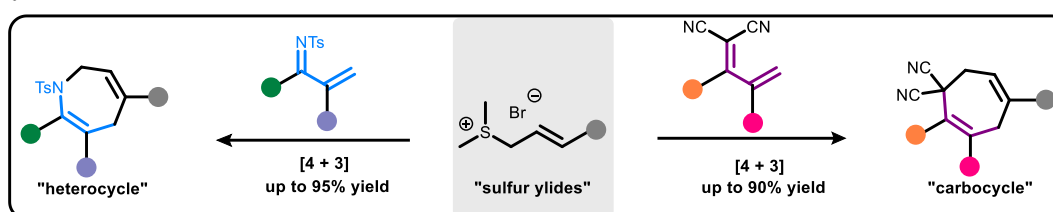


Construction of Seven-Membered Cycles through Base Promoted [4+3] Domino Annulation of Crotonate-derived Sulfur Ylides with Diene

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Supporting Information



ABSTRACT: A sequential [4+3] domino annulation of crotonate-derived Sulfur Ylides with Diene has been reported. With base promoted, this general method can realize the synthesis of highly functional none-fused cycles including nitrogen-heterocycles and carbocycles which are widely and important in pharmaceutical molecules with excellent yield respectively, showing a great application potential. Meanwhile, this is also a supplementary to sulfur ylide chemistry as the C3 synthesizer.

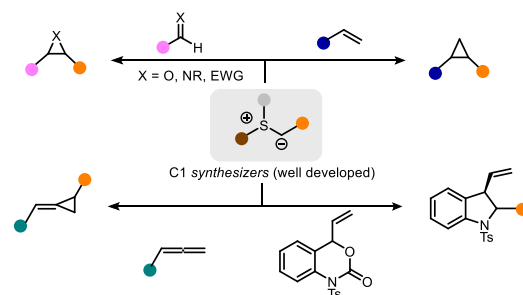
Sulfur ylides are among the most significant and widely applied chemical reagents participated in the field of organic synthetic chemistry.¹ The chemistry of this type of reagents has evolved dramatically over the past 50 years since the pioneering work of Johnson, Corey and Chaykovsky in the 1960s² as the well-known Johnson-Corey-Chaykovsky reaction. Based on that, sulfur ylides can react with polar substrates, for example, aldehydes,³ ketones,⁴ imines⁵ and electron-deficient alkenes⁶ to produce a wide range of significant small-ring molecules such as epoxides, aziridines, cyclopropanes and so on⁷. More importantly, their synthetic potential has been well applied in the synthesis of numerous bioactive natural products and pharmaceuticals.⁸ So, developing the novel and extensive methods is greatly meaningful.

In the past decade, sulfur ylide has mainly participated in many cycloaddition reactions but always as the C1 synthesizers⁹ which are attributed to inherent properties as nucleophilic 1,1-dipolar species as shown in Scheme 1a. Although some elegant work has been reported, the specific structure of sulfur ylides limited the possibility of building large-membered ring molecules.

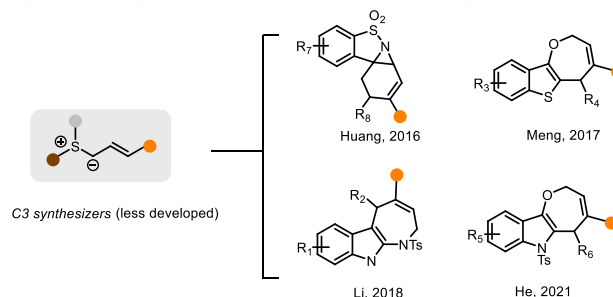
In order to address this issue, a new type of crotonate-derived sulfur ylide was developed in recent years.¹⁰ Because of the introduction of allylic part, the negative carbon dipolar would tend to tautomerize to other position with the base involved as the C3 synthesizers through a domino process (Scheme 1b).

Scheme 1. Recent advances in the catalytic cyclization reactions of sulfur ylides as the C1 or C3 synthesizers

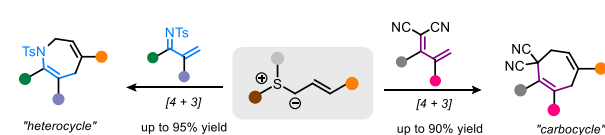
a) Common sulfur ylides participate in cycloaddition reactions as C1 synthesizers



b) Crotonate sulfur ylides participate in cycloaddition reactions as C3 synthesizers



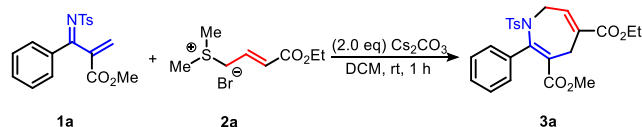
c) This work: Base promoted [4+3] annulation of Crotonate-derived Sulfur Ylides



For example, Huang^{11a} reported a original annulation domino reaction of crotonate-derived sulfur ylide and α,β -unsaturated cyclic ketimines for the construction of cyclic 2-alkenyl aziridines. Meng^{11b} developed a novel NaH promoted domino reaction between thioaurones and crotonate-derived sulfonium salts, which has been the first example of using a crotonate-derived sulfonium salt as a C3 synthon in a [4+3] annulation reaction. A variety of 2,5-dihydrobenzo [4,5] thieno [3,2-b] oxepines were obtained. Li^{11c} developed a novel [4 + 3] annulation of iminoindoline-derived aza-dienes with crotonate sulfonium salts to construct azepino[2,3-b] indole cores. He^{11d} has developed a Cs₂CO₃ promoted [4+3] cascade annulation reaction of crotonate-derived sulfur ylides with 2-ylideneoxindoles to synthesize a series of oxepino [3,2-b] indoles. Inspired by the previous work, we envisioned a base promoted [4+3] domino annulation of crotonate-derived sulfur ylides with functional diene to synthesize a series of none-fused cycles including nitrogen-heterocycles and carbocycles (Scheme 1c).

We evaluated our investigation with a model reaction between 1-azadiene **1a** and crotonate-derived sulfur ylide **2a** in the presence of Cs₂CO₃ in dichloromethane at room temperature for 1 h to obtain nitrogen-heterocycles **3a** (X-ray crystallographic analysis, CCDC 2145522) in 95% isolated yield (Table 1, entry 1). Some screening data of the reaction conditions were shown in Table 1. This reaction could not occur without base participated (entry 2). We changed the base to Et₃N, DABCO, K₂CO₃, but an unsatisfactory result was acquired with the yield of 54%, 32%, 84% separately (entry 3). The different solvents such as MeCN, DMF also were investigated with the yield of 78%, 80% separately. When chose alcohols solvent such as MeOH, less than 5% of the product was obtained (entry 4). We tried to reduce the amount of base to 1.0 eq, but the yield was decreased correspondingly to 48% (entry 5). When the temperature was raised to 60 °C, we found that the raw material **2a** began to decompose and the by-products began to increase. So that leads to a decrease in the 25% yield of **3a** (entry 6).

Table 1. Screening Data of the Reaction Conditions to Synthesize Nitrogen-Heterocycles^a



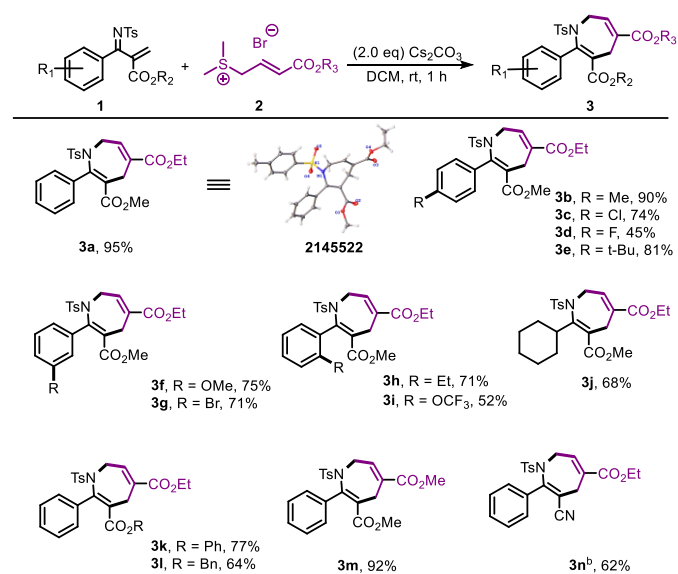
entry	deviation from initial conditions	yield of 3a ^b (%)
1	none	95
2	No base	N.D.
3	Et ₃ N, DABCO, K ₂ CO ₃	54, 32, 84
4	MeCN, MeOH or DMF instead of DCM	78, <5, 80
5	1.0 eq based	48
6	60 °C instead of room temperature	25

^aReaction conditions: **1a** (0.10 mmol, 1.0 eq), **2a** (0.12 mmol, 1.2 eq), Cs₂CO₃ (0.20 mmol, 2.0 eq), DCM (0.5 mL), r.t, 1 h. N.D. = not detected. DMF = N, N'-dimethylforma. ^bIsolated yield was reported.

With these optimized conditions in hand, we then examined the generality of similar substrates. As shown in scheme 2, different substituent azadiene **1** was used under the standard condition. For example, Electron-donating group including *para*-methyl **3b** (90%), *para*-tertiary butyl **3e** (81%), *meta*-methoxy

3f (75%), *ortho*-ethyl **3h** (71%) showed a satisfactory result. What's more, typical electron-withdrawing group such *para*-fluorine **3d** (45%), trifluoromethoxy **3i** (52%) was also tolerated. Some halogen group, *para*-Cl **3c** (74%), *meta*-Br **3g** (71%). Alkyl substituted like cyclohexane **3j** also showed a good yield of 68%. To our delight, the ester group from azadiene showed good compatibility similarly represent in **3k** and **3l**. Then, we evaluated the scope of crotonate-derived sulfur ylide (**3m**) by changing the ester group, which proved there is not any effect too. Replacing an ester group with a cyanide group could also trigger the reaction (**3n**).

Scheme 2. Scope of the Nitrogen-Heterocycles^a

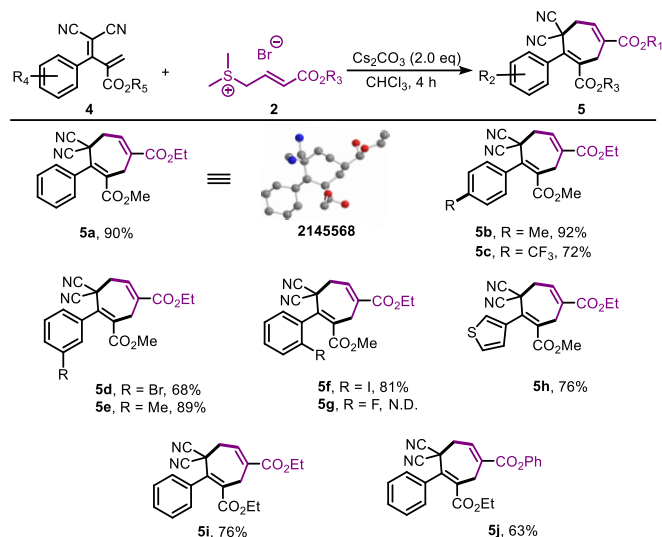


^aReaction conditions: **1** (0.10 mmol, 1.0 eq), **2** (0.12 mmol, 1.2 eq), Cs₂CO₃ (0.2 mmol, 2.0 eq), DCM (0.5 mL), r.t, 1 h. ^bReact for 12 h.

Subsequently, we focus on the structure of seven-membered carbocycles. The diene **4** and sulfur ylide **2** were chosen to participated in the [4+3] domino annulation under similar conditions (Specific experimental conditions were screened by reference to SI). Surprisingly, we could obtain the carbocycles **5a** (X-ray crystallographic analysis, CCDC 2145568) with the isolated yield of 90% meanwhile. This exciting result encouraged us to continue our further exploration by employing the different substitutions (Scheme 3). Electron-donating group including methyl at *para* **5b** or *meta* position **5e** show a good result for over 92%, 89% yield separately. The electron-withdrawing group CF₃ **5c** could also be tolerated towards this reaction. When move the fluorine group to *ortho* position, there was no any product can be observed (**5g**). Some halogen groups (**5d** and **5f**) performed a preferable result. Some representative heterocycles such as thiophene are also suitable for this reaction **5h**. The ester group from diene and sulfur ylide showed no effect towards this reaction **5i** and **5j**.

Based on our experimental results and previous related studies,^{11b,12} a possible mechanism for this type of [4+3] annulation reactions was proposed (Scheme 4). Firstly, deprotonation of

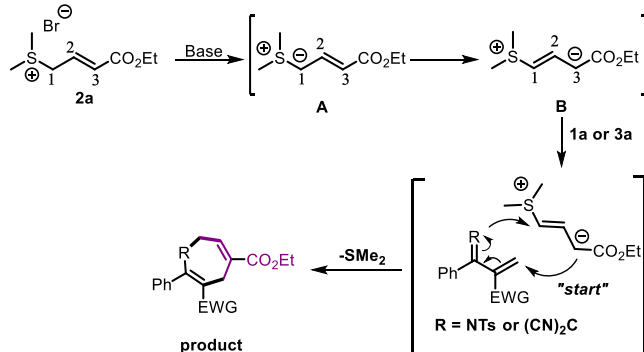
Scheme 3. Scope of the Seven-membered Carbocycles^a



^aReaction conditions: **4** (0.10 mmol, 1.0 eq), **2** (0.12 mmol, 1.2 eq), Cs_2CO_3 (0.2 mmol, 2.0 eq), CHCl_3 (0.5 mL), r.t., 4 h.

crotonate-derived sulfur ylides **2a** results in a carbanion allylic ylide intermediate **A** in the presence of a base (such as Cs_2CO_3 , NaH). Carbanion allylic ylide intermediates **B** is formed by tautomerism from sulfur ylide intermediate **A**. Then, an intermolecular Michael addition of carbanion allylic ylide intermediate **B** as C3 synthons to functional diene as the start step. Followed by the nucleophilic site of diene attacks the carbanion allylic ylide to implement a closed cycle process and one equivalent of SMe_2 was separated from the system to complete the whole domino process. Finally, the highly functional none-fused cycles including nitrogen-heterocycles or carbocycles are obtained.

Scheme 4. Plausible Reaction Mechanism^a



In summary, we have developed an inventive example of domino annulation reaction of crotonate-derived sulfur ylides and dienes to generate highly functional none-fused seven-membered cycles such as nitrogen-heterocycles and carbocycles with moderate to excellent yields. The advantages of the current reaction include available and easy-synthesized materials, mild reaction conditions, good functional groups tolerance, and extensive substrate scope. In addition, this is also a supplementary to sulfur ylide chemistry as the C3 synthesizer, and we are confident that this type of reaction has important application

potential in the synthesis of natural products and bioactive molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental details, materials characterization and copies of relevant NMR spectra for all products, 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.

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