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Sulfur as a Bridge: Synthesis of Medium Rings *via* a Bicyclic Sulfonium Ion

Hongwei Zhou,[a,]* Yanpeng Xing,[a] Le Liu,[a] and Junjie Hong[a]

[a] Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310007, People's Republic of China
Fax: (+ 86)-571-8892-0271; e-mail: zhouhw@zju.edu.cn

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This paper is dedicated to the memory of Prof. Xian Huang.

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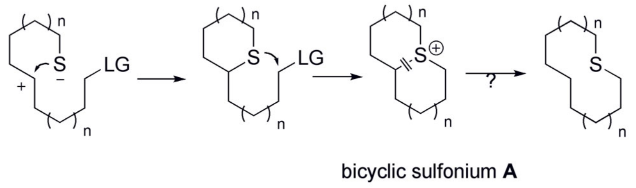
Abstract: A facile and efficient synthesis of medium rings *via* a bicyclic sulfonium ion was developed. Spectroscopic evidence for the formation of an intermediate sulfonium moiety is provided. The sulfur atom served as a "bridge" to access the medium ring system and could be removed after use *via* a Ramberg–Bäcklund process. As a result of the readily available starting materials, simple operation, and mild conditions, these reactions should be an appealing strategy in organic synthesis.

Keywords: bicyclic sulfonium species; cyclization; medium ring synthesis; medium rings; sulfur participation

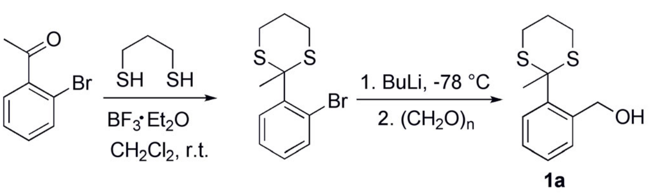
Cyclic structures of various ring sizes are quite significant in organic and bioorganic chemistry as they are the structural core of a large number of biologically important natural products and are often incorporated into drugs.[1] While five- and six-membered carbocycles are most common, seven-, eight-, nine- and ten-membered or larger cycles occupy an important fraction of these compounds.[2] The synthetic protocols to five- and six- membered cycles *via* the different types of cyclizations are familiar to the organic community, but the construction of eight-, nine- and ten-membered or larger ring compounds are not as abundant. This may be ascribed to the fact that traditional ring-closure strategies are effective for five- or six- membered systems, but problematic for medium or larger ring systems owing to the high transannular interactions and an unfavorable entropy factor. In brief, to bring the two ends of a reactant together is difficult for medium ring-closure.[3] Recently, an excellent report by Woerpel gave spectroscopic evidence for the formation of a bicyclic sulfonium ion in a 4-thio-substituted tetrahydropyran acetal system, in which the bridged sulfonium ion experienced a ring-openning even at low temperature.[4] This knowledge stimulated us to propose a bicyclic sulfonium species **A**, in which the central carbon-sulfur bond could be broken to release a medium ring (Scheme 1).

The formation of the bicyclic sulfonium **A** might be not difficult because it is a five- or six-membered ring closure strategy. If this proposal could work, the sulfur atom would behave like a bridge to make the distant span close.

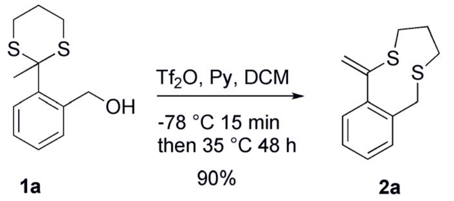
On the basis of this proposal and our previous understanding of sulfur participation,[5,6] we were stimulated to choose [2-(2-methyl-1,3-dithian-2-yl)phenyl]-methanol (**1a**) as the starting material, which could be synthesized *via* the reaction of [2-(2-methyl-1,3-dithian-2-yl)phenyl]lithium with paraformaldehyde (Scheme 2).



Scheme 1. Proposal of synthesis of medium rings.



Scheme 2. Synthesis of the substrate **1a**.



Scheme 3. Synthesis of **2a**.

Using **1a** as the starting material, we examined the cyclization reaction in the presence of triflic anhydride and pyridine in dichloromethane at −78 °C. We observed the complete consumption of **1a** on TLC in 15 min, but did not observe the expected product. We chose a stronger base triethylamine and kept the reaction mixture at 35 °C for 48 h. As expected, 6-methylene-3,4,6,9-tetrahydro-2*H*-benzo[*g*][1,5]dithionine (**2a**) was isolated in 90% yield (Scheme 3).

During this examination, we found that the hypothesized bicyclic sulfonium is quite stable before the addition of triethylamine. Thus, after the treatment of **1a** with triflic anhydride and pyridine-d_5 in dichloromethane at −78 °C, we removed the volatile dichloromethane in vacuum at room temperature and charged CDCl$_3$ for the NMR experiments. The ^{1}H NMR spectroscopy of the reaction mixture confirmed that the bridged bicyclic sulfonium was formed. Downfield shifts were observed for the protons adjacent to the sulfur atom (Ha to Ha′), demonstrating the presence of an electron-withdrawing functionality on sulfur. Also, the single peak of the methylene group adjacent to the benzene ring of **1a** was changed to two double peaks of the intermediate (Hb to Hb′), showing an obvious AB system. In addition, on the ^{13}C NMR spectroscopy of reaction mixture, a downfield shift was observed for the quaternary carbon (C1 to C1′) and an upfield shift for the methylene carbon adjacent to the benzene ring (C2 to C2′), consistent with the formation of bicyclic sulfonium (Table 1, Figure 1, Figure 2, Figure 3 and Figure 4).

Based on these results, we propose a plausible pathway as shown in Scheme 4. Treatment of **1a** with triflic anhydride and pyridine gave a trifluoromethanesulfonate and the sulfur atom attacked the trifluoromethanesulfonate to afford a bridged bicyclic sulfonium **A**. The bicyclic sulfonium **A** offered the nine-membered product **2a** *via* an E2 process in the presence of triethylamine.

Table 1. NMR shifts from **1a** to bicyclic sulfonium.

Compounds	^{1}H NMR [ppm]	^{13}C NMR [ppm]
1a	Ha (2.79, 2.98); Hb (5.14)	C1 (52.5); C2 (62.8)
Bicyclic sulfonium	Ha′ (2.86, 4.15); Hb′ (4.79, 5.14)	C1′ (71.7); C2′ (45.4)

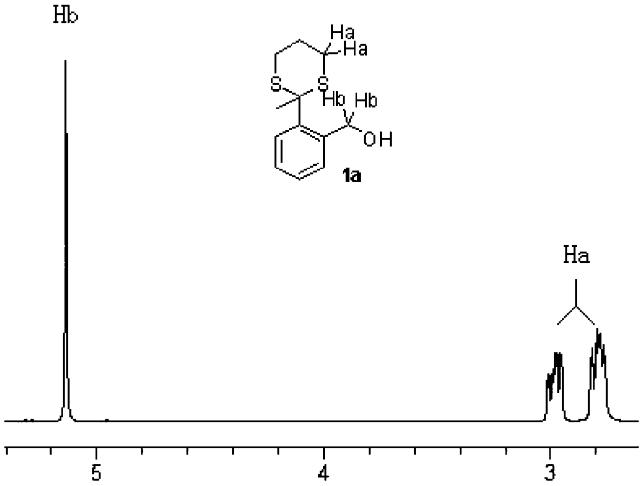


Figure 1. ^{1}H NMR of **1a** about Ha and Hb.

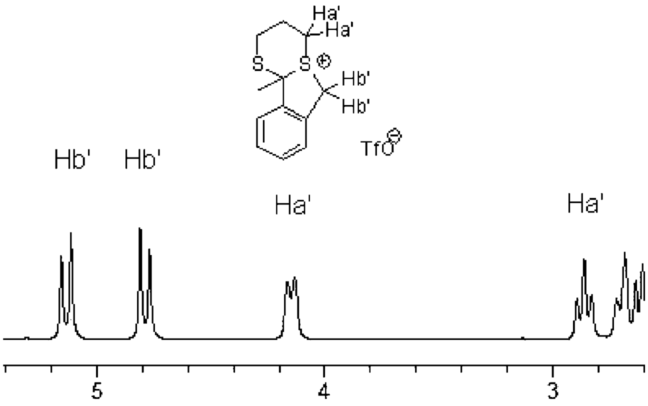


Figure 2. ^{1}H NMR of bicyclic sulfonium about Ha′ and Hb′.

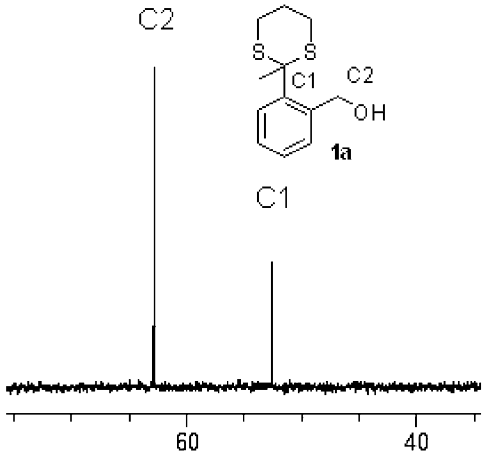


Figure 3. ^{13}C NMR of **1a** about C1 and C2.

With this result in hand, we examined the scope of the reaction and obtained a series of medium rings in

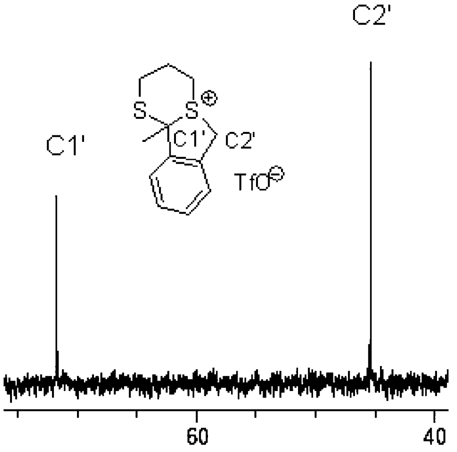
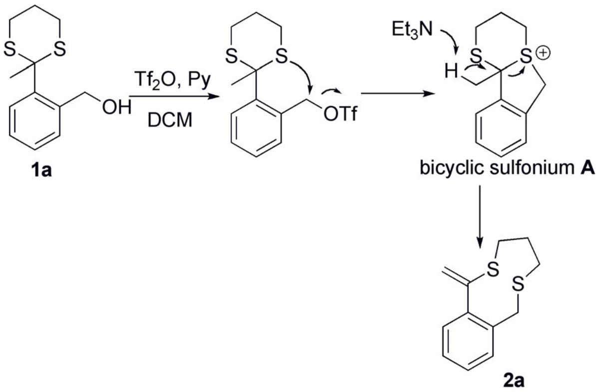


Figure 4. ^{13}C NMR of bicyclic sulfonium about C1′ and C2′.

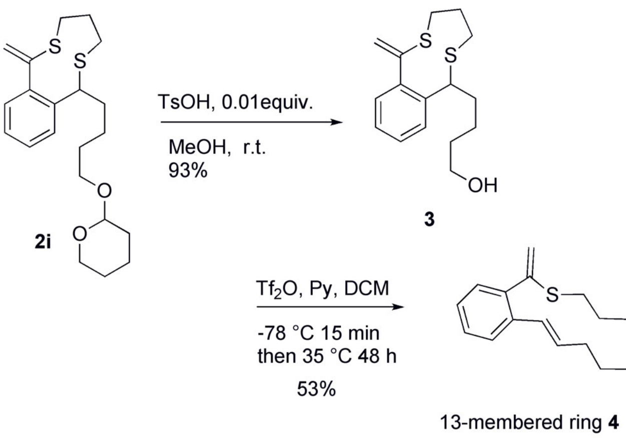


Scheme 4. Plausible mechanism.

moderate to good yields under mild conditions (Table 2).

The formation of the carbon-carbon double bond *via* the E2 process is highly stereoselective and the stereochemistry of the products **2b** and **2g** was established by NOESY experiments.

It is noteworthy that the product **2i** (entry 9, Table 1), containing a latent hydroxy group, might be transformed to the precursor of a new substrate which could undergo another "bicyclic sulfonium-open" process. Thus, we treated **2i** with TsOH/methanol at room temperature affording 4-(6-methylene-3,4,6,9-tetrahydro-2*H*-benzo[*g*][1,5]dithionin-1-yl)butan-1-ol (**3**) as the substrate and conducted the reaction under similar conditions. As expected, (*E*)-6-methylene-3,4,6,11,12,13-hexahydro-2*H*-benzo[*g*]-[1,5]dithiacyclotridecine (**4**) was obtained in 53% yield. This result means that the sulfur atom was used as the "bridge" again. Theoretically, the bridge of sulfur could be used for many times to afford large rings provided that a suitable substrate was pre-designed (Scheme 5).



Scheme 5. Synthesis of 13-membered ring.

[2-(2-Methyl-1,3-oxathian-2-yl)phenyl]methanol (**5a**), in which one of the two sulfur atoms of **1a** was replaced by an oxygen, could be thought of as a promising expansion of **1a**, and reasonably, one of the two sulfur atoms of the substrate might also be replaced by a carbon (Table 3).

The sulfur atom, which serves as a bridge in these reactions, is also a very useful part of the products prepared by the above protocols and could be used as a convenient handle for further generation of chemical diversity. We treated **6d** with *m*-CPBA in dichloromethane followed by a Ramberg–Bäcklund process[7] and obtained 1-phenylcyclohepta-1,3-diene (**7**) in 58% yield. This result demonstrates that the bridge of sulfur could be removed after use to give a new ring system without a sulfur atom (Scheme 6).

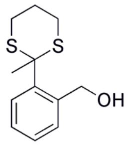
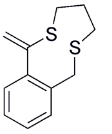
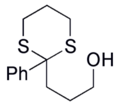
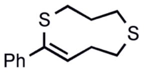
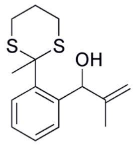
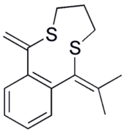
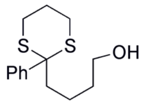
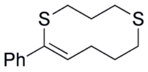
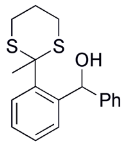
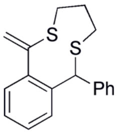
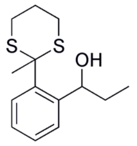
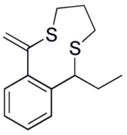
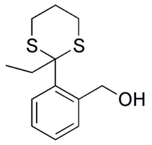
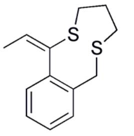
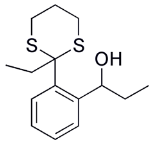
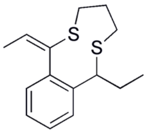
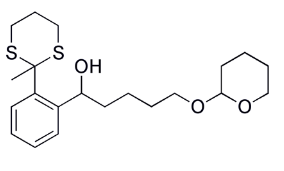
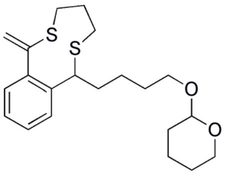
In summary, we have developed a facile and efficient synthesis of medium rings *via* bicyclic sulfonium species. Spectroscopic evidence for the formation of an intermediate sulfonium ion is provided. The sulfur atom served as a "bridge" to access the medium ring system and could be removed after used *via* a Ramberg–Bäcklund process. As a result of the readily available starting materials, simple operation, and mild conditions, these reactions should be an appealing strategy in organic synthesis.

Experimental Section

General Procedure for Synthesis of 2a

To a stirred solution of **1a** (0.5 mmol) in 5 mL of dry pyridine/dichloromethane (1:20) was added trifluoromethanesulfonic anhydride (0.15 mL) by syringe at −78 °C under an N_2 atmosphere. After stirring for 15 min at −78 °C, the reaction mixture was allowed to stir for 30 min at room temperature. Then triethylamine (0.8 mL) was added and the reaction mixture was stirred at 35 °C for 48 h. The reaction mixture was diluted by 10 mL dichloromethane, washed successively with 2N hydrochloric acid (2×10 mL) and water (1×

Table 2. Synthesis of medium rings.[a]

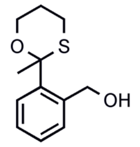
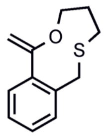
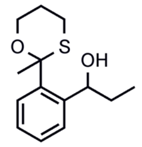
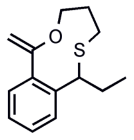
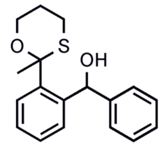
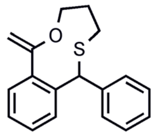
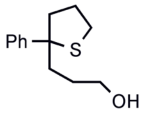
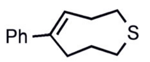
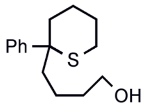
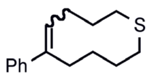
Entry		Substrate		Product	Yield [%]
1	**1a**		**2a**		90
2	**1b**		**2b**		46
3	**1c**		**2c**		77
4	**1d**		**2d**		58
5[b]	**1e**		**2e**		51
6	**1f**		**2f**		87
7	**1g**		**2g**		90
8	**1h**		**2h**		61
9	**1i**		**2i**		60

[a] All reactions were run under the following conditions, unless otherwise specified: 0.5 mmol of **1**, 5 mL of pyridine/DCM (1:20) and 0.15 mL of Tf_2O at –78 °C for 15 min followed by warming to room temperature, then charged 0.8 mL of triethylamine at 35 °C for 48 h under a N_2 atmosphere.

[b] Stirring at 35 °C for 60 h.

10 mL), then dried with anhydrous Na_2SO_4. After evaporation, chromatography on silica gel (hexane/dichloromethane: 15/1) of the reaction mixture afforded **2a**; yield: 100 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30–7.23$ (m, 3H), 7.18–7.16 (m, 1H), 5.65 (s, 1H), 5.09 (s, 1H), 3.83 (s, 2H), 3.04–3.01 (t, $J = 5.6$ Hz, 2H), 2.42–2.39 (t, $J = 5.8$ Hz, 2H), 1.84–1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 145.5, 141.1, 138.0, 129.0, 128.9, 128.7, 126.8, 114.6, 37.2, 33.8, 33.6, 28.7; IR (neat): $\nu = 2921$, 1594, 1482, 1067, 757 cm^{-1}; HR-MS;: $m/z = 222.0532$, calcd. for $C_{12}H_{14}S_2$: 222.0537.

Table 3. Synthesis of medium rings containing one sulfur atom.[a]

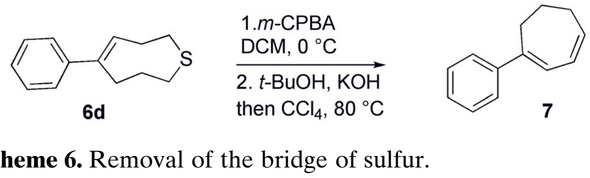
Entry	Substrate		Product		Yield [%]
1	**5a**		**6a**		58
2	**5b**		**6b**		69
3	**5c**		**6c**		52
4[b]	**5d**		**6d**		93
5[c,d]	**5e**		**6e**		45

[a] All reactions were run under the following conditions, unless otherwise specified: 0.5 mmol of **5**, 5 mL of pyridine/DCM (1:20) and 0.15 mL of Tf_2O at −78 °C for 15 min followed by warming to room temperature, then treated with 0.8 mL of triethylamine at 35 °C for 48 h under an N_2 atmosphere.

[b] The stereochemistry of **6d** was established by a NOESY experiment.

[c] 0.8 mL of DBU instead of Et_3N was added and stirring was at 35 °C for 72 h.

[d] An *E*/*Z* ratio (13:87) was observed and the stereochemistry of **6e** was established by a NOESY experiment.



Scheme 6. Removal of the bridge of sulfur.

Acknowledgements

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