Tetrahedron Letters Vol. 22, pp 973 - 976
0040-4039/81/0301-0973$02.00/0

SOME THOUGHTS ON THE MECHANISM OF ACETAL FORMATION AND RELATED REACTIONS: EXTENSION OF BALDWIN'S RULES FOR RING CLOSURE

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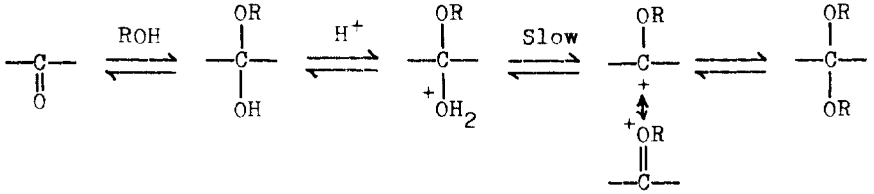
Abstract : Extension of Baldwin's rules for ring closure to dioxolane formation and related reactions has been attempted. A plausible mechanism has been arrived at on the basis of available literature evidence and earlier work reported from our laboratory.

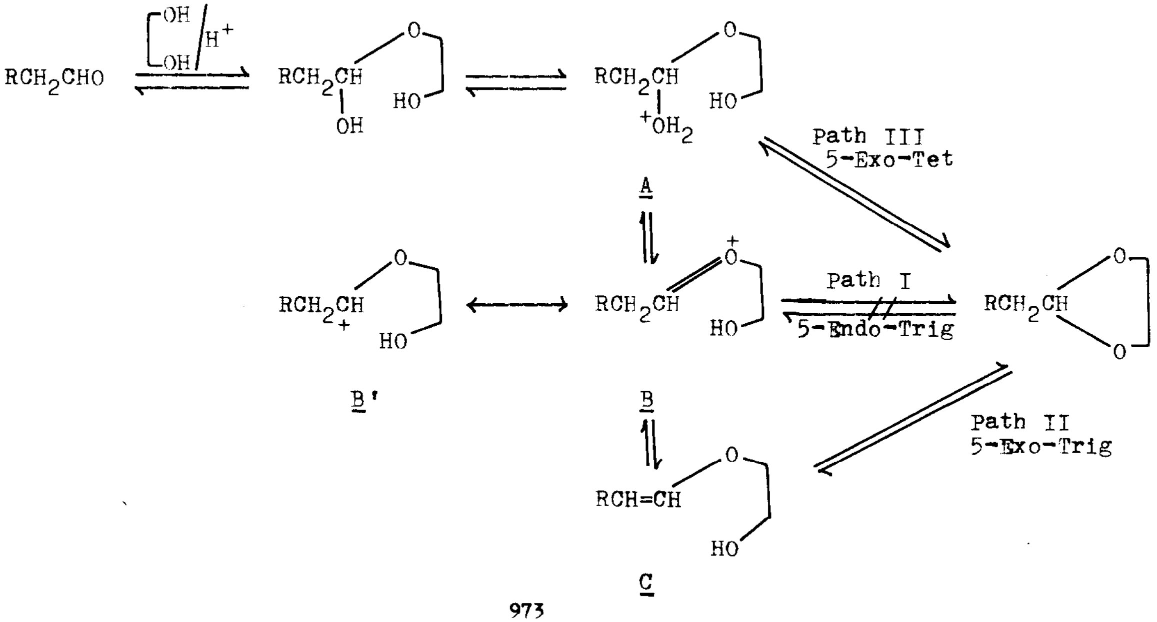
Conversion of carbonyl groups to acetals is a common strategy for the protection of aldehydes and ketones. The mechanism of acetal formation has been extensively investigated and it has now been established[1] as shown in Scheme 1. It has been shown that the elimination of **a water** molecule is the rate determining step.

Scheme 1



When the mechanism is extended to the formation of dioxolanes, it presents some problems which are summarized in Scheme 2.

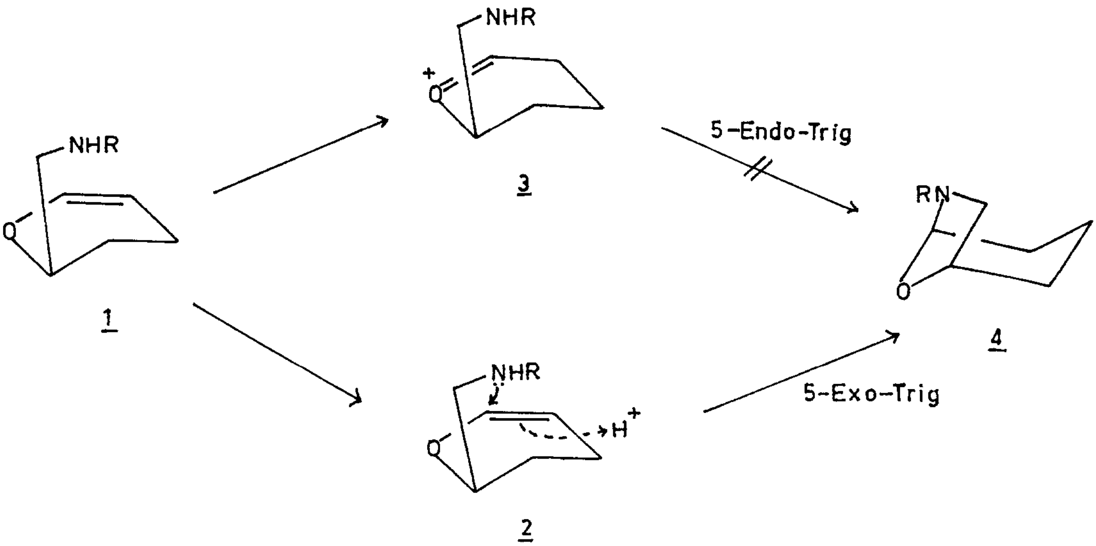
Scheme 2



The protonated hemiacetal A could loose a mole of water through the participation of the lone pair of electrons on the neighbouring oxygen. Such a structure would have two resonance hybrids viz. B and B'. Therefore one would expect a double bond character between the carbon and oxygen. Cyclization of this intermediate (Path I) would be a 5-Endo-Trig cyclization, which is 'unfavourable' by Baldwin's rules for ring closure[2]. The intermediate B could loose a proton and become an enol ether C, which could cyclize via a 'favourable' 5-Exo-Trig cyclization (Path II). Alternatively the protonated hemiacetal A could directly cyclize via another 'favourable' 5-Exo-Tet cyclization (Path III).

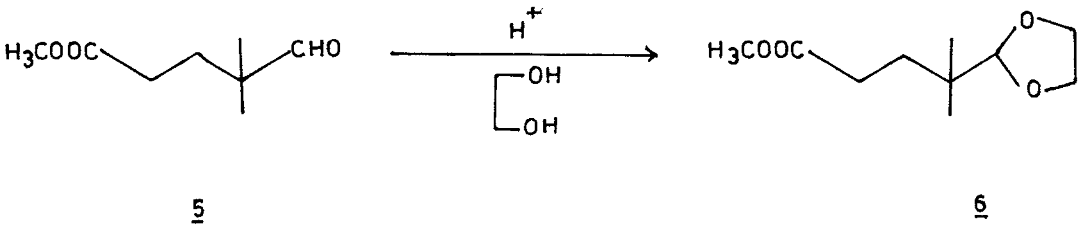
A model for Path II is available from a recently reported facile cyclization of the enol ether 1 under acid catalyzed conditions to give the bicyclic oxazolidines 4[3] (Scheme 3). Here cyclization via 3 is not 'favourable' 5-Endo-Trig[4], whereas cyclization via 2 is 'favourable' 5-Exo-Trig. By this analogy, if we consider Path II as a preferred route for dioxolane formation reactions, the aldehyde 5 should be unreactive under the usual conditions (Equation 1). However this reaction proceeds in 60% yield[5]. Since Path II is not available for

Scheme 3



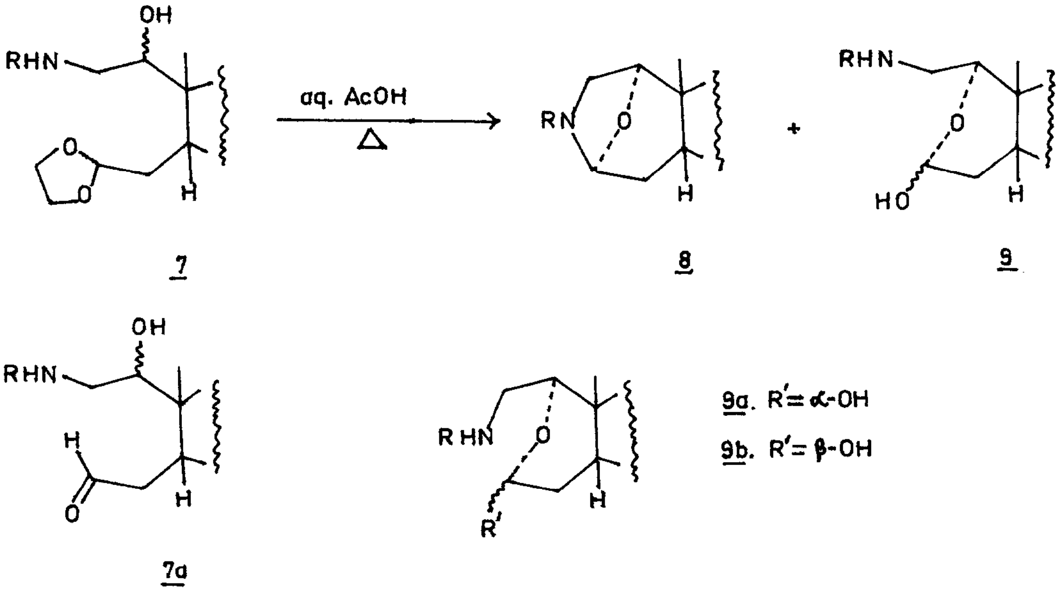
aldehyde 5 and Path I is not 'favourable' by Baldwin's rules[2] the only path now available is Path III.

Equation 1



That Path III is preferred in such reactions could be infered from the observation of Hara and Oka[6]. When they treated 7 with 75% aqueous acetic acid under reflux conditions, they obtained 8 and 9 each in 45% yield (Scheme 4). The result could be rationalized as follows. The aldehyde group in the intermediate 7a could take two orientations leading to two hemiacetals 9a and 9b. Of these 9a has

Scheme 4



R = CH_2Ph

the required stereochemistry for cyclization (5-Exo-Tet cyclization require an attack at 180° leading to S_N2 displacement). It should be noted here that though the aldehyde 7a has two α-protons available and therefore could go to an intermediate analogues to compound 1, the reaction does not proceed to completion, suggesting that such reactions prefer Path III and not Path II.

Acknowledgement:

One of us (C.P.R.) would like to thank U.G.C. (New Delhi) for financial support.

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4. It could be argued that the process is also a favoured 7-Exo-Trig cyclization. A study of molecular models indicates that the required geometry (attack at an angle of 109°) is not attainable for structure 3. It should therefore be described only as 5-Endo-Trig system.

5. Unpublished results.

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(Received in UK 18 December 1980)