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

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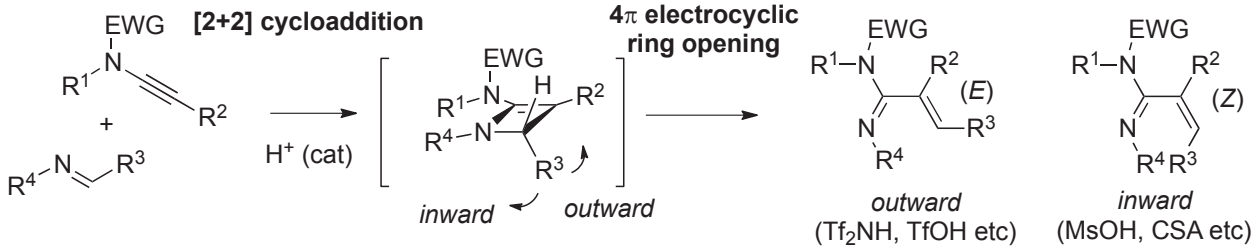
Abstract – Dibenzo[*b,h*][1,4]oxazonines and the thiazonine congener were synthesized from cyclic imines with ynamides by acid-mediated domino [2+2] cycloaddition—4π electrocyclic ring opening reaction. The reaction enables two carbon-enlargement of the cyclic imine substrates. The X-ray crystallography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

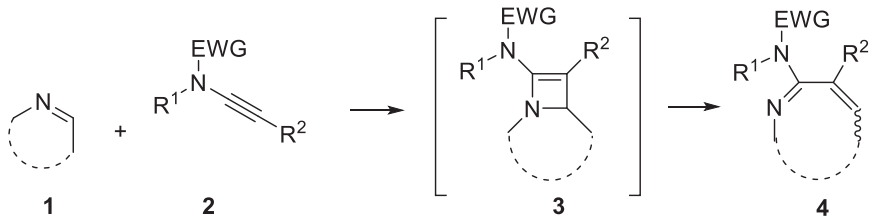
Benzo-fused heterocyclic compounds have gathered much attention in the field of medicinal chemistry as well as synthetic chemistry. Although benzo-fused 6- and 7-membered heterocycles, such as quinolines, isoquinolines and benzaepines, are utilized as privileged scaffolds for drugs, medium-sized (8-11 membered) congeners have been less explored.[1-5] Design and synthesis of the less explored unique heterocyclic skeletons will contribute to the expansion of chemical space.[6] Previously, we have reported a domino [2+2] cycloaddition—4π electrocyclic ring opening reaction[7-11] of acyclic aldimines with ynamides to give α,β-unsaturated amidines via azetine intermediates (Scheme 1). We made clear that the reaction is activated by a strong Brønsted acid such as triflic imide (Tf_2NH) and sulfonic acids and,



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

Dedicated to Prof. Dr. Kaoru Fuji on the occasion of his 80th birthday

moreover, the torquoselectivity in the 4π electrocyclic ring opening of azetine intermediates giving *trans*- or *cis*-α,β-unsaturated amidines can be controlled by the catalyst.[8] 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_2NH-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.[12,13] 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.

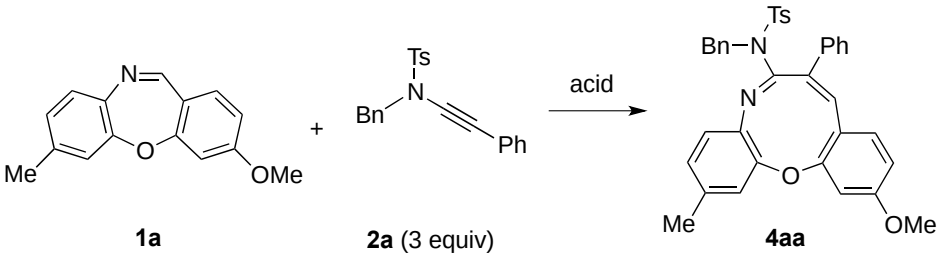


Scheme 2. This work: Synthesis of medium-sized cyclic amidines

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_2NH. 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 4π 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,[14] was chosen as a cyclic imine substrate. The reaction of **1a** (1 equiv) with ynamide **2a** (1 equiv) in the presence of Tf_2NH (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_2NH, and trace formation of the adduct of **1a** with **2a** (*m/z* = 601 $[M+H]^+$). When 3 equivalents of **2a** was used, imine **1a** was fully consumed within 30 min at ambient temperature to give **4aa**[15] 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_2NH (20 mol%) resulted in the production of a trace amount of **4aa** but decomposition of **2a** (entry 5). Methanesulfonic acid instead of Tf_2NH resulted in recovery of **1a** and **2a**

(entry 6). Lewis acids such as $BF_3{\cdot}OEt_2$ and $Zn(OTf)_2$ promoted the reaction much slower than Tf_2NH to give **4aa** in 38 and 28% yields, respectively. Although it was found that the Lewis acid catalysts potentially turn over the reaction (TON = 1.4–1.9) 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**



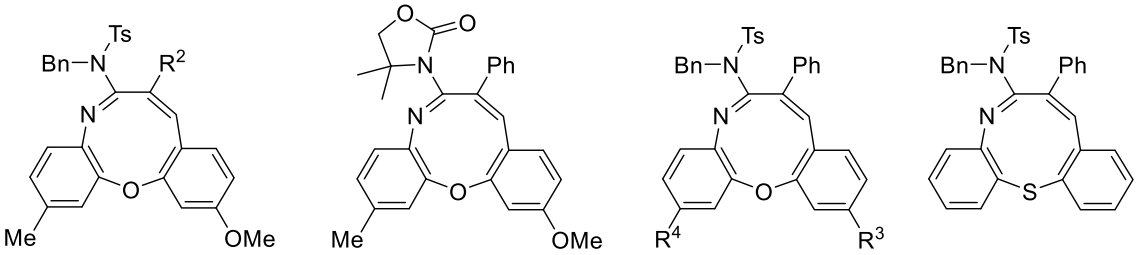
1a **2a** (3 equiv) **4aa**

entry	acid (equiv)	solvent	temp.	time (h)	% yield of **4aa**[b]
1[a]	Tf_2NH (1.0)	CH_2Cl_2	rt	0.5	trace[c]
2	Tf_2NH (1.0)	CH_2Cl_2	rt	0.5	68
3	Tf_2NH (1.0)	CH_2Cl_2	0 °C	0.5	40
4	Tf_2NH (1.0)	$ClCH_2CH_2Cl$	50 °C	0.5	27
5	Tf_2NH (0.20)	CH_2Cl_2	rt	0.5	trace[c]
6	MsOH (1.0)	CH_2Cl_2	rt	0.5	0
7	$BF_3{\cdot}OEt_2$ (0.20)	$ClCH_2CH_2Cl$	rt	15	38
8	$Zn(OTf)_2$ (0.20)	$ClCH_2CH_2Cl$	50 °C	60	28

[a] 1.0 equivalent of **2a** was used. [b]Isolated yields. [c]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[a]



4ab (R^2 = Me): 75%
4ac (R^2 = H): 20%
4ad (R^2 = 4-$CF_3C_6H_4$): 57%

4ae: 50%

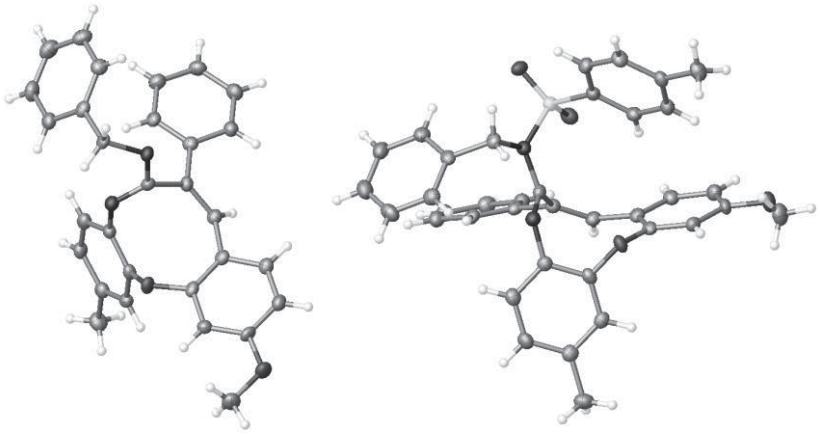
4ba (R^3 = CF_3, R^4 = H): 35%
4ca (R^3 = H, R^4 = Cl): 70%

4da: 35%

[a]Standard conditions:**1** (1.0 equiv), **2** (3.0 equiv), Tf_2NH (1.0 equiv), CH_2Cl_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 Tf_2NH. 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**)[16] and its analogy in ^{1}H NMR spectra. Although the central oxazonine ring of **4** seems to be 10π 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.



top view[a] side view

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

[a]*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 Tf_2NH, and then was reacted with ynamide **2** to afford tetracyclic azetinium intermediate **3**·H^+ via keneniminium **5** by stepwise [2+2] cycloaddition.[7,8] The thermal conrotatory 4π 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 Tf_2NH,[8] the inward rotation of the hydrogen on the nitrogen atom of **3**·H^+ would be preferred to produce *trans,cis*-**6**·H^+ rather than outward product *cis,trans*-**7**·H^+. The *trans/cis* stereochemistry of the C=N bond of **6**·H^+ readily epimerizes to give *cis,cis*-**4**·H^+ by its resonance effect,[17] and the *cis* geometry is much more stable than the *trans* geometry.

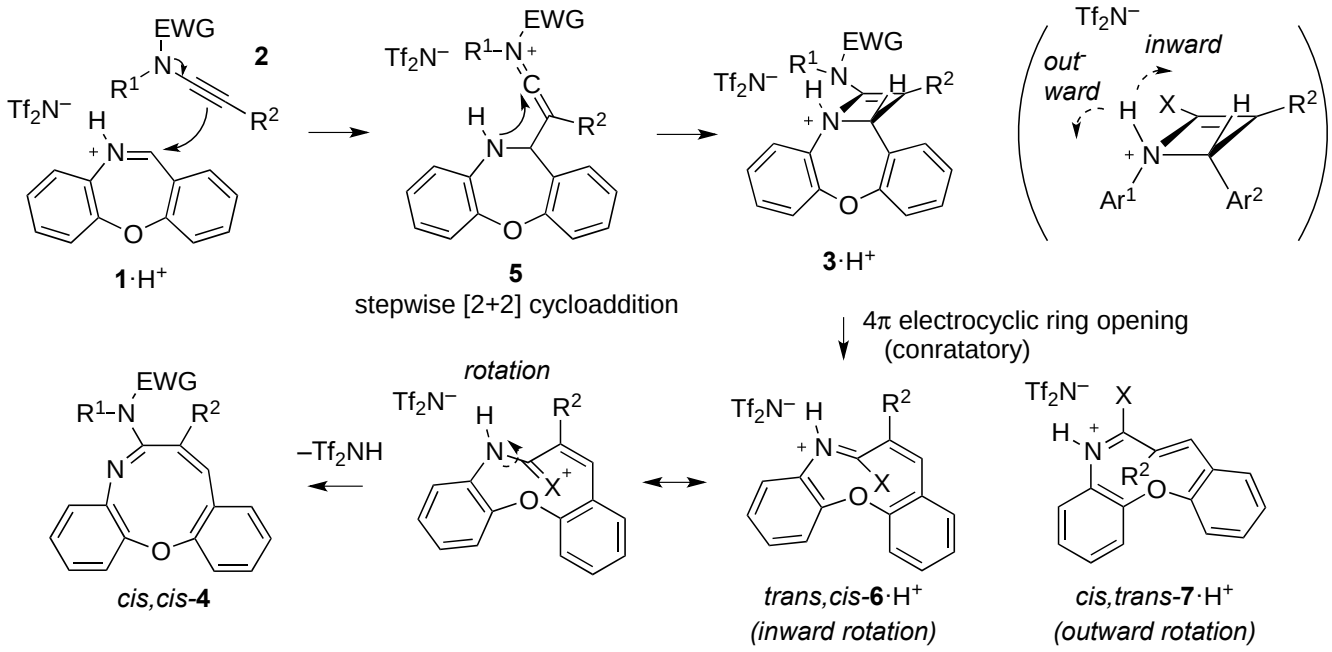


Figure 2. Proposed reaction mechanism for the formation of **4**. X = N(R^1)EWG

In summary, we have achieved the synthesis of benzo-fused 9-membered heterocycles from cyclic imines and ynamides by Tf_2NH-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.

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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.

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15. Data of **4aa**: Colorless prisms, mp 207–208 °C (recrystallization from AcOEt/hexane). TLC R_f = 0.42 (hexane/acetone 2:1). ^{1}H NMR: δ 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}C NMR: δ 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 cm^{-1}. HRMS (ESI) *m/z* [M + H]$^+$ Calcd for $C_{37}H_{33}N_2O_4S^+$ 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.
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