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Vinyl Radical Cyclization onto Imino Group. Selective 6-Endo Cyclization onto Aldimines Leading to 3-Methylenepiperidines

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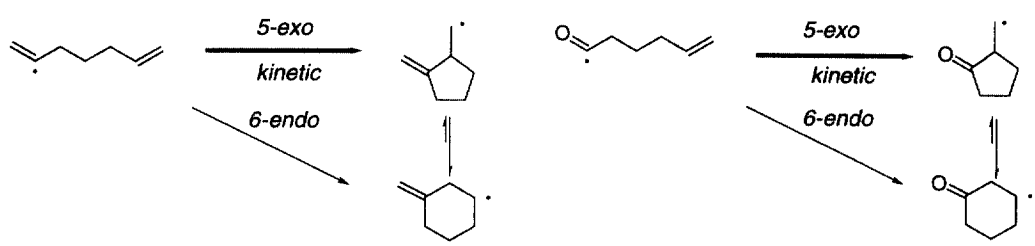
Abstract: When 5-exo/6-endo type of vinyl radical cyclization onto aldimine N=C bond was examined using tin hydride mediated radical reaction conditions, selective 6-endo cyclization took place to lead to 3-methylene-piperidines. On the other hand, vinyl radical cyclization onto ketimine N=C bond did not take place.

Early studies by Beckwith[1] and Stork[2] have shown that under tin hydride mediated reaction conditions 5-exo/6-endo type of vinyl radical cyclization onto C=C bond gives a mixture of both 5-exo and 6-endo products. The kinetic work by Beckwith[1] revealed that formation of six-membered ring is the result of the further isomerization of the initially formed five-membered ring radical (left-hand side of Scheme 1). More recently Crich's group reported preferential formation of 5-exo product when the reaction was conducted in their very rapid radical quenching system using PhSeSePh-Bu_3SnH, reconfirming us that the five-membered ring closure is kinetically favored.[3] Analogous 5-exo/6-endo type of acyl radical cyclization also gives a 5-exo/6-endo mixture (right-hand side of Scheme 1), and there is an agreement as to that 5-exo cyclization of acyl radicals onto C=C is kinetically favored process.[4]



Scheme 1. Vinyl and Acyl Radical Cyclizations onto C=C

As a potent tool for *N*-heterocycle synthesis, much attention has been paid on radical cyclizations onto N=C and the systematic study on alkyl radical cyclizations has been done by Bowman's group.[5] We have recently found that 5-exo/6-endo type of acyl radical cyclization onto N=C took place in selective 5-exo

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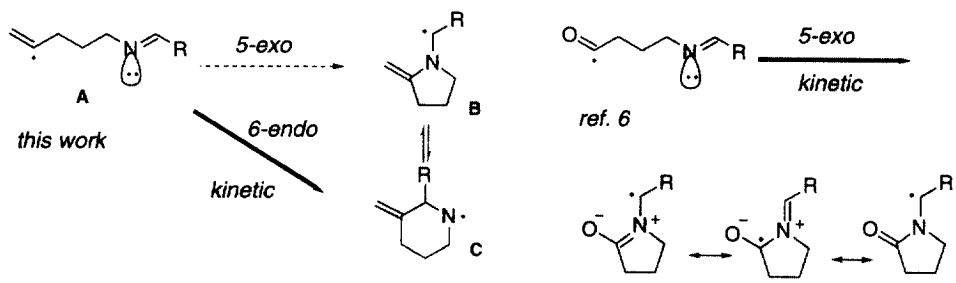
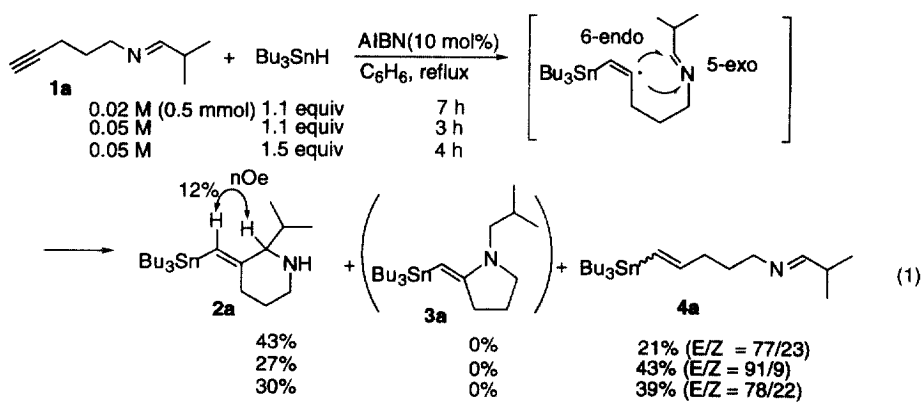
manner leading to 2-pyrrolidinones (right-hand side of Scheme 2).[6] Experiments at different concentrations did not produce six-membered ring product and therefore cyclized radical via 5-exo (*N*-philic mode) is most likely formed via a kinetically favored process. To account for the selective cyclization, we are inclined to polar cyclization mechanism including attack of nitrogen lone pair to carbonyl carbon of acyl radicals.[6] Then, we became curious at knowing what mode of selectivity the related vinyl radical cyclization onto N=C would exhibit. In this paper we report that 5-exo/6-endo type of vinyl radical cyclization onto aldimine N=C proceeds selectively in 6-endo manner (*C*-philic mode) leading to 3-methylenepiperidines (left-hand side of Scheme 2), showing an opposite selectivity to the related acyl radical cyclization onto N=C bond.



Scheme 2. Vinyl and Acyl Radical Cyclizations onto N=C

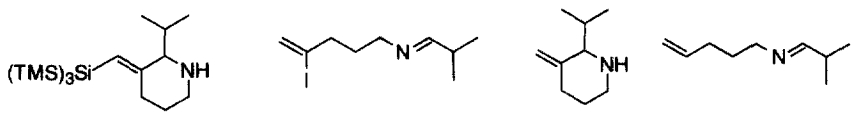
An azaenyne **1a** was prepared from 5-amino-1-pentyne and isobutyroaldehyde under acid-catalyzed azeotropic conditions and subjected to radical hydrostannylation. Thus, when **1a** (0.02 M) was treated with tributyltin hydride and a catalytic amount of AIBN, six membered ring product **2a** was formed in 43% yield as a single stereoisomer along with hydrostannylation product **4a** (21%) (eq 1). Curiously, five-membered ring product **3a** was not detected in the reaction mixture. Even at higher concentration (0.05 M), again **3a** was not formed and the yield of hydrostannylation product **4a** was increased.[7]



(1)

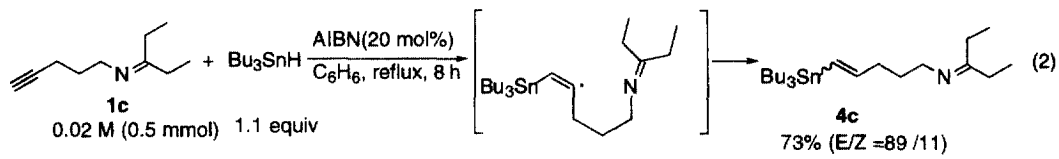
Hydrosilylation of **1a** with $(TMS)_3SiH$ also gave **2a'** as the sole cyclization product. Similarly, five-membered ring product was not formed when vinyl iodide **1b** was exposed to the radical reaction (0.02

M, 80 °C, 2.5 h), where 3-methylenepiperidine **2b** was obtained in 30 % yield together with a comparable amount of reduced **4b**.



2a' **1b** **2b** **4b**

The results from these experiments using aldimines indicate that (i) only product via 6-endo cyclization is observed in the 5-exo/6-endo type of vinyl radical cyclizations onto N=C bond, (ii) the 6-endo cyclization process appears kinetically favored, but, nevertheless, (iii) the cyclization is not very fast, judging from the fact that vinyl radical reduction by tributyltin hydride is largely competitive. We also tested the case of a ketimine **1c**, with a thought that steric congestion at C-6 position would allow us to observe 5-exo cyclization onto N-C double bond. Contrary to our expectation, however, neither 5-exo nor 6-endo cyclization took place and only product obtained was simple hydrostannylation product **4c** (73% yield) (eq 2). This suggests that 6-endo cyclization to sterically crowded imine carbon is highly inefficient, but still it does not lead to 5-exo cyclization. These results show similarities with the related aryl radical cyclization onto imine N-C bonds previously reported by Warkentin and coworkers.[8]

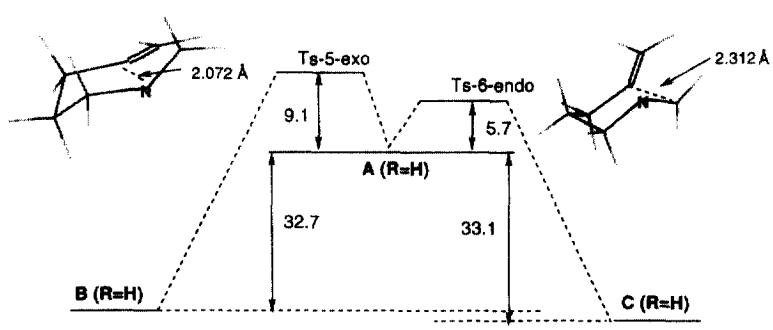


1c
0.02 M (0.5 mmol) 1.1 equiv

4c
73% (E/Z =89 /11)

(2)

Ab initio MO study was carried out for 6-aza-7-heptadiene-2-yl system using the level of UHF/3-21G (Scheme 3). The results suggested that (i) there is no significant thermodynamic preference for six-membered radical (0.34 kcal/mol more stable than five-membered ring radical), (ii) chair-form transition states are deduced for both 5-exo/6-endo cyclizations, and (iii) the transition state barrier favors 6-endo radical cyclization to 5-exo cyclization by 3.4 kcal/mol, which is supportive of six-membered radical being



Scheme 3. Calculated Energies at UHF/3-21G Level (kcal/mol)

kinetically favored.

In summary, we have demonstrated that unlike the cyclization onto C=C (Scheme 1), vinyl radical cyclization onto aldimine N=C bond took place selectively in 6-endo fashion. However, the observed 6-endo cyclization process largely competes with H-abstraction. In the case of a ketimine, neither 6-endo nor 5-exo cyclization was observed. Thus, both the slow 6-exo and reluctant 5-exo cyclization processes appear characteristic of 6-aza-heptadiene-2-yl systems. The 6-endo selectivity is contrasting to the corresponding acyl radical cyclization onto N=C proceeding in 5-exo mode,[6] and this may support indirectly the polarity governed cyclization mechanism for the acyl radical case.

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5. For alkyl radical cyclizations onto imino group, see: Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959-7980.

6. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838-5839.

7. 2-Isopropyl-3-[(tributyltin)methylidene]piperidine (**2a**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J* = 6.6 Hz), 0.88 (t, 15H, *J* = 7.3 Hz), 1.01 (d, 3H, *J* = 6.6 Hz), 1.30 (sex like, 6H, *J* = 7.3 Hz), 1.46-1.51 (m, 6H), 1.58-1.65 (m, 1H), 1.78 (dqnint, 1H, *J* = 4.2, 12.8 Hz), 2.04-2.11 (m, 2H), 2.18 (br s, 1H), 2.29 (dt, 1H, *J* = 4.8, 12.6 Hz), 2.79-2.82 (m, 2H), 2.91 (ddd, 1H, *J* = 3.3, 11.0, 13.0 Hz), 5.44 (s, 1H, J_{SnH}= 36.6 Hz); ^{13}C NMR(68 MHz, $CDCl_3$) δ 10.23(t), 13.73(q), 19.52(q), 20.68(q), 25.91(d), 27.33(t), 29.27(t), 30.78(t), 33.51(t), 41.04(t), 71.28(t), 120.50(d), 157.57(s); IR(neat) 1608 cm^{-1}; MS (EI) *m/z* 428 (M^+, 1), 386 (69), 372 (22), 152 (85), 138 (84), 96 (29). Anal. Calcd for $C_{21}H_{43}NSn$: C, 10.12; H, 58.90; N, 3.27. Fonnd: C, 10.21; H, 58.95; N, 3.50. 2-Isopropyl-3-methylenepiperidine (**2b**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.56-1.75 (m, 2H), 1.82-1.87 (br, 1H), 2.03-2.12 (m, 1H), 2.21 (dt, 2H, *J* = 4.9, 9.9 Hz), 2.72-2.79 (m, 2H), 2.92 (ddd, 1H, *J* = 3.6, 9.6, 12.9 Hz), 4.66 (s, 1H), 4.73 (s, 1H); ^{13}C NMR (68MHz, $CDCl_3$) δ 19.14(q), 20.67(q), 25.93(d), 29.99(t), 31.56(t), 41.67(t), 66.87(d), 108.00(t), 148.48(s) IR(neat) 1658 cm^{-1}; MS (EI) *m/z* 139 (M^+, 2), 124 (2), 96 (100); HRMS (EI) *m/z* 139.1352 ($C_9H_{17}N$ requires 139.1361).

8. Warkentin et al. reported that the related aryl radical cyclization onto aldimines occurs in 6-endo selective mode, whereas the cyclization onto ketimines is highly inefficient. On the other hand, unlike the present vinyl radical case, 6-endo cyclization of aryl radicals is very rapid (ca. 10^8 s^{-1} at 80 °C). (a) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123-2126. (b) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291-321. For some other examples of aryl radical cyclizations, see: (c) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315-316. (d) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149-152.