

# [3 + 2]-Annulation of Prop-2-ynylsulfonium Salts: Access to Hydroindol-5-ones Containing a Methylthio Group

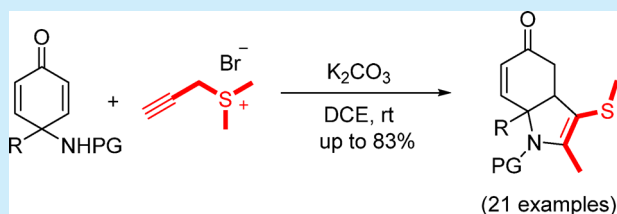
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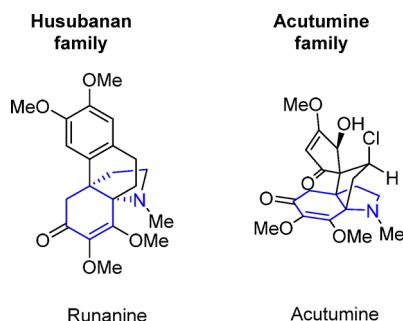
**S** Supporting Information

**ABSTRACT:** An unprecedented [3 + 2]-annulation of prop-2-ynylsulfonium salts and *p*-quinamines was developed, affording a series of hydroindol-5-ones with a methylthio group in moderate to good yields under mild conditions. In this reaction, the prop-2-ynylsulfonium salt acts as a novel C<sub>2</sub> synthon and sulfide does not serve as a leaving group, which provides facile access to organosulfur compounds.



Hydroindol-5-one scaffolds exist widely in the polycyclic alkaloids isolated from medicinal herbs. Hasubanan and acutumine alkaloids are representative examples (Scheme 1).<sup>1</sup>

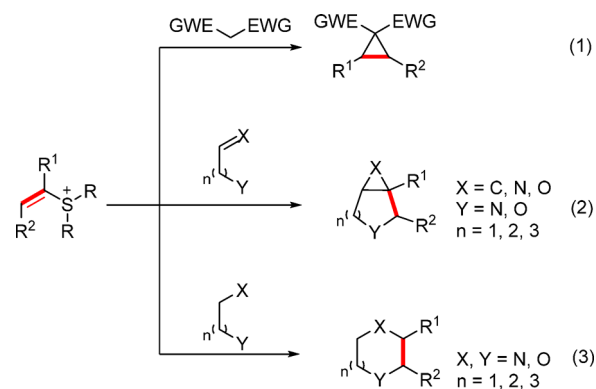
**Scheme 1. Representative Polycyclic Alkaloids Containing Hydroindol-5-one Scaffolds**



These densely functionalized small molecules exhibit promising biological properties. For example, acutumine alkaloid has selective T-cell cytotoxicity and antiemetic activity.<sup>2</sup> Therefore, the synthesis of such structures has been of interest to the chemical community for many years.<sup>3</sup>

As C<sub>1</sub> synthons, sulfur ylides have been widely used as methylene-transfer reagents in the construction of three-membered ring compounds with C = X (X = C, N, O, etc.) double bonds.<sup>4</sup> In recent years, Aggarwal's, Xiao's, and other groups have reported the significant application of sulfur ylides as C<sub>2</sub> synthons. According to their research, vinylsulfonium salts could react with active methylene compounds containing electron-withdrawing groups to give substituted cyclopropane derivatives (Scheme 2, eq 1).<sup>5</sup> Upon reaction with  $\alpha$ -,  $\beta$ -, and  $\gamma$ -aminoaldehydes, hydroxyaldehydes, or similar olefins or imines, epoxide-, cyclopropane-, or aziridine-fused heterocycles can be obtained, which also provides a key strategy for the total synthesis (Scheme 2, eq 2).<sup>6</sup> When amino alcohols or diamines are used in the reaction with vinylsulfonium salts, a series of

**Scheme 2. Application of Vinylsulfonium Salts as C<sub>2</sub> Synthons**

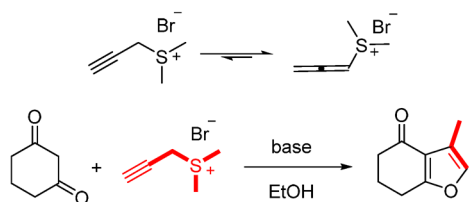


heterocycles containing nitrogen and oxygen atoms can be constructed (Scheme 2, eq 3).<sup>7</sup> For all the reactions mentioned above, vinylsulfonium salts are directly used or generated in situ. Therefore, the development of new kinds of sulfur ylides as C<sub>2</sub> synthons and their applications in more reaction types are underexplored.

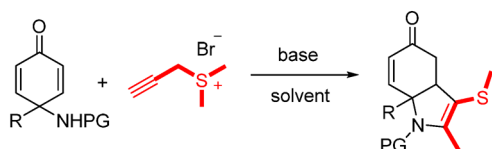
It has been reported that prop-2-ynylsulfonium salts could transform into allenic sulfonium salts and react with enolate anions of  $\beta$ -diketones to afford substituted furans (Scheme 3).<sup>8</sup> Inspired by their previous work and on the basis of our continuous interest in exploring new reactions of sulfur ylides,<sup>9</sup> we developed a novel [3 + 2]-annulation reaction<sup>10</sup> of prop-2-ynylsulfonium salts and *p*-quinamines<sup>11</sup> to generate S-containing hydroindol-5-ones. In this reaction, sulfide does not serve as leaving group compared with traditional reactions of sulfur ylides, which provides the possibility for the

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## Scheme 3. Reactions of Prop-2-ynylsulfonium Salts

Previous work:<sup>8</sup>

This work:



construction of organosulfur compounds with biological and chemical properties.<sup>12</sup>

At the outset of this investigation, we employed *p*-quinamine **1a** with prop-2-ynylsulfonium salt **2a** in the presence of Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) in CH<sub>3</sub>CN at room temperature. The reaction gave the [3 + 2]-annulation product **3a** in 41% yield as well as *N*-methyl product **4a** in 17% yield after 3 h (Table 1, entry 1). When the reaction time was extended to 24 h, pleasingly, the yield of **3a** improved to 53% (Table 1, entry 2). Subsequent screening of bases showed that K<sub>2</sub>CO<sub>3</sub> could give a better yield of 58% (Table 1, entries 3–8). Solvents such as DCM, DCE, DBM, and CHCl<sub>3</sub> all proceeded with the desired

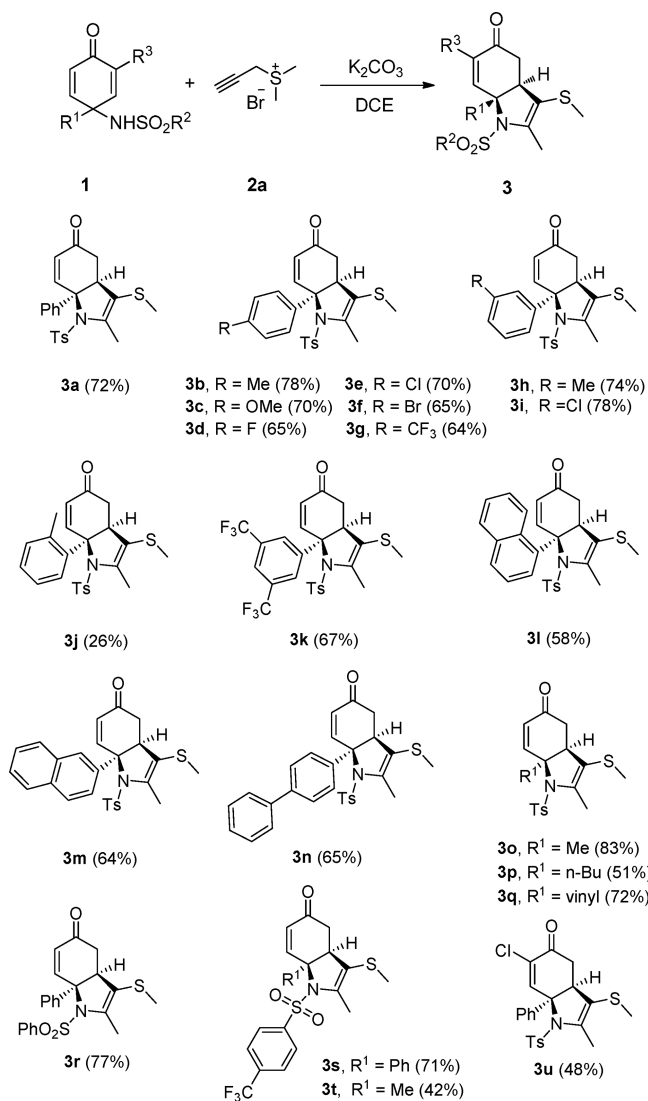
Table 1. Screening of the Reaction Conditions<sup>a</sup>

					yield <sup>b</sup> (%)	
entry	base	solvent	time (h)	1a/2a/base	3a	4a
1	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	3	1:2:2	41	17
2	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	24	1:2:2	53	18
3	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	24	1:2:2	58	13
4	Et <sub>3</sub> N	CH <sub>3</sub> CN	24	1:2:2	52	NP
5	DABCO	CH <sub>3</sub> CN	24	1:2:2	26	trace
6	K <sub>3</sub> PO <sub>4</sub>	CH <sub>3</sub> CN	24	1:2:2	49	28
7	NaOH	CH <sub>3</sub> CN	24	1:2:2	41	15
8	KOH	CH <sub>3</sub> CN	24	1:2:2	43	22
9	K <sub>2</sub> CO <sub>3</sub>	DCM	24	1:2:2	68	trace
10	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:2:2	72	trace
11	K <sub>2</sub> CO <sub>3</sub>	DBM	24	1:2:2	59	trace
12	K <sub>2</sub> CO <sub>3</sub>	CHCl <sub>3</sub>	24	1:2:2	52	trace
13 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:2:2	69	NP
14	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:1.5:2	68	trace
15	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:3:2	67	trace
16	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:2:1.5	68	trace
17	K <sub>2</sub> CO <sub>3</sub>	DCE	24	1:2:3	73	trace

<sup>a</sup>Unless otherwise noted, reactions of **1a** (0.20 mmol) and **2a** were carried out in 2 mL of the solvent at 20 °C. <sup>b</sup>Isolated yields. <sup>c</sup>The reaction temperature was 10 °C.

products, among which DCE gave the best yield of 72% of **3a** with a trace amount of **4a** (Table 1, entry 10). Lowering the reaction temperature to 10 °C gave a lower yield of 69% (Table 1, entry 13). Changing the loading of prop-2-ynylsulfonium salt **2a** and bases did not give better yields (Table 1, entries 14–17).

The generality of this prop-2-ynylsulfonium salts involved [3 + 2]-cycloaddition reaction was examined. As summarized in Scheme 4, a wide range of *p*-quinamines can be employed in

Scheme 4. Scope of the Reactions<sup>a,b</sup>

<sup>a</sup>Reactions of **1** (0.20 mmol) and **2a** (0.40 mmol) were carried out in the presence of K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) in 2 mL of 1,2-dichloroethane.

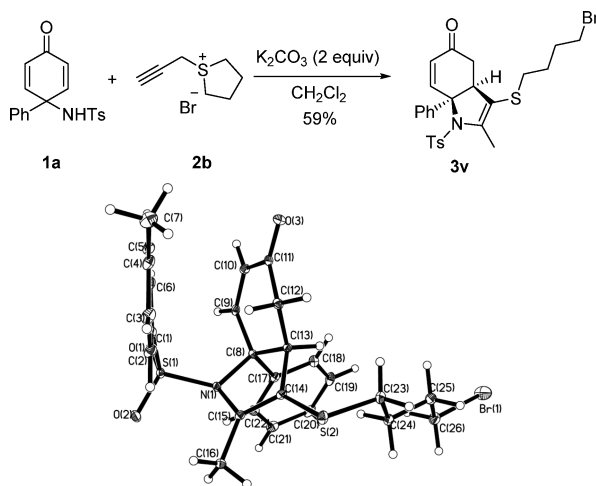
<sup>b</sup>Isolated yields are shown.

this transformation. *p*-Quinamines bearing either electron-rich or electron-deficient substituents at the para and meta position of the benzene ring were well-tolerated, producing the desired products in good to high yields (**3b–i**). However, when *p*-quinamine with Me at the ortho position of the benzene ring was employed in the reaction, a reduced yield of 26% was obtained, probably because of steric hindrance (**3j**). Substrates **1** with a 3,5-bis(trifluoromethyl)-substituted phenyl ring could also be transformed into the corresponding product in 67%

yield (**3k**). Further investigation showed that *p*-quinamines bearing naphthyl groups or a biphenyl group (**3l–n**) were also efficient for the transformation. Different alkyl groups were also introduced into substrates **1**. The yields decreased with the increase of the chain  $R^1$  length because of steric hindrance (**3o–q**). The protecting group of the sulfamide functional group could also be changed and worked well in the reaction (**3r–t**). *p*-Quinamine with  $R^3 = \text{Cl}$  was also a suitable substrate for this conversion, producing the corresponding cycloaddition product in moderate yield (**3u**).

To further broaden the scope of the reaction, tetrahydrothiophene sulfonium salt **2b** was employed in the reaction in the presence of  $\text{K}_2\text{CO}_3$  in dichloromethane at room temperature. Ring-opened product **3v** with a Br atom at the terminal of the chain was obtained in 59% yield (Scheme 5). The structure and stereochemistry of **3v** were characterized by a combination of NMR, HRMS, and single-crystal X-ray analysis.<sup>13</sup>

**Scheme 5.** Reaction of **1a** and 1-(Prop-2-yn-1-yl)tetrahydro-1*H*-thiophene-1-ium Bromide

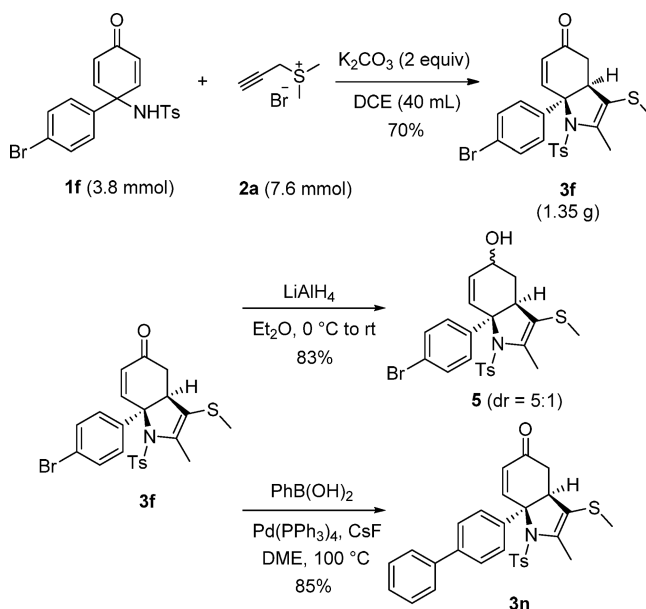


To investigate the synthetic utility of this reaction, a gram-scale version of the reaction using substrates **1f** and **2a** was carried out, and compound **3f** was obtained in 70% yield (Scheme 6). Some transformations were conducted using product **3f**. Upon treatment of **3f** with  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$ , reduction product **5** was generated in 83% yield with 5:1 diastereoselectivity. Moreover, product **3n** could also be obtained from **3f** via a Suzuki cross-coupling reaction in 85% yield.

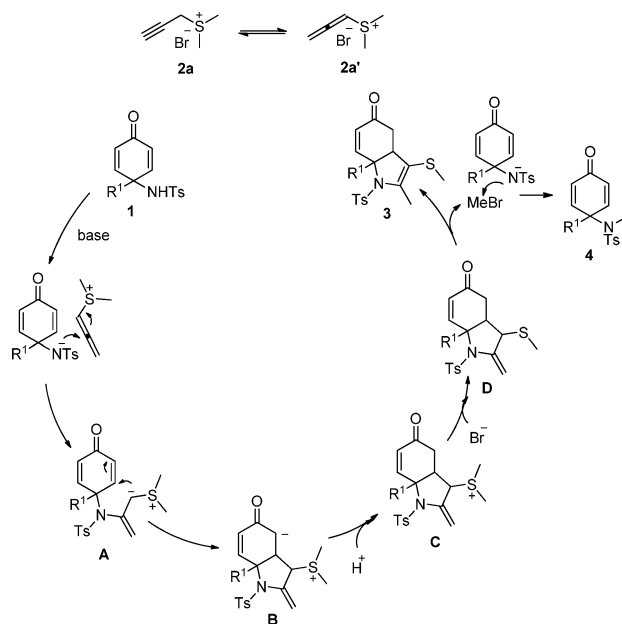
A possible mechanism is depicted in Scheme 7. Prop-2-ynylsulfonium salt **2a** first isomerizes into allenic sulfonium salt **2a'**. Conjugate addition of the N anion to **2a'** generates intermediate **A**, which then undergoes intramolecular nucleophilic addition to form intermediate **B**. Subsequent protonation of **B** give intermediate **C**. The methyl group of the  $\text{Me}_2\text{S}$  sulfonium would be attacked by  $\text{Br}^-$  to yield intermediate **D**,<sup>14</sup> which then undergoes double-bond isomerization to afford the final product **3**. The  $\text{Br}^-$  of  $\text{MeBr}$  proceeds via nucleophilic substitution by the N anion to generate *N*-methyl product **4**.

In conclusion, we have developed a method to construct hydroindol-5-ones containing a methylthio group via [3 + 2] annulation of prop-2-ynylsulfonium salts and *p*-quinamines. Prop-2-ynylsulfonium salts can isomerize into allenic sulfonium

**Scheme 6.** Gram-Scale Synthesis and Further Transformation of **3f**



**Scheme 7.** Plausible Reaction Mechanism



salts and act as a novel  $\text{C}_2$  synthon in the reaction, which broadens the chemistry of sulfur ylides. Moreover, sulfides do not serve as leaving groups compared with traditional reactions, which provides access to organosulfur compounds. Further studies applying this method to the synthesis of molecules with biological activity are underway 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.6b03667.

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

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

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### Notes

The authors declare no competing financial interest.

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- (13) CCDC 1489814 (**3v**) 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](http://www.ccdc.cam.ac.uk/data_request/cif).
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