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Synthesis of Bicyclo[4.1.0]tetrahydropyridazines by a Sequential [4 + 2] and [1 + 2] Annulation Reaction of Azoalkenes and Crotonate-Derived Sulfur Ylides

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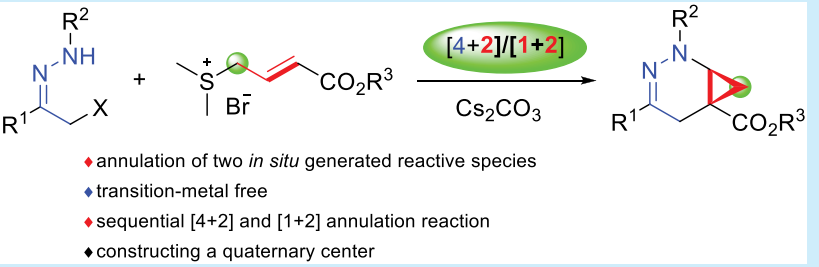
Supporting Information



ABSTRACT: The base-induced unprecedented tandem [4 + 2] and [1 + 2] annulation reaction of in situ formed 1,2-diaza-1,3-dienes and crotonate-derived sulfur ylides is reported. This protocol provides a novel and practical method for the synthesis of cyclopropane-fused tetrahydropyridazines with a quaternary carbon center in synthetically useful yield. In this tandem reaction, three new bonds were formed in one pot, and the crotonate-derived sulfur ylide serves as a C3 synthon.

Pyridazines and tetrahydropyridazines represent an important family of N−N bond-containing six-membered heterocycles that show a broad range of pharmaceutical activities,[1] such as cannabinoid CB1 receptor antagonists[1a] and influenza neuraminidase inhibitory activity (Figure 1).[1b] Furthermore, as ubiquitous subunits, cyclopropanes, in particular, cyclopropane-fused nitrogen heterocycles, are found in various drug molecules.[2] 3-Azabicyclo[4.1.0]heptane derivatives have shown potential in medicinal chemistry, such as triple reuptake inhibitor (GSK1360707),[2b] inducible nitric oxide synthase inhibitors,[2c] and HIV-1 non-nucleoside reverse transcriptase inhibitors (Figure 1).[2d]

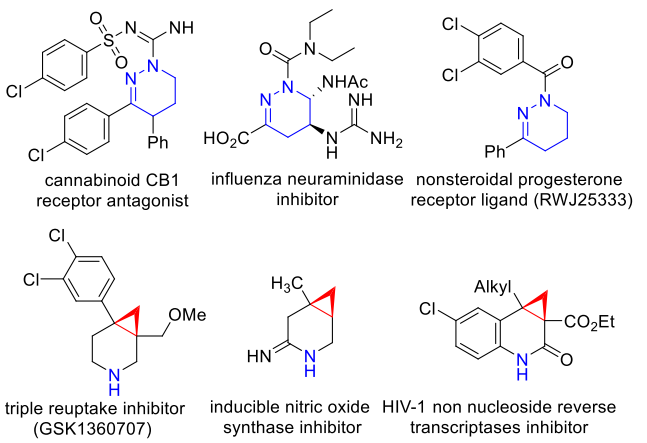
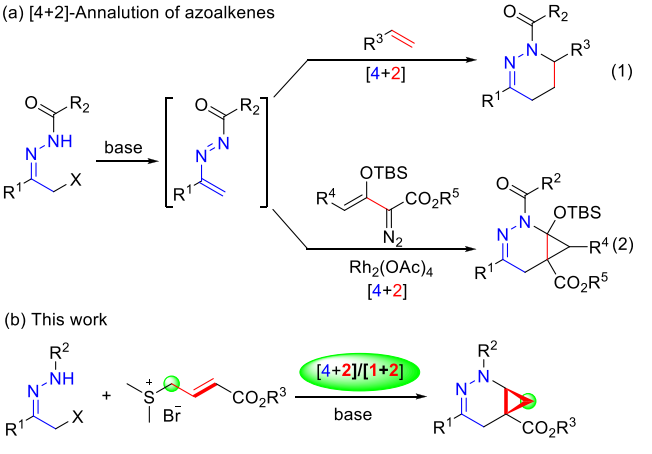


Figure 1. Biologically active tetrahydropyridazines and cyclopropane-fused nitrogen heterocycles.

To date, several efficient approaches have been developed for the synthesis of the privileged tetrahydropyridazine skeleton.[1,3] The recently discovered [4 + 2] annulation of in situ generated azoalkenes with alkenes is particularly attractive because of the high efficiency and step economy (Scheme 1a, pathway 1).[4] Azoalkenes (1,2-diaza-1,3-dienes) can be mildly

Scheme 1. Annulation Reactions Involving Azoalkenes



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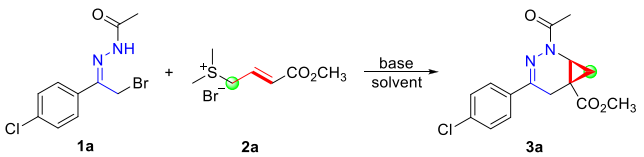
generated by treating α-halogeno hydrazones with a base, which have been recognized as a class of powerful and versatile four-atom building blocks for the synthesis of various valuable multi-nitrogen-containing heterocycles.[4−7] However, efficient and economic methods for the construction of cyclopropane-fused tetrahydropyridazines are limited so far. Great progress has only been achieved for the synthesis of structurally diverse bicyclo[4.1.0]tetrahydropyridazines through the dirhodium-(II)-acetate-catalyzed [4 + 2] cycloaddition of azoalkenes with enol diazoacetates by Doyle and Xu,[8] and the resulting cyclopropane-fused tetrahydropyridazines were converted to tetrahydro-1,2-diazepines by ring expansion (Scheme 1a, pathway 2). Therefore, the pursuit of practical approaches to rapidly access intriguing cyclopropane-fused tetrahydropyridazines is still highly desired. On the basis of these elegant studies involving azoalkene as well as our continuous efforts on tandem annulations[9] involving sulfur ylides,[6a] herein we report a novel transition-metal-free, tandem [4 + 2] and [1 + 2] annulation reaction of in situ formed 1,2-diaza-1,3-dienes and cronate-derived sulfur ylides,[10,11] delivering valuable cyclopropane-fused tetrahydropyridazines. To the best of our knowledge, this is the first example of a cronate-derived sulfur ylide[10] as a 1,2-C2 synthon as well as a C1 synthon in the generation of a cyclopropane skeleton.

Crotonate-derived sulfur ylides are a well-known class of versatile building blocks and have been typically used as C1, C2, or C3 synthons in various cascade annulation processes for the synthesis of structurally diverse cyclic compounds.[11] In our preliminary screening, the α-bromo *N*-acetyl hydrazone **1a** and crotonate-derived sulfonium salt **2a** were employed as the model substrates to optimize the reaction conditions (Table 1). Because the base plays a vital role in the formation of the azoalkenes and sulfur ylides, cesium carbonate was initially selected as the base in various solvents at room temperature. To our delight, an unprecedented product **3a** was isolated in 56% yield when the reaction took place in acetonitrile (Table 1, entry 4), whose structure was elucidated from spectroscopic data and verified unambiguously by X-ray diffraction analysis (CCDC 1941157). This interesting result encouraged our further exploration because there are few general methods for the synthesis of bicyclo[4.1.0]tetrahydropyridazine derivatives. Subsequently, various bases were tested. Unfortunately, other inorganic bases, such as Na_2CO_3, K_2CO_3, *t*-BuOK, and NaOH led to a decrease in yield (Table 1, entries 8−11). Organic base Et_3N seemed to be inefficient in this reaction. (Table 1, entry 12). Further optimization disclosed that an increase in the amount of sulfonium salt and base has a beneficial effect and resulted in 65% yield (Table 1, entry 13). Gratifyingly, the yield was increased to 83% when the reaction was performed at 35 °C (Table 1, entry 14). No better results were obtained whether the reaction was performed at higher or lower temperature (Table 1, entries 15 and 16).

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	base	solvent	3a, yield (%)[b]
1	Cs_2CO_3	toluene	trace
2	Cs_2CO_3	CH_2Cl_2	15
3	Cs_2CO_3	$CHCl_3$	52
4	Cs_2CO_3	CH_3CN	56
5	Cs_2CO_3	DMF	50
6	Cs_2CO_3	DMSO	44
7	Cs_2CO_3	CH_3OH	trace
8	Na_2CO_3	CH_3CN	trace
9	K_2CO_3	CH_3CN	20
10	*t*-BuOK	CH_3CN	15
11	NaOH	CH_3CN	45
12	Et_3N	CH_3CN	trace
13	Cs_2CO_3	CH_3CN	65[c]
14	Cs_2CO_3	CH_3CN	83[c,d]
15	Cs_2CO_3	CH_3CN	53[e]
16	Cs_2CO_3	CH_3CN	trace[f]

[a]Unless otherwise noted, reactions were conducted with **1a** (0.20 mmol), **2a** (0.30 mmol), and base (0.60 mmol) in solvent (2.0 mL) at rt under Ar for 8 h. [b]Isolated yield based on **1a**. [c]2.5 equiv of **2a** and 4.0 equiv of Cs_2CO_3 were used. [d]At 35 °C, 8 h. [e]At 50 °C, 8 h. [f]At 0 °C, 24 h.

With the optimized reaction conditions in hand (Table 1, entry 14), the generality and scope of the tandem [4 + 2]/[2 + 1] annulation reaction were investigated by reacting α-halo hydrazones **1** with crotonate-derived sulfonium salts **2**. The results are summarized in Scheme 2. The investigation with respect to the scope of the α-halo hydrazones revealed that not only α-bromo-hydrazone **1a** but also α-chloro-hydrazone **1a′** is a suitable azoalkene precursor during the process of tandem annulation. Various *N*-acetyl α-bromo hydrazones bearing para, meta, or ortho substituents with both electron-deficient and electron-rich character at the benzene rings were well tolerated and furnished the bicyclo[4.1.0]tetrahydropyridazine derivatives in moderate to good yield. In particular, α-bromo-hydrazones bearing a functional group at the para position on the aryl ring showed higher reactivity than their ortho- or meta-substituted counterparts (**3a** vs **3h** and **3l**; **3c** vs **3i**). For instance, sterically hindered *o*-chlorine-substituted congener **1l** led to the corresponding product **3l** in 32% yield. In addition, 2-naphthyl-substituted α-bromo-hydrazone **1m** also worked well under the optimized reaction conditions, producing the corresponding product **3m** in 84% yield. More importantly, cyclic α-bromo-hydrazones **1n** and **1o** derived from α-bromo-1-tetralone and α-bromo-4-chromanone could successfully take part in the tandem annulation reaction and afforded the interesting polycyclic adducts **3n** and **3o** in 85 and 95% yield, respectively. Besides aryl groups, a *tert*-butyl-substituted hydrazone **1p** was successfully converted into the corresponding tetrahydropyridazine **3p** in 92% yield. However, primary and secondary alkyl-substituted hydrazones are not suitable azoalkene precursors for this transformation, probably due to the lower reactivity.[12] Moreover, it was found that the reactions proceeded efficiently when sulfonium salt **2b** was employed, leading to the desired products in excellent yield (**3q−s**). Further screening revealed that the reactivity of the reaction is significantly influenced by an N-protecting group on the α-bromo-hydrazones **1**: *N*-Boc α-bromo-hydrazone delivers the adduct **3t** in 70% yield, whereas *N*-tosyl α-bromo-hydrazone **1u** does not participate in this transformation under these initially developed reaction conditions. Additionally, the reaction of a methyl-substituted crotonate-derived sulfonium salt **2c** with **1a** under standard conditions led to complicated mixtures. No desired product **3v** was observed, which may be

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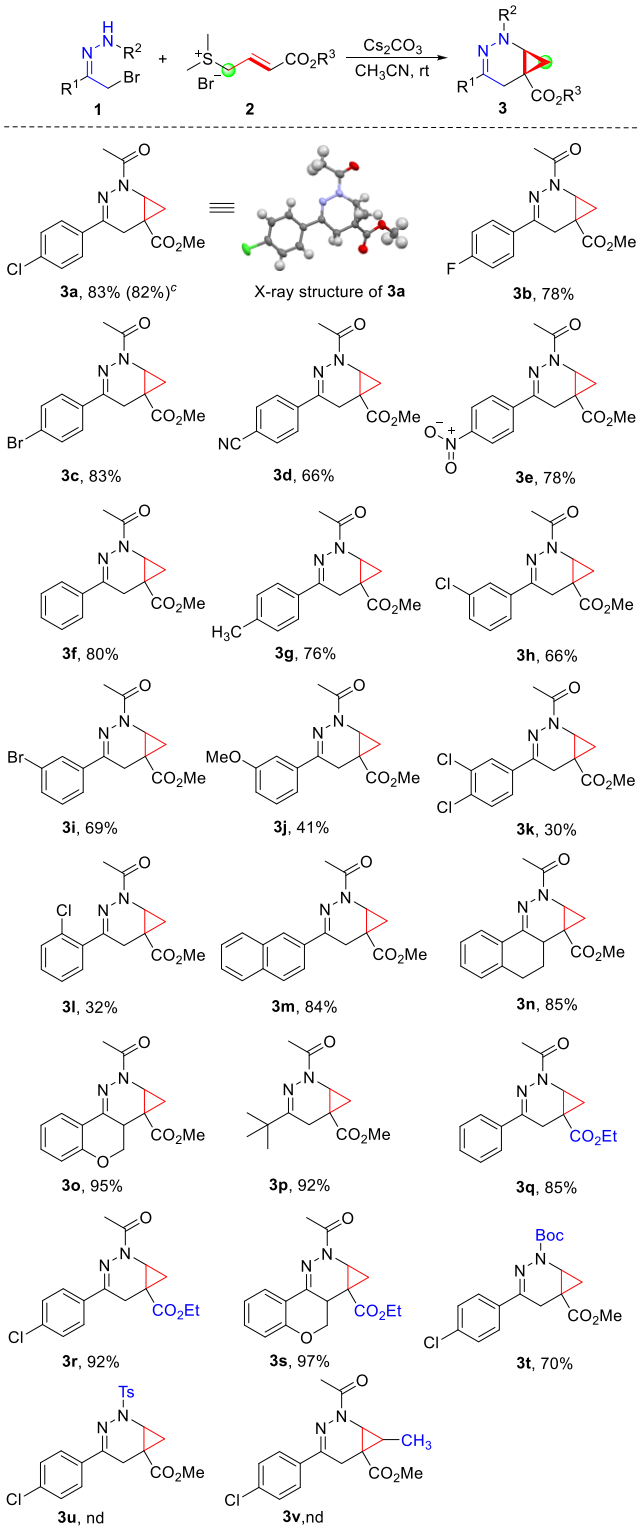
Scheme 2. Substrate Scope[a,b]

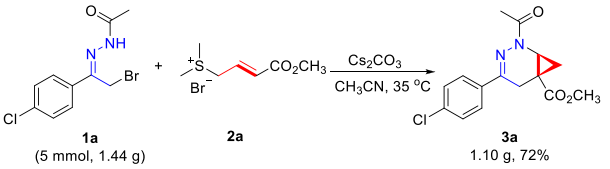


[a]Unless noted otherwise, reactions were conducted with **1** (0.20 mmol), **2** (0.50 mmol), and Cs_2CO_3 (0.80 mmol) in CH_3CN (2.0 mL) at 35 °C under Ar for 8 h. [b]Isolated yield based on **1**. [c]α-Chloro hydrazones were used.

due to the steric hindrance of **2c**, showing the limitation of this reaction.

As indicated in Scheme 3, a gram-scale reaction of α-bromohydrazone **1a** (1.44 g, 5 mmol) and sulfonium salt **2a** was

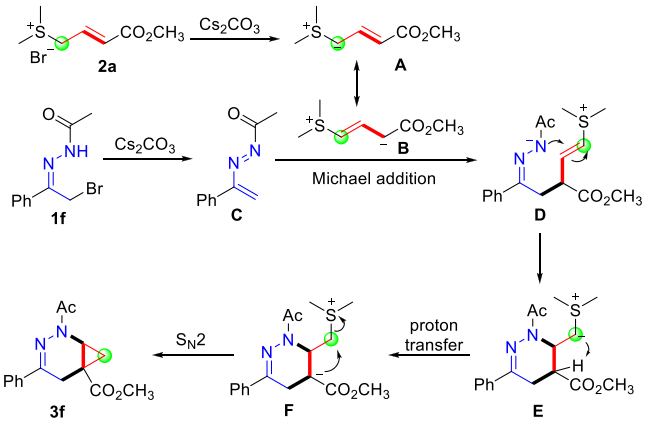
Scheme 3. Gram-Scale Experiment



conducted under the optimal reaction conditions, which still afforded bicyclo[4.1.0]tetrahydropyridazine **3a** in 72% yield.

On the basis of our deuterium exchange experiment results (see the Supporting Information) and the previous reports, a plausible reaction mechanism for this novel tandem reaction is depicted in Scheme 4. Initially, crotonate-derived sulfonium

Scheme 4. Proposed Plausible Mechanism



salt **2a** underwent deprotonation in the presence of cesium carbonate to generate an allylic ylide with two resonance structures **A** and **B**, which then reacted with in situ formed 1,2-diaza-1,3-diene **C** to generate ylide **E** via Michael addition and intramolecular nucleophilic addition, sequentially. Finally, a proton transfer was followed by an intramolecular S_N2 nucleophilic substitution to deliver the bicyclo[4.1.0]-tetrahydropyridazine **3f**.

In summary, the efficient construction of a challenging cyclopropane-fused tetrahydropyridazine is developed through an unprecedented sequential [4 + 2] and [1 + 2] annulation reaction of 1,2-diaza-1,3-dienes and cronate-derived sulfur ylides. This protocol provides a novel transition-metal-free method for the synthesis of value bicyclo[4.1.0]-tetrahydropyridazines possessing a quaternary carbon center in one step. The development of an asymmetric version of this tandem reaction is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02661.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1941157 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing

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data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(12) Data not shown in Scheme 2; see the Supporting Information.

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