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THE STUDY OF INTRAMOLECULAR FREE RADICAL CYCLIZATION OF α-SULFENYL RADICAL

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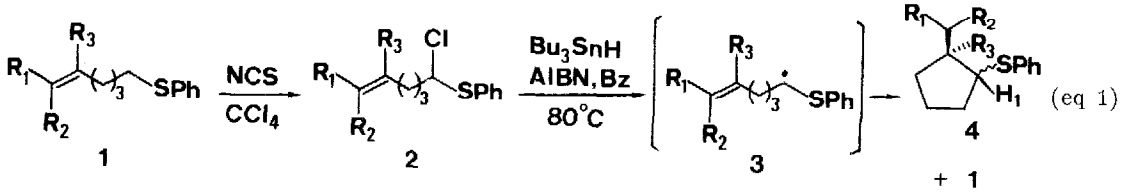
Abstract: α-Sulfenyl radical can be generated from α-chlorosulfide or dithioacetal. The olefin substituent effect on the intramolecular radical cyclization of this type was studied.

Free radical reactions have enjoyed their popularity in recent years.[1] In particular, the use of intramolecular free radical cyclizations to construct five-membered rings has received the most attention. We focused our attention on the generation and cyclization of radicals carrying α-sulfur functional group. The presence of such group in the cyclization product opens the possibility for further transformations. Examination of the literature, we have found only a few scattered reports involving this type of free radicals.[2,3] Herein we wish to report our results in the area of α-sulfenyl radical cyclizations.

Initially, we generated the desired radical from α-chlorosulfides. Thus, when chlorosulfide **2a**, prepared[4] almost quantitatively from **1a**[5] (eq 1), was treated with tributyltin hydride in the presence of 5 mol% of azobisisobutyronitrile (AIBN) in benzene (0.05 M) at 80°C gave 45% yield of **4a** as a 35/65 mixture of *cis* and *trans* isomer, respectively.[6] In addition was isolated 29% of **1a** which was derived from hydrogen abstraction of radical **3** from tributyltin hydride.[7] We were not able to detect any six-membered ring product. In order to provide an authentic sample of phenyl cyclohexyl sulfide (**5**) for comparison and to determine the stereochemistry of **4**, we adopted an alternative route to synthesize **4a** and **5**. Thus, **5** was prepared (50%) according to Walker's procedure[8] from cyclohexanol (*N*-phenylthiosuccinimide, tributylphosphine, THF). Similarly, *cis*- and *trans*-**4** were prepared from *trans*- and *cis*-2-methylcyclopentanol, respectively, in 80 and 17% yield.[9]

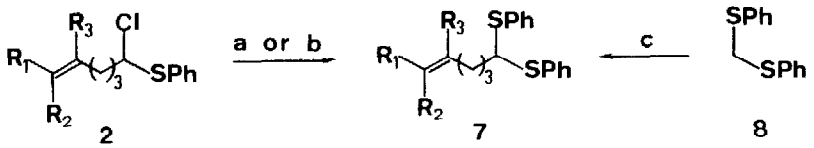
When we tried to optimize the cyclization of **2a**, a dehydrochlorinated product **6** was sometimes present in varying amounts. This diene sulfide is probably formed via an ionic process. In fact, when we carried out the reaction (0.05 M) in the presence of 0.2~1 equivalent of anhydrous triethylamine,[10] the formation of **6** was successfully depressed.



1 2 3 4 + 1 (eq 1)

a, $R_1=R_2=R_3=H$; **b**, $R_1=R_2=H$, $R_3=CH_3$; **c**, $R_1=R_3=H$, $R_2=CH_3$; **d**, $R_1=CH_3$, $R_2=R_3=H$
e, $R_1=R_2=CH_3$, $R_3=H$; **f**, $R_1=R_3=H$, $R_2=CO_2Et$; **g**, $R_1=CO_2Et$, $R_2=R_3=H$

Scheme I



a, $R_1=R_2=R_3=H$; c, $R_1=R_3=H$, $R_2=CH_3$; d, $R_1=CH_3$, $R_2=R_3=H$; e, $R_1=R_2=CH_3$, $R_3=H$
(a) PhSH, $ZnCl_2$, CCl_4 (**7a**: 70%) (b) NaSPh, DMF (**7c**: 67%, **7d**: 57%) (c) *n*BuLi (1.1 equiv), HMPA (1.1 equiv), THF, -50°C; 5-iodopentene (1.2 equiv), -50°C → RT (**7a**: 92%)

However, as the reaction concentration became more dilute (< 0.02 **M**), **6** was unavoidable. To solve this problem, we felt that dithioacetal **7a** (Scheme I) may provide a better alternative.[11] This dithioacetal can be prepared either from **2a** by exchange reaction[12] or by alkylation of the anion of diphenylthiomethane[13] (**8**). Reaction of **7a** with tributyltin hydride (Table I) indeed gave **4a** (54%) with the same *cis/trans* ratio as obtained from **2a**.

We subsequently studied the effect of olefin substitution on the cyclization and the results are summarized in Table I. In general the dithioacetals are better substrates for radical cyclization than chlorosulfides. Unfortunately, the reaction of dithioacetal with tri-*n*-butyltin hydride appeared slower and at more dilute conditions (≤ 0.02 **M**) starting material was recovered even after prolonged heating. Being a nucleophilic radical[1a] the cyclization of α-sulfenyl radical with electron deficient olefin (entry 9, 10)[14] is faster and proceeded to give only the cyclization product even at higher concentration.

The assignments of the stereochemistry of **4c**, **4e**, and **4f** were made by comparison of the chemical shift of H-1 with that of *cis*- and *trans*-**4a**. For the *cis* ones, H-1 all appeared at lower field within δ 3.79 ± 0.07 ppm, and that of the *trans* ones all appeared at higher field within δ 3.01 ± 0.09 ppm.[15] It is noted that for the cyclization of **7a**, *trans*-**4a** was the major product (entry 2, Table I); however, the seemingly sterically more congested *cis*-**4e** enhanced its weight in the cyclization product derived from **7e** (entry 8, Table I). Yet, in the case of **2g** (entry 10, Table I), *cis*-**4f** became the major product.

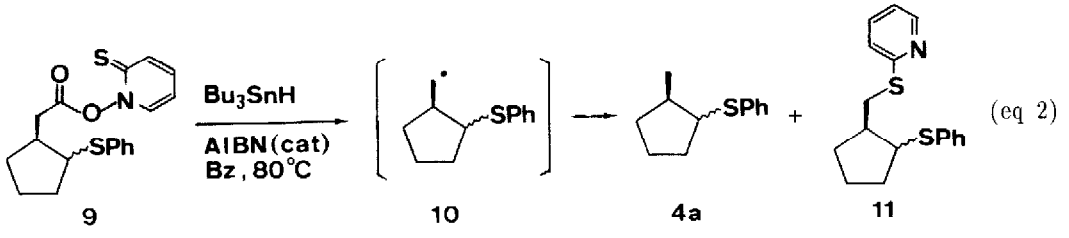
Although initially we felt that the fact that we did not observe six-membered ring product indicated the kinetic nature of these cyclizations; however, confused by the stereochemical outcomes, we felt that it may be essential to probe the reversibility of our process before drawing any conclusion. Thus, a *cis* enriched mixture of **4f** (*c*/*t* = 65/35) was hydrolyzed (KOH/MeOH/H_2O) and converted to **9** according to Barton's procedure.[16] When **9** was treated with tributyltin hydride (eq 2) we were able to isolate **4a** (19% from **4f**) with the same ratio of *cis* and *trans* isomers as

In order to provide a rationale for the stereoselectivity observed here one can adopt the Beckwith model[18] assuming a chair transition state as shown in **A** or **B**. For cyclizations that are faster as in entry 10 (Table I), an early transition state is proposed in which the distance between C-5 and C-1 is longer and the steric interaction between the phenysulphenyl group and C-3 hydrogen is more important and raises the energy of **B** relative to **A** and *cis*-**4**

Table I Intramolecular free radical cyclizations of α-phenylsulphenyl radicals.[a]

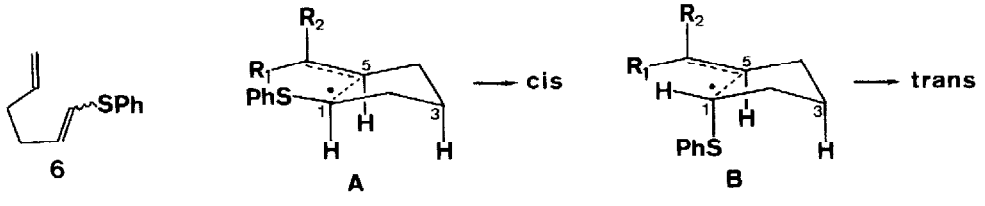
entry	substrate	cyclization product (yield%; *c*/*t* ratio)[c,d]	reduction product (yield%)[c]	% elimination[c,e]
1[b]	**2a**	**4a** (45; 35/65)	**1a** (29)	--
2	**7a**	**4a** (54; 35/65)	**1a** (29)	--
3[b]	**2b**	--	**1b** (30)	33
4[b]	**2c**[f]	**4c** (20; 35/65)	**1c** (26)	36
5	**7c**[g]	**4c** (48; 35/65)	**1c** (26)	--
6[b]	**2d**	**4c** (29; 35/65)	**1d** (34)	3
7	**7d**[h]	**4c** (51; 35/65)	**1d** (32)	--
8	**7e**[i]	**4e** (55; 45/55)	**1c** (17)	--
9[b,j]	**2f**[k]	**4f** (67; 55/45)	--	--
10[b,j]	**2g**[k]	**4f** (83; 65/35)	--	--

[a]Reactions were performed by slow addition (6 h) of a solution of tributyltin hydride (1.5 equiv) and AIBN (0.05 equiv) to a solution of the substrate in benzene heated at 80°C with final concentration of 0.05 M. [b]Triethylamine (0.2 equiv) was added. [c]Isolation yield. [d]Ratios were determined by ^{1}H NMR spectrum integration. [e]Geometry of the olefins were not determined. [f]A mixture of *cis* and *trans* isomers (*c*/*t* = 85/15). [g]Prepared from **2c**. [h]Prepared from **2d**. [i]Prepared from **8**. [j]Final concentration was 0.1 M. [k]See ref 14.



(eq 2)

is the major product. For slower cyclizations as in entry 2,5 and 7 (Table I), a late transition state is proposed in which the distance between C-5 and C-1 is shorter and the eclipsing interactions between the substituents on C-1 and C-5 are more important. Transition state **A** now has higher energy and *trans*-**4** becomes the major product. We believe that our cyclization is the first model that demonstrates how the degree of bond formation in the transition state is effecting the stereochemical course.[19]



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5. The sulfides were prepared in high yields from the corresponding alcohols via mesylate formation (MsCl, Et_3N, CH_2Cl_2) and displacement of the mesyl group (NaSPh, EtOH).
6. The ratio was determined by ^1H NMR spectrum integration.
7. Note that this represents a rare case that the straight reduction product can be reused.
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9. The stereochemical assignments were based on Walker's (ref. 8) mechanism which involved a backside attack that resulted in inversion of the stereochemistry.
10. Since the chlorosulfide is moisture sensitive, we suspect that the exclusion of chloride ion is assisted by HCl which came from the reaction of the chlorosulfide with moisture.
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14. Chlorosulfides **2f** and **2g** were prepared from 2-hydroxytetrahydropyran according to the following sequence: (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 (88%), (ii) MsCl, Et_3N, CH_2Cl_2, 0°C (96%), (iii) PhSNa, EtOH, 0°C (82%), with separation of *cis* and *trans* isomer, (iv) NCS, CCl_4.
15. Chemical shift (ppm) of H-1 (in $CDCl_3$): *cis*-**4a**, 3.62; *cis*-**4c**, 3.69; *cis*-**4e**, 3.72; *cis*-**4f**, 3.76; *trans*-**4a**, 2.93; *trans*-**4c**, 3.12; *trans*-**4e**, 3.28; *trans*-**4f**, 3.10.
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19. We thank the National Science Council of the Republic of China for financial support. Helpful discussions with Prof. D. H. R. Barton is also acknowledged.

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