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8-Endo versus 5-Exo Cyclization of Unsaturated Acrylate Esters upon Reaction with t-BuHgI/KI

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Abstract: Free radical addition of t-BuHgI/KI to 1-vinyl-4-pentenyl acrylates in DMSO followed by a photostimulated reaction with Ph_2S_2 leads to the formation of free radical cyclization products **3** by the 8-endo mode and/or **5** by the 5-exo mode. Copyright © 1996 Elsevier Science Ltd

Alkylmercury halides have been demonstrated to be excellent free radical precursors.[1] Reaction of t-BuHgI with acrylates (**1**) occurs readily in the dark at room temperature in the presence of I^- to yield the corresponding adduct organomercurials **2** in excellent yield(Equation 1).[2] The adduct **2**, without isolation, can undergo further photostimulated free radical condensations with various substrates.[3] Moreover, photostimulated free radical cyclization becomes possible by use of PhSSPh because of its low reactivity towards electrophilic radicals (uncyclized radicals) and high reactivity towards nucleophilic radicals (cyclized radicals, $R_c\cdot$) allowing chain reactions (2)-(4) to occur.[2] This allows for an examination of the cyclization of various electrophilic radicals generated from **2**. Herein we report results on the 8-endo cyclization reactions[4-5] of 4-pentenyl acrylate esters and the competition with 5-exo cyclization[3,6-8] for doubly unsaturated acrylates. The results are summarized in Table 1 and 2.[9]

$$\text{t-BuHgI} + \underset{\mathbf{1}}{CH_2{=}CH_2CO_2R} \xrightarrow[\text{DMSO}]{\text{KI}} \underset{\mathbf{2}}{\text{t-BuCH}_2\text{CH(HgI)CO}_2\text{R}} \tag{1}$$

$$\underset{\mathbf{2}}{\text{t-BuCH}_2\text{CH(HgI)CO}_2\text{R}} + \text{PhS}^\bullet \longrightarrow \text{t-BuCH}_2\text{CH(CO}_2\text{R)}^\bullet + \text{PhSHgI} \tag{2}$$

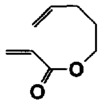
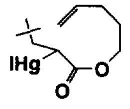
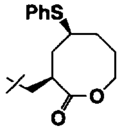
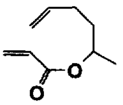
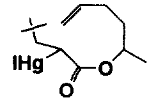
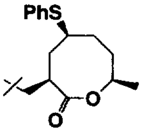
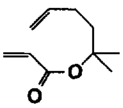
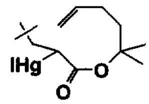
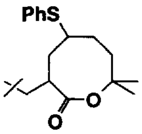
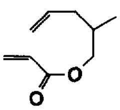
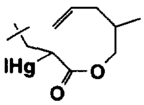
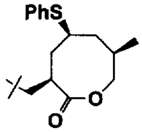
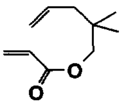
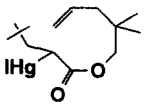
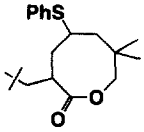
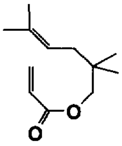
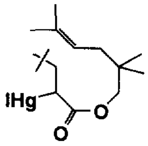
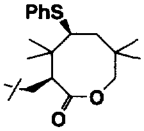
$$\text{t-BuCH}_2\text{CH(CO}_2\text{R)}^\bullet \xrightarrow{\text{cyclization}} R_c^\bullet \tag{3}$$

$$R_c^\bullet + \text{PhSSPh} \longrightarrow \underset{\mathbf{3}\text{ or }\mathbf{5}}{R_c\text{SPh}} + \text{PhS}^\bullet \tag{4}$$

Cyclization in the 8-endo mode showed some sensitivity to methyl substitution in the pentenoxy function (Table 1). The formations of the all cis products, e.g., **3b,g,h**, are not easily rationalized by a transition state involving a s-trans conformation of the adduct radical, where the substituents are quasi-equatorial (see **6**, R = Me or vinyl).[4] Instead, cyclization via the s-cis conformation **7** is suggested. Thus, cyclization is hindered when R_2 or $R_5 = R_6$ are methyl groups. The major effect of gem dialkyl substitution ($R_1 = R_2 = Me$ or $R_3 = R_4 = Me$)

is to lower the stereoselectivity in the reaction of the cyclized radical with Ph_2S_2. Introduction of methyl groups at the terminal olefinic carbon ($R_5 = R_6 =$ Me) hinders 8-endo cyclization from occurring without causing 7-exo cyclization to occur. Structures of all products were assigned by ^1H, 2D COSY and NOESY spectra.[10]

Table 1. 8-Endo Cyclization of Acrylates **1**.

Entry	Acrylate **1**	Adduct **2** (Yield)[a,b]	Product **3**(Yield)[a,c]
1	 (**1a**)	 (**2a**, 95%)	 (**3a**, 35%)
2	 (**1b**)	 (**2b**, 95%)	 (**3b**, 65%)
3	 (**1c**)	 (**2c**, 90%)	 (**3c**, 31%) cis/trans =2.5:1
4	 (**1d**)	 (**2d**, 95%)	 (**3d**, 45%)
5	 (**1e**)	 (**2e**, 95%)	 (**3e**, 63%) cis/trans =3.8:1
6	 (**1f**)	 (**2f**, 95%)	 (**3f**, 25%)[d]

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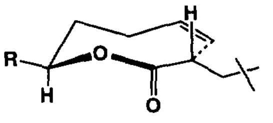
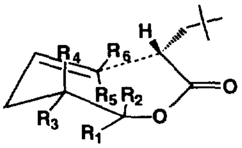
[a] Yield based on the corresponding acrylate **1** with toluene as the internal stantard. [b] Reaction condition: t-BuHgI (1.2 eq), KI (3 eq) and acrylate **1**(1 eq) were dissolved in DMSO-d6 and kept at r.t. for 30 min. [c] Reaction condition: Photolysis of **2** with Ph_2S_2 (2 eq) for 6-10 hours.[d] Major products are the disproportionation products of the uncyclized adduct radical.

The competitions of 8-endo/5-exo cyclizations are summarized in Table 2. Bicyclic products **5** are formed by 5-exo cyclization followed by subsequent cyclization in a 6-exo mode. The stereochemistry of **5** requires the cyclization to possess the transition state **8**. Now the substituent $R_2 =$ Me enhances the 5-exo cyclization (Thorpe-Ingold effect) while $R_4 =$ Me hinders cyclization. Thus, for the reaction of **1g**, both the conformation

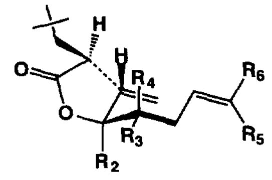
7 (R_1 = vinyl) and **8** ($R_2 = R_3 = R_4$ = H) are accessable and two cyclization products **3g** and **5g** are obtained in comparable amounts. For **1h** ($R_3 = R_4$ = Me), the methyl group R_4 destabilizes **8** and only 8-endo



6

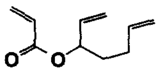
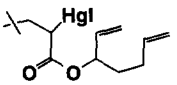
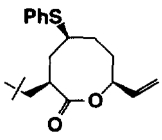
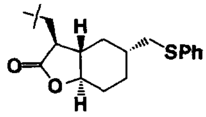
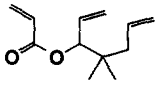
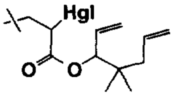
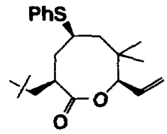
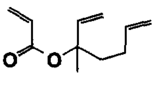
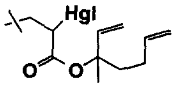
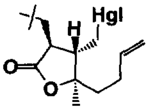
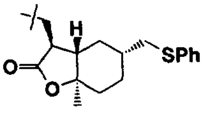
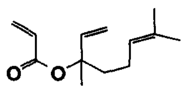
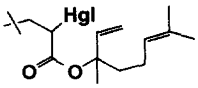
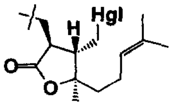
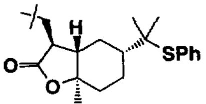
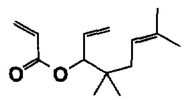
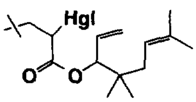
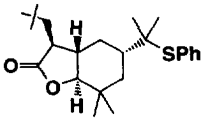


7



8

Table 2. 5-Exo/8-Endo Cyclizations of Acrylates **1**.

Entry	Acrylate 1	Adducts (Yield)[a,b]	Products (Yield)[a,c]
1	 (**1g**)	 (**2g**, 90%)	 (**3g**, 30%) +  (**5g**, 25%)
2	 (**1h**)	 (**2h**, 90%)	 (**3h**, 45%)
3	 (**1i**)	 (**2i**, 55%) +  (**4i**, 36%)	 (**5i**, 50%)
4	 (**1j**)	 (**2j**, 45%) +  (**4j**, 40%)	 (**5j**, 40%)
5	 (**1k**)	 (**2k**, 90%)	 (**5k**, 50%)

[a, b, c] See Table 1.

cyclization occurs. In the case of **1i,j**, the comformation **7** is destabilized by the methyl group R_2 and only product **5** could be isolated. In fact, the 5-exo cyclization reaction occurred even in the first stage of the reaction and both uncyclized intermediate **2i,j** and cyclized organomercurial **4i,j**[11] were obtained in comparable amounts. However, when R_2 becomes large, such as a t-butyl group, cyclization is no longer observed. Introduction of terminal methyl groups in **1k** eliminated the 8-endo cyclization observed for **1g** and the bicyclic product **5k** was the only product observed.

In conclusion, substitutions on the pentenoxy function of **1** play an important role in the 8-endo/5-exo cyclizations of acrylates **1**.[12]

Acknowledgement: We are grateful for the financial support provided by the National Science Fundation.

REFERENCES and NOTES

1. Russell, G.A. *Acc.Chem.Res.* **1989**, 22, 1-8.
2. The adduct **2** could be observed by the ^{1}H NMR monitoring of the reactions in DMSO-*d6*. They also reacted with NH_4I or $NaBH_4$ to give t-$BuCH_2CH_2CO_2R$ in almost quantitative yield.
3. Russell, G.A.; Li, C.; Chen, P. *J.Am.Chem.Soc.* **1995**, 117, 3645-3646.
4. Lee, E.; Yoon, C.H.; Lee, T.H. *J.Am.Chem.Soc.* **1992**, 114, 10981-10983.
5. Pirrung, F.O.H.;Hiemstra, H.;Speckamp, W.N.;Kaptein, B.;Schoemaker, H.E. *Synthesis* **1995**, 458-472.
6. Belletire, J.L.; Mahmoodi, N.O. *Tetrahedron Lett.* **1989**, 30, 4363-4366.
7. Clough J.M.; Pattenden, G.; Wight, P.G. *Tetrahedron Lett.* **1989**, 30, 7469-7472.
8. Hanessian, S.; Di Fabio, R.; Marcoux, J.-F.; Prud'homme, M. *J.Org.Chem.* **1990**, 55, 3436-3438.
9. Typical Procedure: 4-Pentenyl acrylate (**1a**, 70 mg, 0.5 mmol) was added to the solution of t-BuHgI (231 mg, 0.6 mmol) and KI (249 mg, 1.5 mmol) in DMSO (5 mL) and the solution was kept at room temperature for 30 min. PhSSPh (218 mg, 1.0 mmol) was added and the mixture was photostimulated for 10 h with a 275W fluorescent sunlamp. Water (40 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3X50 mL). The combined organic phase was washed with brine (40 mL) and dried over $MgSO_4$. After the removal of the solvent, the crude product was purified by thin layer chromatography on silica to give the pure product **3a** (53 mg, 35%) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ0.794 (9H, s), 0.942 (1H, dd, J=1.5, 10.5), 1.480-1.567 (1H, m), 1.699-1.965 (5H, m), 2.091 (1H, dd, J=3.9, 10.2), 2.475-2.546 (1H, m), 3.370-3.412 (1H, m), 4.001-4.049 (1H, m), 4.732-4.799 (1H, m), 7.186-7.363 (5H, m). ^{13}C NMR ($CDCl_3$) δ29.30, 30.66, 31.62, 32.99, 42.85, 44.48, 46.51, 47.65, 66.04, 126.97, 129.03, 131.40, 135.51, 179.94. EI-MS: m/z 306 (M^+, 18), 291(5), 197(100), 71(54). HRMS calcd for $C_{18}H_{26}O_2S$: 306.1654. Found: 306.1661.
10. NOE is observed in **3b,g,h** between the α-methine hydrogens and both other methine hydrogens. This NOE is not observed in the trans isomers of **3c** or **3e**.
11. The organomercurial **4i** or **4j** could be trapped by PhSeSePh (2 eq.) to give the corresponding monocyclized selenide compounds, whose stereochemistry was demonstrated by their NOESY spectra.
12. All the new compounds **3** and **5** gave satisfactory ^{1}H, ^{13}C NMR and HRMS.

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