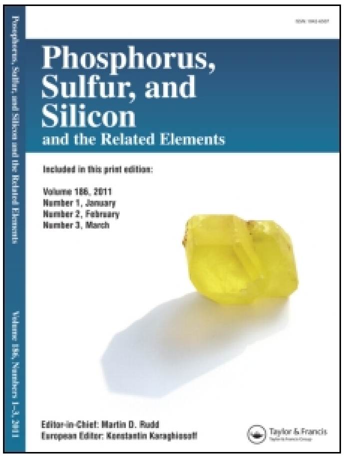

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SOLVENT EFFECTS IN REACTIONS OF DIKETONES WITH WITTIG AND WITTIG-HORNER REAGENTS

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SOLVENT EFFECTS IN REACTIONS OF DIKETONES WITH WITTIG AND WITTIG-HORNER REAGENTS

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In a series of reactions between Wittig or Wittig-Horner (Wadsworth-Emmons) reagents and diketones it was found that out of the five solvents tested, for the Wittig reagents, namely dichloromethane, toluene, ethanol, dimethylformamide, and pyridine, only pyridine had a significant effect on the Z:E ratio of isomeric products, percent Z isomer being increased. In contrast to the Wittig reagents out of the three reactions with Wittig Horner reagents, two always gave as the only products those in which both carbonyl groups were replaced. Isomerization of products sometimes occurred and dimethylformamide particularly enhanced this feature of the reaction.

INTRODUCTION

Although the reaction of phosphorus ylides with carbonyl compounds to give alkenes was discovered more than forty years ago[1] its use and scope have continued to expand into a wide variety of areas of synthesis. What was once thought to be a straightforward reaction leading to unambiguous products and having an accepted, well-established mechanism has proved to be more complex. Attempts to control the stereochemistry of alkene formation (*Z* versus *E*) have been successful in same cases, especially with reactive ylides[2]. Some of the techniques which have been used to influence the stereochemistry of the reactions resulting in a particular alkene

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* Corresponding Author.

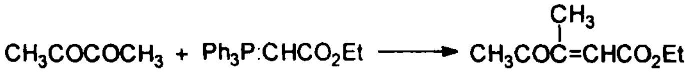
are variations in solvent, addition of soluble salts, variations in temperature and changing the group R in the reagent $R_3P{=}CHZ$. As far as the Wittig-Horner reaction is concerned trans or *E* products predominate although some stereochemical control has been achieved.[3] Sometimes changing the base used to generate the phosphonate carbanion reverses the stereochemical preference[4], and a change of temperature may also reverse the *Z*:*E* preference.[5]

Whereas reactive ylides frequently give a greater percentage of *Z* isomers[6], stable ylides react with aldehydes generally to give predominantly *E* isomers.[7] Reactive ylides readily react with ketones but ylides of the type used in this study do not readily do so. It has been found that methyl alkyl ketones react with ethoxycarbonylmethylene triphenylphosphorane to give 60 to 66% *E* isomer and that yields were increased by acid catalysts.[8] To date there has been no attempt to control or influence the stereochemistry of the reaction between stabilized ylides and either ketones or diketones.

RESULTS AND DISCUSSION

The present work aims at investigating one factor, solvent choice, which may influence the stereochemistry of the reaction between some selected diketones and stabilized Wittig reagents, as well as in some cases comparing the results with those obtained from the corresponding Wittig-Horner reagents.

The results are very interesting and indicate that a dramatic change in *Z*:*E* ratio can be achieved in some cases by changing the solvent but that there may also be complicating factors. The reaction of diacetyl (**1**) and ethoxycarbonylmethylene triphenylphosphorane (**2**) is one example where the Z:E ratio can be influence by the change of solvent as shown in table I.



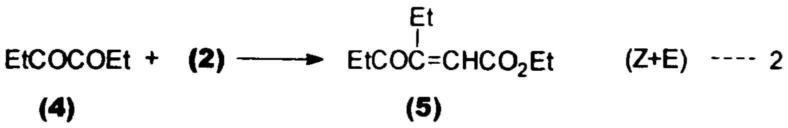
$$CH_3COCOCH_3 + Ph_3P{:}CHCO_2Et \longrightarrow CH_3CO\overset{CH_3}{\overset{|}{C}}{=}CHCO_2Et \quad \text{----} \; 1$$

(1) **(2)** **(3)**

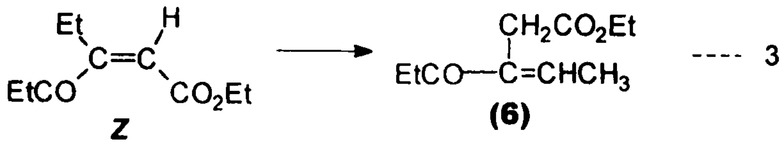
TABLE I Dependence of Z:E ratio on solvent for the reaction of (**1**) with (**2**)

Solvent	*% Yield*	*Z:E ratio of (3)*
dichloromethane	86	35:65
toluene	94	32:68
ethanol	81	34:66
dimethylformamide	84	27:73
pyridine	85	64:36

Thus the basic solvent pyridine clearly favoured the *Z* isomer whereas the *E* isomer predominated in all other cases. Could this solvent bring about a similar change for other diketones? We tried the same series of solvents using 3,4-hexanedione (**4**) and (**2**) and found rather unexpectedly that the % *E* isomer varied between 27 and 31%. Moreover the Z isomer isomerized in some solvents:



$$\underset{(\mathbf{4})}{\mathrm{EtCOCOEt}} + (\mathbf{2}) \longrightarrow \underset{(\mathbf{5})}{\mathrm{EtCO}\overset{\mathrm{Et}}{\mathrm{C}}\mathrm{=CHCO_2Et}} \quad (\mathrm{Z+E}) \text{ ---- } 2$$



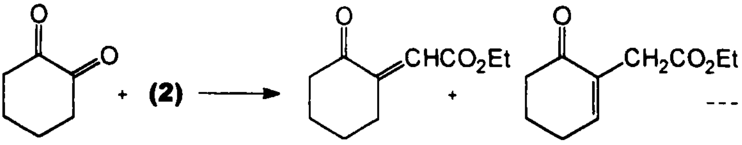
The results were as shown in Table II

TABLE II Dependence of product ratios on solvent for the reaction of (**4**) with (**2**)

Solvent	*% Yield*	*Ratio of:*		
		Z-(5)	*E-(5)*	*(6)*
dichloromethane	79	69	29	2
toluene	81	51	31	18
ethanol	53	73	27	0
dimethylformamide	85	2	30	68
pyridine	74	73	27	0

It was established that Z- (**5**) isomerized to (**6**) by heating a sample of the former alone in DMF. Again pyridine favoured the *Z* isomer and its isomerization to (**6**) in this solvent did not occur.

As a final example for this Wittig reagent and a 1,2-dione it was reacted with 1,2-cyclohexanedione (**7**) and again there was a complicating factor of isomerization in some of the solvents, but not all of them (see Table III).



(7) **(8 *E+Z*)** **(9)** ---- 4

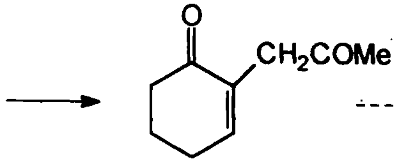
TABLE III Dependence of product ratios on solvent for the reaction of (**7**) with (**2**)

Solvent	*% Yield*	*Ratio of*		
		Z-(8)	*E-(8)*	*(9)*
dichloromethane	85	4	96	0
toluene	61	12	88	0
ethanol	73	14	82	4
dimethylformamide	83	7	59	34
pyridine	65	22	78	0

When (**7**) was reacted with acetylmethylene triphenylphosphorane (**10**) it gave *only* isomerized product (**11**) whichever of the five solvents were used; yields varied between 58% in dimethylformamide and 97% in dichloromethane.

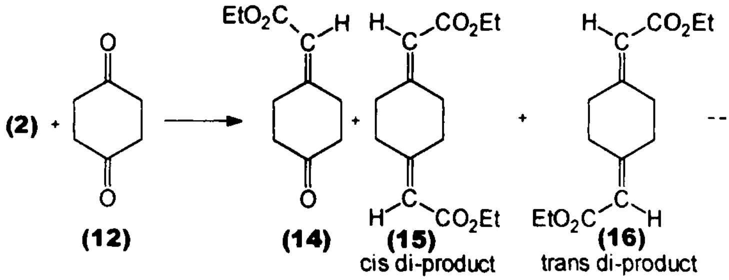
(7) + $Ph_3P{:}CHCOMe$ ⟶

(10)



(11) ---- 5

Although *Z:E* isomerism is not possible for products formed from 1,4-cyclohexanedione (**12**) it was of interest to see whether initially formed exocyclic double bonds would migrate under the conditions of the Wittig reaction since it had been previously noted that such migrations do occur for exocyclic ethoxycabonyl methylene groups but not for exocyclic cyanomethylene groups.[9] With this in mind, we reacted (**12**) with (**2**), with (**10**) and with cyanomethylenetriphenyl phosphorane (**13**), in each case using a molar ratio of 1,4-cyclohexanedione: Wittig reagent of 1:1. Equations 6 to 8 summarize the products formed.



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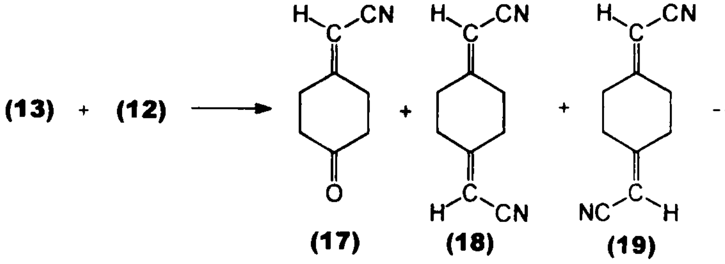

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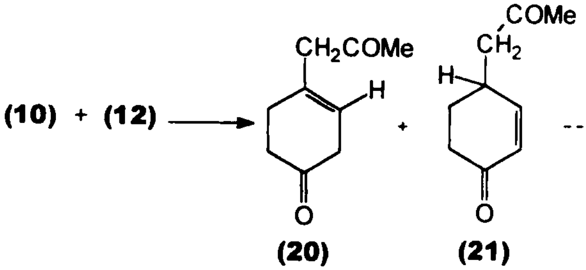

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Table IV, V and VI summarize these results. As can be seen there are two unusual features for these reactions. One is the occurrence of reaction at both carbonyl groups in spite of using a 1:1 molar ratio and this was very extensive in the case of Wittig reagent **(13)**. The other feature is the lack of an exocyclic acetylmethylene product, which is analogous to the result from 1,2-cyclohexanedione. It appears that exocyclic acetylmethylene groups have a marked tendency to rearrange to endocyclic unsaturated ketones.

TABLE IV Dependence of product ratios on the solvent for the reaction of **(12)** with **(2)**

Solvent	*% Yield*[a]	*Product (14)*	*cis di-product (15)*	*trans di-product (16)*
Dichloromethane	93	93	4	3
Toluene	80	96	2	2
Ethanol	79	88	8	4
Dimethylformamide	83	91	4	5
Pyridine	88	99	trace	trace

a. Based on the no. of moles of (2) used.

TABLE V Dependence of product ratios on the solvent for the reaction of **(12)** with **(13)**

Solvent	*% Yield*[a]	*Product (17)*	*cis di-product (18)*	*trans di-product (19)*
Dichloromethane	79	50	21	29
Toluene	68	44	22	34
Ethanol	39	54	40	6
Dimethylformamide	54	38	47	15
Pyridine	37	49	42	9

a. Based on the limiting reagent (13).

TABLE VI Dependence of product ratios on the solvent for the reaction of **(12)** and **(10)**

Solvent[a]	*% Yield*	*Product (20)*	*Product (21)*
toluene	38	92	8
dimethylformamide	33	3	97

a. Reaction in the other solvents resulted in viscous oils of uncertain composition.

Finally since the Wittig reagents sometimes gave unexpected results it was of interest to see whether the more reactive Wittig-Horner reagent would behave analogously. The molar ratios of diketone to Wittig-Horner reagents were kept at 1:1 and the solvent used was absolute ethanol. The results are:

(12) + $(EtO)_2P(O)C^-HCO_2Et\ Na^+$ ⟶ **(15)** + **(16)** ---- 9

(22) Ratio 46 : 54

88% Yield based on no. of moles of **(22)** used

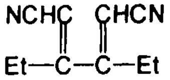
(12) + $(EtO)_2P(O)C^-HCN\ Na^+$ ⟶ **(17)** + **(18)** + **(19)** ---- 10

(23) Ratio 55 : 32 : 12

84% Yield based on no. of moles of **(23)** used

It is of interest to note that for reaction number 9 no trace of product **(14)** was detected even on testing and working up the mixture two minutes after completion of addition of the reagent. In contrast reaction 10 yielded 55% of the mono product **(17)**. This difference can only be attributed to a difference in the intermediates formed, possibly due to a difference in stabilities of the various conformations.

(4) + **(23)** ⟶



$$Et{-}\overset{\overset{\Large NCHC}{\|}}{C}{-}\overset{\overset{\Large CHCN}{\|}}{C}{-}Et$$

---- 11

(24)

100% EE isomer
74% Yield based on **(23)**

4-Cyanomethylidyne 3-hexanone was not obtained, although Taylor[10] did obtain 3-cyanomethylidyne 2-butanone from diacetyl and the corresponding Wittig reagent **(13)** which he then reacted with the corresponding Wittig-Horner reagent **(23)** to give *EE* (major) and *EZ* (minor) products. In contrast to our result in which the Wittig-Horner reagent **(23)** with 3,4-hexanedione **(4)** gave only the *EE* isomer **(24)**, (74% yield), Taylor found that **(4)** and the Wittig reagent **(13)** gave both *EE* **(24)**(38%) and the corresponding *EZ* isomer (29%). Clearly in this case the Wittig-Horner reagent was more selective than the Wittig reagent.

All the new products were identified by the usual means but it is useful to point out some salient features of their spectra, which have not been spotlighted by previous authors dealing with these types of compounds.

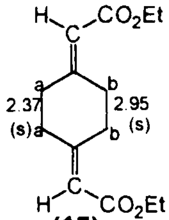
IR spectra

Z γ-keto α,β-unsaturated esters have higher ketonic carbonyl frequencies (1705–1710 cm^{-1}) than the corresponding *E* isomers (1690 cm^{-1}). For the same class the C=C frequency is about 5 cm^{-1} higher for the *Z* isomer (1640–1645 cm^{-1}) than for the *E* isomer (1635–1640cm^{-1}).

^{1}H NMR spectra

E and *Z* isomers were differentiated by means of the well documented differences in their vinyl H δ values, accentuated in γ-keto α,β-unsaturated esters because of the proximity of two groups containing C=O. However, other features of this class of compound are the lower δ values for hydrogens of the ethoxyl group in *Z* isomers as compared to *E* isomers.

Proton NMR was most useful in differentiating **(15)** from **(16)** and **(18)** from **(19)**, which could otherwise have been rather difficult to do.



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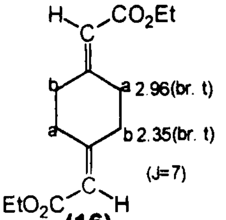
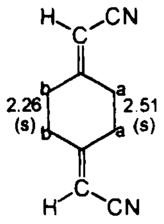
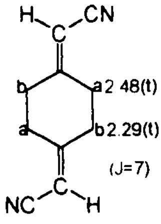


(16)

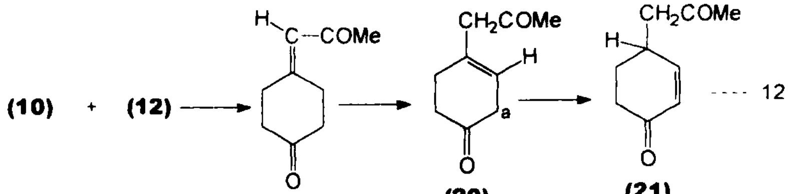


(18)



(19)

The essential features were the coupling of ring protons which only occurred in the trans isomers thus clearly differentiating them from the cis compounds. We have not attempted to establish the mechanisms involved in the formation of some of the unexpected products. We believe that probably the following sequence of reactions occurred, which would account for the formation of compound **(21)**.



(20) **(21)**

Hydrogen atoms at position (**a**) in (**20**) are both α-ketonic and allylic and hence would be susceptible to extraction by base especially in the aprotic solvent DMF in which (**21**) is formed as the major isolable product.

In reactions 7,9,10 and 11 major or sole products formed were those resulting from reaction at both carbonyl groups; in three of these cases the reactions involved the Wittig-Horner reagents (reactions 9,10 and 11) and three involved nitrile compounds (**7,10** and **11**). It seems that either the mono-products, such as (**14**) and (**17**), are so extremely reactive as compared to diketones that they are consumed at a much faster rate, which does not seem very likely, or that the ylide attacks an ionic coordinated intermediate formed from the first mole of ylide and the diketone.

There is no obvious mechanism which would account for the direct formation of *Z* isomers in pyridine and at the same time allow for the predomination of *E* isomers in other solvents. Reversible betaine formation may not occur in the case of stabilized ylides[11]and therefore any arguments based on this phenomenon would have to be well substantiated. It may well be that *E* isomers are formed initially but that on heating in the basic pyridine medium these are isomerized in some cases to *Z* isomers. It has previously been shown that[12] isomerization (*Z* to *E* and *E* to *Z*) for unsaturated esters does occur under the influence of bases.

In conclusion our study has indicated some possible guidelines for syntheses involving diketones and either stabilized Wittig reagent or Wittig-Horner reagents. Firstly, pyridine generally enhances *Z* isomer formation, and double bond migration is much less prone to occur in this solvent than in the others studied. Secondly, use of the high boiling solvents, toluene and DMF under reflux, especially the latter, results in more double bond migration in some case, and therefore these solvents should be avoided. Lastly reaction at both carbonyl groups is a complicating factor in several reactions when a 1:1.05 molar ratio of diketones to ylide was used and is more prone to occur with Wittig-Horner reagents than with

Wittig reagents. It is noticeable that this complication occurs with 1,4-cyclohexanedione but not with 1,2-cyclohexanedione.

EXPERIMENTAL SECTION

General

Melting points were done using a Fisher Johns melting point apparatus and are uncorrected. ^{1}**H NMR** spectra were recorded on either 90 MHz or 200 MHz spectrometers using $CDCl_3$as solvent. ^{13}**C NMR** spectra were recorded on a 50 MHz – spectrometer using the APT technique and as coupled or decoupled spectra. **IR** spectra were recorded on a Perkin Elmer 1430 ratio recording spectrometer. **GLC** analyses were performed using a Varian 3700 gas chromatogram with 3%SE on chromosorb WHP packing for the detection of different products, and GP 10% SP 2330 for the detection of Ph_3PO, using nitrogen as the carrier gas at a flow rate of 30 cm^3 per minute, and a flame-ionization detector. The initial column temperature was 120° for two minutes and then it was raised by 8° per minute. Peak areas were integrated with a Varian 4270 integrator. UV-spectra were determined on a Beckman spectrometer UV 5240. TLC were run on silica coated plates with fluorescent indicators. Visualising agents used were: UV light, iodine vapour, spraying with 1% $KMnO_4$ in 10% acetic acid, dilute 2,4-dinitrophenylhydrazine reagent and in some cases anhydrous $CoCl_2$ in dry acetone when phosphorus compounds were to be detected.[13] The solvent system used for TLC was diethyl ether (DE): petroleum ether (30–40) (PE) in a ratio of 1:3 or 1:8. All reactions were carried out under anhydrous conditions and under dry nitrogen.

General Experimental Procedure for Wittig reactions

In general the reactions were carried out by dissolving the phosphorane in a solvent (dimethylformamide, absolute ethanol, toluene, dichloromethane or pyridine) and then adding the diketone solution to it. The molar ratio of reactants was 1 mole of Wittig reagent to 1.05 moles of diketone. The resulting solution was then heated under reflux and monitored by titration until the phosphorane was consumed. The solvent was evaporated, low boiling petroleum ether or in some cases cold diethyl ether was added and the precipitated triphenylphosphine oxide was filtered yielding the crude ester. Isolation of *E* and *Z* esters and other products was done by chromatography using a silica gel column ≈ 50–70 cm high × 2.5 cm diameter and eluting with a ether: petroleum ether mixtures of varying ratios.

The products were identified by the combined use of GLC, NMR, IR and elemental analyses. In order to determine the ratios of product GLC's were run on (**a**) the product mixture after removal of triphenylphosphine oxide and (**b**) the fractions from the column chromatography. The results from (**a**) gave directly the ratios of products, which were identified in the usual way. The results from (**b**) enabled the purity of fractions to be precisely determined and indicated the order of elution from the column. Pure fractions were used for running spectra, preparing derivatives and for analysis.

General Experimental procedure for the Wittig-Horner reactions

The molar ratio of reactants was ≈1.05 moles of Wittig-Horner reagent to 1 mole diketone unless otherwise indicated. The reactions were done in absolute ethanol. The Wittig-Horner reagent was added to a solution of sodium which had been dissolved in absolute ethanol; this mixture was then added slowly to a solution of the diketone in ethanol. The reaction mixture was stirred throughout the period of addition. The reactions were monitored by TLC. The work-up was done by evaporating most of the ethanol and then pouring the reaction mixture into distilled water and finally extracting with pet. ether. Separation, purification, measurement of product ratios and identification was carried out in a similar manner to that described above.

Experimental Results

1- Reactions of diacetyl with ethoxycarbonylmethylenetriphenylphosphorane

The mixture of *E*+*Z* ethyl 3-methyl 4-oxo 2-pentenoate was analyzed before separation. A typical analysis for a mixture was as follows: Calculated for $C_8H_{12}O_3$: C 61.52%, H 7.74%. Found C 61.72%, H 7.82%.

TABLE VII Effect of changing the solvent on the reaction time, percent yield and E:Z ratios

Solvent	*Reaction time*	*% yield*	*Ratio of*	
			Z (3)	*Z (3)*
Dimethylformamide	45 min. Δ	83.5	72.7	27.3
ethanol	25 min. Δ	80.5	66.0	34.0
toluene	2.25 hr. Δ + overnight r.t.	94.0	68.0	32.0
dichloromethane	2.0 hr Δ + overnight r.t.	85.5	65.0	35.0
pyridine	9 hr at 50–60°C + 5 d. r.t.	84.8	36.0	64.0

***E* ethyl 3-methyl 4-oxo 2-pentenoate** had the following properties: **IR** (thin layer) (ν cm^{-1}): 1725 (s) C=O of α,β-unsaturated ester, 1690 (m) C=O of α,β-unsaturated ketone, 1640 (w) C=C. **^{1}H-NMR** (90 MHz) δ: 6.42 (s with fine splitting, C=CH, 1H), 4.23 (q, C-CH_2-O, J=7.0, 2H), 2.35 (s, CH_3-CO, 3H), 2.18 (d with fine splitting, CH_3-C=C, 3H), 1.31 (t, CH_3-C, J=7.1, 3H). **t_R** 6.77.

***Z* ethyl 3-methyl 4-oxo 2-pentenoate** had the following properties: **IR** (thin layer) (ν cm^{-1}): 1715 (s) with shoulders at 1725 and 1705 C=O of α,β-unsaturated ester, and C=O of α,β-unsaturated ketone, 1645 (m) C=C. **^{1}H-NMR** (90 MHz), δ: 5.62 (s with fine splitting, C=CH, 1H), 4.12 (q, C-CH_2-O, J=7.3, 2H), 2.27 (s, CH_3-CO, 3H), 1.95 (d with fine splitting, CH_3-C=C, 3H), 1.27 (t, CH_3-C, J=7.1, 3H). **t_R** 7.80. **^{13}C-NMR** (50 MHz), for **(E+Z) ethyl 3-methyl 4-oxo 2-pentenoate** in $CDCl_3$, δ: 199.77 (s, >C=O, ketonic), 166.21 (s, >C=O ester), 150.54 (s, >$\underline{C}$=CH), 126.47 (d, >C=$\underline{C}$H), 60.79 (t, -$\underline{C}H_2$-O), 26.14 (q, $\underline{C}H_3$-C=O), 14.26 (q, $\underline{C}H_3$-C=C) 13.20 (q, $\underline{C}H_3$-CH_2-0, one isomer), 13.04 (q, $\underline{C}H_3$-CH_2-0, second isomer). **UV** λ_{max}($CHCl_3$)nm (for a mixture of E & Z isomers) = 265, (ε/dm^3 $mole^{-1}$ cm^{-1} 3060). Both products decolourized acidified $KMnO_4$and gave yellow orange spots on TLC plate when sprayed with 2,4-DNPH. 2,4-DNPH derivatives were prepared from both E and Z isomers and recrystallized from ethyl acetate; melting points were 209° and 143–145° respectively.

2- Reactions of 3,4-hexanedione with ethoxycarbonylmethylenetriphenylphosphorane

***E* ethyl 3-ethyl 4-oxo 2-hexenoate** had the following properties: (Found C, 65.05, H, 8.97 for $C_{10}H_{16}O_3$ requires C, 65.19, H, 8.754).

n_D^{22} = 1.4590. **IR** (thin layer) (ν cm^{-1}): 1725 (vs) C=O of the α,β-unsaturated ester, 1690 (vs) α,β-unsaturated ketone, 1635 (m) C=C ^{1}**H-NMR** (80 MHz), δ: 6.41 (s, C=C$\underline{H}$, 1H), 4.22 (q, Me-C$\underline{H}_2$-O, J= 7.1, 2H), two overlapping q≡ 4H, at 2.76 (q, Me-C$\underline{H}_2$-CO, J= 7.3) and at 2.70 (Me-C$\underline{H}_2$-C=C, J= 7.2), 1.20 (three overlapping triplets ≡9H centred at about 1.16 probably corresponding to: t at 1.31, C$\underline{H}_3$-CH_2O, J=7.0, t at 1.11, C$\underline{H}_3$-CH_2-CO, J= 7.2, t at 1.02, C$\underline{H}_3$-CH_2-C=C, J= 7.35). ^{13}**C NMR**, δ: 202.68 (s, C=O ketonic), 165.97 (s, >C=O ester), 156.37 (s, $\underline{C}$=CH), 124.41 (d, C=$\underline{C}$H), 60.76 (t, CH_2-O), 31.84 (t, $\underline{C}H_2$-C=O), 20.54 (t, $\underline{C}H_2$-CH=C), overlapping signals at δ= 15.48 to δ= 4.41, due to overlapping quartets of the three methyl groups. t_R 7.17.

TABLE VIII Effect of changing the solvent on the reaction time, percent yield and E:Z ratios

Solvent	*Reaction time*	*% Yield*	*E (5)*	*Z (5)*	*I (6)*
dimethylformamide	1 hr. Δ + 2 d r.t.	85	30.0	2.3	68.7
ethanol	1.5 hr Δ + 2 d. r.t.	53	27.0	73.0	–
toluene	12 hr. Δ + 4 d. r.t.	81	30.5	51.3	18.2
dichloromethane	13 hr Δ + 4 d. r.t.	79	29.4	68.7	1.9
pyridine	11 hr at 50–70°C + 5 d. r.t.	74	27.4	72.6	–

Z ethyl 3-ethyl 4-oxo 2-hexenoate had the following properties: [Calculated for $C_{10}H_{16}O_3$: C 65.19%, H 8.754%. Found C 65.05%, H 8.89%] **IR** (thin layer) (ν cm^{-1}): 1725 (s. shoulder) C=O α,β-unsaturated ester, 1710 (vs) C=O α,β-unsaturated ketone, 1640 (shoulder) (ms) C=C.

^{1}**H-NMR** (200 MHz), δ: 5.67 (t, C=C$\underline{H}$, J=1.7, 1H), 4.15 (q, Me-C$\underline{H}_2$-O, J=7.2, 2H), 2.62 (q, Me-C$\underline{H}_2$-C=O, J=7.2, 2H), 2.31 (qd, C=C-C$\underline{H}_2$, J=7.4 and 1.6, 2H), 1.26 (t, C$\underline{H}_3$-CH_2-O, J=7.3, 3H), 1.15 (t, C$\underline{H}_3$-CH_2-C=O, J=7.8, 3H), 1.12 (t, C$\underline{H}_3$-CH_2-C=C, J=7.6, 3H). t_R 8.77.

3-ethoxycarbonylmethylene 2-hexene 4-one had the following properties: [Calculated for $C_{10}H_{16}O_3$: C 65.19%, H 8.754%. Found C 64.55%, H 8.74%]. n_D^{22} = 1.4564. **IR** (thin layer) (ν cm^{-1}): 1740 (vs) C=O ester, 1675(vs) C=O α,β-unsaturated ketone, 1650 (shoulder) C=C. **UV** λ_{max}($CHCl_3$)nm 242, (ε/dm^3 $mole^{-1}$ cm^{-1} 3060). ^{1}**H-NMR** (200 MHz), δ: 6.90 (q, C=C$\underline{H}$, J=6.9, 1H), 4.08 (q, Me-C$\underline{H}_2$-O, J=7.1, 2H), 3.31 (s, C=C-C$\underline{H}_2$-C=O, 2H), 2.68 (q, Me-C$\underline{H}_2$C=O, J=7.3, 2H), 1.86 (d, C$\underline{H}_3$-C=C, J=7.0, 3H), 1.20 (t, C$\underline{H}_3$-CH_2-O, J=7.1, 3H), 1.06 (t,

$C\underline{H}_3$-CH_2-C=O, J= 7.3, 3H). ^{13}**C-NMR** (50 MHz) decoupled, δ: 181.00 (>C=0 ketonic), 171.18 (>C=O ester), 139.76 (>$\underline{C}$=CH), 136.19 (>C=$\underline{C}$H), 60.50 (CH_3-$\underline{C}H_2$-O), 30.75 (C=C-$\underline{C}H_2$-CO), 29.75 (-$\underline{C}H_2$-CO), 14.68 ($\underline{C}H_3$-CH_2-O), 13.81 ($\underline{C}H_3$-C=C), 8.23 ($\underline{C}H_3CH_2$-C=O). **t$_R$** 9.95. The products decolourized acidified $KMn0_4$ and gave yellow-orange spots when sprayed with 2,4-DNPH on a TLC plate.

3- Reactions of 1,4-cyclohexanedione with ethoxycarbonylmethylene-triphenylphosphorane

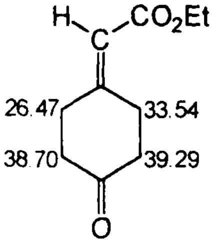
TABLE IX Effect of changing the solvent on the reaction time, percent yield and E:Z ratios

Solvent	*Reaction time*	*% Yield*	*14*	*16*	*15*
dimethylformamide	7 hr. Δ + 1 d r.t.	83	91.0	4.8	4.1
ethanol	5 hr Δ + overnight. r.t.	79	87.5	4.3	8.2
toluene	7.5 hr. Δ + 3 d. r.t.	80	96.3	1.9	1.8
dichloromethane	8.5 hr Δ + 3 d. r.t.	93	93.0	3.2	3.8
pyridine	15 hr at 50–70°C + 6 d. r.t.	87.6	98.7	0.07	0.06

The mono-product: **4-ethoxycarbonyl methylidyne cyclohexanone (14)** had the following properties: [Calculated for $C_{10}H_{14}0_3$: C 65.9%, H 7.74%, found C 65.63%, H 7.65%.]. **M.pt.**: 54–55°C. **IR** (nujol) (ν cm^{-1}), 1710 (vs) α,β-unsaturated ester, 1690 (shoulder) ketone, 1645 (m) C=C. **UV** $\lambda_{max}(CHCl_3)$nm 240, (ε/dm^3 mole^{-1} cm^{-1} 3060). ^{1}**H-NMR** (80 MHz), δ: 5.81 (m, C=C$\underline{H}$, J=1.2Hz, 1H), 4.15 (q, J=7.1Hz, $OC\underline{H}_2Me$, 2H), 3.19 (t of d, J= 6.7 & 1.4Hz, cis -$C\underline{H}_2$-C=C-CO_2Et, 2H), 2.70–2.38 (overlapping signals due to two -CH_2- in the ring next to C=O and a CH_2 next to C=CH, 6H), 1.28 (t, $C\underline{H}_3$-CH_2-O, J=7.1, 3H). ^{13}**C-NMR** (50 MHz), δ: 210.50 (ketonic -$\underline{C}$=O), 166.23 (ester -$\underline{C}$OO-), 156.93 (>$\underline{C}$=C), 116.11 (C=$\underline{C}$H), 59.66 (-O$\underline{C}H_2$-), 39.29 (-CH_2-C=O), 38.70 (-CH_2-C=O), 33.54 (-CH_2-C=C), 26,47 ($\underline{C}H_2$-C=C), 13.95 (-CH_3). **t$_R$** 14.6.

The mono-product: **4-ethoxycarbonylmethylidyne cyclohexanone** decolorized $KMn0_4$.

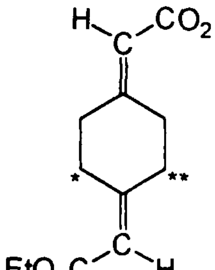
The 2,4-DNPH of the mono-product was prepared and then recrystallized from ethyl acetate yielding a solid of **M.pt.**: 180–182°C. [Calculated for $C_{16}H_{18}N_4O_6$: N 15.46%, Found: N 15.55%].



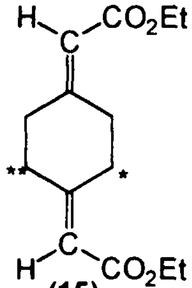
* Probable assignments

(14)

Trans-1,4-di(ethoxycarbonyl-methylidyne) cyclohexane (16), crystals, gave the following results: (Calculated for $C_{14}H_{20}O_4$: C 66.48%, H 7.93%, found C 66.44%, H 7.96%). **M.pt.**: 66°C. **IR** (nujol) (νcm^{-1}): 1715 (vs) C=O, 1655 (vs) C=C, 1255 (s) C-O as. str., 1170 (vs) C-O sym. str. **UV** λ_{max}($CHCl_3$)nm 245, (ε/dm^3 $mole^{-1}$ cm^{-1} 3040). **^{1}H-NMR** (200 MHz), δ: 5.68 (s, C=C$\underline{H}$, 2H), 4.1 (q, O-C$\underline{H}_2$-Me, J=7.1, 4H), 2.96 (broad t, -C$\underline{H}_2{}^*$-C=C, J=6.9, 4H), 2.35 (broad t, -C=C-C$^{**}\underline{H}_2$, J=6.7, 4H), 1.24 (t, C$\underline{H}_3$-CH_2-, J=7.1, 6H)(see fig. 16 below). **^{13}C-NMR** (50 MHz) decoupled, δ: 166.59 (>C=O), 160.06 (>$\underline{C}$=CH), 114.54 (C=$\underline{C}$H), 59.46 (O-CH_2), 35.72 (-$\underline{C}^*H_2$), 29.30 (=C-$^{**}\underline{C}H_2$)13.97 (-CH_2-$\underline{C}H_3$). (see fig.16 below). t_R 16.1.



(16)
trans-isomer



(15)
cis-isomer

Cis-1,4-di(ethoxycarbonyl methylidyne) cyclohexane (15), an oil, gave the following results: (Calculated for $C_{14}H_{20}O_4$: C 66.48%, H 7.93%, found C 66.04.%, H 8.11%). **IR** (thin layer) (ν cm^{-1}): 1715 (s) α,β-unsaturated ester, 1648 (m) C=C. **UV** λ_{max}($CHCl_3$)nm 241, (ε/dm^3 mole^{-1} cm^{-1} 3040). ^{1}**H-NMR** (200 MHz), δ: 5.67 (s, C=C$\underline{H}$, 2H), 4.14 (q, Me-C$\underline{H}_2$-O, J=7.2, 4H), 2.95 (s, C$^*\underline{H}_2$-C=C, 4H), 2.37 (s, C=C-C$^{**}\underline{H}_2$, 4H), 1.26 (t, C$\underline{H}_3$-CH_2-, J=7.3, 6H). (see fig. 15 above). ^{13}**C-NMR** (50 MHz) decoupled, δ: 166.60 (C=O), 159.46 (>$\underline{C}$=CH), 114.81 (C=$\underline{C}$H), 59.74 (O-CH_2), 37.29 ($^*\underline{C}H_2$-C=C), 28.91 (-$^{**}\underline{C}H_2$-C=C), 14.34 ($\underline{C}H_3$-CH_2-). (see fig. 15 above). t_R 16.5.

4- Reactions of 1,2-cyclohexanedione with ethoxycarbonylmethylenetriphenyl-phosphorane

TABLE X Effect of changing the solvent on the reaction time, percent yield and E:Z ratios

Solvent	*Reaction time*	*% Yield*	*E (8)*	*Z (8)*	*9*
Dimethylformamide	6 hr. Δ + 2 d. r.t.	83	59	7.4	33.6
ethanol	4 hr Δ + 1 d. r.t.	73	81.6	14.4	4.0
toluene	8 hr. Δ + 2 d. r.t.	61	87.7	12.35	–
dichloromethane	8 hr Δ + 4 d. r.t.	85.2	96.4	3.6	–
pyridine	15 hr at 50–70°C + 6 d. r.t.	65	78.0	22.0	–

Only product **8** (E isomer) was isolated in a pure form, products **8** (Z isomer) and **9** were difficult to separate from **E-8**, and thus spectroscopic analyses of a mixture of all three products were done. **IR** (thin layer) (ν cm^{-1}) of the mixture of products: 1735–1720 (vs) ester, 1680 (vs) ketone, shoulders at 1650, 1640 and 1620 C=C. ^{1}**H-NMR** (80 MHz), of the mixture of products obtained from the reaction in dimethylformamide δ: Peaks due to the isomer **9**: 6.83 (broad **t**, C=C$\underline{H}$, J=4), 3.16 (d, C$\underline{H}_2$-CO_2Et, J=0.5) and at 3.06 (probably due to C=C-C$\underline{H}_2$, ring). Peak due to the E-isomer of **8**: 6.43 (t, C=C$\underline{H}$ of **E-8**, J=2.3). Peak due to the Z- isomer of **8**: 5.63 (poorly resolved signal, C=C$\underline{H}$of **Z-8**). Signals for ring methylene groups of the three isomers overlapped. t_R 12.4, 13.73 and 14.3 for **E-8**, **9** and **Z-8** respectively.

E-ethyl 2-(2-oxocyclohexylidene) acetate (E-8) had the following properties: [Calculated for $C_{10}H_{14}O_3$: C 65.91%, H 7.74%. Found C 65.47%, H 7.85%]. **IR** (thin layer) (ν cm^{-1}): 1720 (vs) C=O of the α,β-unsaturated ester, 1700 (vs) α,β-unsaturated ketone, 1630 (m) C=C. ^{1}**H-NMR** (200 MHz), δ: 6.47 (t, C=C$\underline{H}$, J=2.2), 4.20 (q, -C$\underline{H}_2$-O, J=6.7), 3.10 (m, ring-C$\underline{H}_2$ adjacent to >C=C, 2H), 2.54 (t, C$\underline{H}_2$-C=O, J=6.8, 2H), multiplets centred at about 1.9 ring -C$\underline{H}_2$- groups, 1.30 (t, C$\underline{H}_3$-CH$_2$-O, J=7.1). **t$_R$** 12.40. The products decolourized acidified KMnO$_4$ and gave yellow and orange spots when sprayed with 2,4-DNPH on a TLC plate.

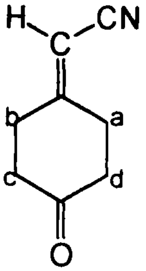
5- Reactions of 1,4-cyclohexanedione with cyanomethylenetriphenylphosphorane

TABLE XI Effect of solvent on the % yield and the rates of reactions

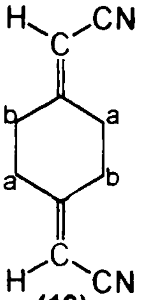
Solvent	*Reaction time*	*% Yield*	*17*	*19*	*18*
dimethylformamide	4 hr. Δ	54	37.7	15.4	46.9
ethanol	0.5 hr Δ	38.5	53.8	6.2	40.0
toluene	4.5 hr. Δ + overnight r.t.	68	43.7	34.5	21.8
dichloromethane	12 hr Δ + 2 d. r.t.	79	49.5	29.1	21.4
pyridine	14 hr Δ + 3 d. r.t.	37	48.5	9.0	42.5

The mono-product **4-cyanomethylidyne cyclohexanone (17)** gave the following results: A yellow spot when sprayed with 2,4-DNPH on a TLC plate, **r$_f$** value (pet. ether: ether 3:1) 0.130. [Calculated for C_8H_9ON: N 10.36%, found N 10.07%]. **IR** (nujol) (ν cm^{-1}) showed: 2200 (s) C≡N, 1710–1715 (s) ketone, 1625 (s) C=C. **UV** λ_{max}(CHCl$_3$)nm 240, (ε/dm^3 mole^{-1} cm^{-1} 3060). ^{1}**H-NMR** (200 MHz), δ: 5.315 (s, C=C$\underline{H}$, 1H), 2.88 (t, -C$\underline{H}_2$- at position **a**, 2H, J=7.1), 2.68 (t, C$\underline{H}_2$- at position **b**, 2H, J=6.9), 2.51 and 2.475 (two t, -C$\underline{H}_2$- at position **c**and **d**, 4H, J=7.3 and 7.1). (The last four are possible assignments). ^{13}**C-NMR** (50 MHz), δ: 181.00 ($\underline{C}$=O), 162.46 ($\underline{C}$=CH), 116.07 (C≡N), 95.77 (C=$\underline{C}$H), 39.17 (-CH$_2$- at position **a**), 38.80 (-CH$_2$- at position **b**), 32.23 (-$\underline{C}$H$_2$- at position **d**), 29.70 (-$\underline{C}$H$_2$- at position **c**). (The last four are possible assignments). **t$_R$**10.74.

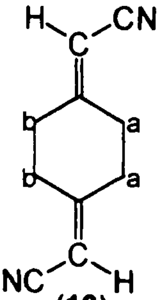
The di-products of **1,4-dicyanomethylidyne cyclohexane (18 and 19)** were very difficult to separate. The mixture gave the following results: [Calculated for $C_{10}H_{10}N_2$: C 75.92%, H 6.37%, N 17.71%, found C 74.82%, H 6.48%, N 17.5%]. **IR** (KBr) (ν *cm^{-1}) showed: 3040 (=C-H), 2960 (>C-H),* 2210 (s) C≡N, 1630 (s) C=C. **UV** λ_{max}(CHCl$_3$)/nm 242. ^{1}**H-NMR** (200 MHz), δ: 5.06 (s, C=CH, 2H), 2.505 (s) and 2.48 (t, J=7.1) overlapping (C-C$\underline{H}_2$-C at position **a**, 4H), 2.29 (t, J=7.0) and 2.26 (s) overlapping (C-C$\underline{H}_2$-C at position **b**, 4H). ^{13}**C-NMR** (50 MHz), δ: 163.29,



(17)



(19)



(18)

163.23 ($\underline{C}$=CH, two di-isomers), 116.18 ($\underline{C}$≡N), 106.43 ($\underline{C}$≡N), 94.99 (C=$\underline{C}$H), 34.81 (-$\underline{C}H_2$- at position **a** for **18**), 34.43 (-$\underline{C}H_2$- at position **a** for **19**), 32.195 (-$\underline{C}H_2$- at position **b** for **19**), 31.84(-CH_2-at position **b** for **18**). (The last four are possible assignments). t_R 22.12 and 24.96 for **19** and **18** respectively.

6- Reactions of 1,2-cyclohexanedione with acetylmethylenetriphenylphosphorane

TABLE XII

Solvent	*% yield of (11)*	*Reaction time*
dimethylformamide	58	10 hr. Δ + over n. r.t.
ethanol	57	25 hr Δ + 3 d. r.t.
toluene	81	4 hr. Δ
dichloromethane	97	25 hr Δ + 3.5 d. r.t.
pyridine	95	12 hr Δ + 2 d. r.t.

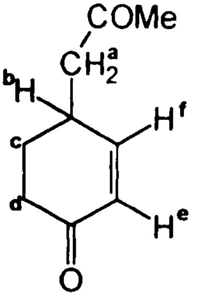
Neither the Z nor the E 2-acetylmethylidyne cyclohexanone was isolated. The only product obtained was **2-acetonyl 2-cyclohexene-1-one (11)** which had the following properties: **IR** (thin layer) (ν cm^{-1}): 1710 (vs) C=O ketonic, 1670(vs) C=O ketonic (ring), 1630 (shoulder) C=C. ^{1}**H-NMR** (270 MHz), δ: 6.7 (t, CH=C, J=5 Hz, 1H), 3.1 (s, 2H at position b), 2.3 (m, 4H at position d and f), 2.05 (s, 3H at position a), 1.9 (broad quintet, –2H at position e, J=6Hz). **MS** m.wt. 152, requires m.wt. 152. Iodoform test: +ve. 2,4-DNPH: +ve. t_R 13.67.

7- Reactions of 1,4-cyclohexanedione with acetylmethylenetriphenylphosphorane

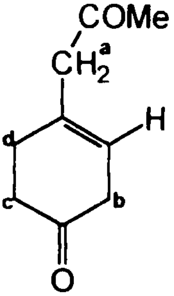
Using the same experimental conditions as in other experiments all reaction mixtures became extremely dark and none of the expected products could be isolated for reactions carried out in ethanol, dichloromethane and pyridine. However, the reaction carried out in dimethylformamide gave 31.7% of **21** with a trace of (0.86%) **20**, plus unidentified products (31.7%) and unreacted diketone (26.7%), while the reaction carried out in PhMe gave 1% **21**, 35% **20** plus 5% unidentified products and 56% unreacted diketone by glc.

Both **21** and **20** gave the following results: **MS** m.wt.152, requires m.wt.152. **IR** (thin layer)(ν cm^{-1}) of the mixture of products: 1725 (shoulder) isolated ring C=O, 1715 (vs) acetyl C=O, 1680 (vs) conjugated ring C=O, 1640 (shoulder) C=C.

21 was found to be **4-acetonyl 2-cyclohexene-1-one** and gave the following: ^{1}**H NMR** (200 MHz), δ: 6.76 (d with fine structure, C=CH at position f, J = 10.2, 1.3, 1H), 5.93 (d of d, C=CH at position e, J = 10.1, 2.3, 1H), 2.95 (m, -CH-at position b, J difficult to determine, 1H), 2.58 (d, $-CH_2-$ at position a, J = 7.4, 2H), 2.39 (m, $-CH_2-$ at position d, 2H), 2.15 (s, $-CH_3$, 3H), 2.10 (m, one hydrogen of the $-CH_2-$ at position c, 1.63 (m, the second hydrogen of the $-CH_2-$ at position c). Iodoform test: +ve. $\mathbf{t_R}$ 16.42.



structure (**21**)



structure (**20**)

20 was found to be **4-acetonyl 3-cyclohexene-1-one** and gave the following: ^{1}**H NMR** (200 MHz), δ: 5.56 (t with fine structure, C=CH), 3.18 (broad s, $-CH_2-$ at position a), 2.89 (m, $-CH_2-$ at position b), 2.44 (multiplets, hydrogens at positions c and d), 2.17 (s, -CH_3). lodoform test: +ve. t_R17.09. 2,4-DNPH: +ve.

8- Reaction of triethylphosphonoacetate with 1,4-cyclohexanedione

Triethylphosphonoacetate (5.645 g, 5.0 ml, 0.0252 moles) was added to a solution of sodium (0.513 g, 0.0223 moles) which had been dissolved in absolute ethanol (50 ml). This mixture was then added slowly to a solution of 1,4-cyclohexanedione (2.38 g, 0.0212 moles) in absolute ethanol (about 10 ml) over a period of 20–30 minutes. The reaction was worked up after 2 minutes, 3 hrs., 48 hrs and in all case did not result in the isolation of the mono-product **14** and only products **16** and **15** were obtained. The percentage of **16** ranged from 52 to 56.0 and of **15** from 44 to 48. The melting point, analytical and spectral data and retention times of **16** and **15** agreed with those in experiment 3.

9- Reaction of diethyl(cyanomethylene)-phosphonate with 1,4-cyclohexanedione

Diethyl (cyanomethylene)-phosphonate (4.56 g, 4.16 ml, 0.0252 moles) was added to a solution of sodium (0.579 g, 0.0252 moles) which had been dissolved in absolute ethanol (about 40 ml). This mixture was then slowly added to a solution of 1,4-cyclohexanedione (2.69 g, 0.024 moles) in ethanol (about 20 ml) over a period of 20–30 min. The reaction mixture was stirred under nitrogen and after 1 hr of mixing a ppt. started to form. The reaction was complete after 2 hrs of addition. The total weight of the crude products was 2.73g (53.3% of which was mono-product, 43.2% di-product and 3.5% unreacted diketone). The di-products obtained could not be separated by column chromatography. The physical properties, analytical data, spectral data and retention times agreed with those given in experiment 5.

10- Reaction of diethyl (cyanomethylene)phosphonate with 3,4-hexanedione

Diethyl (cyanomethylene)-phosphonate (4.560 g, 4.160 ml, 0.0257 moles) was added to a solution of sodium (0.579g, 0.0252 moles) which had been dissolved in absolute ethanol (about 40 ml). This mixture was then slowly added to a solution of 3,4-hexanedione (2.74 g, 2.90 ml, 0.0240 moles) in absolute ethanol (about 20 ml) over a period of 20–30 min. The reaction was complete after 1.5 hr. The main product was EE (or ZZ) 3,4-di(cyanomethylidene) hexane (1.49g, 74%) and it had the following properties: **M.pt** 99°. **IR** (nujol) (ν cm^{-1}): 2220 (vs) C≡N, 1580 (s) C=C. **UV** λ_{max} ($CHCl_3$)/nm 265. ^{1}**H-NMR** (200 (MHz), δ: 5.48 (s, C=CH, 2H), 2.59 (q, -$\underline{CH_2}$-, J=7.7, 4H), 1.09 (t, $\underline{CH_3}$-C. J=7.6, 6H). ^{13}**C-NMR** (50 MHz), δ:162.15 ($\underline{C}$=CH), 115.93 (C≡N), 99.74 (C=$\underline{C}$H), 25.395 (-CH_2-), 12.93 (-CH_3). $\mathbf{t_R}$ 15.8.

There were two unidentified products at $\mathbf{t_R}$ 7.75 and 16.9 which did not contain any phosphorus.

11- Effect of different solvents on the rate of the reaction of ethoxycarbonyl-methylenetriphenylphosphorane and diacetyl

Equal molar quantities of ethoxycarbonylmethylenetriphenylphosphorane (2.2g, 95%, 6.0x10^{-3} moles) were dissolved in equal volumes (20 ml) of dichloromethane or absolute ethanol or dimethylformamide or toluene. Diacetyl (0.54 g, 0.55 ml, 6.27 × 10^{-3}moles) was added to the four solutions in the ratio of 1:1.045, Wittig to diketone. The reactants were allowed to react at R.T. under nitrogen and were monitored by titration. The results are shown in table XIII

TABLE XIII Percent Reaction

Time	*dichloromethane*	*ethanol*	*dimethylformamide*	*toluene*
5 min.	26	86	26	(inhomogeneous)
0.5 hrs	69	100	73 (40 min)	69
1.5 hrs	81			77
2.0 hrs	86		75	85.5
8.0 hrs	86		83.5	90
24 hrs	94		94	94
48 hrs	94		94	94
72 hrs	94		94	94

The reactions were worked up the usual way and they gave the following % yields of mono-products: in dichloromethane 75, in ethanol 73, in dimethylformamide 69, and in toluene 91.5. The ratio of E:Z isomers of the mono-products was found by GLC to be in these solvents

73:27 in dichloromethane, 74:26 in ethanol, 78:22 in dimethylformamide and 72:28 in toluene.

12- Isomerization of Z-ethyl-3-ethyl-4-oxo-2-hexenoate to 3-ethoxycarbonylmethylene-2-hexene-4-one

0.1g of the crude product obtained from the reaction of ethoxycarbonylmethylenetriphenylphosphorane with 3,4-hexanedione in dichloromethane, was heated under nitrogen in 5 ml dimethylformamide. The reaction was monitored by GLC and the % of each component was determined at 0 hours, after 7.5 hours of heating and 1 day at room temperature and finally after 7.5 hours heating and 100 hours at room temperature. For these three determinations the percentage of E ethyl 3-ethyl 4-oxo 2-hexenoate (t_R 6.67) were 26, 26 and 26 respectively, for the Z isomer (t_R 8.26) 71, 66 and 50 respectively and for

3-ethoxycarbonylmethylene 2-hexene 4-one (t_R 9.66) 3, 8 and 24 respectively.

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