Organic LETTERS

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Ring Enlargement Reaction of *C,N*-Cyclic-*N′*-acyl Azomethine Imines with Sulfonium Ylide: An Efficient Synthesis of 3-Benzazepine Derivatives

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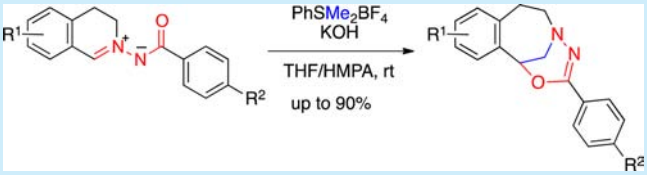
Supporting Information

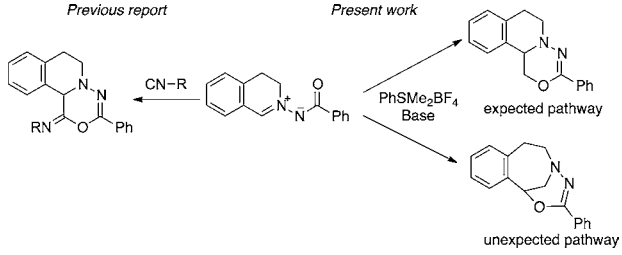
ABSTRACT: Highly efficient formation of 3-benzazepine derivatives has been achieved, based on the ring expansion reaction of *C,N*-cyclic-*N′*-acyl azomethine imines with sulfonium ylide generated *in situ* from the corresponding sulfonium salt. The reactions proceeded smoothly to afford the tricyclic 3-benzazepine derivatives in good to high yields. A wide range of *C,N*-cyclic *N′*-acyl azomethine imines were applicable to this reaction.



Benzazepines, which have a 7-membered aza-heterocyclic fused aromatic ring, are of interest because of their biological activity and use as building blocks for natural product synthesis and drug discovery.[1] The 1-substituted tetrahydro-3-benzazepine derivatives are known to act as dopamine receptor agonists and antagonists.[2] An example is SCH-23390.[3] These compounds also are active in animal models of neurological disorders such as Parkinson's disease[4] and Alzheimer's disease.[5] In the area of natural products synthesis, syntheses of alkaloids with a benzazepine skeleton, such as aphanorphine,[6] cephalotaxine,[7] and lennoxamine,[8] have been investigated because of their interesting chemical structures and useful biological activities. Several synthetic procedures have been developed for 3-benzazepine derivatives, including a simple condensation reaction,[9] reductive cyclization to form azepine carbon−nitrogen bonds,[10] cyclization via aromatic substitution such as the Friedel−Crafts reaction,[6d,11] intramolecular Heck reaction,[12] or ring expansions such as the Beckmann rearrangement of *α,β*-tetralone oxime.[13] Among these reactions, migration and insertion-based ring expansion is one of the most efficient methods for constructing the substituted 3-benzazepine skeletons from isoquinoline derivatives.[14] The present report describes the highly efficient formation of 1-substituted tetrahydro-3-benzazepine derivatives by an unexpected ring expansion reaction of a *C,N*-cyclic-*N′*-acyl azomethine imine with sulfonium ylide (Scheme 1).

The [5 + 1] cycloaddition reaction between isocyanide and a *C,N*-cyclic-*N′*-acyl azomethine imine as an "isocyanophile" has been developed previously.[15] Thus, a molecule containing both nucleo- and electrophilic characteristics on the same carbon atom was expected to act as a C1 source, similar to an isocyanide, and reaction with the *C,N*-cyclic-*N′*-acyl azomethine imine was expected to afford the corresponding [5 + 1] cycloadduct.

Scheme 1. Working Hypothesis

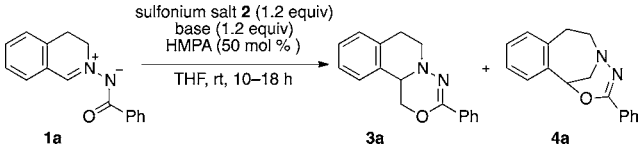


Based on this hypothesis, the initial reaction of *C,N*-cyclic-*N′*-acyl azomethine imine **1a**[16] with trimethylsulfonium iodide (**2a**) and dimsyl anion generated *in situ* by NaH in DMSO was attempted (Table 1).[17] The desired cycloadduct **3a** was obtained in 8% yield. Surprisingly, a ring-expanded 3-benzazepine derivative **4a** also was obtained in 38% yield (Table 1, entry 1). The structure of **4a** was determined unambiguously using X-ray crystallographic analysis (Figure 1). The reaction using NaH as a base in THF also afforded **4a** in 23% yield (Table 1, entry 2). Using KH as a base, **4a** was obtained selectively in 32% yield (Table 1, entry 3). When dimethylphenyl sulfonium tetrafluoroborate (**2b**)[18] was employed as a sulfonium salt, the reaction proceeded cleanly to produce the 3-benzazepine derivative **4a** in 74% yield (Table 1, entry 4). When 1.2 equiv of 18-crown-6 were added to capture potassium cations, the product was obtained in 70% yield (Table 1, entry 5). The use of 50 mol % HMPA, which can coordinate the potassium cation, improved the chemical yield to 86% (Table 1, entry 6). Bases other than KH also were evaluated to generate sulfonium ylide for the ring expansion reaction in THF (Table 1, entries 7−11). The use of KOH

Received: August 7, 2014
Published: September 8, 2014

dx.doi.org/10.1021/ol502347n | *Org. Lett.* 2014, 16, 4854−4857

Table 1. Results from Optimization Reactions



entry[a]	2, sulfonium salt	base	3a yield (%)	4a yield (%)
1[b,c]	**2a**, Me_3SI	NaH[d]	8	38
2[c]	**2a**, Me_3SI	NaH	8	23
3[c]	**2a**, Me_3SI	KH	–	32
4[c]	**2b**, $C_6H_5SMe_2BF_4$	KH	–	74
5[e]	**2b**, $C_6H_5SMe_2BF_4$	KH	–	70
6	**2b**, $C_6H_5SMe_2BF_4$	KH	–	86
7	**2b**, $C_6H_5SMe_2BF_4$	KOH	–	82
8	**2b**, $C_6H_5SMe_2BF_4$	KO*t*-Bu	–	messy
9	**2b**, $C_6H_5SMe_2BF_4$	NaH	–	nr
10	**2b**, $C_6H_5SMe_2BF_4$	*n*-BuLi	–	messy
11	**2b**, $C_6H_5SMe_2BF_4$	LDA	–	38
12	**2c**, 4-$ClC_6H_4SMe_2BF_4$	KOH	–	trace
13	**2c**, 4-$ClC_6H_4SMe_2BF_4$	KH	–	51
14	**2d**, 4-$MeC_6H_4SMe_2BF_4$	KH	–	80
15	**2d**, 4-$MeC_6H_4SMe_2BF_4$	KOH	–	nr

[a]Using 1.2 equiv of **2**, base, and 50 mol % of HMPA unless otherwise noted. [b]DMSO was used as a solvent instead of THF. [c]In the absence of HMPA. [d]Dimsyl anion in DMSO was generated *in situ*. [e]1.2 equiv of 18-crown-6 was used instead of HMPA.

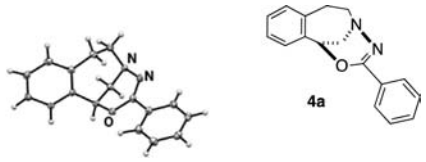
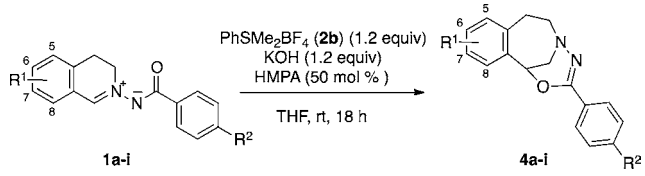


Figure 1. X-ray structure of compound **4a**.

afforded the product in high yield (Table 1, entry 7); however, KO*t*-Bu and NaH were not effective (Table 1, entries 8 and 9, respectively). *n*-Butyllithium and LDA were ineffective in this reaction, although the product was obtained in 38% yield when LDA was used (Table 1, entries 10 and 11, respectively). These results indicate KH and KOH are the preferred bases for this reaction system (Table 1, entries 6 and 7, respectively). Sulfonium ylide derivatives (i.e., sulfonium salts containing electron-withdrawing or -donating groups on the aromatic ring) were examined for the efficient ring expansion reaction of a *C,N*-cyclic-*N*′-acyl azomethine imine (Table 1, entries 12–15). When a sulfonium salt with an electron-withdrawing group on the aromatic ring **2c**[18] was used with KOH as a base, very low reaction efficiency was observed (Table 1, entry 12). However, KH was a more beneficial base in this case, affording the product in 51% yield (Table 1, entry 13). The sulfonium salt containing an electron-donating group, **2d**,[18] showed the same reactivity as **2b** in the presence of KH, affording the product in 80% yield (Table 1, entry 14). However, for **2d**, KOH did not generate the corresponding sulfonium ylide (Table 1, entry 15).

Reactivity toward various azomethine imines with dimethylphenyl sulfonium ylide was examined by treatment using 1.0 equiv of azomethine imines **1a–i** and 1.2 equiv of **2b** in the presence of KOH to generate the sulfonium ylide (Table 2), because KOH was easier to handle than KH. The *C,N*-cyclic *N*′-acyl azomethine imines containing 5-, 6-, and 7-methyl substituents reacted to yield the corresponding heterocycles

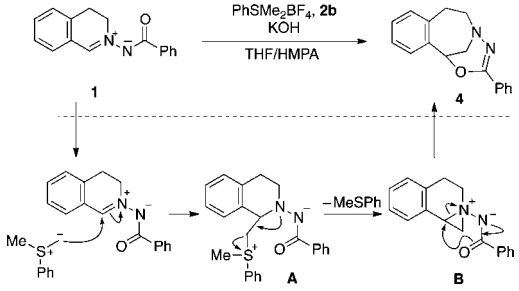
Table 2. Scope of *C,N*-Cyclic-*N*′-acyl Azomethine Imine Reactions



entry	1, R^1, R^2	4, yield (%)
1	**1a**, H, H	**4a**, 82
2	**1b**, 5-Me, H	**4b**, 83
3	**1c**, 6-Me, H	**4c**, 90
4	**1d**, 7-Me, H	**4d**, 86
5	**1e**, 8-Me, H	**4e**, 46
6	**1f**, 6-MeO, H	**4f**, 74
7	**1g**, 7-Br, H	**4g**, 80
8	**1h**, H, Me	**4h**, 87
9	**1i**, H, Cl	**4i**, 73

(Table 2, entries 2–4). The only exception was the reaction using the 8-methyl substituent, which was very slow (Table 2, entry 5). The *C,N*-cyclic *N*′-azomethine imine **1f** having an electron-donating group also was tested (Table 2, entry 6). The *C,N*-cyclic *N*′-azomethine imine **1g** with an electron-withdrawing group on the aromatic ring reacted smoothly to afford product **4g** in 80% yield (Table 2, entry 7). The influence of the substituent on the benzoyl group on the nitrogen also was examined. Results showed that a methyl group on the aromatic moiety was more effective than a chloride and afforded products in 87% and 73% yields, respectively (Table 2, entries 8 and 9). Thus, the electron density of the *N*′-acyl moiety plays an important role in the cyclization.

Scheme 2. Proposed Reaction Mechanism

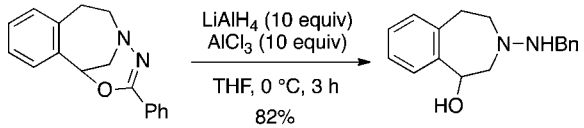


Scheme 2 presents the proposed mechanism for the ring enlargement reaction of *C,N*-cyclic-*N*′-acyl azomethine imines with sulfonium ylide. In this mechanism, sulfonium ylide, generated from the corresponding sulfonium salt with a base, reacts with C=N$^+$ of the azomethine imine to afford **A**. The nitrogen atom of the isoquinoline moiety attacks the α-position of the sulfonium cation to form the aziridinium cation **B**. Finally, nucleophilic attack of the amidocarbonyl oxygen on the C1 position caused the isoquinoline skeleton to undergo ring opening to yield the corresponding 3-benzazepine derivative **4**.

The oxadiazine ring of the product **4a** readily opened to afford the 1-hydroxy-3-benzazepine derivative **5** under reductive conditions (Scheme 3). Thus, hydrogenation in the presence of Raney-Ni, or Pd/C, and reduction in the presence of $LiAlH_4$ did not work well and only starting **4a** was recovered quantitatively. Fortunately, the reductive opening of the

dx.doi.org/10.1021/ol502347n | *Org. Lett.* 2014, 16, 4854–4857

Scheme 3. Reduction of 4a to 1-Hydroxy-3-tetrahydrobenzazepine 5



4a 5

oxadiazine ring proceeded smoothly using $LiAlH_4$ with $AlCl_3$[2e,9a] at 0 °C to afford 1-hydroxy-3-tetrahydrobenzazepine **5** in 82% yield. The skeleton of this molecule has been reported to possess activity as a NR2B-selective NMDA receptor antagonist.[2b,c]

In summary, a synthetic method for the highly efficient formation of tricyclic 1-substituted tetrahydro-3-benzazepine derivatives has been developed, based on the ring expansion reaction of a *C,N*-cyclic-*N*′-acyl azomethine imine with sulfonium ylide generated from the corresponding sulfonium salt. The reactions proceeded smoothly to afford the tricyclic 3-benzazepine derivatives in good to high yields. A wide range of *C,N*-cyclic *N*′-acyl azomethine imines were successfully applied to this reaction. This method is promising for the synthesis of biologically active tetrahydro-3-benzazepine compounds.

■ ASSOCIATED CONTENT

Supporting Information

General procedure, NMR spectra, and X-ray structure of **4a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Young Scientists (B) (24750037) and a Grant in-Aid for Scientific Research (B) (24350022) from the Japan Society for the Promotion of Science.

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