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Cycloaddition Reaction of 2-Vinylazetidines with Benzyne: A Facile Access to 1-Benzazocine Derivatives

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ABSTRACT

The cycloaddition reaction of 2-vinylazetidines with benzyne proceeded smoothly without a catalyst, and various benzazocine derivatives were isolated in good to high yields. The scope of the reaction, as well as the reactions of other arynes, has been studied.

The 1-benzazocine structure is found in many biologically active compounds,[1] and various synthetic approaches have been reported. A multistep synthesis, involving olefin metathesis,[2] a Mizoroki−Heck reaction,[3] or other reactions,[4] is frequently required to synthesize benzazocine derivatives, and the development of a new and efficient synthesis of these compounds is highly desirable.

We have been interested in the ring-expansion reactions of 2-vinylazetidines which afforded nitrogen-containing heterocyclic compounds. For example, the reaction of 2-vinylazetidine with electron-deficient alkynes[5] or tosyl isocyanate[6] gives eight-membered nitrogen-containing heterocyclic compounds, and the palladium-catalyzed reaction of 2-vinylazetidine with phenyl isocyanate afforded a six-membered nitrogen-containing heterocyclic compound.[7] The ring-expansion reaction of 2-alkenylazetidium salts yielded azepane derivatives.[8]

Recently, Greaney and co-workers reported that benzyne could promote aza-Claisen reactions: the ring expansion reactions of some five- and six-membered cyclic vinylamines proceeded, and the formation of unsaturated nine- and ten-membered cyclic amines was observed.[9] These results prompted us to study the ring expansion reaction of 2-vinylazetidines. In this paper we report the synthesis of 1-benzazocine derivatives by the reaction of 2-vinylazetidines with benzyne.

We first explored the reaction of 1-benzyl-2-vinylazetidine (**1a**)[6] with benzyne (**2a**), employing 2-(trimethylsilyl)-phenyl trifluoromethanesulfonate (**2a′**) as the precursor.[10] Reaction conditions were screened, and the results are summarized in Table 1.

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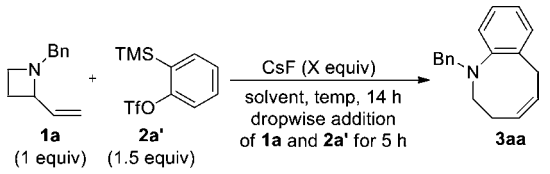
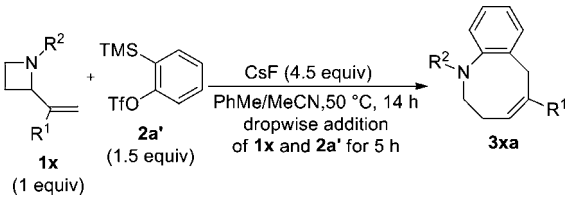
Table 1. Optimization of the [6 + 2] Cycloaddition Reaction



entry	solvent	X (equiv)	temp	yield[a]
1	PhMe/MeCN (1:1)	3	50 °C	76%
2	PhMe/MeCN (1:1)	4.5	50 °C	81%
3	PhMe/MeCN (1:1)	4.5	rt	51%
4	PhMe/MeCN (1:1)	4.5	80 °C	79%
5	MeCN	4.5	50 °C	63%
6	PhMe	4.5	50 °C	0%

[a] Isolated yield.

Table 2. Reactions of Various 2-Vinylazetidines with Benzyne



entry	1x	R^1	R^2	3xa	yield[a]
1	**1a**	H	Bn	**3aa**	81%
2	**1b**	Me	Bn	**3ba**	73%
3	**1c**	Ph	Bn	**3ca**	43%
4	**1d**	H	PMB	**3da**	78%
5	**1e**	H	*n*-Octyl	**3ea**	41%
6	**1f**	H	Cy[b]	**3fa**	59%

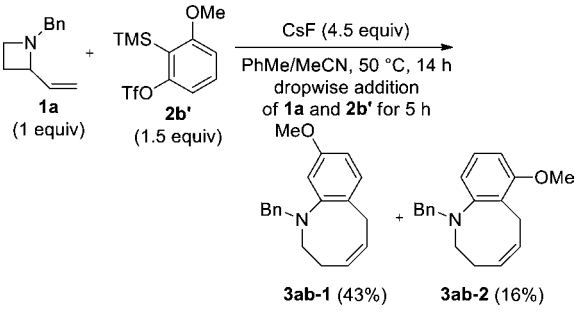
[a] Isolated yield. [b] Cyclohexyl.

To a suspension of CsF (3 equiv) in a 1:1 mixture of toluene and acetonitrile was slowly added (5 h) a solution of 1-benzyl-2-vinylazetidine (**1a**) and benzyne precursor (**2a′**), and the mixture was stirred at 50 °C for an additional 14 h. The ring expansion reaction proceeded smoothly, and the corresponding 1-benzazocine derivative (**3aa**) was isolated in 76% yield (entry 1). It is noteworthy that the reaction proceeded selectively and the formation of a quinoline derivative was not observed. When a larger amount (4.5 equiv) of CsF was used, compound **3aa** was isolated in 81% yield (entry 2). The yield of **3aa** decreased when the reaction was carried out at room temperature or at 80 °C (entries 3 and 4). We also studied the solvent effect on the reaction. When acetonitrile was selected as the solvent, compound **3aa** was isolated in 63% yield (entry 5). On the other hand, compound **3aa** was not isolated when the reaction was carried out in toluene (entry 6). The lower yields of **3aa** in solvents other than toluene−acetonitrile could be attributed to the solubility of CsF. Thus, the presence of a large amount of fluoride ion in acetonitrile induced side reactions, and the solubility of CsF was very low in toluene, preventing the formation of benzyne.

The generality of the cycloaddition was examined by carrying out the reaction of 2-vinylazetidine with various substituents. The results are summarized in Table 2. Cycloaddition of **1b** (R^1 = Me)[6] with benzyne proceeded smoothly, and **3ba** was isolated in 73% yield (entry 2). The yield of the product decreased when the phenyl group[6] was introduced as the substrate (entry 3). We also studied the reactions of various *N*-substituted 2-vinylazetidines. Thus, the reaction of **1d** (R^2 = *p*-methoxybenzyl (PMB)) with benzyne gave **3da** in 78% yield (entry 4). The corresponding benzazocine derivatives were isolated in lower yields when the octyl or cyclohexyl group[11] was introduced as the substituent (entries 5 and 6).

Next, we studied the reaction of vinylazetidine **1a** with various arynes. The reaction of **1a** with 3-methoxybenzyne (**2b**) proceeded with moderate regioselectivity, and **3ab-1** was isolated as the major product (Scheme 1). It is noteworthy that the nitrogen atom of the azetidine attacked the *meta* position of the methoxy group exclusively.

Scheme 1. Reaction of **1a** with **2b′**



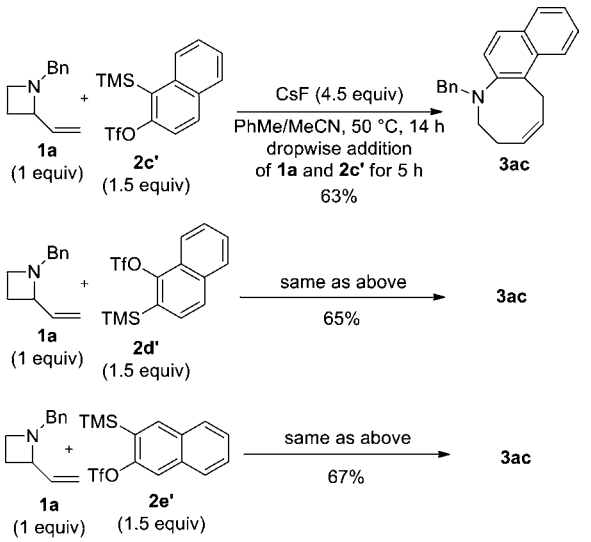
We also studied the reaction of **1a** with naphthalyne. Thus, the reaction of **1a** with **2c′** in the presence of CsF gave **3ac** in 63% yield, and other isomers were not isolated (Scheme 2). A similar result was obtained in the reaction of **1a** with **2d′**, supporting the formation of 1,2-naphthalyne as the intermediate.

To gain insight into the mechanism of this reaction, we carried out the reaction of **1a** with **2a′** in deuterated acetonitrile (Scheme 3).[9] The NMR analysis as well as the mass spectroscopic analysis revealed that a 1:1 mixture of **3aa** and **3aa-D** was isolated in a 43% combined yield. The result indicated that the uptake of the proton from acetonitrile proceeded during the reaction.

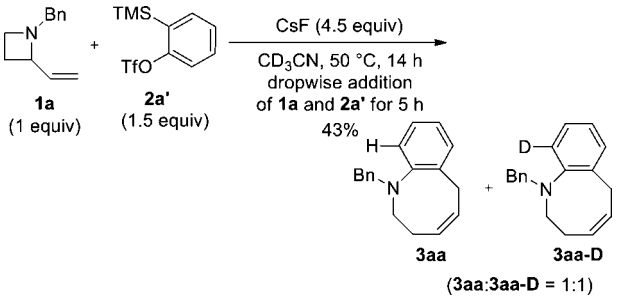
Based on our results and closely related studies,[9] a possible mechanism of this reaction is shown in Scheme 4. The reaction is initiated by the nucleophilic attack of the nitrogen atom of vinylazetidine to benzyne. The zwitterionic species would be protonated to give an azetidinium salt. The isolation of the ammonium salt by the reaction of allylamine with benzyne has been reported by Greaney and

(11) Inman, G. A.; Butler, D. C. D.; Alper, H. *Synlett* **2001**, 914–919.

Scheme 2. Reaction of **1a** with Naphthalynes

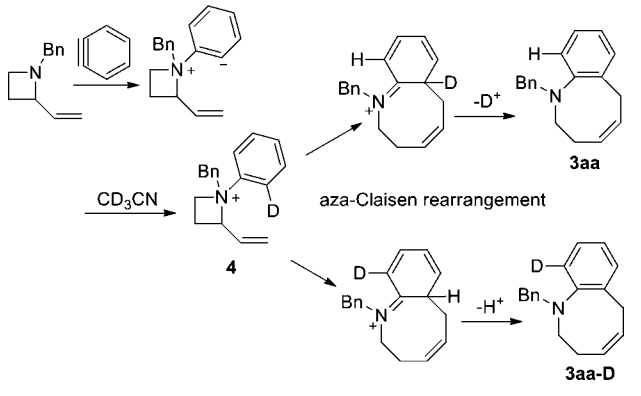


Scheme 3. Reaction of **1a** with **2a′** with Acetonitrile-d_3



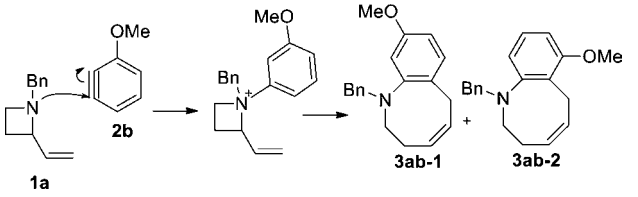
co-workers.[9] The azetidinium salt would rearrange under the reaction conditions to provide the ring expansion product. When the rearrangement of **4** proceeded, half of the incorporated deuterium would be lost and an equimolar mixture of **3aa** and **3aa-D** would be isolated.

Scheme 4. Proposed Mechanism for the [6 + 2] Cycloaddition

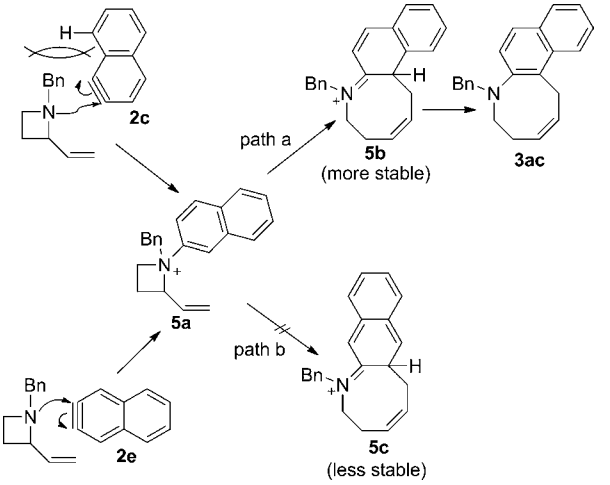


The regioselective reactions of arynes would be explained in terms of the electronic effect and the steric effect of the substituents. Thus, the attack of the nucleophile (azetidine) would occur at the *meta* position to the methoxy group of 3-methoxybenzyne (**2b**) (Scheme 5).[12] Subsequent rearrangement would proceed via the less sterically hindered transition state, providing **3ab-1** as the major product.[13]

Scheme 5. Regioselective Reaction of **2b**



Scheme 6. Regioselective Reactions of **2c** and **2e**



The regioselective reactions of naphthalynes could be explained by considering the stability of the intermediates (Scheme 6). Thus, the attack of the nucleophile toward 1,2-naphthalyne would occur at the C-2 position which is less sterically hindered, and **5a** would be formed.[12] The rearrangement of **5a** would preferentially give **5b** as another intermediate, since the aromaticity is preserved in the structure:[14] if **5c** were formed as the intermediate, the aromatic nature would be lost. The formation of **3ac** as the product would be explained by the deprotonation of **5b**. The reaction of **1a** with 2,3-naphthalyne would also

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give **5a** as the intermediate, and **3ac** would be isolated as the product.

In summary, we have developed a new and simple method for the synthesis of benzazocine derivatives by the [6 + 2] cycloaddition reaction of 2-vinylazetidines with benzyne. The reaction proceeds by the dropwise addition of 2-vinylazetidine and the benzyne precursor to a suspension of CsF at 50 °C, and no catalyst is required. Further extension of this reaction to the synthesis of other medium-sized heterocycles is ongoing.

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Supporting Information Available. Experimental procedures including the synthesis of vinylazetidines, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.