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## SYNTHESIS OF DIBENZOXAZONINES BY DOMINO [2+2] CYCLOADDITION— $4\pi$ ELECTROCYCLIC RING OPENING REACTION OF CYCLIC IMINES WITH YNAMIDES

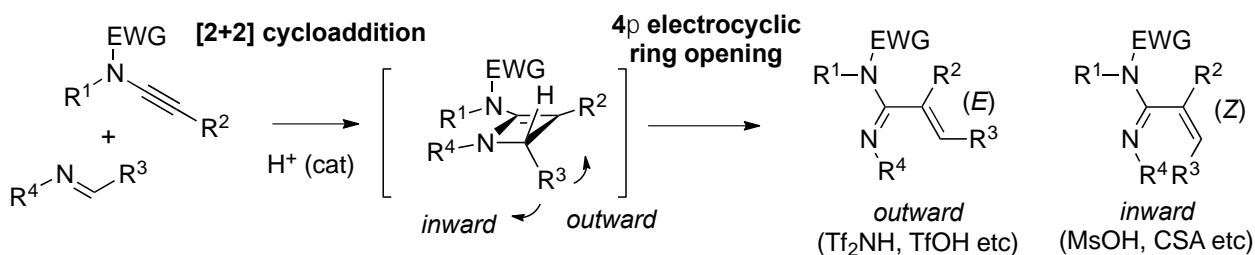
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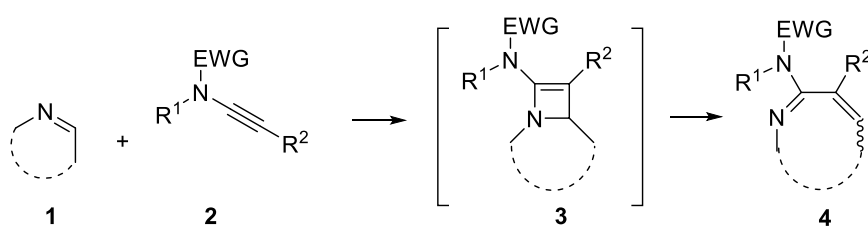
**Abstract** – Dibenzo[*b,h*][1,4]oxazonines and the thiazonine congener were synthesized from cyclic imines with ynamides by acid-mediated domino [2+2] cycloaddition— $4\pi$  electrocyclic ring opening reaction. The reaction enables two carbon-enlargement of the cyclic imine substrates. The X-ray crystallography made clear that the oxazonine skeleton has a unique bent-conformation.

Benzo-fused heterocyclic compounds have gathered much attention in the field of medicinal chemistry as well as synthetic chemistry. Although benzo-fused 6- and 7-membered heterocycles, such as quinolines, isoquinolines and benzaepines, are utilized as privileged scaffolds for drugs, medium-sized (8-11 membered) congeners have been less explored.<sup>1-5</sup> Design and synthesis of the less explored unique heterocyclic skeletons will contribute to the expansion of chemical space.<sup>6</sup> Previously, we have reported a domino [2+2] cycloaddition— $4\pi$  electrocyclic ring opening reaction<sup>7-11</sup> of acyclic aldimines with ynamides to give  $\alpha,\beta$ -unsaturated amidines via azetine intermediates (Scheme 1). We made clear that the reaction is activated by a strong Brønsted acid such as triflic imide ( $\text{Tf}_2\text{NH}$ ) and sulfonic acids and,



**Scheme 1.** Our previous study; Domino [2+2] cycloaddition— $4\pi$  electrocyclic ring opening reaction of acyclic imines with ynamides

moreover, the torquoselectivity in the  $4\pi$  electrocyclic ring opening of azetine intermediates giving *trans*- or *cis*- $\alpha,\beta$ -unsaturated amidines can be controlled by the catalyst.<sup>8</sup> We envisioned that the domino reaction of cyclic imines **1** instead of acyclic ones with ynamides **2** would give medium-sized cyclic amidines **4** (Scheme 2). As a related work, in 2015, Li, Sun and coworkers nicely reported that Tf<sub>2</sub>NH-catalyzed ring expansion of 5- and 6-membered cyclic hemiacetals and hemiaminals with silyl ynol ethers affording 7- and 8-membered lactones and lactams, respectively.<sup>12,13</sup> The reaction includes the formation of iminiums, [2+2] cycloaddition and ring-opening reaction. In this paper, we describe the concise synthesis of 9-membered azacycles such as dibenzoxazonines by two-carbon enlargement of 7-membered cyclic imines.

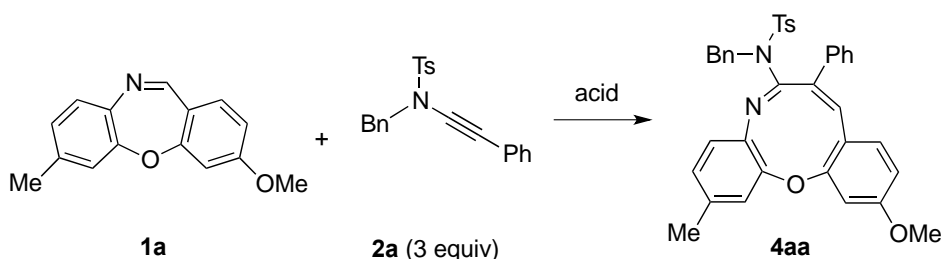


**Scheme 2.** This work: Synthesis of medium-sized cyclic amidines

At the outset of our study, the reaction of 3,4-dihydroisoquinoline, a 6-membered cyclic imine, with ynamides **2** was attempted in the presence of Tf<sub>2</sub>NH. However, recovery of 3,4-dihydroisoquinoline was resulted under any conditions tested (catalyst amount, reaction temperature and reaction time were examined). It can be concluded that  $4\pi$  electrocyclic ring opening reaction cannot proceed owing to the severe strain of the expected aza-*trans*-cyclooctadiene product **4**. Next, 7-membered benz[*b,f*][1,4]oxazepane **1a**, which was easily prepared from 2-amino-5-methylphenol and 2-fluoro-4-methoxybenzaldehyde,<sup>14</sup> was chosen as a cyclic imine substrate. The reaction of **1a** (1 equiv) with ynamide **2a** (1 equiv) in the presence of Tf<sub>2</sub>NH (1 equiv) resulted in messy (Table 1, entry 1). Monitoring the reaction by TLC indicated that consumption of ynamide **2a** was much faster than that of imine **1a**. Mass spectrum of the crude mixture also suggested decomposition of **2a** into the corresponding amide by hydration, which would be initiated by protonation with Tf<sub>2</sub>NH, and trace formation of the adduct of **1a** with **2a** ( $m/z = 601$  [M+H]<sup>+</sup>). When 3 equivalents of **2a** was used, imine **1a** was fully consumed within 30 min at ambient temperature to give **4aa**<sup>15</sup> in 68% yield (entry 2). The reactions at 0 °C or 50 °C decreased the yield of *cis,cis*-**4aa** (entries 3 and 4). Neither [2+2] cycloadduct **3** nor the *cis,trans/trans,cis* stereoisomers of **4aa** were obtained in the crude mixture. The structure of **4aa** was determined to have dibenzo[*b,h*][1,4]oxazonine skeleton by X-ray crystallographic analysis (*vide infra*). The reaction with Tf<sub>2</sub>NH (20 mol%) resulted in the production of a trace amount of **4aa** but decomposition of **2a** (entry 5). Methanesulfonic acid instead of Tf<sub>2</sub>NH resulted in recovery of **1a** and **2a**

(entry 6). Lewis acids such as  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{Zn}(\text{OTf})_2$  promoted the reaction much slower than  $\text{Tf}_2\text{NH}$  to give **4aa** in 38 and 28% yields, respectively. Although it was found that the Lewis acid catalysts potentially turn over the reaction ( $\text{TON} = 1.4\text{--}1.9$ ) because they would not initiate decomposition of **2a** by protonation (entries 7 and 8).

**Table 1.** Optimization of reaction conditions to give **4aa** from **1a** and **2a**

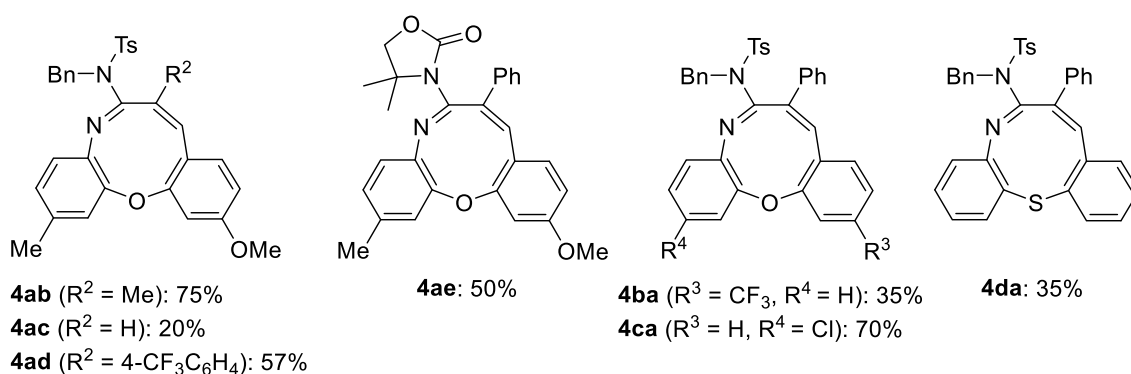


entry	acid (equiv)	solvent	temp.	time (h)	% yield of <b>4aa</b> <sup>b</sup>
1 <sup>a</sup>	$\text{Tf}_2\text{NH}$ (1.0)	$\text{CH}_2\text{Cl}_2$	rt	0.5	trace <sup>c</sup>
2	$\text{Tf}_2\text{NH}$ (1.0)	$\text{CH}_2\text{Cl}_2$	rt	0.5	68
3	$\text{Tf}_2\text{NH}$ (1.0)	$\text{CH}_2\text{Cl}_2$	0 °C	0.5	40
4	$\text{Tf}_2\text{NH}$ (1.0)	$\text{ClCH}_2\text{CH}_2\text{Cl}$	50 °C	0.5	27
5	$\text{Tf}_2\text{NH}$ (0.20)	$\text{CH}_2\text{Cl}_2$	rt	0.5	trace <sup>c</sup>
6	$\text{MsOH}$ (1.0)	$\text{CH}_2\text{Cl}_2$	rt	0.5	0
7	$\text{BF}_3 \cdot \text{OEt}_2$ (0.20)	$\text{ClCH}_2\text{CH}_2\text{Cl}$	rt	15	38
8	$\text{Zn}(\text{OTf})_2$ (0.20)	$\text{ClCH}_2\text{CH}_2\text{Cl}$	50 °C	60	28

<sup>a</sup> 1.0 equivalent of **2a** was used. <sup>b</sup> Isolated yields. <sup>c</sup> Oligomers of **2a** and hydration adduct of **2a** (amide) were formed as major by-products.

Next, the scope of the reaction was explored (Table 2) under the optimal conditions shown in Table 1,

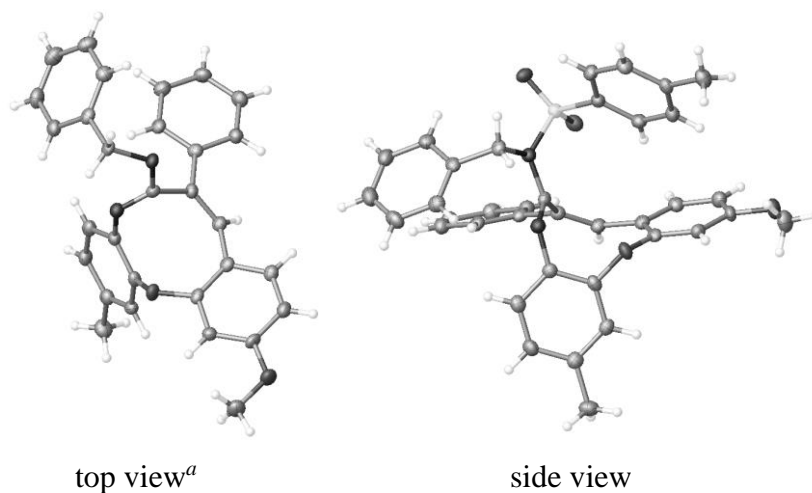
**Table 2.** Scope of the reaction<sup>a</sup>



<sup>a</sup> Standard conditions: **1** (1.0 equiv), **2** (3.0 equiv),  $\text{Tf}_2\text{NH}$  (1.0 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, 30 min.

entry 2. Aryl- and alkyl-substituted ynamides provided the corresponding dibenzoxazonines **4ab** and **4ad** in good to moderate yield, whereas ethynamide gave **4ac** in lower yield due to rapid decomposition of the terminal ynamide by  $\text{Tf}_2\text{NH}$ . Ynamide bearing oxazolidinone moiety is also a suitable substrate as well (**4ae**). Benzoxazepanes having different substituents also gave the corresponding tricycles **4ba** and **4ca** in moderate yield. *S*-Containing heterocycle **4da** can be also obtained from benzothiazepine.

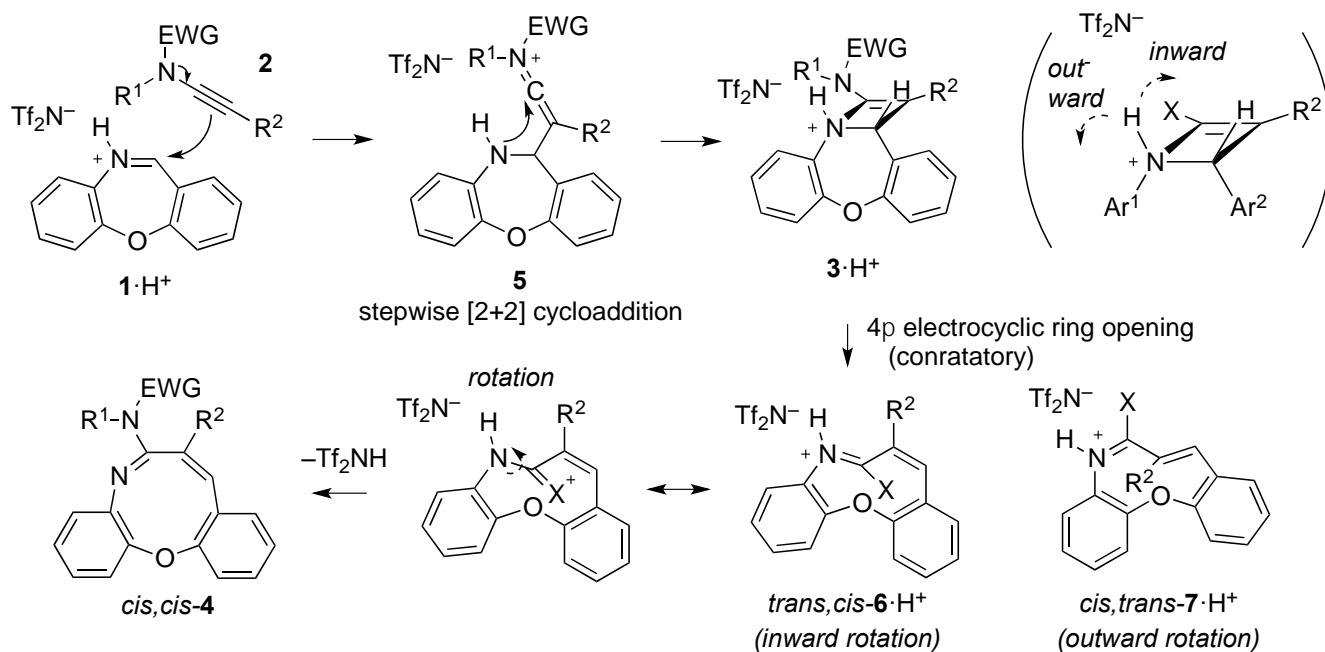
It was determined that both of C=N and C=C double bonds in the 9-membered heterocyclic ring of **4** to be *cis*-configuration by X-ray crystallography (for **4aa**, **4ac**, **4ba** and **4da**)<sup>16</sup> and its analogy in  $^1\text{H}$  NMR spectra. Although the central oxazonine ring of **4** seems to be  $10\pi$  aromatic system, the X-ray crystallographic analysis revealed that the 9-membered ring has a perpendicularly bent conformation along the nitrogen and oxygen atoms (Figure 1 for the crystal structure of **4aa**). Thus, the 9-membered ring would not have aromatic character.



**Figure 1.** X-Ray crystallographic structure of **4aa**

<sup>a</sup>*p*-Toluenesulfonyl group on the nitrogen atom was omitted for clarity.

Our proposed reaction mechanism was summarized in Figure 2. The cyclic imine **1** was activated by protonation from  $\text{Tf}_2\text{NH}$ , and then was reacted with ynamide **2** to afford tetracyclic azetinium intermediate  $\mathbf{3}\cdot\text{H}^+$  via keneniminium **5** by stepwise [2+2] cycloaddition.<sup>7,8</sup> The thermal conrotatory  $4\pi$  electrocyclic ring opening allows two sense of rotations of the substituents, inward versus outward rotations. According to our previous study in the similar reaction promoted by  $\text{Tf}_2\text{NH}$ ,<sup>8</sup> the inward rotation of the hydrogen on the nitrogen atom of  $\mathbf{3}\cdot\text{H}^+$  would be preferred to produce *trans,cis*- $\mathbf{6}\cdot\text{H}^+$  rather than outward product *cis,trans*- $\mathbf{7}\cdot\text{H}^+$ . The *trans/cis* stereochemistry of the C=N bond of  $\mathbf{6}\cdot\text{H}^+$  readily epimerizes to give *cis,cis*- $\mathbf{4}\cdot\text{H}^+$  by its resonance effect,<sup>17</sup> and the *cis* geometry is much more stable than the *trans* geometry.



**Figure 2.** Proposed reaction mechanism for the formation of **4**. X = N(R<sup>1</sup>)EWG

In summary, we have achieved the synthesis of benzo-fused 9-membered heterocycles from cyclic imines and ynamides by Tf<sub>2</sub>NH-mediated domino [2+2] cycloaddition—4π electrocyclic ring opening reaction. We also made clear that the 9-membered ring has a bent conformation. We believe that the skeleton can offer a new chemical space in medicinal chemistry field.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

Supplementary data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26393/101/2>.

## REFERENCES AND NOTES

- I. A. Perillo, M. C. Caterina, and A. Salemo, *ARKIVOC*, 2018, **i**, 288.
- A. Sharma, P. Appukkuttan, and E. Van der Eycken, *Chem. Commun.*, 2012, **48**, 1623.
- P. Das, S. Gondo, P. Nagender, H. Uno, E. Tokunaga, and N. Shibata, *Chem. Sci.*, 2018, **9**, 3276.
- B. A. Aderibigbe, I. R. Green, T. Mabank, M. J. van Rensburg, G. L. Morgans, M. A. Fernandes, J. P. Michael, and W. A. L. van Otterlo, *Tetrahedron*, 2017, **73**, 4671.

5. K. Okuma, H. Kinoshita, H. Nogahara, and K. Shioji, [Eur. J. Org. Chem.](#), 2016, 2264.
6. P. Kirkpatrick and C. Ellis, [Nature](#), 2004, **432**, 823.
7. N. Shindoh, Y. Takemoto, and K. Takasu, [Chem. Eur. J.](#), 2009, **15**, 7026.
8. N. Shindoh, K. Kitaura, Y. Takemoto, and K. Takasu, [J. Am. Chem. Soc.](#), 2011, **133**, 8470.
9. Y. Kuroda, N. Shindoh, Y. Takemoto, and K. Takasu, [Synthesis](#), 2013, **45**, 2318.
10. N. Arichi, K. Yamada, Y. Yamaoka, and K. Takasu, [J. Am. Chem. Soc.](#), 2015, **137**, 9579.
11. T. Ito, M. Tsutsumi, Y. Yamada, H. Takikawa, Y. Yamaoka, and K. Takasu, *Angew. Chem. Int. Ed.*, *in press*.
12. W. Zhao, Z. Li, and J. Sun, [J. Am. Chem. Soc.](#), 2013, **135**, 4680.
13. W. Zhao, H. Qian, Z. Li, and J. Sun, [Angew. Chem. Int. Ed.](#), 2015, **54**, 10005.
14. Y. R. Jorapur, G. Rajagopal, P. J. Saikia, and R. R. Pal, [Tetrahedron Lett.](#), 2008, **49**, 1495; Y.-C. Lin, N.-C. Li, and Y.-J. Cherng, [J. Heterocycl. Chem.](#), 2014, **51**, 808.
15. Data of **4aa**: Colorless prisms, mp 207–208 °C (recrystallization from AcOEt/hexane). TLC  $R_f$  = 0.42 (hexane/acetone 2:1).  $^1\text{H}$  NMR:  $\delta$  7.42 (d,  $J$  = 8.3 Hz, 2H), 7.29 (d,  $J$  = 6.0 Hz, 2H), 7.22–7.17 (m, 4H), 7.11–7.08 (m, 4H), 6.92 (d,  $J$  = 8.6 Hz, 1H), 6.84 (d,  $J$  = 7.7 Hz, 2H), 6.72–6.68 (m, 3H), 6.61 (dd,  $J$  = 8.3, 2.6 Hz, 1H), 6.47 (d,  $J$  = 8.0 Hz, 1H), 6.42 (s, 1H), 4.97 (d,  $J$  = 14.9 Hz, 1H), 4.83 (d,  $J$  = 14.6 Hz, 1H), 3.89 (s, 3H), 2.39 (s, 3H), 2.14 (s, 3H) ppm.  $^{13}\text{C}$  NMR:  $\delta$  160.5, 156.4, 155.5, 146.5, 143.7, 140.4, 137.9, 136.4, 136.1, 134.1, 133.6, 129.1, 128.9, 128.8, 128.3, 127.9, 128.8, 128.7, 127.2, 126.4, 125.3, 120.8, 119.9, 117.8, 109.5, 107.0, 55.5, 50.1, 21.6, 20.8 ppm. IR (neat): 1705, 1613, 1501, 1447, 1346, 1292, 1269, 1161, 1130  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$   $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{37}\text{H}_{33}\text{N}_2\text{O}_4\text{S}^+$  601.2156; Found 601.2149. X-Ray: *orthorhombic*, *Pbca*;  $a$  = 10.0384(4),  $b$  = 20.7792(8),  $c$  = 28.4695(11);  $V$  = 5938.5(4),  $Z$  = 8,  $D_x$  = 1.331,  $R$  = 0.0559,  $wR_2$  = 0.1318, GOF = 1.018. CCDC number 1936865.
16. CCDC 1936865, 1936866, 1936867, 1936868, and 1936869 (**4aa**, **4ab**, **4ac**, **4ba**, **4da**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
17. I. D. Cunninham and A. F. Hagarty, *J. Chem. Soc., Perkin Trans. 2*, 1986, 537.