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Sequential Annulation Domino Reaction of Sulfur Ylides and α,β-Unsaturated Cyclic Ketimines: Synthesis of Cyclic 2-Alkenyl Aziridines

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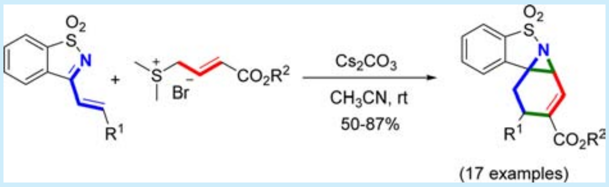
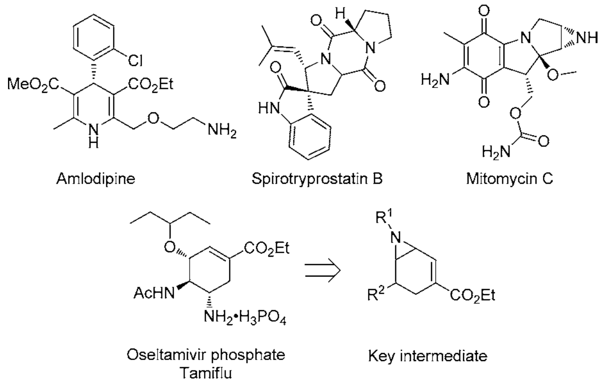
Supporting Information

ABSTRACT: A sequential annulation domino reaction of sulfur ylides and α,β-unsaturated cyclic ketimines for the construction of cyclic 2-alkenyl aziridines has been developed. Readily accessible starting materials, a one-pot procedure, excellent functional group compatibility, and mild conditions make this transformation a powerful tool for the synthesis of cyclic 2-alkenyl aziridines.



Nitrogen-containing heterocyclic skeletons represent privileged structural motifs in biologically active natural products, pharmaceuticals, and agrochemicals.[1] Molecules such as amlodipine, spirotryprostatin B, and mitomycin C (Scheme 1) are typical examples with significant pharmaceutical activity.[2]

Scheme 1. Representative Pharmaceuticals with Nitrogen-Containing Heterocyclic Skeletons

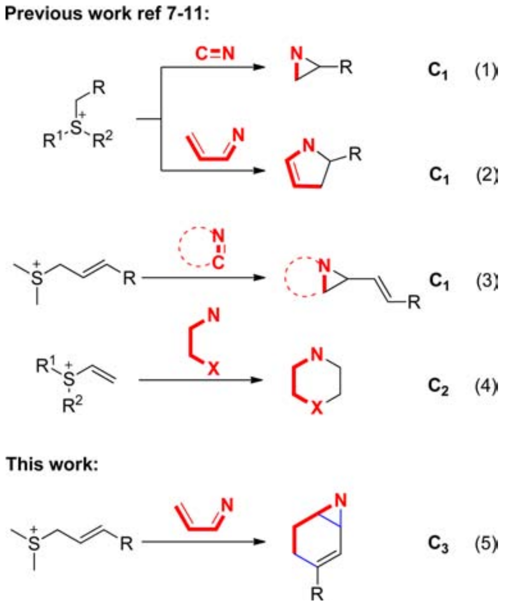


Moreover, nitrogen-containing heterocycles are also fascinating intermediates in organic synthesis, serving as precursors of many biologically active compounds.[3] Oseltamivir phosphate (Tamiflu), an orally active neuraminidase inhibitor, can effectively treat and prevent seasonal influenza virus infections.[4]

Recent practice shows that Tamiflu is active against the avian H5N1 influenza as well as the swine H1N1 influenza.[5] Among the developed methods to synthesize Tamiflu, cyclic 2-alkenyl aziridines are the key intermediates.[6] However, the synthetic route for this intermediate is usually tedious. Therefore, the development of alternative approaches to such nitrogen-containing heterocycles that start from simple materials and are highly efficient has drawn extensive attention from the chemical community.

First applied in the 1960s, sulfur ylides have been widely used as methylene-transfer reagents in the construction of three-membered-ring compounds.[7] The reaction of sulfur ylides with imines is an important synthetic method for the construction of aziridines (Scheme 2, eq 1).[7a,b,d] Later researches broadened the application scope of sulfur ylides.[8] For example, Xiao and co-workers reported a [4 + 1] annulation of sulfur ylides and α,β-unsaturated imines for the enantioselective construction of a series of pyrrolines (Scheme 2, eq 2)[9] in which the sulfur ylide

Scheme 2. Representative Examples of Annulations Involving Sulfur Ylides



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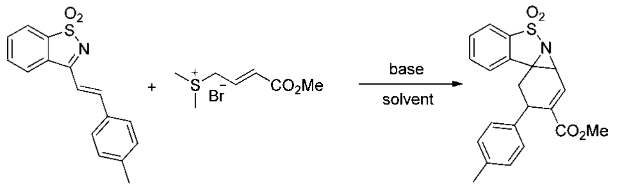
acts as a C_1 synthon in the construction of five-membered azaheterocycles. Recently, Tang and co-workers developed a diastereoselective annulation reaction using allylic sulfur ylides and cyclic ketimines (Scheme 2, eq 3).[10] Allylic sulfur ylides reacted as C_1 synthons in the construction of fused vinyl aziridines. In 2008, Aggarwal's group reported a novel reaction of biselectrophilc vinyl sulfonium salts and *β*-amino alcohols/thiols/amines delivering six-membered azaheterocycles (Scheme 2, eq 4).[11] Notably, this transformation represents the application of sulfur ylides as C_2 synthons in the synthesis of nitrogenous heterocycles. Inspired by their excellent work and on the basis of our continuous interest in developing new sequential annulation domino reactions to construct bicyclic skeletons[12] and exploring new reactions of sulfur ylides,[13] we have developed a novel annulation of crotonate-derived sulfonium salts and *α*,*β*-unsaturated cyclic ketimines[14] to generate cyclic 2-alkenyl aziridines (Scheme 2, eq 5). To the best of our knowledge, this is the first example of sulfur ylides acting as C_3 synthons[15] in the constructing of nitrogen-containing heterocycles.

Our study commenced with the reaction between *α*,*β*-unsaturated cyclic ketimine **1a** and sulfonium salt **2a** (2.5 equiv) in the presence of Cs_2CO_3 (3 equiv) in CH_3CN at room temperature (Table 1, entry 1). Pleasingly, the reaction gave cyclic 2-alkenyl aziridine **3a** in 87% yield. Subsequent screening of bases and solvents did not give a better yield (entries 2–8). Then we tried to conduct the reaction at 0 °C, which provided a yield of 74% (entry 9). When the loading of **2a** was decreased to 2 equiv, the reaction proceeded with a lower yield of 68% (entry 10), whereas the reaction gave nearly the same yield (84%) when the loading of Cs_2CO_3 was decreased to 2 equiv (entry 11).

Table 1. Screening of the Reaction Conditions[a]

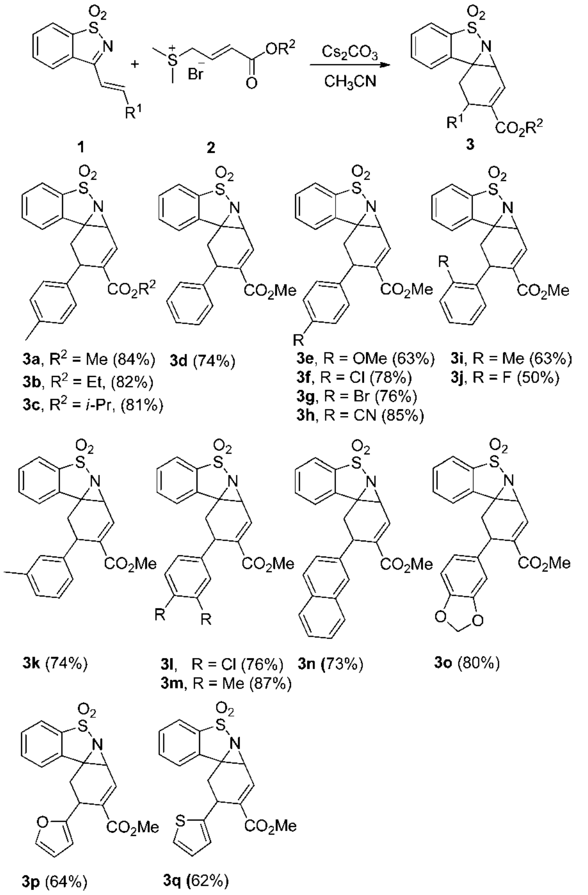


1a **2a** **3a**

entry	solvent	base	**1a**/**2a**/base	yield (%)[b]
1	CH_3CN	Cs_2CO_3	1:2.5:3	87
2	CH_3CN	K_2CO_3	1:2.5:3	18
3	CH_3CN	*t*-BuOK	1:2.5:3	13
4	CH_3CN	Et_3N	1:2.5:3	74
5	CH_3OH	Cs_2CO_3	1:2.5:3	45
6	$CHCl_3$	Cs_2CO_3	1:2.5:3	50
7	toluene	Cs_2CO_3	1:2.5:3	13
8	THF	Cs_2CO_3	1:2.5:3	29
9[c]	CH_3CN	Cs_2CO_3	1:2.5:3	74
10	CH_3CN	Cs_2CO_3	1:2:3	68
11	CH_3CN	Cs_2CO_3	1:2.5:2	84

[a] Unless otherwise noted, reactions of **1a** (0.10 mmol) and **2a** were carried out in the presence of Cs_2CO_3 in 1 mL of the solvent at room temperature. [b] Isolated yields. [c] The reaction temperature was 0 °C.

Scheme 3. Scope of the Reaction[a,b]



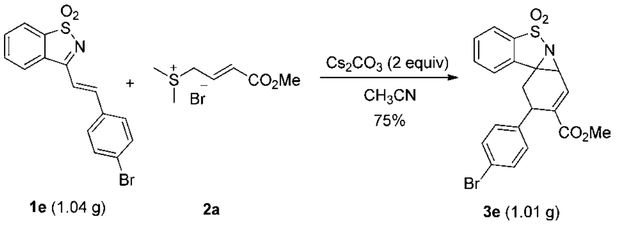
[a] Reactions of **1** (0.20 mmol) and **2** (0.50 mmol) were carried out in the presence of Cs_2CO_3 (0.40 mmol) in 2 mL of CH_3CN. [b] Isolated yields are shown.

With the optimal conditions in hand, we next examined the substrate generality of this domino annulation between sulfur ylides and *α*,*β*-unsaturated cyclic ketimines (Scheme 3). We found that increasing the size of the ester group in sulfonium salt **2** did not affect the yield (**3a**–**c**). *α*,*β*-Unsaturated cyclic ketimines with either electron-rich or electron-deficient substituents at the para position of the benzene ring were well-tolerated, producing the desired products in good yields (**3a**, **3e**–**h**). In the case of different substituents at the ortho position of the benzene ring, reduced yields were obtained, probably because of steric hindrance (**3i** and **3j**). Substrate **1k** with Me at the meta position on the phenyl ring was also transformed into the corresponding cyclic 2-alkenyl aziridine **3k** in 74% yield. Moreover, substrates **1** with 3,4-dichloro- and 3,4-dimethyl-substituted phenyl rings produced the corresponding products in good yields (**3l** and **3m**). Further investigation proved that an *α*,*β*-unsaturated cyclic ketimine bearing a naphthyl group was also a suitable substrate for this conversion (**3n**). In addition, heterocycle-bearing *α*,*β*-unsaturated cyclic ketimines were also efficient for the transformation, and the desired products were isolated in moderate yields (**3o**–**q**). The structure and stereochemistry of **3l** was characterized by a combination of NMR, HRMS, and single-crystal X-ray analysis (see S-Figure 1 in the Supporting Information).[16]

To further investigate the synthetic utility of this reaction, a gram-scale version of the reaction using substrates **1e** and **2a** was carried out, and compound **3e** was obtained in 75% yield (Scheme 4).

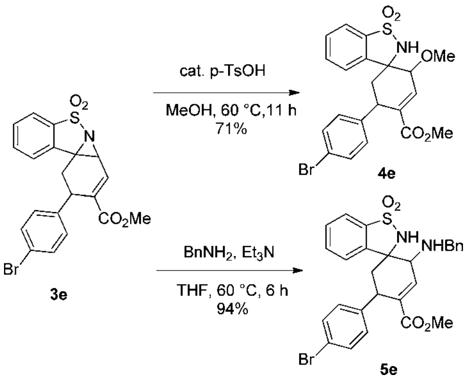
The obtained cyclic 2-alkenyl aziridines are potential intermediates for the construction of Tamiflu since aziridines can easily undergo nucleophilic ring opening to generate

Scheme 4. Scaled-Up Synthesis



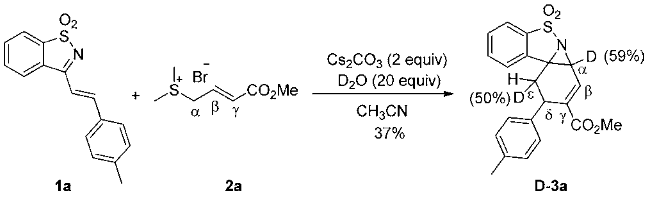
corresponding structures. Some transformations were conducted using product **3e** (Scheme 5). Treatment of cyclic 2-alkenyl aziridine **3e** in methanol in the presence of *p*-TsOH resulted in opening of the aziridine ring, affording product **4e** in 71% yield. Using benzylamine as the nucleophile afforded product **5e** bearing a 1,2-diamine structure, which represents an important subunit in many biological compounds.[17]

Scheme 5. Synthetic Transformations



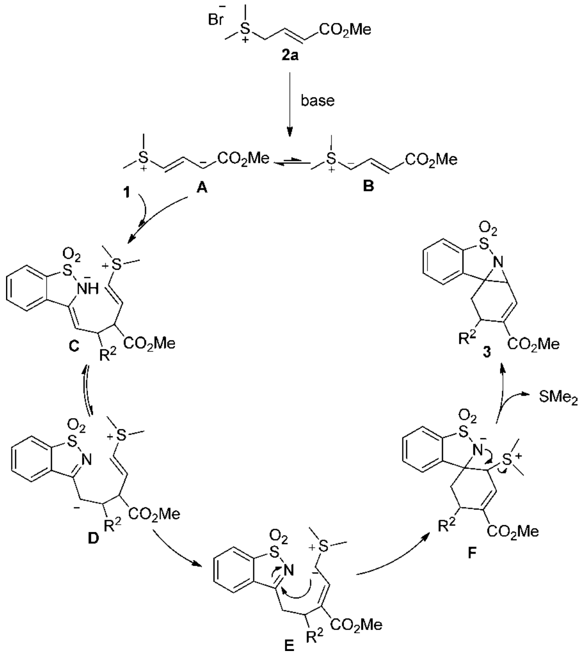
To gain insight into the reaction mechanism, we conducted the domino reaction with **1a** and **2a** in the presence of 20 equiv of D_2O. The deuterated product **D-3a** was obtained in a reduced yield of 37%, probably because of interactions between D_2O and the sulfonium salt. ^1H NMR analysis showed 59% deuterium incorporation at the α-position and 50% deuterium incorporation at the ε-position, unveiling the possibility of the involvement of a carbanion intermediate (Scheme 6). A plausible mechanism for this reaction is proposed in Scheme 7. Under the treatment of base, sulfonium salt **2a** could be transformed into allylic ylides **A** and **B**, which then undergo a Michael addition to the α,β-unsaturated cyclic ketimines to form intermediate **C**. Then a series of proton transfers leads to intermediates **D** and **E**. The subsequent intramolecular nucleophilic addition and elimination of Me_2S could further give the final product **3**.

Scheme 6. Control Experiments



In conclusion, we have developed a novel sequential [3 + 3] and [1 + 2] annulation domino reaction of sulfur ylides and α,β-unsaturated cyclic ketimines for the first time, which provides a rapid, efficient, and selective route to nitrogen-containing heterocycles. In this reaction, the crotonate-derived sulfur ylides act as C_3 synthons and participate in the synthesis of cyclic 2-alkenyl aziridines in good to excellent yields under mild conditions. Moreover, this reaction has a broad substrate scope. The developed method achieves the highly efficient synthesis of cyclic 2-alkenyl aziridines in a one-pot procedure. We believe that this novel annulation reaction will be the method of choice for the synthesis of molecules with pharmacological importance. Further studies to expand the scope of the sulfur ylides are currently ongoing.

Scheme 7. Plausible Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01045.

Crystallographic data for **3l** (CIF)

Experimental details, characterization data for new compounds, copies of NMR spectra, and X-ray crystal structure of **3l** (PDF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1419912 (**3l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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