JOC*Article*

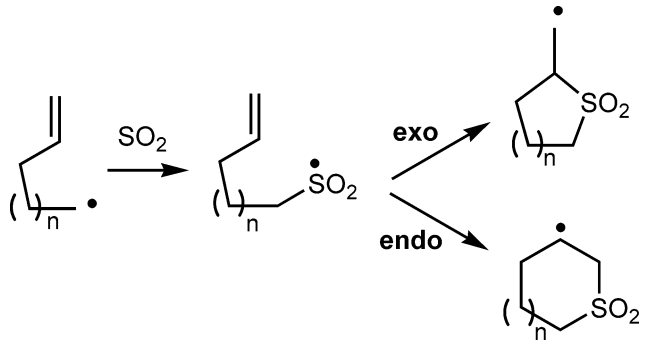
Radical [*n* + 1] Annulations with Sulfur Dioxide

Anna Tsimelzon and Rebecca Braslau*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California, 95064

braslau@chemistry.ucsc.edu

Received September 28, 2005

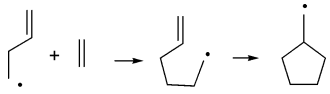


A new methodology for [*n* + 1] radical annulation using sulfur dioxide as a geminal radical acceptor/donor is presented. This methodology provides a novel route to the formation of five-, six-, and seven-membered cyclic sulfones utilizing a radical chain mechanism under very mild conditions.

Introduction

Radical chain reactions are highly efficient processes: generation of a small amount of an initiating radical can effect conversion of a large amount of substrate. Further efficiency is obtained if the reaction is convergent. Most radical acceptors are double-bond systems, which generate a new radical on the atom adjacent to the site of addition. Not surprisingly, the first convergent annulations were [3 + 2] systems in which a three-atom unit undergoes a tandem addition cyclization sequence with an olefin to form a five-membered ring[1] (Scheme 1).

SCHEME 1. [3 + 2] Radical Annulation



There are only a few functional groups that undergo radical addition resulting in the formation of a new radical at the same atom as the initial addition: geminal radical acceptor/donors (Figure 1). In 1991, Curran[2] introduced methodology for radical [*n* + 1] annulation using isonitriles as the one-atom radical acceptor/donor **1**. This was developed into a very efficient entry to the campotothecins[3] and mappicines.[4] Ryu[5] extended this strategy to the use of carbon monoxide as the radical donor/acceptor. Using a slightly different strategy, Kim[6] accomplished [4 + 1] radical annulations using bissulfonyl oxime ethers as a 2-fold one-atom radical acceptor. We now report [*n* + 1] annulations using sulfur dioxide as a radical acceptor/donor. Heterocyclic compounds containing SO_2 as part of the ring are of particular

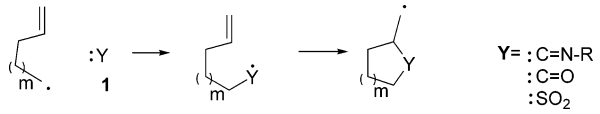


FIGURE 1. [*n* + 1] Radical annulation.

(1) Rheault, T. R.; Sibi, M. P. *Synthesis* **2003**, 803−819.

(2) (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127−2132. (b) For reviews, see: McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215−3229. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194.

(3) (a) Du, W.; Curran, D. P. *Synlett* **2003**, 1299−1302. (b) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem.−Eur. J.* **1998**, *4*, 67−83. (c) Curran, D. P.; Liu, H.; Josien, H.; Ko, S. B. *Tetrahedron* **1996**, *52*, 11385-11404. (d) Curran, D. P.; Ko, S. B.; Josien, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2683−2684.

(4) (a) Zhang, Q. S.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774−5781. (b) Zhang, W.; Luo, Z. Y.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450.

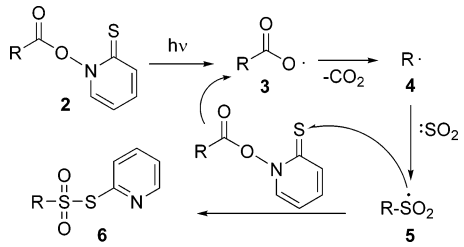
(5) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018−1019. (b) For reviews, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069. Also, see ref 2b and 2c.

(6) Kim, S.; Yoon, J. Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982−5983.

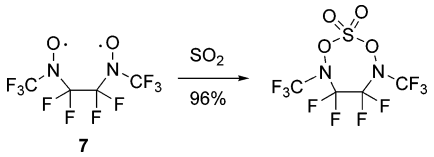
(7) (a) Koteva, K. P.; Cantin, A. M.; Neugebauer, W. A.; Escher, E. *Can. J. Chem.* **2001**, *79*, 377−387. (b) Balsamo, A.; Cercignani, G.; Gentili, D.; Lapucci, A.; Macchia, M.; Orlandini, E.; Rapposelli, S.; Rossello, A. *Eur. J. Med. Chem.* **2001**, *36*, 185−193. (c) Alpegiani, M.; Bissolino, P.; Corigli, R.; Del Nero, S.; Perrone, E.; Rizzo, V.; Sacchi, N.; Cassinelli, G.; Franceschi, G.; Baici, A. *J. Med. Chem.* **1994**, *37*, 4003−4019. (d) Finke, P. E.; Ashe, B. M.; Knight, W. B.; Maycock, A. L.; Navia, M. A.; Shah, S. K.; Thompson, K. R.; Underwood, D. J.; Weston, H.; Zimmerman, M.; Doherty, J. B. *J. Med. Chem.* **1990**, *33*, 2522−2528. (e) Buynak, J. D. *Curr. Med. Chem.* **2004**, *11*, 1951−1964. (f) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503−7524.

10.1021/jo052035t CCC: $30.25
Published on Web 11/17/2005

SCHEME 2. Radical Addition to SO_2 Using the Thiohydroxamic Ester System



SCHEME 3. Bis Addition of Perfluorinated Nitroxide to SO_2

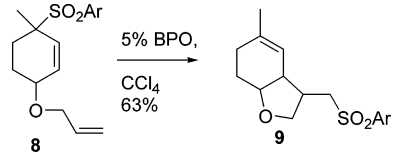


interest because of the presence of this structural motif in the cephalosporins[7] as well as in other pharmaceutically active compounds, such as TRUSOPT (dorzolamide hydrochloride).[8]

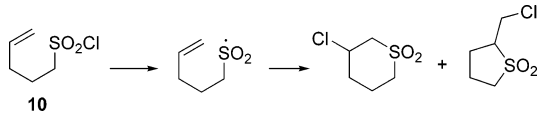
Carbon radicals add readily to the sulfur lone pair of sulfur dioxide. For example, Barton and Zard[9] used their thiohydroxamic ester system to trap SO_2 in a radical chain sequence (Scheme 2). Photolysis of thiohydroxamic ester **2** in dichloromethane saturated with SO_2 gas results in homolytic cleavage of the oxygen−nitrogen bond. The acyloxy radical **3** undergoes decarboxylation to afford carbon radical **4**, which adds to SO_2. The sulfur-centered radical **5** adds to the thiocarbonyl of the starting material, affording product **6** and perpetuating the radical chain. Primary, secondary, and tertiary radicals were shown to add to SO_2 in good yields. This work clearly demonstrates that SO_2 behaves as a one-atom radical acceptor/donor in a fashion similar to that of isonitriles and carbon monoxide. In fact, radical polymerizations between olefin monomers and SO_2[10] have been known since Kharash's work in the 1940s. In another example, Smith has shown that SO_2 can act as a 2-fold geminal radical acceptor in the bis addition of persistent perfluorinated nitroxides such as **7** to neat SO_2[11] (Scheme 3).

Aryl sulfonyl radicals are common intermediates in synthetic methodology, often participating as the chain-carrying species. A representative example is the cyclization of bisallylic ether **8**, mediated by an aryl sulfonyl radical to afford bicyclic product **9** (Scheme 4).[12] Alkyl

SCHEME 4. Example of Aryl Sulfonyl Radical-Mediated Cyclization



SCHEME 5. Sulfonyl Radical Cyclization

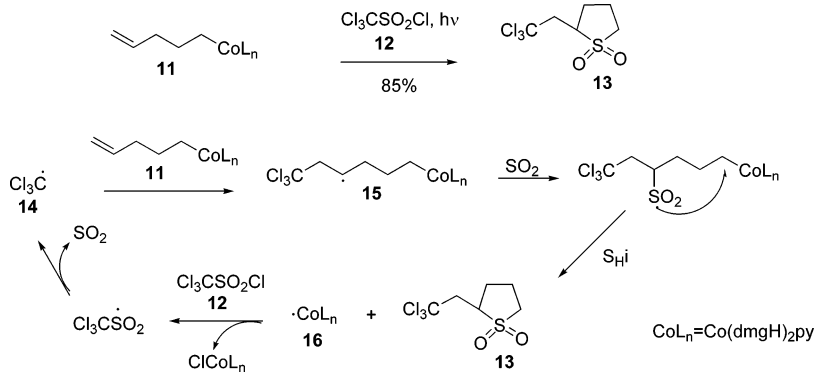


sulfonyl radical chain reactions are less common and sometimes proceed with SO_2 extrusion[13] to generate reactive alkyl radicals that can be harnessed for atom abstraction or other chain-carrying roles. Walton[14] demonstrated sulfonyl radical cyclizations from sulfonyl chloride substrates (Scheme 5). For example, chlorine radical abstraction from sulfonyl chloride precursor **10** gives predominantly 6-endo-trig closure. This 6-endo closure may be an inherent kinetic preference, or it may be the result of equilibration via a reversible cyclization step. Johnson[15] demonstrated radical annulations with SO_2 utilizing cobaloxime chemistry in 1984. For example, pent-4-enylcobaloxime **11** was irradiated in the presence of tricholoromethanesulfonyl chloride **12** to produce sulfolane **13** (Scheme 6). The mechanism is as follows: trichloromethyl radical **14** adds to pent-4-enylcobaloxime **11** to produce secondary carbon radical **15**, which adds to SO_2. Cyclization via an S_Hi mechanism (substitution homolytic intramolecular) produces sulfolane **13** and cobalt-centered radical **16**. Abstraction of chloride from trichloromethanesulfonyl chloride followed by SO_2 extrusion regenerates trichloromethyl radical **14** and SO_2. Cyclizations using α,ω dienes were also examined using cobaloximes as catalysts.

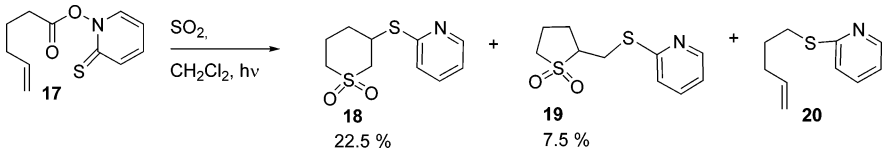
Results and Discussion

As outlined above, the precedent exists for both carbon radical addition to SO_2 and sulfonyl radical cyclization onto a tethered olefin. Thus, a convergent [*n* + 1] cyclization with SO_2 was pursued, beginning with thiohydroxamic ester **17** (Scheme 7). Photolysis of ester **17** in dichloromethane saturated with sulfur dioxide formed an inseparable 3:1 mixture of products **18** and **19**

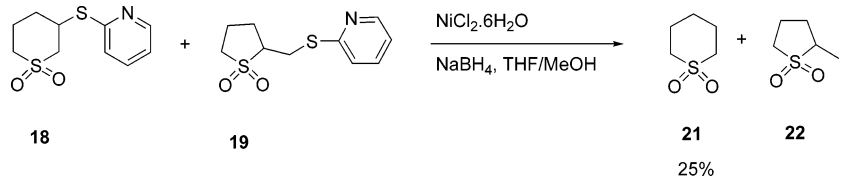
SCHEME 6. Cobaloxime-Mediated SO_2 Radical Annulation



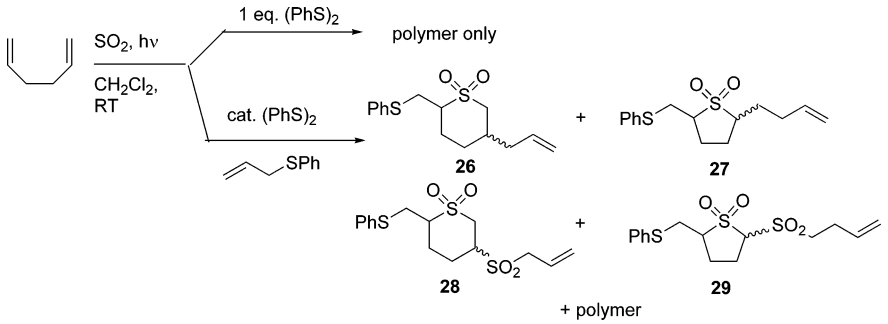
SCHEME 7. [n + 1] SO_2 Radical Annulation Using the Thiohydroxamic Ester System



SCHEME 8. Reductive Desulfurization of [n + 1] Annulation Products 18 and 19



SCHEME 9. Reactions of 1,5-Hexadiene with SO_2 Mediated by a Phenylthiyl Radical



resulting from both 6-endo and 5-exo cyclization in a combined 30% yield. In addition, product **20** was formed from the direct addition of the carbon radical to the starting material **17**. In a separate experiment without SO_2, thiohydroxyamic ester **17** rearranged upon heating to produce sulfide **20**,[16] providing an authentic sample for spectroscopic identification in the crude reaction mixture containing cyclic sulfones **18** and **19**.

To determine the identity of the major product, the mixture of cyclic sulfones **18** and **19** was reduced with nickel boride[17] generated in situ to produce the known unsubstituted cyclic sulfones **21** and **22** (Scheme 8). The major product was the 6-endo derived material **21** isolated in 25% yield.

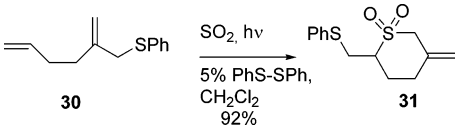
With this encouraging example of [5 + 1] cyclization using the parent 4-pentenyl radical, additional substrates **23**−**25** (Figure 2) were prepared and subjected to similar reaction conditions. Disappointingly, none of the desired cyclization products were obtained: only direct trapping products analogous to compound **20** were isolated, in addition to recovered starting material.

Because of the limited success of the substrates based on thiohydroxamic ester chemistry, an alternative initiation/termination approach was investigated. Simple thiyl radical addition to olefins is a reversible method for the generation of carbon radicals. Treatment of 1,5-hexadiene with diphenyl disulfide in dichloromethane saturated with SO_2 under photolysis gave no detectable cyclization products, but produced a white insoluble polymer[10] (Scheme 9). The use of catalytic disulfide and 1 equiv of allyl phenyl sulfide gave a complex mixture of products in low yield in addition to a significant amount of insoluble polymeric material. ^{1}H NMR and mass spectral data suggested the formation of products incorporating both one and two molecules of SO_2, tentatively assigned as structures **26**−**29**.

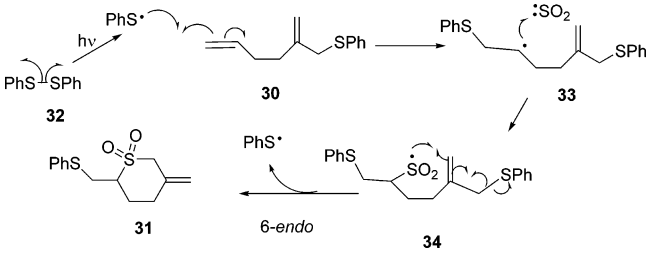
To avoid incorporation of a second equivalent of SO_2, a rapid termination step was needed following the desired [n + 1] cyclization. Thus, substrate **30** bearing an allylic sulfide was prepared. In addition to providing a clean final step for the cyclization, substitution on the allylic sulfide trap can be used to direct the endo/exo regioselectivity of the cyclization. Upon irrradiation of substrate **30** in the presence of catalytic diphenyl disulfide in

(8) Tsai, J.-C.; Chang, H.-W. *J. Ocul. Pharmacol. Ther.* **2001**, *17*, 499−504.
(9) Barton, D. H. R.; Lacher, B.; Misterkiewicz, B.; Zard, S. Z. *Tetrahedron* **1988**, *44*, 1153−1158.
(10) (a) Kharasch, M. S.; Friedlander, H. N. *J. Org. Chem.* **1948**, *13*, 882−885. (b) Hwang, J. S.; Tsonis, C. P. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1417−1421. (c) Tsai, J. Y.; Shevlin, P. B. *J. Org. Chem.* **1998**, *63*, 3230−3234.
(11) Arfaei, A.; Smith, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1791−1794.
(12) Smith, T. A. K.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 319−325.
(13) (a) For a review, see: Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Compt. Rend.* **2001**, *4*, 547−555 and references therein. (b) Montermini, F.; Lacote, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 921−923. (c) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem.−Eur. J.* **2004**, *10*, 3606−3614. (d) Kim, S.; Lim, C. J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1219−1222. (e) Ouvry, G.; Zard, S. Z. *Chem. Commun.* **2003**, 778−779. (f) Andraos, J.; Barclay, G. G.; Medeiros, D. R.; Baldovi, M. V.; Scaiano, J. C.; Sinta, R. *Chem. Mater.* **1998**, *10*, 1694−1699.
(14) Culshaw, P. N.; Walton, J. C. *Tetrahedron Lett.* **1990**, *31*, 6433−6436. Culshaw, P. N.; Walton, J. C. *J. Chem Soc., Perkin Trans. 2* **1991**, 1201−1208.
(15) Ashcroft, M. R.; Bougeard, P.; Bury, A.; Cooksey, C. J.; Johnson, M. D.; Hungerford, J. M.; Lampman, G. M. *J. Org. Chem.* **1984**, *49*, 1751−1761.
(16) Okano, T.; Ishihara, H.; Takakura, N.; Tsuge, H.; Eguchi, S.; Kimoto, H. *J. Org. Chem.* **1997**, *62*, 7192−7200.
(17) Back, T. G.; Yang, K.; Krouse, H. R. *J. Org. Chem.* **1992**, *57*, 1986−1990.

SCHEME 10. [5 + 1] 6-Endo-Trig Radical Annulation



SCHEME 11. Mechanism of the [5 + 1] 6-Endo-Trig Radical Annulation



dichloromethane saturated with SO_2, cyclization took place exclusively in the 6-endo mode to afford the desired product **31** in 92% yield (Scheme 10). The reaction product was extremely clean, containing only the catalytic diphenyl disulfide as an impurity.

The mechanism of this reaction is illustrated in Scheme 11. Diphenyl disulfide **32** undergoes homolytic cleavage upon photolysis to produce a catalytic amount of thiyl radical. The thiyl radical adds to the monosubstituted olefin of substrate **30** to afford carbon radical **33** that is captured by SO_2 to form sulfonyl radical **34**. This sulfur-centered radical cyclizes in a 6-endo fashion onto the olefin of the allylic sulfide; rapid fragmentation produces the desired product **31** and generates another thiyl radical that perpetuates the chain. Note that in this cyclization, the thiyl radical is the chain-carrying species. Addition of a thiyl radical to the monosubstituted olefin initiates the cyclization sequence. However, addition of a thiyl radical to the allylic sulfide also occurs but is a degenerate reaction.[18]

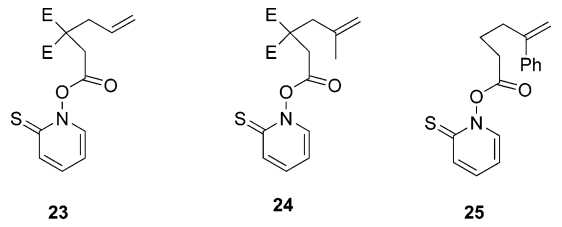


FIGURE 2. Failed annulation substrates.

Encouraged by this extremely clean and efficient reaction, a number of substrates were prepared incorporating both olefins and acetylenes and using linear or branched allylic sulfides as the terminating functionality. Retrosynthetically, the requisite allylic sulfides were prepared from the corresponding allylic alcohols. These were prepared either by a metalation−alkylation sequence or by olefination and reduction. The synthesis of substrates **30**, **38**, **42**, **46**, and **50** is depicted in Scheme 12. Thus, methallyl alcohol **35** was doubly deprotonated with 2.1 equiv of *n*-BuLi in the presence of *N,N,N,N*-tetramethylethylenediamine followed by C-alkylation with either allyl or propargyl bromides to obtain compounds **36** or **37**.[19] Allylic alcohol **41** was assembled by Horner−Wadsworth−Emmons olefination of aldehyde **39** to give the α,β-unsaturated ester **40**; DIBAL-H reduction afforded alcohol **41**.[20] Similarly, yne-enol **45**[21] was prepared by Swern oxidation of 4-pentyn-1-ol **43**, followed by olefination and reduction. The synthesis of dienol **49** began with an S_N2 reaction between 5-bromopentene **47** and deprotonated methyl diethylphosphonoacetate, followed by a Horner−Wadsworth−Emmons olefination with formaldehyde to afford α,β-unsaturated ester **48**. Reduction with DIBAL-H afforded allylic alcohol **49**.[22] The allylic sulfide cyclization substrates were prepared

SCHEME 12. Preparation of Radical Annulation Substrates 30, 38, 42, 46, and 50

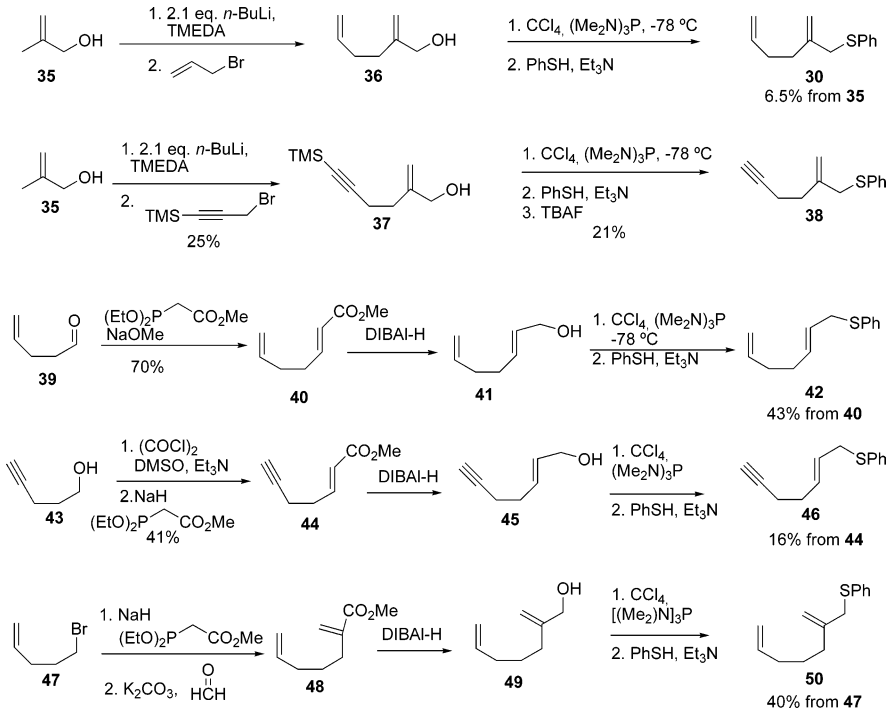
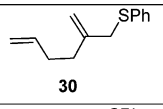
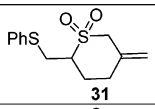
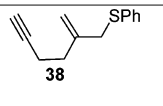
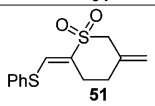
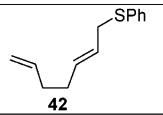
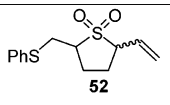
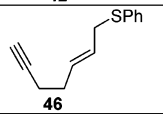
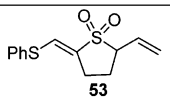
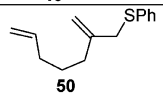
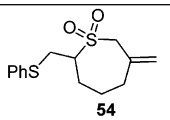


TABLE 1. [n + 1] SO_2 Radical Annulations

Substrate	Product	Reaction time	Yield
 **30**	 **31**	17 h	92%
 **38**	 **51**	63 h	18% *E*
 **42**	 **52**	17 h	92% 4:1 *cis:trans*
 **46**	 **53**	63 h	20% *E* + S.M.
 **50**	 **54**	40 h	50%

according to the procedure of Castro:[23] allylic alcohols were treated with hexamethylphosphorus triamide and carbon tetrachloride to form the allylic alkyloxyphosphonium chlorides, which are stable at −70 °C. These were displaced in situ by thiolate.

With the substrates in hand, a series of [n + 1] cyclizations were examined (Table 1). The acetylenic branched allylic sulfide **38** underwent [5 + 1] cyclization to afford the 6-endo product **51** as a single isomer in 18% yield on a 42 mg scale after purification by preparative thin-layer chromatography (TLC). The ACD[24] simulation of the ^{1}H NMR spectra of the *E* and *Z* isomers of vinyl sulfide **51** predicted a chemical shift for the vinylic sulfide proton of δ 7.28 ppm for the *E* isomer and δ 5.79 ppm for the *Z* isomer. Product **51** displayed a singlet at δ 7.52 ppm, indicating that the cyclization product possessed the *E* configuration. The ^{1}H NMR of the crude product showed only the desired product and diphenyl disulfide as an impurity, implying that the yield should be substantially higher on a larger scale. Although the thiyl radical is expected to add more quickly to the unsubstituted sp^2 hybridized olefin compared to the sp hybridized acetylenic terminus, only the latter leads to the consumption of starting material and the formation of the product whereas the former is a degenerate reaction.

Linear allylic sulfide **42** underwent [4 + 1] cyclization to form the 5-*exo*-sulfolane **52** in 92% yield as an inseparable mixture of diastereomers in a 1:1 ratio, as determined by ^{1}H NMR. Similarly, the acetylenic analogue substrate **46** cyclized in the expected [4 + 1] mode to afford the 5-exo product **53** as a single isomer in 20% yield after 63 h. The reaction did not go to completion; the ratio of the starting material to the product was 2:1. However, extended reaction times did not enhance the yield but instead afforded complex mixtures. The *E* configuration of the vinyl sulfide was again assigned by examination of the ^{1}H NMR spectrum. Experimentally, the sp^2 hydrogen of the vinylic sulfide came at δ 7.35 ppm; ACD[24] predicted a chemical shift of δ 7.39 ppm for the *E* isomer and δ 6.07 ppm for the *Z* isomer. The identity of this peak was confirmed by homonuclear decoupling experiments. Irradiation of the peak at δ 7.35 ppm resulted in simplification of the two peaks at δ 2.22 and δ 2.01 ppm, corresponding to the diastereotopic allylic methylene protons in the ring. Conversely, irradiation at δ 2.22 ppm caused the doublet of doublets at δ 7.35 ppm to collapse to a doublet. Likewise, irradiation at δ 2.01 ppm also resulted in a doublet at δ 7.35 ppm.

The formation of five- and six-membered rings by radical cyclization is well precedented. However, the formation of larger rings is more challenging because of substantially slower cyclization rates.[25] Pleasingly, substrate **50** underwent [6 + 1] cyclization to give exclusively the 7-endo product **54**. The ^{1}H NMR analysis of the crude reaction mixture showed only the product and diphenyl disulfide. Purification by preparative TLC afforded 50% of the pure product on a small scale.

Summary

The ability to form five-, six-, and seven-membered cyclic sulfones by this [n + 1] radical annulation strategy demonstrates a new convergent approach to these heterocycles under very mild conditions. The exo vs endo selectivity can be tuned by selection of either a linear or a branched allylic sulfide terminating group. In addition, the phenyl sulfide group in the final products provides a functional handle that can be utilized in subsequent steps for further elaboration of the cyclized material. This [n + 1] radical annulation strategy should be amenable to other substrates capable of rapid fragmentation as the cyclization terminating step. In summary, this work demonstrates the use of SO_2 as a one-atom geminal acceptor/donor in radical [n + 1] annulations to prepare five- to seven-membered cyclic sulfones under extremely mild conditions.

Experimental Section

Cyclization to Form 3-(2′-Pyridylsulfide)-1,1-dioxythiacyclohexane 18 and 2-Methyl-(2′-pyridylsulfide)-1,1-dioxythiacyclopentane 19. In a 50 mL quartz tube was put 22 mL of CH_2Cl_2 cooled to −40 °C; the solvent was saturated with SO_2 gas until the volume increased by 30%. Hex-5-enoic acid 2-thioxo-2*H*-pyridin-1-yl ester **17** (300 mg, 1.31 mmol), dissolved in 1 mL of CH_2Cl_2, was added to the saturated SO_2 solution. The tube was closed with a glass stopper, and the resulting yellow solution was irradiated with a 250 W tungsten−halogen lamp until the color disappeared (about 1 h). The solvent was removed in vacuo, and the crude mixture was analyzed by ^{1}H NMR. The ratio of the two cyclization products was determined to be 3:1. The crude mixture was dissolved in a minimal amount of CH_2Cl_2, and hexanes were added. The product immediately formed a precipitate that was filtered and dried to afford 195 mg (0.80 mmol, 61% yield) of a white solid.

(18) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **1997**, *69*, 645−650.
(19) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421−9438.
(20) Crandall, J. K.; Mayer, C. F. *J. Org. Chem.* **1970**, *35*, 3049−3053.
(21) Huang, H.-L.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 805−810.
(22) Schomaker, J. M.; Borhan, B. *Org. Biomol. Chem.* **2004**, *2*, 621−624.
(23) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 2296−2298.
(24) *Advanced Chemistry Development (ACD/Labs) Software Solaris*, version 2.0; Advanced Chemistry Development, Inc.: Toronto, Ontario, Canada, 1994−2005; http://www.acdlabs.com/.
(25) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941.

^{1}H NMR indicated that the ratio of the two cyclization products after precipitation was enhanced to 9:1. The major isomer was further characterized by DEPT, COSY, and HETCOR experiments (see Supporting Information).

A. Major Isomer. TLC: 1:1 hexanes/ethyl acetate; UV; R_f = 0.13. IR ($CDCl_3$): 3155, 1572, 1469, 1332, 1135, 706 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (ddd, J = 1.0 Hz, 2.0 Hz, 5.0 Hz, 1H), 7.83 (td, J = 7.5 Hz, 2.0 Hz, 1H), 7.74 (dt, J = 1.0 Hz, 7.5 Hz, 1H), 7.44 (ddd, J = 1.0 Hz, 5.0 Hz, 7.5 Hz, 1H), 4.26 (tt, J = 2.5 Hz, 12.5 Hz, 1H), 3.79−3.76 (m, 1H), 3.28 (t, J = 13.0 Hz, 1H), 3.13 (dq, J = 14.5 Hz, 2.75 Hz, 1H), 2.98 (td, J = 13.5 Hz, 2.5 Hz, 1H), 2.63 (br d, J = 15.0 Hz, 1H), 2.36−2.32 (m, 1H), 2.13 (qt, J = 12.5 Hz, 4.0 Hz, 1H), 1.84 (qd, J = 13.5 Hz, 3.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2, 150.2, 138.5, 131.9, 125.4, 66.4, 51.0, 50.9, 24.4, 21.9 ppm. HRMS (M + 1) calcd for $C_{10}H_{14}NO_2S_2$, 244.0469; found, 244.0461.

Direct Trapping Product 4-(2-Pyridinothio)-1-pentene[16] (20). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.42 (m, 1H), 7.47−7.45 (m, 1H), 7.18−7.14 (m, 1H), 6.97−6.94 (m, 1H), 5.82−5.73 (m, 1H), 5.08−4.96 (m, 2H), 3.16 (t, J = 7.5 Hz, 2H), 2.21−2.12 (m, 2H), 1.86−1.71 (m, 2H) ppm.

Reduction to Prepare Tetrahydrothiopyran 1,1-Dioxide 21[14b] and 2-Methyltetrahydrothiophene 1,1-Dioxide 22. On the basis of the procedure of Back,[17] the mixture of compounds **18** and **19** (100 mg, 0.41 mmol) was dissolved in 10 mL of THF. To this solution was added $NiCl_2 \cdot H_2O$ (684 mg, 2.88 mmol) dissolved in 6 mL of methanol. The resulting mixture was cooled to 0 °C, and $NaBH_4$ (326 mg, 8.61 mmol) was added in portions. The reaction mixture was stirred for 15 min, and then the solvent was evaporated. The resulting black solid was resuspended in a 1:1 methanol/chloroform mixture and was filtered through Celite. Purification by flash column chromatography using 50:1 methylene chloride/methanol gave 14 mg (0.10 mmol, 25% yield) of tetrahydrothiopyran 1,1-dioxide **21**.

TLC: 99:1 methylene chloride/methanol; PAA stain; R_f = 0.5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00−2.98 (m, 4H), 2.11−2.09 (m, 4H), 1.64 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.2, 24.3, 23.9 ppm.

General Procedure for SO_2 Cyclization. The preparation of 5-methylene-2-phenylsulfanylmethyltetrahydrothiopyran 1,1-dioxide **31** is a representative example: (2-Methylenehex-5-enylsulfanyl)benzene **30** (80 mg, 0.39 mmol) and diphenyl disulfide (4.0 mg, 0.02 mmol) were dissolved in 6 mL of dichloromethane and placed into a 15 mL heavy-walled glass pressure vessel. The solution was cooled to −78 °C, and 6 mL of SO_2 gas was condensed into the reaction mixture using a dry ice condenser. The mixture became yellow in color. The dry ice condenser was removed, and the pressure vessel was sealed and irradiated with a 450 W Hg lamp for 17 h. During the photolysis, the solution turned brown in color. The mixture was cooled to −78 °C, and the pressure vessel was slowly opened to the air and left standing in the hood at room temperature until all of the SO_2 gas had evaporated. Volatiles were removed in vacuo to give 101 mg (0.36 mmol, 92% yield) of the title compound as a brown oil.

TLC: 5:1 hexanes/ethyl acetate; UV; I_2; R_f = 0.36. IR ($CDCl_3$): 2962, 1711, 1440, 1364, 899, 748 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.26 (m, 5H), 5.11 (s, 1H), 5.05 (s, 1H), 3.80 (dd, J = 13.5 Hz, 2.2 Hz, 1H), 3.71 (d, J = 13.5 Hz, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.02 (tt, J = 11.5 Hz, 3.0 Hz, 1H), 2.87 (dd, J = 14.2 Hz, 11.2 Hz, 1H), 2.55−2.50 (m, 2H), 2.15−2.11 (m, 1H), 1.81−1.74 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.8, 134.1, 129.5, 129.4, 127.0, 117.7, 60.6, 60.2, 32.7, 29.1, 27.5 ppm. HRMS calcd for $C_{13}H_{17}O_2S_2$, 269.0670; found, 269.0665.

Acknowledgment. We thank the National Science Foundation (CHE-0078852) and Research Corporation (RA0336) in addition to equipment grants from the NSF (BIR-94-19409) (NMR) and a supplement grant from NIH (CA52955) (ESITOFMS) for providing financial support for this project. We also thank Professor Yian Shi for helpful discussions on the synthesis of 2-methylenehex-5-en-1-ol **36**.

Supporting Information Available: General experimental; detailed experimental procedures for the preparation of compounds **17**, **30**, **36**−**38**, **40**−**42**, **44**−**46**, and **48**−**54**; and the ^{1}H NMR and ^{13}C NMR spectra of compounds **18**, **31**, and **51**−**54** along with HETCOR and COSY spectra of **18**. Additionally, HETCOR, COSY, and NOESY spectra for compound **52** are also available. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052035T