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COMMENTS ON THE REACTION OF ETHYL 4-(DIETHOXYPHOSPHINYL)-3-OXOBUTANOATE AND RELATED PHOSPHONATE ESTERS WITH ENALS

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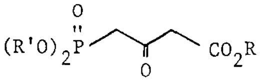
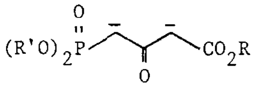
Abstract: The reaction pathways followed by the mono- and dianions of 4-phosphinyl-3-oxobutanoates during their condensation with α,β-unsaturated carbonyl compounds are discussed.

In recent publications it was communicated that 4-(diethoxyphosphinyl)-3-oxobutanoate (1) forms a dianion (3) upon treatment with two molar equivalents of sodium or potassium hydride in tetrahydrofuran (THF).[1-3]



(1) (R=R'=Et)
(2) (R=R'=Me)

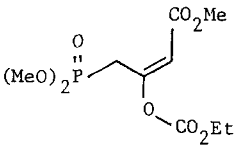


(3) (R=R'=Et)
(4) (R=R'=Me)

During our on-going investigations that centre around the condensation of (1) and related phosphonate esters with α,β-unsaturated aldehydes and other carbonyl compounds, it became evident that the dianion (3) cannot be generated under the above conditions.

We have found that the phosphonate (1), which was pretreated with one molar equivalent of sodium or potassium hydride, condensed with appropriate α,β-unsaturated carbonyl compounds to produce reaction products that resulted from interaction with the corresponding α- and γ-monoanions (5) and (6). These results, which are discussed at a later stage in this paper, strongly indicate that deprotonation of (1) produces an equilibrium mixture of (5) and (6). Addition of a second equivalent of base did not lead to further deprotonation, not even when the temperature of the reaction mixture was gradually raised to 60°C. Treatment of the phosphonate

(5) (6)



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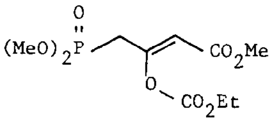
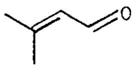


(8)

(2) with one or two molar equivalents of sodium hydride followed by two equivalents of ethyl chloroformate, yielded similar product mixtures which could not be separated but were isolated as such by column chromatography on silica gel and distillation. Analysis of the product mixtures by ^{13}C and ^{31}P n.m.r. and high resolution mass spectrometry revealed that only mono-ethoxycarbonylated products were formed and that both mixtures comprised the phosphonates (7) (64%) $\{\delta_c$ 28,08 (dt, P-CH$_2$, J_{PC} 136,1 Hz)$\}$ and (8) (16%) $\{\delta_c$ 32,33 (dt, P-CH$_2$, J_{PC} 138,5 Hz)$\}$ as the major reaction products. These results indicate that the dianion (3) is not produced under these conditions and that the γ-anion (6) is apparently more reactive towards ethyl chloroformate than the α-anion (5).

It was furthermore found that when the phosphonate (1) was added to a suspension of two molar equivalents of sodium hydride in THF, treatment of the resulting equilibrium mixture of monoanions (5) and (6) with one molar equivalent of 3-methylbut-2-enal (9), led to the evolution of hydrogen gas after an induction period of about five minutes. After acidic work-up of the reaction mixture the stereochemically pure (4E)-ketoester (10) (53%), the condensation product of the α-monoanion (5), and the cyclic aldehyde dimer (12) (22%) were isolated as pure reaction products. The ketoester (10) was produced in only 21% yield when the phosphonate (1) was successively treated with only one molar equivalent each of sodium hydride and the enal (9). Condensation of crotonaldehyde with the phosphonate (2) in the presence of two molar equivalents of sodium hydride gave the pure (4E,6E)-ketoester (13) in 47% yield, which came nowhere near a yield of 91% previously claimed by Bodalski and co-workers,[1] for the synthesis of the corresponding ethyl ester (14) via condensation of the phosphonate (1) with crotonaldehyde under the same reaction conditions.



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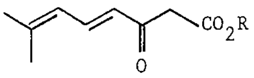
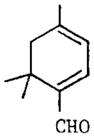


(10) (R=Et)
(11) (R=Me)



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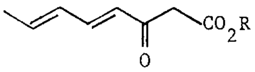
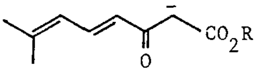


(13) (R=Me)
(14) (R=Et)

In accordance with previous findings,[1,3] our results demonstrate that substantially higher yields of ketoesters (10) and (13) can indeed be achieved when the phosphonates (1) and (2) are treated with two molar equivalents of sodium hydride prior to the addition of the carbonyl compounds. We ascribe the beneficial effect of the second molar equivalent of sodium hydride to its ability to generate the ketoester enolates (15) and (16) rather than the dianions (3) and (4).[1,2] Deprotonation of the product ketoesters by sodium hydride eliminates the possi-



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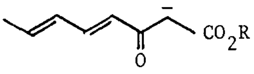

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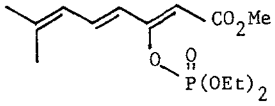
(17) (18)



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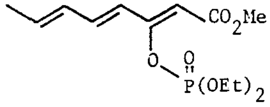
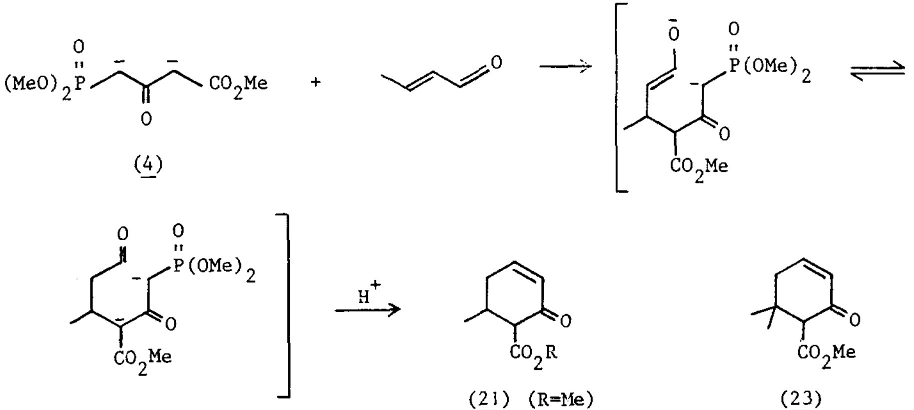


(20)

bility of protonation of the phosphonate anions (17) and (18) by the more acidic reaction products, e.g. (11) and (13), and thereby preventing the premature termination of the phosphonate condensation reactions.[5]

Formation of the stereochemically pure enol phosphates (19) (42%) and (20) (47%) upon successive treatment of the phosphonate (2) with two molar equivalents of sodium hydride, one molar equivalent each of 3-methylbut-2-enal (9) or crotonaldehyde, and quenching of the reaction mixtures with diethyl chlorophosphate prior to acidic work-up, provided conclusive evidence for the presence of the ester enolates (15, R=Me) and (16, R=Me) in significant quantities in the above reaction mixtures.

Formation of the dianions (3) and (4) can easily be achieved by successive treatment of the corresponding phosphonates (1) and (2) with equimolar quantities of sodium hydride and butyllithium.[6] Condensation of the phosphonate dianion (4) with the enal (9) at room temperature produced the ketoester (11) in a significantly higher yield of 69%. The ketoester (13) was formed in 40% yield when the dianion (4) was condensed with crotonaldehyde under the same reaction conditions. A significant by-product of the latter reaction was the cyclic ketoester (21) (11%), which most probably resulted from rapid Michael addition of the highly nucleophilic phosphonate dianion (4) to crotonaldehyde, followed by an intramolecular Horner-Wittig condensation.



(4)

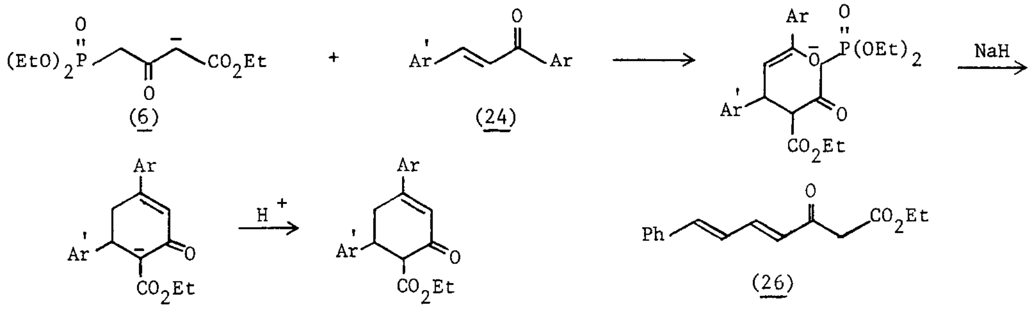
(21) (R=Me)

(22) (R=Et)

(23)

It is not surprising that neither we nor Bodalski and co-workers[1,2] isolated any of the cyclic ketoesters (21) or (22) as by-products when the phosphonates (1) and (2) were treated with two molar equivalents of sodium hydride (conditions for monoanion formation) prior to condensation with crotonaldehyde. Reaction of the phosphonate dianion (4) with the enal (9) did not yield the corresponding cyclic ketoester (23) in a detectable quantity, most probably as a consequence of enhanced steric interaction at the β-carbon atom of the enal (9) as compared to crotonaldehyde.

In a recent communication[7] it was reported that a series of chalcones (24) was successfully annulated by treatment with the phosphonate (1) in the presence of two or three molar equivalents of sodium hydride, to produce the corresponding cyclic ketoesters (25). The formation of these products can adequately be rationalized against the background of the foregoing discussions.



(6)

(24)

(25)

(26)

Condensation of the monoanion of the phosphonate (1) in the presence of an excess of base with an α,β-unsaturated carbonyl compound possessing a sterically hindered carbonyl group, e.g. the chalcones (24), leads to initial Michael addition of the γ-anion (6) to the enones (24), followed by energetically favoured intramolecular Horner-Wittig condensations as compaired to the classical intermolecular olefinations. When the sterically less hindered α,β-unsaturated aldehydes, e.g. crotonaldehyde or enal (9), are utilized as substrates under conditions of monoanion formation, classical Horner-Wittig olefinations become the favoured reaction paths to produce the corresponding acyclic products (10) and (14). It is therefore not suprising that Taylor and Davies[3] isolated the acyclic ketoester (26) as the reaction product of the phosphonate (1) and cinnamic aldehyde in the presence of a molar excess of potassium hydride.

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References and Notes

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