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Chemistry of Tetrathiomolybdate: Aziridine Ring Opening Reactions and Facile Synthesis of Interesting Sulfur Heterocycles

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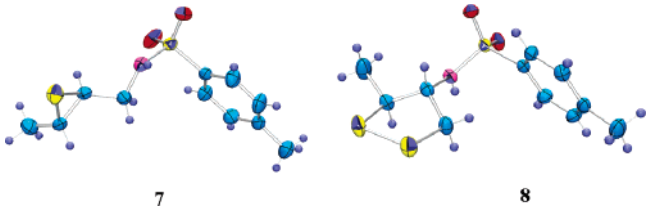
There has been a great interest in the sulfur and nitrogen containing compounds because of their potential biological activity and pharmaceutical significance. Aziridines are the most widely used chiral building blocks for the synthesis of various amino acids, heterocycles, and alkaloids.[1a] Although nucleophilic ring opening of aziridines[1b] has been known for over three decades, there are only a few reports on nucleophilic ring opening of aziridines by sulfur reagents.[1] In this communication, we report our results of a comprehensive study of regio- and stereospecific ring opening of aziridines with benzyltriethylammonium tetrathiomolybdate,[2] $[BnEt_3N]_2MoS_4$ (**1**), an efficient sulfur transfer reagent. Use of the reagent **1** in tandem and multistep processes in a one-pot operation for synthesis of novel heterocyclic systems is also delineated.

To demonstrate the regio- and stereospecificity in the ring opening of aziridines with **1**, (±)-*cis*-*N*-tosyl-1-isopropyl-2-methylaziridine[3] **2** was treated with **1** (1 equiv; CH_3CN, 28 °C, 10 h) to afford exclusively the *anti*-*β*-aminodisulfide **3** in 80% yield. In the case of (±)-*trans*-*N*-tosyl-1-isopropyl-2-methylaziridine[3] **4**, the *syn*-*β*-aminodisulfide **5** was obtained in 85% yield under the given reaction conditions. We believe that reagent **1** attacks the aziridine from the less hindered side in a stereospecific manner followed by opening of the second aziridine ring. The intermediate **X** undergoes an internal redox process[4] to form the *β*-aminodisulfide **5** (Scheme 1).

Following the successful ring opening of simple aziridines with **1**, this methodology was extended to the reaction of *N*-tosyl aziridinemethanol tosylate **6** with **1**, which afforded *trans*-thiirane **7** as the major product and the cyclic disulfide **8** as the minor product (Figure 1) with excellent regio- and stereocontrol. In the course of this thiaaza-Payne[5]-type rearrangement to form **7**, nitrogen migration occurs from C3, C2 to C1 position (Scheme 3).

In the case of *N*-tosyl homoaziridinemethanol tosylate **9**, tetrahydrothiophene **10** was isolated as a single product in 88% yield. To demonstrate the utility of this methodology, the aziridine derivative[6] **11** was subjected to regiospecific aziridine ring opening and subsequent intramolecular cyclization to afford thiabicyclic derivative **12** in 85% yield, which is a precursor for sulfur containing unnatural amino acids.Since tetrathiomolybdate **1** converts aziridine into *β*-aminodisulfide, it is of interest to carry out a tandem aziridine opening−disulfide formation−reduction[7a]−Michael[7b] reaction on an aziridino epoxide with **1**. Accordingly, treatment of *trans*-aziridino-epoxide[8] **13** with **1** in the presence of methyl acrylate **14** led to the formation of the product **15** in 80% yield (Scheme 5).

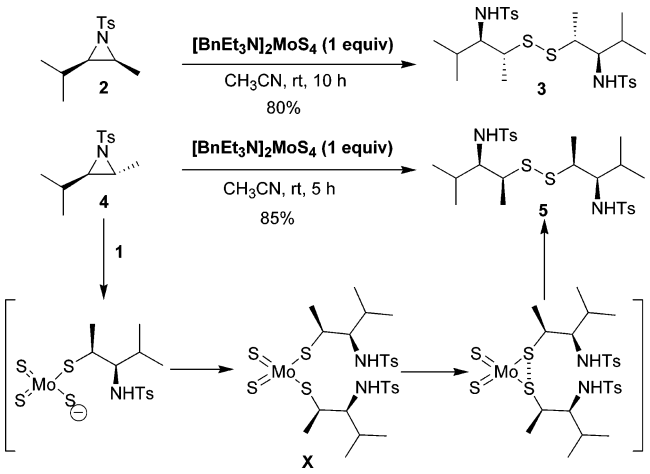
By incorporating a suitable Michael acceptor in the same aziridine, intramolecular 1,4 addition can be performed as a single-pot operation. Thus, treatment of diastereomeric mixture of carvone-derived aziridine **16** with tetrathiomolybdate **1** (2 equiv; CH_3CN, 28 °C, 3 h) yielded two diastereomers of thiabicyclononane derivatives **17** and **18** (1:1) in 88% yield.The *cis*-aziridino epoxide[8] **19** underwent a facile ring opening of aziridine and epoxide[9] rings



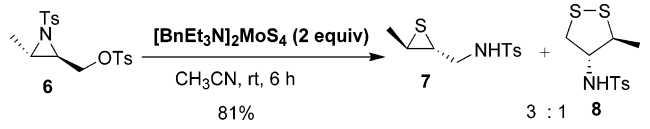
7 **8**

Figure 1. ORTEP diagram of compounds **7** and **8**.

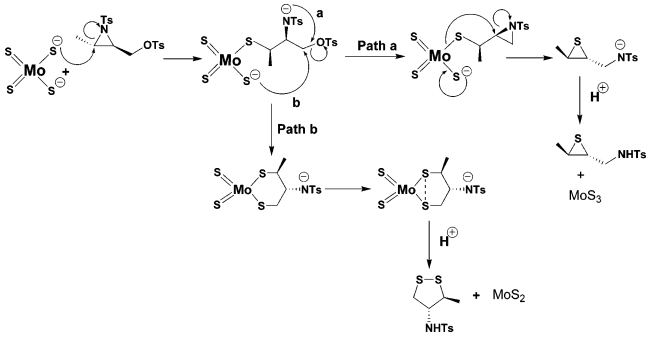
Scheme 1. Regio- and Stereospecific Aziridine Ring Opening



Scheme 2. Thiaaza-Payne-Type Rearrangement



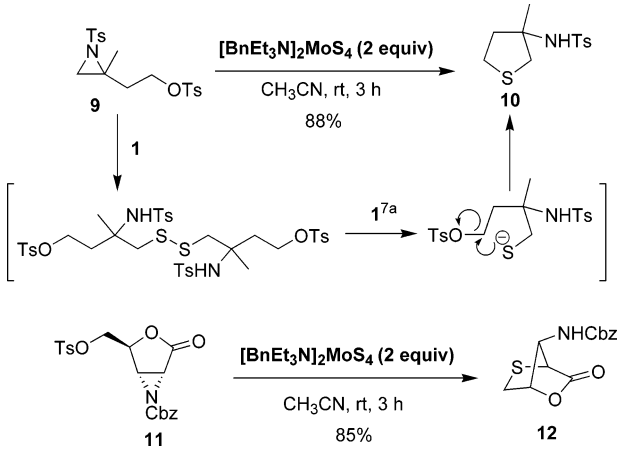
Scheme 3. Tentative Mechanism for the Formation of **7** and **8**



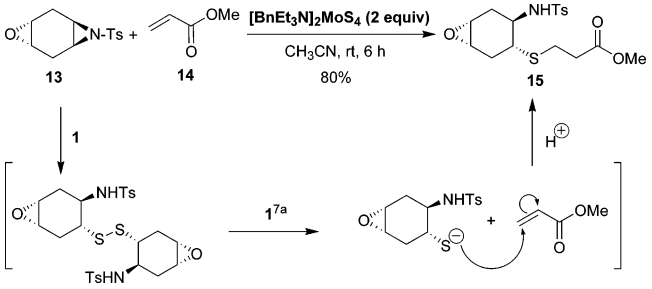
with tetrathiomolybdate **1** (2 equiv; CH_3CN:EtOH, 1:1; 28 °C, 12 h) to afford a functionalized, bridged bicyclic disulfide[10] **20** in 90% yield. This is the first report of the synthesis of a functionalized, conformationally locked disulfide in a single-step operation.The *cis*-aziridino epoxide derivative **21** was synthesized from (*R*)-(−

10.1021/ja052969z CCC: $30.25

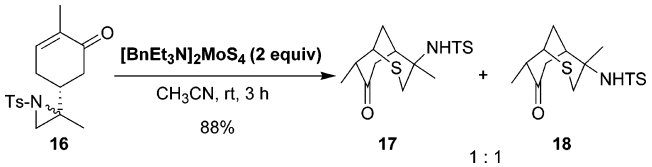
Scheme 4. Synthesis of Tetrahydrothiophene Derivatives



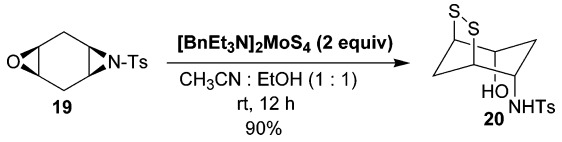
Scheme 5. Tandem Aziridine Opening−Disulfide Formation−Reduction−Michael Addition in One Pot



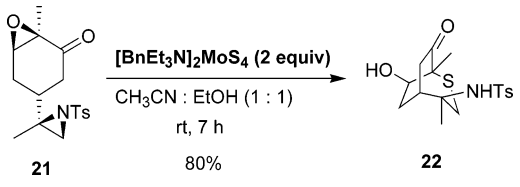
Scheme 6. Synthesis of Thiabicyclononane Derivatives **17** and **18**



Scheme 7. Synthesis of Bridged Bicyclic Disulfide **20**

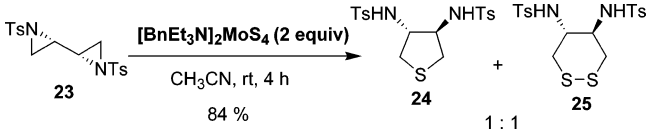


Scheme 8. Synthesis of Thiabicyclononane Derivative **22**

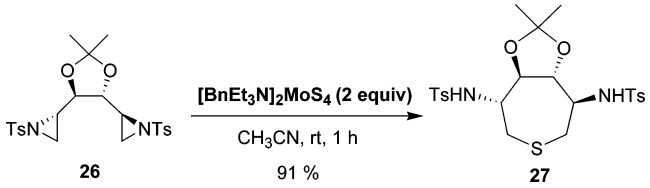


)-carvone in two steps as colorless crystals in optically pure form, and the structure was confirmed by single-crystal X-ray analysis. Treatment of **21** with tetrathiomolybdate **1** (2 equiv; CH_3CN:EtOH, 1:1; 28 °C, 7 h) led to aziridine ring opening in the usual manner, whereas ring opening of epoxide from the more hindered side afforded thiabicyclononane derivative **22** as a single diastereomer in 80% yield. The reaction of bisaziridine[11] **23** with tetrathiomolybdate **1** was next investigated, and it was interesting to observe

Scheme 9. Reaction of Bisaziridine **23** with **1**



Scheme 10. Reaction of Bisaziridine **26** with **1**



that, in this case, cyclic monosulfide **24** and disulfide[12] **25** were isolated (1:1) in 84% yield.In further expanding the scope of this reaction, bisaziridine[13] **26** was treated with tetrathiomolybdate **1** (2 equiv; CH_3CN, 28 °C, 1 h) to give thiepane **27** as the only product in 90% yield. We have demonstrated here an easy and efficient methodology for the synthesis of a thiepane[14] derivative under mild conditions, which is a potential HIV-1 protease[15] and glycosidase inhibitor.[16]

In summary, we have reported an extensive study on nucleophilic ring opening of various aziridines with tetrathiomolybdate **1** and demonstrated the utility of this methodology for the synthesis of a number of interesting sulfur heterocycles with high regio- and stereocontrol.

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Supporting Information Available: Experimental procedures, CIF files, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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