## **Regiochemical Studies on Halocyclization** Reactions of Unsaturated Sulfides

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Key words: Electrophilic cyclizations, halocyclizations, sulfur cyclizations, unsaturated sulfides, halosulfones

Abstract: The regiochemistry of halocyclization reactions for olefinic and acetylenic sulfides has been examined.

Electrophilic cyclizations of unsaturated compounds 1, where X=O, NH, or S, has proved to be an efficient method for constructing heterocyclic structures of type 3.1 These reactions are generally viewed as proceeding through a stepwise electrophilic addition-dealkylation sequence involving cationic intermediate 2. Although a large amount of mechanistic and synthetic work has already been reported for unsaturated oxygenand nitrogen-systems (1, X=O, NH),<sup>2</sup> electrophilic cyclizations of unsaturated <u>sulfides</u> (1, X=S) have remained relatively unexplored.<sup>3,4</sup> Ring closures of this type are generally controlled by a combination of stereoelectronic and steric effects, as summarized by Baldwin.<sup>5</sup> However, since Baldwin's Rules are best applied to systems which contain only first row elements, it remains unclear as to what effect sulfur's larger atomic size and greater polarizability may have on the regiochemistry of cyclization. Judging from the limited number of examples which have appeared in the literature, electrophilic additions of sulfur groups to internal multiple bonds typically favor five-membered rings over other possible ring sizes. It should be pointed out that most of these examples involve the formation of *bicyclic* ring systems, whose regiochemistry is likely to be the result of constraints imposed by the pre-existing ring. We therefore set out to study the regiochemistry of halocyclizations for *conformationally flexible* unsaturated sulfides.



The substrates used for these studies were prepared in a few steps from commercial materials.<sup>6</sup> The halogenation reactions were conducted at room temperature by adding one molar equivalent of bromine (or iodine) dropwise to a solution of the unsaturated sulfides in CH<sub>2</sub>Cl<sub>2</sub>. Due to the volatile nature and instability of the resulting halosulfides<sup>7</sup>, the cyclic adducts were oxidized promptly to their halosulfone derivatives using *m*-chloroperoxybenzoic acid (mCPBA). The products were chromatographed on silica gel and characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Our results are discussed in more detail below.

**Four-exo versus Five-endo Ring Closures:** We first examined the reactions of 3-butenyl benzylsulfides with elemental bromine (see below). Each of these substrates was found to react rapidly with bromine to give five-membered ring bromosulfides, which after oxidation afforded excellent overall yields of bromosulfones. We did not isolate any of the four membered ring adducts or uncyclized bromination products.



When these brominations were carried out using 3-butynyl analogues, complex mixtures of products were obtained due to the instability of the resulting vinylsulfides towards bromine. However, these cyclizations could be accomplished efficiently using iodine as the electrophilic reagent to give the five-membered ring adducts in quantitative yields. Thus, halocyclizations of both olefinic and acetylenic sulfides show a strong preference for forming the five-membered ring over the more highly strained four-membered ring.



Five-exo versus Six-endo Ring Closures: We next turned our attention to the halogenation reactions of 4-pentenyl and 4-pentynyl sulfides. Upon treatment of the pentenyl substrates with bromine, mixtures of five- and six-membered rings were obtained, along with small amounts of acyclic dibromides in some instances. Interestingly, for the first three entries shown below, the six-membered ring product predominates, in contrast to what has been reported for the formation of bicyclic ring systems.<sup>3</sup> However, disubstitution at the terminal olefin site leads to a slight preference for exo ring closure (see last entry below).

Ph~s~~~	1) Br <sub>2</sub> (1 eq) CH <sub>2</sub> CH <sub>2</sub> 2) mCPBA (2.5 eq)		+ <b>C R R</b> + <b>B r</b> +	
	R=R'=H	(8%)	(82%)	(10%)
	R = CH₃; R' =H	(10%)	(87%)	(2%)
	R = Ph; R' =H	(10%)	(85%)	
	R = R = CH <sub>3</sub>	(60%)	(40%)	-

In contrast to these pentenyl cyclizations, the iodination reactions of 4-pentynyl sulfides proceeded with complete regiocontrol to give only the five-membered ring products. These cyclic iodosulfides undergo fairly rapid isomerization to the six-membered ring and must therefore be oxidized to the sulfones without delay.



Six-exo versus Seven-endo Ring Closures: To complete these studies, we also examined the halogenations of 5-hexenyl and 5-hexynyl sulfides. Not surprisingly, the bromination reactions of the hexenyl derivatives produced large amounts of acyclic dibromides due to the diminished rate of cyclization relative to olefin bromination. Nevertheless, the major cyclization product from these reactions is the six-membered ring.



To examine whether these cyclization reactions could be occurring via a dibromide intermediate, the dibromosulfides were prepared (by slow addition of one equivalent of bromine to the olefin) and subjected to the usual cyclization conditions (see below). Upon treatment with one equivalent of bromine, each of the dibromides underwent clean cyclization to produce <u>seven</u>-membered ring adducts exclusively.<sup>8</sup> From this, we conclude that the above cyclizations of the *unsaturated* sulfides do not involve dibromide intermediates, but more likely proceed by way of a bromonium-like species.



Furthermore, it seemed reasonable to expect that the regiochemistry of these 5-hexenyl cyclizations could be altered by simply reversing the order of addition of the reagents. This turned out to be the case. Thus, by adding the sulfide slowly to a concentrated solution of  $Br_2$  (one equivalent), the seven-membered ring adducts are produced in essentially quantitative yields (see above). Under these conditions, the cyclizations undoubtedly proceed via dibromosulfide intermediates through an  $S_N^2$ -type displacement process.<sup>9</sup> Lastly, we studied the iodination reactions of 5-hexynyl benzylsulfide derivatives. Unlike the olefinic analogues above, these substrates cyclized without difficulty to give quantitative yields of six-membered ring cycloadducts, with none of the seven-membered ring product or acyclic diiodides being isolated.



The following table summarizes our results on the regiochemistry of these sulfide halocyclization reactions, using the nomenclature of Baldwin. We will report on additional aspects and applications of this methodology at a later time.<sup>10</sup>

olefinic sulfides	acetylenic sulfides	
5-endo-trig > 4-exo-trig	5-endo-dig > 4-exo-dig	
6-endo-trig > 5-exo-trig	5-exo-dig > 6-endo-dig	
6-exo-trig > 7-endo-trig	6-exo-dig > 7-endo-dig	

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- 6. The preparation and experimental data of all new compounds will be described in a full paper.
- 7. The bromosulfide cycloadducts do not equilibrate under the reaction conditions. Thus, after standing in the
- presence of benzyl bromide (1 eq) and bromine (1 eq), each can be recovered unchanged after 24 hours.
  8. Curiously, this conversion does not occur in the absence of Br2. We speculate that bromine may aid in the displacement via a polarization effect.
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- 10. We thank the donors of the Petroleum Research Fund, administered by the ACS, for the financial support of this research.

(Received in USA 17 December 1992; accepted 29 December 1992)