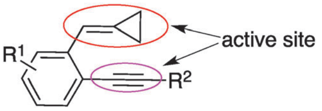

Fig. 1 2-Alkynylaryl methylenecyclopropane.

In the meantime, 2-alkynylbenzaldoxime has continuously drawn our attention since it can easily undergo 6-*endo* cyclization in the presence of an electrophile or a catalytic amount of a Lewis acid.[7] The following [3+2] cycloaddition or nucleophilic addition could afford various N-heterocycles with molecular complexity starting from 2-alkynylbenzaldoximes.[8] Combined with the reactivity of 2-alkynylaryl methylenecyclopropane, we conceived that 2-alkynylbenzaldoxime could be involved in the reaction of 2-alkynylaryl methylenecyclopropane under suitable conditions for the assembly of complex small molecules. In the presence of a catalytic amount of silver triflate, 2-alkynylbenzaldoxime **1** would undergo 6-*endo* cyclization to produce isoquinoline *N*-oxide. We anticipated that the following [3+2] cycloaddition of 2-alkynylaryl methylenecyclopropane would occur to generate an isoquinoline-based compound.

The initial studies are summarized in Table 1. A silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime **1a** with 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a** was selected as the model. In the beginning, the reaction was performed at 75 °C in DMF. To our delight, a product was obtained and isolated in 31% yield (Table 1, entry 1). The structural illustration using X-ray diffraction analysis (Fig. 2) revealed that the compound was 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinoline **3a**. Upon this transformation, the core structures of isoquinoline and 1,3-dihydroisobenzofuran were incorporated into one molecule with the formation of four new bonds. Therefore, we proposed a possible mechanism, which is shown in Scheme 1. As mentioned above, 2-alkynylbenzaldoxime **1** would undergo 6-*endo* cyclization to produce isoquinoline *N*-oxide **A** in the presence of a catalytic amount of silver triflate. Then 2-alkynylaryl methylenecyclopropane **2** would react with isoquinoline *N*-oxide **A** through [3+2] cycloaddition to afford compound **B**. The cleavage of the N–O bond would generate the radical species **C**,

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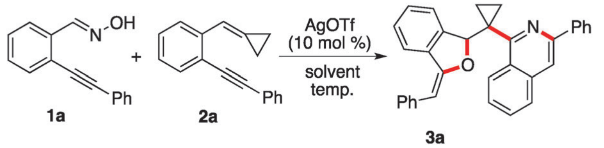
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**. CCDC 973694. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00691g

Table 1 Initial studies for the reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a** with 2-alkynylbenzaldoxime **1a**



Entry	T (°C)	Solvent	Yield[a] (%)
1	75	DMF	31
2[b]	75	DMF	Trace
3	75	DMA	44
4	75	DMSO	53
5	75	THF	Trace
6	75	MeCN	24
7	75	Toluene	Trace
8	75	CF_3CH_2OH	NR
9	75	$(CF_3)_2CHOH$	NR
10	25	DMSO	NR
11	50	DMSO	Trace
12	90	DMSO	54
13	100	DMSO	67
14	110	DMSO	60
15	120	DMSO	58
16[c]	100	DMSO	76
17[d]	100	DMSO	69
18[e]	100	DMSO	NR

[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**. [b] In the presence of 2,2,6,6-tetramethylpiperidin-1-olate (TEMPO). [c] In the presence of 1.5 equivalent of 2-alkynylbenzaldoxime **1a**. [d] In the presence of 1.5 equivalent of 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a**. [e] Without the addition of AgOTf.

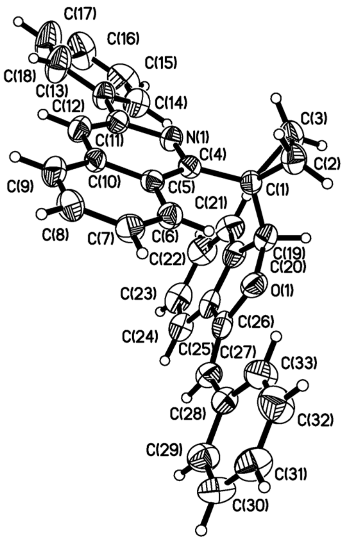
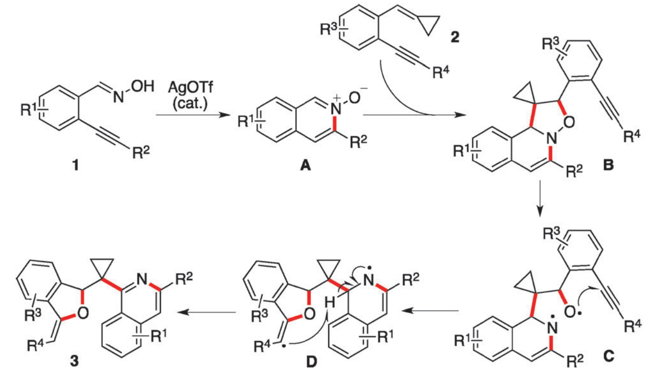


Fig. 2 X-ray ORTEP illustration of compound **3a** (30% probability ellipsoids).

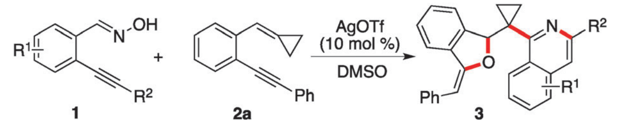


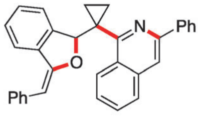
Scheme 1 A possible mechanism for the silver-catalyzed reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)arene with 2-alkynylbenzaldoxime.

which would then proceed through intramolecular addition of triple bond to furnish the intermediate **D**. The subsequent transformation would produce the corresponding 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines **3**.

With this interesting result in hand, we further investigated its optimized conditions. To verify the radical process, 2,2,6,6-tetramethylpiperidin-1-olate (TEMPO) was added to the reaction. As expected, the reaction failed to give rise to the desired product (Table 1, entry 2). When the reaction occurred in other solvents, it was found that the transformation worked efficiently in DMSO leading to the corresponding product **3a** in 53% yield (Table 1, entry 4). The result could be improved when the reaction temperature was changed (Table 1, entries 10–15). Compound **3a** could be obtained in 67% yield when the reaction was performed at 100 °C (Table 1, entry 13). The yield could be increased to 76%

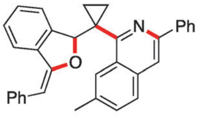
Table 2 Scope investigation for the reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a** with various 2-alkynylbenzaldoximes **1**[a]



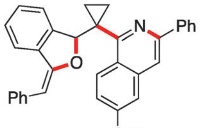


3a, 76% yield

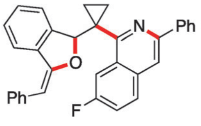
3b, 78% yield



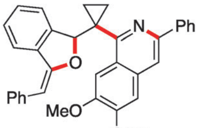
3c, 93% yield



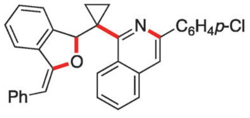
3d, 86% yield



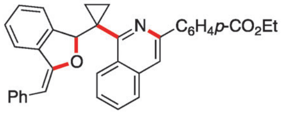
3e, 88% yield



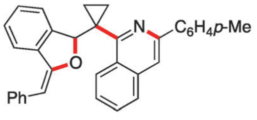
3f, 70% yield



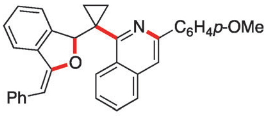
3g, 80% yield



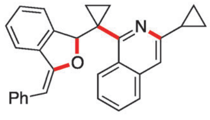
3h, 83% yield



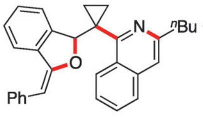
3i, 85% yield



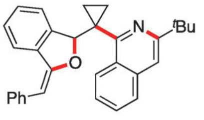
3j, 80% yield



3k, 77% yield



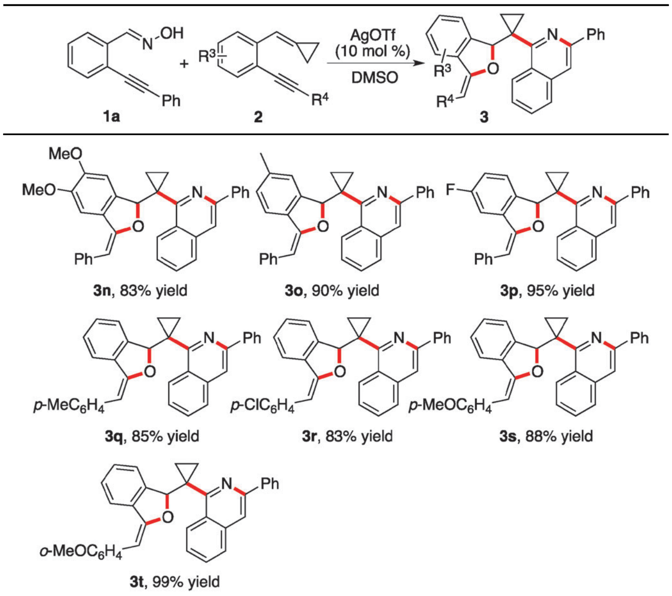
3l, 75% yield



3m, 82% yield

[a] Isolated yield based on 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a**.

Table 3 Scope investigation for the reaction of 2-alkynylbenzaldoxime **1a** with various 1-((cyclopropylidenemethyl)-2-alkynyl)arenes **2**[a]



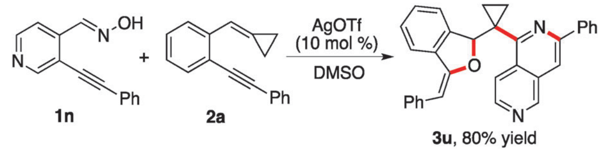
[a] Isolated yield based on 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2**.

when the amount of 2-alkynylbenzaldoxime **1a** added was 1.5 equivalents (Table 1, entry 16). The presence of silver triflate was essential for the successful conversion (Table 1, entry 18).

With the optimal conditions established, we embarked upon exploring the substrate scope of this reaction. The results are summarized in Tables 2 and 3. Firstly, reactions of 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a** with various 2-alkynylbenzaldoximes **1** were evaluated (Table 2). All reactions worked well to furnish the expected products **3** in good to excellent yields. Different functional groups including fluoro, chloro, methyl, methoxy, and ester were all compatible under the standard conditions. For example, the ester-substituted product **3h** was afforded in 83% yield. For the substitutions attached onto the triple bond of 2-alkynylbenzaldoximes **1**, not only aryl groups but also alkyl groups (*n*-butyl, *t*-butyl, and cyclopropyl) were tolerated during the reaction process.

Reactions of other 2-alkynylaryl methylenecyclopropanes with 2-alkynylbenzaldoxime **1a** were then examined (Table 3). All reactions proceeded smoothly. Again, different substitutions on the 2-alkynylaryl methylenecyclopropanes were compatible during the transformation. Generally, the yields of all products were excellent. For instance, 1-((1,3-dihydroisobenzofuran-1-yl)-methyl)isoquinoline **3t** was obtained in a quantitative yield.

We also explored the reaction of pyridinyl-substituted oxime **1n** with 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a** under the standard conditions (Scheme 2). As expected, the reaction worked well to generate the corresponding product **3u** in 80% yield.



Scheme 2 Reaction of substrate **1n** with 1-((cyclopropylidenemethyl)-2-alkynyl)arene **2a**.

In summary, we have described a facile route to prepare 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines *via* a silver(I)-catalyzed reaction of 1-((cyclopropylidenemethyl)-2-alkynyl)arene with 2-alkynylbenzaldoxime. The reaction proceeds through a radical process to provide the corresponding products in good to excellent yields. Currently, the library construction of 1-((1,3-dihydroisobenzofuran-1-yl)methyl)isoquinolines is ongoing in our laboratory.

Financial support from the National Natural Science Foundation of China (No. 21032007, 21372046) is gratefully acknowledged.

Notes and references

1 (*a*) D. P. Walsh and Y.-T. Chang, *Chem. Rev.*, 2006, **106**, 2476; (*b*) P. Arya, D. T. H. Chou and M.-G. Baek, *Angew. Chem., Int. Ed.*, 2001, **40**, 339; (*c*) S. L. Schreiber, *Science*, 2000, **287**, 1964; (*d*) M. D. Burke and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 46; (*e*) S. L. Schreiber, *Nature*, 2009, **457**, 153; (*f*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74; (*g*) C. Cordier, D. Morton, S. Murrison, A. Nelson and C. O'Leary-Steele, *Nat. Prod. Rep.*, 2008, **25**, 719; (*h*) W. R. J. D. Galloway, A. I. Llobet and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80; (*i*) S. Oh and S. B. Park, *Chem. Commun.*, 2011, **47**, 12754.

2 For reviews, see: (*a*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890; (*b*) E. Negishi, C. Coperet, S. Ma, S. Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365; (*c*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*d*) R. Grigg and V. Sridharan, *J. Organomet. Chem.*, 1999, **576**, 65; (*e*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217; (*f*) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (*g*) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, 551; (*h*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*i*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*j*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006; (*k*) L. F. Tietze, M. A. Düfert, T. Hungerland, K. Oum and T. Lenzer, *Chem.–Eur. J.*, 2011, **17**, 8452; (*l*) J. Panteleev, L. Zhang and M. Lautens, *Angew. Chem., Int. Ed.*, 2011, **50**, 9089.

3 For recent selected examples: (*a*) S. Li, Y. Luo and J. Wu, *Org. Lett.*, 2011, **13**, 3190; (*b*) Q. Xiao, Y. Luo, Q. Ding and J. Wu, *Adv. Synth. Catal.*, 2013, **355**, 2321; (*c*) Y. Luo and J. Wu, *Org. Lett.*, 2012, **14**, 1592; (*d*) G. Qiu, G. Liu, S. Pu and J. Wu, *Chem. Commun.*, 2012, **48**, 2903; (*e*) G. Qiu, Y. He and J. Wu, *Chem. Commun.*, 2012, **48**, 3836.

4 B. Yao, Y. Li, Z. Liang and Y. Zhang, *Org. Lett.*, 2011, **13**, 640 and references cited therein.

5 For selected reviews on MCPs, see: (*a*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (*b*) A. de Meijere, S. I. Kozhushkov and A. F. Khlebnikov, *Top. Curr. Chem.*, 2000, **207**, 89; (*c*) P. Binger, P. Wedemann, S. I. Kozhushkov and A. de Meijere, *Eur. J. Org. Chem.*, 1998, 113; (*d*) A. de Meijere and S. I. Kozhushkov, *Eur. J. Org. Chem.*, 2000, 3809; (*e*) I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111; (*f*) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213; (*g*) E. Nakamura and S. Yamago, *Acc. Chem. Res.*, 2002, **35**, 867; (*h*) L.-X. Shao and M. Shi, *Curr. Org. Chem.*, 2007, **11**, 1135; (*i*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117; (*j*) S. Yamago and E. Nakamura, *Org. React.*, 2002, **61**, 1; (*k*) A. de Meijere, S. I. Kozhushkov, T. Spath, M. von Seebach, S. Lohr, H. Nuske, T. Pohomann, M. Es-Sayed and S. Brase, *Pure Appl. Chem.*, 2000, **72**, 1745; (*l*) M. Shi, J.-M. Lu, Y. Wei and L.-X. Shao, *Acc. Chem. Res.*, 2012, **45**, 641.

6 For selected examples: (*a*) B. Hu, S. Y. Xing and Z. W. Wang, *Org. Lett.*, 2008, **10**, 5481; (*b*) M. E. Scott, Y. Bethuel and M. Lautens, *J. Am. Chem. Soc.*, 2007, **129**, 1482; (*c*) L. Yu, J. D. Meng, L. Xia and R. Guo, *J. Org. Chem.*, 2009, **74**, 5087; (*d*) L. Lu, G. Chen and S. Ma, *Org. Lett.*, 2006, **8**, 835; (*e*) S. Ma and J. Zhang, *Angew. Chem., Int. Ed.*, 2003, **42**, 183; (*f*) S. Ma, L. Lu and J. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 9645; (*g*) E. Smolensky, M. Kapon and M. S. Eisen, *Organometallics*, 2007, **26**, 4510; (*h*) I. Nakamura, B. H. Oh, S. Saito and Y. Yamamoto,

Angew. Chem., Int. Ed., 2001, **40**, 1298; (*i*) T. Kurahashi and A. de Meijere, *Angew. Chem., Int. Ed.*, 2005, **44**, 7881; (*j*) X. Huang and H. Zhou, *Org. Lett.*, 2002, **4**, 4419; (*k*) B. Hu, J. L. Zhu, S. Y. Xing, J. Fang, D. Du and Z. W. Wang, *Chem.–Eur. J.*, 2009, **15**, 324; (*l*) M. Jiang, L.-P. Liu, M. Shi and Y.-X. Li, *Org. Lett.*, 2010, **12**, 116; (*m*) M. Jiang and M. Shi, *Org. Lett.*, 2010, **12**, 2606.

7 (*a*) Z. Huo, H. Tomeba and Y. Yamamoto, *Tetrahedron Lett.*, 2008, **49**, 5531; (*b*) H.-S. Yeom, J.-E. Lee and S. Shin, *Angew. Chem., Int. Ed.*, 2008, **47**, 7040; (*c*) H.-S. Yeom, S. Kim and S. Shin, *Synlett*, 2008, 924; (*d*) Q. Ding and J. Wu, *Adv. Synth. Catal.*, 2008, **350**, 1850.

8 For selected examples: (*a*) H. Ren, Y. Luo, S. Ye and J. Wu, *Org. Lett.*, 2011, **13**, 2552; (*b*) S. Ye, H. Wang and J. Wu, *ACS Comb. Sci.*, 2011, **13**, 120; (*c*) Q. Xiao, S. Ye and J. Wu, *Org. Lett.*, 2012, **14**, 3430; (*d*) S. Ye, K. Gao and J. Wu, *Adv. Synth. Catal.*, 2010, **352**, 1746; (*e*) Z. Chen, X. Yu, M. Su, X. Yang and J. Wu, *Adv. Synth. Catal.*, 2009, **351**, 2702; (*f*) Q. Ding, Z. Wang and J. Wu, *J. Org. Chem.*, 2009, **74**, 921.