Nitrogen Heterocycles

An Efficient Synthesis of Bicyclic Amidines by Intramolecular Cyclization**

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Bicyclic amidines and guanidines are organic superbases utilized in various synthetic transformations. Recently, chiral guanidines have been widely explored as non-metal-containing bases in asymmetric synthesis[1] as well as in asymmetric phase-transfer catalysis.[1d,2] In spite of great success in catalysis with chiral guanidine derivatives, asymmetric reactions with chiral derivatives of bicyclic amidines[3] have not been widely studied, possibly because of the difficulty of synthesizing chiral bicyclic amidines. The nucleophilic character of bicyclic amidines[3c,4] further broadens their utility as catalysts. Considering the potency of chiral bicyclic amidines as organocatalysts, the development of an efficient protocol for the synthesis of these compounds would greatly contribute toward the progress in this area.[5]

For the formation of a bicyclic amidine, the starting material should have two nitrogen-containing functionalities that can assemble intramolecularly to form an amidine core at the ring junction. Previous reports[3,6] indicate that the intramolecular attack of a free amino group on a lactam in the presence of a strong acid (*p*-toluenesulfonic acid or $TiCl_4$)[6a] in refluxing xylene, and the intramolecular attack of a Boc-protected amino group (Boc = *t*-butoxycarbonyl) to a thiolactam under acidic conditions[3a,b,6c] are reliable (Scheme 1). However, the former method requires harsh reaction conditions, and the latter, too many steps from readily available organic materials although the reaction conditions are mild. We report a concise synthetic procedure for bicyclic amidines starting from readily available tethered azido lactams by means of an intramolecular cyclization (Scheme 1), which provides easy access to various achiral and chiral bicyclic amidines under mild reaction conditions. The direct use of an azido function, instead of an amino group, plays a key role in our reaction design. We also describe mechanistic aspects of the reaction based on an in situ IR study.

We focused on the use of an azido group as the nucleophile in the intramolecular cyclization.[7,8] Although

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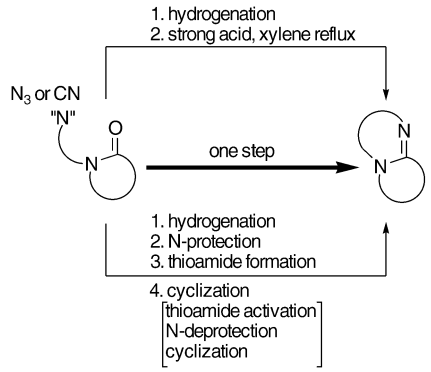


Scheme 1. Strategies for the formation of bicyclic amidines. Top: An amino group serves as the nucleophile; cyclization under harsh conditions. Middle: An azido group functions directly as the nucleophile in a mild and efficient, one-step conversion. Bottom: The lengthy reaction sequence features thioamide formation and protection–deprotection of the amino group.

the intramolecular aza-Wittig reaction of an azido group on an imide carbonyl under Staudinger conditions has been reported,[9] the conditions were not effective for the simple amide carbonyl **1a**.[10] The cyclized product **2a** was obtained in less than 10% yield, and the iminophosphorane was the main product when either triphenylphosphane or tributylphosphane were employed (Table 1, entries 1 and 2).[11] To overcome the intrinsic low reactivity of the amide, chemoselective activation was necessary. Unlike the thiolactam method,[12] direct use of an azido group enables chemoselective activation of the amide because the azido unit is not affected by many kinds of electrophilic reagents. In this design, the azido group serves as a nucleophile[7] or a 1,3-dipole[8] that undergoes cyclization with an activated amide moiety, followed by the extrusion of molecular nitrogen to afford the bicyclic amidine.

Table 1: Bicyclic-amidine-forming reaction with azido lactam **1a**.

Entry	Reagent	Solvent	T [°C]	t [h]	Yield [%]
1	Ph_3P	xylene	reflux[a]	24	<10
2	Bu_3P	xylene	reflux[a]	24	<10
3	$POCl_3$	CH_2Cl_2	RT	24	32
4	PCl_5	CH_2Cl_2	RT	24	<5
5	$(COCl)_2$	CH_2Cl_2	0 to RT[b]	24	81
6	$(COCl)_2$	$(CHCl)_2$	0 to RT[b]	24	76
7	$(COCl)_2$	THF	0 to RT[b]	24	<10
8	$(COCl)_2$	toluene	0 to RT[b]	24	11
9	$(COCl)_2$	CH_3CN	0 to RT[b]	24	37
10	$(COBr)_2$	CH_2Cl_2	0 to RT[b]	4	68
11	$(COBr)_2$	$(CHCl)_2$	0 to RT[b]	4	92

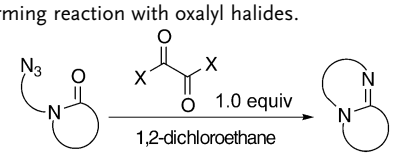
[a] The reagent was added at room temperature (RT), and the reaction mixture was stirred at the same temperature for the first hour before it was heated to reflux. [b] Reagent was added at 0°C, and the reaction mixture was stirred at this temperature for the first hour before it was allowed to warm to room temperature.

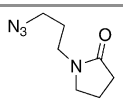
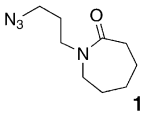
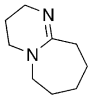
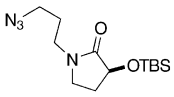
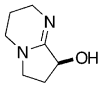
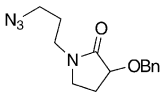
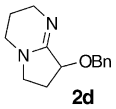
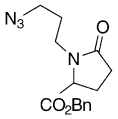
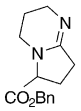
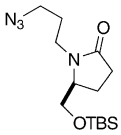
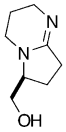
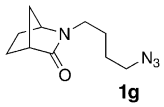
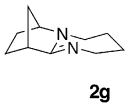
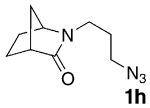
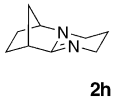
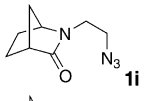
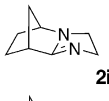
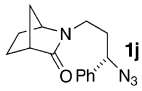
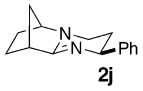
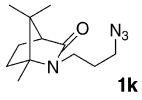
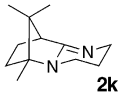
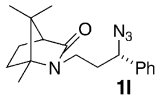
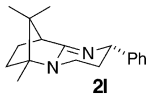
Initially, various reagents were screened in reactions with the achiral substrate **1a** to determine if they activate the amide moiety. Phosphorus oxytrichloride (entry 3) and phosphorus pentachloride (entry 4), common reagents for Vilsmeier's salt formation, resulted in low yields. Among the other reagents tested, oxalyl chloride (1 equiv) was effective for the formation of a chloroiminium intermediate, leading to clean formation of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **2a**) in 81% yield at room temperature (Table 1, entry 5). At the initial stage of the reaction, it was essential to keep the reaction temperature at 0°C for 1 h, otherwise a side reaction occurred triggered by enamine formation[13] from the chloroiminium intermediate, and the reaction mixture became complicated. Among the solvents investigated, CH_2Cl_2 and 1,2-dichloroethane gave the best results (entries 5–8). The use of oxalyl bromide in 1,2-dichloroethane was the most effective, and **2a** was obtained in 92% yield within 4 h after workup with anisole/MeOH (entry 11).

We then applied these optimized conditions to the synthesis of various achiral and chiral bicyclic amidines from tethered azido lactams (Table 2). The substrates for this amidine-forming reaction were easily prepared by S_N2 substitution of azidoalkyl tosylate with the parent lactam.[14] The present bicyclic-amidine-forming reaction has broad substrate generality. Bicyclo[4.3.0] (entries 1, 2, and 4–8), bicyclo[5.4.0] (entry 3), and polycyclic amidine ring systems (entries 9–15) were obtained in good yield. Oxalyl bromide gave better results than oxalyl chloride, especially for the less reactive substrates. For example, the reaction of **1g** with oxalyl bromide afforded **2g** in 82% yield after 4 h (entry 10), while the use of oxalyl chloride gave **2g** in only 18% yield (entry 9).[15] The formation of five- and seven-membered rings required more forcing conditions than the formation of six-membered rings (entry 11 vs entries 9, 10, and 12). The ester functionality was tolerated under these reaction conditions (entry 7). The phenyl group at the position α to the azido group did not interfere with the cyclization; the desired cyclic amidines were obtained in good yield without halogenation of the aromatic ring (entries 13 and 15). Thus, functionalized achiral bicyclic amidines **2d** and **2e** (entries 5–7), functionalized chiral bicyclic amidines **2c** and **2f** (entries 4, 8), and chiral polycyclic amidines **2g**–**2l** (entries 9–15) were synthesized efficiently under mild conditions. Preparation of the polycyclic amidine **2k** from the same substrate **1k** by the thiolactam method[3a] required four steps, and **2k** was obtained in 43% overall yield.[16] It is noteworthy that our method accomplished the same conversion in a single step with 88% yield after simple extraction (entry 14).

Having achieved an efficient process for the formation of bicyclic amidines, we performed several model experiments to gain mechanistic insight into the reaction. Considering the smooth reaction of the bicyclic substrates **1g**–**1l** (Table 2, entries 9–15), in which based on Bredt's rule[17] enamine formation should not occur, the involvement of an enamine intermediate was rationally excluded. In situ IR spectroscopy with **1a** illustrated the possible reaction course (Figure 1a–d).[18] As shown in Figure 1a, the addition of oxalyl bromide to **1a** in 1,2-dichloroethane at 0°C caused the chemoselective transformation of the lactam ($\tilde{\nu} = 1683\ cm^{-1}$, C=O stretch)

Table 2: Bicyclic-amidine-forming reaction with oxalyl halides.



Entry	Substrate	Product	Reagent [X]	T [°C]	t [h]	Yield [%]
1[a]	 **1a**	 **2a**	Cl	RT	24	81
2			Br	RT	4	92
3	 **1b**	 **2b**	Br	RT	6	87
4[b]	 **1c**	 **2c**	Br	50	4	84
5[a]	 **1d**	 **2d**	Cl	RT	24	78
6			Br	RT	6	88
7	 **1e**	 **2e**	Cl	RT	24	86
8[b]	 **1f**	 **2f**	Br	RT	4	91
9	 **1g**	 **2g**	Cl	70	48	18
10			Br	70	4	82
11	 **1h**	 **2h**	Cl	RT	24	94
12[c]	 **1i**	 **2i**	Br	60	4	77
13	 **1j**	 **2j**	Br	RT	4	80
14[a]	 **1k**	 **2k**	Cl	50	24	88
15[c]	 **1l**	 **2l**	Br	50	3	92

[a] CH_2Cl_2 was used as solvent. [b] TBS = tert-butyldimethylsilyl. [c] Reaction was conducted with 1.5 equiv reagent.

into the bromoiminium intermediate ($\tilde{\nu} = 1644\ cm^{-1}$, C=O stretch)[19] without affecting the azido group ($\tilde{\nu} = 2104\ cm^{-1}$, N=N stretch). When the reaction mixture was warmed from 0 °C to 25 °C (Figure 1b), the peaks derived from the bromoiminium intermediate and azido function diminished gradually, accompanied by evolution of N_2 gas. Two new peaks appeared at $\tilde{\nu} = 1679\ cm^{-1}$ and $\tilde{\nu} = 1637\ cm^{-1}$, which were assigned to **2a**·HBr (C=N stretch) and **2a**·Br_2 (C=N stretch), respectively.[20] To test the validity of this assignment, the following experiments were performed. As shown in Figure 1c, model substrate **1m**, which lacks an azido group, was treated with oxalyl bromide and followed by in situ IR spectroscopy. Although the bromoiminium intermediate ($\tilde{\nu} = 1644\ cm^{-1}$) formed smoothly at 0 °C, it remained unchanged even after the reaction mixture had been warmed from 0 °C to 25 °C. Therefore, the new peaks in Figure 1b ($\tilde{\nu} = 1679,\ 1637\ cm^{-1}$) were not derived from the hydrolysis of the bromoiminium intermediate nor from oxalyl bromide. As shown in Figure 1d, **2a**·Br_2 prepared from **2a** and Br_2 was easily solvolyzed to **2a**·HBr within 10 min by the addition of MeOH at 25 °C. The result suggested that **2a**·HBr ($\tilde{\nu} = 1679\ cm^{-1}$) in Figure 1b arises from the hydrolysis of **2a**·Br_2 ($\tilde{\nu} = 1637\ cm^{-1}$) by moisture under the conditions of the in situ IR study. Under strictly anhydrous conditions the final product in the reaction mixture was expected to be **2a**·Br_2.[21] This assumption was supported by the following observation. After the reaction was complete, the addition of anisole to the reaction mixture resulted in the smooth formation of 4-bromoanisole in equimolar amout to **1a**, which implied that some brominating agent, such as **2a**·Br_2, was present in the reaction mixture.[22]

On the basis of the above results, the plausible reaction mechanism is outlined as in Scheme 2. First, bromoiminium intermediate **3a** is formed cleanly by the action of oxalyl bromide on **1a** without affecting the azido group. The involvement of the enamine intermediate **4a** was excluded as mentioned above, and two possibilities for the cyclization step remain. One possibility is the intramolecular 1,2-addition of the azido group to give the bicyclic intermediate **5a**, followed by a 1,2-shift of Br and extrusion of molecular nitrogen (Scheme 2, pathway a). The other possibility is the intramolecular [3+2] cycloaddition to afford tetrazolium intermediate **6a**, and subsequent retro-[3+2] reaction with a concomitant 1,2-shift of Br (Scheme 2, pathway b). Considering the nature of azido functionality as a 1,3-dipole and previous reports concerning the [3+2] cycloaddition of azides,[7] pathway b is assumed to be more favorable for the

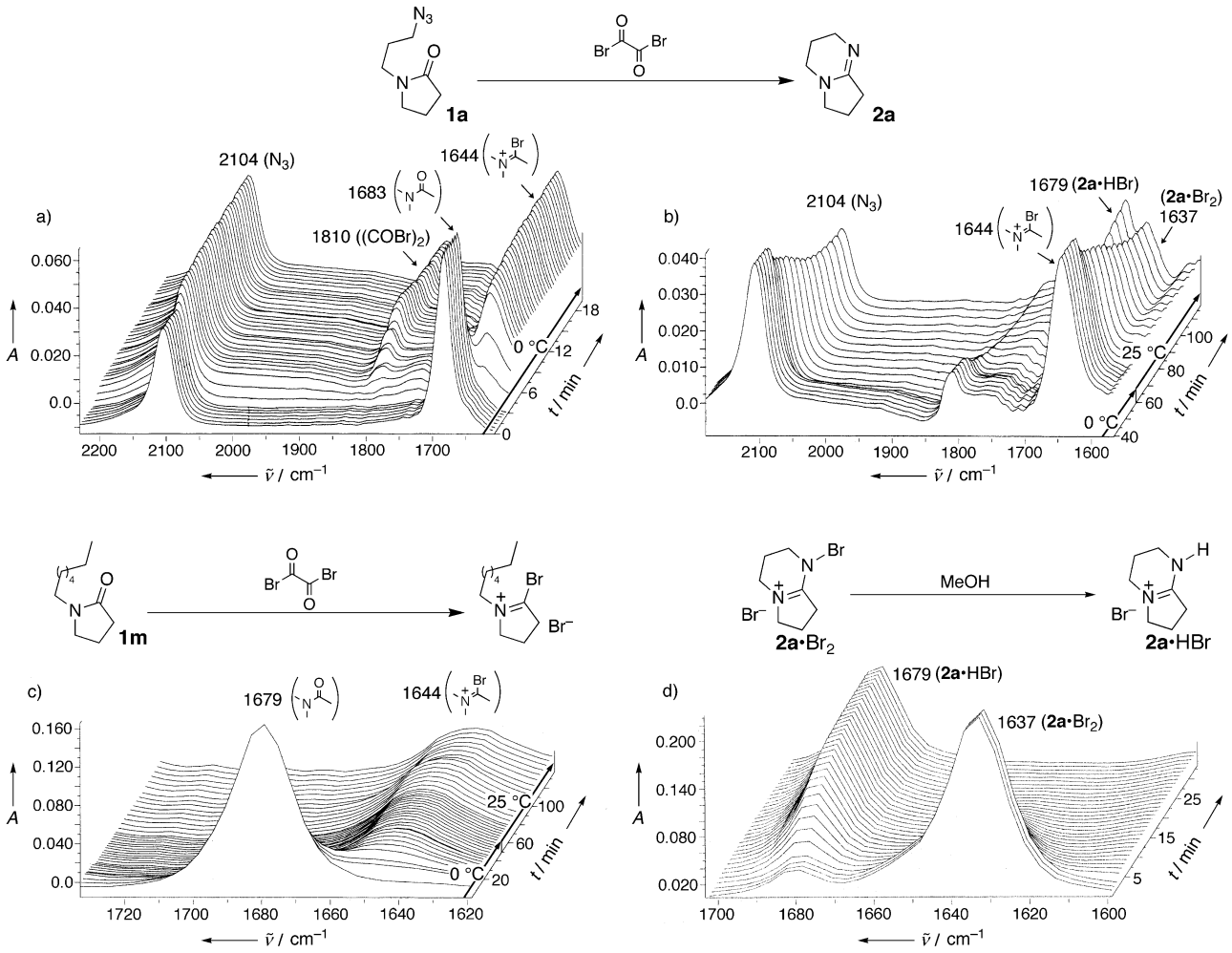
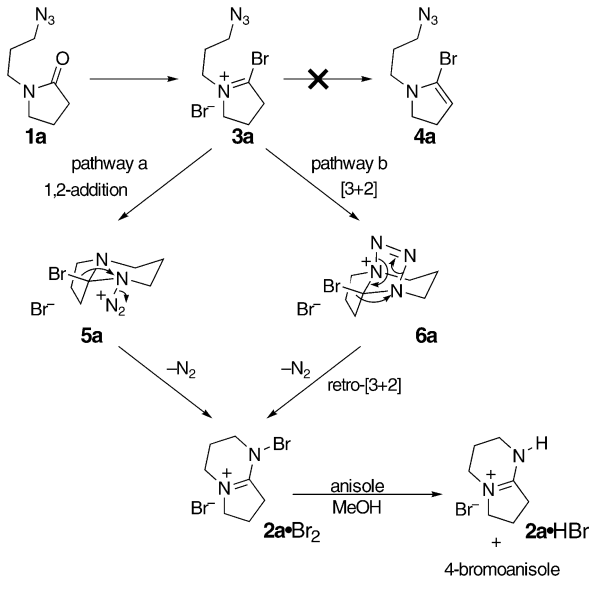


Figure 1. In situ IR study of the amidine-forming reactions in 1,2-dichloroethane as shown. Reaction temperatures: a) 0 °C, b) 60 min at 0 °C then 25 °C, c) 50 min at 0 °C then 25 °C, d) 25 °C.



Scheme 2. Plausible reaction mechanism.

present bicyclic-amidine-forming reaction. In our in situ IR study, neither intermediate **5a** nor **6a** was observed. Thus, the possibility of pathway a cannot be excluded. The resulting brominating species **2a**·Br_2 in the reaction mixture was scavenged with anisole.

In summary, we have developed an efficient method for the synthesis of bicyclic amidines by the intramolecular attack of an azido group on a lactam function. The present reaction conditions allow for facile cyclization without unmasking the azido group to give the amine. This enables the synthesis of various achiral and chiral bicyclic amidines under mild conditions and with a small number of steps compared with the previous methods. Mechanistic studies using in situ IR spectroscopy shed light on the possible reaction pathway. The application of chiral bicyclic amidines to asymmetric catalysis is in progress.

Experimental Section

Representative procedure for the synthesis of bicyclic amidines: To a solution of azido lactam **1a** (103.3 mg, 0.612 mmol, 0.1M) in 1,2-

dichloroethane (6.1 mL) under an Ar atmosphere was added a solution of oxalyl bromide in dichloromethane (306 μL, 2.0 M, 0.612 mmol) dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, it was warmed to room temperature and stirred for 4 h at the same temperature. The resulting mixture was quenched with anisole (133 μL, 1.22 mmol) and MeOH (1.2 mL) at 0 °C and stirred for 30 min at room temperature. The resulting mixture was concentrated to half of the original volume and extracted with 1 M aq HCl. The aqueous extract was washed with CH_2Cl_2 and concentrated under reduced pressure. The resulting residue was passed through Amberlite IRA 400 (OH^-) with MeOH as the eluent. Evaporation of the organic solvent gave the pure amidine **2a** (70.2 mg, 0.565 mmol, 92% yield).

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Keywords: azides · chirality · cyclization · nitrogen heterocycles

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[16] Synthetic procedure reported by Kotsuki et al. (in ref. [3a]) was as follows; 1. hydrogenation of the azide, 2. Boc protection of the resulting amine, 3. thioamide formation with Lawesson's reagent, 4. activation of thioamide (MeI) followed by Boc deprotection and cyclization (trifluoroacetic acid).

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[18] In situ IR spectra were recorded on a ReactIR 4000 instrument from ASI Applied Systems.

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[21] **2a**·Br_2 was also detected with an electrospray ionization mass spectrometer by directly sampling the reaction mixture. The peak at $m/z = 203$, 205 ([$\mathbf{2a}^+ + Br$]) derived from **2a**·Br_2 was detected although its relative intensity was weak compared to the peak at $m/z = 125$ ([$\mathbf{2a}^+ + H$]) derived from **2a**·HBr.

[22] Oxalyl bromide alone did not brominate anisole.