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Stereochemical Control in Intramolecular Ene Reactions of Crotyl Propargyl Ether Systems

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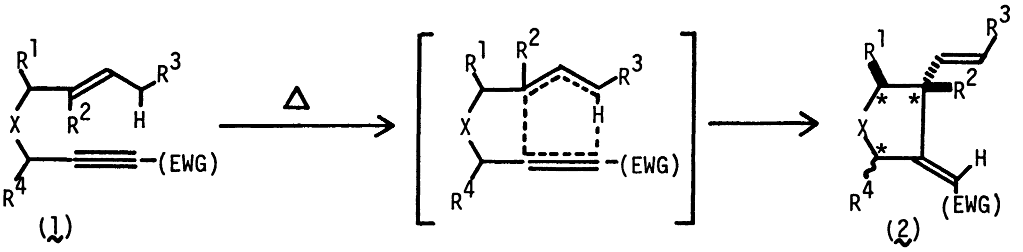
Stereochemical features are described of the title reactions leading to the γ-alkylidene-β-vinyloxolanes. Of particular interest is the high 1,2-trans diastereoselectivity observed for the (α-alkyl)crotyl and (α,β-dialkyl)crotyl ether systems with methoxycarbonyl group at the acetylenic terminus which remarkably facilitates the ene cyclization.

Recently the intramolecular ene reaction has been emerging as one of efficient tools for (carbo)cyclizations.1,2) However, the stereochemistry of this type of pericyclic reaction has not been fully explored, compared with mechanistically-related intramolecular Diels-Alder reactions.2) As part of a program designed to develop the intramolecular ene reaction into a new and stereoselective methodology for five-membered cyclization, we have been investigating the stereochemistry of the ene cyclization as formulated in Eq. 1, where an acetylenic bond acts as an internal enophile.3,4) Our major concerns are associated with stereocontrol over the newly created chiral centers. Disclosed herein are the stereochemical observations on the thermal ene cyclization of propargyl ether systems **1** [X=O] with and without methoxycarbonyl group at the acetylenic terminus.

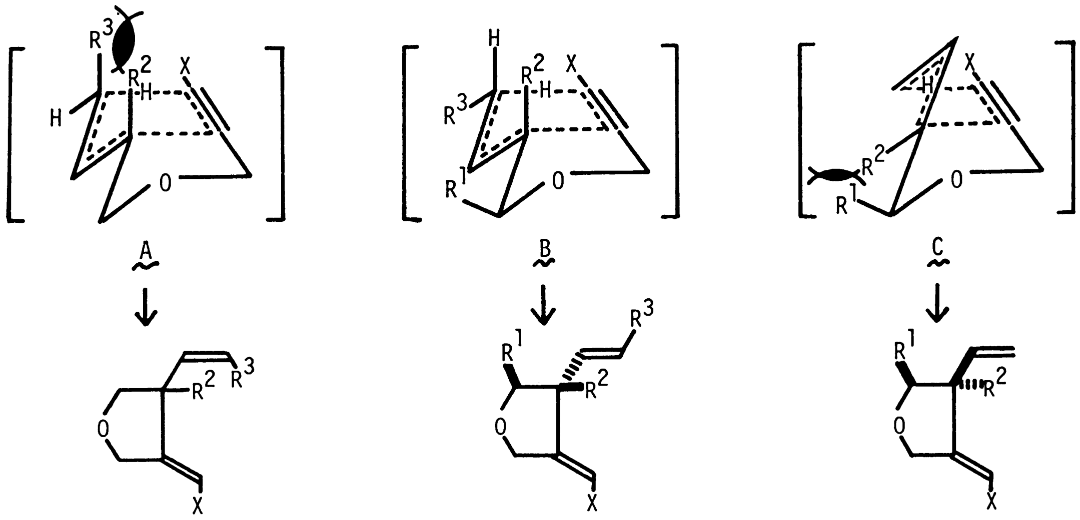


(1)

Substrate ethers (**1**) with a variety of substitution patterns were prepared by the standard methods5) and heated in toluene under argon atmosphere in sealed tubes. Table I summarizes the products and their stereochemistries, which reveal the following significant features of the present ene cyclization.

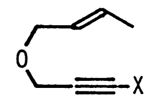
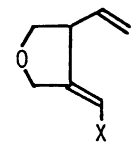
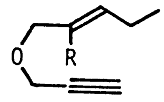
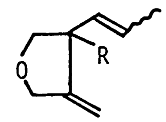
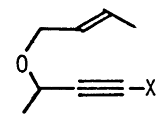
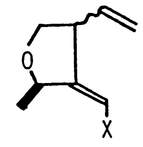
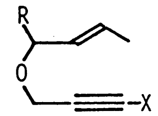
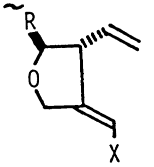
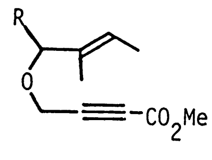
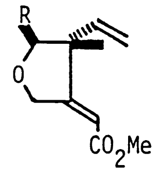
(a) The ene cyclization is remarkably facilitated by the introduction of methoxycarbonyl group at the acetylenic terminus (e.g., entry 1 vs. 2), as previously reported for related ene reactions.3c) (b) Entry 3 is of special interest because the formation of **2c** as a sole product indicates that the ene cyclization involving the acetylenic enophile prevails over the counterpart involving the olefinic enophile.6) (c) The ene cyclization results in the exclusive formation of (*Z*)-geometry with respect to the newly formed alkylidene part7) (e.g., entries 2 and 3). (d) With respect to the newly created vinylic part, on the other hand, relatively high levels of (*E*)-selection was observed (entries 4 and 5). Of particular interest is the remarkably enhanced (*E*)-selectivity observed in entry 5. (e) The ene cyclization provides only low levels of 1,3-asymmetric induction (entries 6 and 7). (f) In contrast, relatively high levels of 1,2-asymmetric induction, i.e., trans diastereoselection,8) were observed (entries 8-14). Particularly noteworthy is the remarkably high diastereoselectivity observed with the substrates bearing the bulky α-substituents (R^{1}) (entries 11-14). It should be noted here that quaternary centeres can be generated stereoselectively as observed with the (β-methyl)crotyl ether systems (entries 13 and 14).

Among these stereochemical observations, the trends (d) and (f) are of synthetic value and of mechanistic interest. The two trends are reasonably explicable in terms of the possible transition states (**A**, **B**, and **C**) as follows.



Of the two transition states **A** and **B**, the latter leading to the (*E*)-vinylic part is sterically more favorable since the former would suffer a large pseudo-1,3-diaxial repulsion of $R^{2}\leftrightarrow R^{3}$. The larger 1,3-repulsion in **A** (R^{2}=CH_3) than that in **A** (R^{2}=H) accounts for the enhanced (*E*)-selectivity observed for **1e**. Of the two transition states **B** and **C**, on the other hand, the endo transition state (**B**) leading to the trans-configuration is sterically less congested because the exo transition state (**C**) would suffer a gauche interaction of $R^{1}\leftrightarrow R^{2}$. The larger gauche repulsion in **C** (R^{1}=*i*-Pr or Ph) than that in **C** (R^{1}=CH_3) is responsible for the enhanced trans-selectivity observed for **1k**-**1n**. Thus, we believe that the bicyclic transition-state model might provide a guiding principle for explaining and predicting the stereochemistry of the present type of five-membered ene cyclization in general.

Table 1. Thermal Ene Cyclization of Ethers 1

Run	Substrate	Temp/°C	Time/h	Product[a)]		
					Yield/%[b)]	Stereochemistry
						
1	1a, X=H	250	6	2a	95	
2	1b, X=CO_2Me	200	1	2b	98	
3	1c, X=CH_3	250	17	2c	41	Only *Z*[c,d)]
						
4	1d, R=H	200	14	2d	93	87 : 13[e,f)]
5	1e, R=CH_3	200	48	2e	58	>95 : <5[e,f)]
						
6	1f, X=H	200	52	2f	83	60 : 40[c,g)]
7	1g, X=CO_2Me	170	24	2g	77	60 : 40[c,g)]
						
8	1h, X=H, R=CH_3	200	5.5	2h	73	76 : 24[c,h)]
9	1i, X=$SiMe_3$, R=CH_3	200	4.5	2i	71	81 : 19[c,h)]
10	1j, X=CO_2Me, R=CH_3	130	24	2j	90	86 : 14[c,h)]
11	1k, X=CO_2Me, R=*i*-Pr	130	24	2k	90	>95 : <5[h,i)]
12	1l, X=CO_2Me, R=Ph	130	24	2l	97	93 : 7[h,i)]
						
13	1m, R=*i*-Pr	130	24	2m	93	90 : 10[h,i)]
14	1n, R=Ph	130	24	2n	88	92 : 8[h,i)]

a) All the products were characterized by IR and ^{1}H and ^{13}C NMR. b) Isolated yield after column chromatography. c) Determined by ^{1}H NMR. d) The (*Z*)-geometry of the alkylidene part was proved by the single peak due to the methyl which appeared as a triple doublet (J=1.2 and 7.8 Hz). e) Determined by capillary GLC (XE-60, 30 m). f) Refers to the *E*/*Z* ratio for the vinylic part. The configuration of the major isomer (separated by preparative GLC) was assigned to *E* on the basis of IR absorption at 965 cm^{-1}. g) Stands for the diastereomeric ratio. No attempt was made to assign the stereochemistry. h) Refers to the trans/cis ratio. For the stereochemical assignments, see Ref. 8. i) Determined by HPLC (Zorbax SIL, hexane/ethyl acetate).

In summary, this work has now revealed the stereochemical features of the thermal ene cyclization leading to the five-membered rings. On the basis of these observations, we are currently investigating applications of this methodology to natural product synthesis.

References

1) Review: W. Oppolzer and V. Snieckus, Angew. Chem., Int. Ed. Engl., 17, 476 (1978).

2) D. F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions," Springer-Verlag, Berlin (1984).

3) No example has been reported for the ene cyclization of the present ether systems 1 [X=O]. However, a few reports have appeared on similar ene cyclizations of related substrates. a) 1 [X=C(CN)OSiR$_3$)]: G. Stork and G. Kraus, J. Am. Chem. Soc., 98, 6747 (1976); b) 1 [X=CH$_2$]: C. A. Townsend, T. Scholl, and D. Arigoni, J. Chem. Soc., Chem. Commun., 1975, 921; c) 1 [X=CH$_2$]: B. B. Snider and T. A. Killinger, J. Org. Chem., 43, 2161 (1978); d) 1 [X=NR]: W. Oppolzer, E. Pfenninger, and K. Keller, Helv. Chim. Acta, 56, 1807 (1973).

4) For a similar ene-type cyclization of 1 [X=C(CO$_2$Me)$_2$ or NR] catalyzed by palladium complexes, see: B. M. Trost and M. Lautens, J. Am. Chem. Soc., 107, 1781 (1985); Tetrahedron Lett., 26, 4887 (1985); B. M. Trost and S.-F. Chen, J. Am. Chem. Soc., 108, 6053 (1986).

5) K. Mikami, K. Azuma, and T. Nakai, Tetrahedron, 46, 2303 (1984). For the method for the introduction of methoxycarbonyl group at the acetylenic terminus, see: M. J. Taschener, T. Rosen, and C. H. Heathcock, Org. Synth., 64, 108 (1985).

6) The higher enophilic reactivity of acetylenic bond than that of olefinic bond is precedented (cf. Ref. 3c).

7) The (Z)-selectivity is consistent with the "cis-addition principle" widely accepted for the ene reaction in general: H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., 8, 556 (1969).

8) The trans-configuration of the major diastereomer was assigned through comparison of its ^{13}C NMR spectrum with that of the minor diastereomer. The configuration of the isomer of which C_α resonates at lower fields was assigned to trans on the basis of the ^{13}C NMR trends reported for closely-related oxolane derivatives: E. L. Eliel, V. S. Rao, and K. M. Dietrusiewicz, Org. Magn. Reson., 12, 461 (1979). The δ-values of C_α for the trans and cis isomers are as follow; 2h: 80.19, 78.35; 2i: 79.48, 77.48; 2j: 78.94, 77.05; 2k: 87.61, 87.39; 2l: 84.57, 82.73.
The trans-configuration of the major diastereomer of 1m was ascertained by 500 MHz 2-D NOE spectroscopy (NOESY), where a cross peak between the α-methine proton and the vinylic proton was observed. In contrast, the cross peak was not observed in the NOESY of the minor cis-1m.
The major diastereomer of 1n of which the β-methyl ^{1}H NMR signal appears at a remarkably higher field was assigned to the trans isomer on the basis of a ring-current effect of the benzene nucleus.

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