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NEIGHBOURING GROUP EFFECTS ON REGIOSELECTIVITY OF WITTIG REACTIONS WITH MALEIC ANHYDRIDES

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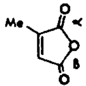
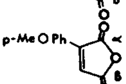
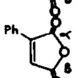
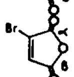
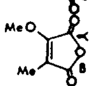
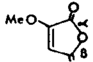
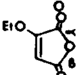
Abstract: Condensations of stabilized Wittig reagent 1 with a variety of substituted maleic anhydrides are discussed. It is proposed that the alkoxy substituents can act as Lewis bases towards the phosphorus of the ylid. Such complexation, stabilizing the transition state for the reaction at the neighbouring carbonyl function, is an important factor in regioselectivity control.

Our investigation of the reductions of unsymmetrically substituted maleic anhydrides by metal hydrides (1) led us to the conclusion that regioselectivity observed in these reactions can be linked to two principal factors: (a) intrinsic reactivities of the two carbonyl functions represented by the relative sizes of the LUMO coefficients on the carbon atoms of the two carbonyl groups; (b) the activating chelating effect of a counter ion.

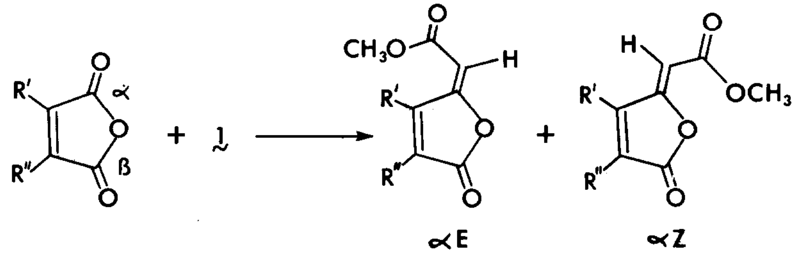
In an attempt to test if these factors play a role in the control of other nucleophilic additions we examined the regioselectivity of the condensation of stabilized phosphorane 1 with a number of maleic anhydrides. The results are listed in Table 1.

$Ph_3P = CHCOOR$ 1

Table 1. Condensations of $Ph_3P{=}CHCOOMe$ with Unsymmetrically substituted Maleic Anhydrides

Anhydrides[d]		Products						
		C_α		C_β		Ratio	% Yield[a]	Ref
		%E	%Z	%E	%Z	α:ß		
	2	-	6	87	7	6:94	84	2
			10	69	21	10:90	89	3
	3	-	-	100	-	- 100[b]	86	
	3a	-	-	100		100[b]	85	
	4	-	10	90	-	10:100[b]	10[c]	
	5	29	71	-	-	100 -	77	2
	6	33	67	-	-	100 -	36	2
	7	28	72	-	-	100 - [b]	86	
	8	30	70	-	-	100 - [b]	71	

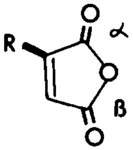
a) Yield of isolated enol-lactone; b) Analysed by G.C. (OV-101) and H^1nmr; c) Polymerization occurs under the reaction conditions; d) All anhydrides were either purchased from Aldrich Chemical Company or prepared by previously reported procedures (see references 2 and 6).



The reactions of phosphorane 1 (R=Me) with anhydrides 2, 5 and 6 have been investigated by Knight and Pattenden (2). The high selectivity for the α-carbonyl function in the condensations with 5 and 6 was interpreted in terms of the steric effects of the alkyl or aryl substituent, complemented by the electronic effect of the methoxy-group, deactivating the β-carbonyl function through the "vinylogous ester" system (2).

The condensations of ylid 1 with methyl-, phenyl- and bromomaleic anhydrides support the hypothesis that the steric effect of the substituent plays an important role in controlling regioselectivity of these reactions. The importance of steric effects is particularly evident in the case of methylmaleic anhydride, in which the high C_β-selectivity, presumably due to the steric effect, fails to be compensated by the higher "intrinsic reactivity" of the α-carbonyl function (see Table 2).

Table 2. Calculated Values of LUMO Coefficients at the Carbon Atoms of the two Carbonyl Functions



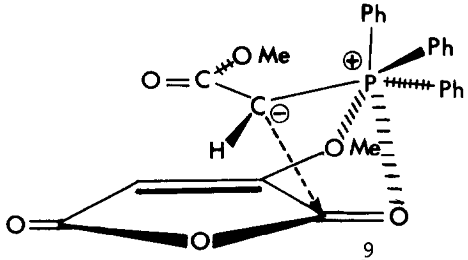
R	C_α	C_β	Higher "intrinsic reactivity"
Me	0.356	-0.348 [a]	C_α
CH_3O-	0.386	-0.342 [a]	C_α
Ph	0.215	-0.251 [b]	C_β
Cl	0.338	-0.338 [a]	-

(a) Reference 1; (b) *Ab initio* molecular orbital calculations using the Gaussian 82 programme with a minimal STO-3G basis set (4). The geometry for the parent maleic anhydride was obtained from the crystallographic data (5). Standard bond lengths and angles were used for the substituents.

Thus, steric control appears to be more important than the relatively weak electronic effect. The situation is reversed in the cases of the methoxy- and ethoxymaleic anhydrides, where the reaction occurs entirely at the sterically unfavourable α-carbonyl group. The preference for the α carbonyl function in these anhydrides may be explained by the higher intrinsic reactivity of the α-carbonyl group. However, as the steric congestion makes the attack at the C_α unfavourable, the 100% selectivity for this function is somewhat puzzling.

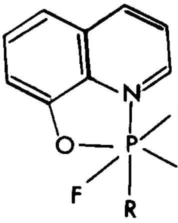
The high selectivity for the α-carbonyl group observed in the metal hydride reductions of 5, 6, 7, 8 (2,6,7) was attributed to the enhancement of the C α reactivity resulting from the chelation of the α-carbonyl and the adjacent alkoxy substituent by a counter ion (Na^+ or Li^+) present in the reaction medium (1). The chelation, however, cannot explain the highly selective condensations with the stabilized ylids, since these reactions take place in the absence of a counter ion.

We propose that the formation of a donor-acceptor complex 9 between the oxygen atom of the alkoxy group and the electron-deficient phosphorus of the ylid lowers the energy of the transition state thus promoting the reaction at the adjacent α-carbonyl group.

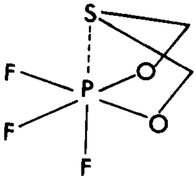


9

The well-known fact that an electron-deficient phosphorus in fluorophosphorane derivatives ($PhPF_4$) can act as a Lewis acid towards such bases as R_2O or R_2S to yield neutral, hexacoordinated adducts (8,9,10) and that such complexes, for example 10 and 11, have actually been isolated (11), supports the proposed transition state 9.



10 R = F, Ph



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The formation of intermediate(s) in the reactions of stabilized phosphoranes with maleic anhydrides is reversible (12). However, although reversibility may play a role in the stereochemical control, it appears to have no effect on the regioselectivity of these reactions.

The reaction pathway via transition state 9, in which an electron-deficient phosphorus is stabilized by electron donation from the neighbouring alkoxy group, is clearly a considerably lower energy route than the one leading to the condensation at C_β. Thus, the combination of electronic factors favouring C_α and the stabilization of the transition state leading to the condensation at the same (αCO) carbonyl group are responsible for these highly regioselective reactions.

We are presently investigating condensations of phosphorane 1 with a variety of unsymmetrical cyclic anhydrides bearing strategically placed electron-donor substituents (-OR, -SR, -NR) to establish the feasibility and effectiveness of such regioselectivity control in Wittig reactions.

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12. We have studied the reversibility of the phosphorane 1 condensation with various substituted maleic anhydrides ($-OCH_3$,-Ph, pCH_3OPh-). In all cases the formation of an intermediate is accomplished within a few minutes at -5°C. The reactions may be followed by monitoring colour changes. The reactants are colourless, the intermediate(s), usually yellow, orange or red. The intermediates decompose relatively slowly (0.5-2 hrs.) and irreversibly to the product enol-lactones. When the intermediates are treated with benzaldehyde or acetaldehyde important quantities of methyl cinnamate or methyl crotonate are recovered, in addition to the enol-lactones. Details of the crossover experiments and the NMR studies of these reactions will be discussed in a full paper.

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