Tetrahedron Letters,Vol.24,No.46,pp 5035-5038,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

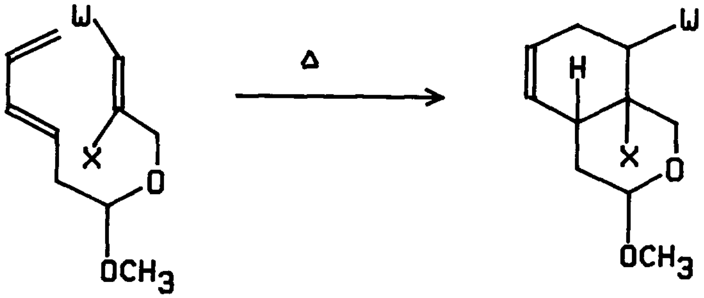
STEREOCONTROL IN THE INTRAMOLECULAR DIELS-ALDER REACTION VI: USE OF MIXED ACETALS AS ESTER EQUIVALENTS IN THE CONNECTING CHAIN

Robert K. Boeckman, Jr.*[1] and Christopher J. Flann

Department of Chemistry
University of Rochester
Rochester, New York 14627

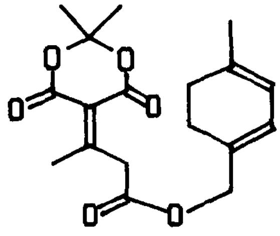
Abstract: The feasibility of the use of an acetal as the linking group for the diene and dienophile in the Intramolecular Diels-Alder reaction has been demonstrated. Although some limitations were encountered, in general the mixed acetals examined showed excellent thermal stability with no tendency to undergo elimination of methanol even at temperatures in excess of 200°C for several hours providing the expected cycloadducts in good to excellent yield.

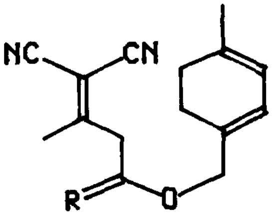
Recent studies in our laboratories[2] as well as others[3] have established that intramolecular 4 + 2 cycloaddition occurs extremely sluggishly if at all when an unconjugated ester is present as the linking group. The nature of this barrier is presumably electronic[2], but detailed mechanistic information is not yet available to substantiate this hypothesis. Such a limitation places a severe restriction on the utility of this method for the preparation of a variety of complex polycyclic lactones whose convergent synthesis would otherwise appear ideally suited to the methodology. Thus, we were led to investigate other linking groups which would function as equivalents (after further manipulation) of an ester, but would be free of the unfavorable stereoelectronic bias. We chose to examine the mixed acetal as such an equivalent (Eqn. 1) since the resulting cyclic systems are generally readily convertible to the lactone by hydrolysis and oxidation[4]. Furthermore, the acetal can serve as a convenient protecting group for the lactone system during subsequent synthetic operations.



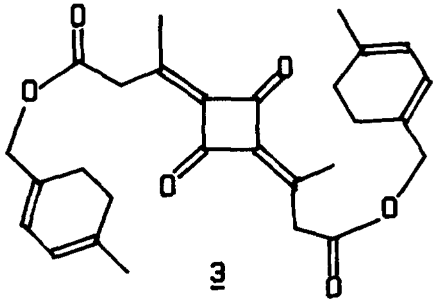
(1)

The need for an alternative to the ester as the linking group was graphically demonstrated by our observation in connection with synthetic work directed toward the trichothecanes that even the highly activated Meldrum's acid ester 1 and the related dinitrile ester 2 failed to undergo intramolecular 4 + 2 cycloaddition. Ester 1 afforded the ketene dimer 3 (48%)

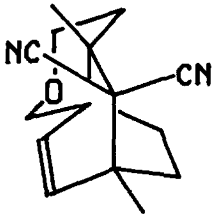

1

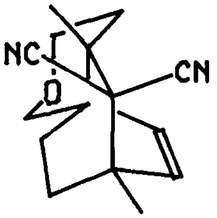

2 R=O

4 R=H_2

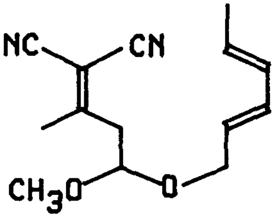

3

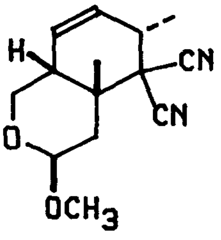
upon heating at 230°C for 5h whereas 2 polymerized after 5h at 150°C^{5,6}. In contrast, the related ether 4 smoothly underwent cyclization at 200°C (5h) affording the adducts 5 and 6 (2.2:1) in 85% yield^{6,7}.

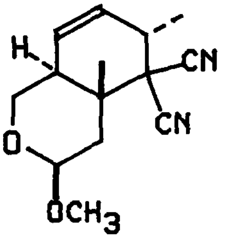

5


6

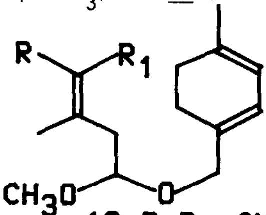
We prepared the required mixed acetals by alkoxymercuration-demercuration of 1-methoxy-1-buten-3-one^{8}, followed by Knoevenagel condensation with malononitrile^{9}. For example, use of sorbyl alcohol in this procedure afforded the diene acetal 7 in 51% overall yield (unoptimized). Thermolysis of 7 in toluene at 200°C for ∿20h cleanly afforded the desired cyclo-


7

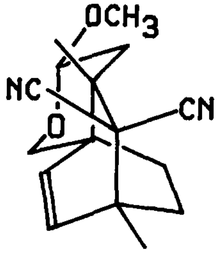

8


9

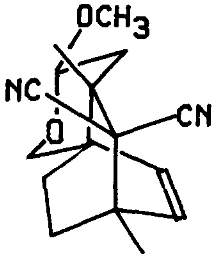
adducts 8 and 9 (1.6:1) in 70% yield^{6,7}. In this instance, remarkably only a single configuration at the acetal center was observed. In the case of the more highly substituted diene acetal 10, obtained as described above using the required cyclohexadienyl methanol[10], thermolysis at 210°C for 22h also smoothly provided the mixture (1.8:1) of cycloadducts 11 (2.75:1; ax/eq. OCH_3) and 12 (2.75:1; ax/eq. OCH_3) in 80% yield[6,7]. It is interesting to note that there is apparently a stereoelectronic preference, in these two cases, for axial disposition of the methoxy group in the transition state. No evidence of competing elimination of methanol was observed. Even systems with a single electron withdrawing group undergo cycloaddition if sufficiently activated. For example, the E aldehyde acetal 13 affords the adducts 14 (1:1; ax/eq. OCH_3) and 15 (1:1; ax/eq. OCH_3) in a ratio of 12.8:1 (50%) upon heating at 210°C (8h).



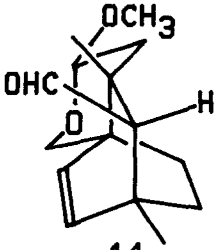
10 $R = R_1 = CN$
13 $R = CHO; R_1 = H$
16 $R = CO_2Et; R_1 = H$
17 $R = H; R_1 = CO_2Et$
19 $R = H; R_1 = CHO$



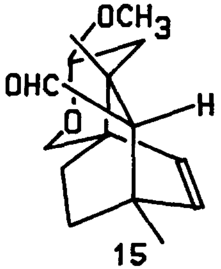
11



12

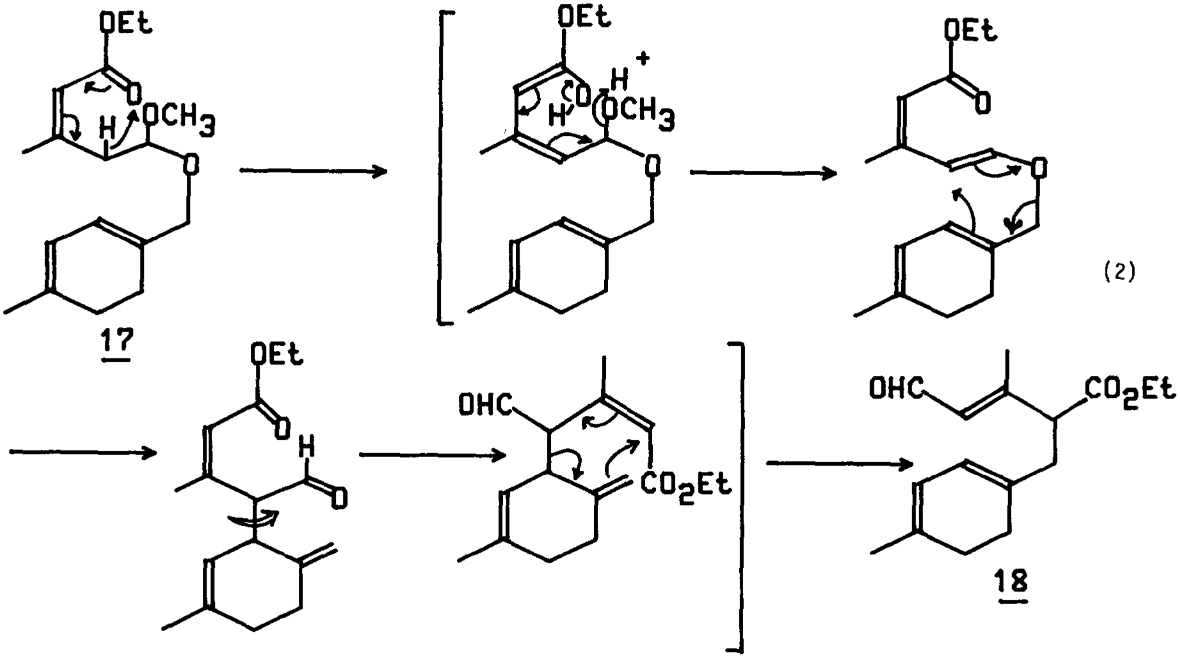


14



15

In this latter case, the related E-ester 16 was recovered unchanged after 48h at 230°C, testimony to the small tendency toward thermal elimination of methanol from acetals of this type. If, however, high temperatures are utilized ($\geq\sim$250°C) then elimination of methanol does begin to occur but no cycloaddition is observed. In contrast, the isomeric Z-ester, upon heating at 250°C, affords quite smoothly not the expected cycloadduct but ester aldehyde 18, the product of an interesting tandem Claisen-Cope process[11] which occurs after elimination of methanol (Eqn. 2). We attribute the significantly more facile elimination of methanol from 17 vs. 16 to the ability of 17 to initiate the elimination by means of a 1,5 sigmatropic hydrogen shift. This hypothesis is substantiated by the observation that the Z-aldehyde 19 undergoes facile isomerization to E-aldehyde 15 at 150°C.



(2)

Further applications of this methodology to the synthesis of intermediates leading to the trichothecane nucleus are under investigation presently and will be reported in due course.

Acknowledgment. This investigation was generously supported by research grants from the National Science Foundation (CHE-81-19823) and the National Cancer Institute (CA-29108) of the National Institutes of Health to whom we are extremely grateful.

References.

1) Research Career Development Awardee (CA-00702) of the National Cancer Institute of the National Institutes of Health.
2) Boeckman Jr., R.K.; Demko, D.M. J. Org. Chem. **1982**, 47, 1789.
3) Ciganek, E. Org. React. **1983**, in press.
4) Stork, G.; Mook Jr., R.; Biller, S.A.; Rychnovsky, S.O. J. Am. Chem. Soc. **1983**, 105, 3741.
5) It has been shown that at high temperatures methylene meldrums acid derivatives decompose to methyleneketenes which readily dimerize. See Brown, R.F.C.; Eastwood, F. W.; Harrington, K.J. Aust. J. Chem. **1974**, 27, 2373.
6) All new products gave satisfactory spectral data and exact mass or combustion analyses.
7) The high reactivity of geminal cyano group in the Diels-Alder reaction has been shown: Boeckman Jr., R.K.; Ko, S.S. J. Am. Chem. Soc. **1982**, 104, 1033. The ratios of stereoisomers were determined by an NOE experiment. Irradiation of the appropriate methyl group resulted in a 5-10% enhancement of the olefinic protons for the syn isomer (e.g., 5, 11, and 15).
8) Boeckman Jr., R. K.; Flann, C.J. Tetrahedron Lett. **1983**, in press.
9) For examples of Knoevenagel condensations see Johnson, J.R. Org. React. **1942**, 1, 210. For use of potassium fluoride as a catalyst see Rand, L.; Swisher, J.V. J. Org. Chem. **1962**, 27, 3505.
10) The allylic alcohol was prepared via Diels-Alder reaction of the known 1-bromo-3-methyl-1,2 butadiene (Jacobs, T.L.; Petty, W.L. J. Org. Chem. **1963**, 28, 1360) with methyl acrylate in refluxing toluene (55%) followed by reduction of the resulting unsaturated ester with DIBAL-H (75%).
11) Ziegler, F.E.; Piwinski, J.J. J. Am. Chem. Soc. **1982**, 104, 7181.

(Received in USA 15 August 1983)