Tetrahedron Letters,Vol.29,No.34,pp 4229-4232,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Anionic Oxy-Claisen Rearrangement of a Tricyclic α-Allyloxy Ketone

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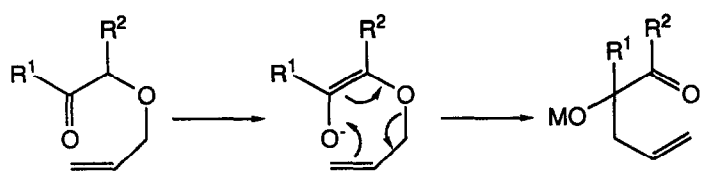
Summary: Preparatively useful reaction conditions for the anionic oxy-Claisen rearrangement of an α-allyloxy ketone (**6**) possessing acidic α- and α'-hydrogens are described. The reaction rate and efficiency are strongly influenced by both solvent and counterion. The product, **8**, although formally the product of [3,3]-sigmatropic rearrangement of enolate **7**, may in fact arise via a [2,3]-Wittig followed by one or more [1,2]-acyloin rearrangements.

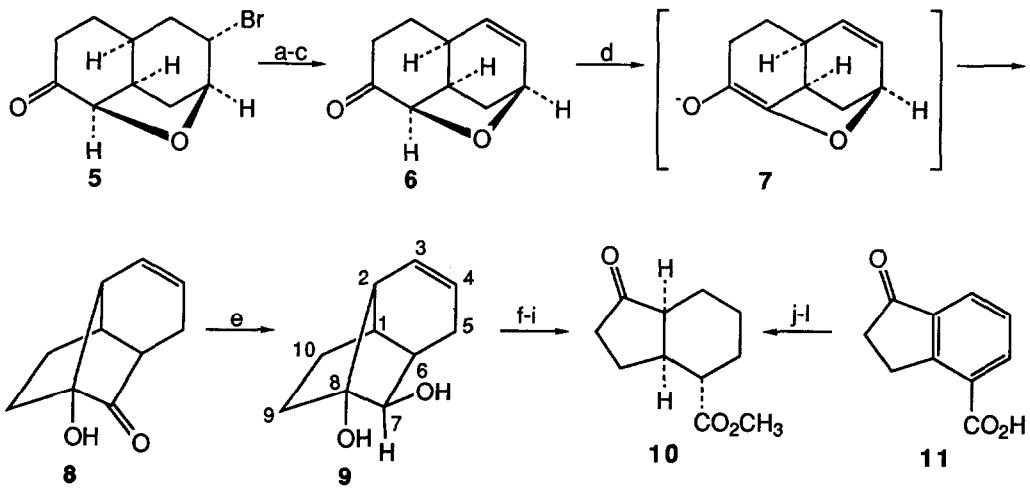
The Claisen rearrangement has enjoyed widespread use in organic synthesis as a method for the formation of carbon-carbon bonds.[2] Its popularity results from its high regio- and stereospecificity as well as its compatibility with a wide range of substitution patterns and functional groups. Substituents can in some cases increase the rate and stereospecificity of the reaction. One such example is the oxido substitutent at C-1 (e.g., **2**) which imparts a considerable rate acceleration to the rearrangement.[3] This variant leads eventually to an α-hydroxy-γ,δ-unsaturated carbonyl compound (**4**). Koreeda and Luengo have studied the anionic oxy-Claisen rearrangement.[4] In their study, the regioselectivity of enolate generation (**1**→**2**) was not an issue, because the model ketone bore $R^1 = C_6H_5$. The generality of this method would be enhanced by information regarding the more complicated case in which the ketone **1** possesses acidic hydrogens on both the α- and α'-carbons.



1 **2** **3** M = K, Na, Li
4 M = H

We have encountered an example of the oxy-anion Claisen rearrangement in which the regiochemistry of enolate generation is an important consideration, and find that proper selection of reaction conditions is critical for the success of the rearrangement. We have semi-quantitatively studied the rate and efficiency of this process as a function of base strength, counterion, and solvent, and report our results herein. These results suggest that ambiguities in the regiochemistry of enolate generation need not be a problem if enolate generation is accomplished under conditions in which enolate regioisomers are able to interconvert.

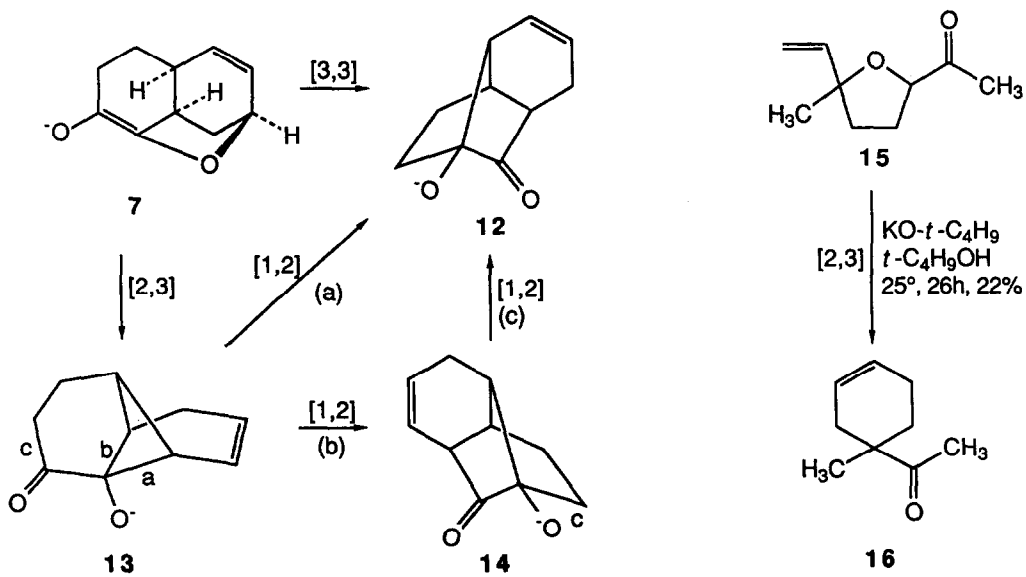
The tricyclic α-allyloxy ketone **6** was prepared from **5**[5,6] by a three-step sequence involving reduction of the ketone function, base-promoted elimination of HBr, and regeneration of the ketone by oxidation.[7] The obvious one-step conversion of **5** to **6** under basic conditions was precluded by the base-sensitivity of **6**. Further investigation defined basic conditions under which **6** was converted predominantly to a single product, **8**. The indicated structure of **8** is supported by spectroscopic data[8] as well as its conversion as shown to **10**, an authentic sample of which was prepared from ketoacid **11**.[9]



a. $NaBH_4$, EtOH, 5°, 0.25h; b. KO-t-C_4H_9, C_6H_6, 60°, 0.75h; c. i) $(COCl)_2$, DMSO/CH_2Cl_2,-60°, 2 min, ii) Et_3N,-60°, 5 min,25°, 1h(71%, 3 steps); d. 10 equiv KO-t-C_4H_9, THF, 50° (94%); e. $NaBH_4$, EtOH, 25°, 1h(94%); f. 10% Pd/C, EtOH, 50 psi H_2, 25°, 2h(100%); g. $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2,-45°, 0.25h; h. CrO_3, H_2SO_4, CH_3COCH_3, H_2O, 25°, 5 min; i. CH_2N_2, Et_2O, 25°, 0.25h (57%, 3 steps); j. CH_2N_2, Et_2O, 0°; k. 10% Rh/C, EtOH, 1000 psi H_2, 100°, 1h; l. PCC, CH_2Cl_2, 25°, 1h.

The rearrangement of **6** to **8** afforded an opportunity to investigate the anionic oxy-Claisen rearrangement of a substrate in which difficulty might be expected in achieving regioselective deprotonation of the starting α-allyloxy ketone. In fact, the strongly basic metal hydride/methanol conditions which were successful in simpler examples (15 equiv KH, 10 equiv CH_3OH, THF, 25°)[4] when applied to **6** afford at most traces of **8** along with a variety of other unidentified products. This result is consistent with formation under these conditions of the enolate regioisomer of **7** which is incorrect for the anionic oxy-Claisen rearrangement. In sharp contrast, exposure of **6** to an excess (10 equiv) of potassium *tert*-butoxide in THF afforded **8** in 94% yield with a half-life of ca. 2 min at 50°.[10] A dependence of the rate on solvent and counterion[4] was observed, a critical factor in the selection of preparatively useful conditions. For example, substitution of sodium *tert*-butoxide for the potassium salt under otherwise identical conditions led less efficiently to **8** with a half-life of 20 min. Reaction with lithium *tert*-butoxide afforded only 10% of **8** after several hours, the formation of several by-products preventing measurement of a meaningful half-life. Substitution of toluene for THF resulted in a significant further rate retardation, yielding with lithium *tert*-butoxide only 1% of **8** after 2 h.

Several mechanistic pathways are possible for the conversion of **6** to **8** under basic conditions. The simplest of these is enolate formation followed by Claisen rearrangement of enolate **7** to alkoxide **12**, whose protonation would afford **8**. Alternatively, [2,3]-Wittig rearrangement of enolate **7** would afford the acyloin **13** which could rearrange to alkoxide **12** by ring expanion with migration of bond a, or by migration of bond b to provide **14** which could in turn undergo a second [1,2] rearrangement involving bond c to yield alkoxide **12**. In favor of the latter multistep sequence is the previous observation that in a closely related system (e.g. **15**->**16**) [2,3]-Wittig rearrangement predominated over [3,3]-Claisen rearrangement.[11] Furthermore, the acyloin rearrangement required for the interconversion of **14** and **12** is known to occur under mild conditions in the parent bicyclo[2.2.1]heptane ring system.[12] The absence of the protonated form of **13** as an isolable product of this reaction does not argue against its intermediacy owing to its expected thermodynamic instability; the absence of the protonated form of **14**[13] may result from a kinetic preference for migration of bond a (allyl migration) of **13** or may reflect a subtle thermodynamic balance in favor of **8**.[14] The substantial ring strain present in enolate **7** enhances the liklihood of non-concerted pathways, such as the allyl radical/semiquinone anion suggested by Koreeda and Luengo[4] as a possible intermediate. The present study leaves these mechanistic questions unresolved.



The results described herein illustrate a circumstance under which strongly basic conditions are deleterious to the anionic oxy-Claisen rearrangement. In the present case, and by extension presumably in others as well, weaker bases such as alkoxide are preferable, affording sufficient enolate to achieve preparatively useful rates of rearrangement under conditions of enolate equilibration. Finally, the specific rearrangement described herein represents an unusual entry into the ring system present in a family of naturally occurring sesquiterpenes derived from campherenone[15,16].

References and Endnotes

1. Fellow of the Alfred P. Sloan Foundation, 1988-1990; ICI Award Recipient, 1988.
2. (a) Rhoads, S.J.; Raulins, N.R. *Org. React.* **1975**, *22*, 1; (b) Bennett, G.B. *Synthesis* **1977**, 589; (c) Ziegler, F.E. *Acc. Chem. Res.* **1977**, *10*, 227; (d) Bartlett, P.A. *Tetrahedron* **1980**, *36*, 1; (e) Lutz, R.P. *Chem. Rev.* **1984**, *84*, 205.
3. For leading references to both experimental and theoretical studies of this effect, see references 2 and 3 in the Koreeda and Luengo paper cited here as reference 4.
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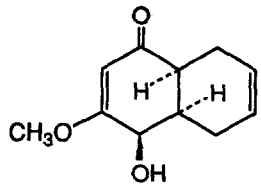
5. (a) Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* **1987**, *28*, 3065; (b) Pratt, D.V.; Hopkins, P.B. *J. Am. Chem. Soc.* **1987**, *109*, 5553; (c) Pratt, D.V.; Hopkins, P.B. submitted.
6. The bromoketone **5** was prepared from 17[5a] by the sequence: 1) NBS, THF, 10°, 1h; 2) $LiAlH_4$, THF, 0°, 1h; 3) PTSA·H_2O, CH_2Cl_2, 25°, 1h; 4) 10% Pd/C, 1 atm H_2, EtOH, 25°, 0.5h (28%, 4 steps); intermediates were characterized by ^1H NMR.



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7. All compounds are racemic and, unless otherwise specified, were characterized by IR, ^1H NMR, and low resolution MS; compounds **5**, **6**, **8**, and **10** gave satisfactory high resolution MS.
8. Spectroscopic data for **6**, **8**, **9**, and **10** are as follows: **6**: IR ($CHCl_3$): 3040-2860 (CH), 1710 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89 (1H, m),1.98 (3H, m),2.17 (1H, dm,J=16 Hz), 2.65-2.8 (3H, m),3.92 (1H, broad s), 4.44 (1H, m), 5.56 (1H, d, J=13 Hz), 6.66 (1H, dd, J=8 Hz, 13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.13, 32.34, 36.24, 36.49, 42.40, 71.45, 82.28, 131.78, 133.39, 208.88; LRMS (ei): m/e164 (M+), 146 (M-H_2O), 136 (M-CO), 79 (100%); HRMS (ei): m/ecalc'd 164.0837, found 164.0836; **8**: IR ($CHCl_3$): 3525 (OH), 1785 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.3-1.5 (3H, m), 1.6-1.8 (2H, m),1.9 (1H, dd, J=16 and 4 Hz), 2.0 (1H, d, J=4 Hz), 2.15 (1H, m),2.3 (1H, m),2.8 (1H, s), 5.2 (1H, m),5.6 (1H, dd, J=12 and 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.7, 31.5, 37.5, 47.5, 48.0, 92.7, 126.5, 126.6, 218.2; LRMS (ei): m/e 164 (M+), 149, 129; HRMS (ei): m/ecalc'd 164.0837, found 164.0836; **9**: ^1H NMR (500 MHz, $CDCl_3$): δ 1.3 ($H_{9\text{-endo}}$, $H_{10\text{-endo}}$, m),1.9 ($H_{9\text{-exo}}$, $H_{10\text{-exo}}$, m),1.94 (H_1, ddd, $J_{1,2}$=2 Hz, $J_{1,3}$=3 Hz, and 6 Hz), 2.14 (H_2, dddd, $J_{1,2}$=2 Hz, $J_{2,3}$=7 Hz, $J_{2,4}$=2 Hz, and $J_{2,7}$=2 Hz), 2.28 (H_{5a}, dddd, $J_{3,5a}$=1 Hz, $J_{4,5a}$=5 Hz, $J_{5a,5b}$=18 Hz, and $J_{5a,6}$=3 Hz), 2.37 (H_{5b}, dddd, $J_{3,5b}$=3 Hz, $J_{4,5b}$=2 Hz, $J_{5a,5b}$=18 Hz, and $J_{5b,6}$=6 Hz), 2.53 (H_6, ddd, $J_{5a,6}$=3 Hz, $J_{5b,6}$=6 Hz, and $J_{6,7}$=6 Hz), 3.71 (H_7, dd, $J_{2,7}$=2 Hz and $J_{6,7}$=6 Hz), 5.79 (H_3, dddd, $J_{2,3}$=7 Hz, $J_{3,4}$=10 Hz, $J_{3,5a}$=1 Hz, and $J_{3,5b}$=3 Hz), 5.85 (H_4, dddd, $J_{2,4}$=2 Hz, $J_{3,4}$=10 Hz, $J_{4,5a}$=5 Hz, and $J_{4,5b}$=2 Hz); **10**: IR ($CHCl_3$): 3040-2850 (CH), 1730 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (1H, m),1.25 (2H, m),1.58 (1H, m),1.64 (1H, m),1.73-1.94 (3H, m),2.16 (1H, m),2.23 (1H, m),2.40 (1H, dd, J=8 Hz, 19 Hz), 2.68 (2H, m), 3.68 (3H, s); LRMS (ei): m/e 196 (M+), 164, 136 (100%); HRMS (ei): m/e calc'd 196.1100, found 196.1095.
9. Aono, T.; Araki, Y.; Imanishi, M.; Noguchi, S. *Chem. Pharm. Bull.* **1978**, *26*, 1153. The indicated relative configurations of the stereocenters of **10** are based upon mechanistic considerations and the spectroscopic identity of **10** prepared from both **8** and **11**.
10. Reactions were 60 mM in alkoxide, 6 mM in **6**. Kinetic measurements for K and Na are for 3 half lives. The **6**:**8** ratio was monitored by workup of a small aliquot followed by capillary GC analysis; control experiments demonstrated that the GC conditions did not alter the **6**:**8** ratio.
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12. Nickon, A.; Nishida, T.; Lin, Y. *J. Am. Chem. Soc.* **1969**, *91*, 6860.
13. Decoupling and nOe ^1H NMR studies on **9**[8] eliminate the possibility that protonated **14** is actually the rearrangement product.
14. Molecular mechanics calculations (MM2) predict **8** is 1.6 kcal/mole more stable than protonated **14**.
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16. We thank the Dreyfus Foundation, Research Corporation, and the Donors of the Petroleum Research Fund administered by the American Chemical Society for financial support.

(Received in UK 25 March 1988)