of (−)-carvone, the absolute configuration of the natural product should be opposite of that shown (vide supra). The highly stereocontrolled synthesis proceeded in 17 steps from (−)-carvone in 3.5% overall yield (average yield/step 82%) without the use of protecting groups. Studies are currently under way to improve the sequence as well as to investigate the isopropenyl to ester conversion and will be reported in due course.

Acknowledgment. We thank Professors Leo Paquette and David Hart of The Ohio State University for their assistance in obtaining some of the optical rotations. We also thank Dr. Dick Weisenburger of The Ohio State University Chemical Instrument Center for the high-resolution mass spectrum of (−)-upial. In addition, we thank Everett Santee for aid in obtaining the high-field NMR spectral data and the NSF (Grant DMR-82-194454) for funds for the 400-MHz spectrometer. Lastly, we acknowledge Professors P. J. Scheuer and S. C. Welch for the exchange of experimental and spectral data.

Anionic Oxy-Claisen Rearrangement of Enolates of α-Allyloxy Ketones. A Remarkable Rate-Accelerating Effect Exhibited by the Nature of the Counterion

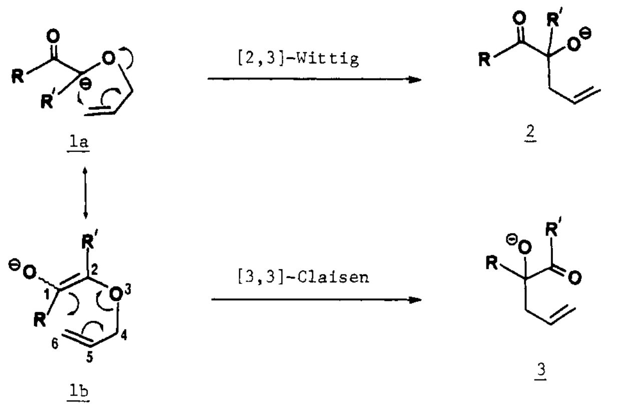
Masato Koreeda* and Juan I. Luengo

Department of Chemistry, The University of Michigan
Ann Arbor, Michigan 48109

Received May 31, 1985

Sigmatropic rearrangements have proven to be powerful, invaluable tools in the stereo- and regiochemically controlled synthesis of a wide range of natural products.[1] In recent years, considerable attention has been focused on substituent effects of these reactions as variants that lead to milder conditions and improved stereoselective outcome.[2] Concurrent to these synthetic investigations, there have been a number of theoretical studies which attempt to correlate the nature of the substituent effect with the mechanism of the sigmatropic reaction.[3] We wish to report herein a potentially highly versatile, novel type of Claisen rearrangement, termed an *anionic oxy-Claisen rearrangement*, utilizing enolates of α-allyloxy ketones, that proceeds at strikingly low temperatures. Furthermore, the reaction was found to be dramatically influenced by the counterion and the solvent employed.

Scheme I



Scheme II

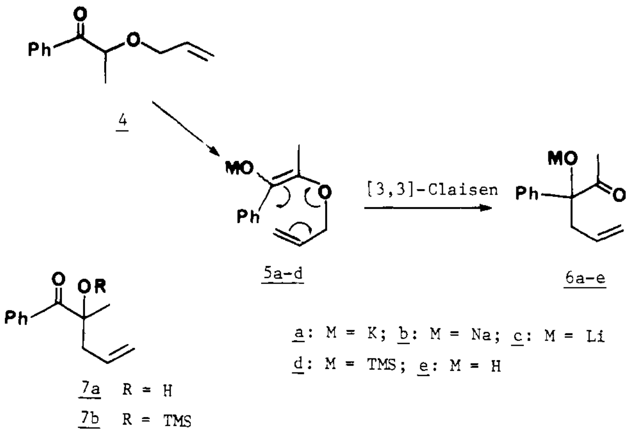


Table I. Results of [3,3]-Claisen Rearrangements of Enolates **5a–c** and Silyl Enol Ether **5d**[a]

entry	solvent	compd	temp, °C	half-life ($t_{1/2}$), h[b]
1	toluene	**5a**, M = K	−23	3.3
2	toluene	**5b**, M = Na	0	2.6
3	toluene	**5c**, M = Li	96.5	1.1
4	toluene	**5d**, M = Me_3Si	71	0.5
5	THF	**5a**, M = K	−42	6.2
6	THF	**5a**, M = K	−23	<0.1
7	THF	**5b**, M = Na	−23	2.4
8	THF	**5c**, M = Li	67	1.3

[a] All the reactions were carried out at 0.025 M concentration of substrates by treatment with 15 equiv of metal hydride and 10 equiv of methanol. [b] Times listed for **5a–c** refer to half-lives derived from the first-order rate constants obtained in the range of 10–90% conversion of **4**. All the reactions of **5a–c** except for entry 6 were preceded by an induction period (0.5–1.5 h) which is believed to account for the generation of the enolates from **4**.

The enolates of α-allyloxy ketones present an intriguing case where two competing modes of sigmatropic rearrangement processes are conceivable (Scheme I). Thus, of the two resonance forms of these enolates, **1a** may be envisioned as an α-(allyloxy) α-carbanion which is capable of undergoing a [2,3]-Wittig rearrangement to give rise to α-alkoxy ketone **2**.[4] Whereas **1b** may

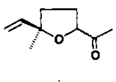
---

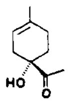
[1] (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *ACS Monogr.* **1983**, *180*. For reviews on [3,3]-sigmatropic rearrangements, see: (b) Rhoads, S. J.; Raulins, N. R. *Org. Reac.* (*N. Y.*) **1975**, *22*, 1. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. For a review on [2,3]-sigmatropic rearrangements, see: (f) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. For mechanistic studies of sigmatropic rearrangements, see: (g) Gajewski, J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981.

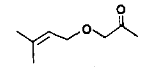
[2] Electron-donor substituents at carbons 1, 2, and 6 have an accelerating effect on the Claisen rearrangement. 1-Donor: (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427. 2-Donor: (b) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030. (c) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 471. (d) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (e) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (f) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866. 6-Donor: (g) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002. (h) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276. 1,2-Bisdonor: (i) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (j) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. Both electron-acceptor and electron-donor substituents at carbon 3 accelerate the Cope rearrangement: (k) Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 211. (l) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

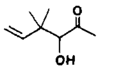
[3] (a) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877. (b) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984. (c) Delbecq, F.; Anh, N. T. *Nouv. J. Chim.* **1983**, 505. (d) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (e) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11. (f) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.

[4] Two examples of [2,3] Wittig rearrangement of the enolates of acetonyl allyl ethers to 3-hydroxy 5-en-2-ones have been reported by Thomas and Dubini (Thomas, A. F.; Dubini, R. *Helv. Chim. Acta* **1974**, *57*, 2084). Thus treatment of ketone i with Grignard reagents or potassium tert-butoxide


i

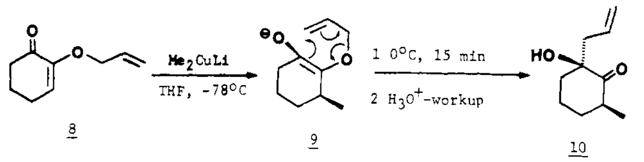

ii


iii


iv

resulted in the formation of compound ii. Although in this particular example the corresponding [3,3]-Claisen rearrangement is not feasible due to the rigidity of the system, the authors extended the method to the acyclic ketone iii. The reaction of iii with potassium *tert*-butoxide gave iv (product of [2,3] rearrangement) as the only isolable product.

Scheme III

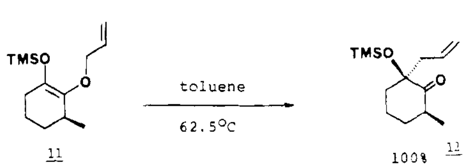


be viewed as a 1-oxy-3-oxa-1,5-hexadiene and may undergo a [3,3]-Claisen rearrangement providing the isomeric α-alkoxy ketone **3**. The latter process is particularly unique as it corresponds formally to an intramolecular S_N2' addition to an allylic ether by the carbon bearing the enolate oxygen.

The system that we have examined extensively is α-(allyloxy)propiophenone (**4**)[5] in which the ketone bears a single acidic hydrogen. Treatment of **4** with excess metal hydride (total 2–15 equiv) in the presence of a small amount of methanol (1–10 equiv) effected the quantitative conversion of the resulting enolate **5a**, **5b** or **5c** to the hydroxy ketone **6e** after aqueous quenching. This indicates that the rearrangement through the [3,3]-Claisen mode is clearly favored in this system (Scheme II). In the range of 10–90% conversion of **4**, the reaction was found to follow the first-order kinetics.[6] Only a trace amount of the product **7a** (<2%), resulting from the [2,3]-Wittig rearrangement, was detectable in all cases except for those using lithium hydride in toluene at 96.5 °C and in THF at reflux (entries 3 and 8 in Table I, respectively), where **7a** comprised up to 20% of the product mixture.[7]

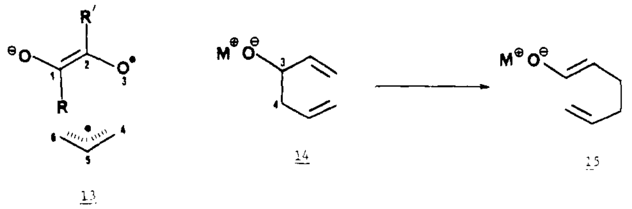
The results summarized in Table I show that there is a dramatic rate acceleration of the reaction as a function of the electron-donating ability of the OM group at C-1. Thus, while the rearrangement proceeded smoothly at −23 °C with potassium hydride in toluene, virtually no rearrangement reaction was observable at the same temperature with sodium hydride in toluene. Somewhat surprisingly, the rearrangement using lithium hydride in toluene required temperatures as high as 90 °C, which were even higher than those required for the rearrangement of the corresponding silyl enol ether **5d**. A similar propensity for rate acceleration was observed in the marked dependence of the rate of the rearrangement on the solvent employed. When THF was used as a solvent at the same concentration in lieu of toluene, the conditions required for the rearrangement were even milder (entries 5–8). The potassium enolate **5a** in THF was found to undergo [3,3]-Claisen rearrangement even at −42 °C. To our knowledge, this represents by far the lowest temperature ever recorded for a Claisen rearrangement of any type.

We have also developed, as an application of this novel Claisen rearrangement, a tandem 1,4-conjugative addition–Claisen rearrangement sequence using 2-(allyloxy)-2-cyclohexenone (**8**)[8] (Scheme III). Thus, treatment of **8** with 1 equiv of lithium dimethyl cuprate in THF at −78 °C followed by warming of the resulting enolate **9** to 0 °C resulted, within 15 min, in the smooth formation of the hydroxy ketone **10** as a single stereoisomer in virtually quantitative yield. As expected, the corresponding silyl enol ether **11** required a temperature as high as 62.5 °C to achieve a half-life of 1.6 h in its rearrangement to **12**.[9]



The remarkable rate acceleration in the [3,3]-Claisen rearrangement delineated above is clearly a manifestation of the effect exerted by the alkoxy anion over the transition state of the reaction. Theoretical studies have postulated that the Claisen rearrangement proceeds via an early transition state which resembles a radical pair arising from homolytic cleavage of the O3–C4 bond.[3f] Application of this concept to the present system would provide an allyl radical and an oxy–oxaallyl radical–anion pair **13**. Interestingly, the latter is in fact a semidione,[10] a stable radical anion obtainable by one-electron reduction of an α-dione, which can also be viewed as a vinylogous organic derivative of the superoxide ion.[11] Therefore, it may be reasonable to attribute the observed rate-accelerating effect, to a significant extent, to the contribution of this exceptionally stable radical anion **13** to the transition state of the reaction.

It is of interest to recognize the analogy between the present system and the well-known case of the anionic oxy-Cope rearrangement. Evans and Golob[21] observed a similar rate-accelerating effect as the donor properties of the alkoxy group were increased in the [3,3]-sigmatropic rearrangement of the metal alkoxide **14** to the enolate **15**. The bond-forming processes are in opposite directions in these two reactions due to the inherent bias exerted by the oxygen of the allyl ether. However, the mechanistic aspects operating on the transition states of both systems are strikingly similar with regard to the effect of the metal alkoxide group. For the anionic oxy-Cope rearrangement, it has been proposed that the oxy substituent has the effect of decreasing the adjacent bond strength, thereby stabilizing the transition state by weakening the C3–C4 bond which is formally cleaved in the process.[12] This postulate should be extendable to the present Claisen process **1b** → **3** as the oxy anion at C1 in **1b** is "vinylogously" adjacent to the O3–C4 bond and thus should also exert a similar debilitating effect on this bond, resulting in the rate acceleration of the reaction. Accordingly, we propose to name this novel type of Claisen variant an "anionic oxy-Claisen rearrangement".



In summary, we have demonstrated that the novel anionic oxy-Claisen rearrangement described herein represents a unique process which proceeds at unprecedented low temperatures. Furthermore, the tandem conjugative addition–anionic oxy-Claisen sequence should find numerous synthetic applications.

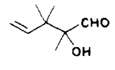
Acknowledgment. We are grateful to the National Institutes of Health (AM-30025) for support of this work and to the National Science Foundation for its contribution to the purchase of a Bruker 300-MHz NMR spectrometer.

---

(5) Obtained by methylation (LDA, THF, −78 °C; MeI, HMPA) of (allyloxy)acetophenone. For the preparation of (allyloxy)acetophenone, see: Kachinski, J. L. C.; Salomon, R. G. *Tetrahedron Lett.* **1977**, 3235.

(6) The rearrangement was monitored by periodically working up aliquots of the reaction mixture followed by its analysis by 300-MHz ^{1}H NMR. The integration of the various peaks was averaged, and the ratio of **4** and **6e** determined.

(7) At this point, the reasons for the discrepancy of our results with those reported by Thomas and Dubini[4] remain unclear. Note, however, that a [3,3] anionic oxy-Claisen rearrangement of the enolate of ketone iii would give v,



v

a compound containing two adjacent quaternary centers.

(8) Ikeda, M.; Takahashi, M.; Ohno, K.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull.* **1982**, *30*, 2269.

(9) Compound **12** was correlated to **10** by desilylation under neutral conditions (ammonium fluoride, water/ethanol, 65 °C).

(10) Russell, G. A. In "Radical Ions"; Kaiser, E. T., Kevan, L., Eds.; Wiley: New York, 1968; pp 87–150.

(11) Sawyer, D. T.; Gibian, M. J. *Tetrahedron* **1979**, *35*, 1471.

(12) (a) Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3319. (b) Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994.