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CONDENSATION OF ETHYL AND METHYL 4-(TRIPHENYLPHOSPHORANYLIDENE)-3-OXOBUTANOATE WITH ENALS

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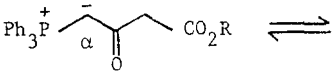
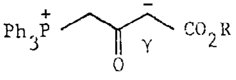
Abstract: The manipulation of the mode of reaction of 4-(phosphoranylidene)-3-oxobutanoates with enals and a resulting new synthesis of ethyl β-safranate have been explored.

A recent literature report[1] on the anionic activation of ethyl 4-(triphenylphosphoranylidene)-3-oxobutanoate (1)[2,3] and its utilization for Z-stereoselective Wittig olefinations of aliphatic aldehydes, prompted us to disclose some of our own findings in a related investigation.

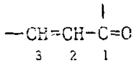


(1) (R=Et)

(2) (R=Me)



(3)

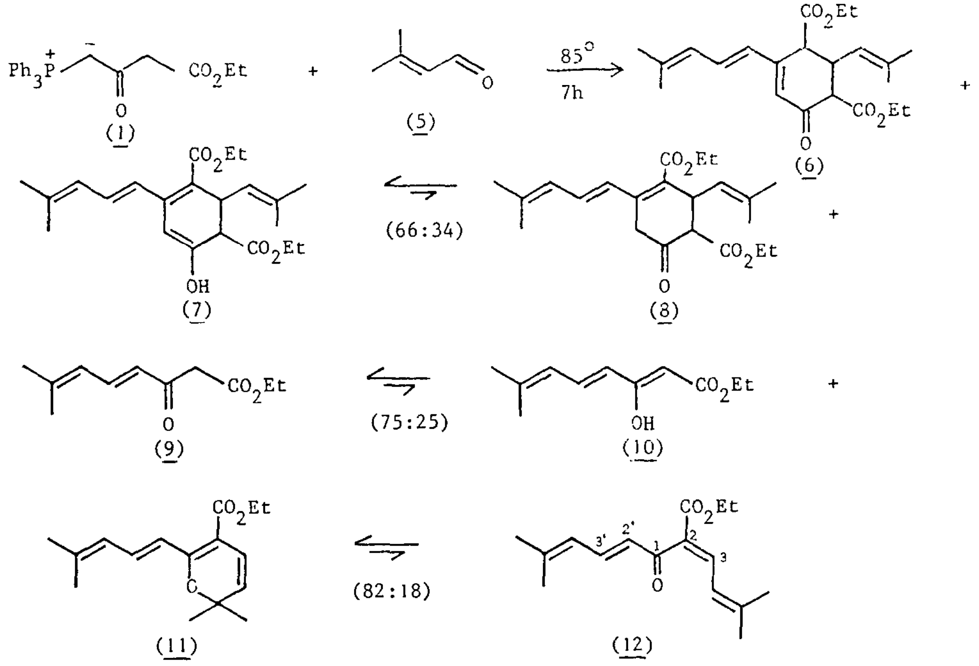


$$-\overset{3}{C}H=\overset{2}{C}H-\overset{1}{C}=O$$

(4)

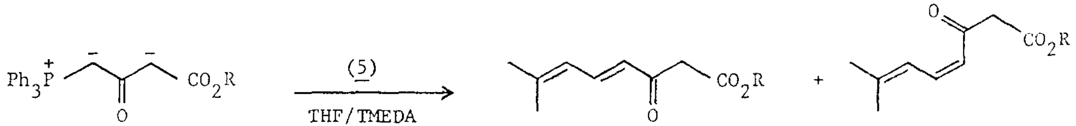
This investigation is directed at the manipulation of the mode of reaction of phosphonium ylides (1) and (2), and the corresponding phosphonate anions, with α,β-unsaturated carbonyl compounds. These ambident nucleophiles have the intrinsic structural properties that might lead to C_α-C_1, C_α-C_3, C_γ-C_1, or C_γ-C_3 interaction with appropriate α,β-unsaturated carbonyl systems (4).

SCHEME I



Condensation of the phosphonium ylide (1) with an excess of 3-methylbut-2-enal (5) produced a complex product mixture which was separated by chromatography into four major fractions. According to ^1H and ^{13}C n.m.r. analyses these fractions consisted of the pure ketodiester (6) (12%) and 66:34, 75:25 and 82:18, equilibrium mixtures of the esters (7) and (8) (19%), (9) and (10) (6%), and (11) and (12) (18%), respectively.[4] By independent synthesis we were able to show that condensation ($PhCO_2^-$/TEBAC) of the keto-enol mixture of esters (9) and (10) with aldehyde (5) produced the same equilibrium mixture of (11) and (12) as above, which reacted with ylide (1) in a Michael-Wittig condensation to yield the diester (6) and a 66:34 tautomeric mixture of (7) and (8). In close resemblance to the chemical behaviour of the corresponding phosphonate anion,[5] it is believed that the ketodiester (6) is formed by an initial Michael addition of γ-ylide (3) (R=Et) to the enone tautomer (12) *via* C_γ-C_3 interaction, followed by transylidation and intramolecular Wittig condensation. Not to our surprise, no reaction product that could be related to C_γ-$C_{3'}$ interaction was formed in a detectable quantity. In order to establish the relationship between ketodiester (6), (7), and (8) a pure sample of (6) and one molar equivalent of ylide (1) were heated (75°C) in benzene to produce a product mixture which consisted of the ester (6) (52%) and 33% of the same tautomeric mixture of (7) and (8) as above.

In an effort to enhance the nucleophilic character[1] and perhaps also the likelihood for Michael-Wittig condensations with enals, the ylide (2) was treated with lithium diisopropylamide in THF/TMEDA and the ensuing dianion (13) condensed with enal (5) at room temperature. Under these circumstances the reaction proceeded rapidly to produce a 74% yield of ketoesters (14) and (16) as a 1:1 E/Z mixture after ten minutes. No indications could however be found that the Michael-Wittig product (18) was formed in a significant quantity, while the stereochemical outcome of this Wittig condensation resembles the reaction pattern of nonstabilized phosphonium ylides with aldehydes.[6] The effect of soluble lithium ions in the reaction mixture, which is known to favour trans-oxaphosphetane formation,[7] was probably largely sequestered by the solvating power of the solvent (THF/TMEDA). Condensation of the dianion (13)



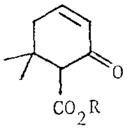
(13) (R=Me)

(14) (R=Me)

(15) (R=Et)

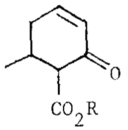
(16) (R=Me)

(17) (R=Et)



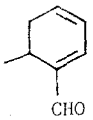
(18) (R=Me)

(19) (R=Et)

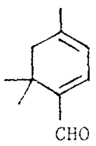


(20) (R=Me)

(21) (R=Et)



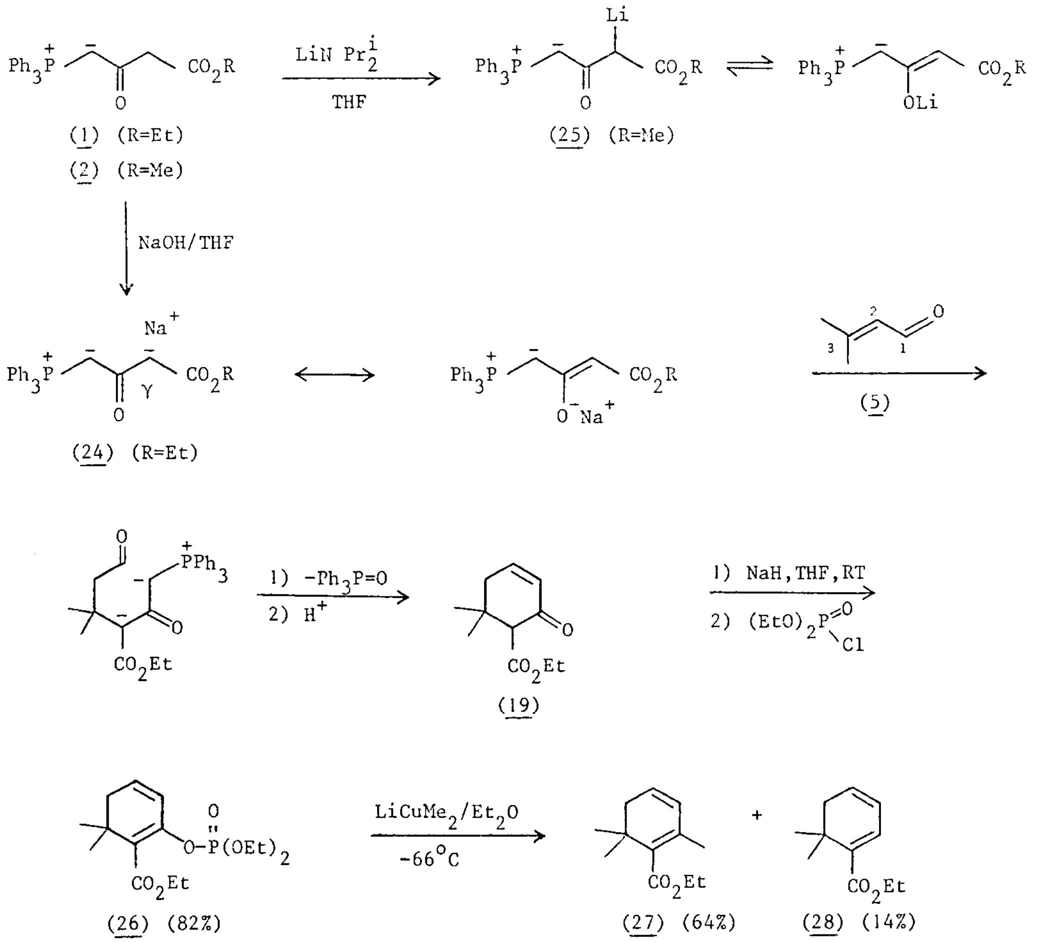
(22)



(23)

with crotonaldehyde which possesses a sterically less hindered β-carbon atom, gave a 31% yield of the Michael-Wittig reaction product (20) while the corresponding open-chain (E)- and (Z)-δ-ketoesters were formed in a combined yield of only 1,5%. Crotonaldehyde underwent an appreciable amount of self-condensation in the stronger basic reaction medium, which was demonstrated by isolation of the dimer (22) in 15% yield.

It was recently communicated[8] that ylide (1), after treatment with two molar equivalents of sodium hydride followed by the addition of a few drops of water, condensed with α,β-unsaturated aldehydes in a Michael-Wittig fashion to produce a series of 6-carboalkoxycyclohex-2-en-1-ones, e.g. (21), in modest yields. However, we found that ylide (1) underwent a smooth Michael-Wittig condensation with crotonaldehyde in the presence of dry, powdered sodium hydroxide in THF to produce the cyclic ketoester (21) in a significantly higher yield of 66%. Condensation under the same reaction conditions of the ylide (1) with enal (5), which is sterically more hindered at the β-carbon atom, yielded for the first time to our knowledge the cyclic ketoester (19) in a modest yield (21%), together with a 1:1 mixture of the ketoesters (15) and (17) in a combined yield of only 13% and the enal dimer (23)(15%).



The synthetically important diverse chemical outcome of the reactions of the enal (5) with ylides (1) and (2), after initial treatment of the latter compounds with powdered sodium hydroxide and lithium diisopropylamide, respectively, can at least partially be ascribed to the marked difference in ionic character of the intermediate sodium and lithium enolates (24) and (25). Condensation of the relatively more covalent lithium enolate (25) with enal (5) can be expected to proceed with substantially enhanced reactivity *via* C_α-C_1 attack, to produce the normal Wittig olefination products (14) and (16). In contrast, the ionic sodium enolate (24) reacted with enal (5) *via* a Michael-Wittig condensation (C_γ-C_3 attack) to yield the cyclic ketoester (19) as the major reaction product.

Successive treatment of the ketoester (19) with sodium hydride and diethyl chlorophosphate gave the pure enolphosphate (26) in high yield.[9] The enolphosphate (26) reacted with lithium dimethylcuprate[9] at low temperature to produce the important synthetic reaction intermediate, ethyl β-safranate (27), which can be converted by standard reaction procedures to β-damascenone, a constituent of Bulgarian rose oil and a useful compound for the creation of modern fragrances.[10,11] Ketoester (28), which may formally be regarded as a reduction product of the enolphosphate (26), was formed as a minor byproduct. Formation of related reduction products was encountered as a general side reaction when a series of conjugated enolphosphates was treated with lithium dimethylcuprate under similar reaction conditions.[12]

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4. All reaction products were isolated as pure compounds which exhibited satisfactory analytical and spectroscopic data. Ketoester (6) showed: δ_C 14.2, 14.25, 18.2, 18.9, 25.9, 26.5(Me), 39.2, 46.2, 55.7(CH), 60.9, 61.4(CH_2), 121.5, 125.6, 126.3, 128.6, 134.1(:CH), 137.2, 143.6, 153.1(:C<), 170.1, 170.2, 194.1(C:O). Enolester (7) showed: δ_C 14.1, 14.3, 18.15, 18.8, 25.8, 26.9(Me), 34.2, 46.5(CH), 60.2, 60.9(CH_2), 97.4(:C<), 122.2, 124.8, 125.7, 130.0, 130.2(:CH), 132.0, 140.2, 142.3(:C<), 165.4(:COH), 171.2, 171.9(C:O).
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