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Stereoselectivity of the Thia-Sommelet [2,3]-Dearomatization

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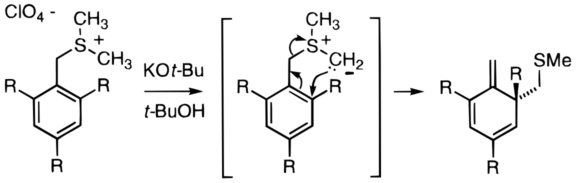
Aromaticity is a powerful driving force in organic chemistry, and for this reason, most reactions of unactivated monobenzenoid aromatics lead to substitution rather than addition. When [2,3]-sigmatropic rearrangements are directed toward substituted positions they provide a powerful means of effecting aromatic additions without rearomatization. This process results in the formation of quaternary stereogenic centers. The [2,3]-sigmatropic dearomatization of benzyl ylides was first demonstrated with the Sommelet−Hauser reaction[1−5] and later through the analogous Moffatt−Olofson[6−14] reaction of phenoxysulfonium ylides. These reactions have achieved prominence while the parent rearrangement of benzylsulfonium ylides has received little attention (eq 1).[15,16] It is suprising that this reaction has only been reported at room temperature[16,17] or above[18−20] since [2,3]-rearrangements of sulfonium ylides can be highly exothermic (by as much as 75 kcal/mol) with low activation energies.[18]



(1)

1a R = Me
1b R = *i*-Pr

2a R = Me
2b R = *i*-Pr

Stereoselective[19−27] and enantioselective[28] [2,3]-sigmatropic rearrangements of allylsulfonium ylides have been studied, yet symmetrical benzylsulfonium salts provide a clear opportunity for asymmetric induction which has not previously been exploited. As a first step toward this goal, we have investigated the scope and stereoselectivity of thia-Sommelet dearomatizations with cyclic and acyclic sulfonium salts. We have found the thia-Sommelet rearrangement to be quite facile even at low temperature. With endocyclic sulfonium ylides the thia-Sommelet dearomatization proceeds with exceptional diastereoselectivity, attributable to a preference for an endo-like transition state.

Sulfonium substrates were prepared by addition of thioether to the corresponding solution of benzylic bromide in acetone. Addition of 1 equiv of silver triflate drives the alkylation to completion by removal of the nucleophilic bromide counterion. The resulting sulfonium triflate salts were then recrystallized from ethyl acetate.

The ylides were generated by deprotonation of the corresponding sulfonium triflate salts in 4:1 THF/*N*,*N*′-dimethylpropylene urea at −78 °C with 1.05 equiv of lithium diisopropylamide (LDA). Kinetic deprotonation is essential for mild rearrangement conditions because the thermodynamically more stable sulfonium benzylides do not rearrange unless they are heated.[29−31] In such cases, heating presumably facilitates tautomerization. Attempts to establish the kinetic selectivity of the deprotonation of **1a** with LDA by quenching the ylide with CD_3CO_2D were complicated by the extreme facility of the rearrangement, which is fast at −78 °C. The corresponding cyclic sulfonium ylides rearrange at slightly slower rates but the reaction is still complete within minutes.[32−34]

A variety of sulfonium ylides were generated at −78 °C and allowed to rearrange as the solution warmed to room temperature. The isolated yields of dearomatized products are excellent, especially considering the steric congestion and potential sensitivity of the products. There are three important differences between the thia-Sommelet dearomatization of sulfonium ylides and the Sommelet−Hauser dearomatization of ammonium ylides. First, there was no evidence of competing Stevens-type [1,2]-rearrangements which compete with Sommelet−Hauser rearrangements and [2,3]-rearrangements of (benzyloxy)methyl anions.[35] Second, E2 elimination was not a prevalent side reaction except for substrate **3a**. Third, the hexatriene products of the thia-Sommelet dearomatization are substantially more stable than the corresponding products of the Sommelet−Hauser rearrangement, which are unstable to silica gel. Products **1b**−**7b** are only slightly sensitive to acid. Addition of 5 mol % camphorsulfonic acid to a solution of **1b** in benzene induces slow decomposition with a half-life of about 1 day. Similar effects are noted in unpurified deuteriochloroform but not benzene or ethyl acetate.

[†] UCI X-ray Crystallography Facility.

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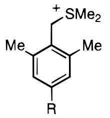
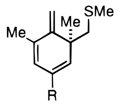
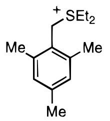
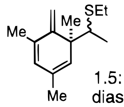
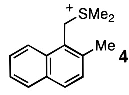
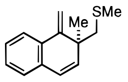
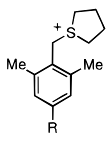
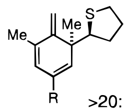
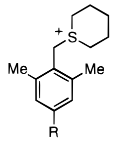
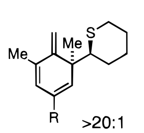
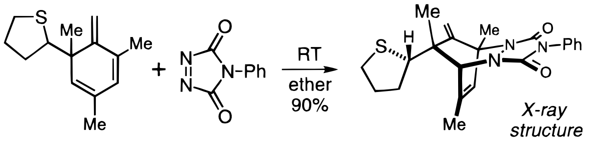
Table 1. Sommelet Rearrangement of Sulfonium Salts with LDA (THF, −78−0 °C)

SULFONIUM		TRIENE		YIELD
	**1a** R = Me		**1b** R = Me	93%
	2a R = H		**2b** R = H	94%
	**3a**	 1.5:1 diast.	**3b**/**3c**	36%[a]
	**4a**		**4b**	90%
	**5a** R = Me	 >20:1 diast.	**5b** R = Me	87%
	6a R = H		**6b** R = H	87%
	**7a** R = Me	 >20:1 diast.	**7b** R = Me	88%
	8a R = H		**8b** R = H	90%

[a] Elimination was a major side reaction.

Exceptional stereoselectivity is realized with the cyclic sulfonium salts **5a**−**8a**, but not with the acyclic diethylsulfonium salt **3a**. To establish a model for the origin of diastereoselection the hexatriene **5b** was reacted with *N*-phenyl-1,2,4-triazoline-3,5-dione to afford a single Diels−Alder adduct **9** (eq 2) which was crystallized from ethyl acetate. The dienophile had more difficulty in discriminating between the methyl and thiomethyl groups in diene **1b**, leading to two diastereomeric adducts in a 1.9:1.0 ratio. X-ray structure determination showed unambiguously that the methyl and sulfur substituents of **5b** possess an anti relationship and confirmed the addition of the dienophile from the same face as the methyl group. Trienes **6b**, **7b**, and **8b** have been tentatively assigned anti stereochemistry in analogy to that of **5b**.



5b **9** (2)

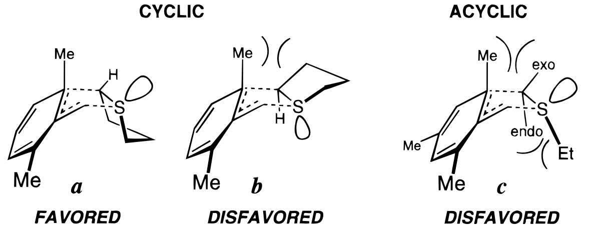


Figure 1. Transition states for cyclic and acyclic thia-Sommelet rearrangements.

The anti relationship in **5b**−**8b** requires that the rearrangement proceed through endo transition state ***a*** as shown in Figure 1. Theoretical studies (MP2/6-31+G*//HF/6-31+G*) by Houk and Wu predicted that in the five-membered ring transition state for [2,3]-sigmatropic rearrangement of sulfonium ylides the sulfur lone pair prefers an exo orientation.[18,36] This important preference creates two entirely different situations for cyclic substrates **5a**−**8a** and acyclic substrate **3a**. For cyclic sulfonium ylides, the effects of lone pair preference and eclipsing are collusive. Transition state ***a*** is preferred because of the favorable lone pair orientation and minimization of eclipsing interactions between sp^3 carbons. Transition state ***b*** suffers from an unfavorable endo lone pair in addition to an unfavorable eclipsing interaction. For acyclic substrates, the lone pair preference and eclipsing interactions do not act in concert. In satisfying the preference for an exo lone pair, as in transition state ***c***, both the exo and endo positions are compromised by eclipsing interactions. When extended to the corresponding [2,3]-sigmatropic rearrangement of allyl oxonium ylides, this analysis explains the poor stereoselectivity observed for acyclic oxonium ylides[37] and predicts that good stereoselectivity will be achieved for endocyclic oxonium ylides.

If the racemization of the chiral ylide intermediate (by sulfur inversion) is fast relative to the rearrangement, then the prospects for asymmetric induction will be dim. In fact, the prospects are bright. Trost has previously demonstrated faithful transfer of stereochemistry in [2,3]-rearrangements of aliphatic sulfonium ylides.[19] While the rearrangement of benzylsulfonium ylides should be energetically more demanding than that of allylsulfonium ylides, the rearrangement is still predicted to be much faster than racemization. Using density functional theory (b3lyp/6-31+G*//b3lyp/6-31+G*),[38] the activation energy for inversion of dimethylsulfonium methylide is predicted to be 22 kcal/mol at room temperature, similar to theoretical[39] and experimental values[40,41] reported for stabilized sulfonium ylides. Unlike racemization, the thia-Sommelet rearrangement is fast even at low temperature; therefore, attention can now be directed toward enantioselective ylide generation as a means of controlling the absolute stereochemistry.

In conclusion, we have shown that thia-Sommelet dearomatization may be carried out by deprotonation with LDA at low temperature leading to formation of hexatrienes containing quaternary stereogenic centers in excellent yields. Cyclic sulfonium ylides give excellent diastereocontrol leading to products in which the ortho substituent and sulfur possess an anti relationship. This diastereocontrol is explainable in terms of two important effects in the transition state: the preference for an exo lone pair and the minimization of eclipsing interactions. Asymmetric induction should be possible due to the rapidity of the first-order thia-Sommelet rearrangement relative to the first-order racemization of the chiral ylide intermediate.

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Supporting Information Available: Procedures and characterization data, summary data for ab initio calculations, and crystallographic data for adduct **9** (28 pages). See any current masthead page for ordering and Internet access instructions.

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