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THE STUDY OF INTRAMOLECULAR FREE RADICAL CYCLIZATIONS OF α-SULFONYL AND α-SULFINYL RADICALS

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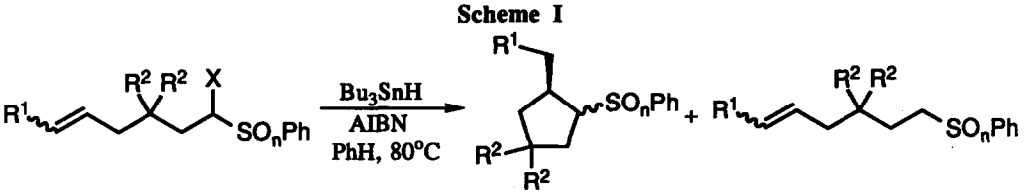
Abstract: α-Sulfonyl and α-sulfinyl radicals can be generated from the corresponding α-halosulfones and α-halosulfoxides. Our results indicate that these radicals cyclize very efficiently.

Free radical reactions have emerged as an important synthetic technique due to the recent intensive studies.[1] We have devoted ourselves in the study of intramolecular free radical cyclizations involving carbon radicals that carry α-sulfur functional groups.[2-5] In this communication we wish to report our success in the generation and cyclization of α-sulfonyl and α-sulfinyl radicals.[4,5]

We first prepared chlorosulfoxide **1b** (Scheme I) as a mixture of two diastereomers (1/2) from the corresponding chlorosulfide **1d**[2] via MCPBA oxidation (85%). Further oxidation of **1b** with potassium permanganate gave chlorosulfone **1a** (66%).[6] As shown in Table I (entry 1), initially we took **1a** (0.1M in benzene, 80°C) and treated it with tributyltin hydride (0.1M in benzene, 0.1 equiv AIBN) using the condition previously worked for α-sulfenyl radical cyclization[2] with slow addition of the stannane over 6 h. Although we successfully obtained the desired cyclization product, however, we found that this result was difficult to reproduce. With intensive variation of the conditions we then realized that these types of radical generation and

Scheme I



a	**1a**	R^1=R^2=H	X=Cl	n=2	**4a**	**7a**
	1b	R^1=R^2=H	X=Cl	n=1	**4b**	**7b**
b	**1c**	R^1=R^2=H	X=SPh	n=0	**4c**	**7c**
	1d	R^1=R^2=H	X=Cl	n=0		
	2a	R^1=H R^2=CO_2Me	X=Br	n=2	**5a**	**8a**
	2b	R^1=H R^2=CO_2Me	X=Br	n=1	**5b**	
	2c	R^1=H R^2=CO_2Me	X=SPh	n=0	**5c**	**8c**
c	**3a**	R^1=CO_2Et R^2=H	X=Cl	n=2	**6a**	**9a**
b	**3b**	R^1=CO_2Et R^2=H	X=Cl	n=1	**6b**	
	3c	R^1=CO_2Et R^2=H	X=Cl	n=0	**6c**	

(a) $KMnO_4$ (1.5 equiv), acetone, RT, 1 h (b) MCPBA (1 equiv), CH_2Cl_2, 0°C, 2 h (c) MCPBA (2 equiv), CH_2Cl_2, 0°C, 3 h

cyclization were extremely sensitive to the presence of oxygen.[7] Even with careful deoxygenation, we still recovered appreciable amount of unreacted **1a** (20%) under the condition mentioned above. Compare with the result of the corresponding α-sulfenyl radical (entry 11), the cyclization/reduction ratio for α-sulfonyl radical is higher which indicates that α-sulfonyl radical is more reactive. This is consistent with the known fact that α-sulfenyl radical is more stable than α-sulfonyl radical.[8]

In fact, we found that when we performed the cyclization of **1a** (entry 2) under the same condition except with a faster stannane addition rate (1 h), all the starting material was consumed. More reduction product (31%) was obtained this time. Further more, we could perform the cyclization (entry 3) under a more concentrated condition (0.4 **M** **1a**, 0.4 **M** stannane) with a fast stannane addition rate (2h) and still obtained similar result as in entry 2. Under this latter set of condition, chlorosulfoxide **1b** also cyclized reasonably well (entry 7). To our knowledge this is the first example that an α-sulfinyl radical is involved in intramolecular cyclization.

In the presence of Thorpe-Ingold effect[9] bromosulfone **2a**[5e] (entry 4) and bromosulfoxide **2b**[10] (entry 8) cyclized very efficiently as judged from the high cyclization/reduction ratio. Interestingly, in the presence of an electron deficient olefin the presumably also electron deficient α-sulfonyl and α-sulfinyl radical (entry 5,6,9,10) still cyclized extremely well irrespective of the olefin geometry. However, this is not surprising according to the kinetic studies of Giese.[11]

In order to determine the stereochemistry of the cyclized products we first took the previously prepared sulfides *cis*- and *trans*-**4c** and oxidized each with two equivalents of MCPBA to give sulfones *cis*- and *trans*-**4a**, respectively.[12] Treatment of *cis*- and *trans*-**4c** with one equivalent of MCPBA each gave a 1/1 mixture of two diastereomeric sulfoxides (**4b**).[12] It is interesting to note that moderate stereoselectivity was observed in the formation of *cis*- and *trans*-**4b** via cyclization. Controlled experiment indicated that these sulfoxides did not interconvert with each other under the reaction condition; thus, the selectivity observed here reflects the inherent selectivity due to the sulfur chiral center of sulfoxide. Previously,[2] we have determined the stereochemistry of *cis*- and *trans*-**6c** via ^{1}H NMR chemical shift correlations. Again, using the oxidation process described above we were able to correlate **6c** with **6a** and **6b**. For the stereochemistry of **5a** and **5b**, we first carried out the cyclization of dithioacetal **2c**[13] (entry 12). The ^{1}H NMR spectrum of the major cyclization product **5c** showed the presence of a quartet at δ 3.72 (J = 7 Hz, C(1)-H) in good correlation with similar type of *cis* sulfides such as **4c** in which the same proton appeared at δ 3.62 (q, J = 7 Hz).[2] Similarly, in *trans*-**5c** C(1)-H appeared at δ 3.06 (q, J = 7 Hz); whereas C(1)-H in *trans*-**4c** occurred at δ 3.02 (q, J = 7 Hz). With the stereochemical assignment of **5c** felt secured, the stereochemistry of **5a** and **5b** were determined via correlations from **5c** by oxidations.[12]

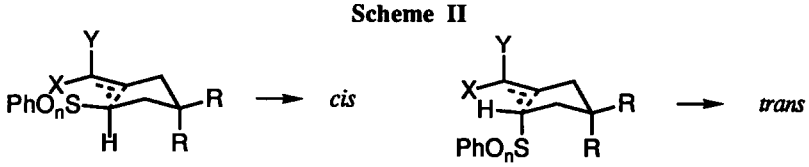
In our last report,[2] from the results of our study of α-sulfenyl radicals we concluded that for faster cyclizations the percentage of the *cis* cyclization product would increase while for slower cyclizations the percentage of the *trans* cyclization product would increase. We also observed this trend in this study. Thus, for the sulfone series (entry 3-6), the Thorpe-Ingold effect enhances the cyclization rate in entry 4 and the *cis*/*trans* ratio of **5a** increases as compared with that of **4a** (entry 3). In the case of entry 5 with electron withdrawing group attached to the olefin, according to Giese,[11] the rate of cyclization is also faster than the unsubstituted case (entry 3) and the *cis*/*trans* ratio in **6a** is also higher. In the case of entry 6, the *Z*-geometry at olefin enforces the carbethoxy group at pseudoaxial position in the chair transition state[14] and the resulting unfavorable 1,3-diaxial interaction increases the absolute energy level of the two low energy transition states[14] **A** and **B** (Scheme II, n = 2, R = X = H, Y = CO_2Et). Therefore, the cyclization rate of (*Z*)-**3a** is slower than that of (*E*)-**3a** but probably still faster than that of **1a** and the *cis*/*trans* ratio of **6a** lies inbetween. Similar trend was observed in the sulfoxide

Table I Intramolecular cyclizations of radicals carrying α-sulfur functionalities.[a,b]

		cyclization products	diastereomer ratio[c]		reduction product
entry	substrate	(% yield; *c*/*t* ratio)	*cis*	*trans*	(% yield)
1[d,e]	**1a**	**4a** (54; 30/70)			**7a** (19)
2[f]	**1a**	**4a** (53; 30/70)			**7a** (31)
3	**1a**	**4a** (46; 30/70)			**7a** (31)
4[g]	**2a**	**5a** (70; 70/30)			**8a** (4)
5	(*E*)-**3a**	**6a** (81; 70/30)			(*E*)-**9a** (2)[h]
6	(*Z*)-**3a**	**6a** (73; 50/50)			(*E*)-**9a** (1)[h]
7	**1b**[i]	**4b** (46; 50/50)	2/3	1/2	**7b** (43)
8	**2b**[i]	**5b** (60; 65/35)	1/2	2/3	
9	(*E*)-**3b**[i]	**6b** (70; 75/25)	1/4	1/2	
10	(*Z*)-**3b**[i]	**6b** (88; 70/30)	1/5	4/5	
11[d,j]	**1c**	**4c** (54; 35/65)			**7c** (29)
12[d]	**2c**	**5c** (92; 55/45)			**8c** (3)

[a]Reactions were performed by slow addition (2 h) of a solution of tributyltin hydride (1.5 equiv) and AIBN (0.1 equiv) in benzene (0.4 M) to a solution of the substrate in benzene (0.4 M) heated at 80°C, and then heated for another 2 h. [b]Yields are isolation yield and ratios were determined by isolation or ^{1}H NMR integration. [c]Diastereomers are epimeric at sulfur; however at this point we do not know the exact stereochemical relationship at sulfur with respect to the other two chiral centers. [d]Stannane (0.1 M in benzene) and AIBN (0.1 equiv) was added over 6 h to the substrate (0.1 M in benzene) at 80°C. [e]Starting material (**1a**) was recovered (20%). [f]Stannane (0.1 M in benzene) and AIBN (0.1 equiv) was added over 1 h to the substrate (0.1 M in benzene) at 80°C. [g]See also reference 5e. [h]Determined by ^{1}H NMR integration. [i]Mixture of two diastereomers (3/7 in (*E*)-**3b**; 1/3 in (*Z*)-**3b**). [j]Results from reference 2.

Scheme II



A **B**

series (entry 7-10). However, comparison of the stereochemical results of the α-sulfonyl , α-sulfinyl and α-sulfenyl radical cyclizations (entry 3, 7, 11) indicates no apparent regularity and this may reflect a delicate balance between the steric effect and inherent radical reactivity factor.

In conclusion, we demonstrated that α-sulfonyl and α-sulfinyl radicals could be generated from the corresponding α-halosulfones and α-halosulfoxides. These radicals are quite reactive and cyclize very efficiently. Since the required α-chlorosulfones and α-chlorosulfoxides can be prepared from the easily available α-chlorosulfides,[15] our approach constitutes an easy entry into the manifold of α-sulfur radicals.

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13. Dithioacetal **2c** was prepared by sequential alkylation of dimethyl malonate with 2-bromoethyl phenyl sulfide (76%) and allyl bromide (71%) followed by chlorination (NCS, CCl_4) and sulfur exchange (PhSH, $ZnCl_2$, CCl_4; 59%).
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