Tetrahedron Letters,Vol.27,No.45,pp 5455-5458,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

INTRAMOLECULAR MICHAEL ADDITION OF CYCLIC β-KETOESTER ON CONJUGATED ACETYLENIC KETONE.

Jean-François Lavallée,[1] Gilles Berthiaume,[1] and Pierre Deslongchamps
Laboratoire de synthèse organique, Département de chimie, Faculté des Sciences,
Université de Sherbrooke, Sherbrooke, QC, Canada J1K 2R1

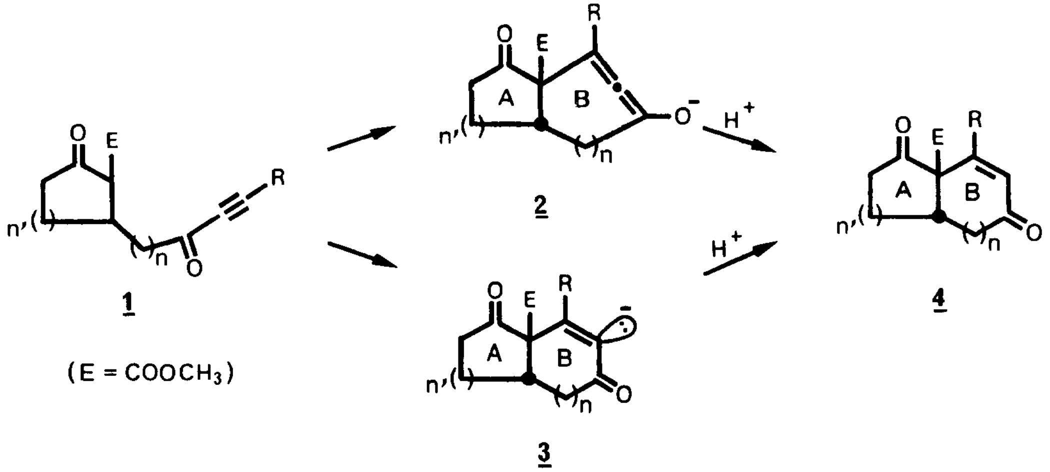
Fritz Grein

Department of Chemistry, University of New Brunswick,
Fredericton, N.B., Canada E3B 6E2

ABSTRACT. A study on the base-catalyzed intramolecular Michael addition of β-ketoester-ynone 1 (n' = 1-2, n = 0-3) is reported.

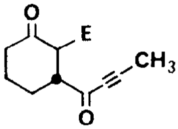
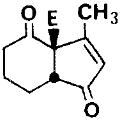
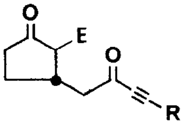
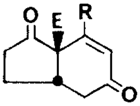
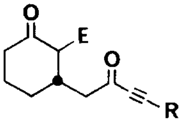
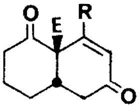
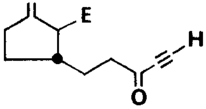
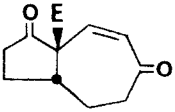
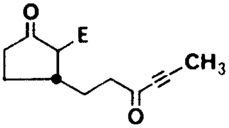
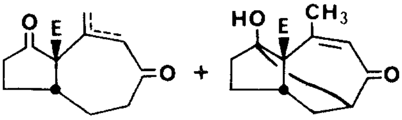
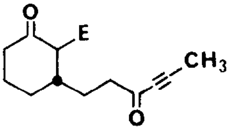
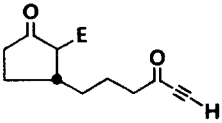
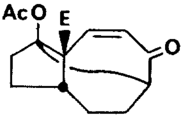
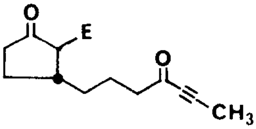
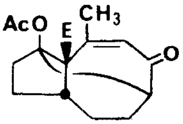
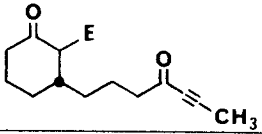
Stereoelectronic principles[2] predict that the first intermediate generated in the nucleophilic addition on a conjugated acetylenic ketone (ynone) should be an allenic enolate which on protonation produces the corresponding α,β-unsaturated ketone (enone). Since allene cannot be accommodated without considerable strain in rings smaller than cyclooctane[3-4], the intramolecular Michael addition on ynone to produce small rings is not expected to take place. Contrary to this conclusion, we wish to report experimental results which show that small rings are readily formed from the intramolecular nucleophilic addition on ynones. We wish to propose also that these successful intramolecular processes take place via a new stereoelectronically controlled pathway.

We have studied the cyclization of the cyclic five- and six-membered β-ketoester-ynone 1 (n' = 1 and 2, n = 0-3). The cyclizations were carried out with cesium carbonate at room temperature and are reported in the Table. The results show clearly that the formation of five and six-membered rings (entries 1-6) takes place with ease and in good yield. They also indicate that seven (entries 7-9) and eight-membered (entries 10-12) rings can be produced but in very low yield. An A/B cis junction was observed in all cases.



(E = $COOCH_3$)

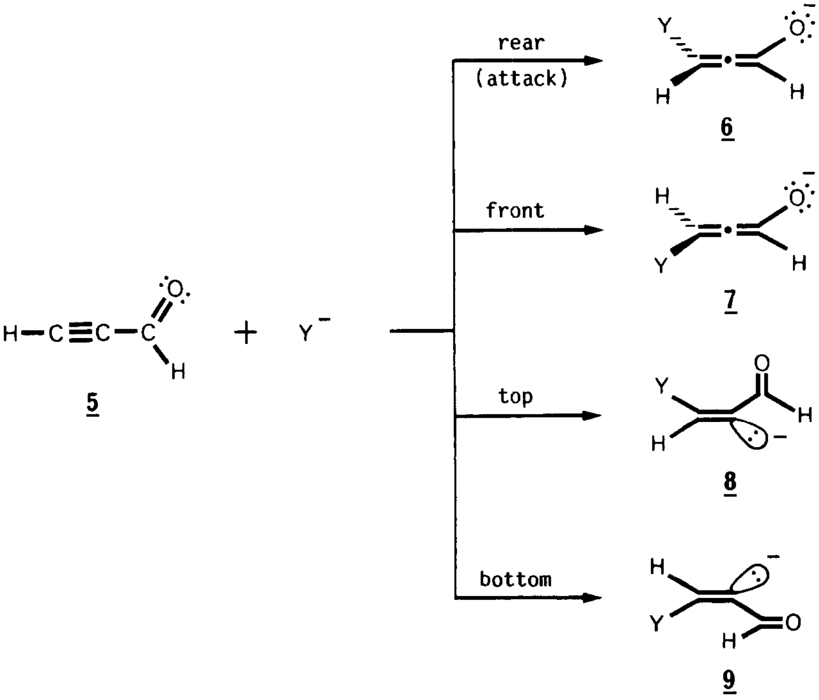
TABLE 1. CYCLIZATION OF β-KETOESTER-YNONES (E = $COOCH_3$)

Entry	Starting material	Method	Reaction time (h)	Yield	Products
1		A	0.75	82	
					
2	R = H	B	0.5	55	
3	R = CH_3	B	2	87	
					
4	R = H	A	2.5	47	
5	R = CH_3	A	2	89	
6	R = $(CH_2)_2-CH_2OAc$	A	5	75	
7		B	1	13	
8		B	30	10	 ratio 7:3
9		A	16	0	——
10		C	30	7	
11		C	96	1	
12		A	72	0	——

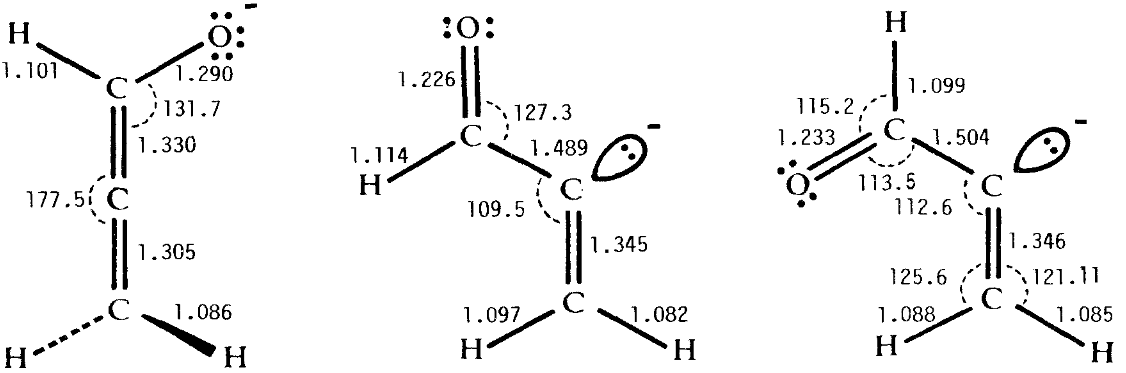
A: Cs_2CO_3, THF:DMF (1:1). B: Cs_2CO_3, CH_3CN. C: conditions B followed by Ac_2O, AcOH, $BF_3 \cdot Et_2O$.

With an enone, it is normally expected that the addition of a nucleophile should take place on the π bond of the triple bond which is conjugated with the carbonyl group. On that basis, the approach of a nucleophile Y^- on an ynone such as 5 can take place from the rear or from the front to produce the two enantiomeric allenic enolates 6 and 7 respectively. On that basis, the formation of bicyclic enone 4 from cyclic β-ketoester 1 should not take place because the intermediate bicyclic allenic enolate ion 2 would be too strained when $n \leqslant 2$. This led us to consider the possibility that the nucleophilic addition might occur on the "non-conjugated π bond" of the triple bond of the ynone. Such an addition can take place from the top or the bottom face of ynone 5 producing the enone-anions 8 and 9 respectively. The non-bonded electron pair in these two anions is not conjugated with the carbonyl group. It is therefore expected that they are less stable than the allenic enolates 6 and 7. The enone-anions should therefore not be observed when it is possible to form the allenic enolates, however, when the latter cannot be produced, it might be possible to generate the formers. The intramolecular version of process 5 → 9, i.e. the pathway 1 → 3 → 4 could indeed lead to the formation of bicyclic enone when $n \leqslant 2$. The anions 8 and 9 may well be less basic than one could first anticipate because they are vinylic anion next to a carbonyl group. Indeed, the inductive effect of this group should reduce the basicity of the vinylic anions which could have a basicity intermediate between vinylic and acetylenic anion.

Theoretical calculations (4-31G^5 geometry opimizations using an IBM version^{6a} of the GAUSSIAN 80^{6b} computer program) were carried out for the allenic enolate (6 or 7, Y = H) and the two geometrically isomeric enone-anions (8 and 9, Y = H). The results are summarized in Fig. 1. They show that the allene enolate is the most stable anion and that the enone-anion 9 is 17 kcal/mol less stable. We concluded that these calculations indicate that the allene



enolate should be the only anion formed normally, but when the formation of this anion is prohibited by other factors, the higher energy enone-anion 9 could well be generated and that would explaine the results described in the Table. Stereoelectronic principles predict that the anion 3 must be produced in a conformation where the newly formed C-C bond must be parallel (i.e. pseudo-axial) to the π system of the ketone group of ring A.[7] Accepting this requirement, examination of molecular models shows that anion 3 is easily constructed when n = 0 or 1. There are however some steric constraints when n = 2, which become much more severe when n = 3. On that basis, formation of five and six-membered rings would occur via the formation of intermediate 3 and the formation, although in low yield, of seven and eight-membered rings would occur via intermediate 3 and 2 respectively.[8-9]



E = -189.8342 a.u.

6 (0 kcal/mol)

E = -189.8072 a.u.

9 (17 kcal/mol)

E = -189.8007 a.u.

8 (21 kcal/mol)

Fig. 1. 4-31G Geometry optimization.

Acknowledgements

Support for this work by the Natural Sciences and Engineering Research Council of Canada (NSERCC) and by the "Ministère de l'Éducation (FCAR)", Quebec, is gratefully acknowledged.

References and notes

1. FCAR predoctoral fellowships: J.-F. Lavallée (1982-86); G. Berthiaume (1982-84, 1985-86).
2. P. Deslongchamps. In Stereoelectronic effects in organic chemistry. Organic Chemistry Series. Vol. 1. Edited by J.E. Baldwin, Pergamon Press: Oxford, England. 1983.
3. P.W. Dillon and G.R. Underwood. J. Am. Chem. Soc. 96, 779 (1974).
4. M. Balci and W.M. Jones. J. Am. Chem. Soc. 102, 7607 (1980).
5. R. Ditchfield, W.J. Hehre, and J.A. Pople. J. Chem. Phys. 54, 724 (1971).
6. (a) P.N. van Kampen, F.A.A.M. de Leeuw, G.F. Smits, and C. Altona. QCPE, 14, 437 (1982). (b) J.S. Binkley, R.A. Whiteside, R. Krishnan, R. Seeger, D.J. DeFrees, H.B. Schlegel, S. Topiol, L.R. Kahn, and J.A. Pople. QCPE, 13, 406 (1981).
7. G. Berthiaume, J.-F. Lavallée, and P. Deslongchamps. Tetrahedron Lett. Preceding communication.
8. All spectra (250 MHz, ^{1}H and ^{13}C, 80 MHz ^{1}H nmr, ir and high resolution mass spectra) are in agreement with the assigned structures. The structure of the cyclization products was established by chemical correlation with the products obtained in reference 7.
9. Five-membered ring formation via the conjugate addition of an oxygen nucleophile to an ynone yielding bullatenone was previously reported: J.E. Baldwin, R.C. Thomas, L.I. Kruse, and L. Silberman. J. Org. Chem. 42, 3846 (1977).

(Received in USA 15 July 1986)