Organic LETTERS

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Stereoselective Construction of Bridged *trans*-aza-Bicyclo[7/6,3/2,1]alkenyl Imines through Ring Expansion aza-Cope Rearrangement

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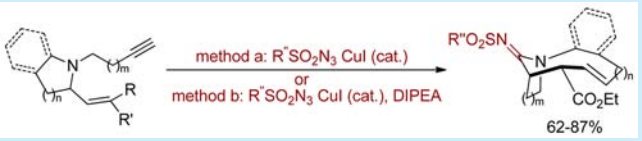
Supporting Information

ABSTRACT: A highly stereoselective method for efficient synthesis of unprecedented bridged bicyclo[7/6,3/2,1]alkenyl amidines is described using cyclic *N*-allyl-aminoalkyne as a substrate. A ketenimine formation/cyclization/aza-Cope rearrangement cascade proceeds either with or without the aid of external DIPEA depending on substrate basicity. Fused bicycloamidines are also obtained via the same protocol using different *N*-allyl cyclic aminoalkynes.



Amidine (Figure 1, **II**) is a unique functional group present in numerous bioactive molecules and functional materials.[1] In comparison with its *N*-isostere, namely, the amide group (**I**), which is one of the most important motifs in nature,[2] amidine possesses one more trivalent nitrogen atom in the place of amide carbonyl oxygen which endows the amidine moiety with more potential for structural and functional diversification. For example, the amide to amidine group switch in Vancomycin aglycon residue-4 enables effective binding to both unaltered peptidoglycan D-Ala-D-Ala and altered ligand D-Ala-D-Lac because the amidine group can act either as a hydrogen-bond acceptor or as a hydrogen-bond donor.[3] Moreover, cyclic amidines (**III**) with two nitrogen atoms in a single ring lacking amide counterparts have been widely used as strong organic bases (exemplified by 1,8-diazabicyclo[5.4.0]-undec-7-ene, DBU)[4] and ligands for proteins[5] and metals.[6] Here, we would like to report the synthesis of a new class of amidines with an unprecedented bridged bicyclic framework (**IV**).

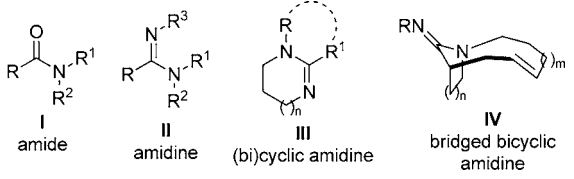
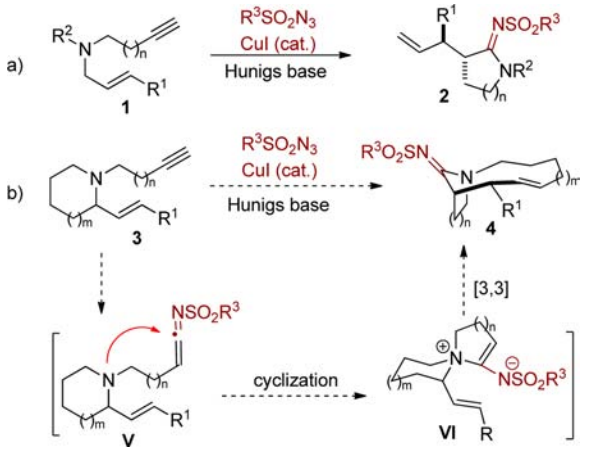


Figure 1. General structures of amide, amidine, (bi)cyclic amidine, and bridged bicyclic amidine.

We have developed an efficient copper catalyzed stereoselective synthesis of functionalized cyclic amidines via a ketenimine formation/cyclization/aza-Cope rearrangement cascade using enynes **1** as substrates (Scheme 1a).[7] Accordingly, it was envisioned that cyclic enyne **3** would react with sulfonyl azide to form ketenimine intermediate **V** utilizing Hünig's base and a catalytic amount of CuI;[7,8] subsequent cyclization would lead to zwitterion **VI**, and finally a [3,3] rearrangement would occur with a concomitant ring expansion to acquire bicyclic amidine **4** (Scheme 1b).[7]

Scheme 1. Synthesis of Monocyclic Amidines (a) and Proposed Ring Expansion for Synthesis of Bridged Bicyclic Amidines (b)



To test this hypothesis, cyclic enyne **3a**, made conveniently from proline, was chosen for initial experiments. When NsN_3 was added to a solution of **3a** in THF in the presence of a catalytic amount of CuI at room temperature, gas bubbling was observed and a clean reaction was obtained in 30 min by TLC. The sole product was isolated in 87% yield and identified as bicyclic amidine **4aNs** (Table 1, entry 1). Replacement of NsN_3 with $TcesN_3$, corresponding ring expansion product **4aTces** was obtained in comparable yield (entry 2). These results corroborated our previously proposed strategy for construction of bicyclic amidines with a bicyclic skeleton from properly designed amino enyne via a ketenimine formation/cyclization/aza-Cope rearrangement cascade. Interestingly, in contrast to

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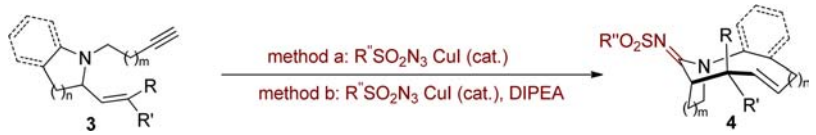
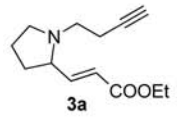
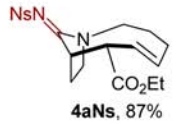
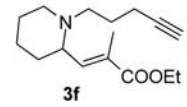
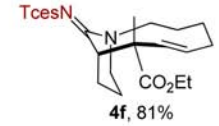
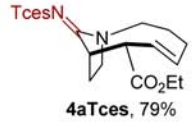
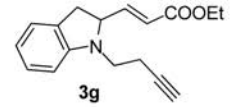
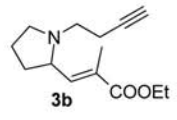
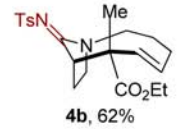
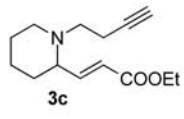
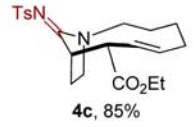
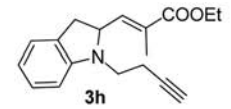
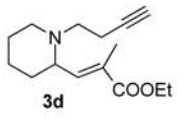
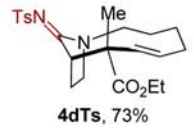
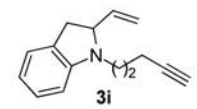
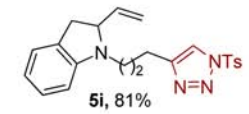
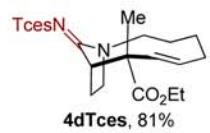
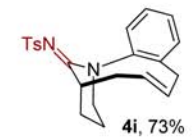
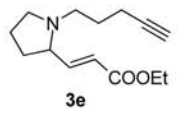
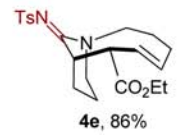
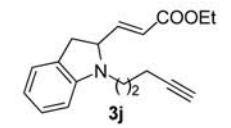
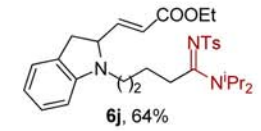
Table 1. Reaction of Cyclic Aminoenynes with Sulfonyl Azides[a]



entry	substrate		product, yield[b]	entry	substrate		product, yield[b]
1	 **3a**	a	 **4aNs**, 87%	8	 **3f**	a	 **4f**, 81%
2	**3a**	a	 **4aTces**, 79%	9	 **3g**	a	 **5g**, 86%
3	 **3b**	a	 **4b**, 62%	10	**3g**	b	 **4g**, 79%
4	 **3c**	a	 **4c**, 85%	11	 **3h**	b	 **4h**, 84%
5	 **3d**	a	 **4dTs**, 73%	12	 **3i**	a	 **5i**, 81%
6	**3d**	a	 **4dTces**, 81%	13	**3i**	b	 **4i**, 73%
7	 **3e**	a	 **4e**, 86%	14	 **3j**	b	 **6j**, 64%

[a]Method **a**: **3** (1.0 equiv), $R'SO_2N_3$ (1.1 equiv), CuI (0.05 equiv), THF (0.1 M), rt. Method **b**: same as method **a** except DIPEA (5 equiv) was added to the reaction. [b]Isolated yields. Ns: 2-nitrobenzenesulfonyl, Tces: trichloroethyoxylsulfonyl, Ts: 4-methylbenzenesulfonyl.

our earlier findings, an external base DIPEA is not required for complete conversion of aminoenyne **3a** to amidine **4a** presumably due to the stronger basicity of cyclic amine compared to noncyclic amines (method a).

Next, more amino enynes were made to explore the substrate scope. Pyrrolidinyl enyne **3b** with trisubstituted alkene reacted smoothly with TsN_3 to give rise to bicycle **4b** with a challenging quaternary all-carbon center (entry 3). When piperidinyl enyne **3c** was submitted to these reaction conditions, correspondingly a one-carbon larger bicyclo[7,2,1] framework was established (entry 4). Similarly, bicyclic amidines **4dTs** and **4dTces** were obtained from the reactions of enyne **3d** with TsN_3 and $TcesN_3$ respectively in 73% and 81% yields (entries 5 and 6). A single crystal of **4dTs** has been obtained and submitted to X-ray diffraction experiments. The relative stereochemistry of **4dTs** was established unequivocally by its X-ray crystal structure (Figure 2a). The ester group is *cis* to the sulfoimino group with respect to the 10-membered ring, and the alknene in the cycle

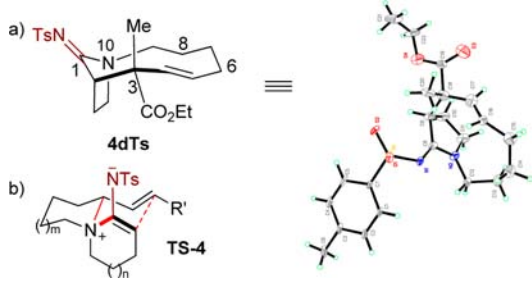


Figure 2. ORTEP presentation of **4dTs** at 20% probability level (a) and proposed transition state for the aza-Cope rearrangement (b).

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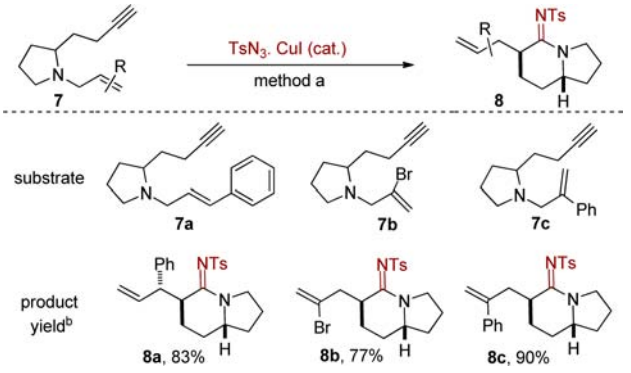
holds a *trans* configuration which was also confirmed by the H−H coupling constant $^3J_{H-H}$ between the two alkene hydrogen atoms. The relative stereochemistry of the remaining bicyclic amidines in Table 1 was assigned by analogy with **4dTs**. It is worth noting that this assignment of stereochemistry is fully in line with a general transition state **TS-4** in which rearrangement proceeds through a thermodynamic favorable chair conformation (Figure 2b). Amino enynes **3e**−**3f** with a *N*-pentyne segment instead of a previous *N*-butyne group delivered corresponding bridged bicyclic amidines with new bicyclo[6,3,1] and bicyclo[7,3,1] skeletons (entries 7 and 8).

However, when aromatic amino enyne **3g** reacted with TsN_3, triazole **5g** was the only product isolated in 84% yield (entry 9),[9] indicating that the cyclic indoline group itself failed to act as an effective internal base to promote the formation of sulfonyl ketenimine in the reaction with sulfonyl azide. To our delight, incorporation of excess DIPEA (5 equiv) as an external base into the reaction system (method b) restored the ketenimine formation/cyclization/aza-Cope rearrangement pathway to deliver benzo-fused bicycle **4g** (entry 10). The same principles also apply to indolinyl substrates **3h**−**3i** to render either triazole or bicyclic amidine exclusively at will (entries 11−13). Interestingly, indolinyl enyne **3j** failed to achieve a related bicyclic amidine even when method b was employed, but instead, linear amidine **6j** was produced (entry 15), which was likely to be derived from the capture of a ketenimine intermediate with external Hünig's base. This result may reflect the additive influence of a weaker nucleophilicity of indoline nitrogen, slower kinetics of six-membered vs five-membered ring cyclization, and the stereoelectronic effect of the ester moiety on the terminal alkene.

Interestingly, when the relative positions of the alkyne and alkene were switched to acquire enynes **7a**−**c**, the same reaction gave another type of bicyclic amidines, namely, fused bicyclic amidines **8a**−**8c** (Scheme 2). The reactions were highly

Scheme 2. Synthesis of Fused Bicyclic Amidines

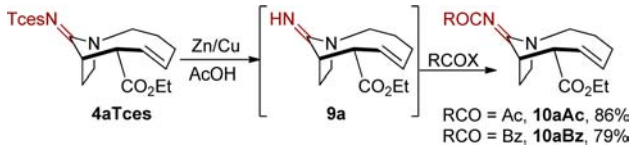


[a]Method **a**: **3** (1.0 equiv), $R'SO_2N_3$ (1.1 equiv), CuI (0.05 equiv), THF (0.1 M), rt. [a]Isolated yields.

stereoselective as well. In all cases, only one single isomer was isolated for each reaction, and their stereochemistry was tentatively assigned as shown by analogy to previously reported stereocontrolled synthesis of α-ally cyclic amidines.[7]

Next efforts were directed toward deprotection of the sulfonyl group and release of the amidine group for further functionalization (Scheme 3). It was found that **4aTs** remained unaffected when refluxed with $PhSH/Na_2CO_3$ in dimethylformamide. **4aNs** with the normally labile Ns group also

Scheme 3. Chemical Operations on the Amidine Nitrogen



survived under these standard deprotection conditions. Strong acidic hydrolysis conditions failed to remove the Ns group, as **4aNs** was recovered after heating in a mixture of H_2SO_4/DMF for 2 h. Realizing that the amidinyl sulfonyl group is very robust against direct action on the sulfur atom, we turn to **Tces** which could be cleaved via a different mechanism. Indeed, by treatment of **4aTces** with a freshly made zinc−copper couple in AcOH/MeOH,[10] with reductive elimination conditions, deprotected product **9a** was obtained smoothly, and without purification, crude **9a** was further elaborated to **10aAc** and **10aBz** in high yields via condensation with corresponding acid chlorides, demonstrating the potential application of these bridged bicyclic amidines and the value of the present synthetic methodology.

In summary, a facile and effective method for the synthesis of structurally unprecedented amidines with bridged bicycle frameworks of *trans*-aza-bicyclo[7/6,3/2,1]alkenes has been described. A ketenimine formation/cyclization/aza-Cope rearrangement cascade converts *N*-allyl cycloaminoalkynes into corresponding bridged bicycloamidines in a highly stereoselective fashion in the context of both the alkene configuration and stereochemistry of ring substitution. This method was also applied to construct fused bicyclic amidines by using similar starting materials with an alkene/alkyne switched structure. It was also demonstrated that the properly selected *N*-sulfonyl group could be cleaved cleanly under suitable conditions to liberate the amidinyl NH group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02798.

Experimental procedures, characterization of new compounds and spectral data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203. (b) Maccallini, C.; Fantacuzzi, M.; Amoroso, R. *Mini-Rev. Med. Chem.* **2013**, *13*, 1305. (c) Schade, D.; Kotthaus, J.; Riebling, L.; Kotthaus, J.; Mueller-Fielitz, H.; Raasch, W.; Koch, O.; Seidel, N.; Schmidtke, M.; Clement, B. *J. Med. Chem.* **2014**, *57*, 759. (d) Sanchez, M. I.; Penas, C.; Vazquez, M. E.; Mascarenas, J. L. *Chem. Sci.* **2014**, *5*, 1901. (e) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, *2010*, 1. (f) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (g) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722. (h) Barker, J.; Kilner, M. *Coord. Chem. Rev.* **1994**, *133*, 219. (i) Singh, B. K. *Int. J. ChemTech Res.* **2009**, *1*, 250. (j) Cho, W.; Cho, H.; Lee, C. S.; Lee, B. Y.; Moon, B.; Kang, J. *Organometallics* **2014**, *33*, 1617. (k) Auer, F.; Nelles, G.; Sellergren, B. *Chem. - Eur. J.* **2004**, *10*, 3232. (l) McKnight, L. E.; Raman, E. P.; Bezawada, P.; Kudrimoti, S.; Wilder, P. T.; Hartman, K. G.; Godoy-Ruiz, R.; Toth, E. A.; Coop, A.; MacKerell, A. D.; Weber, D. J. *ACS Med. Chem. Lett.* **2012**, *3*, 975. (m) Lee, I.; Kim, S.; Kim, S.-n.; Jang, Y.; Jang, J. *ACS Appl. Mater. Interfaces* **2014**, *6*, 17151. (n) Yuan, J.; Venkatraman, S.; Zheng, Y.; McKeever, B. M.; Dillard, L. W.; Singh, S. B. *J. Med. Chem.* **2013**, *56*, 4156.

(2) (a) Greenberg, A., Breneman, C. M., Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: New York, 2000. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(3) Okano, A.; Nakayama, A.; Wu, K.; Lindsey, E. A.; Schammel, A. W.; Feng, Y.; Collins, K. C.; Boger, D. L. *J. Am. Chem. Soc.* **2015**, *137*, 3693.

(4) (a) Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335. (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (c) Khurana, J. M.; Nand, B.; Saluja, P. *Tetrahedron* **2010**, *66*, 5637.

(5) Messer, W. S.; Abuh, Y. F.; Liu, Y.; Periyasamy, S.; Ngur, D. O.; Edgar, M. A. N.; El-Assadi, A. A.; Sbeih; Dunbar, P. G.; Roknich, S.; Rho, T.; Fang, Z.; Ojo, B.; Zhang, H.; Huzl, J. J.; Nagy, P. I. *J. Med. Chem.* **1997**, *40*, 1230.

(6) (a) Aoki, M.; Kaneko, M.; Izumi, S.; Ukai, K.; Iwasawa, N. *Chem. Commun.* **2004**, 2568. (b) Eitel, S. H.; Jautze, S.; Frey, W.; Peters, R. *chem. Sci.* **2013**, *4*, 2218. (c) Bauer, J. M.; Frey, W.; Peters, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 7634. (d) Schrapel, C.; Peters, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 10289.

(7) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Han, M.; Jiang, S.-N.; Cao, J.; Wang, J.-C.; Shen, M.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9284.

(8) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520.

(9) (a) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Zhou, H.; Shen, M.-H. *Org. Lett.* **2015**, *17*, 66. (b) Xu, H.-D.; Xu, K.; Jia, Z.-H.; Zhou, H.; Jiang, P.; Lu, X.-L.; Pan, Y.-P.; Wu, H.; Ding, Y.; Shen, M.-H.; Pan, X.-H. *Asian J. Org. Chem.* **2014**, *3*, 1154. (c) Shen, M.-H.; Pan, Y.-P.; Jia, Z.-H.; Ren, X.-T.; Zhang, P.; Xu, H.-D. *Org. Biomol. Chem.* **2015**, *13*, 4851.

(10) Barrett, A. G. M.; Fenwick, A.; Betts, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 299.

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