ORGANIC LETTERS

2002
Vol. 4, No. 23
4065−4067

Regioselectivity of Ring Closure of 2-Thia- and 2-Sulfonyl-5-methyl-5-hexenyl Radicals

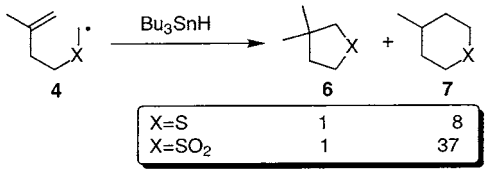
Ernest W. Della* and Sean D. Graney

Department of Chemistry, Flinders University of South Australia, GPO Box 2100, Adelaide SA 5001, Australia

ern.della@flinders.edu.au

Received August 25, 2002

ABSTRACT



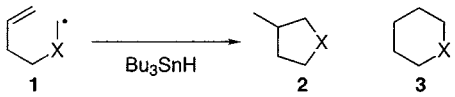
Ring closure of the α-substituted radicals 4 (X = S, SO_2) is observed to be irreversible and to lead to significant amounts of the product of 6-endo cyclization. Indeed, reduction of the sulfonyl-based radical 4 (X = SO_2), in which regioselectivity is believed to be controlled by a combination of both steric and FMO interactions, is found to provide an excellent route to the cyclic sulfone 7 (X = SO_2) in high yield.

The application of radical cyclization of the 5-hexenyl system in organic synthesis leading to the preparation of some quite complex substrates is well-documented.[1] Generally, these rearrangements occur under stereoelectronic control and frequently yield products via a predominant 5-exo mode of ring closure. When a modified radical containing a heteroatom is employed, the procedure can be exploited for the synthesis of heterocyclic compounds, and a number of compounds of commercial and physiological importance have indeed been synthesized in this way. We have previously prepared several novel heterocyclic systems containing nitrogen using both α- and β-ammonio-substituted 5-hexenyl radicals.[2]

While oxygen- and nitrogen-containing radical cyclizations have been studied intensively, an examination of the literature reveals only scattered examples of the synthesis of sulfur-based heterocycles via radical methods. These include cyclizations with a sulfur functionality in the hexenyl chain at the 3-[3] and 4-positions[4] and an example of a sulfonylated radical in the 2-position[5]. Several useful radical cyclizations with a sulfur functionality located α- to the radical center have also been reported, but these yield a cyclic product with the sulfur functionality external to the ring.[6]

More recently, we have reported[7] the results of a parallel study of the cyclization of the 2-thia- and 2-sulfonyl-5-hexenyl radicals **1** (X = S, SO_2) (Scheme 1). It was observed that mixtures containing substantial quantities of both the 5-endo and 6-exo products **2** and **3** (X = S, SO_2), respec-

Scheme 1



(1) (a) For an extensive review on "Radicals in natural product synthesis" see: Curran, D. P.; Fevig, T. L.; Jasperse, C. P. *Chem. Rev.* **1991**, *91*, 1237. (b) Curran, D. P. *Synlett* **1991**, 63. (c) Neumann, W. P. *Synthesis* **1987**, 665. (d) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

(2) (a) Della, E. W.; Smith, P. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 445. (b) Della, E. W.; Smith, P. A. *Tetrahedron Lett.* **2001**, *42*, 481. (c) Della, E. W.; Smith, P. A. *J. Org. Chem.* **2000**, *65*, 6627. (d) Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798. (e) Della, E. W.; Smith P. A.; Knill, A. M. *Chem. Commun.* **1996**, *14*, 1637. (f) Della, E. W.; Knill, A. M. *Tetrahedron Lett.* **1996** *37*, 5805. (g) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529. (h) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1995**, *48*, 2047.

(3) Serra, A. C.; da Silva Correa, C. M. M. *Tetrahedron Lett.* **1991**, *32*, 6653.

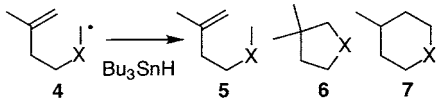
(4) Ponaras, A. A.; Zaim, O. *Tetrahedron Lett.* **2000**, *41*, 2279.

10.1021/ol0267836 CCC: $22.00
Published on Web 10/16/2002

tively, of irreversible ring closure were produced. Interestingly, species **1** (X = SO_2) is much more amenable to ring closure compared to radical **1** (X = S) under similar conditions, giving over 95% cyclized products. Nevertheless, while the mode of cyclization of these radicals is of intrinisic interest, the procedure does not represent a particularly convenient entry into sulfur-substituted heterocyclic compounds in view of the mixture of isomeric products so obtained.

We now report a study on the regiochemistry associated with the cyclization of 5-methyl-substituted radicals **4** (X = S, SO_2) (Scheme 2). By analogy with behavior of the

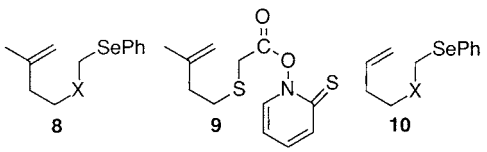
Scheme 2



corresponding all-carbon 5-methyl-5-hexenyl system **4** (X = CH_2), it was anticipated that introduction of a methyl group at C5 would be accompanied by a reduction in the rate of 5-exo ring closure of species **4** (X = S, SO_2), thus giving an enhanced yield of the 6-endo product **7** (X = S, SO_2) compared with isomer **6** (X = S, SO_2). Furthermore, it is noteworthy that in the case of the α-sulfonyl-substituted radical, the strong inductively withdrawing influence of the SO_2R group (s_p value = +0.7)[8] would be expected to impart significant electrophilic character onto the radical. Accordingly, given that these reactions are predicted to proceed via early transition states, regioselectivity is also expected to be dependent upon the favored interaction of the frontier orbitals of the reactants.

The selected precursors to the radicals **4** (X = S, SO_2) under study were the selenides **8** (X = S, SO_2),[9] which were rigorously purified immeditely prior to use. Crich[10] has shown that the presence of PhSeH derived from reaction of $(PhSe)_2$ with Bu_3SnH can introduce undesirable complications. As a precautionary measure, bistributyltin oxide was added to the reaction mixture in view of its demonstrated efficiency as a scavenger of PhSeH.[11] Barton ester **9** was also employed in order to determine whether adventitious diphenyl diselenide might be influencing the extent of cyclization.

Radical Precursors



The results of the behavior of radicals **4** (X = S, SO_2)[12] together with those for **1** (X = S, SO_2) are summarized in Table 1. Inspection of the table reveals that the extent of 6-endo versus 5-exo ring closure is enormously enhanced in the case of the sulfonyl radical **4** (X = SO_2) in which the ratio of the 5-exo to 6-endo product is 1:37, with little of the acyclic reduced species **5** (X = SO_2) detected. Under experimental conditions designed to minimize even further the extent of reduction,[13] the reaction is found to give an excellent yield (86%) of the substituted cyclohexane **7** (X = SO_2)[14] uncontaminated by either isomer **5** (X = SO_2) or isomer **6** (X = SO_2).

Table 1. Product Ratios from Bu_3SnH Reduction of Radicals **1** and **4** (X = S, SO_2)

precursor	radical	concn (M)	*T* (°C)	reduced	5-exo	6-endo
8[a]	**4** (X = S)	0.011	80	38.6	7.1	54.3
9[a]	**4** (X = S)	0.011	80	35.6	8.3	56.2
9[a,b]	**4** (X = S)	0.011	80	75.7	2.7	21.6
8[a]	**4** (X = SO_2)	0.011	80	3.9	2.5	93.6
8[a]	**4** (X = SO_2)	0.044	80	8.9	2.3	88.7
10[7]	**1** (X = S)	0.013	80	17.1	70.1	12.8
10[7]	**1** (X = SO_2)	0.013	80	3.8	73.1	23.1

[a] From this work. [b] Bu_3SnH was used in 5-fold excess.

The data within Table 1 further demonstrate that the ratio of 5-exo to 6-endo products remains constant for radicals **4** (X = S, SO_2) despite changes in concentration, thus indicating that these reactions occur irreversibly under the conditions employed in this study.

It is also of interest to compare the behavior of radicals **4** (X = S, SO_2) with that of other α-substituted 5-methyl-5-

(5) Vacher, B.; Samat, A.; Allouche, A.; Laknifli, A.; Baldy, A.; Chanon, M. *Tetrahedron* **1988**, *44*, 2925.
(6) Ke, B.-W.; Lin, C.-H.; Tsai, Y.-M. *Tetrahedron* **1997**, *53*, 7805.
(7) Della, E. W.; Graney, S. D. *Tetrahedron Lett.* **2000**, *41*, 7987.
(8) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(9) Synthesis of the required substrates and their potential products of reaction will be described in the full paper. The identity of all compounds was established by appropriate combustion data as well as GC and NMR spectroscopic analysis. Spectral data and experimental procedures for new compounds **5** (X = SO_2), **8** (X = S, SO_2), and **9** are provided in Suppporting Information.
(10) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84.
(11) Maxwell, B. J.; Smith, B. J.; Tsanaktsidis, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 425.
(12) Stock solutions of **8** (X = S, SO_2) were prepared in benzene with the addition of bistributyltin oxide[11] and subjected to standard radical cyclization conditions (catalytic amount of AIBN; 1.2 equiv of Bu_3SnH injected over 2 min; reaction temperature = 80°C; reaction time = 2 h; cooling and then quenching with CCl_4 (X = S) or CH_3I (X = SO_2)). Reaction mixtures were analyzed by GC, and product ratios were then determined by utilizing GC response factors for each of the expected products; these response factors were determined using authentic samples of **5**−**7**, which had been prepared by standard procedures. In the case of the Barton ester, precursor **9** was added to a refluxing solution of 1.2 equiv of Bu_3SnH.
(13) A 0.01M solution of (3-methyl-but-3-ene-1-sulfonylmethylselanyl)-benzene **8** (X = SO_2) (0.135 g, 0.43 mmol) in benzene (40 mL) was deoxygenated, heated to reflux (80 °C), and then treated with a solution of Bu_3SnH (0.16 g, 0.54 mmol) in deoxygenated benzene (3 mL) containing a few crystals of AIBN over 15 min. The resulting solution was heated for an additional 3 h and then cooled; the reaction was quenched with CH_3I and the solution concentrated in vacuo. GCMS analysis of the crude product revealed the presence of **6** (X = SO_2) in minute amount (ca. 3%). Flash chromatography on silica (hexane/ether) yielded pure sulfone **7** (X = SO_2) as a white solid (0.055 g, 86%), mp 118−120 °C (lit.[14a] mp 119−120 °C), whose ^1H NMR[14a] and ^{13}C NMR[14b] spectral data were identical to those reported.
(14) (a) Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122*, 4280. (b) Barbarella, G.; Dembech, P. *Org. Magn. Res.* **1984**, *22*, 402.

Table 2. Ratio of Exo/Endo Products from Some 5-Methyl-5-hexenyl Radicals

radical	*T* (°C)	5-exo:6-endo	reference
4 (X = S)	80	12:88	*a*
4 (X = SO_2)	80	2.6:97.4	*a*
4 (X = CH_2)	80	40:60	15
4 (X = CMe_2)	80	68:32	16
4 (X = $^+NMe_2$)	102	72:28	2b

[a] From this work.

hexenyl radicals; these data are included in Table 2. Again, it can be seen that the proportion of 6-endo product derived from radical **4** (X = SO_2) is overwhelming.

While the longer C−S bonds would be expected to facilitate 6-endo closure, as evidenced by the exo/endo ratios produced in the cyclization of radicals **1** (X = S, SO_2),[17] we believe that the high regioselectivity observed in the case of radical ring closure of sulfone **4** (X = SO_2) is a combination of two predominant factors: (a) *steric effects*, which disfavor the 5-exo mode of cyclization as a result of the methyl group attached to C5, in accordance with the effect of a methyl group at C5 in the system **4** (X = CH_2); at the same time, there is no steric encumbrance for 6-endo closure, and (b) *frontier molecular orbital interactions*, in which the presence of the highly electron-withdrawing SO_2 group attached to the radical center confers considerable electrophilic character onto the radical. Thus, in the case of electrophilic radicals such as **4** (X = SO_2), FMO theory suggests[18] that the mode of ring closure is largely determined by the interaction between the radical SOMO and the alkene HOMO. For alkenes of types **1** and **4**, the coefficient of the HOMO at C6 is larger than that at C5, and, accordingly, more favorable bond formation occurs between the radical center and C6, favoring the 6-endo product.

The data collected in Table 2 reveal that the attachment of the two oxygen atoms in **4** (X = SO_2) does not appear to exert the kind of steric effect on the rate of cyclization as displayed by *gem*-dimethyl groups. It is found that the presence of the methyl groups at C2 leads to an enhanced rate of 5-exo ring closure in **4** (X = Me_2)[16] compared with that in **4** (X = CH_2),[15] a phenomenon referred to as the "*gem*-dialkyl effect".[19]

We are currently investigating the behavior of the corresponding sulfoxides **1** and **4** (X = SO).

Acknowledgment. We thank the Australian Research Council for financial support.

Supporting Information Available: Experimental details for the preparation and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0267836

(15) Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535.

(16) Beckwith, A.; L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251.

(17) Wilt has observed that the corresponding α-silyl-based radical **1** (X = $SiMe_2$) leads to mixtures of cyclized products **2** (X = $SiMe_2$) and **3** (X = $SiMe_2$), albeit in very low yield. (a) Wilt, J. *J. Org. Chem.* **1981**, *103*, 5251; *Tetrahedron* **1985**, *41*, 3979. (b) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281.

(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

(19) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.