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CARBANION-ACCELERATED CLAISEN REARRANGEMENTS 3.
VICINAL QUATERNARY CENTERS

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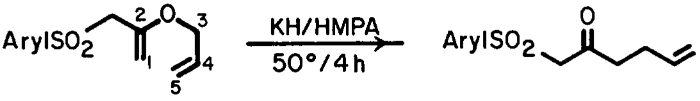
Summary: The preparation and Claisen rearrangement of highly substituted allyl vinyl ethers is described. It is demonstrated that the thermal and anionic versions of the Claisen rearrangement are capable of creating vicinal quaternary centers.

It has been recognized for many years that the aliphatic Claisen rearrangement[1] owes much of its success to a highly favorable enthalpy of reaction (ΔH° - 15 kcal/mol) arising, primarily from the carbon-oxygen double bond energy.[2] This effect is even more pronounced in modern variants[1d,e] which transform ketene acetals into carboxylic acid derivatives. The carbanionic Claisen rearrangement, eq 1, recently documented in these laboratories,[3] is expected to partake of this thermodynamic driving force in still greater measure by virtue of a drop in *ca.* 10 pKa units[4] for **1** to **2**. Thus, the anionic charge not only provides accelerating potential[5] but also contributes to the exothermicity of the reaction.

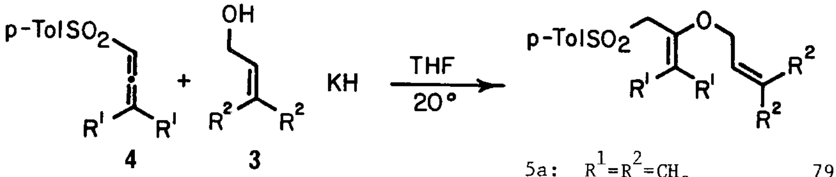


1 **2** (1)

In a recent communication Ponaras[6] has demonstrated a delicate enthalpy balance in the Claisen rearrangement of sterically demanding diosphenol allyl ethers and their carbomethoxyhydrazones. We wish to point out that the aliphatic Claisen rearrangement in both anionic and thermal modes has significant and unrecognized potential for creating vicinal quaternary centers[7] and other strained systems.[8]

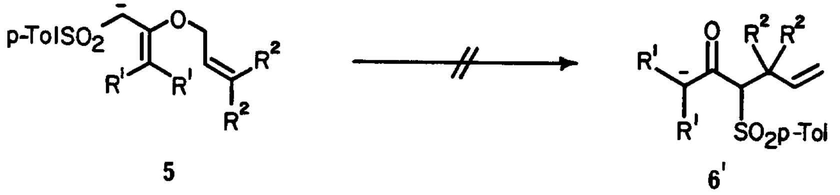
The substrates employed in this study are the tetrasubstituted allyl vinyl ethers **5** prepared as shown in equation 2. Two equivalents of the requisite allylic alcohol **3** (based on sulfone) were added to 0.25 eq of KH (based on sulfone) suspended in THF at 20°C. When the evolution of hydrogen ceased the allenic sulfone, **4**,[11,12] was added. The products **5a**-**d**[11] were isolated by aqueous workup and chromatography in generally good yields.

The results of rearrangements of **5a**-**d** are collected in the Table. Lithium dimsylate was used uniformly as base since each substrate has cis oriented groups in the allyl portion which promote an undesirable side reaction with other counterions.[3b] In each case the Claisen product **6**[11] was smoothly formed as a single regioisomer in very good yield. A moderate rate retardation is noted in changing from methyl to pentamethylene substituents which is slightly more pronounced at C(1) than C(5). Nonetheless it is interesting to note that <u>the net effect of substitution in this manner is accelerating</u>. Anionic rearrangement of the parent sulfone, **1**, requires 4h at 50°C under comparable conditions.[3a,13] The absence of any regioisomer **6'** in these rearrangements is striking in view of the ambident nature of the allyl anion. This



(2)

5a:	$R^1=R^2=CH_3$	79%
5b:	$R^1=CH_3$; $R^2=(CH_2)_5$	88%
5c:	$R^1=(CH_2)_5$; $R^2=CH_3$	84%
5d:	$R^1=R^2=(CH_2)_5$	54%



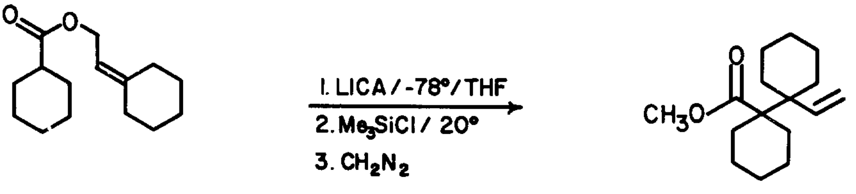
(3)

is yet another manifestation of the thermodynamic driving force associated with the β-keto sulfone anion. In this case the normal rearrangement is even more favorable since the disubstituted allyl anion is *ca.* 3 pka units more basic.[4b] The alternative rearrangement avoids the steric repulsion but produces a simple ketone enolate.

The ease of rearrangement and complete conversion to **6** via anions is noteworthy. However, we have found that **6a** is thermally stable at 150-170°C (0.025 Torr) and **5d** rearranges quantitatively to **6d** in the <u>absence of base</u> (entry 5)! Thus, it is clear that: 1) the strain energy associated with the vicinal quaternary centers in **6a-d** is insufficient to counterbalance the normal enthalpic advantage of rearrangement under any conditions, 2) the strain energy also does not provide a serious kinetic barrier to rearrangement and 3) the strain energy does not offset the normal regiochemical course expected on thermodynamic grounds.

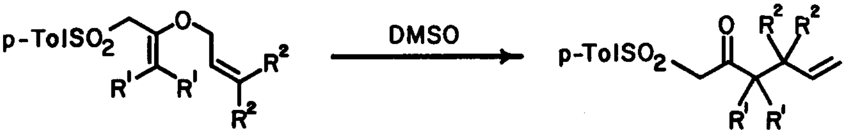
For the purpose of comparison we have also briefly investigated Ireland's ester enolate variant[14] in a similarly demanding test,[15] eq 4. The ester **7**[11] was prepared in 90% yield by reaction of cyclohexylidenemethanol with cyclohexanecarboxylic acid chloride. Rearrangement was effected by stirring the trimethylsilyl ketene acetal[14b,16] (lithium cyclohexylisopropylamide/-78°/THF/Me_3SiCl) for 2 h at 20°C followed by the usual workup. The Claisen rearrangement product **8**[11] was isolated as the methyl ester (CH_2N_2) in 76% yield after chromatography.

In conclusion we have shown that the Claisen rearrangement is a viable reaction for the creation of vicinal quaternary centers ultimately, perhaps, with the expected level of stereocontrol. These results presage an investigation of still-more-highly substituted systems, **5**,



7 8 (4)

in order to establish the limit at which the thermal Claisen is an unfavorable process in the forward direction, while the corresponding anion rearranges completely.



5 6

Table. Claisen Rearrangements of 5a-d[a]

entry	substrate	base (equiv)[b]	temp, °C	time, min	yield,[c] %
1	5a	KH (2.5)/LiCl (16)	50	15	98
2	5b	KH (2.6)/LiCl (12)	50	30	82
3	5c	KH (3.1)/LiCl (14)	50	45	77
4	5d	KH (3.3)/LiCl (14)	50	75	87
5	5d	none	135	90	100

(a) Anionic reactions were run under rigorous exclusion of moisture and oxygen. The reactions were run at 0.09-0.10 M concentrations and were homogeneous throughout. Reaction progress was monitored by TLC until complete and then worked up in the usual way. The products were purified by flash chromatography on silica gel and recrystallized. (b) Lithium dimsylate was prepared freshly from hexane-washed KH at 20°C. (c) Yields of products after chromatographic purification.

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≠Eastman Kodak Graduate Fellow 1981-1984.

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(11) This compound was fully characterized by ^{1}H NMR (220 or 360 MHz), IR and mass spectrometry as well as satisfactory microanalytical data (±0.3%).

(12) The allenic sulfones **4a** ($R^1=CH_3$) and **4c** ($R^1=(CH_2)_5$) were prepared by [2,3] rearrangement (CCl_4, reflux) of the corresponding propargylic sulfinates available in high yield by treatment of the acetylenic carbinols with p-toluenesulfinyl chloride in pyridine.

(13) Qualitative rate studies have shown only minimal differences between HMPA and DMSO for K^+, Na^+ and Li^+ species.

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(15) Ireland has demonstrated the use of this reaction to create vicinal quaternary-tertiary centers with stereocontrol in the context of the synthesis of Lasalocid A. Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivong, S.; Wilcox, C. S. *J. Am. Chem. Soc*. **1983**, *105*, 1988. See also ref. 7.

(16) Rearrangement of the lithium enolate proceeded in poorer yield and was accompanied by the formation of byproducts derived by cyclohexylidene ketene.

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