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Synthesis of Fused Polycyclic 1,4-Benzodiazepines via Metal-Free Cascade [5 + 2]/[2 + 2] Cycloadditions

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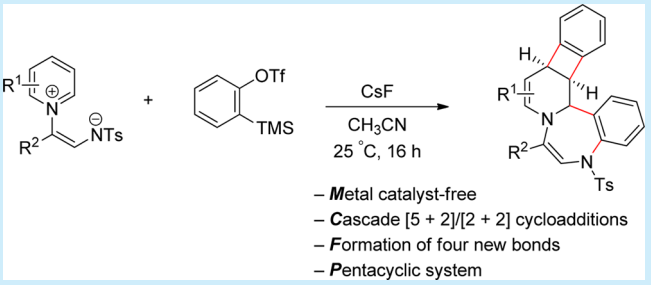
Supporting Information

ABSTRACT: A metal-catalyst-free, mild, and efficient synthetic protocol for polycyclic 1,4-benzodiazepines via cascade [5 + 2]/[2 + 2] cycloadditions between pyridinium zwitterions and arynes is reported. Mechanistic experiments revealed that pyridinium zwitterions act as 1,5-dipoles in [5 + 2] cycloadditions with arynes for the construction of 1,4-benzodiazepines, which further undergo [2 + 2] cycloaddition resulting in the one-pot formation of one C−N bond and three C−C bonds.



Among the wide varieties of heterocyclic compounds, the 1,4-benzodiazepine ring system is a privileged scaffold that constitutes the core structure of many marketed drugs, therapeutic leads, and bioactive natural products.[1] Importantly, the fusion of this seven-membered ring with various carbo- or heterocycles led to the development of scaffolds with a broader spectrum of biological activities.[2] For example, midazolam, alprazolam, and triazolam are imidazole- and triazole-fused tricyclic 1,4-benzodiazepines, known as psychotropic drugs (Figure 1).[3] Moreover, the polycyclic 1,4-benzodiazepine alkaloids bretazenil and circumdatins isolated from *Aspergillus* and *Penicillium* species exhibit excellent pharmacological activities.[4] Thus, the development of methods for the synthesis of fused polycyclic 1,4-benzodiazepines has attracted much attention in the field of medicinal chemistry.

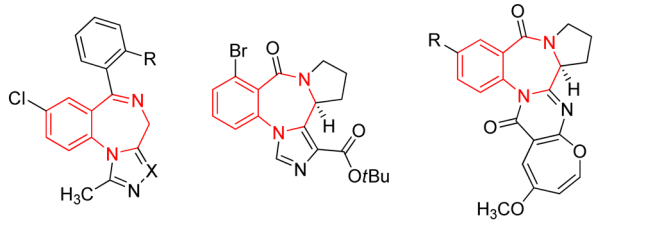


Figure 1. Polycyclic 1,4-benzodiazepines.

Arynes are valuable intermediates in organic synthesis and are involved in a variety of interesting transformation,[5] including Diels−Alder reactions,[6] [2 + 2] cycloaddition,[7] and [3 + 2] cycloadditions.[8] In particular, cycloadditions of benzyne have proved to be an exceptional method for gaining metal-free access to cyclic compounds. In addition, because of its high reactivity, benzyne is well suited for cascade reactions.[9] Thus, the ability to generate molecular complexity in a single operation without the need for a metal catalyst makes benzyne cycloadditions a powerful tool for the synthesis of cyclic compounds. Although [*m* + 2] cycloadditions of benzyne for the construction of four-, five-, and six-membered ring systems have been well studied, to the best of our knowledge, there are very few examples of higher-order cycloaddition,[10] with no reports of [5 + 2] dipolar cycloaddition of benzynes.

Recently, we developed an isolable pyridinium zwitterion (**1**), which can serve as a practical 1,5-dipole in the synthesis of N-heterocyclic compounds.[11] Although the construction of medium-sized heterocyclic rings, especially fused ring systems, is a challenging task because of enthalpic and entropic constraints of the ring closure, catalytic [5 + 2]- and [5 + 3] cycloadditions of pyridinium zwitterions to form seven- and eight-membered N-heterocycles, respectively, have been developed. As part of our interest in the cycloaddition of pyridinium zwitterions for the preparation of heterocyclic compounds, we envisioned that their cycloaddition with arynes could provide fused 1,4-benzodiazepine derivatives.

The present study commenced with the treatment of pyridinium zwitterion **1a** and the benzyne generated in situ from 2-(trimethylsilyl)phenyl triflate **2** in the presence of a fluoride source in DME at room temperature (Table 1).[12] When TBAF or HF-pyridine was used as the fluoride source, only trace amounts of cyclized product **3a** were obtained (entries 1 and 2). Switching the fluoride source to alkali metal fluoride salts KF and CsF furnished **3a** in 32% and 28% yield, respectively (entries 3 and 4). Intriguingly, in THF, the commonly used solvent for the cycloaddition of benzyne, the desired cyclized product **3a** was not observed at all (entry 5), whereas the use of the more polar solvent CH_3CN gave a slightly higher yield (entry 6). Moreover, increasing the loading

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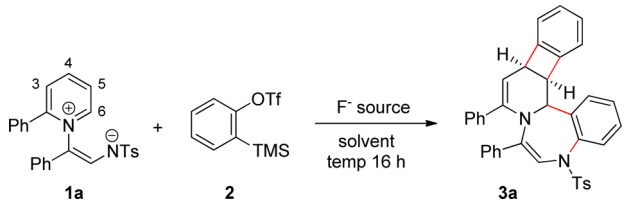
Table 1. Optimization Conditions[a]



entry	equiv of 2	F⁻ [equiv]	solvent	temp (°C)	yield (%)[b]
1	2.4	TBAF [2.4]	DME	25	<1
2	2.4	HF-pyridine [2.4]	DME	25	<1
3	2.4	KF [2.4]	DME	25	32[c]
4	2.4	CsF [2.4]	DME	25	28
5	2.4	CsF [2.4]	THF	25	<1
6	2.4	CsF [2.4]	CH_3CN	25	35
7	2.4	CsF [4.8]	CH_3CN	25	50
8	3.0	CsF [6.0]	CH_3CN	25	45
9	4.8	CsF [9.6]	CH_3CN	25	46
10	2.4	CsF [4.8]	CH_3CN	50	50
11	2.4	CsF [4.8]	CH_3CN	70	45
12	2.4	CsF [4.8]	CH_3CN/C_6H_6	25	9

[a]Reaction conditions: pyridinium zwitterion **1a** (0.2 mmol), benzyne precursor **2** (2.4 equiv), F^- source, and solvent (5.0 mL) for 16 h. [b]NMR yield of **3a** using CH_2Br_2 as an internal standard. [c]18-C-6 (2.4 equiv) was used as an additive.

of fluoride ions to 4.8 equiv afforded the best result (50%, entry 7), while a further increase of benzyne precursor **2** and CsF resulted in slightly reduced yields (entries 8 and 9). Increasing the reaction temperature and using a mixture of CH_3CN and benzene as a solvent were not beneficial (entries 10−12).

Identification of the obtained pentacyclic compound **3a**, resulting from the formation of new bonds at the C4-, C5-, and C6-positions of the pyridinium zwitterion, was established unequivocally by X-ray crystallography (Figure 2).

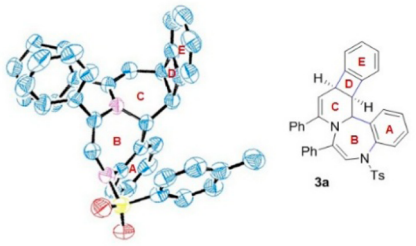
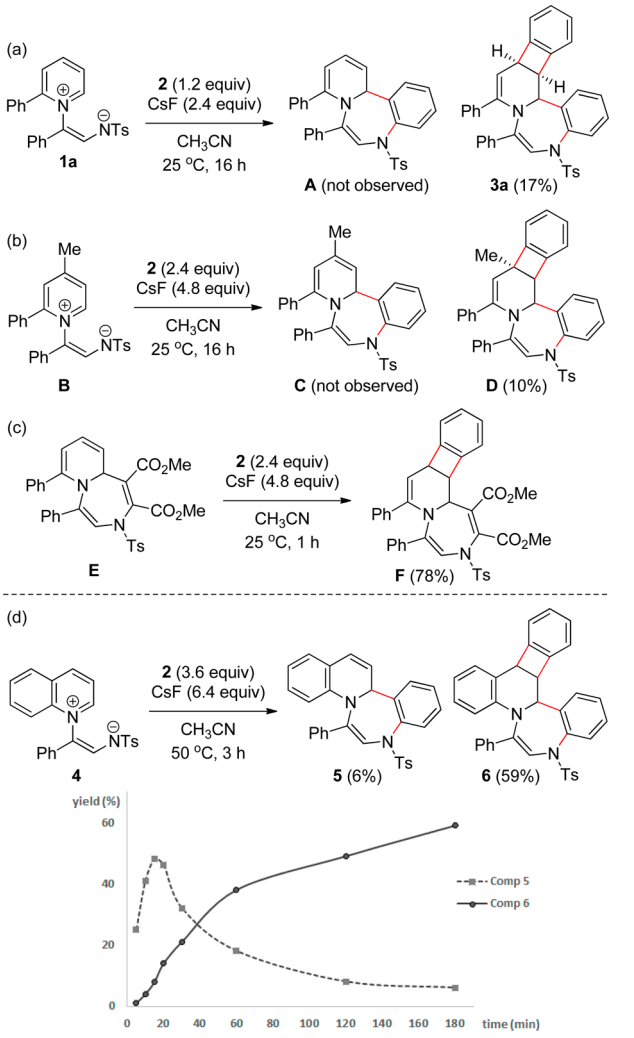


Figure 2. Molecular structure of polycyclic 1,4-benzodiazepine.

To better understand the reaction mechanism, pyridinium zwitterion **1a** was reacted with half of the optimized amount of benzyne (1.2 equiv) (Scheme 1a). Surprisingly, the [5 + 2] cyclized adduct **A** was not observed, and polycyclic product **3a** was isolated in 17% yield. Moreover, when the reaction was carried out using 4-methyl-substituted pyridinium zwitterion **B**, which is sterically hindered for the [2 + 2] cycloaddition, product **C** was not detected (Scheme 1b). It should be mentioned that when the reaction did not proceed efficiently, the pyridinium zwitterion was recovered quantitatively. In an attempt to prove the [2 + 2] cycloaddition of the 1,4-benzodiazepine skeleton and benzyne, compound **E**, which was

Scheme 1. Preliminary Studies for Reaction Mechanism



synthesized by [5 + 2] cycloaddition of **1a** and dimethyl acetylenedicarboxylate, was treated with in situ generated benzyne (Scheme 1c). Contrary to the [5 + 2] cycloaddition, the second [2 + 2] cycloaddition step was complete within 1 h, and the corresponding cyclized product **F** was obtained in 78% yield. The sequential [5 + 2]/[2 + 2] cycloaddition reaction pathway was demonstrated using quinolinium zwitterion **4** and an excess amount of benzyne (Scheme 1d), which afforded the corresponding fused-ring product **6** in 59% yield along with 6% of cyclic compound **5**. Monitoring of the reaction showed that the yield of the final product **6** gradually increased as the amount of [5 + 2] cycloadduct **5** decreased.[12]

Based on our experimental results, a mechanistic rationale for this cascade reaction is proposed in Scheme 2. The [5 + 2] cycloaddition of pyridinium zwitterion **1a** with the benzyne generated in situ from silylaryl triflate **2** leads to the formation of 1,4-benzodiazepine **A**. This first cycloaddition might be the rate-determining step because it involves dearomatization of the pyridinium zwitterion; this explains why the [5 + 2] cycloaddition of pyridinium zwitterion and benzyne does not occur spontaneously at room temperature. Once generated, intermediate **A** immediately cyclizes with another molecule of benzyne, leading to the formation of polycyclic 1,4-benzodiazepine **3a**. Thus, the cascade reaction is driven by

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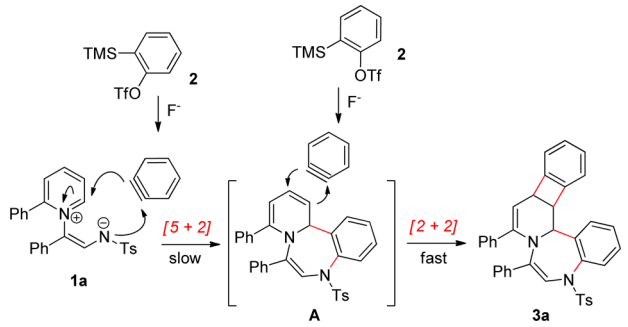
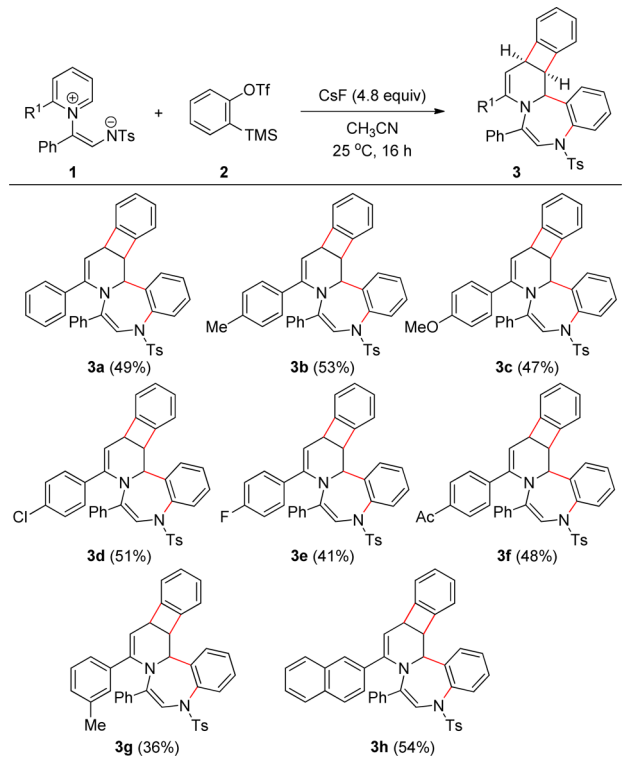
Scheme 2. Proposed Mechanism via Domino Cycloadditions



the second step, i.e., the [2 + 2] cycloaddition, which promotes the overall transformation.

With the optimized conditions in hand and an enhanced mechanistic understanding, we then explored the generality of this cascade cycloaddition reaction for the construction of a variety of polycyclic compounds. First, the electronic and steric effects of the R^1 substituent on the pyridinium ring of **1** were investigated (Scheme 3). The cascade cycloadditions of both

Scheme 3. Cascade [5 + 2]/[2 + 2] Cycloadditions[a,b]

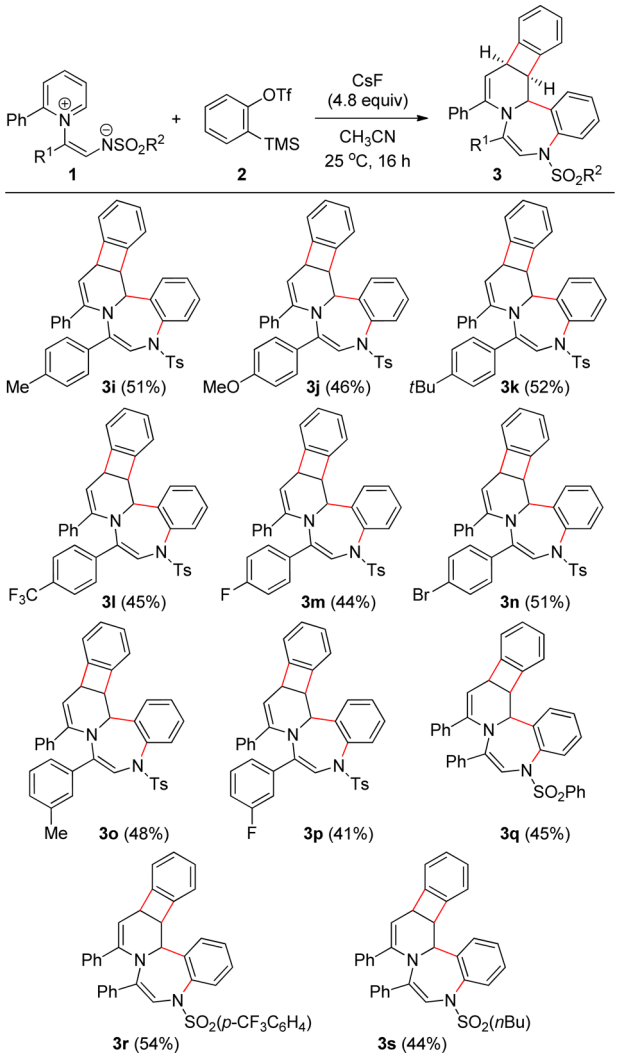


[a]Reaction conditions: pyridinium zwitterion **1** (0.2 mmol), benzyne precursor **2** (2.4 equiv), CsF (4.8 equiv), and CH_3CN (5.0 mL) for 16 h. [b]Isolated yield.

para-methyl- and *para*-methoxy-substituted pyridinium zwitterions proceeded smoothly affording the corresponding polycyclic compounds **3b** and **3c** in 53% and 47% yield, respectively. The scale up experiment was carried out further on 1.0 mmol of pyridinium zwitterion **1b** under the same reaction conditions, and the desired product **3b** was obtained in 48% yield.[12] Halide-substituted polycyclic 1,4-benzodiazepines, which are commonly found in marketed drugs, could also be prepared. In particular, whereas the two-step reaction of chloride-substituted **1d** gave the desired product (**3d**) in acceptable yield, fluoro-substituted benzodiazepine **3e** was obtained in low yield (41%). The electron-withdrawing acetyl group was also well tolerated under the optimized conditions (**3f**). Moreover, a *meta*-tolyl-substituted pyridinium zwitterion provided the corresponding product **3g** in 36% yield. The pyridinium zwitterion bearing a naphthyl group was also a suitable reactant, leading to the formation of cyclic compound **3h** in 54% yield. Unfortunately, the reaction of 2-alkyl substituted pyridine zwitterions and benzyne did not undergo this cascade cycloaddition to afford a multifused cyclic compound.

Next, we explored the substrate scope by varying both the R^1 substituent and the sulfonyl group on the enamide moiety of the pyridinium zwitterion. As summarized in Scheme 4, the efficiency of the cascade reaction was not much influenced by the electronic properties of the substituents, and substrates bearing methyl, methoxy, *tert*-butyl, and trifluoromethyl groups afforded the corresponding products **3i**–**3l** in good yields. Notably, halide-substituted substrates gave cascade products

Scheme 4. Synthesis of Multifused 1,4-Benzodiazepines[a,b]



[a]Reaction conditions: pyridinium zwitterion **1** (0.2 mmol), benzyne precursor **2** (2.4 equiv), CsF (4.8 equiv), and CH_3CN (5.0 mL) for 16 h. [b]Isolated yield.

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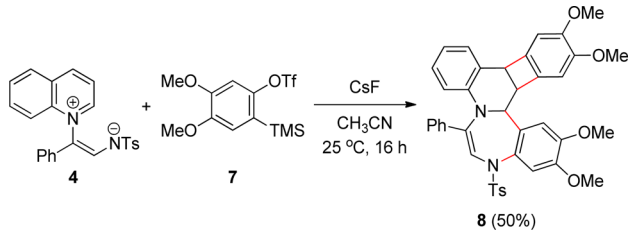
3m and **3n** in 44% and 51% yields, respectively. *meta*-Tolyl- and *meta*-fluorophenyl-substituted pyridinium zwitterions were also well tolerated, providing the corresponding products **3o** and **3p**. Moreover, varying the electronic properties of the sulfonyl group on the pyridinium zwitterion did not significantly affect the product yield (**3q**−**3s**). In addition, the cascade cycloadditions of quinolinium zwitterion **4** with a dimethoxy substituted benzyne precursor (**7**) were successful and afforded polycyclic product **8** in 50% yield (Scheme 5).

Scheme 5. Cycloaddition with Different Aryne Precursor



In conclusion, we have developed a one-pot, mild, and efficient procedure for the synthesis of pentacyclic heterocycles by cascade [5 + 2]/[2 + 2] cycloaddition reactions. In the present method, pyridinium zwitterions act as unique 1,5-dipoles in metal-free [5 + 2] dipolar cycloadditions resulting in the formation of 1,4-benzodiazepines, which further cyclize with arynes via [2 + 2] cycloaddition. We believe that the developed synthetic route to polycyclic 1,4-benzodiazepines will find broad applications in pharmaceutical chemistry as well as in combinatorial chemistry and material science.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01137.

Experimental details, characterization data for new compounds, X-ray crystallographic analysis of the product **3a**, CCDC 1535355 (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information for details.

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