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# Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime with Aryne

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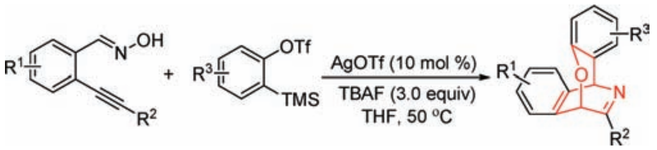
## ABSTRACT



**A novel and unexpected reaction of 2-alkynylbenzaldoxime with aryne in the presence of silver triflate (10 mol %) under mild conditions is discovered. This reaction proceeds through 6-*endo*-cyclization, [3 + 2] cycloaddition, and rearrangement, leading to 2-oxa-6-aza-bicyclo[3.2.2]nona-6,8-diene derivatives in moderate to good yields.**

Currently, generation of *N*-heterocycles with complexity and diversity is in great demand in the process of drug discovery.[1] Thus, continuous efforts have been devoted to the preparation of biologically and pharmaceutically important nitrogen-containing heterocyclic compounds.[2] So far, a variety of efficient and reliable approaches have appeared in this area. Among the strategies, the tandem reaction is regarded as one of the most attactive methods for the formation of *N*-heterocyclic compounds.[3] In the past few years, we have been involved in the preparation of natural product-like compounds via tandem reactions.[4,5] In our previous reports, 2-alkynylbenzaldoxime was demonstrated as a versatile building block for the synthesis of *N*-heterocycles.[5] In the meantime, aryne as a highly reactive species which could be readily prepared *in situ* from 2-(trimethylsilyl)aryl triflate, has been extensively utilized for the generation of a wide range of heterocycles.[6] For instance, arynes have served as dipolarophiles with excellent reactivity in various 1,3-dipolar cycloaddition reactions.[7] The reactions usually proceed under mild conditions, affording a variety of heterocycles in good yields. Since isoquinoline-*N*-oxide can be easily formed from 2-alkynylbenzaldoxime via 6-*endo* cyclization catalyzed

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(1) (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.

(2) 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.

(3) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(4) For recent selected examples, see: (a) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (b) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (c) Luo, Y.; Pan, X.; Wu, J. *Org. Lett.* **2011**, *13*, 1150. (d) Qiu, G.; Ding, Q.; Gao, K.; Peng, Y.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 13. (e) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (f) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (g) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 5238. (h) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950. (i) Yu, X.; Ye, S.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 2050.

(5) (a) Qiu, G.; Ding, Q.; Ren, H.; Peng, Y.; Wu, J. *Org. Lett.* **2010**, *12*, 3975. (b) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746. (c) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem.* **2010**, 6436. (d) Ding, Q.; Wang, Z.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 198. (e) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850. (f) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702. (g) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921. (h) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120.

(6) For reviews on the use of arynes in organic synthesis, see: (a) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 483. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Chen, Y.; Larock, R. C. Arylation Reactions Involving the Formation of Arynes. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: New York, 2009; Chapter 12, p 401. (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.

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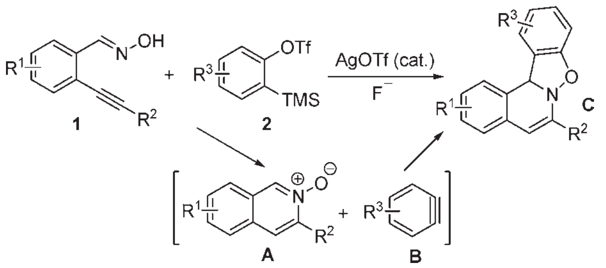
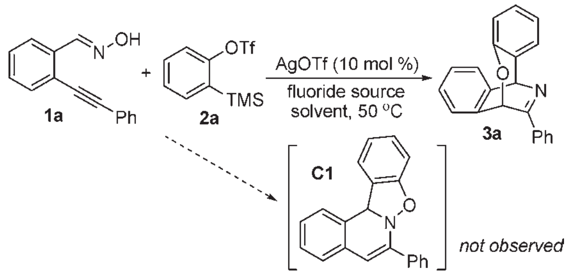
by Lewis acids or promoted by electrophiles,[5,8] we conceived that aryne would be a suitable partner in the reaction of 2-alkynylbenzaldoxime **1**. As illustrated in Scheme 1, in the presence of a silver(I) catalyst and fluoride source, isoquinoline-*N*-oxide **A** would react with aryne **B** via a [3 + 2] cycloaddition, leading to the corresponding fused 1,2-dihydroisoquinoline compound **C**. It is well-known that 1,2-dihydroisoquinoline as a privileged scaffold is found in many biologically active natural products and pharmaceuticals.[9] Prompted by the aryne chemistry[6,7] and the previous reports related to 2-alkynylbenzaldoximes,[5,8] we started to explore the feasibility of the hypothesis shown in Scheme 1.

**Scheme 1.** Proposed Synthetic Route for Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime with Benzyne



The reaction of 2-alkynylbenzaldoxime **1a** with *o*-(trimethylsilyl)phenyl triflate **2a** was initially optimized (Table 1). Since silver triflate has been demonstrated as the most efficient catalyst for isoquinoline-*N*-oxide formation via 6-*endo* cyclization of 2-alkynylbenzaldoxime, the reaction occurred in the presence of 10 mol % of silver triflate and potassium fluoride in acetonitrile at 50 °C (Table 1, entry 1). However, only a trace amount of product was detected. A similar result was observed when the fluoride salt was changed to LiF or NaF (Table 1, entries 2 and 3).

**Table 1.** Initial Studies for Silver Triflate-Catalyzed Reaction of 2-Alkynylbenzaldoxime with Benzyne



| entry | fluoride source | solvent | yield (%)[a] |
|---|---|---|---|
| 1 | KF | MeCN | trace |
| 2 | NaF | MeCN | trace |
| 3 | LiF | MeCN | trace |
| 4 | CsF | MeCN | 30 |
| 5 | AgF | MeCN | complex |
| 6 | $ZnF_2$ | MeCN | trace |
| 7 | $MgF_2$ | MeCN | trace |
| 8 | TBAF | MeCN | 37 |
| 9 | TBAF | toluene | 47 |
| 10[b] | TBAF | toluene | 48 |
| 11 | TBAF | THF | 56 |
| 12[c] | TBAF | THF | 51 |
| 13 | TBAF | DCE | 51 |
| 14 | TBAF | DMF | 17 |
| 15 | TBAF | DMSO | 17 |

[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**. [b] The reaction was performed at 70 °C. [c] The reaction occurred at 30 °C.

To our delight, a product was isolated with 30% yield when the reaction took place in the presence of cesium fluoride (Table 1, entry 4). However, the structure of this product was confirmed as compound **3a** instead of the desired one (**C1**) after structural identification. This interesting result encouraged us to further investigate since there are few reports for the synthesis of 2-oxa-6-azabicyclo[3.2.2]nona-6,8-diene derivatives.[10] The reaction was complex when silver(I) fluoride was used as a replacement (Table 1, entry 5). Utilization of zinc(II) fluoride or magnesium(II) fluoride could not improve the final outcome (Table 1, entries 6 and 7). Gratifyingly, the yield was increased to 37% when TBAF was employed in the reaction (Table 1, entry 8), which indicated that the solubility of the fluoride source might improve the outcome of this tandem reaction. The result could be further improved when the reaction was performed in toluene (47% yield, Table 1, entry 9). A similar outcome was displayed when the reaction occurred at an elevated temperature (70 °C, Table 1, entry 10). Further screening of solvents indicated that the reaction worked most efficiently in THF, giving rise to the corresponding product **3a** in 56% yield (Table 1, entry 11).

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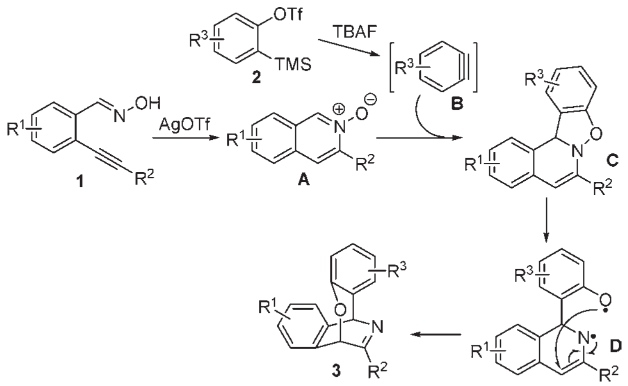
(7) For recent selected examples in aryne 1,3-dipolar cycloadditions, see: (a) Spiteri, C.; Keeling, S.; Moses., J. E. *Org. Lett.* **2010**, *12*, 3368. (b) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234. (c) Kivrak, A.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 7381. (d) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180. (e) Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272. (f) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323. (g) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (h) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (i) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587. (j) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007. (k) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525.

(8) (a) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (b) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924. (c) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.

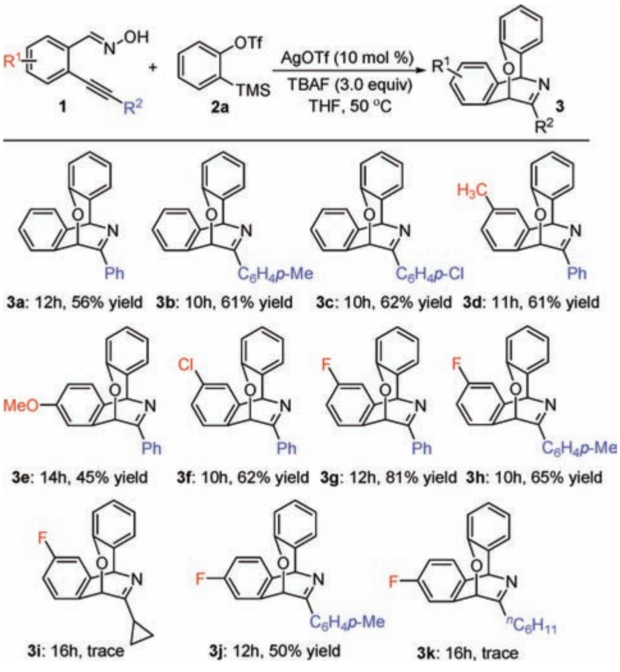
(9) For selected examples, see: (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Australia, 1998; Vol. 1. (b) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954. (c) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780. (d) Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu, K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275. (e) Marchand, C.; Antony, S.; Kohn, K. W.; Cushman, M.; Ioanoviciu, A.; Staker, B. L.; Burgin, A. B.; Stewart, L.; Pommier, Y. *Mol. Cancer Ther.* **2006**, *5*, 287.

(10) (a) Krow, G. R.; Johnson, C. A.; Guare, J. P.; Kubrak, D.; Henz, K. J.; Shaw, D. A.; Szczepanski, S. W.; Carey, J. T. *J. Org. Chem.* **1982**, *47*, 5239. (b) Natsume, M.; Ogawa, M. *Heterocycles* **1980**, *14*, 169.

**Scheme 2.** Possible Mechanism for Silver Triflate-Catalyzed Reaction of 2-Alkynylbenzaldoxime with Benzyne



**Scheme 3.** Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime **1** with *o*-(Trimethylsilyl)phenyl Triflate **2a**[a]



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

The possible mechanism for the formation of this unexpected product **3** with a 2-oxa-6-aza-bicyclo[3.2.2]nona-6,8-diene core structure was described in Scheme 2. As mentioned above, 2-alkynylbenzaldoxime **1** would afford isoquinoline-*N*-oxide **A** in the presence of silver triflate as a catalyst. In the meantime, aryne **B** would be produced *in situ* when *o*-(trimethylsilyl)phenyl triflate **2** was treated with TBAF. Thus, isoquinoline-*N*-oxide **A** reacted with aryne **B** via a [3 + 2] cycloaddition reaction, leading to a fused 1,2-dihydroisoquinoline compound **C**. The N−O bond of intermediate **C** was highly unstable,[11] which would go through cleavage to afford radical **D**. Subsequently, an intramolecular radical addition occurred to furnish the unexpected product **3**.

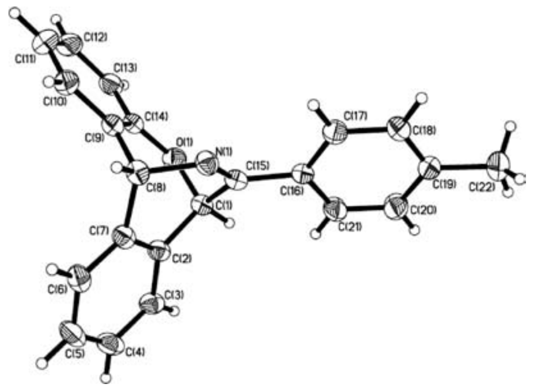
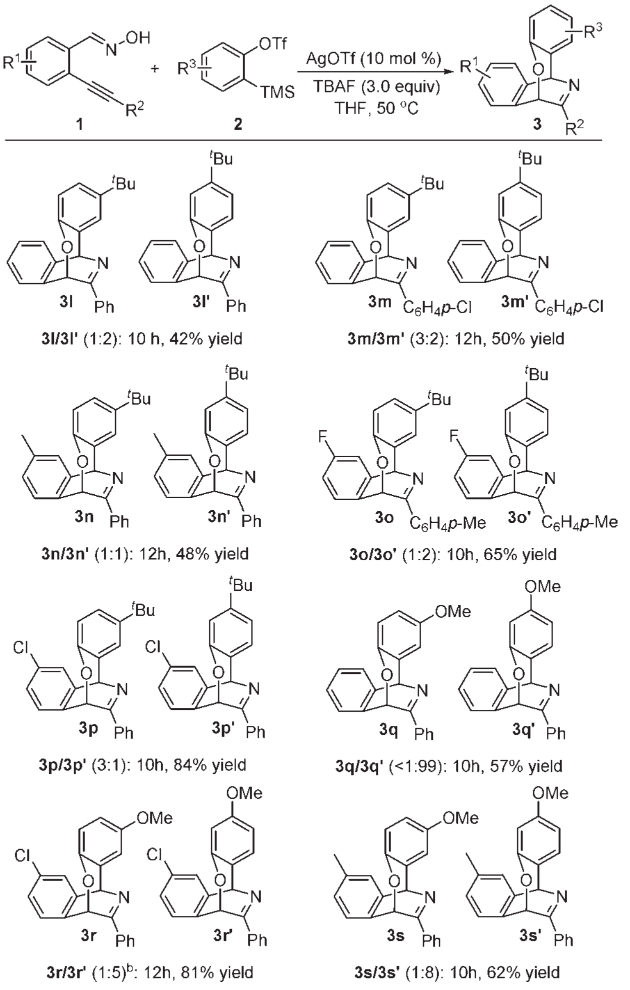


**Figure 1.** X-ray ORTEP illustration of compound **3b**.

**Scheme 4.** Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime **1** with *o*-(Trimethylsilyl)aryl Triflate **2**[a]



[a] Isolated yield based on 2-alkynylbenzaldoxime **1**. The ratio was determined by $^1$H NMR. [b] It is a mixture, which could not be separable.

Next, we examined the scope of this tandem reaction of 2-alkynylbenzaldoxime **1** with aryne under the optimized conditions (10 mol % of AgOTf, 3.0 equiv of TBAF, THF, 50 °C). The results are shown in Schemes 3 and 4. Scheme 3 summarized the silver triflate catalyzed reaction of 2-alkynylbenzaldoxime **1** with *o*-(trimethylsilyl)phenyl triflate **2a**. It seemed that the $R^2$ group attached to the triple bond was crucial for a successful transformation. Only aryl groups were tolerated in the reaction. The structure of compound **3b** (Figure 1) was confirmed by X-ray diffraction analysis meanwhile (see the Supporting Information). A trace amount of product was formed when 2-alkynylbenzaldoxime **1** with an alkyl group (such as cyclopropyl group and *n*-hexyl group) attached to the triple bond was employed in the reaction. Reactions of various 2-alkynylbenzaldoximes **1** with electron-donating and -withdrawing groups in the aromatic ring were explored as well. Methyl-, methoxy-, chloro-, and fluoro-substituted 2-alkynylbenzaldoximes **1** were all good partners for the reaction of *o*-(trimethylsilyl)phenyl triflate **2a**.

In a second set of experiments, the scope of the process with respect to substituted *o*-(trimethylsilyl)aryl triflate **2** was investigated (Scheme 4). For most cases, a mixture of product **3** was generated under the standard experimental conditions. Among the products obtained, the mixture of compounds **3r**/**3r′** could not be separable. Only one isomer **3q′** was obtained (57% yield) when 4-methoxy-2-(trimethylsilyl)phenyl triflate was employed in the reaction of 2-alkynylbenzaldoxime **1a**. This high regioselectivity indicated that the electron effect of the methoxy group played an important role during the process of the [3 + 2] cycloaddition reaction of isoquinoline-*N*-oxide **A** with aryne **B** (Scheme 2).

In summary, we have described a novel reaction of 2-alkynylbenzaldoxime **1** with *o*-(trimethylsilyl)aryl triflate **2** catalyzed by silver triflate. The reaction works efficiently to produce the unexpected 2-oxa-6-aza-bicyclo[3.2.2]nona-6,8-diene derivatives. A possible reaction pathway is proposed, which proceeds through a tandem 6-*endo*-cyclization, [3 + 2] cycloaddition, and rearrangement.

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

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