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Effect of Temperature on 5-*Endo*- and 4-*Exo-Trig* Radical Cyclizations of *N*-Vinylic α-Halo Amides

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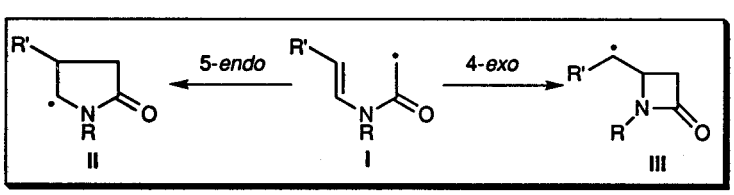
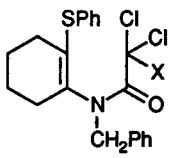
Abstract: The radical **3a** generated from *N*-vinylic trichloroacetamide **1a** provided the 5-*endo-trig* cyclization product **2a** in boiling toluene, whereas, at room temperature, gave the 4-*exo-trig* cyclization product **9**. The results may be explained in terms of the reversibility of 4-*exo* cyclization.

Despite current interest in the chemistry of radical cyclizations leading to carbo- and heterocyclic compounds, there are few reports on the 5-*endo-trig*[1] and 4-*exo-trig*[2] cyclizations of pent-4-enyl radicals and related species. This is probably because the 5-*endo-trig* cyclization is a disfavored process,[3] and the 4-*exo* cyclization is, in general, a reversible process due to the high strain of the cyclized four-membered ring systems, thereby shifting the equilibrium to the starting radicals.[2] Previous reports from our laboratories revealed that the *N*-vinylic carbamoylmethyl radicals **I**, generated from the corresponding α-halo amides, underwent both types of cyclization effectively to give γ-lactams[4] and β-lactams,[5] respectively. In general, the radicals **I** cyclize in a 5-*endo-trig* manner to give five-membered radicals **II**, whereas the 4-*exo* cyclization predominates when a sulfur-substituent is attached to the *N*-vinylic bond. The effectiveness of the 4-*exo* cyclization can be explained in terms of the high stability of the resulting sulfur-substituted radicals **III**. To extend this methodology, we subsequently examined the reactions of α-chloro amides **1** having a sulfur-substituent at the C-2 position of the *N*-(1-cyclohexen-1-yl) group, and found that the course of the cyclizations, *i. e.*, 4-*exo-trig* vs. 5-*endo-trig*, was strikingly affected by the reaction temperature employed.





1a: X = Cl
1b: X = H

A toluene solution of Bu_3SnH (1.3 equiv.) and AIBN (0.3 equiv.) was added slowly to a boiling solution of **1a** in toluene during 3.5 h to give 1,4,5,6-tetrahydro-2*H*-indol-2-one **2a**[6] in 84% yield.

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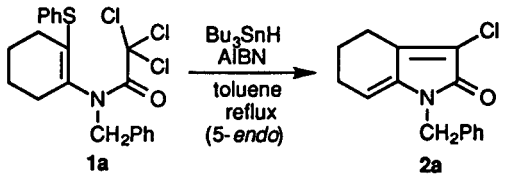
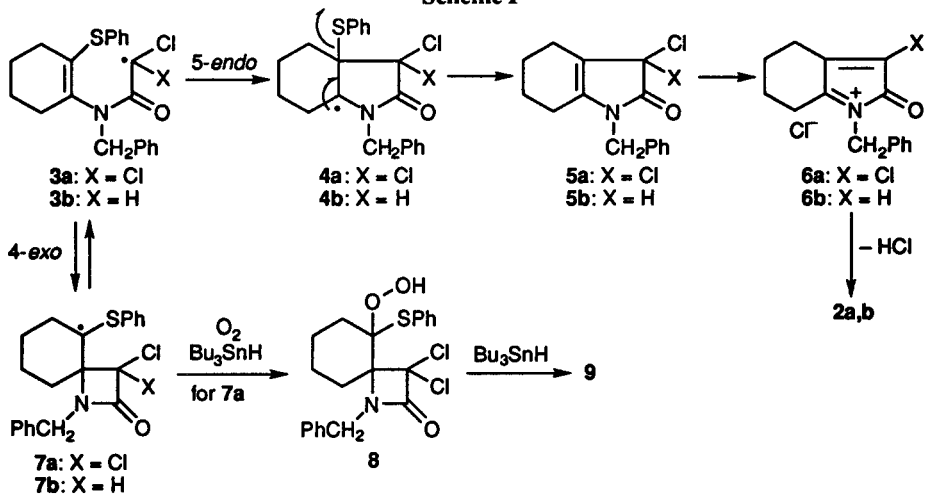
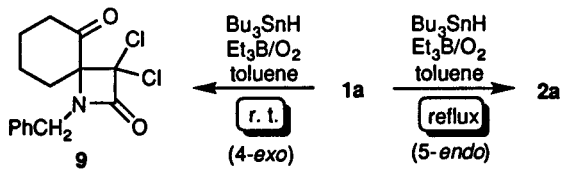


The formation of **2a** from **1a** would involve the 5-*endo-trig* cyclization of the carbamoylmethyl radical **3a** leading to the five-membered radical **4a** (Scheme I). This step is then followed by elimination of benzenethiyl radical to give hexahydroindolone **5a**. Although the exact mechanism for the conversion of **5a** to **2a** is obscure at the moment, one possible explanation may involve the thermal elimination of chloride ion with the aid of an electron-donating nitrogen atom to give acyliminium salt **6a**, which then loses hydrogen chloride to give **2a**.

Scheme I



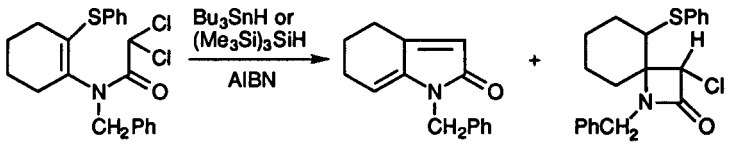
Interestingly, when a toluene solution of **1a** and Bu_3SnH (1 equiv.) was treated slowly with triethylborane (1 equiv.) *at room temperature* under an oxygen atmosphere, spiro β-lactam **9**[6] was obtained in 35% yield along with the recovered **1a** (15%) and its partially dechlorinated product **1b** (10%).



The formation of **9** from **1a** may be explained as proceeding *via* an attack of molecular oxygen (used as a radical initiator for triethylborane) on the radical center of **7a**, generated by the 4-*exo* cyclization of **3a** (Scheme I). Reduction of the resulting hydroperoxide **8** with Bu_3SnH would give ketone **9**. A similar reaction of **1a** *in boiling toluene*, however, gave again the 5-*endo* cyclization product **2a** in 51% yield along with the recovered

1a (24%). These results clearly indicate that the cyclization of **1a** occurs preferentially in a 4-*exo-trig* manner at low (room) temperature, whereas at much higher temperature the 5-*endo-trig* cyclization predominates.

In order to see the effect of substituent(s) α to the carbonyl group of amides on the course of the cyclizations, we next examined the reaction of α,α-dichloro amide **1b** with Bu_3SnH and AIBN in boiling toluene. This was found to give tetrahydroindolone **2b**[6] and β-lactam **10**[6] (a single stereoisomer) in 39 and 18% yields, respectively. The following experiments suggested that the modes of cyclization of **1b** are also dependent upon the reaction temperature employed. Since the reaction of amide **1b** with triethylborane and Bu_3SnH at room temperature was very sluggish, the reactions in boiling toluene or benzene by using AIBN as an initiator were examined. The results are summarized in Table 1, which shows that the relatively low temperature (80 °C) tends to increase the amount of the 4-*exo* cyclization product **10** with decrease in the amount of the 5-*endo* cyclization product **2b** (compare entries 1 and 2, and entries 3 and 4).



1b **2b** **10**

Table 1. Formation of **2b** and **10** from **1b**

Entry	Hydride	Solvent	Temp. (°C)	Yield (%)		2b : 10
				2b	10	
1	Bu_3SnH	toluene	110	39	18	2.2 : 1
2	Bu_3SnH	benzene	80	35	43	1 : 1.2
3	$(Me_3Si)_3SiH$	toluene	110	32	19	1.7 : 1
4[a]	$(Me_3Si)_3SiH$	benzene	80	14	29	1 : 2.1

[a] 35% of **1b** was recovered.

One possible explanation for the results observed for **1a,b** may be derived from the consideration of the reversibility of the 4-*exo* cyclization. Thus, at low temperature, *i. e.*, under the kinetically controlled conditions, radicals **3a,b** cyclize predominantly in a 4-*exo-trig* manner so as to avoid a steric repulsion between the phenylthio group and chlorine atom(s) in the transition state for the 5-*endo* cyclization. On the other hand, at high temperature, the ring-opening of radicals **7a,b** rapidly occurs, and the resulting radicals **3a,b** can cyclize in a 5-*endo-trig* manner to give radicals **4a,b**. A subsequent elimination of benzenethiyl radical from **4a,b** would immediately occur to give **5a,b**, so that the 5-*endo* cyclization of **3a,b** might be irreversible. In the case of amide **1b**, the 4-*exo* cyclization product **10** was formed in substantial quantity even at higher temperature. This is probably because the monochloro substituted radical **3b** is less stable than the dichloro substituted radical **3a**, thereby descending the ability of the ring-opening of **7b** to **3b**.[7]

Thus, we revealed that the reaction temperature played an important role in deciding the course of the cyclizations of *N*-vinylic carbamoylmethyl radicals.[8] It is also relevant to note that the 5-*endo-trig* cyclization of trichloro amide **1a** provides a new entry to 1,4,5,6-tetrahydro-2*H*-indol-2-ones which are versatile intermediates for the synthesis of *Erythrina* and lycorine alkaloids.[9]

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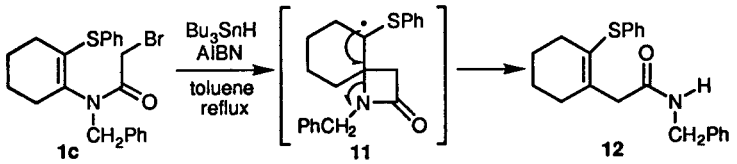
6. Spectral data for products. For **2a**: IR ($CHCl_3$) ν 1701 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.81 (quint, J = 6.3 Hz, 2 H), 2.28 (q, J = 5.5 Hz, 2 H), 2.62 (t, J = 6.6 Hz, 2 H), 4.80 (s, 2 H), 5.58 (t, J = 4.6 Hz, 1 H), 7.20-7.35 (m, 5 H). For **9**: IR ($CHCl_3$) ν 1790, 1725 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.2-1.9 (m, 4 H), 2.0-2.15 (m, 2 H), 2.6-2.8 (m, 2 H), 4.21 (d, J = 15.5 Hz, 1 H), 4.97 (d, J = 15.5 Hz, 1 H), 7.2-7.4 (m, 5 H). For **2b**: IR ($CHCl_3$) ν 1676 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.75-2.65 (m, 6 H), 4.76 (s, 2H), 5.52 (td, J = 4.6, 2.0 Hz), 5.81 (d, J = 2.0 Hz), 7.2-7.45 (m, 5 H). For **10**: IR ($CHCl_3$) ν 1761 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.81-2.24 (m, 8 H), 3.22 (d, J = 16.3 Hz, 1 H), 3.36 (dd, J = 12.5, 3.6, 1 H), 4.22 (d, J = 16.3 Hz, 1 H), 5.13 (s, 1 H), 7.15-7.49 (m, 10 H).
7. α-Bromo amide **1c**, upon treatment with Bu_3SnH and AIBN in boiling toluene, gave a complex mixture of products from which compound **12** was isolated in 16% yield. Formation of **12** from **1c** may be a result of the 4-*exo* cyclization followed by ring-opening of the resulting radical **11**. The detailed mechanism is under investigation.



8. Quite recently, the effect of temperature on the 5-*exo*- and 6-*endo-trig* radical cyclizations onto vinylsilyl ethers has been reported. See: Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 5676.
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