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5-*Exo* versus 6-*Endo* Cyclization of Primary Aminyl Radicals: An Experimental and Theoretical Investigation

Feng Liu, Kun Liu, Xinting Yuan, and Chaozhong Li*

Joint Laboratory of Green Synthetic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

clig@mail.sioc.ac.cn

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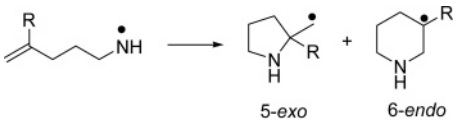

R =	5-*exo*	6-*endo*
H	92	8
Me	73	27
t-Bu	44	56
Cl	7	93

The cyclization of neutral primary pent-4-enylaminyl radicals was investigated experimentally and theoretically. Unlike the corresponding secondary aminyl radicals, primary pent-4-enylaminyl radicals underwent efficient cyclization to afford the pyrrolidine and/or piperidine products in good to high yields. While the simple pent-4-enylaminyl radical gave predominately the 5-*exo* cyclization product, 4-chloropent-4-enylaminyl radicals led to the formation of the corresponding 6-*endo* cyclization products in excellent regioselectivity. Theoretical calculations revealed that the 5-*exo* cyclization rate of primary aminyl radicals is about 3−4 orders of magnitude higher than that of secondary aminyl radicals.

Nitrogen-centered radicals are involved in a number of useful organic transformations.[1] Intramolecular addition of N-centered radicals to C═C double bonds offers a unique entry to N-hetereocycles such as lactams and cyclic amines. In particular, the cyclization in a 5-*exo* mode has been widely investigated and has found important application in natural product synthesis.[2] Different types of N-centered radicals exhibit dramatically different reactivities in these cyclization reactions. While amidyl and sulfonamidyl radicals are electrophilic and highly reactive toward electron-rich C═C double bonds,[3] neutral secondary aminyl radicals are much less reactive and rather nucleophilic. Kinetic study by Newcomb et al. showed that the rate constant for 5-*exo* cyclization of *N*-alkylpent-4-enamidyl radicals is around 2×10^9 s^{-1}.[3a] As a comparison, the rate constant for 5-*exo* cyclization of the *N*-butylpent-4-enylaminyl radical is in the range of 3×10^3 to 4×10^4 s^{-1}.[4,5] However, the rate of secondary aminyl radical cyclization can be increased significantly by the addition of a Brönsted or Lewis acid.[6]

Despite the relatively slow addition of neutral secondary aminyl radicals to C═C bonds, they provide a direct entry to *N*-alkyl pyrrolidines and piperidines and thus have attracted considerable attention.[1,7] However, to our surprise, the cyclization of neutral primary aminyl radicals is far less explored. In fact, only a few separated examples were reported in the literature.[8] The possible difference between primary and secondary aminyl radicals in reactivity remains virtually unknown.

During our investigation on the cyclizations of unsaturated amidyl radicals,[9] we found that the activation energies for 6-*exo* cyclization of *N*-alkyl-substituted hex-5-enamidyl radicals are significantly higher than that of the primary hex-5-enamidyl radical.[9b] More recently, we demonstrated that the regioselectivity of amidyl and sulfonamidyl radical cyclization could be excellently controlled by the vinylic halogen substitution.[9d,f] We were thus motivated to find if (1) primary aminyl radicals would exhibit significantly higher cyclization rates than the corresponding secondary aminyl radicals and (2) the regioselectivity of cyclization of pent-4-enylaminyl radicals could be controlled by vinylic halogen substitution. We report here that, unlike *N*-alkylpent-4-enylaminyl radicals, primary aminyl radicals underwent efficient 5-*exo* and/or 6-*endo* cyclization to furnish the corresponding pyrrolidine and/or piperidine products in good to high yields. Furthermore, the internal vinylic substitution played an important role in controlling the regioselectivity of

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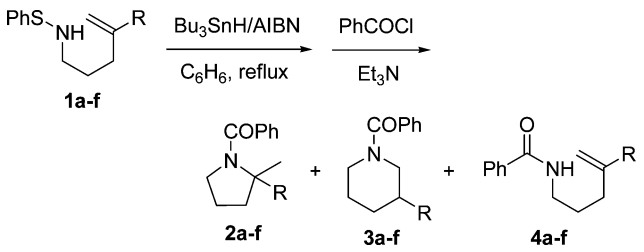
TABLE 1. Cyclization of Pent-4-enylaminyl Radicals



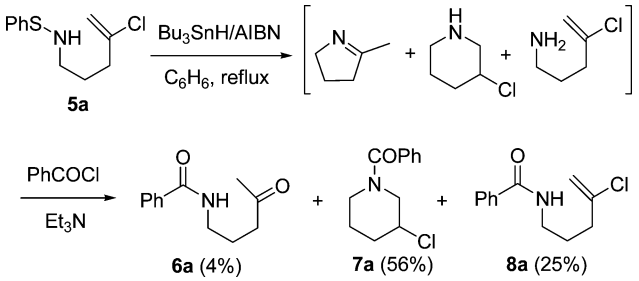
entry	substrate	R	yield (%)[a] 2	3	4
1	**1a**	H	66	6	22
2	**1b**	Me	46	17	29
3	**1c**	*n*-Bu	37	20	32
4	**1d**	*i*-Pr	43	25	20
5	**1e**	*t*-Bu	33	42	17
6	**1f**	Ph	0	84	4

[a] Isolated yield based on **1**.

cyclization. Theoretical calculations in combination with the experimental results offer a detailed understanding of the mechanism of the primary aminyl radical cyclization.

Several methods are available for the generation of aminyl radicals. The older and widely used method is the photolysis or metal-induced reduction of *N*-chloroamines.[1b] However, the radical reactions of *N*-chloroamines are prone to the contamination of ionic processes such as electrophilic halocyclization. The use of *N*-hydroxypyridine-2-thione carbamates (PTOC carbamates) developed by Newcomb and co-workers has served as good precursors for secondary aminyl radicals.[10] Unfortunately, the PTOC carbamates derived from primary amines are very unstable in solution.[11] Therefore, we chose the benzenesulfenamide derivatives as the precursors for primary aminyl radicals.[8b,12] Benzenesulfenamides could be easily prepared in good yield by reaction between amines and *N*-(benzenesulfenyl)-phathalimide.[13] Besides, they were found to be fairly stable and their purification could be carried out with column chromatography on netrual or basic alumina.[8b] Thus, we synthesized *N*-(benzenesulfenyl)pent-4-enylamine (**1a**) according to the above method. It was then subjected to treatment with Bu_3SnH (1.5 equiv) and AIBN (0.2 equiv) in refluxing benzene according to the standard literature procedure.[8b] To facilitate product characterization, the resulting product amines were then trapped by benzoyl chloride with triethylamine as the base to give the corresponding benzamides, which were readily purified by column chromatography on silica gel. We were delighted to find that the cyclization products **2a** and **3a** were achieved in a combined 72% yield along with the direct reduction product **4a** in 22% yield (Table 1). This result is in sharp contrast to that of secondary aminyl radicals as the *N*-butylpent-4-enylaminyl radical gave very poor yield of cyclized product.[8b] It also implied that the cyclization rate of the primary aminyl radical derived form **1a** is much faster than that of the corresponding secondary aminyl radical.

SCHEME 1



As also can be seen from the reaction of **1a**, 5-*exo* cyclization (**2a**) predominated over 6-*endo* cyclization (**3a**) for the pent-4-enylaminyl radical and the product ratio was about 92:8. It is foreseeable that the terminal vinylic substitution will further increase the regioselectivity and efficiency of the 5-*exo* aminyl radical cyclization because of the radical-stabilizing effect of the substituent (also vide infra). Such a trend has been widely observed in radical cyclization reactions. Of interest to us was the internal vinylic substitution effect, which varies dramatically in different cyclization systems. Thus, the 4-alkyl- or phenyl-substituted sulfenamides **1b**−**f** were prepared and subjected to the same procedures indicated above. The results are summarized in Table 1. In all cases, the cyclized products were obtained in good yields. The 4-methylpent-4-enylamine **1b** afforded the mixture of 5-*exo* cyclization product **2b** (46%) and 6-*endo* cyclization product **3b** (17%) (entry 2, Table 1). Although 5-*exo* cyclization was again preferred, the ratio of **2**:**3** was decreased from 92:8 (R = H) to 73:27 (R = Me). Changing the methyl group to a butyl or isopropyl moiety further lowered the regioselectivity to ~65:35 (entries 3 and 4, Table 1). However, with the 4-*tert*-butyl substitution, the regioselectivity of the aminyl radical cyclization was reversed (44:56) to be in favor of 6-*endo* cyclization (entry 5, Table 1). On the other hand, the 4-phenyl-substitutited substrate **1f** gave exclusively 6-*endo* cyclization product **3f** in 84% yield (entry 6, Table 1). The above alkyl-substitution effect is in sharp contrast to that in amidyl radical cyclization[9d] but similar to that in pent-4-enoxyl radical cyclization.[14]

Although the 4-alkyl-substitution encourages the 6-*endo* cyclization, the regioselectivity was poor. We then moved on to test the effect of halogen substitution, which has showed a remarkable control of regioselectivity in the cyclization of amidyl[9d] and sulfonamidyl[9f] radicals. Thus, 4-chloro-substituted amine **5a** was prepared and subjected to the same reaction indicated above. Three products were isolated, the piperidine **7a** (56%) as the 6-*endo* cyclization product, the vinyl chloride **8a** (25%) as the direct reduction product, and the ketone **6a** (~4%) apparently generated from the hydrolysis of the 5-*exo* cyclization product 2-methylenepyrrolidine (Scheme 1). The ratio of 5-*exo* versus 6-*endo* cyclization products (**6a**:**7a**) was therefore determined by HPLC to be 7:93, indicating the overwhelming predominance of 6-*endo* cyclization.

We then tested a number of 4-halogen-substituted substrates and the results are listed in Table 2. The reactions of **5a**−**e** with different substitutions all exhibited high preference of 6-*endo* cyclization with the ratio of *endo*/*exo* ranging from 6:1

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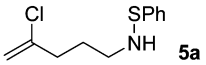
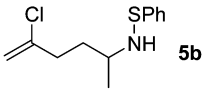
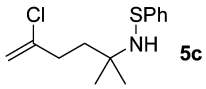
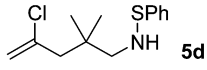
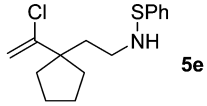
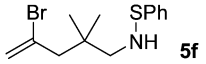
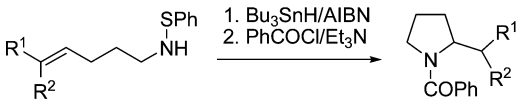
TABLE 2. Cyclization of 4-Halopent-4-enylaminyl Radicals

entry	substrate	yield (%)[a] 6	7	8
1	 **5a**	4	56	25
2	 **5b**	10	62[b]	15
3	 **5c**	7	52	26
4	 **5d**	7	80	5
5	 **5e**	2	66	5
6	 **5f**	–[c]	–[c]	40

[a] Isolated yield based on **5**. [b] Trans:cis = 3:1. [c] Not detected.

to 33:1. The regioselectivity was decreased by the 1-alkyl substitution but increased by the 3-alkyl substitution. This substituent effect parallels that in alkyl radical cyclization and can be well explained analogously according to the work of Beckwith and Schiesser.[15] For the 4-bromo-substituted substrate **5f** (entry 6, Table 2), no desired cyclization product could be obtained probably because of the contamination of the easy reduction of the vinyl bromide by Bu_3SnH.

As a comparison, the 5-chloro-substituted substrate **9a** led to the exclusive formation of the 5-*exo* cyclization product **10a** in 83% yield (eq 1). The 5-methyl or 5,5-dimethyl substitution also enhanced the efficiency and regioselectivity of cyclization and the expected pyrrolidines **10b** and **10c** were also obtained in 87% and 90% yield, respectively (eq 1).

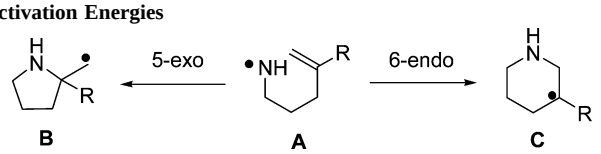


(1)

9a (R^1 = Cl, R^2 = H, *Z*:*E* = 63:37) **10a** (83%)
9b (R^1 = Me, R^2 = H) **10b** (87%)
9c (R^1 = R^2 = Me) **10c** (90%)

The above results clearly demonstrated the efficiency of primary aminyl radical cyclization and the unique effect of Cl substitution in controlling the regioselectivity. To gain more insight into the reactivity of primary aminyl radicals, we turned to density functional calculations for help, which have been shown to be an increasingly important tool in modeling radical reactions and mechanisms.[16,17] All the structures were fully optimized at the UB3LYP/6-31G* level. Once the geometry was reached, the harmonic frequencies were examined to confirm the geometry obtained to be a true minimum or first-order saddle point. The enthalpies and free energies were then calculated at the UB3LYP/6-311++G** level. The zero-point vibrational energy and thermal corrections were also obtained at the UB3LYP/6-311++G** level. The computed activation free energies ($\Delta G^{\ddagger}$) for 5-*exo* and 6-*endo* cyclization are summarized in Table 3. By assuming that the cyclizations are kinetically controlled, the regioselectivities, which are also included in Table 3, could be calculated based on the transition state theory.

TABLE 3. Calculated (UB3LYP/6-311++G//UB3LYP/6-31G*) Activation Energies**



B **A** **C**

		$\Delta G^{\ddagger}$ (kcal/mol)		**B**:**C** (at 80 °C)	
entry	R	5-*exo*	6-*endo*	calcd	expt
1	H	10.2	12.1	94:6	92:8
2	Me	11.0	11.4	64:36	73:27
3	*n*-Bu	10.6	10.7	54:46	65:35
4	*i*-Pr	10.8	10.9	54:46	63:37
5	*t*-Bu	11.3	10.5	24:76	44:56
6	Ph	13.2	9.4	<1:99	<1:99
7	Cl	13.2	10.9	4:96	7:93
8	Br	13.5	10.9	2:98	

As can be seen in Table 3, the activation energies for both 5-*exo* and 6-*endo* cyclization of aminyl radicals A (R = H or alkyl) are around 10−12 kcal/mol. With the increase of bulkiness of the alkyl substituent, the energy differences between the two modes of cyclization become smaller. This can be well interpreted in terms of steric effect. For the phenyl-substituted radical **A**, the activation energy for 6-*endo* cyclization is lowered by 2.6 kcal/mol compared to that of the unsubstituted radical A (R = H), apparently resulting from the powerful radical-stabilizing effect of the phenyl moiety. The calculated ratios of 5-*exo* versus 6-*endo* cyclization products are in good agreement with the experimental data.

As a comparison, the activation free energy for 5-*exo* cyclization of a typical secondary aminyl radical, *N*-butylpent-4-enylaminyl radical, was also computed at the UB3LYP/6-311++G**//UB3LYP/6-31G* level to be 16.5 kcal/mol, about 6.3 kcal/mol higher than that of the corresponding primary aminyl radical **A** (R = H). This strongly implies a 3−4 orders of magnitude increase of 5-*exo* cyclization rate from secondary to primary aminyl radicals. For secondary aminyl radicals, the rate of cyclization is very similar to the rate of reduction of aminyl radicals by Bu_3SnH.[5b,10,11] Poor yield of cyclization is generally obtained. However, for primary aminyl radicals, the dramatic acceleration of the rate of cyclization allows it to compete efficiently with the rate of direct reduction. As a result, a high yield of cyclization can be achieved.

When the alkyl group is switched to the chlorine atom, the activation energy for 5-*exo* cyclization is increased by >2 kcal/

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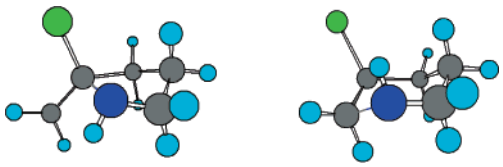
(16) For review articles on use of calculations in radical reactions, see: (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (b) Schiesser, C. H.; Skidmore, M. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 337.
(17) For the recent selected examples, see: (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 9d and 9f.

mol while the activation energy for 6-*endo* cyclization remains almost unchanged. Since chlorine is smaller in size than a methyl group and the radical-stabilizing energy of Cl is only slighter higher than that of Me,[18] the above two effects (steric and radical-stabilizing effects) are not enough to account for the difference between Cl and Me in controlling the regioselectivity. The third effect, the lone pair−lone pair repulsion between chlorine and nitrogen atoms, should add an additional weight to the improvement of regioselectivity. This can be further evidenced from the calculated structures. The computed transition state structures for 5-*exo* and 6-*endo* cyclization of radical **A** (R = Cl) are shown as **TS-1** and **TS-2**, respectively. **TS-1** is in a half-chair conformation while **TS-2** is in a chair conformation. The NH proton is in the axial position in both cases. The N−Cl distance is 2.94 Å in **TS-1** but 3.76 Å in **TS-2**. Moreover, the chlorine atom and the lone pair electron of the nitrogen atom are at the same side in **TS-1** but in the opposite directions in **TS-2**. Therefore, the lone pair−lone pair repulsion is much stronger for 5-*exo* cyclization than for 6-*endo* cyclization.



TS-1 **TS-2**

In summary, the chemistry detailed above has clearly demonstrated the efficiency of 5-*exo* and 6-*endo* cyclization of neutral primary aminyl radicals and the remarkable chlorine substitution effect in controlling the regioselectivity. This finding should encourage the further development of primary aminyl radical-based strategy in organic synthesis.

Experimental Section

Typical Procedure for the Synthesis of *N*-(Benzenesulfenyl)-pent-4-enylamines. *N*-(Benzenesulfenyl)phthalimide (636 mg, 2.49 mmol) was added into the CH_2Cl_2 (8 mL) solution of pent-4-enylamine (234 mg, 2.74 mmol) and the solution was stirred for 2 h at rt. The resulting mixture was then concentrated under reduced pressure and the residue was poured into hexane (20 mL). The mixture was filtered and the precipitate was washed with hexane (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography on basic alumina with hexane−ethyl acetate (10:1, v:v) as the eluent to give *N*-(benzenesulfenyl)pent-4-enylamine (**1a**) as a yellowish liquid. Yield: 264 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (2H, q, J = 7.1 Hz), 2.11 (2H, q, J = 7.1 Hz), 2.86 (1H, br), 2.96 (2H, t, J = 6.4 Hz), 4.95−5.06 (2H, m), 5.73−5.85 (1H, m), 7.12−7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 29.3, 30.9, 51.4, 114.9, 123.7 125.2, 128.6, 138.0, 141.6; EIMS *m*/*z* (rel intensity) 193 (M^+, 13), 160 (22), 138 (54), 109 (100), 84 (14), 77 (15), 65 (26), 39 (18); HRMS calcd for $C_{11}H_{16}NS$ (M + H: 194.0998, found 194.1000.

Typical Procedure for the Cyclization of Pent-4-enylaminyl Radicals. The benzene (10 mL) solution of Bu_3SnH (213 mg, 0.732 mmol) and AIBN (16 mg, 0.097 mmol) was added via the aid of a syringe pump over a period of 5 h into the benzene (20 mL) solution of *N*-(benzenesulfenyl)pent-4-enylamine (**1a**, 94 mg, 0.487 mmol) at reflux. After the addition was complete, the mixture was allowed to cool to room temperature and triethylamine (0.20 mL, 1.30 mmol) was added. The solution was further cooled to 0 °C and benzoyl chloride (102 mg, 0.73 mmol) was added. The mixture was then stirred at rt overnight. After the usual workup, the crude products were separated by column chromatography on silica gel with ethyl acetate−hexane (1:3, v:v) as the eluent to give **2a** (61 mg, 66%),[11] **3a** (5.4 mg, 6%),[19] and **4a** (20 mg, 22%).[20]

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Supporting Information Available: Characterizations of **1**−**10** and the computational results on the cyclizations of radicals **A** and *N*-butylpent-4-enylaminyl radical. This material is available free of charge via the Internet at http://pubs.acs.org.

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