Carbanion-Accelerated Claisen Rearrangements. 2. **Studies on Internal Asymmetric Induction**

Summary: The stereochemical course of Claisen rearrangements of 2 and 3 in the thermal and anionic modes has been studied. The carbanionic processes were shown to be highly stereoselective and dependent upon solvent, counterion, and temperature.

Sir: In a previous communication¹ we demonstrated the rate-accelerating effect of a carbanion in the Claisen rearrangement² (eq 1). The effects of methyl substitution

$$\operatorname{AryISO}_{2} \prod_{i=1}^{2} \prod_{j=1}^{0} \prod_{j=1}^{3} \frac{1. \text{ KH/HMPA}}{50^{\circ}/4 \text{ h}} \quad \operatorname{AryISO}_{2} \prod_{j=1}^{0} 78 \% (1)$$

at C(1), C(3), C(4), and C(5) on the rate of the rearrangement were found to correlate well with those reported for Ireland's ester enolate variant.³ Further, methyl substitution at C(3) gave rise, stereospecifically, to a product with the expected E double-bond geometry.^{3,4} While these observations bode well for the synthetic utility of this process, the most important characteristic of Claisen rearrangements was not addressed, namely, the ability to create vicinal asymmetric centers in a predictable fashion. Such behavior is a hallmark of [3,3]-sigmatropic rearrangements⁵ and has been convincingly documented in the Claisen rearrangement by Schmidt,^{6a,b} Sucrow,^{6c,d} Ireland,^{3,6e} and Bartlett.^{6f} We wish to report that carbanion-accelerated Claisen rearrangements are as stereoselective as their thermal counterparts.

The substrates employed in this study, 2^7 and 3^7 (eq 2),



were selected for ease of synthesis and to facilitate the stereochemical assignment of products. Stirling⁸ has demonstrated that kinetically controlled addition of nucleophiles to sulforyl allenes affords β,γ -unsaturated

(1) Denmark, S. E.; Harmata, M. A. J. Am. Chem. Soc. 1982, 104, 4972

(2) Subsequent to the appearance of our first communication, we were informed of an earlier experiment in which sodium allyl oxide reacted at room temperature with an allenyl phosphonate to give a regioisomeric mixture of Claisen rearrangement products: cf. Cooper, D.; Trippet, S. J. Chem. Soc., Perkin Trans. 1 1981, 2127. We thank Professor Trippett for bringing this to our attention.

(3) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. 1976, 98, 2868.

(4) Katzenellenbogen, J. A.; Christy, K. J. J. Org. Chem. 1974, 39, 3315.

(5) For recent reviews, see; (a) Bartlett, P. A. Tetrahedron 1981, 36, (b) Ziegler, F. E. Acc. Chem. Res. 1977, 10, 227. (c) Bennett, G. B. Synthesis 1977, 589. (d) Rhoads, S. J.; Raulins, R. N. Org. React. (N.Y.)

1975, 22, 1. (6) (a) Vittorelli, P.; Hansen, H.-J.; Schmidt, H. Helv, Chim. Acta Hahne, W. F. J. Org. Chem. 1979, 44, 882.

(7) This compound has been fully characterized by ¹H NMR (220 or 360 MHz), IR, and mass spectroscopy as well as combustion analysis (±0.3%).

(8) (a) Stirling, C. J. M. J. Chem. Soc. 1964, 5856, 5863. hailova, V. N.; Yurevich, V. P.; Bulat, A. D. J. Org. Chem. USSR (Engl. Transl.) 1978, 14, 213. (c) For a recent review on nucleophilic addition to allenes, see: Landor, S. R. In "The Chemistry of Allenes"; Landor, S. R., Ed.; Academic Press: New York, 1982; Vol. 2, pp 361-397.

sulfones. Thus, base-catalyzed addition of (E)- and (Z)-crotyl alcohol⁹ to 1-(p-tolylsulfonyl)-1,2-butadiene¹⁰ gave 2 and 3, respectively, in which the enol ether double bond was expected to be E on the basis of a least-hindered-approach model of attack at the central carbon.^{11,12}

The results of rearrangements of 2 and 3 are collected in Table I. For calibration of the stereoselectivity of carbanionic rearrangements, the thermal Claisen process was performed for comparison (Table I, entries 1 and 5). Both 2 and 3 rearranged smoothly and with high stereoselectivity to 4⁷ and 5,⁷ respectively.¹⁴ The carbanionic rearrangement of 2 in Me_2SO^{17} also proceeded in good yield under milder conditions and with comparable or better stereoselectivity (entry 3). Different counterions only marginally influenced the stereoselectivity in the order $K^+ < Na^+ \sim Li^+$. Carbanionic rearrangement of 3 was plagued by a side reaction which produced 1-(p-tolylsulfonyl)-2-butanone (9) in considerable amounts (entries 6 and 7). However, this side reaction could be completely suppressed by using lithium dimsylate¹⁸ as the base, resulting in a highly selective, clean rearrangement.¹⁹ Thus, while the selection of counterions is critical for a successful reaction, the stereoselectivity is again little perturbed; i.e., $K^+ < Na^+ \sim Li^+$.

The effects of solvent and temperature on the selectivity of the rearrangement were investigated next. Entries 9 and 10 show that neither HMPA nor THF improved the selectivity in rearrangement of K^+2^- . With K^+3^- in THF the selectivity improves (compare entry 6) but the yield is still poor. Finally, we have found that short reaction times at slightly elevated temperatures (compare entries 3, 12, and 13) are the optimum conditions for obtaining the highest yield and stereoselectivity.

The complementarity of stereochemical outcome of carbanionic rearrangements of 2 and 3 is in full accord with the established dogma of a chairlike transition state for this family of reactions.^{5,6,20} Further insight into the nature of the transition state may be gleaned by com-parison of entries 1, 5, 7, and 13. The slower rate of thermal rearrangement of 3 vs. 2 (2-fold) is expected due

(5) (L)- and (L)-crotyl alconol were prepared according to literature methods and were 99% pure by GC analysis.
(10) (a) Smith, G.; Stirling, C. J. M. J. Chem. Soc. C 1971, 1530. (b) Braverman, S.; Mechoulam, H. Tetrahedron 1974, 30, 3883.
(11) The homogeneity of 2 and 3 was assured by sharp melting points (2, mp 86.7-88.0 °C; 3, mp 62.0-62.7 °C) and ¹H and ¹³C NMR spectraecov. troscopy

(12) Similar arguments have been invoked in the addition of cuprates to sulfonyl, sulfinyl, and phosphinyl allenes^{13a-c} and addition of alcohols to allenyl sulfoxides^{13d} and keteniminium ions.^{6f}

(13) (a) Koosha, K.; Berlan, J.; Capmau, M.-L. Comp. Rend. Acad. Sci., Ser. C 1973, 276, 1633. (b) Koosha, K.; Berlan, J.; Capmau, M.-L.; Chodkiewicz, W. Bull. Soc. Chim. Fr. 1975, 1291. (c) Berlan, J.; Battioni, J.-P.; Koosha, K. Tetrahedron Lett. 1976, 3351. (d) Van Rheenan, V.; Shepard, K. P. J. Org. Chem. 1979, 44, 1582.

(14) The assignment of u (R^*, R^*) and l (R^*, R^*) stereochemistry¹⁵ to 4 and 5, respectively, was achieved by desulfonylation¹⁶ (Al(Hg), THF/ HOAc/H₂O) to u-(6)⁷ and l-(7)⁷ diastereomers of 3,4-dimethyl-1-hexen-5-one, which were identified by GC comparison with authentic samples. (15) Prelog, V.; Seebach, D. Angew. Chem., Int. Ed. Engl. 1982, 21, 654

(16) Johnson, C. R.; Kirchoff, R. A. J. Am. Chem. Soc. 1979, 101, 3602. (17) Qualitative rate studies on the carbanionic rearrangement showed

only minimal differences between HMPA and Me_2SO for Li⁺, Na⁺, and K⁺. We have therefore abandoned the use of HMPA or originally reported.1 (18) Lithium dimsylate was prepared by dissolving excess anhydrous

lithium chloride in a solution of potassium dimsylate in Me₂SO. Reactions with lithium dimsylate prepared from n-BuLi were less selective. (19) The origin of 9 is as yet unclear. Presently we favor an intra-

molecular E2 elimination of butadiene. Suppression of this pathway by use of the less basic (more covalent) lithium species is consistent.

(20) For exceptions, see: Bartlett, P. A.; Barstow, J. F. Tetrahedron Lett. 1982, 623 and references cited therein.

[†]Eastman Kodak Graduate Fellow, 1981-1984.

⁽⁹⁾ (E)- and (Z)-crotyl alcohol were prepared according to literature

Table I. Carbanionic Claisen Rearrangements of 2 and 3^a

0 CH3 0 CH3

$\xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{R^2} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{CH_3} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{CH_3} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{CH_3} \xrightarrow{CH_3} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{C} \xrightarrow{H_3} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{P^{-}\text{To} SO_2} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} \xrightarrow{Q} Q$							
		R' 2 or 3	4		5		
entr	y substrate	base (equiv) ^b	solvent	temp, °C	time, h	4:5 ratio ^c	yield, ^d %
1	2	none	Me,SO	100	4	96:4	97
2	2	KH (2.2)	Me SO	20 ^e	4	93:7	79 ^f
3	2	NaH (2.2)	Me.SO	20 ^e	4	98:2	85
4	2	KH (2.2)/́LiCl (4.2)	Me ₂ SO	20 ^e	4	97:3	73
5	3	none	Me,SO	100	8	4:96	89
6	3	KH (2.1)	Me,SO	20 ^e	6.75	14:86	7^{f}
7	3	NaH (2.2)	Me _s SO	50	3	6:94	64 ^{<i>f</i>}
8	3	KH (2.6)/́LiCl (15)	Me ₂ SO	50	1.5	6:94	85
9	2	KH (2.2)	THF	20	24	89:11	78
10	2	KH (2.1)	HMPA	20	2	64:36	83
11	3	KH (1.9)	\mathbf{THF}	20	23	7:93	19 ^{<i>f</i>}
12	2	NaH (2,2)	Me ₂ SO	20	6	95:5	57
13	2	NaH (2.2)	Me ₂ SO	50	0.25	98:2	93

^a All anionic reactions were done under rigorous exclusion of moisture and oxygen. The reaction were run at 0.09-0.12 M concentrations and were homogeneous throughout. Reaction progress was monitored by TLC until complete and then worked up by aqueous extraction in the usual way. The products were purified by flash chromatography on silica gel. ^b Potassium and lithium dimsylate were prepared freshly from hexane-washed KH at 20 °C (see ref 18). Sodium dimsylate was prepared freshly by warming hexane-washed NaH in Me₂SO to 65 °C for 40 min and cooling to 20 °C. ^c Ratios were determined by analytical HPLC (UV detection, 250 nm). ^d Yields of products after column chromatographic purification. ^e The completion of this run was difficult to discern due to an unknown side product that was coincident with starting material. Heating to 50 °C for 2-5 min assured complete conversion. ^f 9 was isolated in this run: entry 2, 13%; entry 6, 65%; entry 7, 24%; entry 11, 28%.



to pseudo-1,3-diaxial interactions between $CH_3C(5)$ and the sulfonylmethylene group. The carbanionic rearrangement of 3 is 12 times slower than that of 2, suggesting a more serious interaction probably due to the strong association with the metal ion and its attendant solvent molecules.

The high stereoselectivity of these rearrangements is striking. Originally we perceived two pitfalls, either of which could destroy stereoselectivity. The first concerned the geometrical integrity of the stabilized allyl anion i



and the second an ex post facto epimerization requiring only equilibrium quantities of dianion ii. Unfortunately, very little information is available concerning structures and rotational barriers of sulfonyl-stabilized allyl anions.^{21,22} Rotation about the C(1)-C(2) bond is stereochemically crucial and we must conclude that either (1) the barrier is extremely high or (2) the E geometry as shown is strongly favored at equilibrium. The relative orientation of the p-toluenesulfonyl group (C(2)–C(6) geometry) is unknown at present, as is its importance in cation chelation or its indirect influence on the C(1)-C(2)geometry. Finally, it is clear that species ii are not accessible in Me₂SO even in the presence of excess base.²³

The results reported herein provide a firm foundation for the investigation of rearrangements employing chiral carbanions and studies on the structure of heteroatomstabilized anions which will be the subject of future reports.

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Registry No. 2, 87039-98-3; 3, 87039-99-4; 4, 87040-00-4; 5, 87040-01-5;]-(p-toluenesulfonyl)-1,2-butadiene, 32140-55-9; lithium dimsylate, 57741-62-5; trans-crotyl alcohol, 504-61-0; cis-crotyl alcohol, 4088-60-2; KH, 7693-26-7; NaH, 7646-69-7; LiCl, 7447-41-8.

(23) The low stereoselectivity of the rearrangement of K^+2^- in HMPA may well be due to the existence of ii in this solvent.

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Synthesis of Dehydrooogoniol, a Female-Activating Hormone of Achlya

The structure of dehydrooogoniol Summary: $(3\beta,11\alpha,15\beta,29$ -tetrahydroxystigmasta-5,24(28)(E)-dien-7one), a female-activating hormone of the water mold Achlya, has been confirmed by synthesis. The starting material was progesterone, which was converted to the 11α , 15β -dihydroxy derivative by microbiological hydroxylation with Aspergillus giganteus (ATCC 10059). The side chain was constructed in a stepwise manner by

^{(21) (}a) Biellmann, J. F.; Ducep, J.-B. Org. React. (N.Y.) 1982, 27, 1.
For studies on the structure of sulfenyl-stabilized anions, see: (b) Biellmann, J. F.; Ducep, J. B. Tetrahedron 1971, 27, 5861. (c) Hartmann, J.; Muthukrishnan, R.; Schlosser, M. Helv. Chim. Acta 1974, 57, 2261. (22) (a) Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978; pp 36-90. (b) Bordwell, F. G.; Branca, J. C.; Johnson, C. R.; Vanier, N. R. J. Org. Chem. 1980, 45, 3884 and references cited therein cited therein.