JOC*Article*

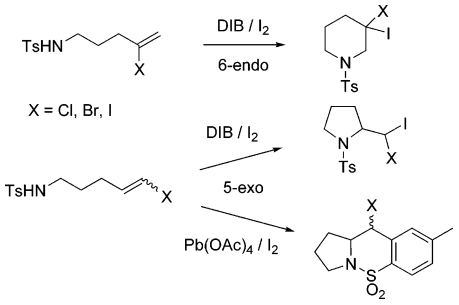
Control of the Regioselectivity of Sulfonamidyl Radical Cyclization by Vinylic Halogen Substitution

Hongjian Lu, Qian Chen, and Chaozhong Li*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, 200032, P. R. China

clig@mail.sioc.ac.cn

Received December 17, 2006



The radical cyclization reactions of unsaturated sulfonamides were investigated. The photolysis of *N*-(4-halo-4-pentenyl)sulfonamides (X = I, Br, or Cl) with (diacetoxyiodo)benzene (DIB) and iodine at room temperature afforded exclusively the corresponding piperidines in 73−98% yield via 6-endo radical cyclization. On the other hand, the reactions of *N*-(5-halo-4-pentenyl)sulfonamides with DIB/I_2 led to the only formation of the pyrrolidine products in 84−99% yield via 5-exo radical cyclization. The vinylic halogen substitution not only successfully inhibits the competing ionic iodocyclization process to allow the radical cyclization to proceed smoothly but also shows a remarkable effect in controlling the regioselectivity of cyclization.

Introduction

Nitrogen-centered radicals are involved in a variety of useful organic transformations. Intramolecular addition of N-centered radicals to C=C double bonds provides a unique entry to N-heterocycles such as lactams and cyclic amines.[1,2] Oxidative generation of N-centered radicals allows the direct use of the parent amines, amides, or sulfonamides, making this methodology more attractive in organic synthesis. For example, Nicolaou and co-workers reported the successful *o*-iodoxybenzoic acid (IBX)-mediated 5-exo cyclization of unsaturated *N*-aryl amides.[2a] Studer et al. extended this methodology to the oxidative cyclization of acylated alkoxyamines.[2d] Different types of N-centered radicals exhibit dramatically different reactivities in these cyclization reactions. For instance, kinetic studies by Newcomb et al. showed that the 5-exo cyclization of 4-pentenamidyl radicals proceeds at a much faster rate ($\sim 10^9$ s^{-1})[3a] than that of the neutral 4-pentenaminyl radicals ($\sim 10^4$ s^{-1}).[3b]

While the cyclizations of aminyl and amidyl radicals have received considerable attention in the past decades, that of sulfonamidyl radicals, to our surprise, is far less explored and only a few examples have been reported in the literature. Chemler and co-workers reported the Cu(II)-mediated oxidative radical cyclization of arylsulfonyl-*o*-allylanilines leading to the formation of tetracyclic products.[4] Closely related examples are the intramolecular sulfonamidyl radical addition onto an aryl ring in which bicyclic heterocycles, such as quinolines, were

(1) (a) Neale, R. S. *Synthesis* **1971**, 1. (b) Esker, J.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, p 1. (c) Zard, S. Z. *Synlett* **1996**, 1148. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (e) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407.

(2) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (b) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (c) Martin, A.; Pérez-Martin, I.; Suárez, E. *Org. Lett.* **2005**, *7*, 2027. (d) Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991. (e) Gaudreault, P.; Drouin, C.; Lessard, J. *Can. J. Chem.* **2005**, *83*, 543. (f) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831.

(3) (a) Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738. (b) Musa, O. M.; Horner, J. H.; Shanhin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862.

(4) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573.

10.1021/jo0625857 CCC: $37.00
Published on Web 03/03/2007

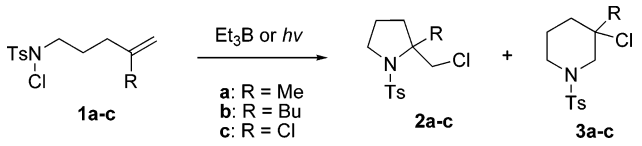
achieved in good yields.[5] Other related works include the addition of *N*-allyl-substituted sulfonamidyl radicals to alkenes yielding the corresponding pyrrolidine derivatives.[6] It should be emphasized that in some cases reported[5a,6c] the above reactions did not proceed when the radicals were switched to amidyl or aminyl radicals, thus demonstrating the unique property of sulfonamidyl radicals and in turn justifying the further investigation on the cyclization of sulfonamidyl radicals.

One of the difficulties that hinder research on sulfonamidyl radicals is that electrophilic cyclization[7] rather than radical cyclization usually predominates for unsaturated sulfonamides under oxidative conditions due to the highly nucleophilic nature of the sulfonamide moiety (also vide infra).[8] In fact, the electrophilic halocyclization of sulfonamides in a 5-exo mode proceeds very rapidly with high efficiency.[9] This seems to discourage the study on the corresponding radical cyclization. During our recent investigation on the behaviors of unsaturated amidyl radicals,[10] we found that vinylic halogen substitutions allowed the regioselective radical cyclization to occur while the electrophilic iodocyclization was retarded.[10d] We were then motivated to find if this remarkable halogen substitution effect could be extended to the cyclization of sulfonamidyl radicals. We report here that vinylic halogen substituted sulfonamides underwent efficient and highly regioselective radical cyclization reactions, which showed dramatically different reactivities and selectivity patterns from the corresponding electrophilic halocyclizations. Theoretical calculations in combination with the experimental results offer a detailed understanding of the mechanism of the sulfonamidyl radical cyclization.

Results and Discussion

To understand the substituent effect on the regioselectivity in the cyclization of sulfonamidyl radicals, we chose *N*-chloro-substituted toluenesulfonamides **1a**−**c** as the model radical precursors. These intermediates were readily prepared in excellent yields from the corresponding sulfonamides by treatment with ^{t}BuOCl/K_2CO_3 in CH_2Cl_2, a modified procedure of literature methods.[11] Compounds **1a**−**c** were fairly stable and could be purified by column chromatography on silica gel. They were then subjected to the treatment of 10 mol % of triethylborane[6c,d] or to UV irradiation[12] in CH_2Cl_2 at low temperature. The results are summarized in Table 1. Both initiation methods yielded similar results (entries 1 and 2, Table 1), confirming the radical nature of the cyclization. With **1a** bearing an internal methyl substituent, both the 5-exo cyclization product **2a** and the 6-endo cyclization product **3a** were produced, and the ratio was about 1:2. Changing the methyl substituent to the butyl group in **1b** showed almost no difference (entry 3, Table 1). The reactions of **1a** and **1b** proceeded smoothly at −78 °C. On the other hand, no reaction was observed for the chloro-substituted substrate **1c** at the low temperature (entry 4, Table 1). Raising the temperature to −20 °C resulted in a clean reaction, and the 6-endo cyclization product **3c** was achieved exclusively in 88% yield (entry 5, Table 1).

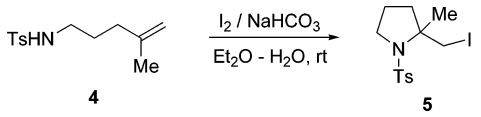
TABLE 1. Radical Cyclization of *N*-Chloro-*N*-(4-pentenyl) Toluenesulfonamides 1a−c



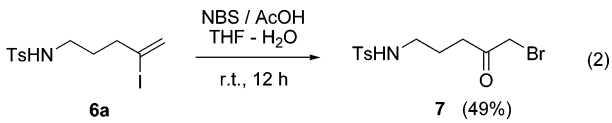
entry	R	conditions[a]	yield (%)[b]	**2**/**3**[c]
1	Me	Et_3B, −78 °C	82	34/66
2	Me	*hν*, −78 °C	98	34/66
3	Bu	*hν*, −78 °C	93	33/67
4	Cl	*hν*, −78 °C or Et_3B, −78 °C	0[d]	
5	Cl	Et_3B, −20 °C	88	0/100

[a] For the direct UV photolysis: **1** (0.3 mmol) in CH_2Cl_2 (10 mL), *hν*, 2 h. For the Et_3B-initiated reactions: **1** (0.5 mmol), Et_3B (0.05 mmol), dry air (5 mL), CH_2Cl_2 (10 mL), 2 h. [b] Isolated yield based on **1**. [c] Determined by ^{1}H NMR (300 MHz). [d] No reaction occurred.

In order to demonstrate the unique selectivity of the above radical cyclization, the corresponding ionic cyclization reactions were also performed. The reaction of sulfonamide **4** under typical iodocyclization conditions (I_2/$NaHCO_3$, Et_2O−H_2O, rt, 2 h) afforded only the 5-exo cyclization product **5** in 95% yield (eq 1). Under similar conditions, the iodo-substituted sulfonamide **6a** remained inert. When a stronger halocyclization condition (NBS/AcOH, aqueous THF solution, rt, 12 h)[7] was employed for **6a**, bromoketone **7** was isolated in 49% yield (eq 2). Apparently, the bromocyclization of **6a** in a 5-exo mode occurred to give the corresponding pyrrolidine intermediate, which then underwent the iodide elimination and subsequent



(1)



(2)

(5) (a) Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 5193. (b) Togo, H.; Harada, Y.; Yokoyama, M. *J. Org. Chem.* **2000**, *65*, 926. (c) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209.

(6) (a) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3865. (b) Kitagawa, O.; Miyaji, S.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2003**, *68*, 3184. (c) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709. (d) Tsuritani, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246.

(7) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, p 363. (c) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (d) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099.

(8) (a) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 3335. (b) Minakata, S.; Daisuke, K.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2002**, *4*, 2097. (c) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (d) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938.

(9) (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063. (b) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491. (c) Cooper, M. A.; Ward, A. D. *Tetrahedron Lett.* **1992**, *33*, 5999.

(10) (a) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229. (b) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625. (c) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983. (d) Hu, T.; Shen, M.; Chen, Q.; Li, C. *Org. Lett.* **2006**, *8*, 2647. (e) Tang, Y.; Li, C. *Tetrahedron Lett.* **2006**, *47*, 3823.

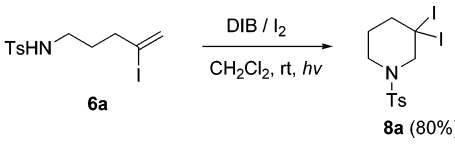
(11) (a) Zimmer, H.; Audrieth, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 3856. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. (d) Goossen, L. J.; Liu, H.; Dress, K. R.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1080.

(12) Neale, R. S.; Marcus, N. L. *J. Org. Chem.* **1969**, *34*, 1808.

hydrolysis to form the final product **7**. The chloro-substituted sulfonamide **6c** was also tested under the above conditions. No reaction was observed.

The above results clearly indicate the different reactivities and selectivity patterns between the radical cyclization and the ionic cyclization. While the electrophilic halocyclization occurs exclusively in a 5-exo mode, the internal vinylic substitution in **1** strongly encourages the radical cyclization in a 6-endo mode. This is particularly the case in the halogen-substituted substrates (**1c** and **6a**). With regard to the reactivity, the halogen-substitution retards both the ionic and radical cyclizations. This should be attributed to the lowered electron density of the C═C double bond. However, the high reactivity of sulfonamidyl radicals allows the cyclization to proceed smoothly while the ionic cyclization is more susceptible to the electron density of the double bond, and in the case of **6c** with a Cl substituent, the reaction is completely inhibited.

In light of the above observations, we then tried to directly use the unsaturated sulfonamides, such as **4** and **6a**, as the substrates for radical cyclization. This should be of more synthetic value than the use of their *N*-chloro derivatives. The photolysis of **4** with (diacetoxyiodo)benzene (DIB)/I_2[5a,b,13] or $Pb(OAc)_4/I_2$[14] at ambient temperature led only to the formation of **5**, indicating that ionic iodocyclization prevailed under these oxidative conditions. On the other hand, when **6a** was irradiated with DIB (1.5 equiv) and I_2 (1.1 equiv) in CH_2Cl_2 at room temperature for 1 h, a clean reaction was observed and the expected 6-endo radical cyclization product **8a** was isolated in 80% yield (eq 3). Thus, a number of vinylic halogen substituted

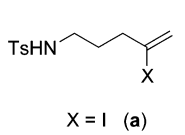
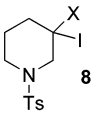
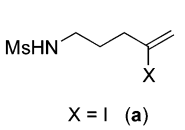
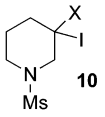
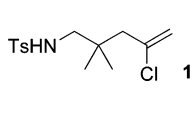
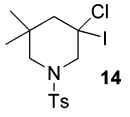
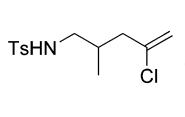
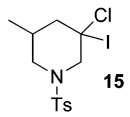
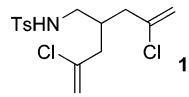
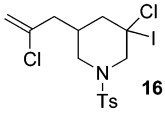


(3)

sulfonamides were subjected to this oxidative condition (eq 3), and the results are listed in Table 2. In all the cases tested, the radical cyclization product piperidines were achieved in high yields. No compounds derived from 5-exo cyclization could be detected. Switching the iodine atom in substrate **6a** to bromine (**6b**) or chlorine (**6c**) yielded similar results (entries 1−3, Table 2). Changing the tosyl group in **6** to the mesyl group in **9** showed almost no difference (entries 4−6, Table 2). The mono- or dialkyl substitution in the substrates did not impose much influence on the reaction outcome (entries 7−9, Table 2). The Cl-substituted sulfonamides generally gave higher product yields than their Br- or I-analogues. This might be attributed to the lower stability of the diiodo- and bromoiodo-containing piperidine products under the reaction conditions.

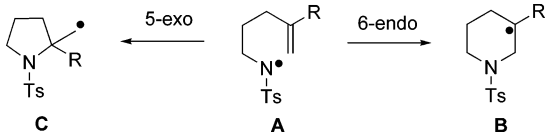
The above results clearly demonstrate the remarkable vinylic halogen substitution effect in controlling the regioselectivity of sulfonamidyl radical cyclization. To gain more insight into the substitution effect, we carried out the density functional calculations on the above sulfonamidyl radical cyclization, which have been demonstrated to be an accurate tool in the theoretical study of radical reactions.[15,16] The calculations were performed at the

TABLE 2. 6-Endo Cyclization of Sulfonamidyl Radicals

entry	substrate	product	yield (%)[a]
			
1	X = I (**a**)		80
2	Br (**b**)		81
3	Cl (**c**)		98
			
4	X = I (**a**)		78
5	Br (**b**)		88
6	Cl (**c**)		93
7			73
8			85[b]
9			76[b]

[a] Isolated yield based on the starting sulfonamides. [b] Two stereoisomers in about a 60:40 ratio determined by ^{1}H NMR (300 MHz).

TABLE 3. Calculated (UB3LYP/6-31G*) Activation Energies



entry	R	E_a (5-exo) (kcal/mol)	E_a (6-endo) (kcal/mol)
1	H	8.1	9.8
2	Me	9.2	8.0
3	Cl	12.4	8.8

UB3LYP/6-31G* level, and the calculated activation energies (E_a) for 5-exo cyclization (from **A** to **C**) and for 6-endo cyclization (from **A** to **B**) (at 298 K) are listed in Table 3.

As can be seen in Table 3, 5-exo cyclization predominates for the *N*-(4-pentenyl) toluenesulfonamidyl radical (**A**, R = H) (entry 1, Table 3). With an internal methyl substituent (R = Me), the reaction pathway is reversed from 5-exo to 6-endo cyclization (entry 2, Table 3). The activation energy difference is about 1.2 kcal/mol. When the methyl group is replaced by a chlorine atom, both of the activation energies are increased

(13) Togo, H.; Kotohgi, M. *Synlett* **2001**, 565.

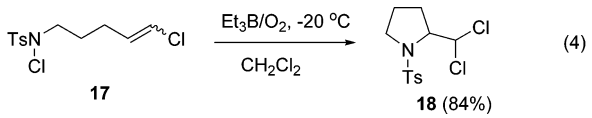
(14) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.

(15) (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (b) Schiesser, C. H.; Skidmore, M. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 337.

(16) (a) Itoh, Y.; Houk, K. N.; Mikami, K. *J. Org. Chem.* **2006**, *71*, 8918. (b) O'Neil, L. L.; Wiest, O. *J. Org. Chem.* **2006**, *71*, 8926. (c) Hartung, J.; Daniel, K.; Rummey, C.; Bringmann, G. *Org. Biomol. Chem.* **2006**, *4*, 4089. (d) Lin, H.; Chen, Q.; Cao, L.; Yang, L.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2006**, *71*, 3328. (e) Liu, L.; Chen, Q.; Wu, Y.-D.; Li, C. *J. Org. Chem.* **2005**, *70*, 1539. (f) Speybroeck, V. V.; De Kimpe, N.; Waroquier, M. *J. Org. Chem.* **2005**, *70*, 3674. (g) References 10b and 10d.

(entry 3, Table 3). However, the energy difference becomes much larger (3.6 kcal/mol). The calculated results are in good qualitative agreement with the experimental data. These results also closely resemble those of amidyl radical cyclization processes,[10d] indicating the generality of the halogen substitution effect in controlling the regioselectivity of N-centered radical cyclization reactions. Moreover, the much better control of regioselectivity by the Cl-substitution could also be interpreted in terms of the lone pair−lone pair repulsion[10d] between the chlorine atom and the nitrogen atom, which is much greater in the 5-exo cyclization (from **A** to **C**) than in the 6-endo cyclization (from **A** to **B**).

The above reactions dealt with the substrates having an internal vinylic halogen substitution. With a terminal vinylic halogen substitution, the unsaturated sulfonamides should be expected to undergo radical cyclization reactions via a 5-exo mode. Indeed, the radical reaction of *N*-chloro-*N*-(5-chloro-4-pentenyl) toluenesulfonamide (**17**, *E*/*Z* = 2:1) at −20 °C afforded exclusively the 5-exo cyclization product **18** in 84% yield, indicating that only 5-exo radical cyclization occurred (eq 4).



17 **18** (84%) (4)

Although this regioselectivity shown in eq 4 is the same as that of ionic halocyclization, it could be envisioned that once the adduct radical **22** is generated from the cyclization of the sulfonamidyl radical **21**, it might attack the phenyl ring to give intermediate **24**, which could be further oxidized to afford the tricyclic compound **25a** as the final product (Scheme 1).[4]

On the basis of the above discussion, we chose compounds **19a**−**d** as the substrates to explore their radical reactions. The reactions of **19a**−**d** with DIB/I_2 afforded the corresponding 5-exo cyclization products **23a**−**d** in excellent yields (Table 4). Both the *Z*- and the *E*-isomers of **19** gave the same products. With the use of the stronger oxidant $Pb(OAc)_4$, we were delighted to find that the tricyclic product **25a** could be achieved in 72% yield when sulfonamide **19a** was photolyzed with 3.5 equiv of $Pb(OAc)_4$ and 0.5 equiv of I_2 in 1,2-dichloroethane at a refluxing temperature for 1 h. Under this optimized condition, tricyclic compounds **25b** and **25c** could be synthesized in 60% and 30% yields from substrates **19b** and **19c**, respectively (Table 4). In the case of **19c**, only the trans isomer **25c** could be isolated

SCHEME 1

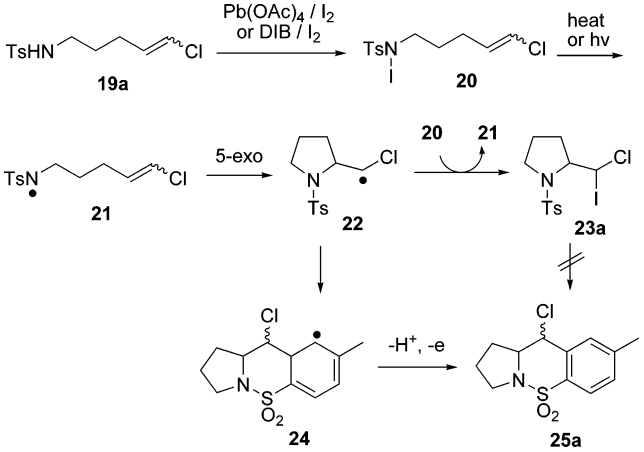
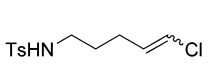
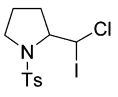
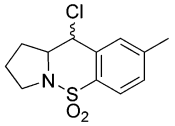
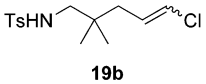
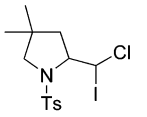
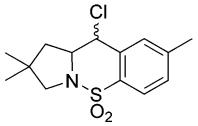
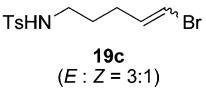
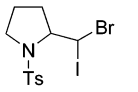
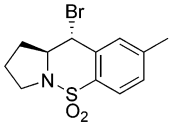
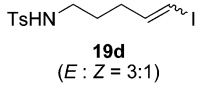
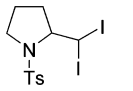


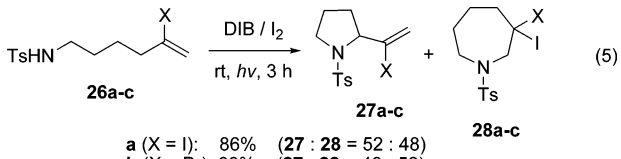
TABLE 4. Reactions of Compounds 19a−d

substrate	product (yield)[a]	
	condition A[b]	condition B[c]
 **19a** (*E* : *Z* = 2:1)	 **23a** (99%)[d]	 **25a** (72%)[e]
 **19b** (*E* : *Z* = 1:1)	 **23b** (90%)[d]	 **25b** (60%)[e]
 **19c** (*E* : *Z* = 3:1)	 **23c** (91%)[d]	 **25c** (30%)
 **19d** (*E* : *Z* = 3:1)	 **23d** (84%)	NT[f]

[a] Isolated yield based on **19**. [b] DIB (1.5 equiv), I_2 (1.1 equiv), CH_2Cl_2, rt, *hν*, 1 h. [c] $Pb(OAc)_4$ (3.5 equiv), I_2 (0.5 equiv), $ClCH_2CH_2Cl$, reflux, *hν*, 1 h. [d] Two stereoisomers in a 1:1 ratio determined by ^1H NMR (300 MHz). [e] Trans/cis = 57/43 determined by ^1H NMR (300 MHz). [f] Not tested.

in relatively low yield, presumably because the cis isomer decomposed under the experimental conditions. The formation of tricyclic products **25a**−**c** illustrates the different reactivity pattern of radical cyclization from the corresponding electrophilic iodocyclization. It should also be noted that the tricyclic compounds **25** are a class of oxicams which are a large family of nonsteroidal anti-inflammatory agents.[17]

In light of the above results, we were motivated to extend the above halogen substitution effect to the 6-exo vs 7-endo cyclization system. The photolysis of sulfonamides **26a**−**c** with DIB/I_2 at rt afforded the expected 7-endo cyclization products **28a**−**c** along with a significant amount of the pyrrolidines **27a**−**c** in overall high yields (eq 5). No corresponding 6-exo



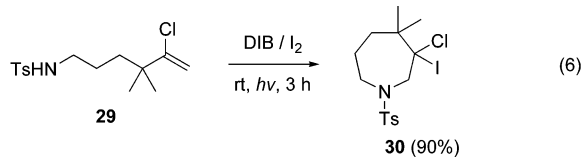
(5)

a (X = I): 86% (**27** : **28** = 52 : 48)
b (X = Br) 88% (**27** : **28** = 48 : 52)
c (X = Cl) 72% (**27** : **28** = 36 : 64)

cyclization products could be detected. Apparently the formation of compounds **27** resulted from the 1,5-H migration of the sulfonamidyl radicals.[1a,5b] In order to avoid the competing intramolecular hydrogen migration process, we further synthesized sulfonamide **29** with a gem-dimethyl substitution at the C-4 position. Its reaction with DIB/I_2 led to the exclusive formation of the 7-endo cyclization product **30** in 90% yield

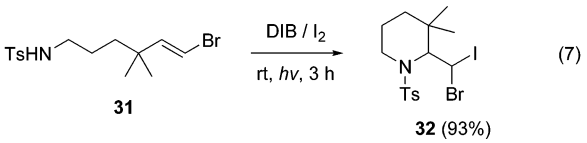
(17) (a) Bakker, W. I. I.; Familoni, O. B.; Padfield, J.; Snieckus, V. *Synlett* **1997**, 1079. (b) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327. (c) Liu, X.; Li, C.; Che, C. *Org. Lett.* **2006**, *8*, 2707.

(eq 6). Under similar conditions, sulfonamide **31**, bearing an



29 **30** (90%) (6)

external vinylic bromine substituent, afforded the 6-exo cyclization product **32** exclusively in 93% yield (eq 7). These



31 **32** (93%) (7)

examples further demonstrate the powerful effect of halogen substitution in controlling the regioselectivity of radical cyclization.

Conclusion

The chemistry detailed above clearly illustrates the different reactivities and selectivity patterns of sulfonamidyl radical cyclization reactions from those of the corresponding electrophilic halocyclization processes. The vinylic halogen substitution successfully inhibits the competing ionic processes to allow the radical cyclization to proceed smoothly. More importantly, the halogen substitution allows the radical cyclization to occur with an excellent regioselectivity, leading to the efficient generation of five-, six-, and even seven-membered cyclic amines. This finding should be of importance to applications in organic synthesis.

Experimental Section

Typical Procedure for the Synthesis of *N*-Chloro Toluenesulfonamides. To a solution of *N*-(4-methyl-4-pentenyl) toluenesulfonamide (253 mg, 1.0 mmol) and K_2CO_3 (0.17 g, 1.2 mmol) in anhydrous CH_2Cl_2 (30 mL) was added ^{t}BuOCl (120 mg, 1.1 mmol). The mixture was stirred in the dark at rt for 2 h. After the removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (10:1, v:v) as the eluent to give pure **1a** as a colorless oil. Yield: 258 mg (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (3H, s), 1.77−1.87 (2H, m), 2.09 (2H, t, J = 7.2 Hz), 2.47 (3H, s), 3.23 (2H, t, J = 6.9 Hz), 4.73 (2H, d, J = 14.7 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.82 (2H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.6, 22.3, 25.1, 34.0, 56.2, 110.8, 129.5, 129.6, 130.2, 144.2, 145.3. EIMS: *m*/*z* (rel intensity) 287 (M^+, 2), 252 (14), 238 (16), 198 (10), 184 (8), 155 (53), 132 (9), 91 (100). HRMS calcd for $C_{13}H_{18}NO_2S$ (M^+ − Cl): 252.1058. Found: 252.1070.

Typical Procedure for the Direct UV Photolysis of *N*-Chloro Toluenesulfonamides. The solution of *N*-chloro-*N*-(4-methyl-4-pentenyl) toluenesulfonamide (**1a**, 86 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL) was photolyzed with the aid of a 125 W high-pressure mercury lamp at −78 °C for 2 h under nitrogen atmosphere. The light was then turned off, and the solution was allowed to warm up to rt. After removal of the solvent, the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:1, v:v) as the eluent to give the products **2a** (29 mg, 34% yield) and **3a** (55 mg, 64% yield). Compound **2a**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (3H, s), 1.63−1.91 (3H, m), 2.25−2.33 (1H, m), 2.43 (3H, s), 3.30−3.46 (2H, m), 3.85−3.89 (2H, m), 7.29 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.5, 22.5, 23.8, 38.3, 49.8, 51.0, 67.9, 127.3, 129.5, 137.9, 143.1. EIMS: *m*/*z* (rel intensity) 287 (M^+, 1), 238 (95), 198 (3), 155 (44), 149 (2), 132 (3), 91 (100), 65 (23). Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; N, 4.87. Found: C, 54.35; H, 6.42; N, 4.67. Compound **3a**: white solid. Mp: 88−90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (3H, s), 1.62−1.97 (4H, m), 2.44 (3H, s), 2.94−3.18 (4H, m), 7.33 (2H, d, J = 7.8 Hz), 7.65 (2H, d, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.5, 22.4, 38.2, 39.5, 45.8, 57.8, 65.7, 127.6, 129.7, 133.8, 143.6. EIMS: *m*/*z* (rel intensity) 287 (M^+, 24), 252 (19), 236 (8), 198 (100), 155 (67), 132 (38), 103 (18), 91 (67). Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; N, 4.87. Found: C, 54.30; H, 6.45; N, 4.79.

Typical Procedure for Et_3B/O_2 Initiated Sulfonamidyl Radical Cyclization. To the solution of *N*-chloro-*N*-(4-chloro-4-pentenyl) toluenesulfonamide (**1c**, 154 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3B (50 μL, 0.05 mmol, 1 M solution in CH_2Cl_2) and dry air (5 mL) at −20 °C under nitrogen atmosphere. The mixture was stirred in the dark at −20 °C for 2 h. After removal of the solvent, the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:1, v:v) as the eluent to give the product **3c** as a white solid. Yield: 135 mg (88%). Mp: 92−94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.88−1.95 (2H, m), 2.26 (2H, t, J = 5.7 Hz), 2.44 (3H, s), 3.08 (2H, t, J = 5.4 Hz), 3.53 (2H, s), 7.34 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.5, 23.0, 43.8, 45.1, 59.9, 84.8, 127.5, 129.8, 134.1, 143.9. EIMS: *m*/*z* (rel intensity) 307 (M^+, 14), 271 (5), 236 (2), 198 (61), 155 (63), 116 (17), 91 (100), 65 (40). Anal. Calcd for $C_{12}H_{15}Cl_2NO_2S$: C, 46.76; H, 4.91; N, 4.54. Found: C, 47.04; H, 4.60; N, 4.17.

Typical Procedure for Sulfonamidyl Radical Cyclization with DIB/I_2. To the solution of DIB (48 mg, 0.15 mmol) in dry CH_2Cl_2 (5 mL) was added iodine (28 mg, 0.11 mmol) at rt under nitrogen atmosphere. The mixture was stirred at rt for 5 min. *N*-(4-Bromo-4-pentenyl) toluenesulfonamide (**6b**, 32 mg, 0.1 mmol) was added, and the resulting mixture was irradiated at rt for 1 h with the aid of a 125 W high-pressure mercury lamp. Aqueous $Na_2S_2O_3$ (5 mL) was then added. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous Na_2CO_3 and brine and then dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:1, v:v) as the eluent to give the product **8b** as a white solid. Yield: 36 mg (81%). Mp: 120−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.70−1.93 (2H, m), 2.20−2.31 (1H, m), 2.44 (3H, s), 2.44−2.53 (1H, m), 2.99−3.17 (2H, m), 3.33 (1H, d, J = 12.6 Hz), 3.70 (1H, d, J = 12.6 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.5, 25.1, 33.5, 45.3, 49.0, 64.3, 127.5, 129.8, 134.1, 144.0. EIMS: *m*/*z* (rel intensity) 444 ($M^+(^{81}Br)$ − 1, 0.3), 442 ($M^+(^{79}Br)$ − 1, 0.2), 318 (64), 316 (67), 237 (6), 207 (4), 155 (73), 91 (100). Anal. Calcd for $C_{12}H_{15}BrINO_2S$: C, 32.45; H, 3.40; N, 3.15. Found: C, 32.42; H, 3.47; N, 3.03.

Typical Procedure for Sulfonamidyl Radical Cyclization with $Pb(OAc)_4/I_2$. To the solution of $Pb(OAc)_4$ (155 mg, 0.35 mmol) in dry 1,2-dichloroethane (10 mL) was added iodine (13 mg, 0.05 mmol) at rt under nitrogen atmosphere. The mixture was stirred at rt for 5 min. *N*-(5-Chloro-2,2-dimethyl-4-pentenyl) toluenesulfonamide (**19b**, 30 mg, 0.1 mmol) was then added. The reaction mixture was irradiated at the refluxing temperature for 1 h with the aid of a 125 W high-pressure mercury lamp. The light was then turned off, and the resulting solution was cooled down to rt. Aqueous $Na_2S_2O_3$ (10 mL) was then added. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous Na_2CO_3 and brine and then dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:1, v:v) as the eluent to give the product **25b** as a white solid as the mixture of two stereoisomers (trans/cis = 57/43 determined by ^{1}H NMR). Yield: 18 mg (60%). Mp: 124−126 °C. ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 1.04/1.20 (3H, 2s), 1.17/1.22 (3H, 2s), 1.51−1.59/2.27−2.35 (1H, 2 m), 1.81−1.95 (1H, m), 2.43/2.46 (3H, 2s), 2.72/3.23 (1H, 2d, J = 9.6 Hz), 3.33/3.47 (1H, 2d, J = 9.6 Hz), 4.22−4.31/4.43−4.51 (1H, 2 m), 4.96/5.55 (1H, 2d, J = 10.5/5.4 Hz), 7.26−7.33 (1H, m), 7.47−7.51 (1H, m), 7.72−7.77 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 21.7/21.6, 26.2/25.8, 26.9/27.2, 36.8/37.6, 43.0/46.5, 57.7/56.3, 61.0/59.6, 62.9/64.6, 123.8/124.6, 129.3/129.5, 129.6/129.8, 133.9/133.5, 135.0, 143.4/143.2. EIMS: *m*/*z* (rel intensity) 299 (M^+, 22), 264 (4), 220 (4), 200 (100), 167 (9), 144 (18), 139 (22), 103 (32). Anal. Calcd for $C_{14}H_{18}ClNO_2S$: C, 56.08; H, 6.05; N, 4.67. Found: C, 56.07; H, 5.98; N, 4.47.

Acknowledgment. This project was supported by the National Natural Science Foundation of China (Grant Nos. 20325207 and 20472109) and by the Shanghai Municipal Committee of Science and Technology (Grant No. 04QMH1418).

Supporting Information Available: Characterizations of **1**−**31** and the computational results on radicals **A**−**C**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0625857