A COMPARATIVE STUDY OF THE REACTION OF SOME
STABILIZED PHOSPHONIUM YLIDS AND PHOSPHONATE
CARBANIONS WITH CONJUGATED ACETYLENIC KETONES

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ABSTRACT

A COMPARATIVE STUDY OF THE REACTION OF SOME STABILIZED PHOSPHONIUM YLIDS AND PHOSPHONATE CARBANIONS WITH CONJU-GATED ACETYLENIC KETONES
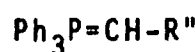
Thomas Chaly

A comparative study has been done of the reaction of ten conjugated acetylenic ketones of the type 18 with two stabilized phosphonate carbanions 19 and the corresponding phosphonium ylids 20, in 1,2-dimethoxyethane as solvent. The products isolated include the 'normal' enynes 21,

$R-C\equiv C-CO-R'$ $(EtO)_2P(O)\bar{C}HR''$ $Ph_3P=CH-R''$
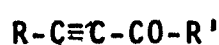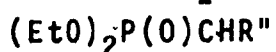
<u>18</u>   <u>19</u>   <u>20</u>
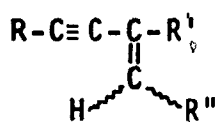
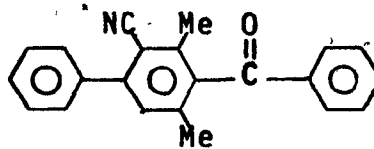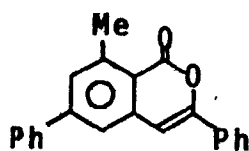(b) R = Me; R' = Ph   (a) R" = CN   (b) R" = COOEt
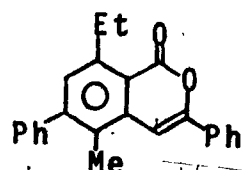
(h) R = Et; R' = Ph

21

45

47

53

and the 'abnormal' products 45 (biphenyl derivative), 47 and 53 (isocoumarin derivatives), all of which were

previously unknown in the literature.

The ylids were much less reactive than the phosphonate carbanions in Wittig-type reactions yielding the 'normal' enynic products 21. In the case of the phosphonate carbanions two of the ketones yield only the 'abnormal' products 45 (from 18b and 19a), 47 (from 18b and 20b) and 53 (from 18h and 20b).

The stereochemistry and the isomer distribution of the enynes were established by the use of NMR spectroscopy. In some cases the E and Z isomers of 21 were separated by column chromatography. The structures were assigned to the 'abnormal' products 45, 47 and 53 on the basis of IR, UV, NMR, Mass spectral data and elemental analysis. Plausible mechanisms for the formation of these products have been postulated. Some factors responsible for the differences in the reactivities of the ylids and the phosphonate carbanions are also discussed.

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INTRODUCTION

The Wittig reaction has now been firmly established in the arsenal of synthetic organic chemistry for the creation of a carbon-carbon double bond. This reaction has been reviewed extensively,[1,2] and involves the condensation-elimination reaction between a phosphorane ("Phosphonium Ylid" or "Phosphine Methylene") and a carbonyl compound to yield an ethylene derivative and a phosphine oxide.

$$R_3P=CR_2' \quad + \quad R_2''C=0 \quad \longrightarrow \quad R_2'C=CR_2'' \quad + \quad R_3P=0$$
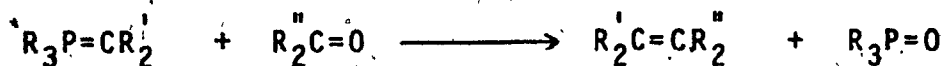
The reaction between a carbonyl compound and a phosphonium ylid was known as early as 1919 when Staudinger[3] found that benzhydrylidenetriphenylphosphorane reacted with phenylisocyanate producing triphenylphosphine oxide and triphenylketenimine. Soon afterwards it was discovered that the same

$$Ph_3P=CPh_2 \nearrow^{Ph-N=C=0} Ph_3PO + Ph-N=C=CPh_2$$
$$\searrow_{Ph_2-C=C=0} Ph_3PO + Ph_2-C=C=CPh_2$$

1
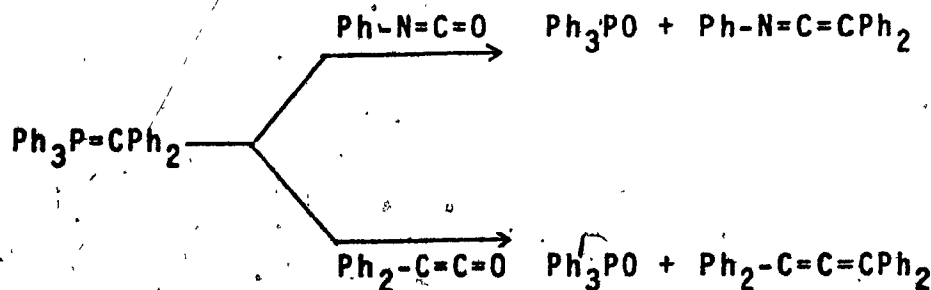
ylid reacted with diphenylketene giving triphenyl-
phosphine oxide and tetraphenylallene.[4]   It was
only in the 1950's that Wittig and coworkers were
able to demonstrate the versatility of the reaction
between a phosphonium ylid and a carbonyl compound.[5,6]
The reaction ,now aptly called the Wittig reaction,is
known; to take place with such wide range of carbonyl
compounds as saturated and unsaturated aldehydes,[7]
aromatic aldehydes,[6,8] aliphatic and aromatic
ketones[8] ,ketenes,[4,9,10] thioketones,[11] iso-
cyanates,[3] and Schiff's base.[12]

The phosphonium ylids are a class of compounds
which contain an anionic carbon attached to a
phosphorus atom which carries a high degree of positive
character,and they are usually represented as hybrid

$$\geq \overset{+}{P}\text{---}\overset{-}{C}\leq \quad \longleftrightarrow \quad \geq P=C\leq$$

$$\underline{1a} \qquad\qquad\qquad \underline{1b}$$
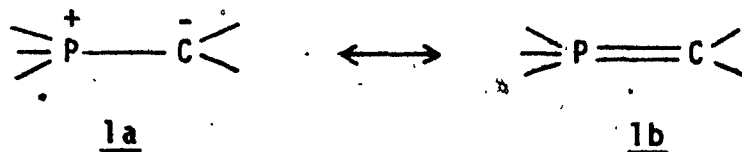
between the dipolar structure 1a and the covalent
structure 1b. Their reactivity is variable,and
depends mainly on the negative character of the

carbon atom <u>alpha</u> to the phosphorus atom.When the groups attached to the α-carbon have electron - withdrawing properties,the delocalization of the electron density of the anionic carbon makes the ylid more stable,and such ylids can be readily isolated and purified.[13]   Ylids which are not thus stabilized are usually prepared <u>in situ</u> for the purpose of the Wittig reaction .In general,the more,stable an ylid is the less reactive it is in Wittig reaction.This reduced reactivity is attributed to the lowered nucleophilicity of the α-carbon due to electron delocalization.

The presence of unsaturation in the carbonyl compound was found not to affect the normal course of the Wittig reaction.Many conjugated carbonyls have been successfully employed in the Wittig synthesis, especially in the fields of terpenes and carotenoids, and the topic has been reviewed.[14.] It must be pointed out,however,that the carbonyl compounds in most instances have been aldehydes,and the ylids were those of high reactivity, being unstabilized by electron-withdrawing substituents.Thus Bohlman and

coworkers [15-17] reacted the aldehydes 2 and 3 with the ylid 4 producing the expected products in the

$$H-C\equiv C-CHO \qquad H-C\equiv C-CH=CH-CHO \qquad Ph_3\overset{+}{P}-\overset{-}{CH}-CH=CH-R$$

$$\underline{2} \qquad\qquad \underline{3} \qquad\qquad \underline{4}$$

$$(R=\underline{n}-Bu;\underline{n}-Hex)$$
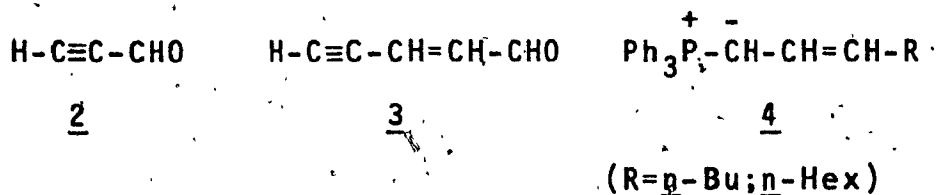
synthesis of several polyenynes.

The methylenecyclopropene derivative 7 has been prepared from the reaction between diphenylcyclo-propenone (5) and carbethoxymethylenetriphenyl-phosphorane [18] (6 ;R = Et).The Wittig reaction between

$$\underline{5} \qquad\qquad \underline{6} \qquad\qquad \underline{7}$$
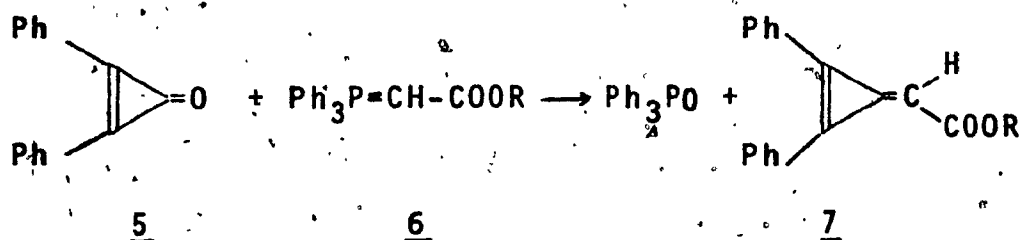
the stable carbomethoxymethylenetriphenylphosphorane (6; R = Me) and the α,β-acetylenic ketone 8 has been made use of by Serratosa [19] in an approach to the

$$\underline{8}$$
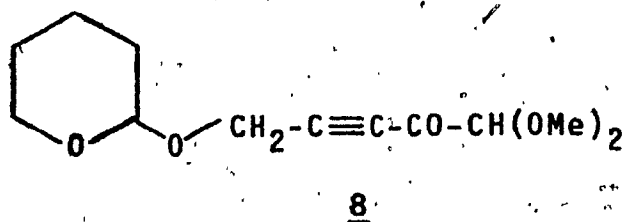
total synthesis of patulin derivatives.Apart from
a few isolated studies such as these there seems to
have been no systematic study of the reaction of α,β-
acetylenic ketones and stabilized phosphonium ylids.

.The versatility of the reaction between phosphoranes
(ylids) and carbonyl compounds in producing a wide
variety of olefinic compounds has given incentive to
the search for other organophosphorus reagents in olefin
synthesis.The most significant outcome has been the
discovery that phosphoryl-stabilized carbanions have
just as wide an applicability,if not more,in the
preparation of olefinic compounds.In addition,these
carbanions offer significant advantages over the
conventional Wittig procedures.The synthetic applications
of phosphoryl-stabilized anions have been reviewed very
recently by Wadsworth.[20]

The anions required for the olefin synthesis are
generally liberated from compounds having active
methylene groups such as phosphonates of the type 9 by
treatment with a base.These anions,having their negative
charges located next to a P(O) group,are stabilized

$$(RO)_2P(O)-CH_2-R' \xrightarrow{\text{B:}} (RO)_2\overset{\overset{O}{\|}}{P}-\overset{-}{C}H-R' \quad \underline{10\ a}$$

$$\updownarrow$$

$$(RO)_2\overset{\overset{O^-}{|}}{P}=CH-R' $$

$$\underline{10\ b}$$
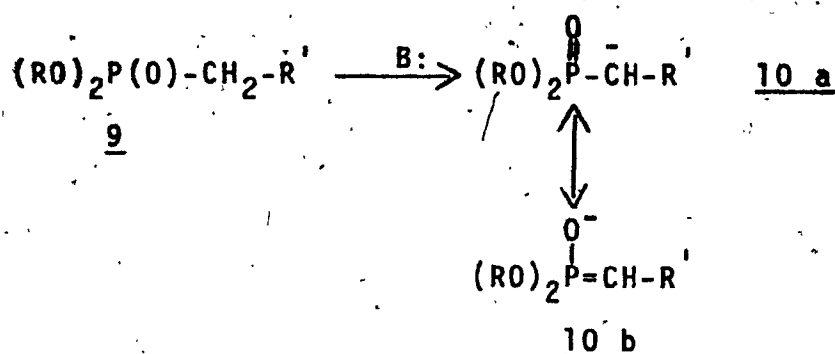
through delocalization of the charges through the phosphoryl group. This stability is undoubtedly derived from the fact that the phosphorus atom can become pentacovalent by use of its d-orbitals (d π-p π bonding). The P(O) group is not as effective as a carbonyl group in stabilizing a negative charge; but if R' in $\underline{9}$ is an electron-withdrawing group such as CN, COOEt or a keto group, the stability of an anion $\underline{10}$ is enhanced due to the delocalization of the negative charges into these groups as well.

.The olefin-forming reaction between a carbonyl compound and a phosphonate carbanion was first reported by Horner and coworkers.[21,22] Diethylbenzylphosphonate ($\underline{11}$) was reacted with benzophenone in presence of sodamide to produce triphenylethylene ($\underline{13}$) in 88% yield. The reaction of the anion from the same phosphonate with

$(EtO)_2P(O)-CH_2-Ph$ $\xrightarrow[\text{2.Ph}_2\text{C=O}]{\text{1.NaNH}_2}$ $(EtO)_2P(O)-O^-$ +

$\underline{11}$ $\underline{12}$

$Ph_2C=CHPh$

$\underline{13}$

$\underline{11}$ $\xrightarrow[\text{2.PhCHO}]{\text{1.}\underline{t}\text{-BuOK}}$ $\underline{12}$ + $PhCH=CHPh$

$\underline{14}$
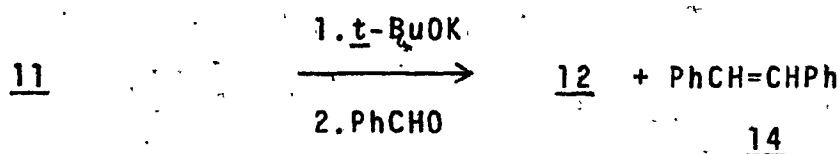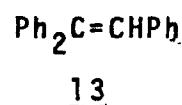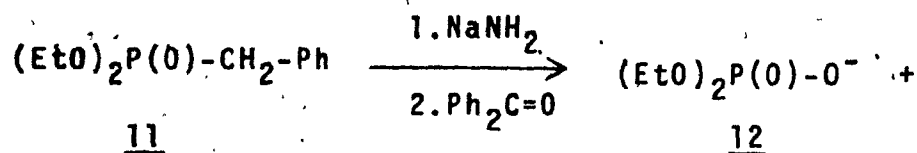
benzaldehyde produced stilbene ($\underline{14}$) in moderate yield.[22]
Later ethylcinnamate was obtained in low yield upon
treatment of ethyl diethylphosphonoacetate ($\underline{15}$) with
benzaldehyde in presence of piperidine.[23] However, in
this work it was incorrectly assumed that the product

$(EtO)_2P(O)-CH_2-COOEt$ $\xrightarrow[\text{2.benzaldehyde}]{\text{1.piperidine}}$ $PhCH=CH-COOEt$

$\underline{15}$ $\underline{16}$
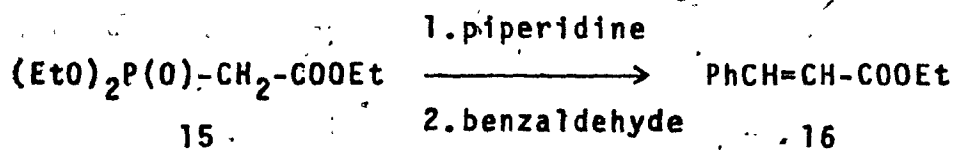
arose from the hydrolysis and subsequent decomposition
of a benzylidene intermediate $PhCH=C(COOEt)P(O)(OEt)_2$.
Soon afterwards Wadsworth and Emmons carried out a
detailed study of the utility of phosphonate carbanions

in olefin synthesis,and demonstrated that the reaction
of the carbanions containing electron-withdrawing
groups with aldehydes or ketones in an aprotic solvent
constituted a useful olefin synthesis.[24] The carbanions
were found to be,in general,more reactive than the
analogous triaryl phosphoranes ("Wittig reagents"),and
the technique offered contain special features which
enhanced the use of these carbanions in olefin synthesis.

In comparison with the phosphoranes the phosphonate
carbanions are less expensive and are reactive towards
a wider variety of carbonyl compounds under milder
conditions.In many instances the reaction takes place
at room temperature and undesirable side products are
minimal.[24] In addition to the availability of the reagents.
and convenient reaction conditions,the workup and isolation
of the olefinic products are also easier than in the
conventional Wittig reaction.Using sodium hydride as the
base and dimethoxyethane as solvent the isolation of the
olefinic products is simpler since the alkali metal
phosphate is readily soluble in water.As indicated by a
number of reviews these carbanions have thus become one of
the most frequently used organophosphorus reagents in

olefin synthesis.[25,26] The procedure has sometimes
been referred to as the Horner-Wittig synthesis,[27] or
the Horner-Emmons,[28] or Wadsworth-Emmons [20] modi-
fication of the Wittig reaction. It is clear that the
P(O)-stabilized anions have been used mainly with a
view to widening and extending the scope of the Wittig
reaction.

There has been no systematic study of the P(O)-
activated olefin synthesis with refrence to α,β-
unsaturated carbonyl compounds. However, there has been
scattered reports of the use of α,β-unsaturated
aldehydes and ketones in such synthesis. The anion 17
from phosphonoacetonitrile has been reacted with the un-
saturated carbonyl systems of steroids,[29] and of
cis-β-ionone.[30] However, in these reactions the stereo-

$(EtO)_2P(O)-\overset{-}{C}H-CN$

17

+

→

HC
|
CN

(ref.29)

17   +   [structure] → [structure]   (ref.30)
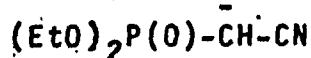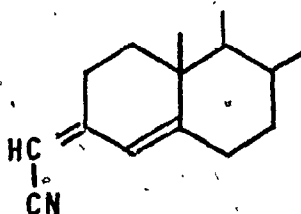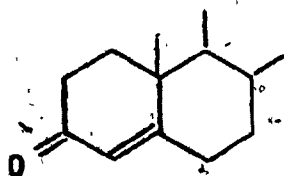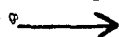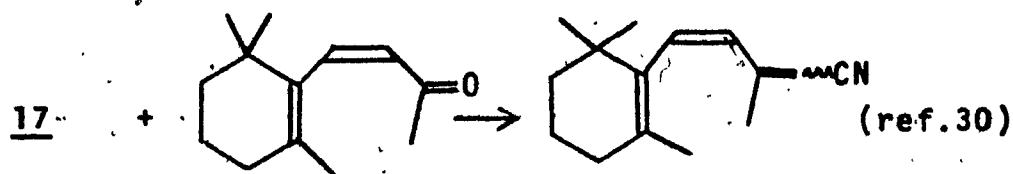
chemistry of the newly formed double bond in the
derivatives has not been established.

    Corey and coworkers have made use of open-chain
α,β-unsaturated   aldehydes with   α,β-unsaturated
phosphonatecarbanions to prepare derivatives of C_{18}
Cecropia juvenile hormone.[31,32]   Similar reactants
have been used by Edwards et al. [33] during the synthesis

$(EtO)_2P(O)-CH_2-C(CH_3)=CHCOOMe$
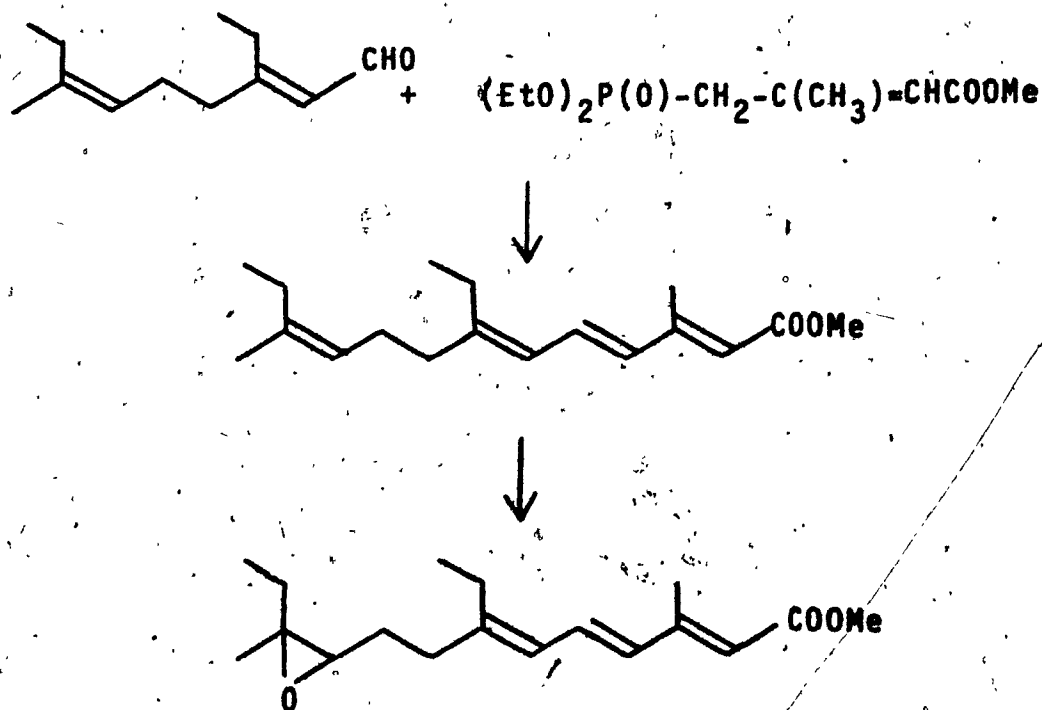
of (+)-trisporic acid β-methyl ester.These reactions
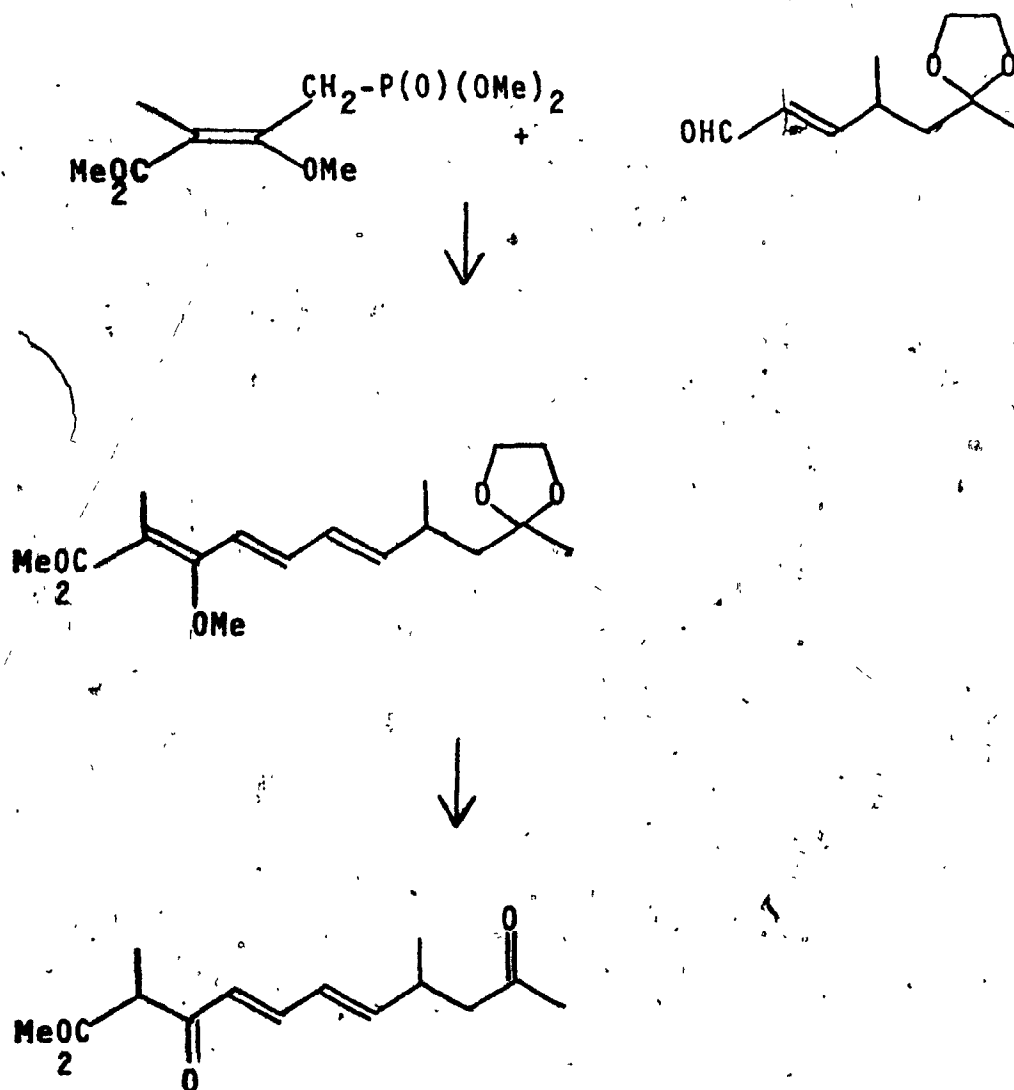
exhibited remarkable _trans_ stereospecicity and
demonstrated that the _trans_-alkylphosphonate
undergoes practically no isomerization upon formation

of its anion and subsequent olefination. Other α,β-unsaturated aldehydes used in making conjugated dienes included cinnamaldehyde [24] and 2-alkylacroleins.[34] The

$$p\text{-}C_6H_4[CH_2P(O)(OEt)_2]_2 \quad + \quad 2PhCH=CH\text{-}CHO$$

$$\downarrow NaOH$$

$$p\text{-}C_6H_4(CH=CH\text{-}CH=CH\text{-}Ph)_2.$$

$$CH_2=C(R)CHO \quad + \quad (EtO)_2P(O)CH_2COOEt$$

$$\downarrow \begin{array}{l} 1.\ EtONa \\ 2.\ EtOH \end{array}$$

$$CH_2=C(R)\text{-}CH=CH\text{-}COOEt \quad + \quad EtO\text{-}CH_2\text{-}CH(R)\text{-}CH=CH\text{-}COOEt$$
$$(50\text{-}60\%)$$
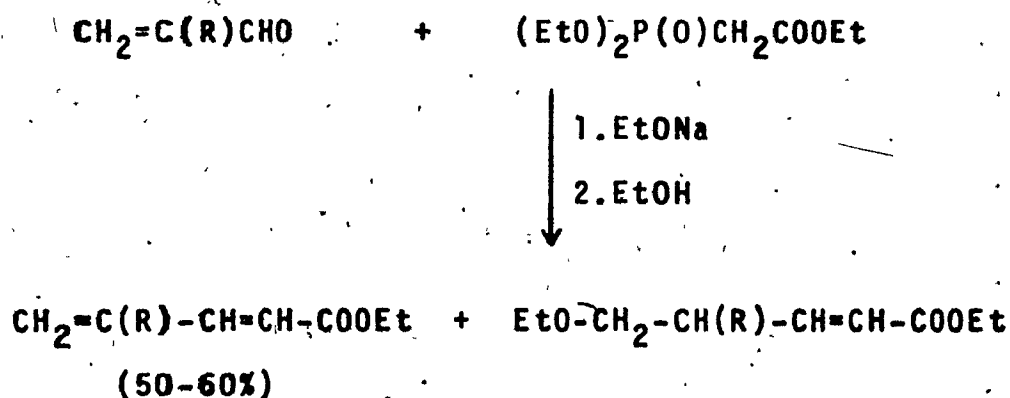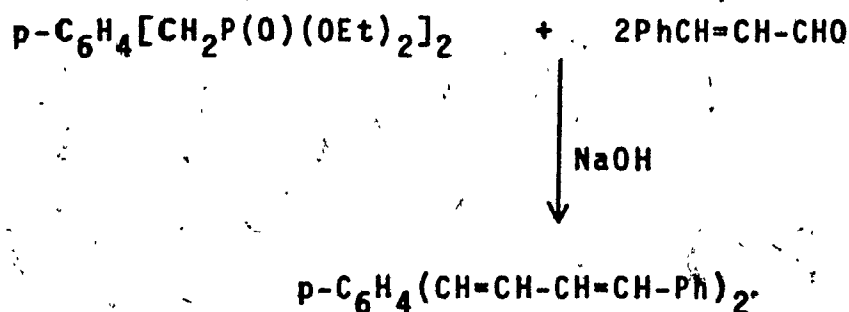
P(O)-activated olefin formation with unsaturated aldehydes has also been employed in the modification of a steroid to a bufodienolide,[35] and in the total synthesis of mycophenolic acid.[36]

CHO
CH-OCH₃

+ (EtO)₂P(O)CH₂COOMe →(EtONa)→

CH=CHCOOMe
CH-OCH₃

HCl
MeOH

OHC

OH
MeO

+ (EtO)₂P(O)CH₂-COOMe

NaNH₂

MeOOC

OH
MeO
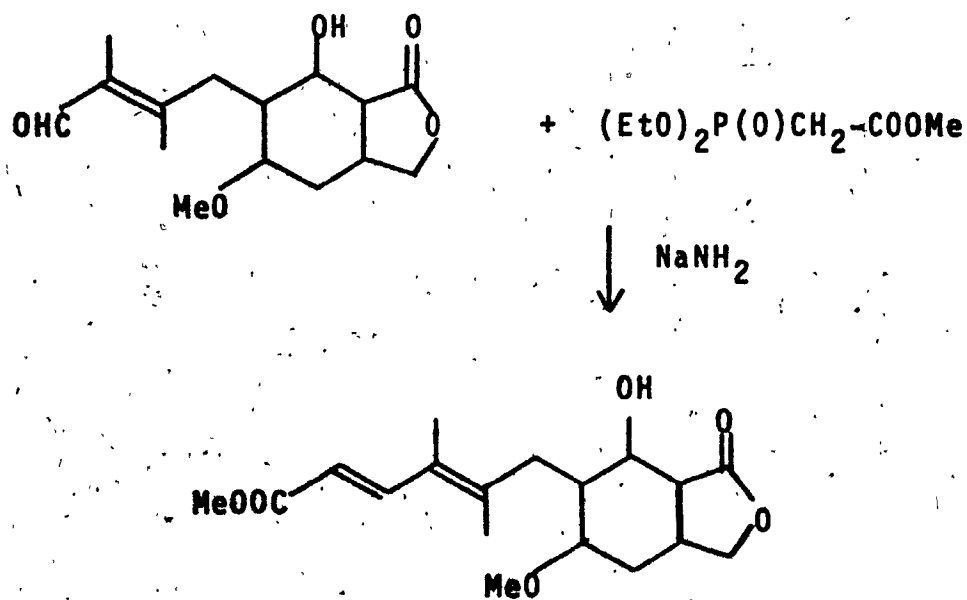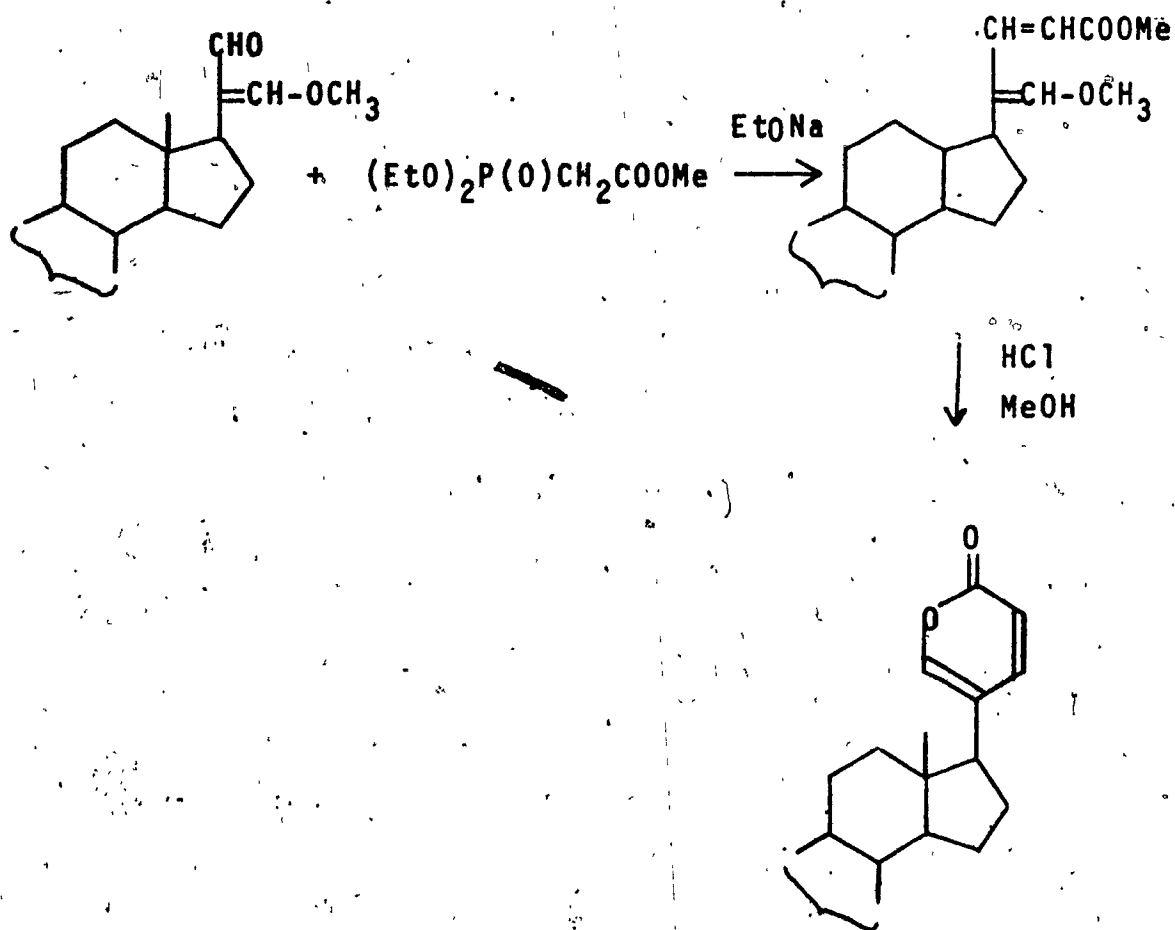
In contrast to α,β-unsaturated aldehydes the course of the reaction with α,β-olefinic ketones is determined by the reaction conditions.[37] In the case of chalcone (benzalacetophenone) phosphonate carbanions gave the expected diene only when the reaction was carried out in diglyme as solvent and sodium hydride as the base , whereas use of solvents such as benzene or ethanol and bases such as sodium ethoxide gave exclusively Michael-type addition products.[38-41] This

$$(EtO)_2P(O)-CH_2R \quad + \quad PhCH=CH-CO-Ph$$

$$\downarrow \quad \begin{array}{c} NaH \\ diglyme \end{array}$$

$$Ph-CH=CH-C(Ph)=CHR \quad (R = Ph; COOEt)$$

latter point will be returned to in the discussion section of this thesis. A rather interesting diene formation has been achieved by the reaction of triethyl phosphonoacetate anion with a β-methyl lactol, which in turn was obtained via condensation of the same anion with the diethyl acetal of pyruv-

aldehyde.[42,43]

$$(EtO)_2CH\text{-}CO\text{-}CH_3 \ + \ (EtO)_2P(O)CH_2\text{-}COOEt$$

$$\downarrow$$

$$(EtO)_2CHC(CH_3)=CH\text{-}COOEt$$

$$\downarrow \ H_3O^+$$

$$\downarrow \ \begin{array}{l}(EtO)_2P(O)CH_2COOEt \\ NaOEt\end{array}$$
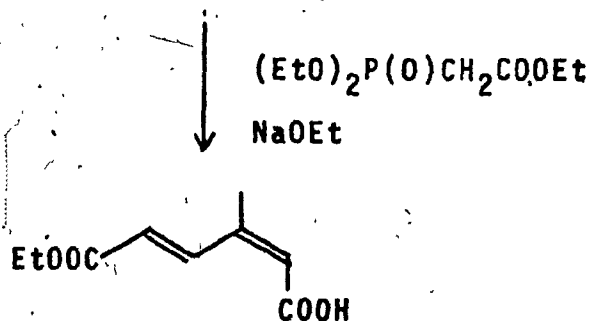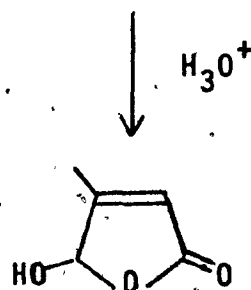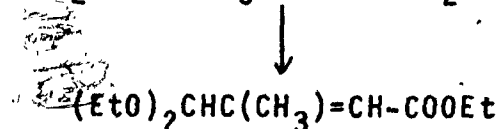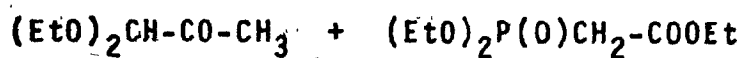
Since the final product is exclusively the cis-trans
half ester, it has been concluded that there is
complete retention of the stereochemistry of the
double bond derived from the lactol.

Although several reports of the reaction of
α,β-olefinic carbonyl compounds with phosphonate

carbanions exist in the literature as mentioned in the foregoing paragraphs, virtually no data are available concerning the reaction of α,β-acetylenic ketones with such carbanions. Therefore it seemed of interest to investigate the reaction between the phosphonate carbanions and a series of acetylenic ketones. If normal olefin-forming reaction takes place the products will be conjugated enynes which are interesting synthetic intermediates.

STATEMENT OF THE PROBLEM

In view of the lack of data in the literature relative to the reaction of α,β-acetylenic ketones with stabilized phosphonate carbanions and stable phosphonium ylids, a systematic study of the reactions of acetylenic ketones of the type 18 with phosphonate

$$R-C\equiv C-\overset{\overset{\displaystyle O}{\|}}{C}-R' \qquad (EtO)_2P(O)-\overset{-}{C}H-R'' \qquad Ph_3\overset{+}{P}-\overset{-}{C}H-R''$$

$$\underline{18} \qquad\qquad\qquad \underline{19} \qquad\qquad\qquad \underline{20}$$
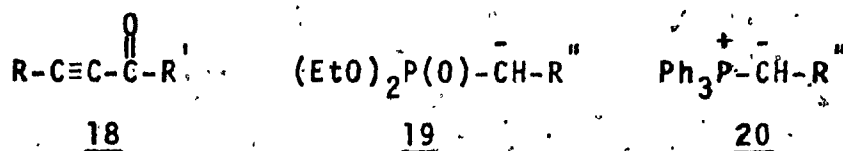
$$(R = CN; COOEt)$$

carbanions 19 and ylids 20 seemed desirable.

The acetylenic ketones chosen were such that the substituents R and R' in 18 included groups such as methyl, ethyl, isopropyl, tert-butyl and phenyl, which provided different steric and electronic requirements for the reaction. The substituents R" in the phosphorus derivatives 19 and 20 were chosen to be the nitrile and carbethoxy groups, so that the expected olefinic products in the reaction would be the enynes 21. It was of interest to compare the yields of the olefinic

17

products with the two types of phosphorus reagents, as
well as the ratio of the E and Z isomers from a given

$$R-C\equiv C-\underset{\underset{H}{\underset{\displaystyle C}{\|}}{\overset{\displaystyle C-R'}{}}}{}$$

R—C≡C—C—R'
                  ‖
                  C
               H⁄   ⁀R"
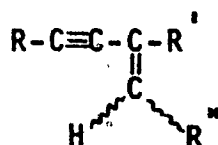
21

(E and Z isomers; R" = CN; COOEt)

acetylenic ketone. A meaningful comparison of the
reactivities of the phosphonate carbanion and the
phosphonium ylid with a given ketone under similar
reaction conditions will be achieved if products are
the same in both cases.

As regards the quantitative analysis of the E
and Z isomers of 21, it was hoped that , even if
complete physical separation were not achieved, NMR
spectroscopy would provide a feasible method, as the
chemical shifts of the hydrogen attached to the C=C
bond in the two isomers would be expected to be
different.

Many of the enynes 21 have not been previously
reported in the literature, and are interesting

synthetic intermediates. Therefore the present study
seemed worthwhile and interesting, and it was thought
that, in addition to expanding the scope of the Wittig-
type reactions as far as the carbonyl compounds are
concerned, it would also add to our knowledge of the
mechanism of these reactions.

DISCUSSION

1. α,β-Acetylenic Ketones

The α,β-acetylenic ketones used in the present study were synthesized following the sequence of reactions outlined in <u>Scheme 1</u>.[44] Reaction of ethyl magnesium bromide with the appropriate terminal acetylene produced the

$$Et-Mg-Br \xrightarrow{R-C\equiv C-H} R-C\equiv C-MgBr \xrightarrow{R'-CHO} R-C\equiv C-\overset{OH}{\underset{}{C}H-R'}$$

$$\xrightarrow{H_2CrO_4} R-C\equiv C-CO-R'$$

$$\underline{18}$$
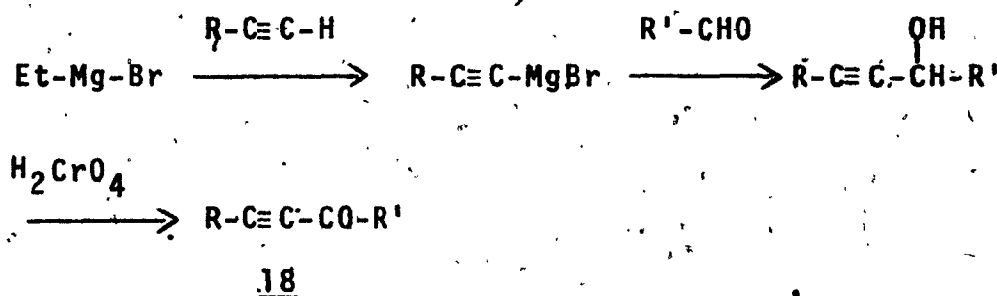
Scheme 1

acetylenic Grignard reagent which was reacted with the appropriate aldehyde to yield the corresponding secondary alcohol. The acetylenic secondary alcohol was oxidized by the procedure reported by Brown and coworkers[45] to produce the acetylenic ketones <u>18</u>. The acetylenic ketones used in the present study are listed in <u>Table I</u>. Many of these ketones were already known in the literature and have been synthesized by other methods.

Table I

α,β-Acetylenic ketones R-C≡C-CO-R' (18)

No.	R	R'	bp^{0}C		* Yield^a	Reference
a	Ph	Ph	46.5-47	(mp)	50 %	44,46
b	Me	Ph	84-92	(1.0 mm)	83 %	44,47
c	Ph	Me	88-108	(1.0 mm)	50 %	44,48
d	Me	Me	28-35	(0.41 mm)^b	65 %	44,49
e	Ph	t-Bu	88-93	(0.08 mm)	46 %	44
f	t-Bu	Ph	100-112	(1.60 mm)	83 %	44,50
g	Me	CH$_2$Ph	97- 103	(1.90 mm)	61 %	44
h	Et	Ph	92-95	(0.77 mm)^b	69 %	--
i	Ph	i-Pr	100-113	(2.00 mm)	56 %	44,51
j	Me	CH=CH Me	94- 102	(16.00mm)	73 %	44,52

a yields reported are from reference 44.

b yield obtained in the present study.

* yield based on alcohol.

2. Triphenyl phosphonium ylids.

Only two phosphonium ylids of the type Ph$_3$P$^+$-CH$^-$-R"(19) were chosen for study in the present work. These are ylids where the R" group in 19 are the electron-withdrawing groups CN and COOEt. By virtue of the fact that these

electron-withdrawing groups are attached to the α-carbon
of the ylid ,the electron density of this carbon atom is
delocalized into the groups making the ylid more stable.
Such stable ylids can be readily isolated and purified.In
the present study the two stable ylids 19a and 19b were
synthesized using methods reported in the literature as
listed in Table II.The groups CN and COOEt for R" were
chosen because the phosphonate carbanions used in the

Table II

Stable triphenyl phosphonium ylids ($Ph_3P^+-CH^--R''$)(19)

No.	R"	mp ^{0}C	Yield(%)	Reference
a	CN	193-195	82	53,54,55
b	COOEt	121-124	95	56, 57

reaction of the acetylenic ketones also had the same two
groups, and one of the objects of the present study was the
comparison of the reactivities of the two types of phospho-
rus derivatives in the olefin-forming reaction with acetyle-
nic ketones.

3. The Wittig Reaction.

The condensation-elimination reaction between a

phosphonium ylid and a carbonyl compound (aldehyde or
ketone) to form an olefin and phosphine oxide is termed
the Wittig reaction. The reaction has been of such versa-
tility that it has enabled the ready synthesis of many
olefinic compounds of great importance to mankind such
as the vitamins, hormones, and pheromones, and for this
reason Wittig shared the 1979 Nobel Prize in chemistry.

The generally accepted mechanism [58] of the Wittig
reaction between a carbonyl compound and a phosphonium
ylid is given in Scheme 2.

Betaine Intermediates   (E and Z Isomers)
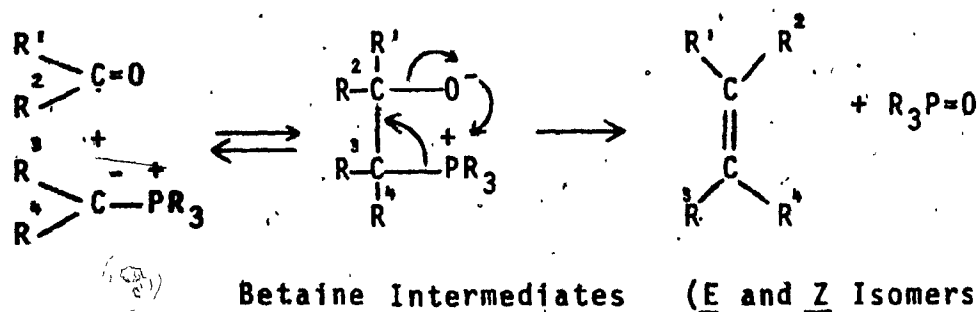
Scheme 2

The reactivity of the ylids is highly variable (as
is the case with the carbonyl components) and depends
mainly on the negative charge on the carbon alpha to the
phosphorus atom. As is evident from Scheme 2 the reacti-
vity of the ylid is related to the basicity of the ylid.
It has been demonstrated that methylenetriphenylphospho-

rane (an "unstabilized ylid ") reacts with most carbonyls [6] , and cyclopentadienylidenetriphenylphosphorane (one of the most stabilized ylids) is unreactive towards aldehydes or ketones[104]. Ylids stabilized by electron-withdrawing groups such as acyl, cyano, carboxylic ester groups do, however, react with aldehydes and ketones to give good to excellent yields of olefinic products, although at a reduced rate compared to the unstabilized phosphorane[1]. In the reaction of benzaldehyde with a series of aoyl substituted phosphoranes, a plot of the ylid basicity versus the rate of reaction was found to be linear.[59] This result is in agreement with other observations,[60] and among other things, indicates that the rate of the overall reaction depends on the rate of the betaine formation (cf. Scheme 2). The rate of betaine formation should be affected by the nucleophilicity of the ylid and the electrophilicity of the carbonyl carbon. There have been many instances in which the betaines have actually been isolated and their structures verified.[61] The reversibility of the betaine formation has also been verified, although only in limited number of cases.[58,59,62,63]

Two other electronic factors which must be taken into consideration (disregarding stereochemical consideration) in the conversion of the betaine (cf. Scheme 2) to olefin and phosphine oxide, are the stabilization of

the incipient double bond in the transition state 22 ,
and the rate at which the anionic oxygen in the betaine
attacks the positive phosphorus atom. In a comparison of
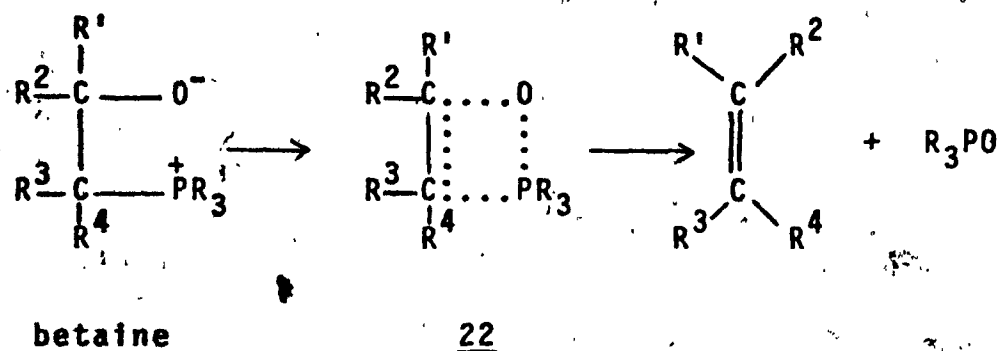
betaine   22

the reaction between the ylid $Ph_3P^+—CH_2$ and benzaldehyde
($R^1 = R^2 = R^3 = H$, $R^4 = Ph$) or benzophenone ($R^1 = R^2 = H$,
$R^3 = R^4 = Ph$) the former afforded lower yield of olefin
along with some betaine whereas the latter gave a high
yield of olefin and no betaine.[64] The implication has been
that the two phenyl groups in benzophenone provided more
stabilization for the olefinic double bond than did the
one phenyl group in the case of benzaldehyde.

In the reaction of two ylids, differing only in the
phosphorus substituents , with a common carbonyl compound,
one should expect the rate of decomposition of the betaine
to depend on the facility with which the negative oxygen

carries out a nucleophilic attack on the positive phos-
phorus. It is evident that the groups attached to the
phosphorus which increase its electron density must
retard the rate of decomposition of the betaines.These
ideas have been borne out by the observation that
methylenetrimethylphosphorane and benzophenone gave only
the betaine, whereas methylenetriphenylphosphorane and
benzophenone afforded only the olefin with little evidence
for a long-lived betaine.[5,65]

4. Stereochemistry of the Wittig Reaction.

The Wittig reaction of a carbonyl compound with a
phosphonium ylid can produce two geometrical isomers with
respect to the newly created double bond (_E_ and _Z_ isomers).
There have been many studies aimed at obtaining information
regarding the factors that contribute to the stereo-
chemistry of the product olefin in Wittig reactions.[66]Most
of these studies involved an aldehyde and a phosphorane
carrying a hydrogen on the ylid carbon so that the result-
ing olefinic product had one hydrogen at each end of the
new double bond. In these situations the two geometrical
isomers of the olefin can be conveniently refered to as the
cis and _trans_ isomers. In this section this terminology
will be used.

In Wittig reactions it has been observed in general

that <u>trans</u> olefins are the predominant products,especially with stable ylids.With unstabilized ylids higher <u>cis</u>/<u>trans</u> ratios have been observed.It must also be pointed out that in certain cases <u>cis</u> olefins are known to isomerize to the <u>trans</u>-isomers under the conditions of the reaction;[58,67] therefore care has to be exercised in the use of the product ratio observed at the end of the reaction.

Various studies have indicated that the stereo-chemistry of the Wittig reaction can be understood in terms of the mechanism discussed earlier (cf.<u>Scheme 2</u>, page 23).One of the more detailed studies has been that of Speziale and Bissing,[58] involving the reaction of benz-aldehyde and the stable ylid $Ph_3P=CH-COOEt$. The formation of the two stereoisomers of the olefin in the reaction can be understood in terms of the intermediates (<u>erythro</u>-and <u>threo</u>-betaines)indicated in <u>Scheme 3</u>.The cis- product

<u>Scheme 3</u>
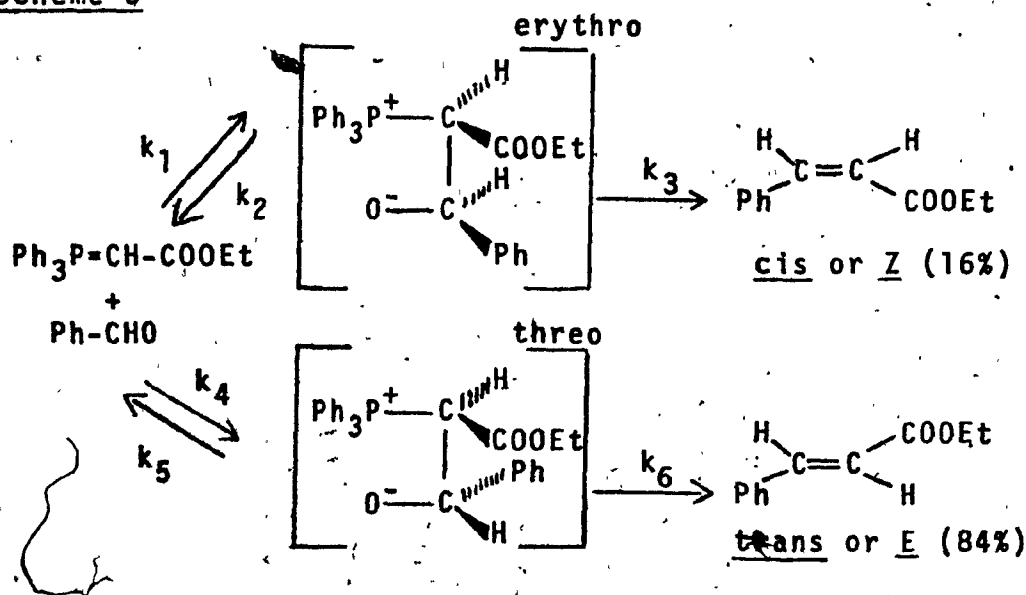
is thought to arise from the erythro-betaine, and the trans-product from the threo-betaine. The threo-betaine is the more stable of the two, being sterically less hindered than the erythro-betaine. The transition state leading to the trans-product from the threo-betaine is also therefore the more stable one than that which leads to the cis-product.

Many other factors are also shown to contribute to the observed stereochemistry of the Wittig reaction. Among these are the reactivities of the carbonyl compound and the ylid, the reaction conditions, and the various rate constants k_1-k_6 for the steps shown in Scheme 3. It appears that there is a delicate balance between the rates of formation of the betaines, their rates of dissociation and their rates of decomposition to olefins. The reversibility of the betaine formation, as well as the interconversion of the two betaines have been established in several instances.[58,62,68] It has also been demonstrated that the decomposition of the betaine involves the cis elimination of Ph_3PO as implied in Scheme 3.[69]

With regard to reaction conditions, it would be expected that any change which will tend to reduce the steric and electronic differences between the isomeric betaines would tend to decrease stereoselectivity; i.e., the cis/trans ratio would be expected to increase. The presence

of <u>excess</u> carbonyl compound or excess ylid has been found
to increase <u>cis/trans</u> ratio.[70,71] Several studies have
indicated that polar aprotic solvents and protic solvents,
or proton-donating catalysts also tend to increase the
<u>cis/trans</u> ratio in the products.[70,72-74]

5.Phosphonate carbanions.

The two phosphonate carbanions chosen for reaction
with α,β-acetylenic ketones were of the type $(EtO)_2P(O)$
$^-CH-R"$

(<u>19</u>).The R" group in these carbanions were the same
electron-withdrawing groups CN(<u>19a</u>) and COOEt(<u>19b</u>)which
were present in the two triphenylphosphonium ylids used
in the reactions with the same acetylenic ketones.These
carbanions were produced immediately prior to the reaction
with the ketones by treating the corresponding active
methylene compounds (phosphonate esters) with sodium
hydride in 1,2-dimethoxyethane.[24] The carbanions <u>19a</u>

$$(EtO)_2P(O)-CH_2-CN \xrightarrow[\text{(DME)}]{\text{NaH}} (EtO)_2P(O)-\overset{-}{C}H-COOEt$$
<u>19a</u>

$$(EtO)_2P(O)-CH_2-COOEt \xrightarrow[\text{(DME)}]{\text{NaH}} (EtO)_2P(O)-\overset{-}{C}H-COOEt$$
<u>19b</u>
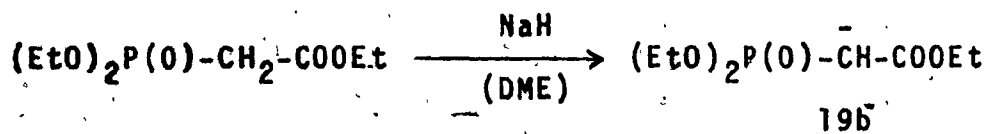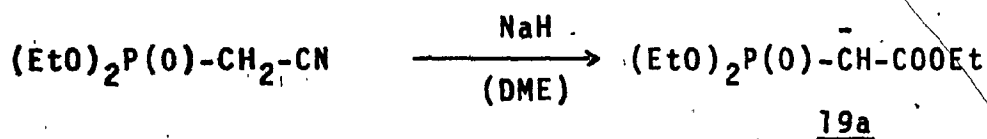
and <u>19b</u> are stabilized by the presence of the electron-

withdrawing groups on the carbanionic carbon.

6.Olefin synthesis with phosphonate carbanions.

As mentioned in the introduction section the phosphonate carbanions as olefin-forming reagents have several advantages over the phosphoranes used in the conventional Wittig reaction.The ever-increasing use of stabilized phosphonate carbanions such as 19a and 19b in olefin synthesis is evidenced by the growing number of publications involving this reaction.Two of the most recent reviews on the topic to which reference has already been made are those by Wadsworth [20] and by Boutagy and Thomas. [25]

Unlike the case of the Wittig reaction,fewer studies have been reported regarding the mechanism and stereochemistry of the reaction of phosphonate carbanions with carbonyl compounds.The mechanism proposed [24,75] is analogous to that of the conventional Wittig reaction and is
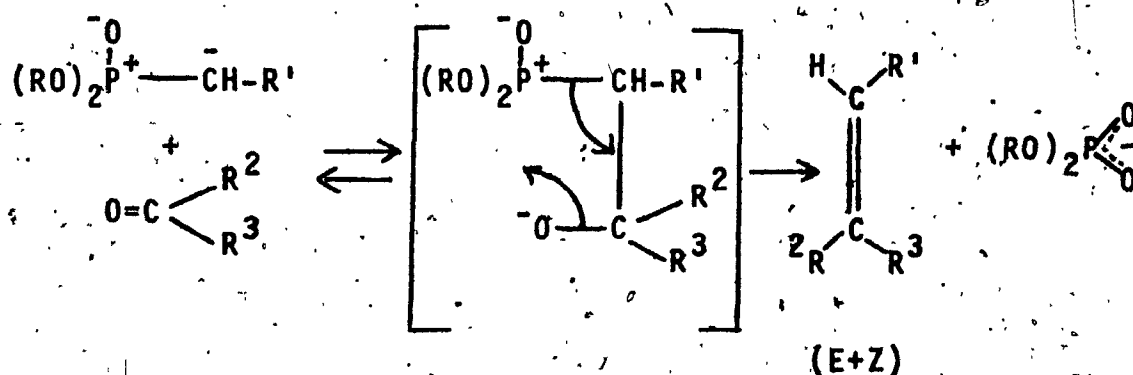
Schéme 4

depicted in Scheme 4. The mechanism is believed to involve a two-step process in which the carbanion reacts with the carbonyl compound in a reversible first step to form an intermediate oxyanion (betaine). The betaine then decomposes irreversibly by oxygen transfer to the phosphorus atom producing the olefin and dialkylphosphate ion. This latter step is thought to be a cis elimination process involving a 4-membered cyclic transition state analogous to that in the Wittig reaction.

It is known that only those phosphonate carbanions in which R' can further stabilize the carbanion (e.g. R'=CN,COOR,COR,Ph) can be employed successfully in olefin synthesis. Reaction of nonstabilized carbanions with aldehydes or ketones does not yield olefins in significant amounts,[76] the conjugate acid of the betaine being produced to a considerable extent in these reactions. This can be interpreted to mean that there is a considerable accumulation of negative charge on the carbon alpha to the phosphorus atom in the transition state for the elimination step.[77]

7. Stereochemistry of phosphonate-olefin formation

The stereochemical pathway of the reactions involving phosphonate carbanions in olefin formation has not been as well documented as that of the conventional Wittig

reaction.Earlier studies of the reaction seemed to indicate that only _trans_ olefins were formed.[22,24,78] It was thought that a mixture of the _cis_ and _trans_ isomers was probably produced,but the _cis_ isomer underwent base catalyzed isomerization to the _trans_-product under the reaction conditions.[24,78] That this is not the case has been verified by later studies.[72,79] Many subsequent studies (see ref.20,76-85 and ref.25,p.91) have shown that the reaction is not stereospecific and that a mixture of geometric isomers can be produced.

The observed stereochemistry of the phosphonate-olefin formation can be accounted for on the basis of the mechanism proposed in _Scheme 4_,the steric effects in the betaine determining to a larger degree the stereochemical course of the reaction,as in the course of the Wittig reaction.These ideas were illustrated in a study of the reaction of the stable ylid $(EtO)_2P(O)-\overset{-}{C}H-CN$ with benzaldehyde,[80] and are given in _Scheme 5_.The intermediate oxyanions (betaines) formed reversibly by the reaction of the phosphonate carbanion and the aldehyde can exist as two diastereomers,the _erythro_-betaine being the precursor of the _cis_-olefin _via_ a _cis_ elimination,and similarly the _threo_-betaine yield the _trans_-isomer.The stable conjugate acids of the _erythro_- and _threo_- betaines (i.e.,1-cyano-2-hydroxy-2-phenylethylphosphonate diastereomers)were

(EtO)$_2$P(O)$\bar{C}$H-CN

+

Ph-CHO
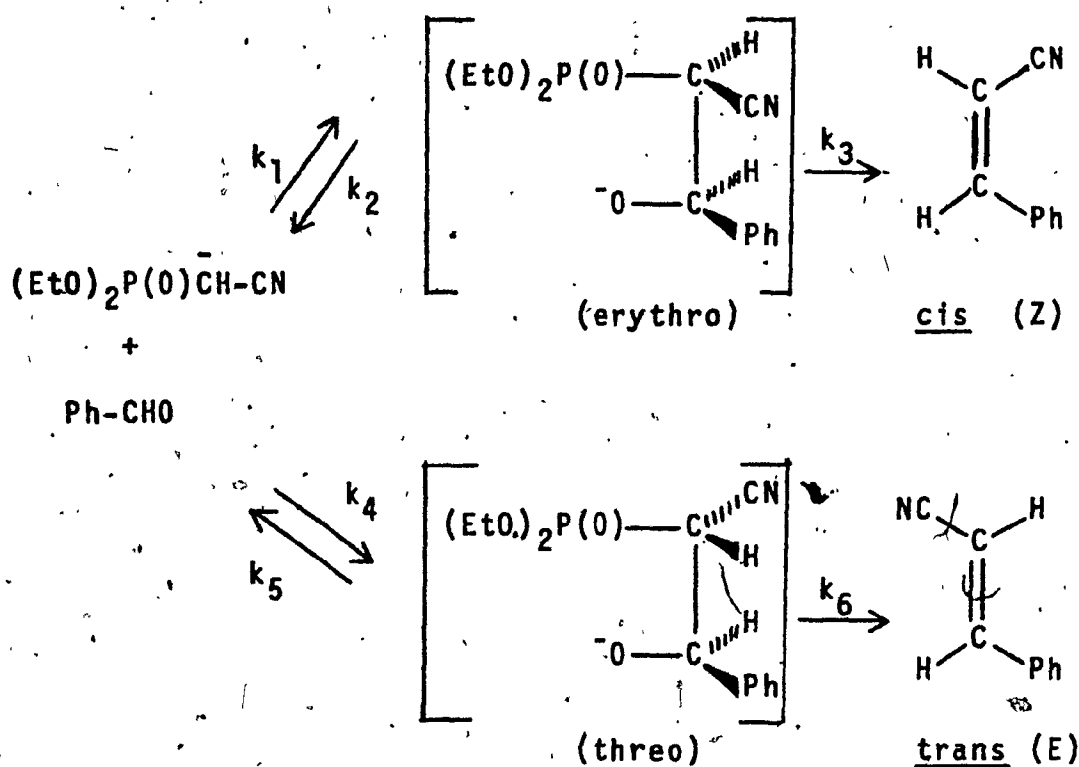
<u>Scheme 5</u>.

indeed isolated and each isomer has been shown to yield the unsaturated nitriles by reaction with aldehydes in presence of base.[80,81] The authors have shown also that these diastereomeric β-hydroxyphosphonates revert partly to benzaldehyde and the anion (EtO)$_2$P(O)-$\bar{C}$H-CN in basic medium to an extent which is solvent-dependent, and partly interconvert directly.[80] The reversibility of the first step has also been amply demonstrated.[82,84]

The isomer ratios observed in these reactions may be

explained by assuming a difference in stability, due primarily to steric effects, between the two diastereomeric betaines. Since the betaines are formed reversibly, the amount of $\underline{Z}$ isomer produced should depend on the relative magnitudes of the various rate constants (cf. Scheme 5.). That this argument is valid follows from the quantitative data on isomer distribution obtained in several studies.[85,86]

A recent study has shown that the oxyanion (betaine) formation from phosphonoesters (e.g. the reaction involving $\underline{19b}$) and benzaldehyde proceeds to a lesser extent than the formation of the oxyanions from phosphononitriles (e.g. the reaction involving $\underline{19a}$) and benzaldehyde.[87] To the extent that the ester group is bulkier than the nitrile, any steric interaction the ester group develops with the phenyl group in the formation of the betaine will be greater causing a decrease in rate. This steric effect will be greater in the erythro diastereomer as it yields the $\underline{Z}$ olefin (cf. Scheme 5). Since both k_3 and k_6 are less for the phosphonoesters than for phosphononitriles retroaldolization becomes more pronounced in the former. The ratio k_3/k_6 (which determines the stereoselectivity at least in part) would be expected to be smaller for the ester, the ester would produce more of the trans $(\underline{E})$ olefin than the nitrile. Indeed the trans isomer is produced almost exclusively in the cinnamates obtained by this

reaction.

Some solvent effects on the isomer ratio of the olefinic products have been observed recently.[70,79,84,85] It has been observed that when epimerization of the diastereomeric oxyanions is impossible,as when there is only one _alpha_ hydrogen in the starting phosphonate,the stereochemistry of the reaction does vary with the solvent.[88,89] The variations with solvent were attributed to a change in the reversibility of the aldol condensation.

8.Choice of solvent in the present study.

The nature of the solvent plays an important role in the Wittig reaction,especially where stabilized ylids are involved.Speziale and Bissing [58] have reported that the Wittig reaction between benzaldehyde and $Ph_3P=CHCOOEt$ was about six times faster in chloroform than in benzene and about a thousand times faster in methanol than in benzene. However,the cis/trans ratio of the olefins were found to be unaffected by aprotic solvents of varying polarities,[72,73] but this ratio was found to increase with protic solvents such as methanol.[73,74] The choice of the medium for the reaction of α,β-acetylenic ketones with the stable ylids as well with the phosphonate carbanions has been the polar aprotic solvent 1,2-dimethoxyethane.This solvent has been shown to be ideally suited for the reaction of phospho-

nate carbanions and carbonyl compounds.[24] Since one of the objectives of the present study was a comparison of the reactions of phosphonium ylids and phosphonate carbanions (both reagents having identical substituents on the carbanionic carbon) with α,β-acetylenic ketones, the reaction conditions including the solvent were kept the same. Being a polar non-protic solvent 1,2 dimethoxyethane will enhance the Wittig reaction, and will exert little influence on the Z/E ratios of the products. Besides, preliminary experiments with 1,3 diphenyl-2-propyn-1-one and the ylids using benzene, chloroform, carbontetrachloride, tetrahydrofuran and dimethoxyethane indicated that dimethoxyethane as the sol-vent gave better results in the present study.

9. Reaction of $Ph_3P=CH-CN$ and $Ph_3P=CHCOOEt$ with α,β-Acetylenic Ketones.

As was pointed out in the introduction section, the normal course of the Wittig reaction has been found to be unaffected by the presence of unsaturation (olefinic or acetylenic) in conjugation with the carbonyl group. Many conjugated carbonyls have been found to give the expected products from the Wittig reaction.[14-19] However, the carbonyl components in most of these cases were aldehydes and the ylid components were not stabilized by strongly electron-withdrawing groups. Thus, both partners in these react-

ions were of high reactivity.

In the present study the carbonyl components in the
Wittig reaction were ketones having their carbonyl func-
tions conjugated with acetylenic functions.All the
ketones given in table I (page 21) were allowed to react
with each of the two ylids under a variety of conditions
described earlier.

1,3-Diphenyl -2-propyn-1-one,Ph-C≡C-CO-Ph (18a) was
refluxed with each ylid for various periods of time under
an atmosphere of nitrogen,in various solvents (cf.Section
8).No expected vinylic products 23 or 24 were detectable
in the reaction mixture.Only varying amounts of triphenyl-
phosphine oxide,and unreacted starting materials were
identified in the reaction mixture.Similar results were

Ph-C≡C-CO-Ph
18a

Ph₃P=CHCN →
Ph-C≡C / C=C \ Ph ... H, CN
23

Ph₃P=CHCOOEt →
PhC≡C / C=C \ Ph ... H, COOEt
24
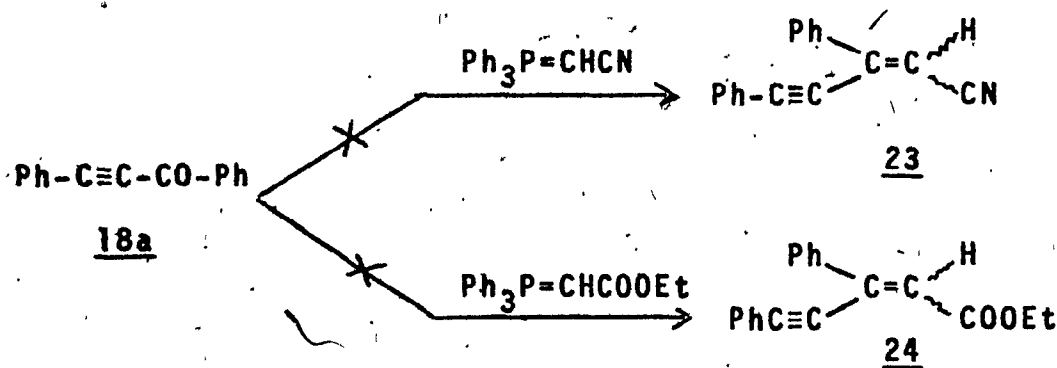
obtained with 1-phenyl-2-butyn-1-one (18b) with both the

ylids.
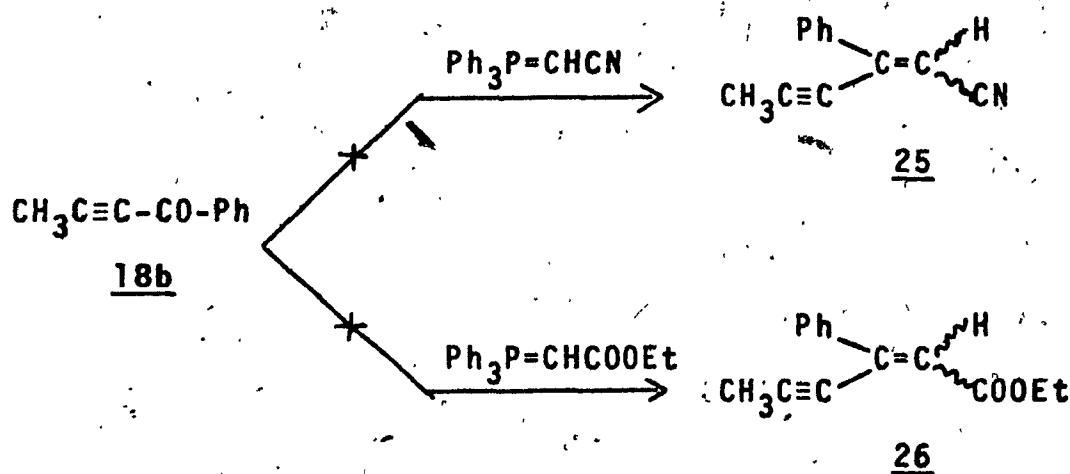
In view of the fact benzoic acid catalyzes the Wittig reaction with ketones and carbethoxymethylenetriphenyl-phosphorane,[90] benzoic acid was added in the reactions of both ketones 18a and 18b with the two ylids. No trace of the expected products 23, 24, 25, or 26 was detected among the products of reaction. As before only triphenyl-phosphine oxide and unreacted ketones were identified.

Unlike ketones 18a and 18b, 4-phenyl-3-butyn-2-one (18c) was found to react with both the ylids in dimethoxy-ethane. When 18c was refluxed with triphenylphosphoranyl-acetonitrile the expected products were isolated in 50% yield. It was possible to obtain samples of the two geometrical isomers of the product 27a and 27b in isomerically pure state for analytical purposes by repeated chromatography of the product over alumina. The products were identified on

Ph-C≡C-CO-CH$_3$ $\xrightarrow{\text{Ph}_3\text{P=CHCN}}$ $\underset{\text{PhC}\equiv\text{C}}{\overset{\text{CH}_3}{>}}\text{C=C}\underset{\text{CN}}{\overset{\text{H}}{<}}$ + $\underset{\text{PhC}\equiv\text{C}}{\overset{\text{CH}_3}{>}}\text{C=C}\underset{\text{H}}{\overset{\text{CN}}{<}}$

18c

27a(Z)   27b(E)

46%   54%
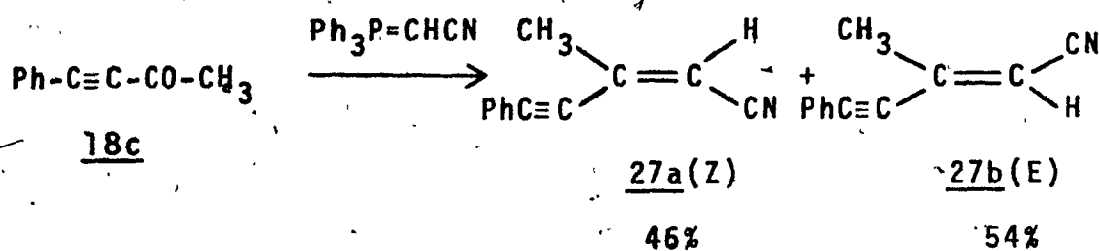
the basis of their IR,NMR,and mass spectra and elemental
analysis.The vinylic hydrogens of the two geometrical
isomers 27a and 27b exhibited signals with chemical shifts
different enough so that quantitative analysis of the iso-
mer ratio by NMR spectroscopy was possible.

The Z (27a) and E (27b) isomers were distinguished on
the basis of the chemical shift values of the substituents
on the terminal double bond,as used by several workers
earlier.[91-95] Generally coupling constants of hydrogens
situated trans with respect to the double bond are observ-
ed to be larger than those for hydrogens situated cis with
respect to it.However,in 27a and 27b the coupling constants
between the CH$_3$ and H on the double bond were extremely
small (≈1 Hz) such that the distinction between the Z and
E isomers based on the values of coupling constants was
not possible.Assignment of the Z and E configurations were
made based on the chemical shift values of the signal for
the CH$_3$ group and for the H atom attached to the double
bond.It has been observed in similar situations that when

a CH_3 group and H-atom are positioned <u>cis</u> with respect to each other the CH_3 signal appears at a higher field (lower δ) than when the two are positioned <u>trans</u> to each other; the signal for the H-atom appears at higher field (lower δ) in the <u>cis</u> arrangement of the CH_3 and H, than for the trans arrangement.[94] The chemical shift values of the CH_3 and H in the two isomers are listed in Table III. As is evident

Table III

Compound	Chemical shift values (δ)	
	CH_3	H
27a	2.12	5.55
27b	2.28	5.62

from Table III the methyl and hydrogen signals in <u>27a</u> are at higher fields than the corresponding signals in <u>27b</u>. Therefore, in <u>27a</u> the CH_3 and H are located <u>cis</u> with respect to the double bond and in <u>27b</u> they are in <u>trans</u> arrangement. Thus it was possible to assign the <u>Z</u> configuration to <u>27a</u> and <u>E</u> configuration to <u>27b</u>.

Carbethoxymethylenetriphenylphosphorane also reacted with $Ph-C\equiv C-CO-CH_3$ in the Wittig manner in dimethoxy-ethane. The olefinic products <u>28</u> were isolated in 49 % yield.
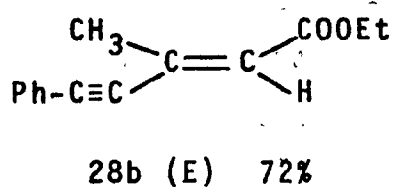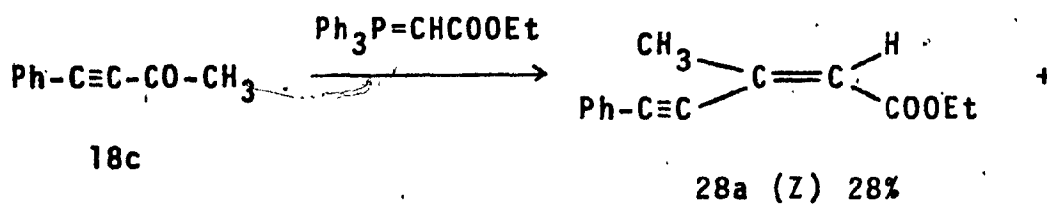
Ph-C≡C-CO-CH₃ $\xrightarrow{\text{Ph}_3\text{P=CHCOOEt}}$

18c

$$\underset{\text{Ph-C}\equiv\text{C}}{\overset{\text{CH}_3}{\diagdown}} C = C \underset{\text{COOEt}}{\overset{\text{H}}{\diagup}} \quad +$$

28a (Z) 28%

$$\underset{\text{Ph-C}\equiv\text{C}}{\overset{\text{CH}_3}{\diagdown}} C = C \underset{\text{H}}{\overset{\text{COOEt}}{\diagup}}$$

28b (E) 72%

The relative amounts of the isomers were estimated from the NMR spectra of the crude reaction mixture after removal of solvent and most of the triphenylphosphine oxide. Complete separation of the isomers was not achieved. However by repeated chromatography it was possible to obtain small amounts of pure sample of E-isomer (28b).The configurational assignments Z and E were made on the basis of the chemical shift values of the CH₃ and H attached to

Table IV

Compound	Chemical Shift Values (δ)	
	CH₃	H
28a	δ 2.15	6.18
28b	δ 2.46	6.37

the double bond as was done in the case of the nitrile products.The results are summarized in Table IV.

Only two other acetylenic ketones (18g and 18i) reacted with $Ph_3P=CH-CN$,and only four others (18d,18g,18h,18i) reacted with $Ph_3P=CHCOOEt$.A summary of the results of the reaction of all the acetylenic ketones used in the present study are given in Table V.In those instances which gave mixtures of the expected olefinic products the relative amounts of the isomers were estimated from the NMR spectra of the crude reaction mixture after removal of the solvent under reduced pressure and removal of the triphenylphosphine oxide by filtration .The yields of products were estimated by taking up the crude product in petroleum ether, filtering off the Ph_3PO,and removing the solvent.The configurational assignments Z and E were made based on the chemical shift values of the vinylic hydrogen,[94] as was done for the products of reaction of ketone 18c with the same two ylids.In the case of those ketones which did not yield any olefinic products only varying amounts of Ph_3PO and unreacted ylid and ketone were identified in the final reaction mixture.Prolonged reaction time or benzoic acid catalysis was not found to have any further effect on the reaction in the case of 1,3 diphenyl-2-propyn-1-one.

From Table V it is evident that most of the conju-

Table V

Reactions of Acetylenic Ketones with the phosphonium ylids

NO.	Ketones	$Ph_3P=CH-CN$ (%yield)[*]	Isomer distribution Z	E	$Ph_3P=CHCOOEt$ (%yield)[*]	Isomer Distribution Z	E
18a	Ph-C≡C-CO-Ph	0	0	0	0	0	0
18b	Me-C≡C-CO-Ph	0	0	0	0	0	0
18c	Ph-C≡C-CO-Me	(38)	46[†]	54[†]	(49)	28	72
18d	Me-C≡C-CO-Me	0	0	0	(24)	40[§]	60[†]
18e	Ph-C≡C-CO-t-Bu	0	0	0	0	0	0
18f	t-Bu-C≡C-CO-Ph	0	0	0	0	0	0
18g	Me-C≡C-CO-CH₂-Ph	(23)	41	59	(26)	48	52
18h	Et-C≡C-CO-Ph	0	0	0	(25)	33~	67
18i	Ph-C≡C-CO-i-Pr	(33)	0	100	(39)	0	100
18j	Me-C≡C-CO-CH=CH-Me	0	0	0	0	0	0

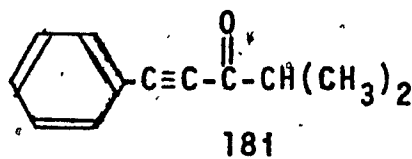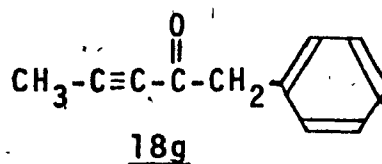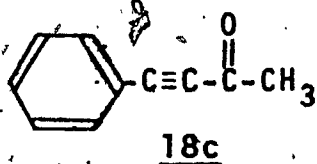* Refers to the total yield of the expected olefinic products.
† Refers to cases where pure samples of the isomers were obtained by chromatography.
§ Isomer which was not observed after chromatography.

-gated acetylenic ketones used in the present study are unreactive in the Wittig reaction towards both of the stable ylids $Ph_3P=CHCN$ and $Ph_3P=CHCOOEt$. Several factors must contribute to the observed lack of reactivity. Considering the general mechanism of the Wittig reaction (cf. Scheme 2, p 23), best results (maximum yield of olefinic product) would be obtained when both components in the reaction (i.e the carbonyl compound and the phosphonium ylid) exhibit maximum reactivity. The reactivity of the carbonyl compound is dependent mainly on the electrophilicity of the carbonyl carbon. In the α,β-acetylenic ketones used in the present study the electrophilicity of the carbonyl carbon must be reduced to a considerable extent by conjugation with the triple bond on one side as well as (in some cases) with phenyl or olefinic groups on the other. The reactivity of the ylid in the Wittig reaction is governed chiefly by the nucleophilicity of the carbanionic carbon. The nucleophilicity of this carbon is reduced substantially when there are strongly electron-withdrawing groups attached to it, as is the case with both the ylids $Ph_3P=CH-CN$ and $Ph_3P=CHCOOEt$ used in the present study. The observed lack of reactivity between the acetylenic ketones and these two ylids is therefore not entirely unexpected.

The few acetylenic ketones that did undergo the

Wittig reaction with the ylids gave only poor yields of
the expected olefinic products.Ph$_3$P=CH-CN reacted only
with the ketones 18c,18g, and 18i giving products in
yields 38 %,23 %,and 33 % respectively. In the reaction

$$\text{(Ph)}-C\equiv C-\overset{O}{\overset{\|}{C}}-CH_3 \qquad 18c$$

$$CH_3-C\equiv C-\overset{O}{\overset{\|}{C}}-CH_2-\text{(Ph)} \qquad 18g$$

$$\text{(Ph)}-C\equiv C-\overset{O}{\overset{\|}{C}}-CH(CH_3)_2 \qquad 18i$$

of 18c it was possible to obtain isomerically pure
samples of the olefinic products 27a and 27b (see NMR
spectra on pages 118 and 119 respectively) by chromato-
graphy. The geometrical isomers of the products from the
reaction of ketone 18g could not be separated by chromato-
graphy. In the reaction of 18i with Ph$_3$P=CH-CN only one
isomer could be detected(IR and NMR spectroscopy) in
the crude product immediately following the reaction.
From the fact that only one isomer is produced , the pro-
duct is assigned the E configuration based on the assump-
tion that only the less sterically hindered betaine is
formed as the intermediate. Considering the two possible
diastereomeric betaines 30a and 30b that could be formed

$$Ph-C\equiv C-CO-\underline{i}-Pr \xrightarrow{Ph_3P=CH-CN} \begin{array}{c} \underline{i}-Pr \\ Ph-C\equiv C \end{array} C=C \begin{array}{c} CN \\ H \end{array}$$

$$\underline{181} \qquad\qquad\qquad\qquad\qquad \underline{29}\ (\underline{E})$$

$$\underline{30a} \qquad\qquad\qquad \underline{30b}$$
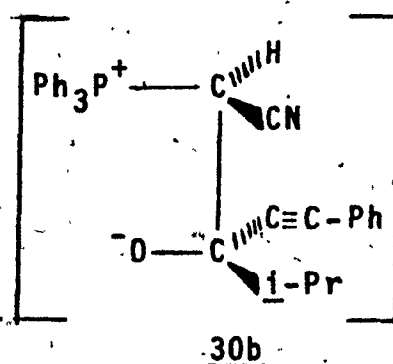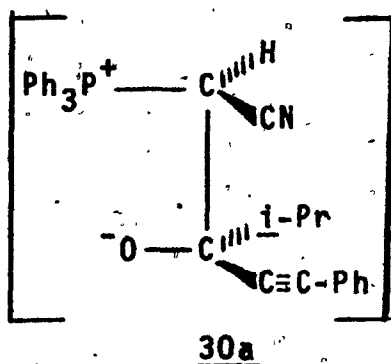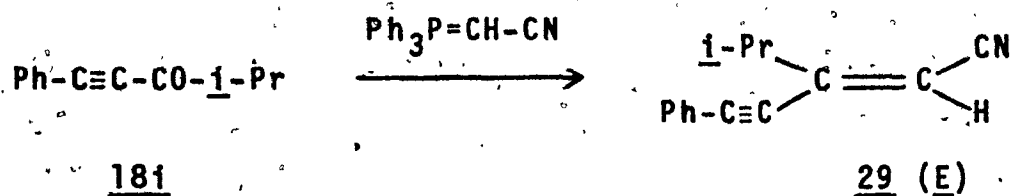
in the reaction, it is not immediately obvious why the $\underline{E}$ isomer (derived from $\underline{30b}$) is produced exclusively. An argument could probably be made that $\underline{30b}$ will provide a more stable transition state leading to the $\underline{E}$ isomer ($\underline{29}$) than would $\underline{30a}$ in giving the $\underline{Z}$ isomer. It is also possible that both $\underline{Z}$ and $\underline{E}$ isomers were produced and that the $\underline{Z}$ product isomerized to the thermodynamically more stable $\underline{E}$ isomer under the conditions of the reaction. Such isomerizations have been known to occur.[58,67]

The ylid $Ph_3P=CHCOOEt$ reacted with all the acetylenic ketones ($\underline{18c}$, $\underline{18g}$, and $\underline{18i}$) with which $Ph_3P=CHCN$ reacted to give olefinic products in approximately the same yields.

In addition, $Ph_3P=CHCOOEt$ reacted also with the ketones $CH_3-C\equiv C-CO-CH_3$ (18d) and $CH_3CH_2-C\equiv C-CO-Ph$ (18h) giving poor yields of products.

Unlike $Ph_3P=CHCN$, the ylid $Ph_3P=CHCOOEt$ did react with $CH_3C\equiv C-CO-CH_3$ (18d) yielding 24 % of the expected olefinic products. The NMR spectrum of the crude reaction product immediately after isolation exhibited vinylic proton resonances at $\delta 5.63$ and $\delta 6.10$ with relative intensities 40 % and 60 % respectively. On the basis of the chemical shift values of the vinyl proton signals as well as those due to CH_3 attached to the double bond[94,95] the predominant isomer is assigned the E configuration. However , after chromatography of the reaction mixture only one isomer (31b, E) could be detected. It was concluded therefore that the thermodynamically less stable Z isomer was converted to the more stable E isomer during chromatography. Such isomerizations have previously been reported.[58,67]

$$CH_3-C\equiv C-CO-CH_3 \xrightarrow{Ph_3P=CHCOOEt}$$

31a (Z) 40 %

31b (E) 60 %
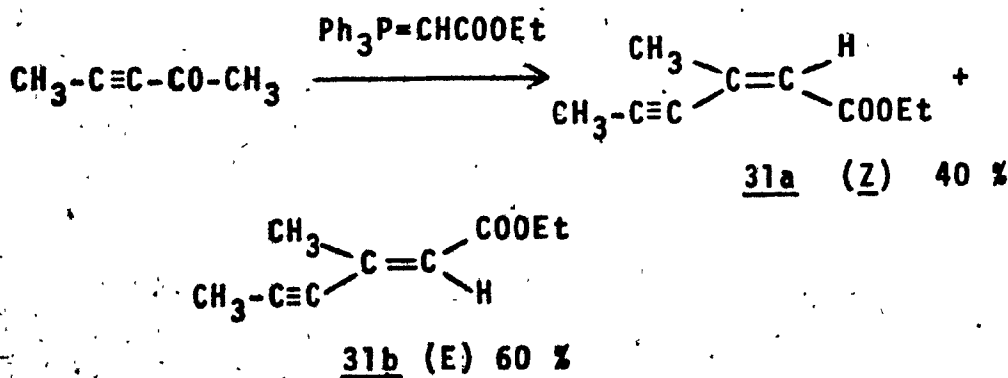
With the ketone 18g the yield of products with Ph$_3$P=CHCOOEt was comparable with that obtained with Ph$_3$P=CHCN (26 % vs 23 %). The vinylic proton signals of the product appeared at δ 6.47 (48 %) and δ 6.75 (52 %) which are attributed to the Z (32a) and E (32b) isomers.respectively. As can be seen there is no appreciable stereoselectivity in the reaction of this ylid also. All attempts to separate the two isomers by chro-

$$CH_3-C\equiv C-CO-CH_2-Ph \xrightarrow{\text{Ph}_3\text{P=CHCOOEt}}$$

18g

32a (Z)   48 %

32b (E)   52 %
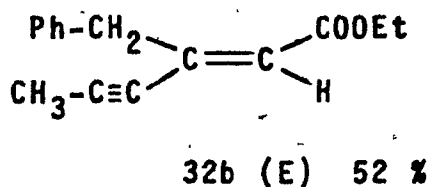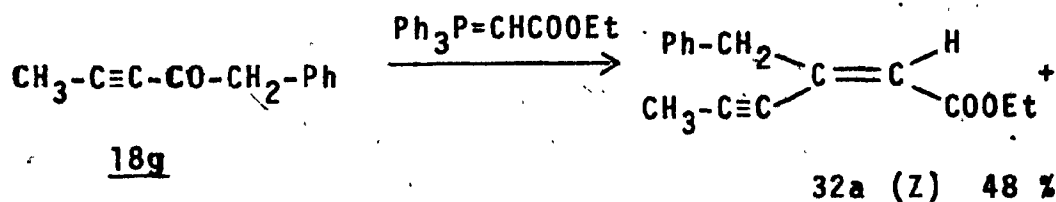
matography were unsuccessful.

Even though ketone 18h did not react with Ph$_3$P=CHCN, it did react with Ph$_3$P=CHCOOEt yielding the expected olefinic products in 25 % yield. The NMR spectrum of the crude reaction product isolated exhibited vinylic proton signals at δ 6.20 (33 %) and δ 6.36 (67 %) which were attributed to the Z (33a) and E (33b) isomers respectively.

Et-C≡C-CO-Ph $\xrightarrow{Ph_3P=CHCOOEt}$

18h

$$\underset{Et-C\equiv C}{\overset{Ph}{}} C = C \underset{COOEt}{\overset{H}{}}$$

33a (Z)   33 %

+

$$\underset{Et-C\equiv C}{\overset{Ph}{}} C = C \underset{H}{\overset{COOEt}{}}$$

33b (E)   67 %
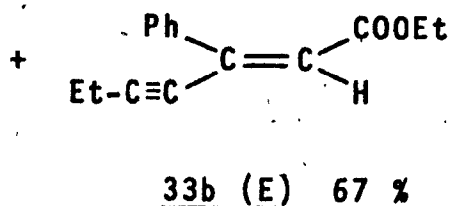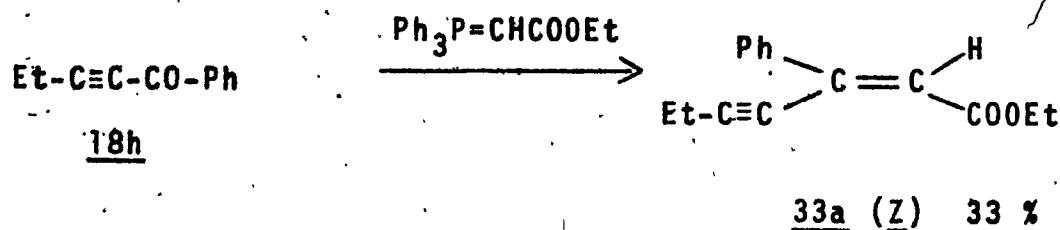
It was not possible to achieve clean separation of the isomers by chromatography.

As in the case of $Ph_3P=CHCN$, ketone 18i reacted with $Ph_3P=CHCOOEt$ in comparable yield (39 %) giving only one isomer (34) under identical reaction conditions. The

Ph-C≡C-CO-i-Pr $\xrightarrow{Ph_3P=CHCOOEt}$

18i

$$\underset{Ph-C\equiv C}{\overset{i-Pr}{}} C = C \underset{H}{\overset{COOEt}{}}$$

34 (E)
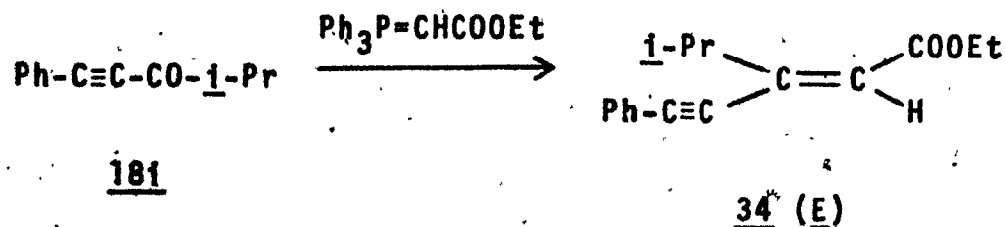
NMR spectrum of the crude product exhibited the vinyl proton resonance at δ 6.22. Considering the fact that only one isomer was obtained , the product was identified

as __34__ with the more stable $\underline{E}$ configuration, based on the assumption that only the less sterically hindered betaine is formed as the intermediate.

It is evident from Table V that the Wittig reaction between α,β-acetylenic ketones and stabilized ylids such as $Ph_3P=CHCOOEt$ is generally ineffective. The few ketones that did undergo the Wittig reaction gave only poor yields of the expected olefinic products. The reduced electrophilicity of the carbonyl carbon in the ketones together with the reduced nucleophilicity of the ylid carbon must contribute to great measure to the ineffectiveness of the Wittig reaction here. Steric factors must also contribute to the lack of reactivity. However, it is rather difficult to predict the extent of this contribution. Certainly in the case of ketone __18e__ (where a __t__-Bu is attached to the carbonyl group) this is a significant factor and both ylids are found to be unreactive with the ketone. However when the carbonyl had CH_3 group (__18c__) and __i__-Pr group (__18i__) both ylids reacted to produce the Wittig products in low yield. No other general trends seem to emerge from Table V regarding the reactivity of the ketones.

In the Wittig reaction involving α,β-unsaturated ketones a few rare examples of unexpected product formation resulting from conjugated addition of the phospho-

-nium ylid to the unsaturated ketone were reported.
Inhoffen and et al.[97] have reported the formation of the
triene(37)in the reaction of methylenecyclohexanone (35)
with the ylid (36) . Methylenetriphenylphosphorane has

$$35 + Ph_3P=CH-CH= \quad \longrightarrow \quad Ph_3PO + 37$$

35 · 36 37
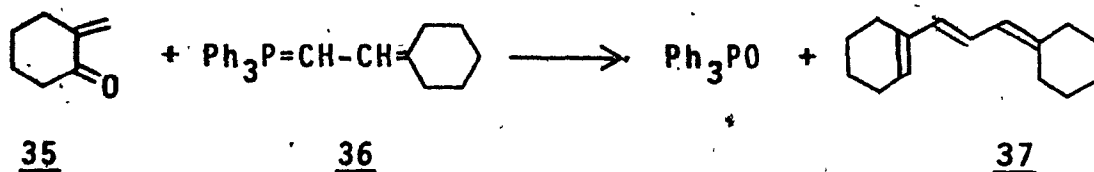
been found to react with mesitoylphenylethylene (38) to
yield the cyclopropyl ketone (39).[98] This author has
suggested that the reaction took the conjugate addition

$$\left\{ \begin{array}{c} 38 \\ + \\ Ph_3P=CH_2 \end{array} \right\} \longrightarrow \left[\begin{array}{c} Mes-CO-\overset{-}{C}H-CH \longrightarrow Ph \\ | \\ CH_2 \longrightarrow P^+Ph_3 \end{array} \right] \longrightarrow$$

$$Ph_3P + Mes-CO \triangle Ph \qquad (mes = Me \quad)$$

39
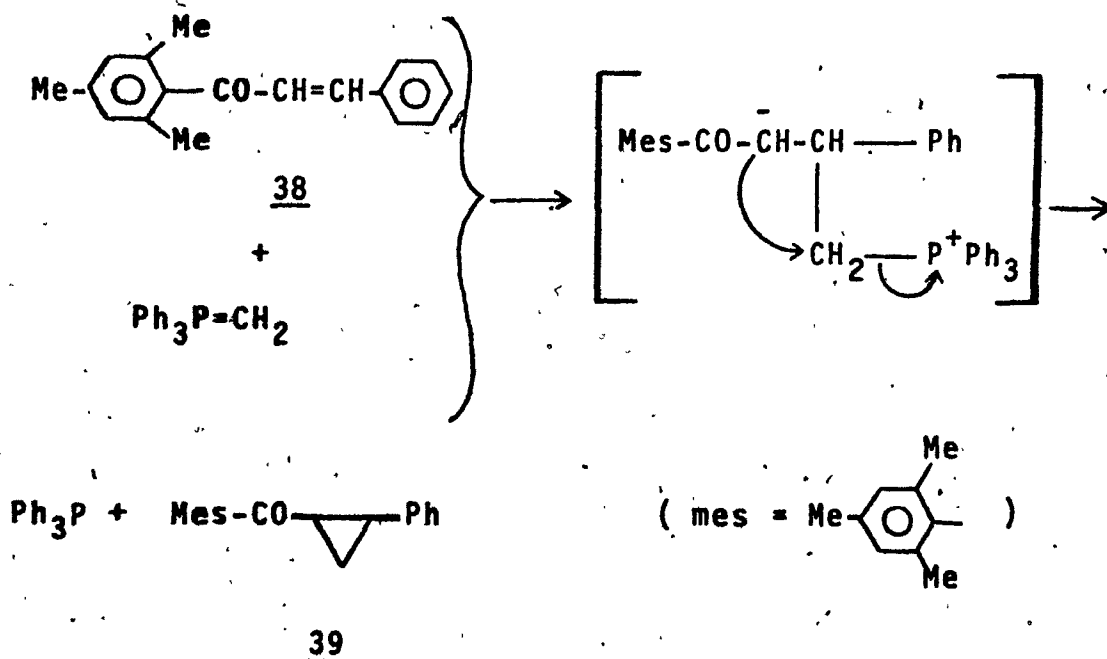
pathway because of the steric hindrance about the
carbonyl group, and that other hindered unsaturated

ketones might form cyclopropanes.

In the present study none of the acetylenic ketones which did react with the two ylids $Ph_3P=CHCN$ and $Ph_3P=CHCOOEt$, yielded any products which might have result-ed from conjugate addition of the ylid to the ketone. The ketone $Ph-C\equiv C-CO-\underline{t}-Bu$ (18e) which has hindered carbonyl failed to react with both the ylids.

In comparing the reactivity of the ylids towards the acetylenic ketones, it is observed (cf. Table V) that $Ph_3P=CHCOOEt$ was more reactive than $Ph_3P=CHCN$. The former reacted with more ketones and gave also slightly better yields of products. The reduced reactivity of the latter can be attributed to its reduced nucleophilicity on account of the better electron-withdrawing property of the nitrile group as compared to the carbethoxy group. The ylid with the carbethoxy substituent shows more stereo-selectivity, producing more of the Z isomers in several cases (e.g. with ketones 18c, 18d, and 18h).

10. Reaction of $(EtO)_2P(O)CHCN$ and $(EtO)_2P(O)CHCOOEt$ with α,β-Acetylenic Ketones.

In recent years the reaction of phosphonate carban-ions with carbonyl compounds has had a wider application

in the synthesis of olefinic compounds than the reaction
of phosphonium ylids and carbonyl compounds.[20,25] One of
the reasons for choosing the phosphonate carbanions over
the phosphonium ylids is that the former are more nucleo-
philic and therefore react better with a wider variety of
carbonyl compounds than do the ylids.[24,78] When electron-
withdrawing groups such as CN or COOR are attached to
carbanionic carbon these phosphonate carbanions have added
stability and are also more reactive in olefin formation.
The increase in reactivity is attributed to the ease of
cycloelimination from the betaine intermediate[20] (cf.
Scheme 5, page 33).

Since the reaction of phosphonate carbanions and
α,β-acetylenic ketones has hitherto been not systemati-
cally studied, two stabilized phosphonate carbanions
$(Eto)_2P(O)\bar{C}HCN$ and $(Eto)_2P(O)\bar{C}HCOOEt$ were allowed to re-
act with the same set of acetylenic ketones as were used
for reacting with the phosphonium ylids $Ph_3P=CHCN$ and
$Ph_3P=CHCOOEt$. Thus a direct comparison between the two
ylids and the two carbanions as to their effectiveness in
olefin-formation with conjugated acetylenic ketones could
be made.

In accordance with expectations the phosphonate
carbanions reacted with a wider range of acetylenic

Table VI

Reaction of Acetylenic Ketones With the Phosphonate Carbanions

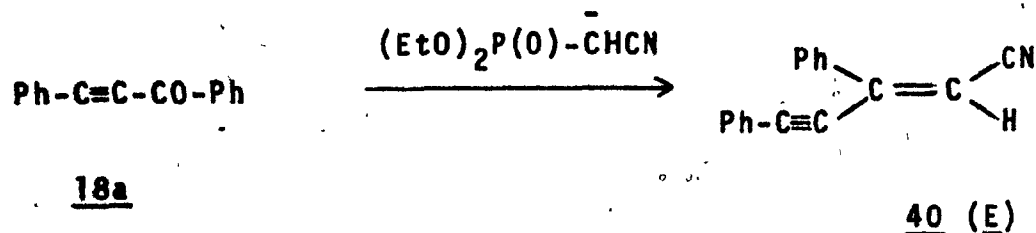| NO.	Ketone	$(EtO)_2P(O)CH-CN$ (%yield)*	Isomer Distribution Z	E	$(EtO)_2P(O)CHCOOEt$ (%yield)*	Isomer Distribution Z	E
18a	Ph-C≡C-CO-Ph	(23)	0	100	(35)	25	75
18b	CH₃-C≡C-CO-Ph	(49)**	0	0	(59)ʸ	0	0
18c	Ph-C≡C-CO-CH₃	(79)	30ˢ	70ˢ	(50)	45	55
18d	CH₃-C≡C-CO-CH₃	(44)	0	100	(31)	0	100
18e	Ph-C≡C-CO-t-Bu	(41)	0	100	(40)	25	75
18f	t-Bu-C≡C-CO-Ph	(36)	33	67	(6)	42	58
18g	CH₃-C≡C-CO-CH₂-Ph	(0)	0	0	(10)	44	56
18h	CH₃-CH₂-C≡C-CO-Ph	(39)	17	83	(38)ʸ	0	0
18i	Ph-C≡C-CO-i-Pr	(0)	0	0	(0)	0	0
18j	CH₃-C≡C-CO-CH=CH-CH₃	(0)	0	0	(0)	0	0

*   Refers to yield of olefinic products resulting from normal reaction

** Abnormal product - biphenyl derivative.

ʸ   Abnormal product - isocoumarin derivative.

ˢ   Pure samples of isomers were separated by chromatography.

ketones producing better yields of products under the same
conditions as were used for the reactions of the same
ketones with the ylids. The results are summarized in
Table VI.

The ketone 18a which was found to be unreactive
towards the two ylids reacted with both the phosphonate
carbanions. Upon refluxing cyanomethylphosphonate carban-
ion with 18a in dimethoxyethane a 23 % yield of the
olefinic product was isolated. The NMR spectrum of the
product (page 122) indicated it to be a single isomer.
Based on elemental analysis, IR and NMR spectra the pro-
duct was assigned the structure 40 . The product was
assigned the E configuration based on the fact that only
the less hindered betaine is formed as the intermediate.
Under identical reaction conditions the carbethoxymethyl-
phosphonate carbanion reacted with 18a yielding 35 % of
a mixture containing both the geometrical isomers of the
olefinic product. The isomer distribution was estimated

$$Ph-C \equiv C-CO-Ph \xrightarrow{(EtO)_2 P(O)-\overset{-}{C}HCN} \begin{array}{c} Ph \\ Ph-C \equiv C \end{array} C = C \begin{array}{c} CN \\ H \end{array}$$

18a

40 (E)

from the NMR spectrum of the reaction product which
exhibited separate signals for the vinylic hydrogens at

δ 6.20(25 %) and δ 6.58 (75 %) . These signals were attri-
buted to the _Z_ and _E_ isomers respectively. Attempts to

$$Ph-C\equiv C-CO-Ph \xrightarrow{(EtO)_2P(O)\bar{C}HCOOEt}$$

18a

41a (Z)
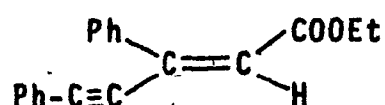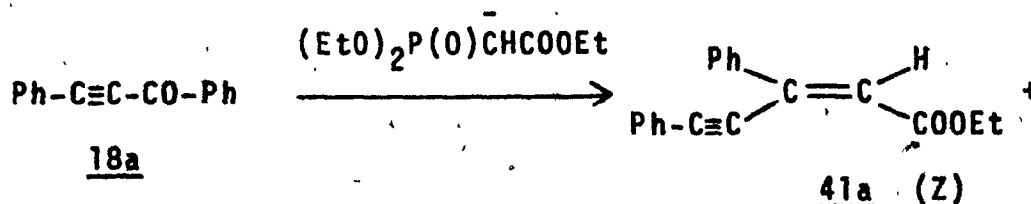
41b (E)

separate the two isomers by chromatographic techniques
were unsuccessful.

1-Phenyl-2-butyn-1-one (**18b**) which did not react
with either of the two ylids did react with both the
carbanions. Under the conditions used diethyl cyanomethyl-
phosphonate carbanion yielded a white crystalline product
(49 % ; mp 123-124° C). The IR and NMR spectra of the
product indicated that it was not the expected olefinic
product **42**. The infrared spectrum (page 132) exhibited
characteristic bands for the C≡N (2220 cm^{-1}) and C=O
(1660 cm^{-1}) groups. The elemental analysis of the product
corresponds to the molecular formula $C_{22}H_{17}NO$. The mass
spectrum indicated the molecular ion peak at m/e 311 (64%).
Other significant peaks were at m/e values 310 (62 %;
M^{+} - H), 296 (11 %; M^{+} - CH_3·), 234 (23 % ; M^{+} - Ph·).

105 (53 % ; PhCO[+]), 77 (100 % ; Ph[+]). The appearance of
a metastable peak in the mass spectrum at m/e 281.7 is
indicative of the process 311⟶296. The NMR spectrum
(page 123) revealed the presence of two CH_3 groups with
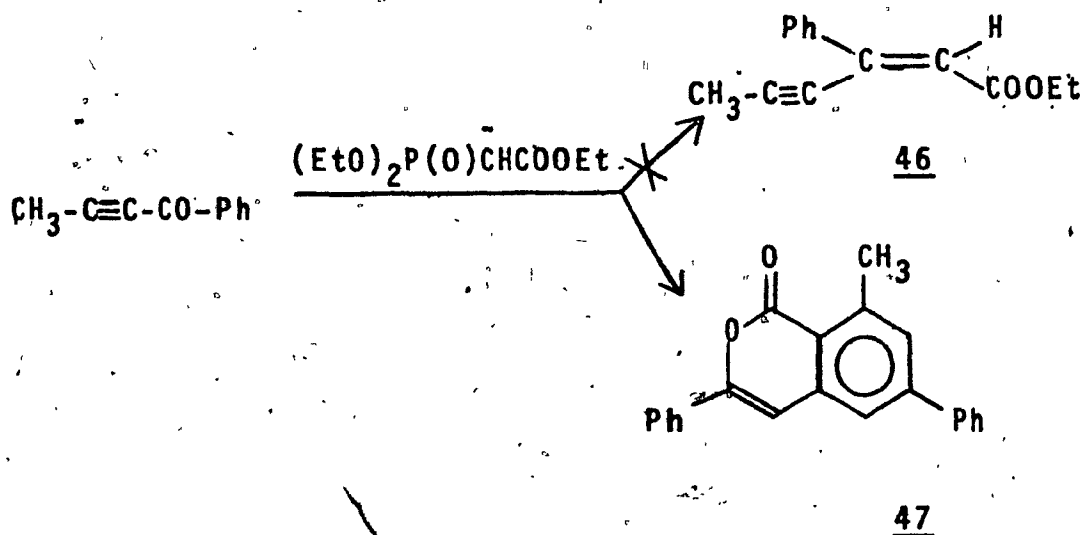the chemical shift values of δ 2.26 and δ 2.46. The aro-
matic region showed the presence of 11 protons, and of
these one appeared as a singlet at δ 7.45. Based on the
foregoing evidence the product was identified as 4-benzoyl-
2-cyano-3,5-dimethylbiphenyl (45). The singlet at δ 7.45
is ascribable to the C-6 proton in 45. The UV spectrum of
the product (page 136) exhibited maxima at 227 nm (ε =
2.3 x 10^{5}), 252 nm (ε = 1.9 X 10^{5}). This is reminiscent
of the UV spectrum of benzoylbiphenyl itself.[99,100]

A plausible mechanism which would account
for the formation of compound 45 from the reaction of
ketone 18b and diethyl cyanomethylphosphonate carbanion
is presented in Scheme 6 . The ketone undergoes conjugate
addition of the carbanion to form a new phosphonate
carbanion 43 which further reacts with a second molecule
of the ketone at the carbonyl function in a normal olefin-
forming reaction producing the intermediate 44 which
undergoes cyclization to the more stable product 45.

$(EtO)_2P(O)-\overset{-}{C}H-CN$ + $CH_3-C\equiv C-\underset{O}{C}-Ph$ **18b**

43

$CH_3-C\equiv C-CO-Ph$

$(EtO)_2PO_2^-$ +

44

  $\equiv$

45
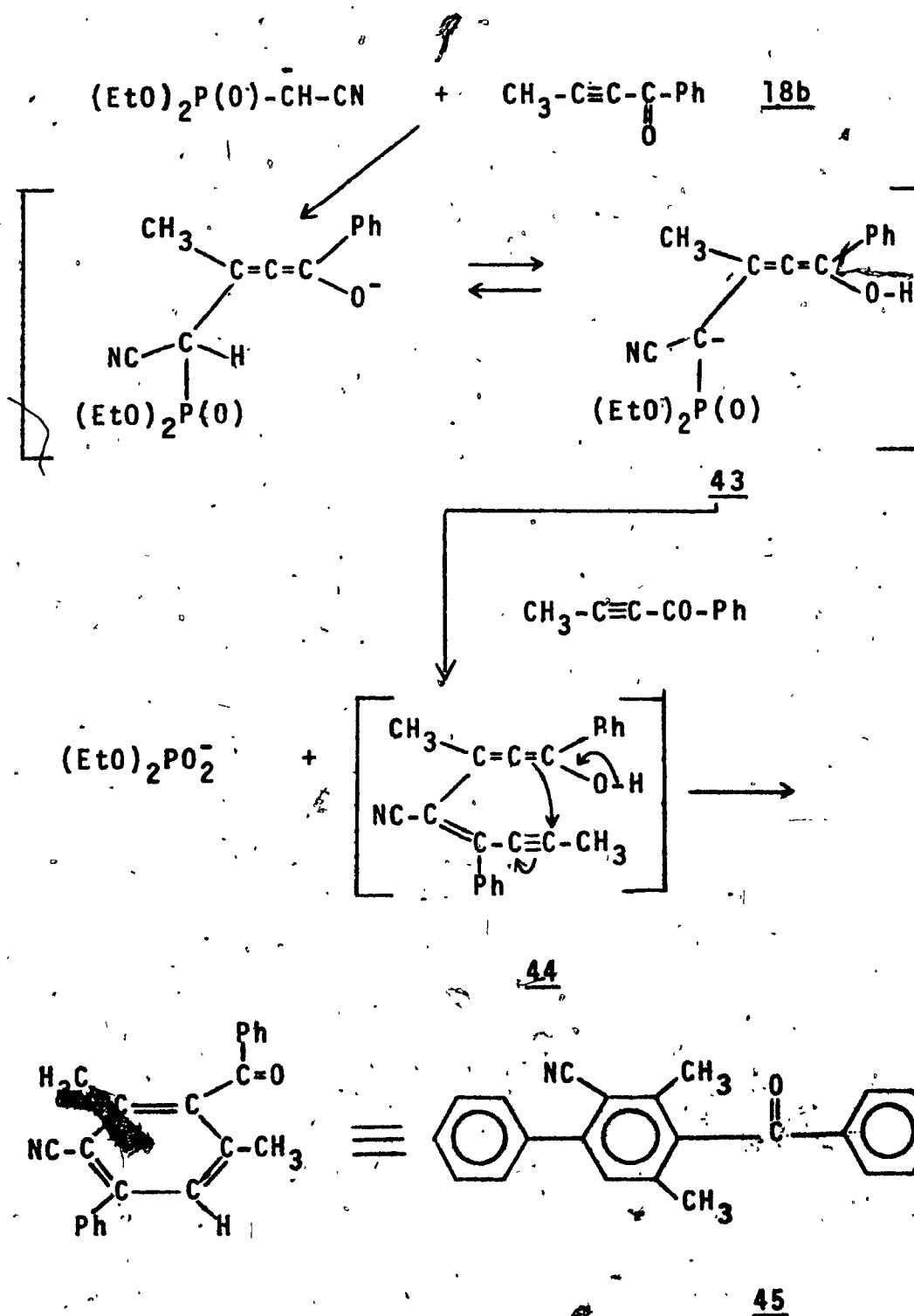
Scheme 6

The carbanion of triethylphosphonoacetate also reacted with the ketone 18b. However, none of the expected olefinic product was detected in the reaction product. Instead, a yellow crystalline solid was isolated (59 % yield) having the mp 125-127 ^{0} C . The elemental

$$CH_3-C\equiv C-CO-Ph \xrightarrow{(EtO)_2P(O)CHCOOEt}$$

$$CH_3-C\equiv C \underset{Ph}{\overset{}{\diagup}} C=C \underset{COOEt}{\overset{H}{\diagdown}}$$

46

47

analysis corresponded to a molecular formula $C_{22}H_{16}O_2$. The IR spectrum of the product (page 130) had character- istic bands for C=O (1730 cm^{-1}) and C=C (1630 cm^{-1}) , but no band due to a C≡C group. The NMR spectrum (page 124.) indicated the absence of any ethyl group in the product , but revealed the presence of one CH_3 group (singlet at δ 2.25). The aromatic region showed the presence of 13 hydrogens , of which one appeared as a well-resolved singlet at δ 7.10 . The mass spectrum revealed the molecular ion at m/e 312 , which is also the base peak. Other significant peaks appear at m/e values

311 ($\sim$ 12 % ; M^+ - H), 284 ($\sim$ 6 % M^+ - CO) and 105

($PhCO^+$) . A metastable peak at m/e 258.5 is attri-

butable to the process 312 $\longrightarrow$ 284. The UV spectrum

(page 137) had absorption maxima at 250 nm ($\epsilon = 1 \times 10^5$),

301 nm ($\epsilon = 0.9 \times 10^5$), 315 nm ($\epsilon = 0.8 \times 10^5$), 348 ($\epsilon =$

0.05×10^5) . Based on the above evidence the product

was identified as 8-methyl-3,6-diphenylisocoumarin 47.

The singlet at δ 7.10 is attributable to the C-4 hydro-

gen of the isocoumarin ring. All the spectral character-

istics described are very similar to those of other

3-aryl substituted isocoumarins.[101]

-The ketone 18h also reacted with the carbanion of

triethylphosphonoacetate giving the unexpected product

with the complete exclusion of the expected olefinic

derivative 48. Here also the product was a yellow crys-

talline solid (38 % yield) having a mp 136^0C.
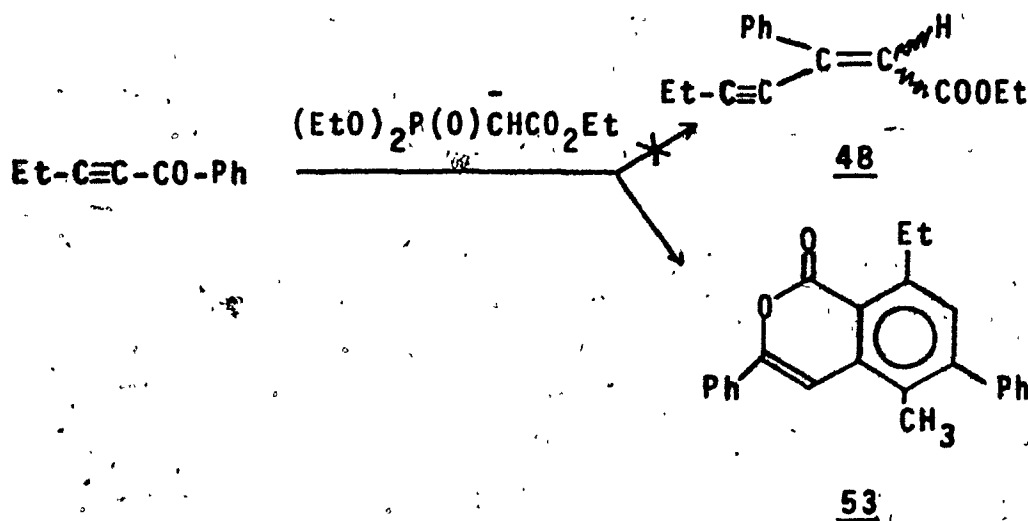
The molecular formula $C_{24}H_{20}O_2$ was arrived at from the elemental analysis and the mass spectrum which disclosed the molecular ion peak at m/e 340, which was also the base peak. Other significant peaks were at m/e 312 (~ 30%; $M^+ - CO$), m/e 297 (~ 20 % ; $M^+ - CH_3$), m/e 105 (~ 20 %; $PhCO^+$). The mass spectrum also revealed a meta-stable peak at m/e 286.3 which is ascribable to the decomposition process 340→312.. The IR spectrum of the product (page 133) exhibited characteristic bands for C=O (1625 cm^{-1}) but no band for a C≡C group. The NMR spectrum (page 125) indicated the presence of one ethyl group (characteristic triplet at δ 1.26 and quartet at δ 2.85), and one methyl group(singlet at δ 2.55). The aromatic region disclosed 12 hydrogens of which one appeared as well-separated singlet at δ 7.38. The UV spectrum (page 138) had maxima at 237 nm (ε= 1.5 x 10^5), 254 nm (ε= 1.8 x 10^5), 304 nm (ε= 1.38 x 10^5), 318 nm (ε= 1.3 x 10^5), 353.(ε = 0.93 X 10^5) . These spectral properties are consistent with a 3-arylisocoumarin.[101,102] The singlet at δ 7.38 is ascribable to the C-4 hydrogen of the isocoumarin ring. The compound was therefore identified as 8-ethyl-5-methyl-3,6-diphenylisocoumarin **53.**

The production of the isocoumarin derivatives **47** and **53** from the reaction of the carbanion of triethyl-

phosphenoacetate and the acetylenic ketones <u>18b</u> and <u>18h</u>
can be rationalized by the sequence of events depicted
in <u>Scheme 7</u>. The carbanion undergoes addition to the triple

R-CH₂-C≡C-C-Ph and related structures

<u>49</u>

Ph-C-C≡C-CH₂-R

<u>50</u>   <u>51</u>

52
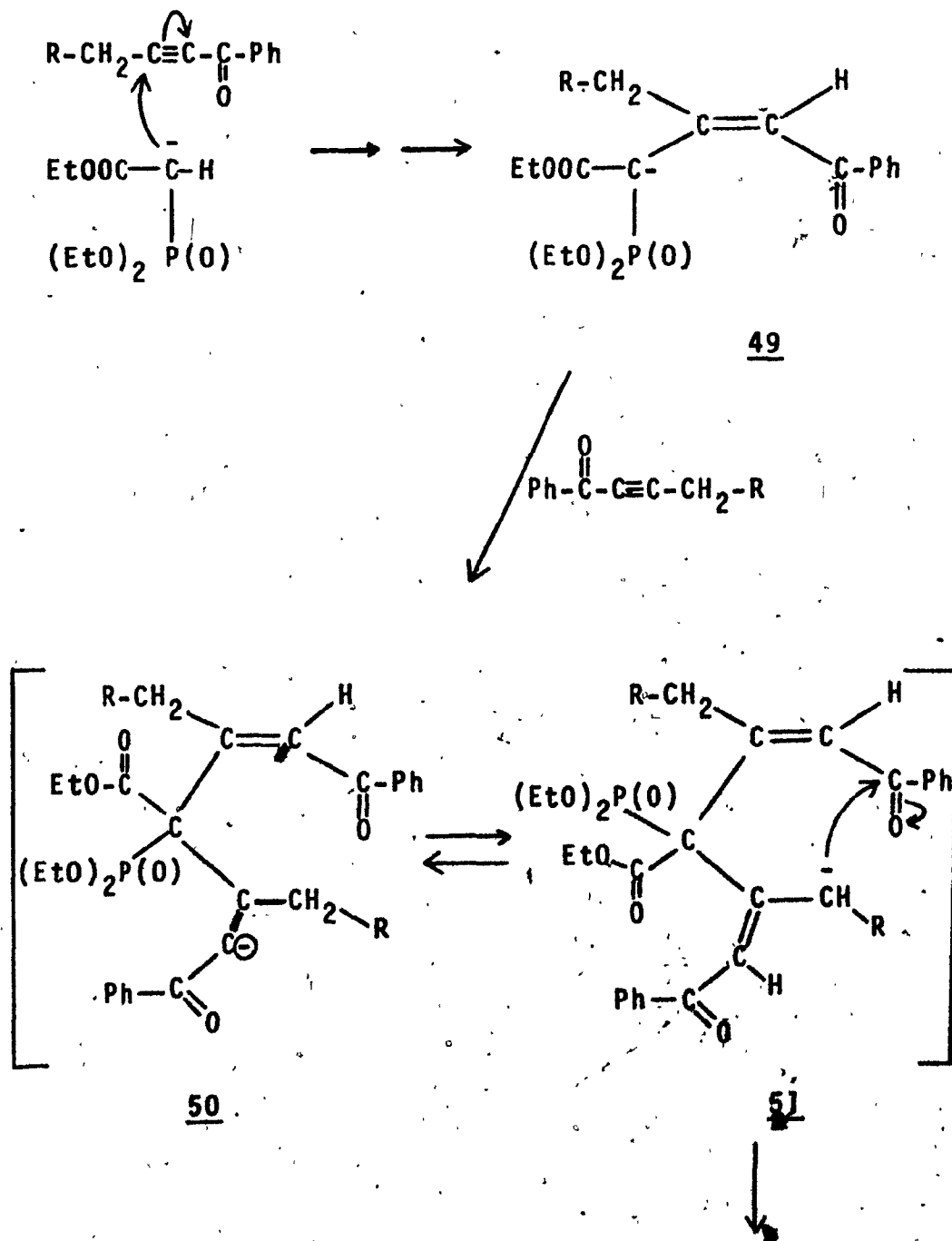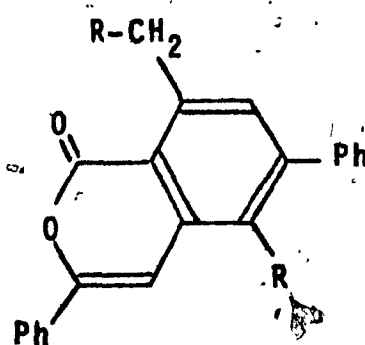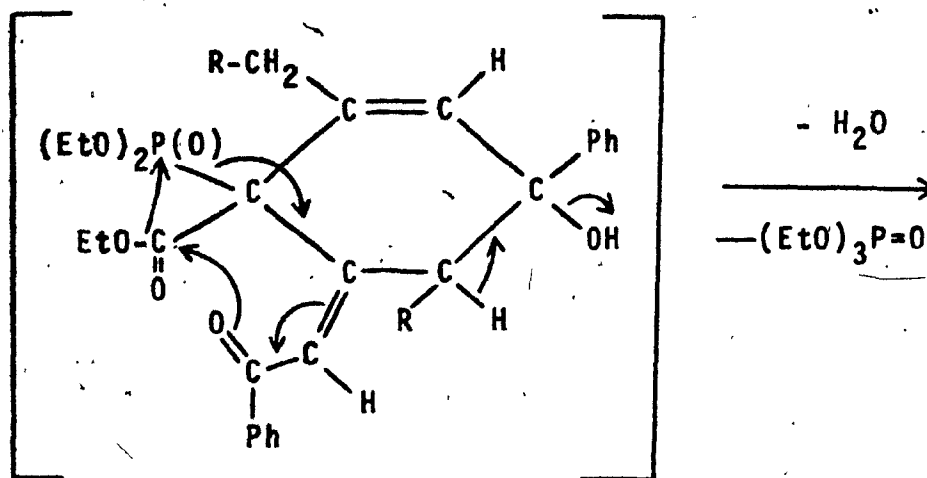
47 (R = H)

53 (R = CH₃)

Scheme 7

bond of the ketone to yield a new carbanion 49 which
undergoes conjugate addition further with another molecule
of the ketone to produce the intermediate 51. This inter-

mediate undergoes cyclization to 52 from which loss of
water and triethylphosphate produces the isocoumarin
derivative 47 or 53.

The carbanion diethylcyanomethylphosphonate reacted
normally with 18h yielding the olefinic products 54
(vinylic proton signals at δ 5.77 and δ 6.08 in 17:83
ratio, NMR spectrum page 126) in contrast to the ketone
18b with the same carbanion where the abnormal biphenyl
derivative 45 was the only product. The difference between
18b and 18h is only in the alkyl group attached to the
acetylenic function (CH_3 in 18b and C_2H_5 in 18h). Why
both ketones react in an analogous manner with the carban-

$$Et-C \equiv C-CO-Ph \quad \xrightarrow{(EtO)_2P(O)\bar{C}HCN} \quad$$

18h

54a (Z) 17 %

54b (E) 83 %
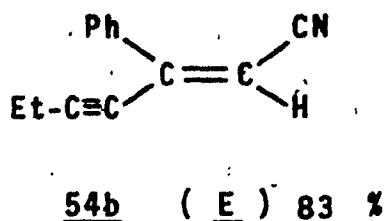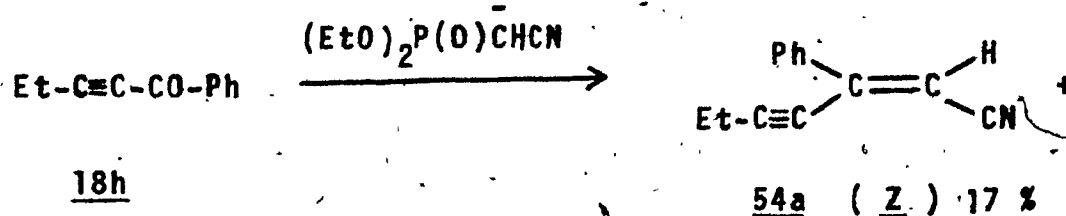
ion of triethylphosphonoacetate, but take entirely
different courses in the reaction with the carbanion of

diethylcyanomethylphosphonate is not entirely clear at present.

Ketone 181 was found to be completely unreactive towards both the phosphonate carbanions as was the case with the two analogous phosphonium ylids. Similarly

$$Ph-C\equiv C-CO-i-Pr \quad \underline{181}$$

with reagents $(EtO)_2P(O)\overset{-}{CH}CN$ and $(EtO)_2P(O)\overset{-}{CH}CO_2Et$ (both reactions crossed out), giving products:

55: $i-Pr$, $Ph-C\equiv C$ / $C=C$ / H, CN

56: $i-Pr$, $Ph-C\equiv C$ / $C=C$ / H, CO_2Et
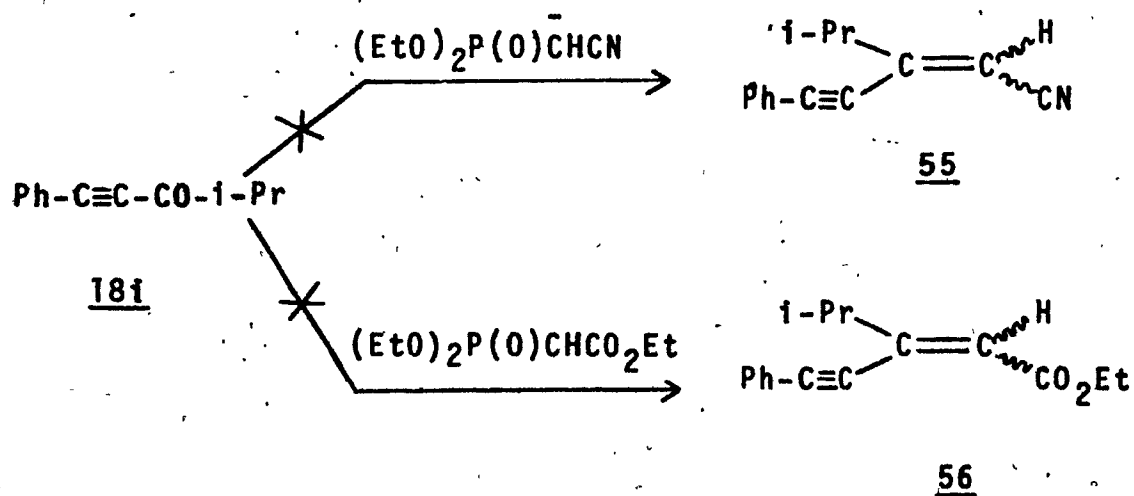
Ph-C≡C-CO-CH=CH-CH$_3$ also did not react with the carbanions to yield the olefinic products 57 and 58. The cyanomethyl-

57: $CH_3-CH=CH$, $Ph-C\equiv C$ / $C=C$ / H, CN

58: $CH_3-CH=CH$, $Ph-C\equiv C$ / $C=C$ / H, $COOEt$
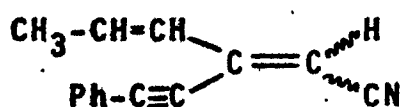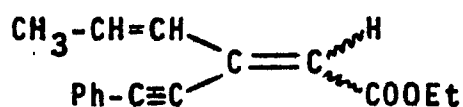
phosphonate carbanion was also unreactive towards ketone

18g. However, the carbethoxymethyl phosphonate carbanion reacted with this ketone giving the expected olefinic products 60 (vinylic proton signals at δ 6.47 and δ 6.75 in the ratio 44:56) although only in 10 % yield. Ketone

$(EtO)_2P(O)\overset{-}{C}HCN$

59

$CH_3-C\equiv C-CO-CH_2Ph$

18g

$(EtO)_2P(O)\overset{-}{\underset{COOEt}{C}H}$

60a (Z) 44 %

60b (E) 56 %
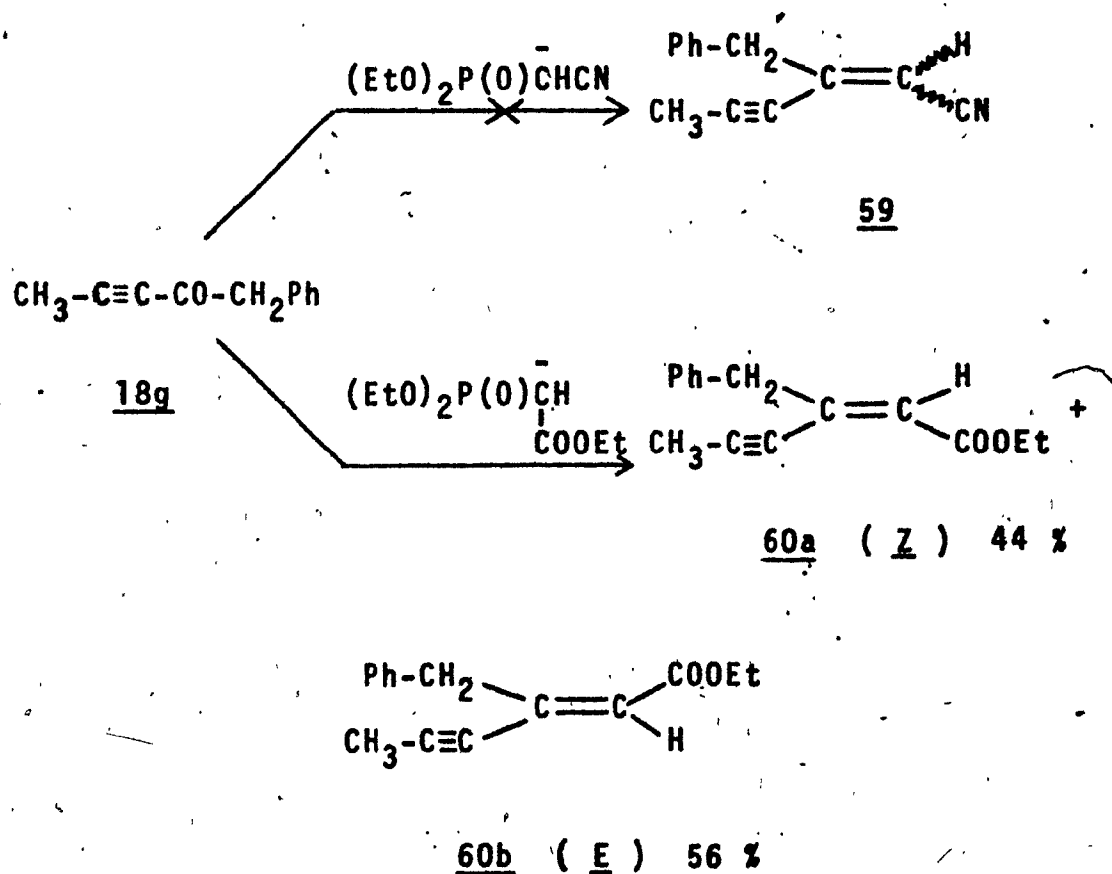
18f which was found to be quite unreactive towards the two phosphonium ylids reacted with both the phosphonate carbanions giving the expected olefinic products 61 and 62 . The vinylic proton signals in the NMR spectrum of 61 were at δ 5.83 (33 %) and at δ 6.26 (67 %) and those in 62 were at δ 6.65 (42 %) and at δ 6.72 (58 %).

$$t\text{-Bu-C}\equiv\text{C-CO-Ph} \xrightarrow[\textstyle 36\%]{(EtO)_2P(O)\overset{-}{C}HCN}$$

18f

61a (Z) 33 %

61b (E) 67 %

$$t\text{-Bu-C}\equiv\text{C-CO-Ph} \xrightarrow[\textstyle 6\%]{(EtO)_2P(O)\overset{-}{C}HCOOEt}$$

18f

62a (Z) 42 %

62b (E) 58 %
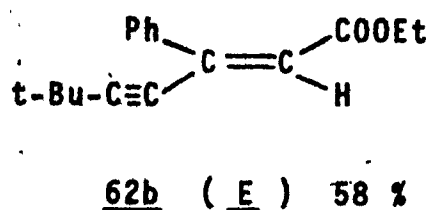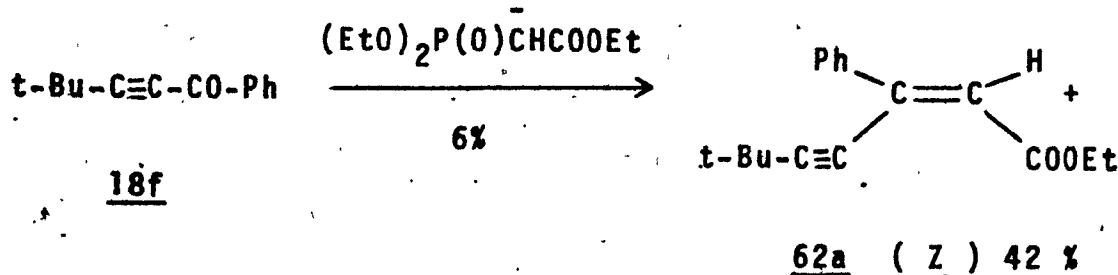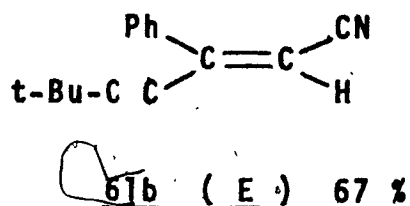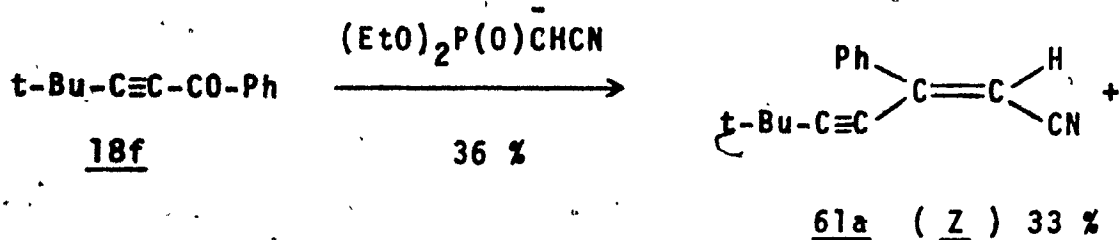
In all these cases the configurational assignments to the olefinic products were made on the basis of the chemical shift of the vinylic hydrogen and also taking into consideration the fact that the less hindered betaine is produced more as the intermediate giving rise to more of the (E)

isomer. With ketone <u>18e</u>, the cyanomethylphosphonate carbanion yielded only one isomer of the olefinic product whose NMR spectrum (page 127) showed vinylic proton signals at δ 5.62. Considering the fact that only one isomer is produced, the product is assigned the (<u>E</u>) configuration.

$$Ph-C\equiv C-CO-t-Bu \xrightarrow{\text{(EtO)}_2P(O)\overset{-}{C}HCN}$$

<u>18e</u>

$$\underset{Ph-C\equiv C}{\overset{t-Bu}{\diagdown}}C=C\underset{H}{\overset{CN}{\diagup}}$$

<u>63</u> (<u>E</u>)
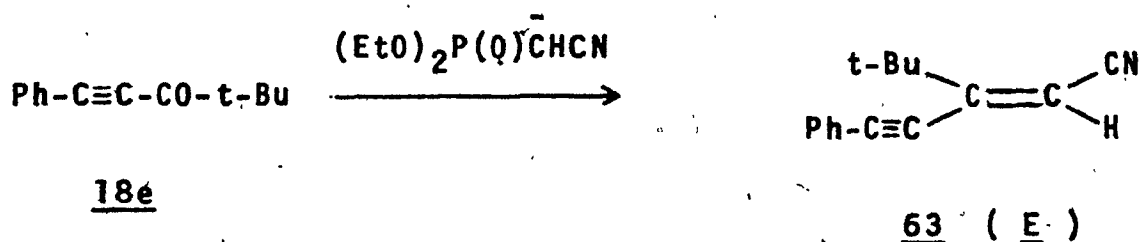
With the carbanion of triethylphosphonoacetate, however, both the expected isomers of the olefinic products <u>64a</u> and <u>64b</u> were produced. The NMR spectrum of the crude

$$Ph-C\equiv C-CO-t-Bu \xrightarrow{\text{(EtO)}_2P(O)\overset{-}{C}HCOOEt}$$

<u>18e</u>

$$\underset{Ph-C\equiv C}{\overset{t-Bu}{\diagdown}}C=C\underset{COOEt}{\overset{H}{\diagup}} +$$

<u>64a</u> (<u>Z</u>) 25 %

$$\underset{Ph-C\equiv C}{\overset{t-Bu}{\diagdown}}C=C\underset{H}{\overset{COOEt}{\diagup}}$$

<u>64b</u> (<u>E</u>) 75 %
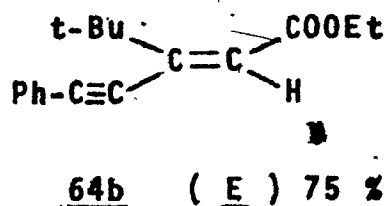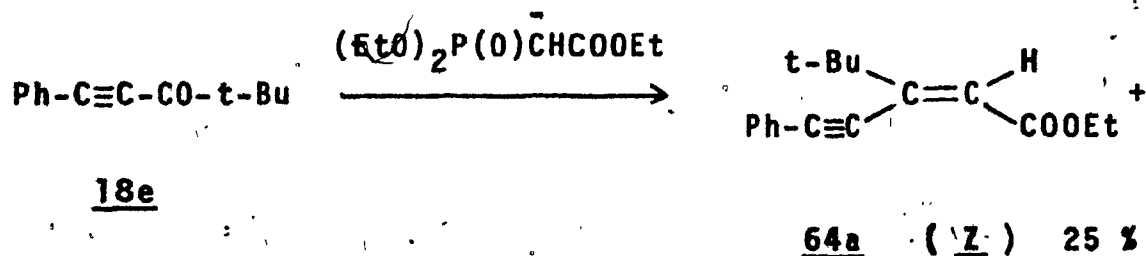
reaction product revealed vinylic proton signals at δ 6.28
(75 %) and δ 6.22 (25 %). After chromatography only
one isomer was obtained in pure form (with vinyl proton
signals at δ 6.28) and was assigned ($\underline{E}$) configuration
considering the chemical shift values as well as the strain
involved in the formation of the transition state ($\underline{erythro}$
and $\underline{threo}$ betaines). With the sterically least hindered
ketone $CH_3-C\equiv C-CO-CH_3$ ($\underline{18d}$) only one isomer of the olefin-
ic product was observed with either of the phosphonate
carbanions. In the NMR spectrum of $\underline{65}$ the vinylic proton

$$CH_3-C\equiv C-CO-CH_3 \xrightarrow{(EtO)_2P(O)\bar{C}HCN} $$

$\underline{18d}$

$$\begin{array}{c} CH_3 \\ CH_3-C\equiv C \end{array} C=C \begin{array}{c} CN \\ H \end{array}$$

$\underline{65}$ ($\underline{E}$)

$$CH_3C\equiv C-CO-CH_3 \xrightarrow{(EtO)_2P(O)\bar{C}OOEt} $$

$\underline{18d}$

$$\begin{array}{c} CH_3 \\ CH_3-C\equiv C \end{array} C=C \begin{array}{c} COOEt \\ H \end{array}$$

$\underline{66}$ ($\underline{E}$)
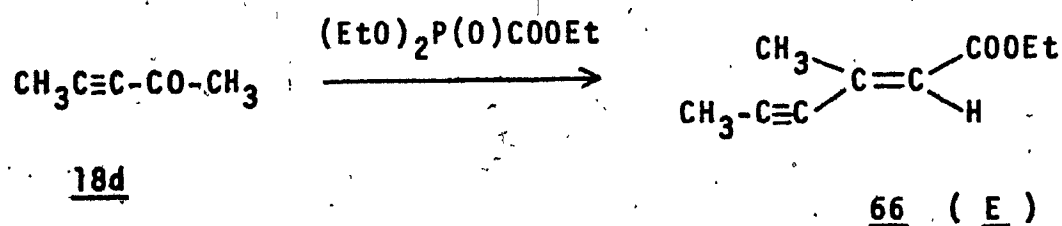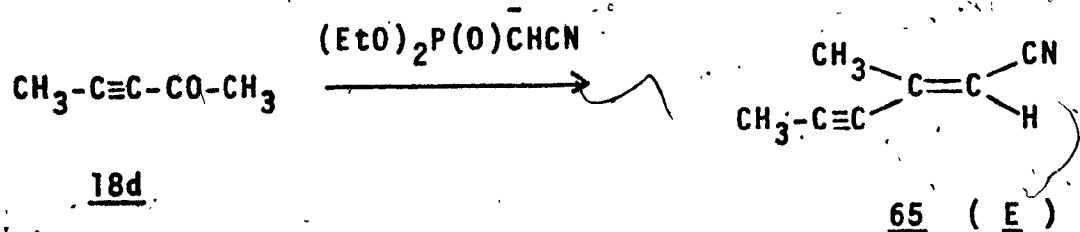
signal appeared at δ 5.58 and the signal for the CH_3 on
the double bond at δ 2.03. Similarly for product $\underline{66}$ the
vinylic proton signal and that for the corresponding CH_3

group were at δ 6.10 and δ 2.04 respectively. Based on
these values the two products were assigned the ($\underline{E}$)
configuration. It is quite possible that both isomers
were produced in each case, but the ($\underline{Z}$) isomer so un-
stable that it underwent fast isomerization to the more
stable isomer under the reaction conditionns.

Ketone $\underline{18c}$ reacted in the normal manner with both the
phosphonate carbanions, as with both the phosphonium ylids
giving the expected olefinic products. It was possible to

Ph-C≡C-CO-CH$_3$ $\xrightarrow{\text{(EtO)}_2\text{P(O)\overset{\bar{}}{C}HCN}}$

$\underline{18c}$

CH$_3$ / C=C \ H, Ph-C≡C / \ CN

$\underline{67a}$ ($\underline{Z}$) 30 %

CH$_3$ / C=C \ CN, Ph-C≡C / \ H

$\underline{67b}$ ($\underline{E}$) 70 %
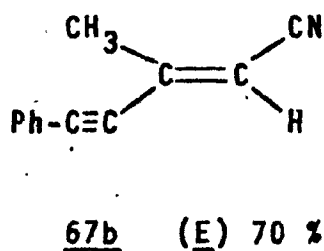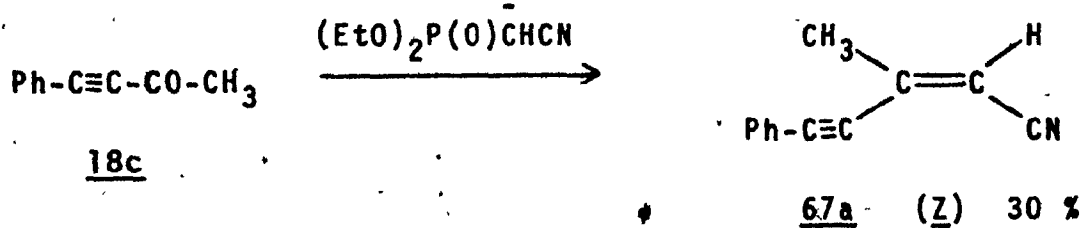
get pure samples of each of the isomeric nitriles $\underline{67a}$
(NMR spectrum, page 119), and $\underline{67b}$ (NMR spectrum,
page 118) by column chromatgraphy. However, it was not

$$Ph-C\equiv C-CO-CH_3 \xrightarrow{(EtO)_2P(O)\bar{C}HCOOEt}$$

18c

68a (_Z_) 45 %

68b (_E_) 55 %
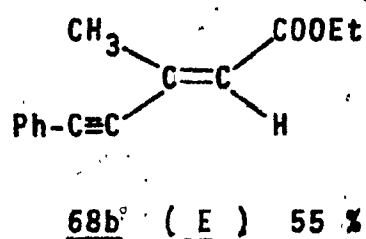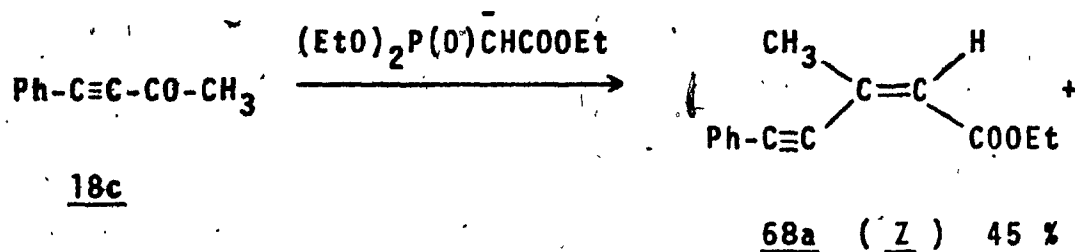
possible to effect a separation of the isomeric ethyl esters **68a** and **68b** by chromatographic techniques.

EXPERIMENTAL

Reagents and Chemicals : - Reagents and chemicals used
in this project were obtained from the following sources.
Aldrich Chemical Co. Inc. : Phenylacetylene, phenyl-
acetaldehyde, isopropylacetylene.

Allied Chemicals Canada, Ltd. : Benzaldehyde.

Anachemia Chemicals Ltd. : Sodium sulphate anhydrous.

Canadian Laboratory supplies Ltd. : Sodium dichromate
dihydrate, acetaldehyde.

Fisher Scientific Co. Ltd. : Magnesium, anhydrous diethyl
ether, molecular sieves, phosphorus pentachloride,
paraffin oil, alumina chromatographic grade.

Mallinckrodt Chemical Works Ltd. : Ammonium chloride,
chloroform, carbon tetrachloride, calcium chloride an-
hydrous.

Most of the reagents were freshly distilled before use.

Melting Points and Boiling Points : Melting points and
boiling points reported are uncorrected. The melting
points were determined using a Gallenkamp MF-370 instru-
ment.

IR and UV Spectra : IR spectra were obtained using
Perkin-Elmer models 137.2 and 599 B. UV spectra were
recorded on an Aminco DW2 instrument using ethanol as

solvent.

Mass Spectra : Mass spectra were done by Ayerst Research Laboratories.

Elemental Analysis : Elemental microanalysis were performed by Ayerst Research Laboratories.

NMR Spectra : All NMR spectra were recorded on a Varian A-60 A spectrometer (solvents : carbon tetrachloride, chloroform or $CDCl_3$). The peaks are designated as singlet (s), doublet (d), multiplet (m) and quartet (q).

Thin Layer Chromatography (TLC) : Analytical TLC was accomplished on standard microscope slides coated in this laboratory with E.Merc Aluminium Oxide GF-254 or E.Merc.Silica Gel GF-254. Mineralit Model SL 2537 lamp with short wave UV filter was used for the detection of the components. The instrument was supplied by Ultra-Violet Products, Inc., South Pasadena, California.

Dry Column Chromatography: Column chromatography was accomplished by the technique described by Low and Goodman.[105] Neutral alumina A-948 (deactivated to Brockman activity III) was used in most cases unless

otherwise specified. A ratio of 1 gram of crude
product to 60 grams of the alumina was usually used.

General

[44]

The acetylenic ketones were prepared following Shearing.
Detailed procedures are given only for reactions that
gave identifiable products and for those reactions that
gave known compounds by new routes. Low boiling petroleum
ether refers to the fraction with boiling range $30-60^0$C
and petroleum ether refers to the fraction with boiling
range $60-75^0$C unless stated otherwise. The term "reduced
pressure" refers to the vacuum obtained with a water
aspirator and an oil pump.Column chromatography implies
the technique of dry column chromatography described
previously.

Preparation of Triphenyl Phosphoranylacetonitrile. [53,54,55]

Triphenylphosphine (66 g, 0.25 mol) was dissolved in
chloroform (50 mL) and chloroacetonitrile (19 g, 0.25
mL) was added and the mixture was refluxed for 3h. The
reaction mixture was then cooled to room temperature and
diethyl ether (400 mL) was added. The solid separated
was filtered and dissolved in water (1000 mL) at
$50-60^0$C. The solution was cooled to room temperature and
a 25 % sodium carbonate solution (100 mL) was added.
The white precipitate thus formed was filtered, washed

with water (3 times) and dried at room temperature. The
ylid thus obtained was recrystallized from ethanol-water
mixture yielding 70 g (92 %) of triphenylphosphoranyl-
acetonitrile, mp 181-182^{0}C.

Preparation of Triphenylphosphoranylethylethanoate.[56,57]

The triphenylphosphine (80 g, 0.3 mol) was dissolved in
200 mL of chloroform. The solution was stirred and while
stirring 52.5 g (~0.3 mol) of ethyl bromoacetate was
added carefully. The reaction was exothermic. The mixture
was then refluxed for 3h. The reaction mixture was then
cooled to room temperature and poured into diethyl ether
(600 mL) with stirring. The oil separated soon solidi-
fied into a granular solid which was filtered, washed
with diethyl ether, dried in air and finally in the oven
at 85^{0}C for 1h yielding 131 g (95 %) of triphenylcarbeth-
oxymethylphosphonium bromide, mp 148-150^{0}C. The salt was
then dissolved in water (350 mL) at 50-60^{0}C, and
cooled to room temperature. 90 mL of 50 % sodium hydro-
xide solution was added rapidly with stirring. The oil
separated solidified on stirring and scratching. The
solid thus obtained was filtered, washed with water (5
times), dried in air for two days, dried again in the
oven at 85^{0}C for 2h yielding 91 g (84 %) triphenyl-
phosphoranylethylethanoate. The ylid thus obtained was
recrystallized from benzene, dried at room temperature

for 2 days and then in the oven at 80^0C for 30 min.

Preparation of 1-phenyl-2-pentyn-1 one[103]. The reaction was
carried out in a 2L 3 necked flask, fitted with a
mechanical stirrer, a dropping funnel and a Dewar con-
denser (with crushed dry ice) equipped with a drying
tube. Ethylmagnesium bromide was prepared in this setup
from 80 g (0.74 mol) of ethyl bromide and 15 g (0.6
mol) of magnesium turnings in a total volume of 450 mL
of anhydrous ether in the usual manner. Ethyl acetylene
was then bubbled through the reaction mixture at the rate
of 150 mL/ min. for 3h. Following this a solution of
63.6 g (0.6 mol) of benzaldehyde in 200 mL of ether was
added dropwise with stirring during 45 min.. The mixture
was then refluxed for a further 1h, cooled to room
temperature and 200 mL of saturated ammonium chloride
solution was added dropwise very carefully. The reaction
mixture was then extracted with ether and the combined
ether layers were washed with water and dried over sodium
sulphate. Evaporation of the solvent yielded 95.4 g (68%)
of 1-phenyl-2-pentyn-1-ol. The alcohol thus obtained was
oxidised with chromic acid using the method of H.C.Brown
et al.[45] The product was poured into water (150 mL) and
stirred well. The oil separated was extracted with ether
(5 X 50 mL) and after drying over sodium sulphate the
solvent was evaporated at reduced pressure. The product

which showed only one spot on TLC, was distilled yielding
41.3 g (69 %) of 1-phenyl-2-pentyn-1-one, bp 92-95^{0}C
(0.77 mm). NMR and IR spectra (C=O 2220 cm^{-1}, C=O
1640 cm^{-1}) confirmed the structure of the ketone.

Reaction of the α-acetylenic Ketones with the ylids-
General Procedure: A 100 mL 3 necked flask was fitted
with a reflux condenser, dropping funnel and an inlet
tube through which nitrogen was passed into the flask.
The ylid (0.01 mol) was transfered into the flask and
25 mL of dimethoxyethane (DME) was added through a
dropping funnel and the mixture was stirred well. A
solution of the ketone (0.01 mol) in the same solvent
(DME, 10 mL) was added dropwise over a period of 20
min.. The mixture was then refluxed for 4h under nitrogen
and the reaction was monitored by IR spectroscopy and TLC.
The reaction mixture was cooled and the solvent was
removed at reduced pressure. After obtaining its NMR and
IR spectra, the crude product was chromatographed over
alumina or silica.

The following reactions were carried out with the
ylids.

Reaction of 1,3-diphenyl-2-propyn-1-one with triphenylphos-
phoranylacetonitrile. From 3.01 g (0.01 mol) of the ylid

and 2.06 g (0.01 mol) of the ketone, after a reflux
time of 8h, and subsequent chromatography over silica
using chloroform as eluent, only 1.80 g of the starting
ketone and 2.55 g of triphenylphosphine oxide were re-
covered. No other product was identified.

Reaction of 1,3-diphenyl-2-propyn-1-one with triphenyl-
phosphoranylethylethanoate. From 3.48 g (0.01 mol) of
the ylid and 2.06 g (0.01 mol) of the ketone, after a,
reflux time of 8h, and subsequent chromatography over
alumina using chloroform as eluent, only 1.86 g of the
starting ketone and 2.48 g of triphenylphosphine oxide
were isolated. No other product was identified.

Reaction of 4-phenyl-3-butyn-2-one with triphenylphospho-
ranylacetonitrile. From 3.01 g (0.01 mol) of the ylid
and 1.44 g (0.01 mol) of the ketone; after a reflux
time of 3h, and subsequent chromatography over alumina
using carbon tetrachloride and chloroform (1:1 v/v) as
eluent, 1.54 g of a brown oil was isolated which was
identified as a mixture of the two geometrical isomers
of the product resulting from the normal Wittig reaction.
By repeated chromatography over alumina using carbon
tetrachloride and chloroform (4:1 v/v) as eluent, 0.821
g of a colourless oil, bp 119^0C (0.32 mm) was separated
and was assigned as the geometrical isomer with the E

configuration. IR (CCl_4, cm^{-1}) : 3030, 2200, 2195, 1600, 1445; NMR (CCl_4) δ 2.28 (3H, d), δ 5.62 (1H, m), δ 7.38- 7.73 (5H, m). Second component separated (0.502 g) was also a colourless oil, bp 120^0C (0.35 mm) and was assigned the $\underline{Z}$ configuration. IR (CCl_4, cm^{-1}) : 3330, 2210, 2205, 2200, 1600; NMR (CCl_4) δ 2.12 (3H,d), δ 5.55 (1H, m), δ 7.38-7.68 (5H, m); MS, m/e 167, 152, 140, 139, 125, 118, 102, 77. Anal. calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.42. Found : C, 86.49; H, 5.23; N, 8.20.

Reaction of 4-phenyl-3-butyn-2-one with triphenylphosphoranylethylethanoate.

From 3.48 g (0.01 mol) of the ylid and 1.44 g (0.01 mol) of the ketone, after a reflux time of 10h, followed by the usual workup and chromatography over alumina using chloroform and carbon tetrachloride (4:1 v/v) as eluent, 0.98 g (48.5 %) of an oil bp 110^0C (0.38 mm) was isolated and was identified as a mixture of the two geometrical isomers resulting from the normal Wittig reaction. IR (CCl_4,cm^{-1}) 3020, 2200, 1700, 1600; NMR (CCl_4) δ 1.16-1.42 (3H, t), δ 2.15 and 2.46 (3H,2d), δ 4.08-4.54 (2H,m), δ 6.18 and δ 6.37 (1H,2m), δ 7.43-8.03 (5H,m). Triphenylphosphine oxide was isolated as an end fraction (2.63 g). Complete separation of the isomers was not achieved. However, by repeated chromatography over alumina using chloroform

and carbon tetrachloride (1:2 v/v) an end fraction (0.52 g) was obtained which was a single geometrical isomer and was assigned the Z configuration. IR (CCl_4, cm^{-1}), 2095, 1700, 1600; NMR (CCl_4) δ 1.16-1.42 (3H,t), δ 2.15 (3H,d), δ 4.08-4.50 (2H,q), δ 6.18 (1H,broad ,s), δ 7.43-7.95 (5H,m); MS, m/e 214, 186, 169, 158, 129. Anal. calcd for $C_{14}H_{14}O_2$: C, 78.47; H, 6.58. Found C, 77.84; H, 6.60.

Reaction of 1-phenyl-2-butyn-1-one with triphenylphosphoranylacetonitrile. From 6.02 g (0.02 mol) of the ketone, after a reflux time of 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, only 2.52 g of the starting ketone and 4.22 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 1-phenyl-2-butyn-1-one with triphenylphosphoranylethylethanoate. From 3.48 g (0.01 mol) of the ylid and 1.44 g (0.01 mol) of the ketone, following a reflux time of 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, only 1.02 g of the starting ketone and 2.22 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 3-pentyn-2-one with triphenylphosphoranylacetonitrile. From 6.02 g (0.02 mol) of the ylid and

1.64 g (0.02 mol) of the ketone, after a reflux time of 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, only 1.34 g of the starting ketone and 5.3 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 3-pentyn-2-one with triphenylphosphoranyl-ethylethanoate. In this experiment 6.96 g (0.02 mol) of the ylid and 1.64 g (0.02 mol) of the ketone were used and the reaction mixture was refluxed for 3.5h. NMR spectrum of the crude product after removal of solvent indicated that the Wittig reaction had taken place producing the two geometrical isomers (vinylic H signals at δ 6.10 and δ 5.63 in the ratio 60:40). Chromatography of this crude product over alumina using hexane and chloroform (1:1 v/v) as eluent yielded 0.672 g (24 %) of a single geometrical isomer and was assigned the E configuration. IR (CCl_4, cm^{-1}) 3000, 2220, 1705, 1610; NMR (CCl_4) δ 1.16-1.42 (3H,t), δ 2.04 (3H,d), δ 2.13 (3H,s), δ 2.42-2.78 (2H,q), δ 6.10 (1H,m). Triphenylphosphine oxide was also isolated as an end product.

Reaction of 1-phenyl-3-pentyn-2-one with triphenyl-phosphoranylacetonitrile. From 3.01 g (0.01 mol) of the ylid and 1.58 g (0.01 mol) of the ketone, after a

reflux time 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, 0.42 g (23 %) of an oil was isolated and was identified as the two geometrical isomers of the Wittig reaction (vinylic H signals at δ 6.12 and δ 5.82 in the ratio 59:41) containing some starting ketone. Triphenylphosphine oxide (2.5 g) and the starting ketone (0.867 g) were also isolated. All attempts at separation of the starting ketone from the product were unsuccessful.

Reaction of 1-phenyl-3-pentyn-2-one with triphenyl-phosphoranylethylethanoate. From 3.48 g (0.01 mol) of the ylid and 1.58 g (0.01 mol) of the ketone, after a reflux time of 10h, after workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, 1.21 g of an oil was isolated and was identified as the two geometrical isomers (vinylic H signals at δ 6.75 and δ 6.47 in the ratio 52:48) of the product of the normal Wittig reaction. Triphenylphosphine oxide (2.41 g) and the starting ketone (0.12 g) were also isolated. The product contained some of the starting ketone and all attempts to separate the ketone from the product were unsuccessful.

Reaction of 1-phenyl-2-pentyn-1-one with triphenyl-phosphoranylacetonitrile. From 6.02 g (0.02 mol) of the

ylid and 3.16 g (0.02 mol) of the ketone, after a reflux time of 20h, and subsequent chromatography over alumina using chloroform and carbon tetrachloride (1:4 v/v) as eluent 2.89 g of the starting ketone and 4.8 g of triphenylphosphine oxide were recovered. No other product was identified.

Reaction of 1-phenyl-2-pentyn-1-one with triphenyl-phosphoranylethylethanoate   In this experiment 3.48 g (0.01 mol) of the ylid and 1.58 g (0.01 mol) of the ketone were used and the reaction mixture was refluxed for 20h. NMR spectrum of the crude product after removal of solvent indicated that the normal Wittig reaction had taken place producing the two geometrical isomers (vinylic H signals at δ 6.36 and δ 6.20 in the ratio 67: 33) in ca 25 % yield. The product contained much starting ketone and triphenylphosphine oxide. It was possible to remove the triphenylphosphine oxide by chromatography. All attempts at separation of the starting ketone from the other products were unsuccessful.

Reaction of 4,4-dimethyl-1-phenyl-1-pentyn-3-one with triphenylphosphoranylacetonitrile.   From 3.01 g (0.01 mol) of the ylid and 1.86 (0.01) of the ketone, after a reflux time of 8h, the usual workup, chromatography over alumina using carbon tetrachloride and chloroform

(1:1 v/v) as eluent, only 1.56 g of the ketone and 2.58 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 4,4-dimethyl-1-phenyl-1-pentyn-3-one with triphenylphosphoranylethylethanoate. From 3.48 g (0.01 mol) of the ylid and 1.86 g (0.01 mol) of the ketone, after a reflux time of 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, only 1.5 g of the ketone and 2.6 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 4-methyl-1-phenyl-1-pentyn-3-one with triphenylphosphoranylacetonitrile. In this reaction 3.01 g (0.01 mol) of the ylid and 1.72 g (0.01 mol) of the ketone were used and the reaction mixture was refluxed for 20h. NMR spectrum of the crude product after removal of solvent indicated that the normal Wittig reaction had taken place producing a single geometrical isomer of the product (vinylic H signal at δ 5.67) in ca 33 % yield. Chromatography of the crude product over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, yielded 0.78 g of the olefinic product. The starting ketone (0.86 g) and triphenylphosphine oxide (2.23 g) were also isolated. The olefinic product contained some

of the starting ketone. All attempts at separation of the
ketone from the olefinic product were unsuccessful.

Reaction of 4-methyl-1-phenyl-1-pentyn-3-one with tri-
phenylphosphoranylethylethanoate. In this raction 3.48 g
(0.01 mol) of the ylid and 1.72 g (0.01 mol) of the ketone
were used and the reaction mixture was refluxed for 20h.
NMR spectrum of the crude product after removal of the
solvent indicated that the normal Wittig reaction had
taken place producing a single geometrical isomer of the
product (vinylic H signals at δ 6.22) in ca 39 % yield.
Chromatography of the crude product over alumina using
hexane and chloroform (1:2 v/v) as eluent, yielded 0.82 g
of the olefinic product followed by the starting ketone
(0.79 g) and triphenylphosphine oxide (2.50 g). The
olefinic product contained a trace amount of the ketone
and all attempts at separation of the starting ketone
from the product were unsuccessful.

Reaction of 4,4-dimethyl-1-phenyl-2-pentyn-1-one with
triphenylphosphoranylacetonitrile. From 3.01 g (0.01
mol) of the ylid and 1.86 g (0.01 mol) of the ketone,
after a reflux time of 20h, removal of solvent and
subsequent column chromatography of the crude product
over alumina using carbon tetrachloride and chloroform
(1:1 v/v) as eluent, only 1.60 g of the starting ketone

and 2.30 g of triphenylphosphine oxide were isolated. No other product was identified.

Reaction of 4,4-dimethyl-1-phenyl-2-pentyn-1-one with triphenylphosphoranylethylethanoate. From 3.48 g (0.01 mol) of the ylid and 1.86 g (0.01 mol) of the ketone, after a reflux time of 20h, workup and chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, were recovered only 1.7 g of the ketone and 2.68 g of triphenylphosphine oxide. No other product was identified.

Reaction of 2-hepten-5-yn-4-one with triphenylphosphoranylacetonitrile. From 6.02 g (0.02 mol) of the ylid and 2.16 g (0.02 mol) of the ketone, after a reflux time of 8h, workup and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:1 v/v) as eluent, only 1.80 g of the starting ketone and 4.61 g of triphenylphosphine oxide were recovered. No other product was identified.

Reaction of 2-hepten-5-yn-4-one with triphenylphosphoranylethylethanoate. From 3.48 g (0.01 mol) of the ylid and 1.08 g (0.01 mol) of the ketone, after a reflux time of 8h, and subsequent chromatography over alumina using carbon tetrachloride and chloroform (1:2 v/v) as eluent,

only 0.90 g of the ketone and 2.30 g of triphenylphosphine oxide. No other product was identified.

Reaction of acetylenic ketones with the carbanion of the phosphonate ester- General procedure:

A 100 mL 3 necked flask was fitted with a reflux condenser, dropping funnel and an inlet tube through which nitrogen was passed into the flask. A suspension of sodium hydride (0.01 mol) was prepared in dry DME (15 mL) under nitrogen while the flask was chilled in an ice bath. A solution of the phosphonate ester (0.01 mol) in dry DME (5 mL) was added dropwise to the above stirred suspension. When the addition was over a solution of the ketone (0.01 mol) in dry DME (5 mL) was added dropwise and the mixture was refluxed for 4h under nitrogen. The reaction was monitored by IR spectroscopy and TLC. The reaction mixture was cooled and poured into ice-cold water (400 mL) with rapid stirring. The product was extracted with ether (5 X 50 mL) and the combined ether layers were dried over sodium sulphate, filtered and the solvent was evaporated at reduced pressure. After obtaining its NMR and IR spectra, the crude product was chromatographed over alumina or silica.

The following reactions were carried out with the phosphonate esters.

Reaction of 1,3-diphenyl-2- propyn-1-one with diethyl phosphonoacetonitrile. From 2.06 g (0.01 mol) of ketone, 1.77 g (o.01 mol) of phosphonate ester and 0.24 g (0.01 mol) sodium hydride, after a reflux period of 4h, 2.20 g of crude product was isolated. Chromatography of this product over alumina using petroleum ether and carbon tetrachloride (1:1 v/v) yielded 1.00 g of the starting ketone and 0.53 g of a brown oil bp 120^0C (0.26 mm) which was identified as one of the geometrical isomers resulting from the normal Wittig reaction and was assigned $\underline{E}$ configuration. IR (CCl_4 cm^{-1}) 3070, 2210, 2220, 1650, 1600; NMR (CCl_4) δ 6.03 (1H,s), δ 7.2-8.08 (10H, m); MS m/e 229, 202, 201, 189, 165, 126, 102; Anal. calcd for $C_{17}H_{11}N$: C, 89.08; H, 4.80; N, 6.11. Found : C, 88.92; H, 4.62; N, 5.99.

Reaction of 1,3-diphenyl-2-propyn-1-one with triethyl phosphonoacetate. In this experiment 4.48 g (0.02 mol) of the phosphonate ester, 0.48 g (0.02 mol) of the sodium hydride and 4.12 g (0.02 mol) of the ketone were used and the reaction mixture was refluxed for 6h. NMR spectrum of the crude product indicated that the normal Wittig reaction had taken place producing the two geometrical isomers of the product (vinylic H signals at δ 6.58 and δ 6.20 in the ratio 75:25) in $\underline{ca}$ 35 % yield. Chromatography of the crude product over alumina using carbon

tetrachloride and chloroform (1:1 v/v) as eluent, yielded 1.88 g of the olefinic product and 2.06 g of unreacted phosphonate ester. The olefinic product contained a trace amount of the phosphonate ester and all attempts at separation of the starting phosphonate ester were un- successful. IR (CCl_4, cm^{-1}) 3040, 1660, 1560, 1580; NMR (CCl_4) δ 1.2-1.5 (3H, m), δ 3.83-4.2 (2H, m), δ 6.20 and 6.58 (1H, 2s), δ 7.25-8.27 (10H,m).

Reaction of 1-phenyl-2-butyn-1-one with diethyl phosphono- acetonitrile. From 3.54 g (0.02 mol) of phosphonoester, 0.48 g (0.02 mol) of sodium hydride and 2.88 g (0.02 mol) of ketone in DME (50 mL), after a reflux time of 4h, 3.95 g of the crude product was isolated. Upon storing this product in the refrigerator overnight white crystal- line substance separated which was filtered and recrystal- lized from methanol yielding 1.21 g of white crystals. This product was identified as 4-benzoyl-2-cyano-3,5-di- methyl biphenyl 45 (page 57) : mp 123-124°C; IR (CCl_4 cm^{-1}) 3040, 2220, 1660; UV λ_{max} (95 % ethanol) 227 nm (ϵ 2.3 X 10^5), 252 (ϵ 1.9 X 10^5); NMR ($CDCl_3$) δ 2.26 (3H,s), δ 2.46 (3H,s), δ 7.45-8.2 (11H, m); MS m/e 311 (64.3 %), 310 (62.5 %), 296 (11.5 %), 234 (22.8 %); Anal. calcd for $C_{22}H_{17}NO$: C, 84.88; H, 5.47; N, 4.50. Found C, 84.70; H, 5.48; N, 4.44.

Reaction of 1-phenyl-2-butyn-1-one with triethylphosphono-
acetate. From 4.48 g (0.02 mol) of the phosphonate ester,
0.48 g (0.02 mol) of sodium hydride and 2.88 g (0.02 mol)
of the ketone in DME (50 mL), after a reflux time of 24h,
4.33 g crude product was isolated. Chromatography of the
product over alumina using chloroform and hexane (3:1 v/v)
as eluent, yielded 1.90 g of the starting ester and 1.99
g of a yellow solid. Recrystallization of the solid
product from methanol afforded 1.86 g of yellow crystals.
This product was identified as 8-methyl-3,6-diphenyliso-
coumarin 47 (page 59): mp 125-127^{0}C; IR (CCl$_4$, cm^{-1})
3040, 1730, 1630, 1600; UV λ_{max} (95 % ethanol) 250 nm
(ϵ=1 X 10^5), 301 (ϵ=0.9 X 10^5), 315 (ϵ=0.8 X 10^5), 348
(=0.5 X 10^5); NMR (CDCl$_3$) δ 2.25 (3H,s), δ 7.10-8.20 (3H,
m); MS m/e 312,284,269,266,242,105. Anal.calcd for
C$_{22}$H$_{16}$O$_2$: C,84.61; H,5.12. Found : C,84.44; H,5.36.

Reaction of 4-phenyl-3-butyn-2-one with diethylphosphono-
acetonitrile. In this experiment 1.77 g (0.01 mol) of
the phosphonate ester, 0.24 g (0.01 mol) of sodium hydride
and 1.44 g (0.01 mol) of the ketone were used and the
reaction mixture was refluxed for 3h. Chromatography of
the crude product obtained over alumina using carbon
tetrachloride and chloroform (4:1 v/v) yielded 0.50 g of
an oil which was identified as the E isomer produced in
the Wittig reaction: bp 116-118^{0}C (0.35 mm);IR (CCl$_4$cm^{-1})

3330, 2200, 2195, 1600; NMR (CCl_4) δ 2.28 (3H, d), δ 5.62 (1H, m), δ 7.38-7.73 (5H, m) and 0.08 g of an oil which was isolated as the $\underline{Z}$ isomer, bp 119-120^{0}C (0.36 mm); IR (CCl_4, cm^{-1}) 3040, 2220, 2195, 1600; NMR (CCl_4) δ 2.12 (3H, d), δ 5.55 (1H, m), δ 7.38-7.68 (5H,m); MS m/e 167, 152, 140, 139, 125, 102, 77. Anal. calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.38. Found C, 86.49; H, 5.23; N, 8.20.

Reaction of 4-phenyl-3-butyn-2-one with triethylphosphono-acetate. From 2.24 g (0.01 mol) of triethylphosphono-acetate, 0.24 g (0.01 mol) sodium hydride and 1.44 g (0.01 mol) of ketone, after a reflux time of 4h, 3.05 g of crude product was isolated. NMR spectrum of the crude product indicated that the normal Wittig reaction had taken place producing the two geometrical isomers of the product in a 50:50 ratio. Chromatography of the crude product over alumina using hexane and chloroform (2:1 v/v) as eluent, gave 0.906 g of starting ketone and 1.01 g (50 %) of a mixture of the olefinic products bp 120^{0}C (0.36 mm); IR (CCl_4, cm^{-1}) 3060, 2200, 1720, 1600; NMR (CCl_4) δ 1.16-1.42 (3H,t), δ 2.15 and δ 2.46 (3H,d), 4.08-4.53 (2H, q), δ 6.18 and δ 6.37 (1H, m), δ 7.42-8.02 (5H, m). Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found C, 77.84 ; H, 6.60. All attempts to separate the two isomers of the product were unsuccessful.

**Reaction of 3-pentyn-2-one with diethylphosphonoaceto-
nitrile.** In this reaction 3.54 g (0.02 mol) of diethyl-
phosphonoacetonitrile, 0.48 g (0.02 mol) sodium hydride
and 1.64 g (0.02 mol) of the ketone were used and the
reaction mixture was refluxed for 16h. NMR spectrum of
the crude product indicated that the normal Wittig react-
ion had taken place producing a single geometrical isomer.
Chromatography of the crude product over alumina using
ether as an eluent gave 1.10 g of starting phosphonate
ester and 1.02 g (44 %) of the olefinic compound, bp 78-
80^0C (15 mm); IR (CCl_4, cm^{-1}) 3060, 2300, 2240, 2220, 1600;
NMR (CCl_4) δ 2.03 (3H, d), δ 2.16 (3H, d), δ 5.58 (1H, m).

Reaction of 3-pentyn-2-one with triethylphosphonoacetate.
From 4.48 g (0.02 mol) of phosphonate ester 0.48 g of
sodium hydride (0.02 mol) and 1.64 (0.02 mol) ketone,
after a reflux period of 16h, 3.85 g of crude product was
isolated. Chromatography of this product over alumina
using hexane and chloroform (1:1 v/v) gave 2.03 g of tri-
ethylphosphonoacetate and 0.43 g of the olefinic compound
in single isomeric form identical to that obtained in the
reaction of 3-pentyn-2-one with triphenylphosphoranyl-
ethylethanoate. IR (CCl_4, cm^{-1}) 2280, 2220, 1710, 1610;
NMR (CCl_4) δ 1.16-1.42 (3H, t), δ 2.04 (3H, d), δ 2.13
(3H, s), δ 2.42-2.78 (2H, q), δ 6.10 (1H, m).

Reaction of 4,4-dimethyl-1-phenyl-1-pentyn-3-one with di-
ethyl phosphonoacetonitrile. In this reaction 1.77 g
(0.01 mol) of diethyl phosphonoacetonitrile, 0.24 g (0.01
mol) of sodium hydride and 1.86 g (0.01 mol) of the
ketone was used and the reaction mixture was refluxed for
4h. NMR spectrum of the crude product indicated that the
normal Wittig reaction had taken place producing a single
geometrical isomer (vinylic H signal at δ 5.62) in ca 41 %
yield. Chromatography of the crude product over alumina
using hexane and chloroform (5:1 v/v) as eluent, yielded
0.924 g of starting ketone and 0.50 g of the olefinic
product, bp 125^0C (0.35 mm); IR (CCl_4, cm^{-1}) 3040, 2960,
2220, 2195, 1590; NMR (CCl_4) δ 1.3 (9H, s), δ 5.62 (1H,
s), δ 7.42-7.92 (5H, m); MS m/e 209, 194, 153, 91, 57;
Anal. calcd for $C_{15}H_{15}N$: C, 86.05; H, 7.22; N, 6.69.
Found : C, 85.40; H, 7.04; N, 6.54.

Reaction of 4,4-dimethyl-1-phenyl-1-pentyn-3-one with
triethyl phosphonoacetate. From 4.48 g (0.02 mol) of
triethyl phosphonoacetate, 0.48 g (0.02 mol) of sodium
hydride and 3.72 g (0.02 mol) of the ketone, after a
reflux period of 4h, 4.8 g of the crude product was
isolated. NMR spectrum of the crude product indicated
that the Wittig reaction had taken place producing the
two geometrical isomers (vinylic H signals at δ 6.28 and
δ 6.22 in the ratio 75: 25). Chromatography of the crude

product over alumina using carbon tetrachloride and $CHCl_3$ (1:2 v/v) yielded 2.10 g of the phosphonate ester and 1.13 g (44 %) of the olefinic product in single isomeric form. IR (CCl_4, cm^{-1}) 3050, 2960, 2200, 1720, 1600; NMR (CCl_4, cm^{-1}) δ 1.05-1.42 (3H, m), δ 1.28 (9H, s), δ 4.12-4.50 (2H, q); δ 6.22 (1H, s), δ 7.43-7.93 (5H, m).

Reaction of 4,4-dimethyl-1-phenyl-2-pentyn-1-one with diethyl phosphonoacetonitrile.   In this reaction 1.77 g (0.01 mol) of diethyl phosphonoacetonitrile, 0.24 g (0.01 mol) of sodium hydride and 1.86 g (0.01 mol) of the ketone were used and the reaction mixture was refluxed for 20h. NMR spectrum of the crude product indicated that the normal Wittig reaction had taken place producing the two geometrical isomers (vinylic H signals at δ 6.26 and δ 5.83 in the ratio 67:33) in ca 36 % yield. The crude product was a mixture of the starting ketone and the product. All attempts at separation of the ketone from the product was unsuccessful.

Reaction of 4,4-dimethyl-1-phenyl-2-pentyn-1-one with triethyl phosphonoacetate.   In this experiment 2.24 g (0.01 mol) of triethyl phosphonoacetate, 0.24 g (0.01 mol) NaH and 1.86 g (0.01 mol) of the ketone were used and the reaction mixture was refluxed for 20h. NMR spectrum of the crude product indicated that the normal Wittig reaction

had taken place producing the two geometrical isomers (vinylic H signals at δ 6.72 and δ 6.65 in the ratio 58:42) in ca 6 % yield. All attempts at separation of the olefinic product by column chromatography were unsuccessful.

Reaction of 1-phenyl-3-pentyn-2-one with diethyl phosphonoacetonitrile. From 1.77 g (0.01 mol) of diethyl phosphonoacetonitrile, 0.24 g (0.01 mol) of sodium hydride and 1.58 g (0.01 mol) of the ketone , after a reflux period of 20h, 2.02 g of a tarry product was obtained, the NMR spectrum of which did not indicate the presence of any olefinic product or of the starting materials.

Reaction of 1-phenyl-3-pentyn-2-one with triethyl phosphonoacetate. In this experiment 4.48 g (0.02 mol) of triethyl phosphonoacetate, 0.48 g (0.02 mol) of sodium hydride and 3.16 g (0.01 mol) of the ketone were used and the reaction mixture was refluxed for 20h. Fractional distillation of the crude product yielded 0.23 g (10 %) of an olefinic product (vinylic H signals at δ 6.75 and δ 6.47 in the ratio 56:44) and 1.82 g of a thick brown liquid which turned into a hard mass at room temperature. The NMR spectrum of the olefinic product revealed the presence of some unreacted ketone and all attempts at separation of this ketone from the product were unsuccessful.

Reaction of 1-phenyl-2-pentyn-1-one with diethyl phos-
phonoacetonitrile. From 5.31 g (0.03 mol) of diethyl
phosphonoacetonitrile, 0.72 g (0.03 mol) of sodium
hydride and 4.73 g (0.03 mol) of the ketone, after a ref-
lux period of 20h, 6.40 g of crude product was isolated.
NMR spectrum of the crude product indicated that the
normal Wittig reaction had taken place producing the two
geometrical isomers (vinylic H signals at δ 6.08 and
δ 5.77 in a ratio 83:17). Chromatography of the crude
product over alumina using carbon tetrachloride and $CHCl_3$
(1:3 v/v) as eluent, yielded 3.70 g of a light yellow oil.
Fractional distillation of this oil gave 0.98 g of the
ketone and 2.12 g (39 %) of the olefinic products, bp 122-
125^{0}C (0.75 mm). IR (CCl_4, cm^{-1}) 3050, 2200, 2220, 1710;
NMR (CCl_4) δ 1.08- 1.53 (3H, m), δ 2.28-2.83 (2H, m),
δ 5.77 and 6.08 (1H, s), δ 7.47-8.27 (5H, m); MS m/e 181,
166, 153, 141, 115, 91, 78; Anal. calcd for $C_{13}H_{11}N$:
C, 86.16; H, 6.12; N, 7.73. Found C, 86.02; H, 5.98; N,
7.65.

Reaction of 1-phenyl-2-pentyn-1-one with triethyl phos-
phonoacetate . In this reaction 6.726 g (0.03 mol)
of triethyl phosphonoacetate, 0.72 g (0.03 mol) of NaH
and 4.74 g (0.03 mol) of the ketone were used. Chromato-
graphy of the crude product over alumina using carbon
tetrachloride and chloroform (3:1 v/v) as eluent yielded

2.23 g of the starting phosphonate ester and 1.80 g of a
yellow oil which solidified on cooling. Recrystallization
of the solid yielded 1.28 g of yellow crystals. This
product was identified as 8-ethyl-5-methyl-3,6-diphenyl-
isocoumarin 53 (page 60), mp 136^0C. IR (CCl_4, cm^{-1}) 3050,
1730, 1625; UV λ_{max}(95 % Ethanol) 237 nm (ϵ= 1.5 X 10^5),
254 (ϵ= 1.8 X 10^5), 304 (ϵ= 1.4 X 10^5), 319 (ϵ= 1.3 X 10^5),
353 (ϵ= 0.93 X 10^5); NMR (CCl_4) δ 1.26 (3H,t), δ 2.55
(3H,s), δ 2.85 (2H,q), δ 7.38-8.28 (12H,m). MS m/e 340,
312, 297, 105; Anal. calcd for $C_{24}H_{20}O_2$: C, 84.67; H,
5.92. Found C, 84.41; H, 6.07.

Reaction of 4-methyl-1-phenyl-1-pentyn-3-one with diethyl-
phosphonoacetonitrile.   In this reaction 3.54 g (0.02 mol)
of diethylphosphonoacetonitrile, 0.48 g (0.02 mol) of
sodium hydride and 3.44 g (0.02 mol) of the ketone were
used and the reaction mixture was refluxed for 18h.
Chromatography of the crude product over alumina using
carbon tetrachloride and chloroform (1:3 v/v) as eluent,
yielded 1.62 g of starting ketone and 2.5 g of a tarry
liquid which solidified to a brittle, insoluble mass upon
keeping at room temperature. No other product was isolat-
ed.

Reaction of 4-methyl-1-phenyl-1-pentyn-3 one with tri-
ethyl phosphonoacetate.   In this reaction 4.483 g

(0.02 mol) of sodium hydride and 3.44 g (0.02 mol) of the ketone were used. The reaction mixture was refluxed for 4h. The crude product obtained was a thick dark brown unidentified liquid which slowly solidified on standing at room temperature to an amorphous insoluble mass.

Reaction of 2-hepten-5-yn-4-one with diethyl phosphono-acetonitrile. From 1.77 g (0.01 mol) of diethyl phos-phonoacetonitrile, 0.24 g (0.01 mol) of sodium hydride and 1.08 g (0.01 mol) of ketone, after a reflux period of 8h and workup only a dark polymeric semisolid material was obtained which was not identified.

Reaction of 2-hepten-5-yn-4-one with triethyl phosphono-acetate. From 2.24 g (0.01 mol) of triethyl phosphono-acetonitrile, 0.24 g (0.01 mol) of sodium hydride and 1.08 g (0.01 mol) of the ketone, after a reflux time of 4h, followed by workup, only a dark polymeric semisolid material was isolated which was not identified.

SUMMARY AND CONCLUSIONS

The present study clearly demonstrates that, under the conditions used, the two stabilized phosphonium ylids $Ph_3P=CHCN$ and $Ph_3P=CHCOOEt$ are considerably less effective in olefin-forming reactions with α,β-acetylenic ketones than the corresponding phosphonate carbanions $(EtO)_2P(O)CH$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CN$

and $(EtO)_2P(O)CHCOOEt$. Even in the case of the phosphonate carbanions the yields of products are only moderate at best. The ylids reacted with fewer acetylenic ketones and gave poor yields of the olefinic products than did the phosphonate carbanions (cf. Tables V and VI).

Comparison of the two ylids indicates that the carbethoxy-stabilized ylid is somewhat more reactive than the nitrile-stabilized ylid. The former reacted with two other ketones in addition to the three that the latter did. One of the factors responsible for the reduced reactivity of the nitrile-stabilized ylid must be the reduced carbanionic character of the ylid carbon on account of the better electron-withdrawing character of the cyano group compared to that of the carbethoxy group. In their reaction with the acetylenic ketones both the ylids took the normal Wittig type olefin-forming pathway. There was no evidence of any abnormal product formation with the

ketones such as those resulting from the initial Michael addition of the ylid to the ketone, which was observed in some rare cases with special α,β-unsaturated ketones with unstabilized ylids.[97,98]

Of the acetylenic ketones used in the present study only Ph-C≡C-CO-i-Pr(18i) and Me-C≡C-CO-CH=CH-Me(18j) failed to yield any identifiable products, the latter yielding much tarry material which probably result from polymerization of the starting ketone or of initially formed Michael adducts. Considering the fact that 18i reacted with both the ylids it is not clear why it was unreactive towards the phosphonate carbanions which are generally known to be more reactive especially when it is observed that both the phosphonate carbanions reacted with the more sterically encumbered ketone Ph-C≡C-CO-t-Bu (18e). The ylids were totally unreactive towards 18e as well as with all those acetylenic ketones having a phenyl group directly attached to the carbonyl group, except Et-C≡C-CO-Ph

(18h) which did react with the ylid stabilized by the COOEt group. Ketone 18g (Me-C≡C-CO-CH$_2$-Ph) did react with both ylids in less than 30 % yields while it reacted only with (EtO)$_2$P(O)CHCOOEt in 10 % yield.

Both phosphonate carbanions yielded 'abnormal'

products with Me-C≡C-CO-Ph (18b), a ketone which was un-
reactive towards both the ylids. With $(EtO)_2P(O)CHCN$ 18b
gave a 4-benzoylphenyl derivative 45 (page 58), with
the complete exclusion of the expected olefinic products.
This product is believed to arise from the initial Michael
type addition of the carbanion to the ketone followed by
the 'normal' reaction at the carbonyl with another mole-
cule of the ketone and subsequent cyclization (cf Scheme 6,
page 58). With $(EtO)_2P(O)CHCOOEt$ also the ketone gave only
'the 'abnormal' product which was identified as an iso-
coumarin derivative 47 (page 59). The product formation
here can be rationalized by the initial conjugate addition
of the carbanion to the ketone followed by another conju-
gate addition of the resulting intermediate to a second
molecule of the ketone and subsequent cyclization and
elimination reactions (cf Scheme 7, page 63). An analog-
ous isocoumarin derivative 53 (page 60) also was isolated
from the reaction of Et-C≡C-CO-Ph (18h) as the sole react-
ion product. This ketone reacted only in the 'normal'
olefin-forming pathway with the carbanion $(EtO)_2P(O)CHCN$.
Thus the ethyl ketone (18h) reacts in the 'normal' manner
with $(EtO)_2P(O)CHCN$ and in the 'abnormal' Michael fashion
with $(EtO)_2P(O)CHCOOEt$, whereas the methyl ketone (18b)
takes the 'abnormal' path with both the carbanions produc-
ing entirely different types of derivatives. A simple
rationale which will explain the differences between the

two ketones as well as between the two phosphonate carbanions is not forthcoming at present. Further studies are needed to unravel all the mechanistic implications in these reactions.

The present study shows for the first time that phosphonate carbanions can undergo conjugate additions to certain α,β-acetylenic ketones yielding novel isocoumarin derivatives or acylbiphenyl derivatives. The 'abnormal' products 45 , 47 and 53 have not previously been reported in the literature. It has been reported recently that α,β-acetylenic ketones react with the sulfur-substituted carbanion dimethyloxosulfoniummethylide $(CH_3)_2\overset{+}{S}(O)\overset{-}{C}H_2$ solely in a Michael fashion to yield initially the allylide intermediates 69 (many of which were isolable)

$$R_1-C\equiv C-CO-R_2 + H_2C=\overset{O}{\overset{\uparrow}{S}}\overset{CH_3}{\underset{CH_3}{\diagdown}} \longrightarrow \underset{\underset{CH_3}{\overset{\uparrow}{\underset{|}{S}}}}{\overset{O}{\underset{|}{CH_3-\overset{\uparrow}{S}=CH}}}\overset{R_1}{\underset{}{}}C=C\overset{\overset{O}{\overset{\parallel}{C}}-R_2}{\underset{H}{}}$$
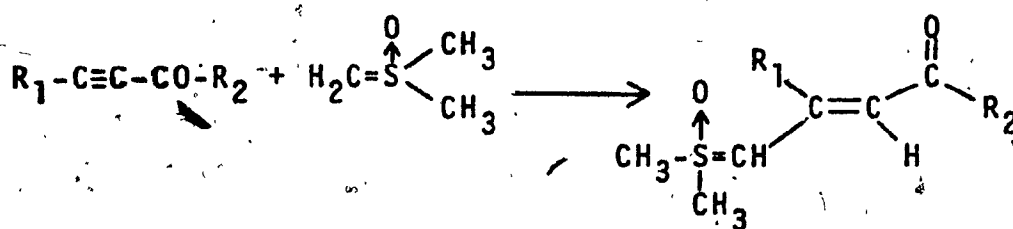
69
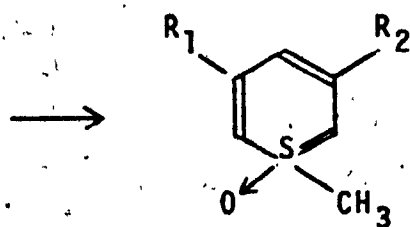
70

which subsequently cyclize to the novel 1,3,5-tri-substituted thiabenzene-1-oxide 70.[103] However, the present study indicates that with phosphonate carbanions Michael additions to acetylenic ketones are exceptions rather than the rule.

SUGGESTIONS FOR FURTHER STUDY

The present study has shown that α,β-acetylenic
ketones are not generally suited for Wittig reactions
with $Ph_3P=CHCN$ and $Ph_3P=CHCOOEt$. However, these ketones
generally give moderate yields of olefinic derivatives
with the phosphonate carbanions $(EtO)_2P(O)\bar{C}HCN$ and
$(EtO)_2P(O)\bar{C}HCOOEt$. To further understand the scope and
limitations of the reaction more acetylenic ketones
with varying substituents both on the carbonyl group
and the acetylenic group (i.e. a greater variety for

$$R-C\equiv C-CO-R' \qquad\qquad (RO)_2P(O)\bar{C}R'R''$$
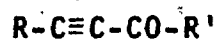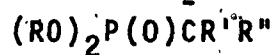
$$\underline{18} \qquad\qquad\qquad \underline{19a}$$

R and R' in 18) as well as a wider variety of phospho-
nate carbanions (e.g. R = Me or Et ; R' = alkyl or
aryl groups ; R" = electron-withdrawing groups such as
CN, NO_2, COOR, COR etc.) need to be examined.

As regards experimental procedure, a reverse
addition technique (i.e. instead of the usual procedure
of adding the ketone to the carbanion solution, slow
addition of the preformed carbanion solution to the
solution of the ketone) merits investigation.

104

This would be particularly interesting in those cases where the 'abnormal' products 45, 47, and 53 were isolated. It would be interesting to see if the yields of these products could be improved.

It is important to synthesize authentic samples of 45, 47 and 53 independently, so that the assignments of structures can be confirmed. The syntheses as well as the study of the chemistry of these compounds will no doubt be interesting projects in themselves,in addition to adding weight to the proposed mechanisms of formation of these products.

Further studies are also indicated in understanding the mechanisms of formation of the abnormal products 45, 47 and 53. In the case of the reaction which produced 45 it would be interesting to use a phosphonate carbanion without an α-H (e.g. $(EtO)_2P(O)\overset{-}{C}CH_3CN$ instead of $(EtO)_2P(O)\overset{-}{C}HCN$. According to the mechanism postulated (cf. Scheme 6, page 58) the α-H is necessary for the conjugate addition of the phosphonate carbanion to the acetylenic ketone. Another interesting experiment would be to use a mixture of two different ketones such as $Me-C\equiv C-CO-Ph$ and $Ph-C\equiv C-CO-Me$ with $(EtO)_2P(O)\overset{-}{C}HCN$ and see if a derivative such as 71 would be among the products (cf. Scheme 8).

$(EtO)_2P(O)\bar{C}HCN + Me-C\equiv C-COPh \longrightarrow$

$$\left[\begin{array}{c} Me \\ | \\ NC-C^- \\ | \\ (EtO)_2P(O) \end{array} C=C=C \begin{array}{c} Ph \\ \\ O-H \end{array}\right]$$

$\xrightarrow{Ph-C\equiv C-CO-Me}$

Me
|
NC—C   C=C=C   Ph
|
C—C≡C—Ph   O—H
|
Me

71
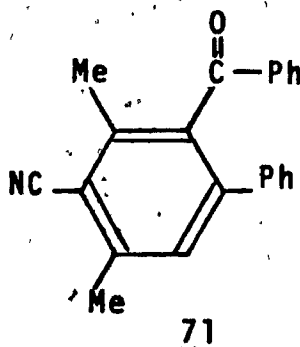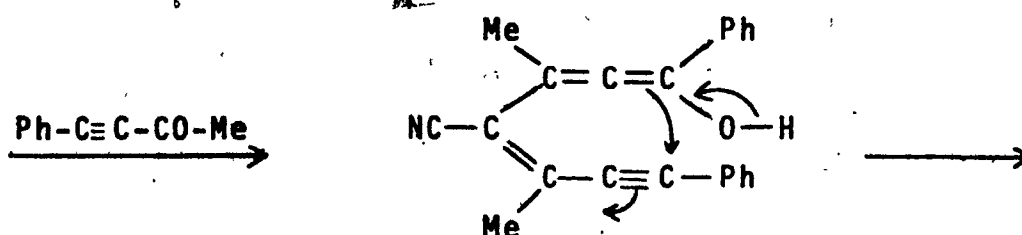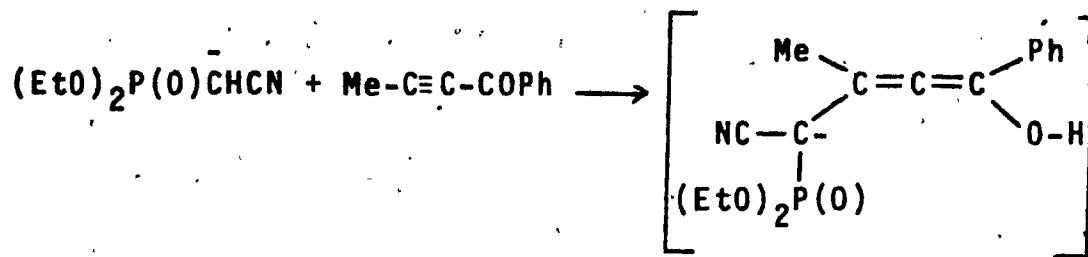
Scheme 8

In those cases where the isocoumarins 47 and 53 were isolated it would also be interesting to use a phosphonate carbanion such as $(EtO)_2P(O)\bar{C}CH_3COOEt$ and to see whether or not a normal reaction pathway is followed. The mechanism postulated for the formation of 47 and 53 (cf. Scheme 7, page 63) also requires the presence of an α-H in the phosphonate carbanion. The mechanism also postulates the formation of $(EtO)_3P=O$ as a product. In this

connection it should be interesting to study the reaction of the carbanion of $(EtO)_2P(O)CH_2COOMe$ and see if the same 47 and 53 are produced with the same ketone. In this case one of the final products would be $(EtO)_2(MeO)P=O$. The mechanism postulated would be on firmer ground if these two phosphates can be identified among the final products. Another test for the mechanism (Scheme 7 , page 62-63) would be using acetylenic ketones having less than two hydrogens in the alkyl group attached to the acetylenic function (e.g. $Me_2CH-C\equiv C-CO-Ph$). Such ketones are not expected to produce the isocoumarin derivative because the final condensation step with the elimination of water is not feasible in these instances.

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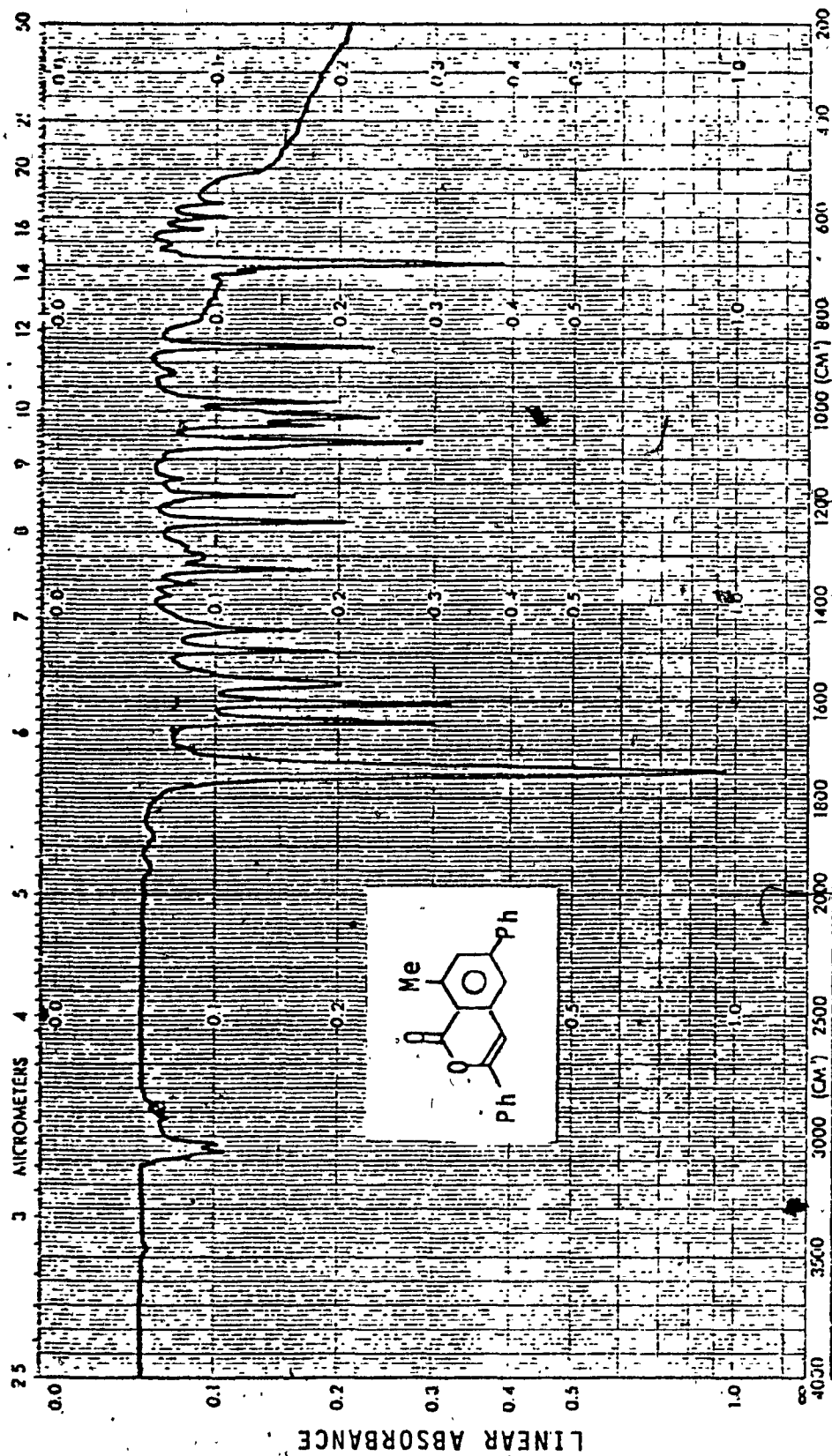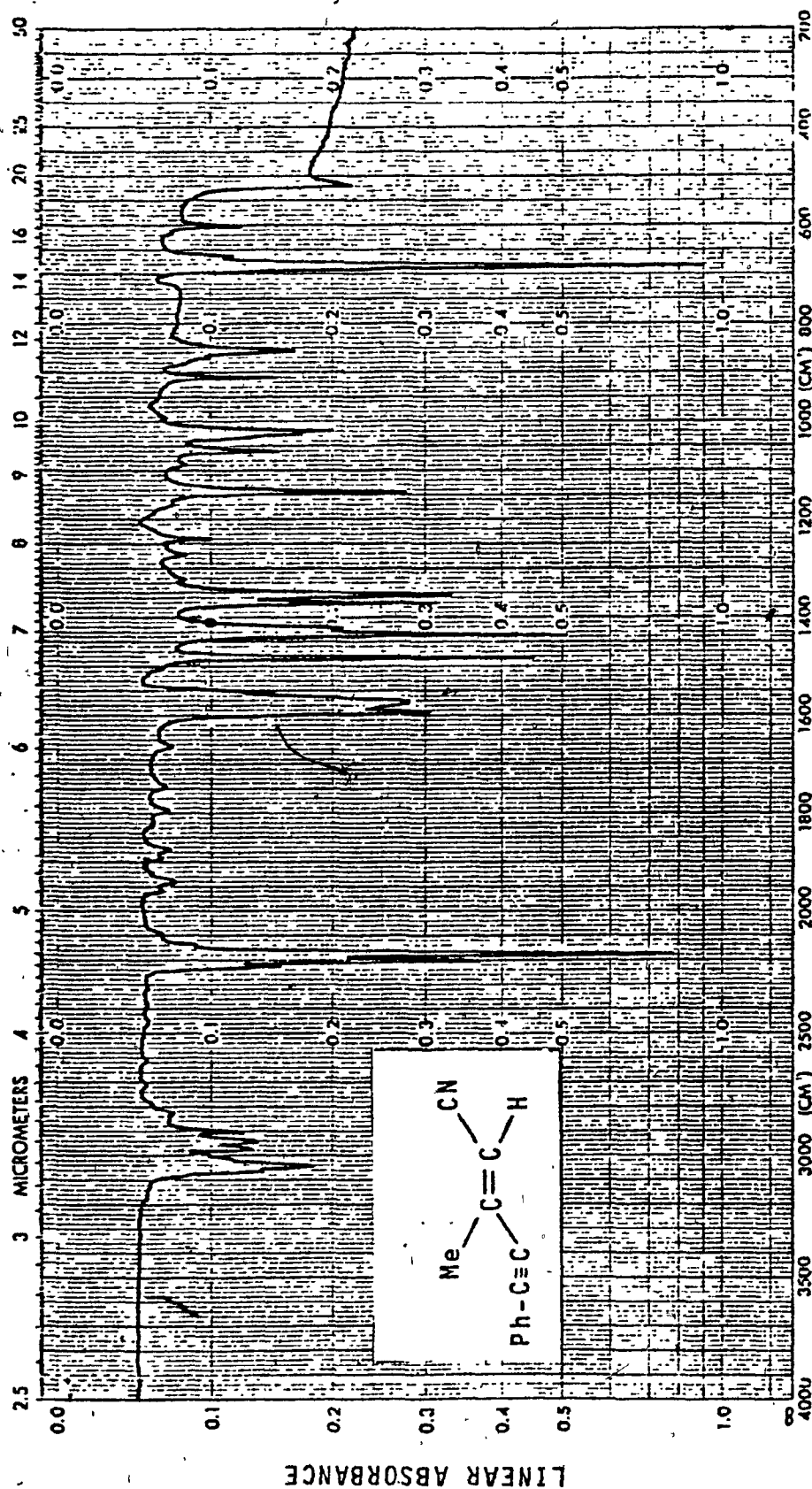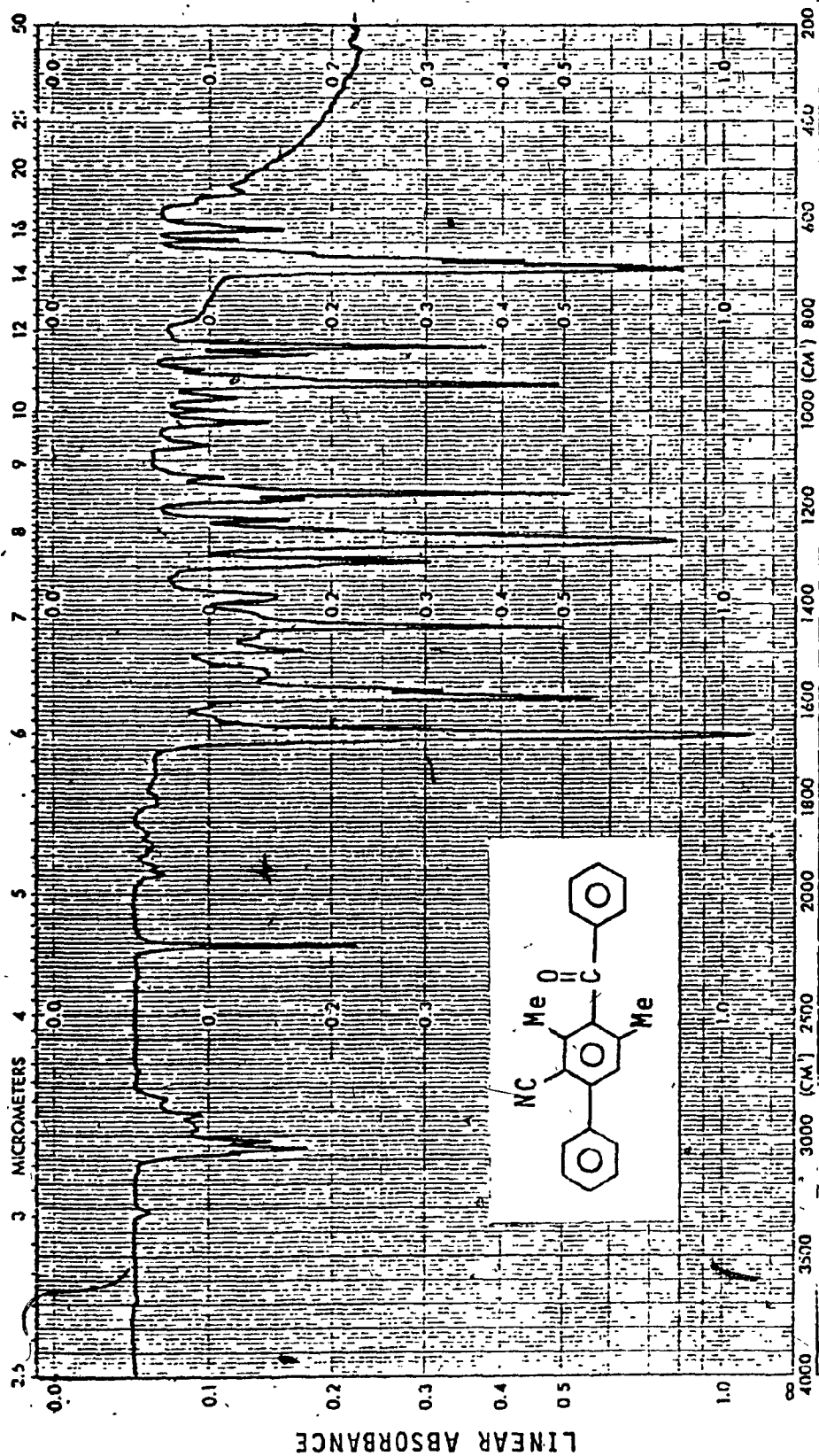
APPENDIX

116
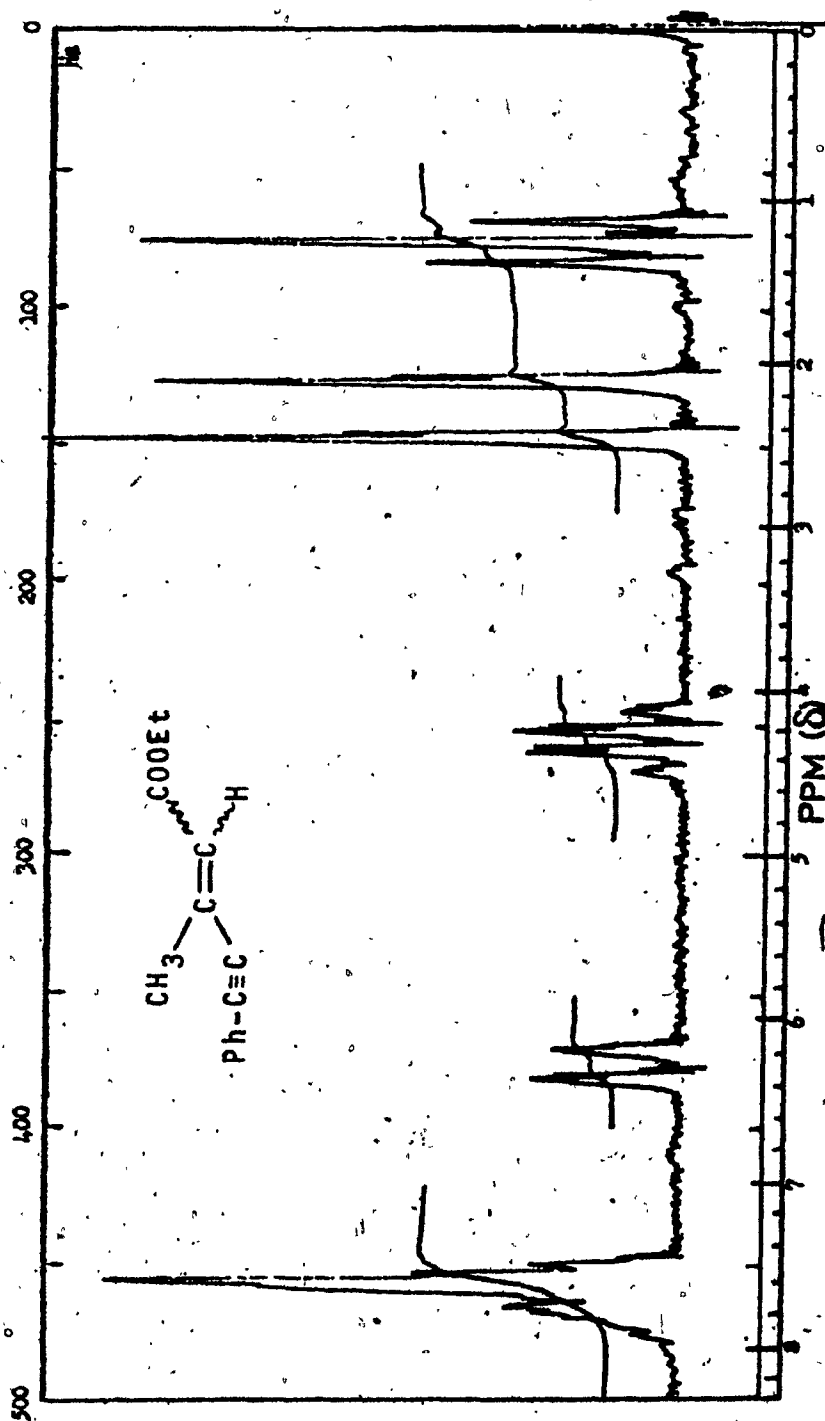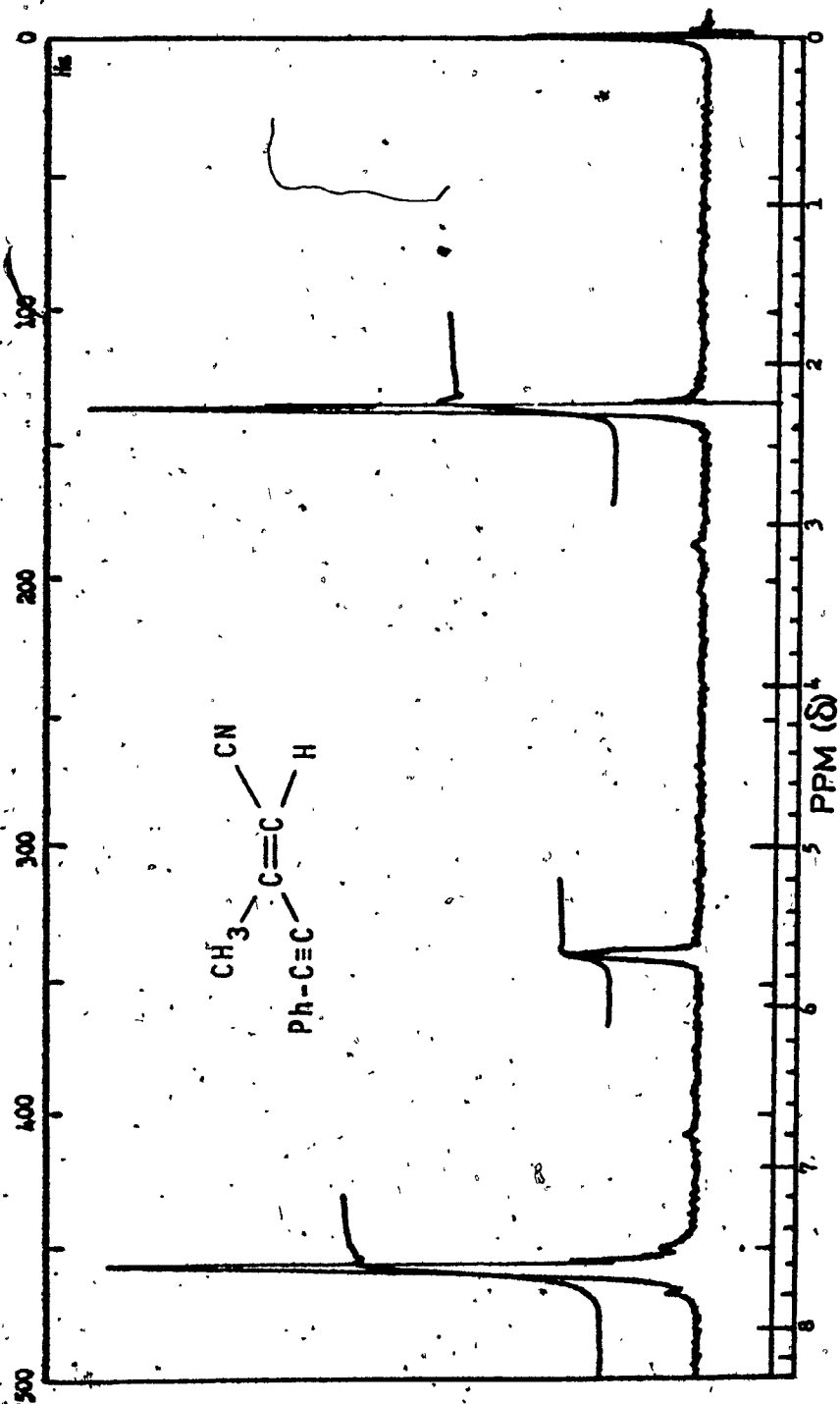
NMR SPECTRUM 1

NMR SPECTRUM 2

NMR SPECTRUM 3

NMR SPECTRUM 4

Structure shown on spectrum:

$$CH_3 \text{ and } Ph-C\equiv C \text{ substituents on } C=C \text{ with } H \text{ and } COOEt$$
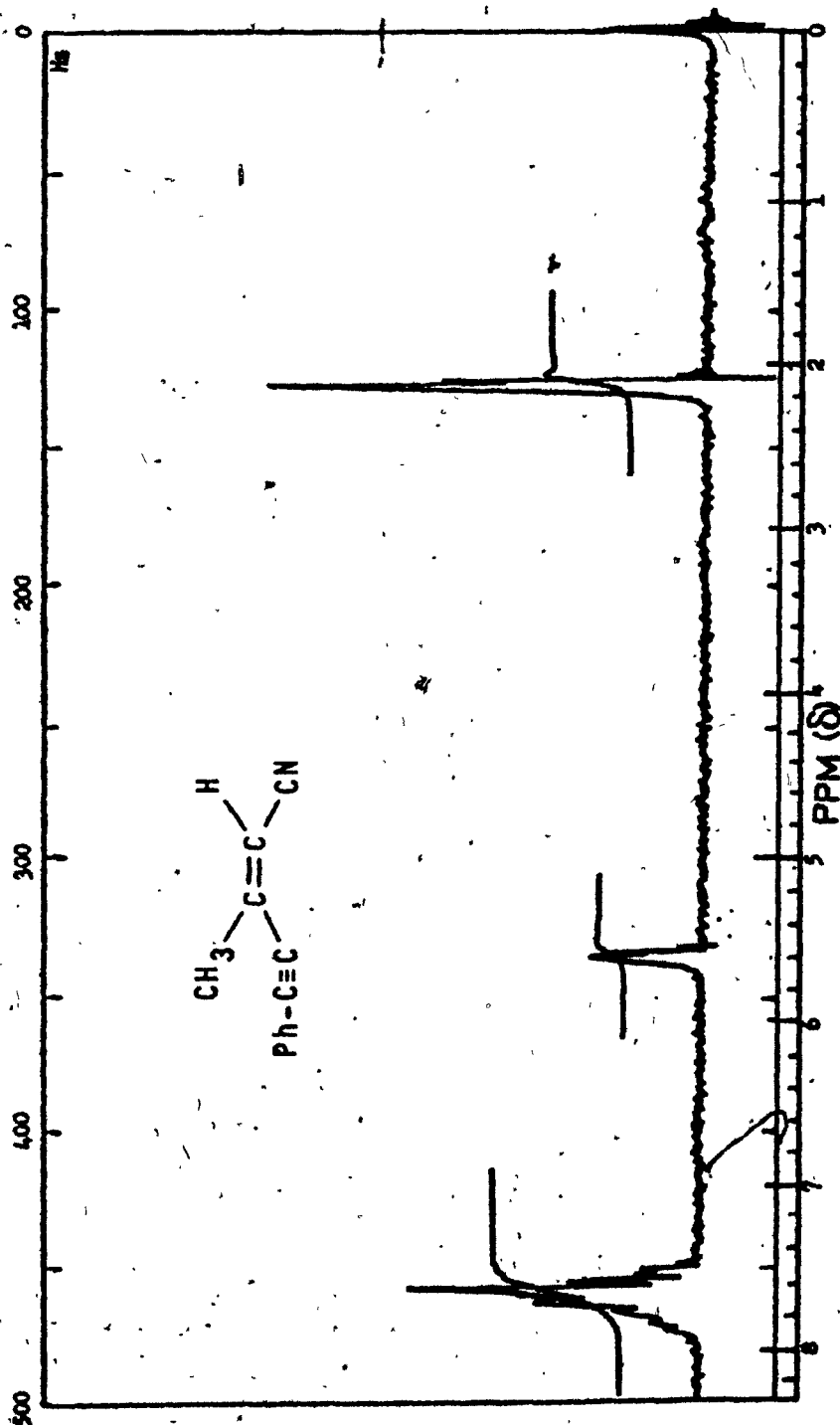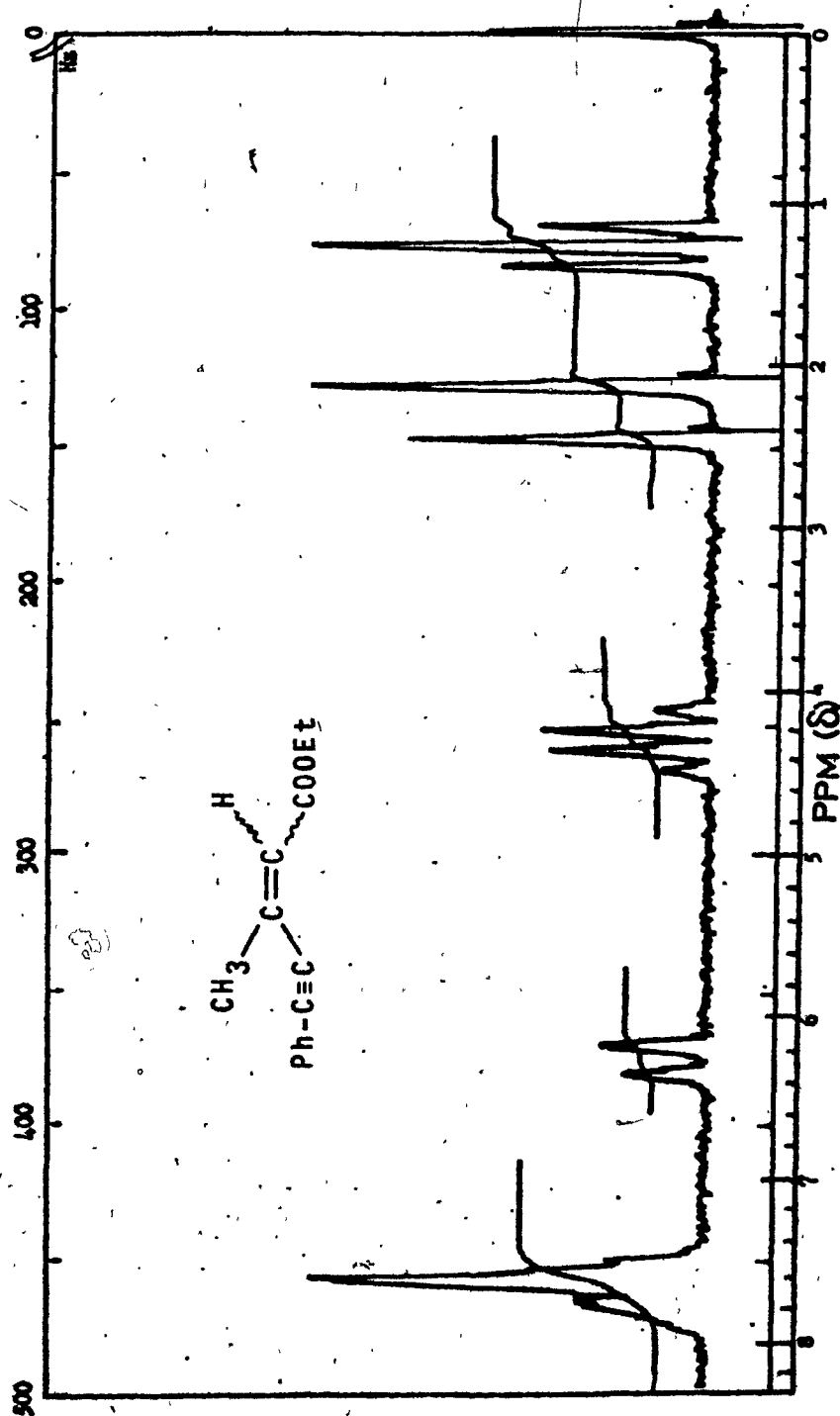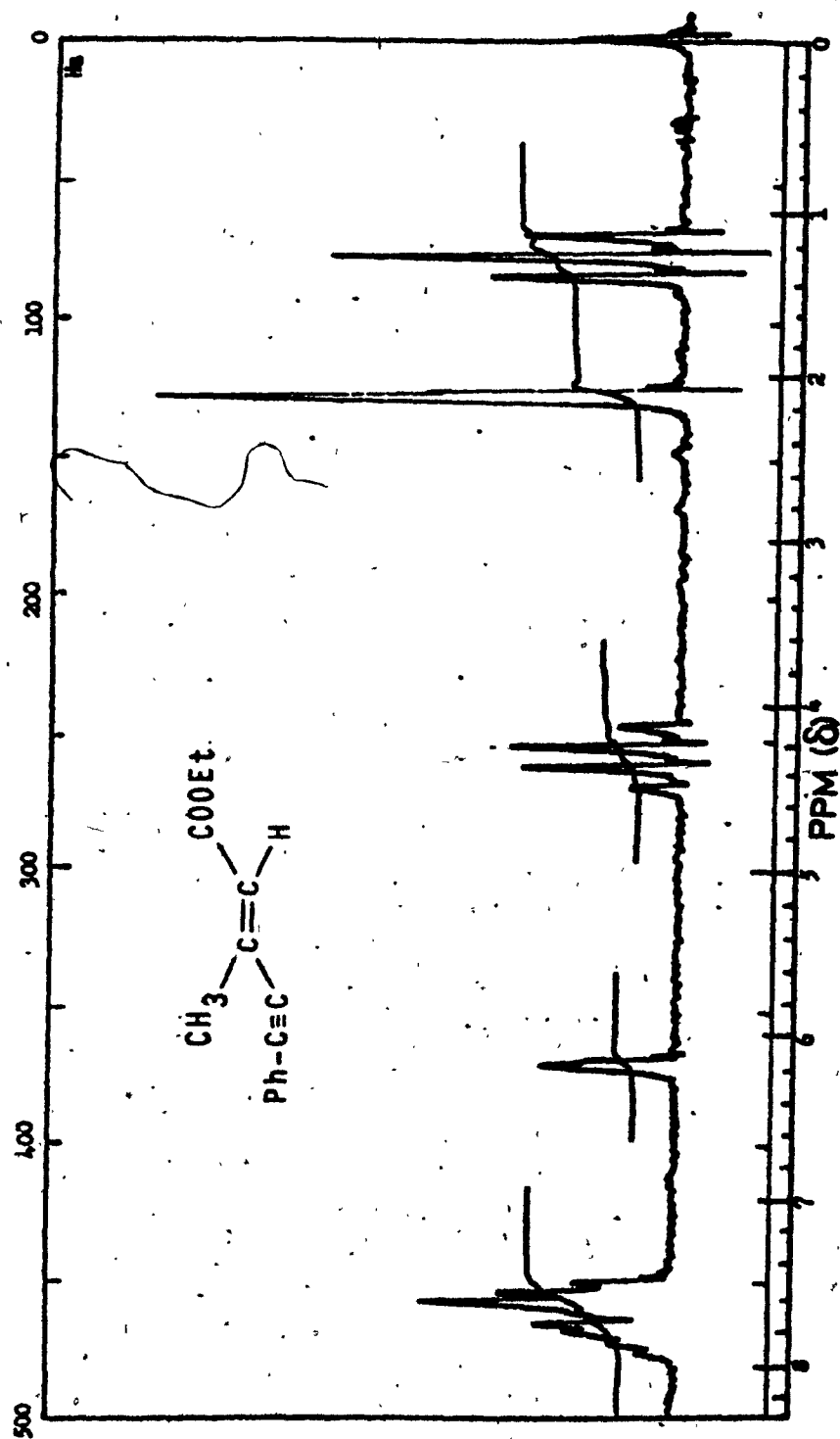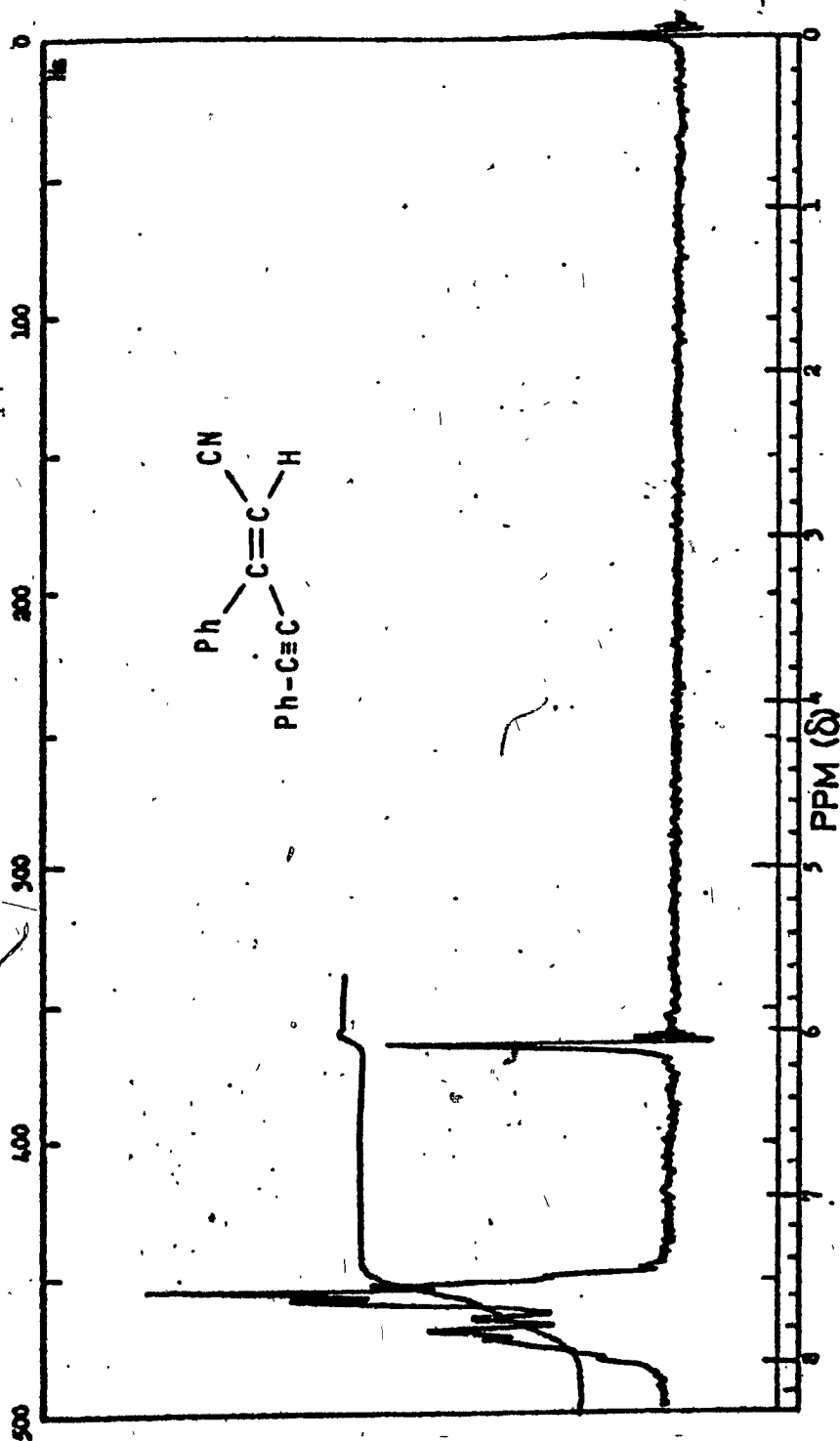
NMR SPECTRUM 5.

NMR SPECTRUM 6
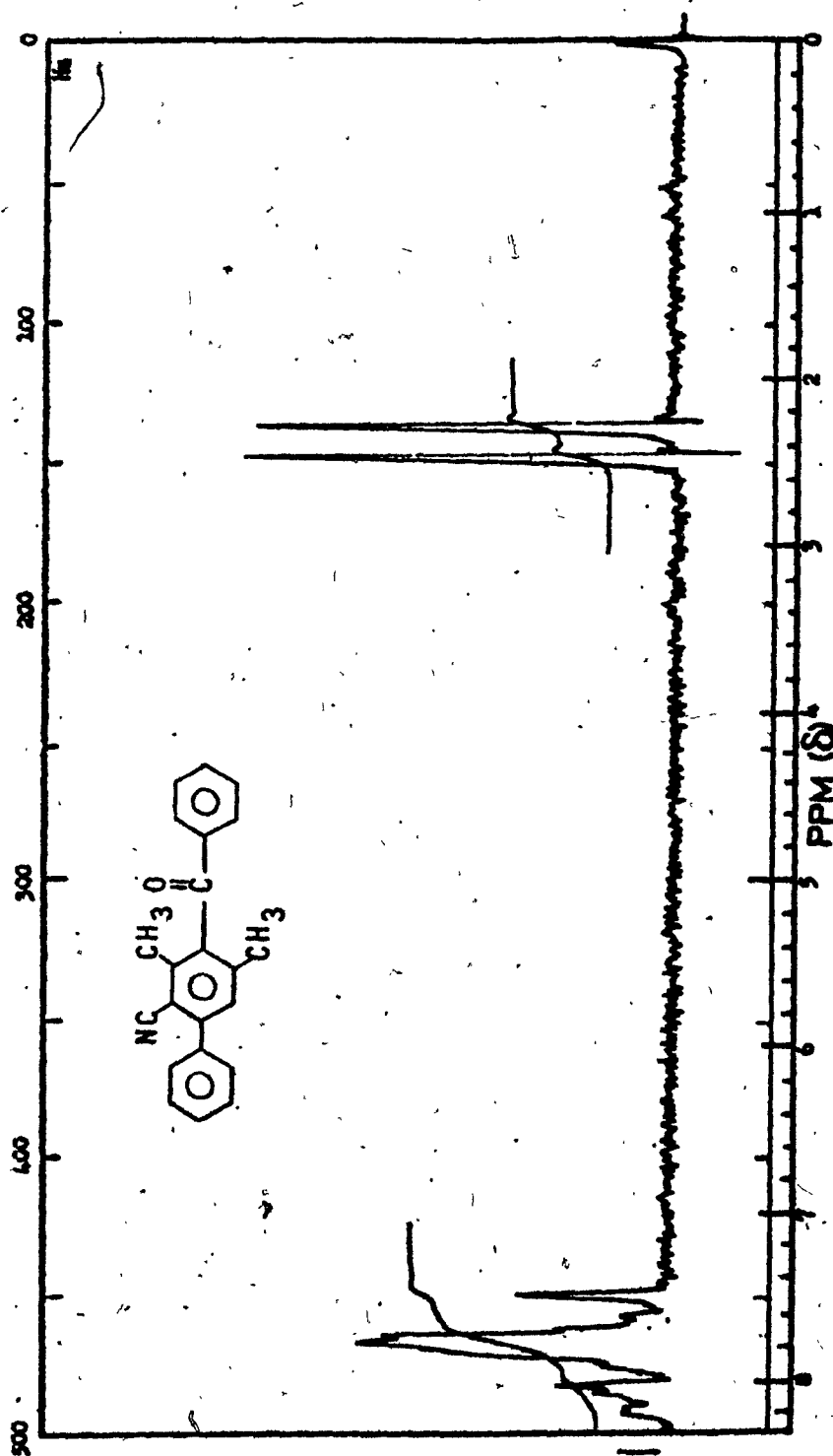
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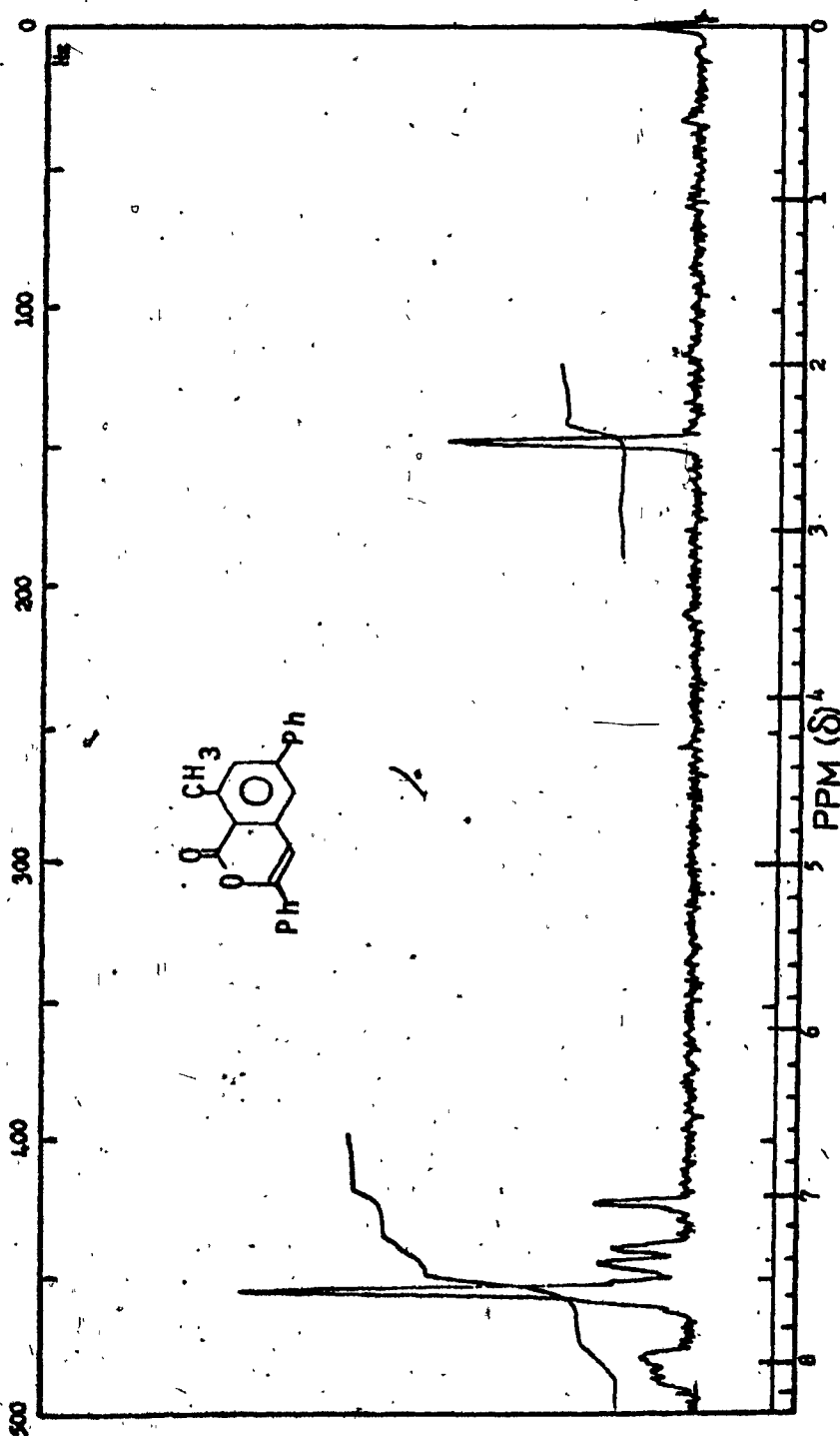
NMR SPECTRUM 8

NMR SPECTRUM 9

Ph⟍   ⟋CN
    C=C
Et-C≡C⟋   ⟍H

NMR SPECTRUM 10

PPM (δ)

$$\text{Ph-C}{\equiv}\text{C} \underset{\text{t-Bu}}{\overset{}{\diagdown}} \text{C}{=}\text{C} \underset{\text{H}}{\overset{\text{CN}}{\diagup}}$$

NMR SPECTRUM 11

$$Ph-C\equiv C-C=C \begin{matrix} COOEt \\ H \end{matrix}$$

with t-Bu on the upper left carbon.
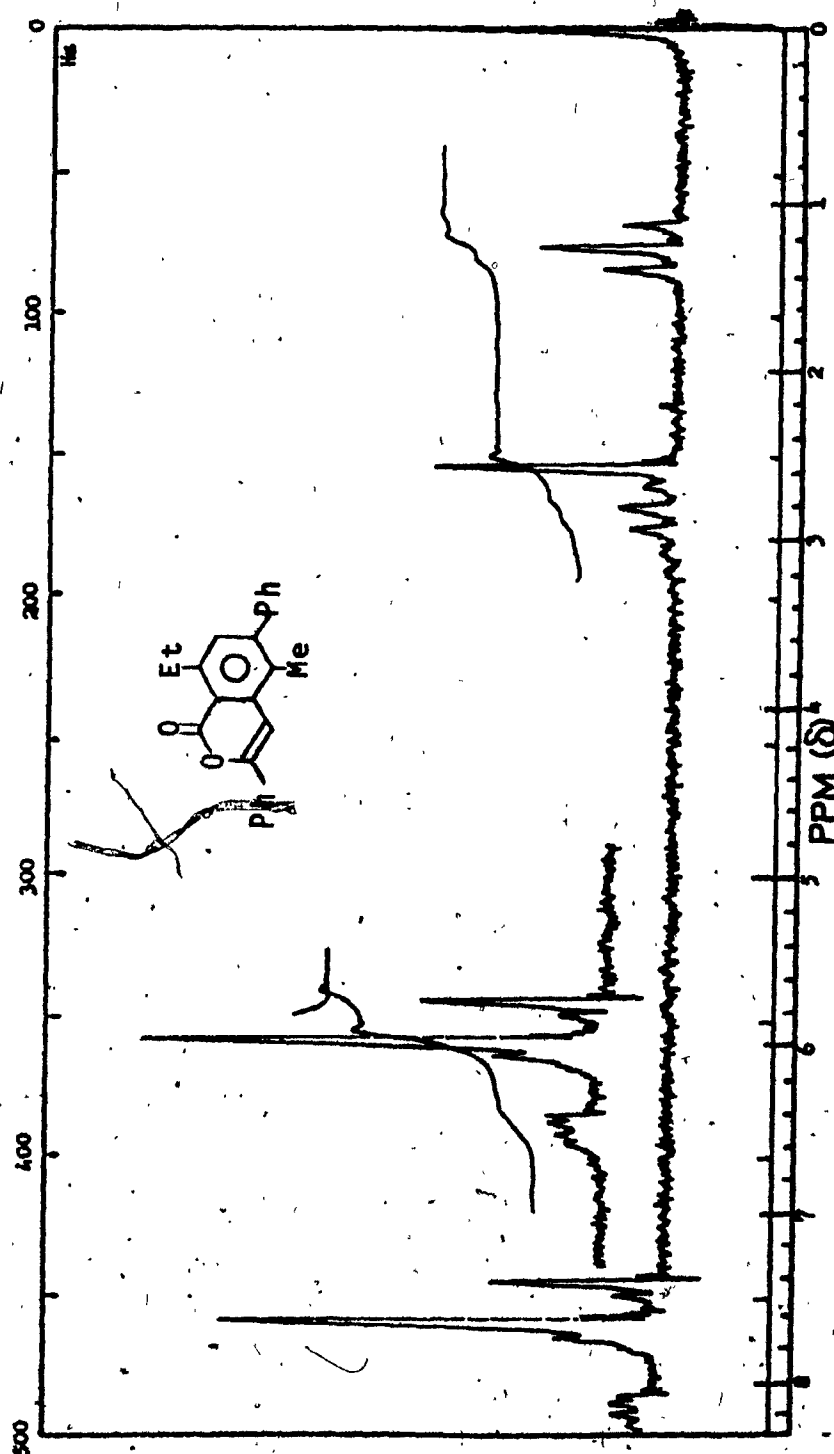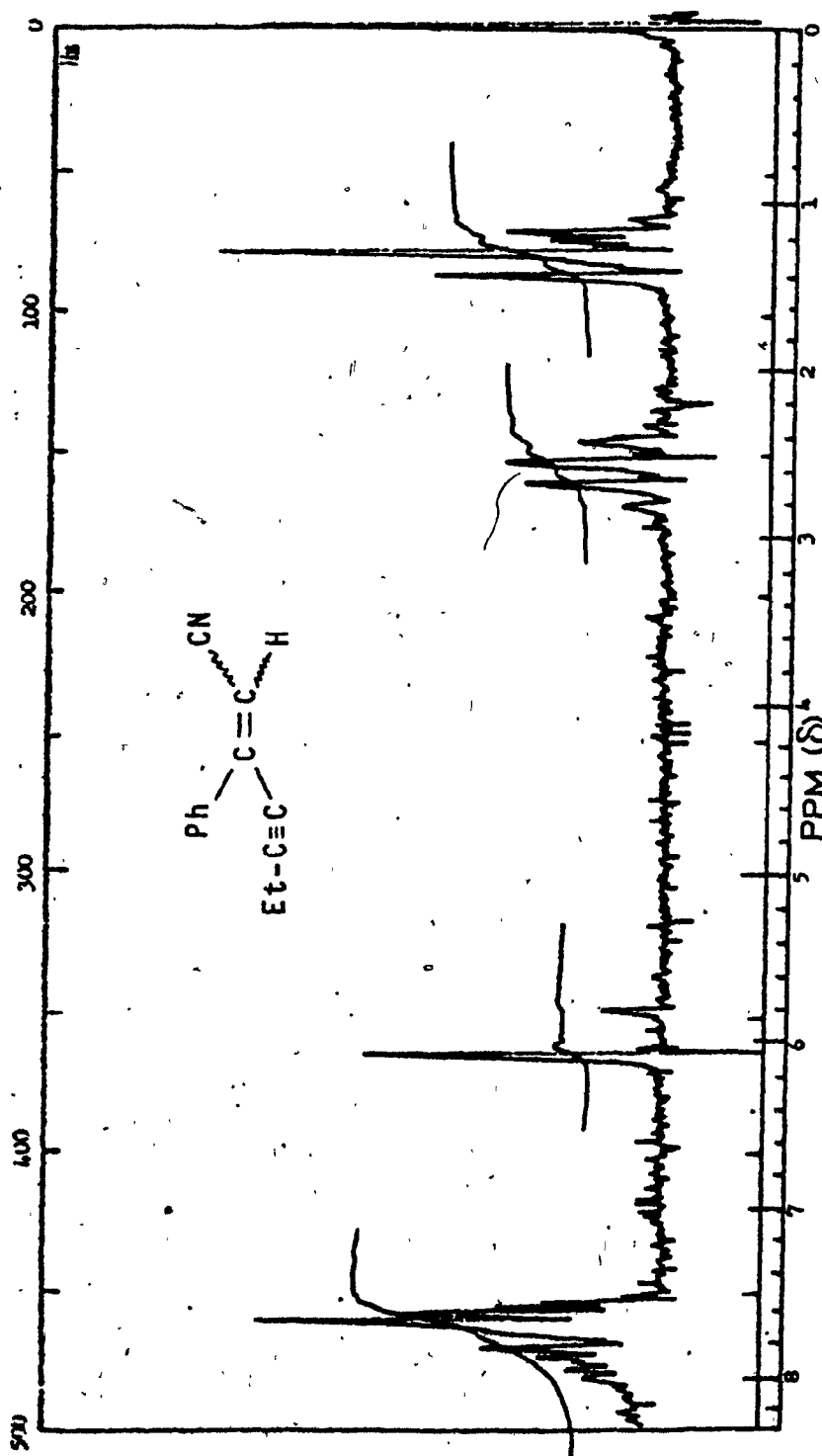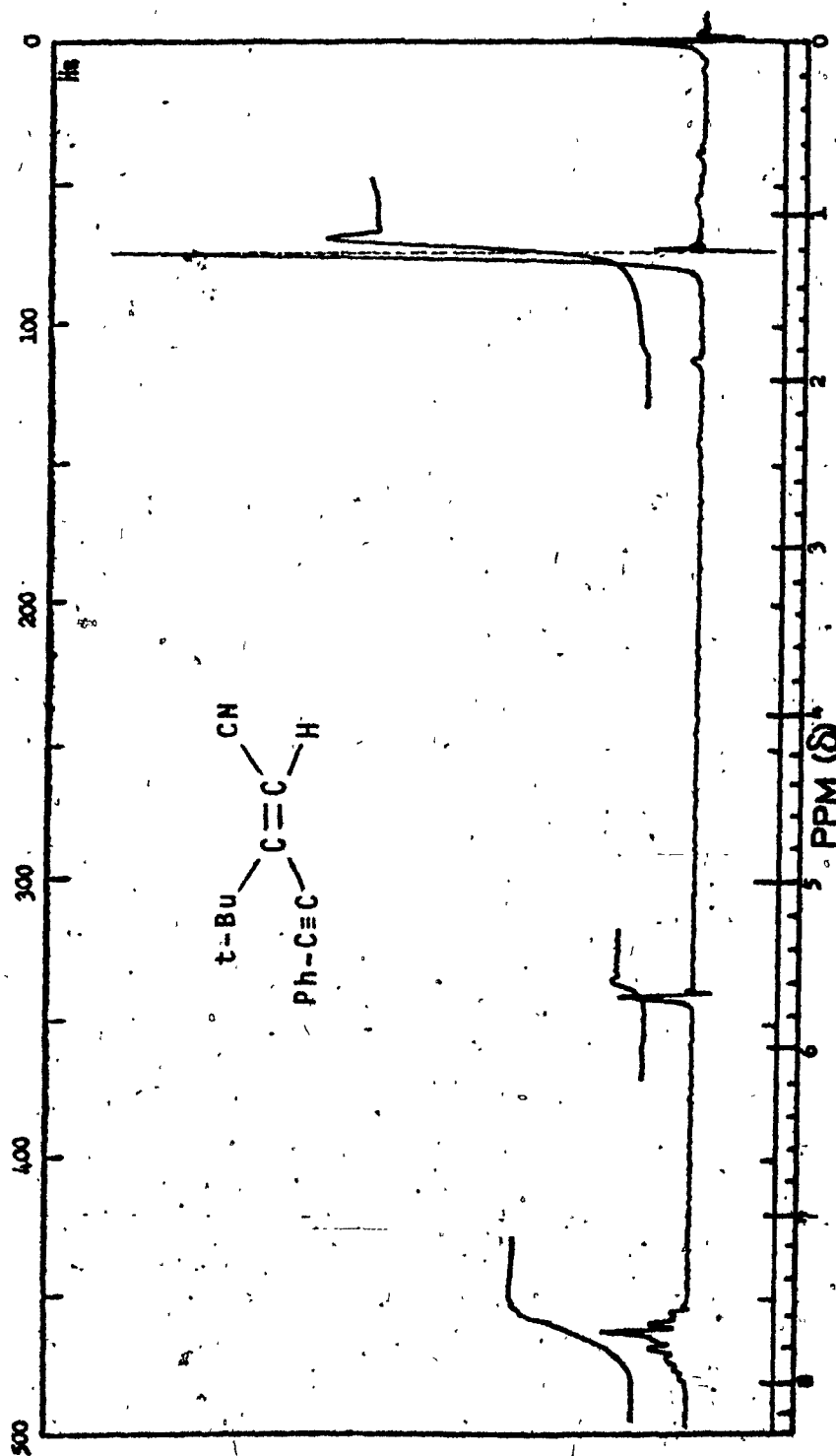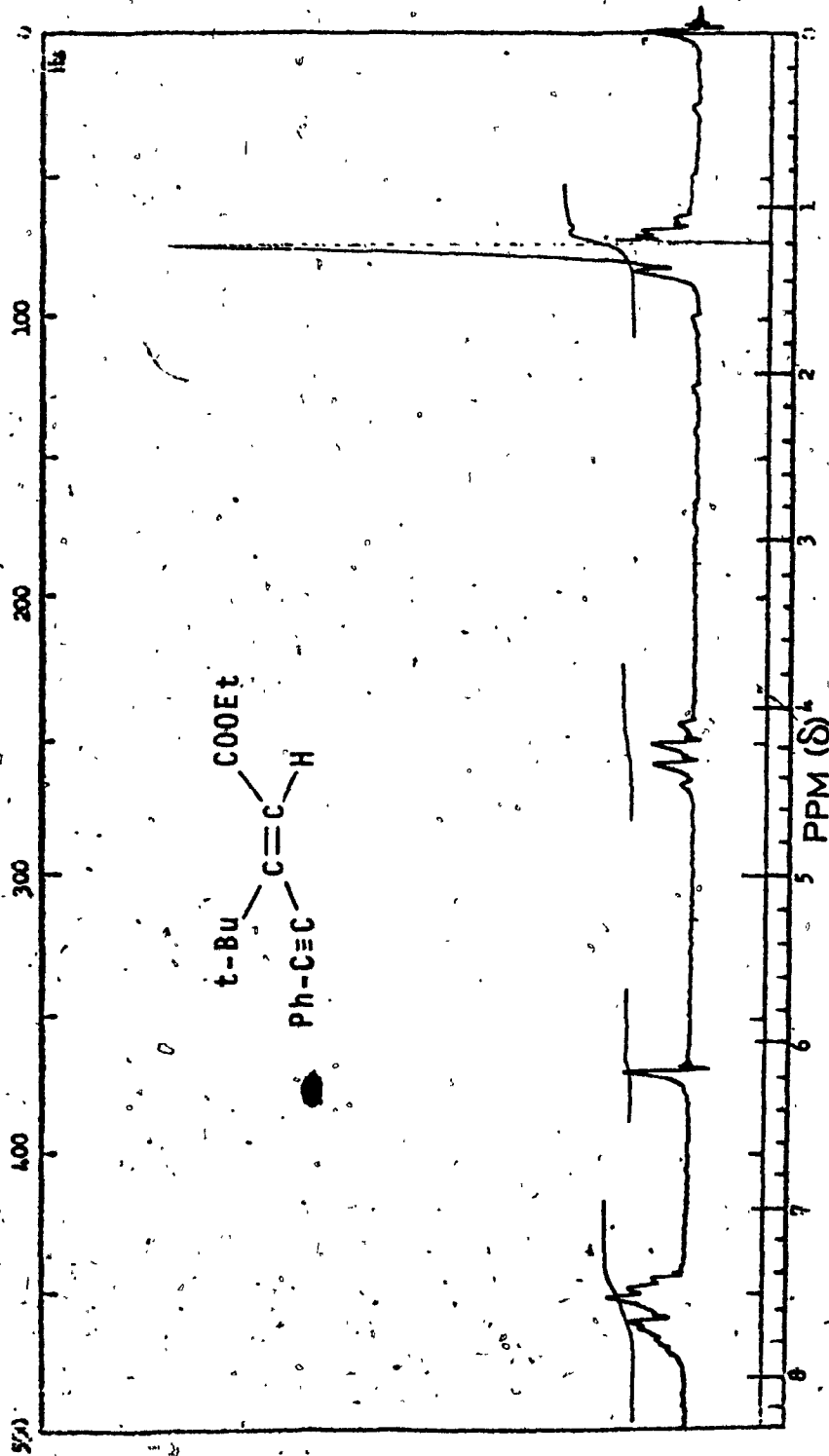
NMR SPECTRUM 12

IR SPECTRUM

129
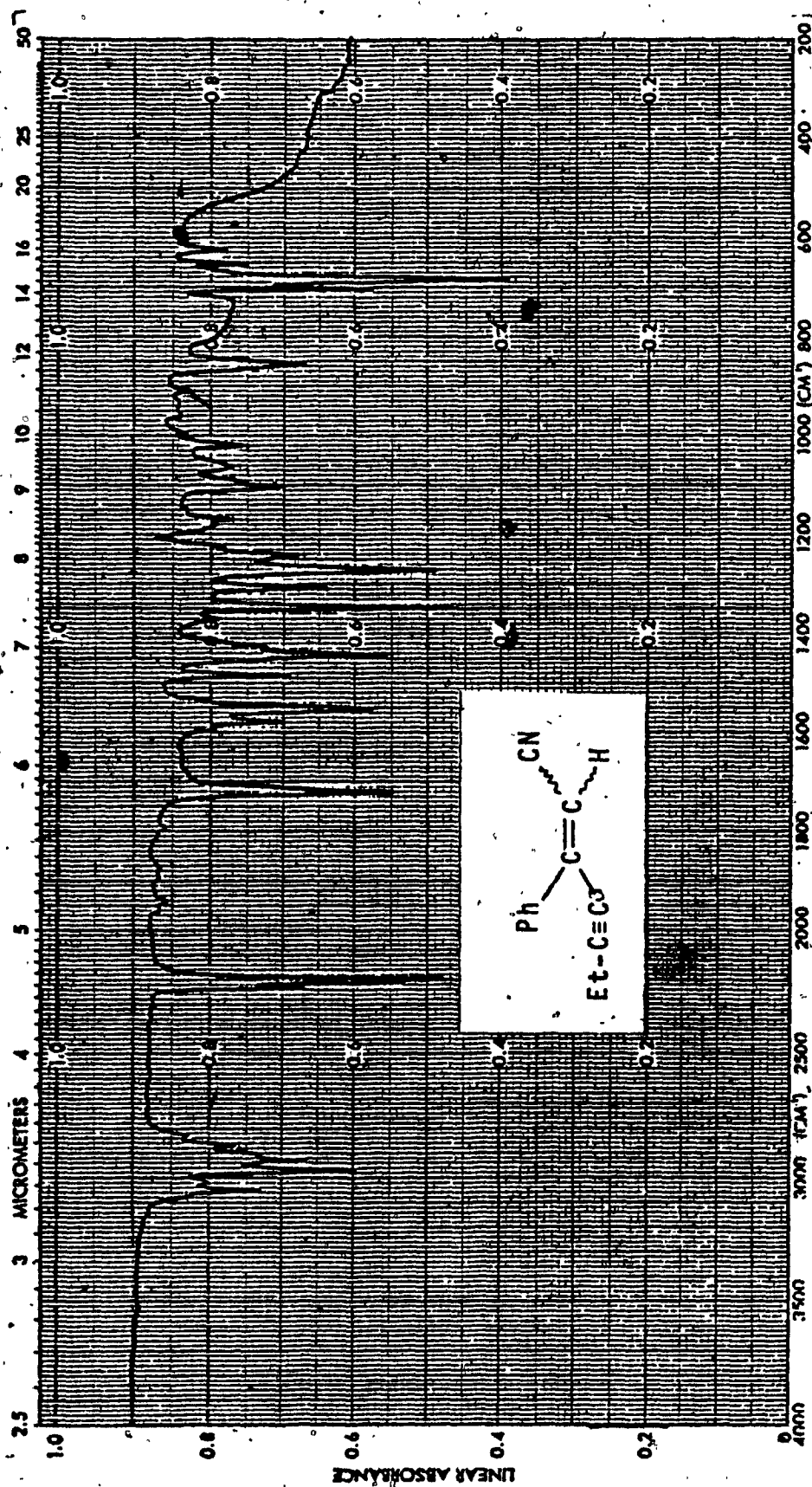
IR SPECTRUM 2

IR SPECTRUM 3

LINEAR ABSORBANCE

MICROMETERS

(CM⁻¹)

(CM⁻¹)
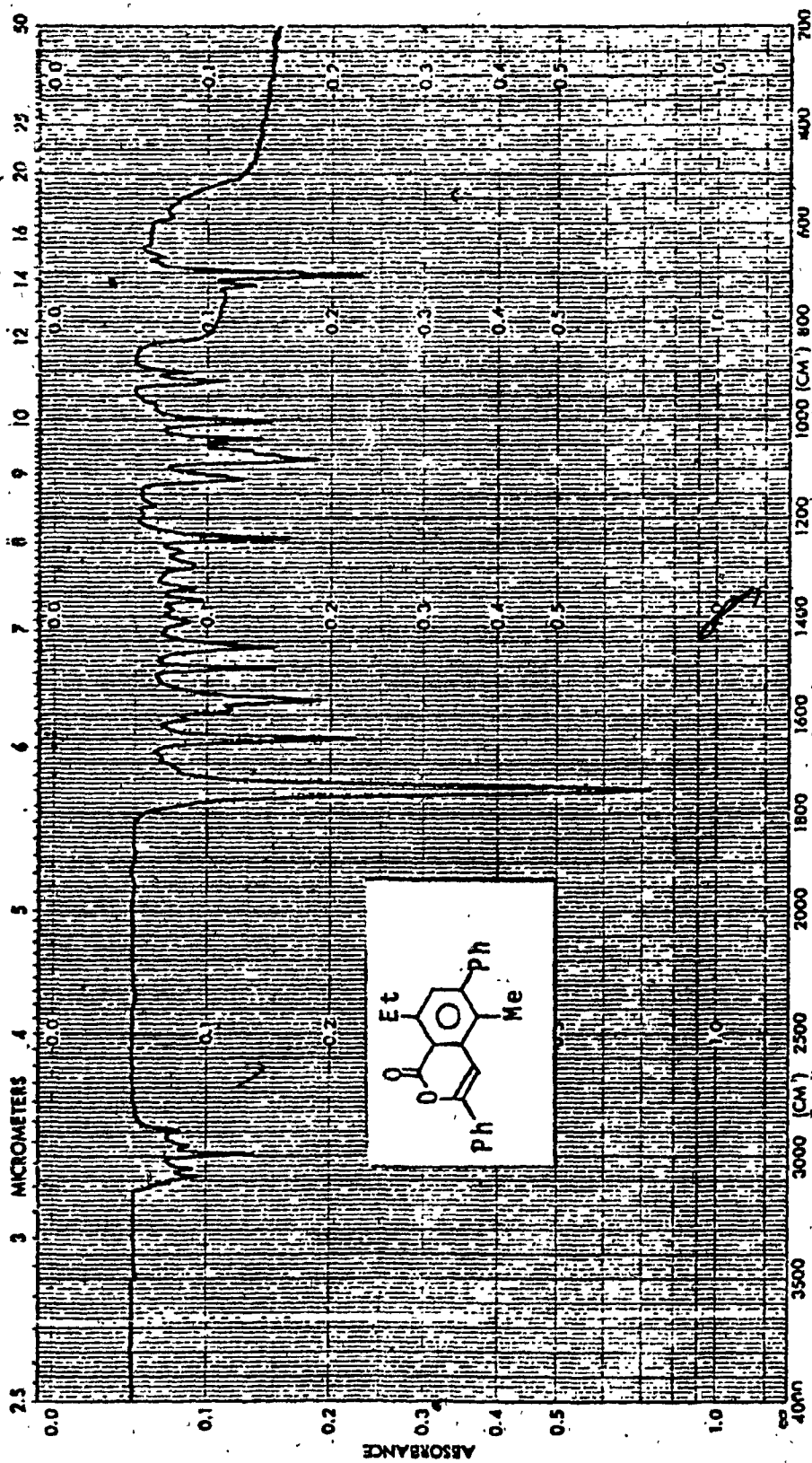
IR SPECTRUM 4

IR SPECTRUM 5
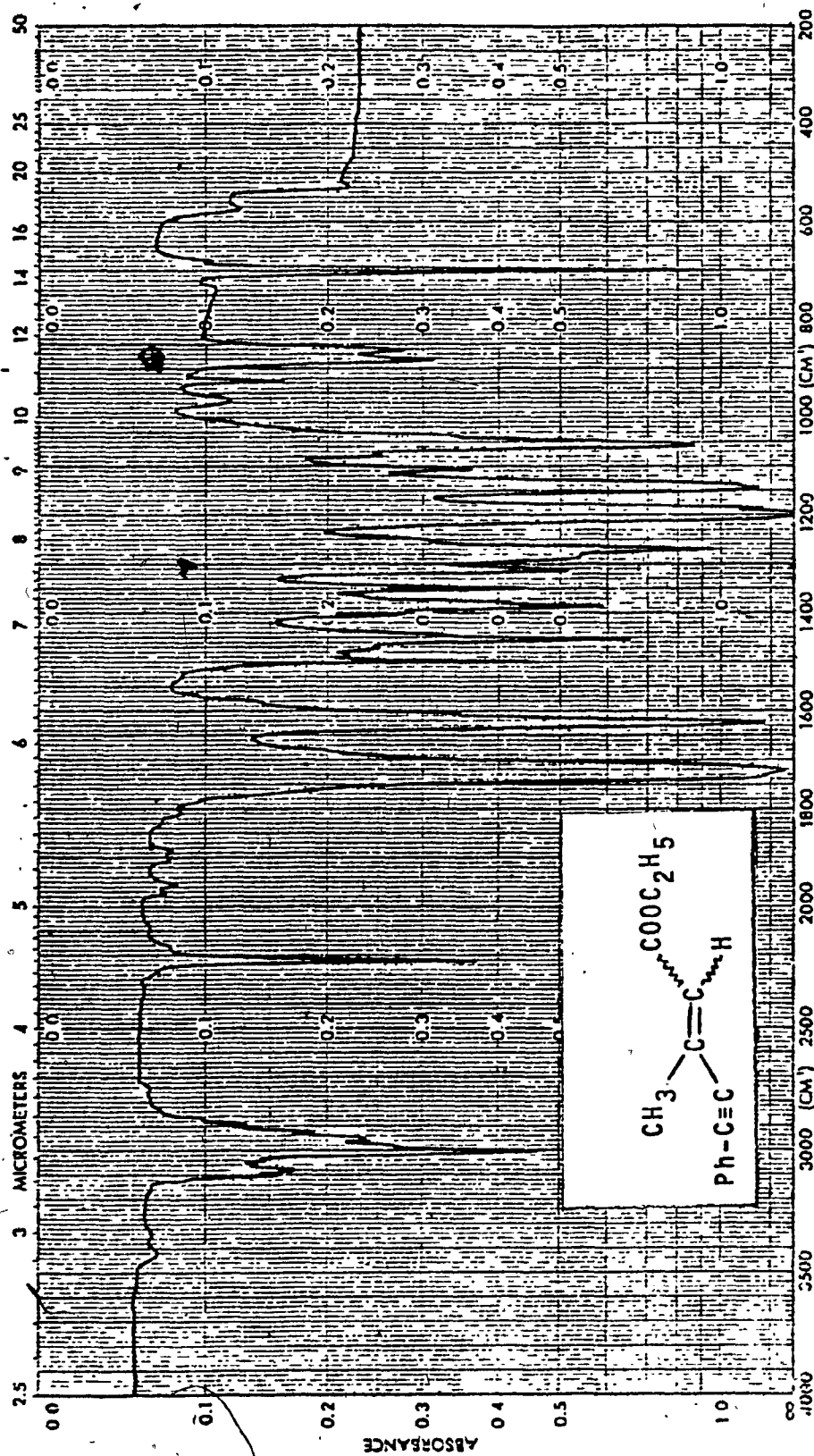
IR SPECTRUM 6

IR SPECTRUM 7

λ (nm)

Absorbance

2.0

1.0

0

220

250

280

310
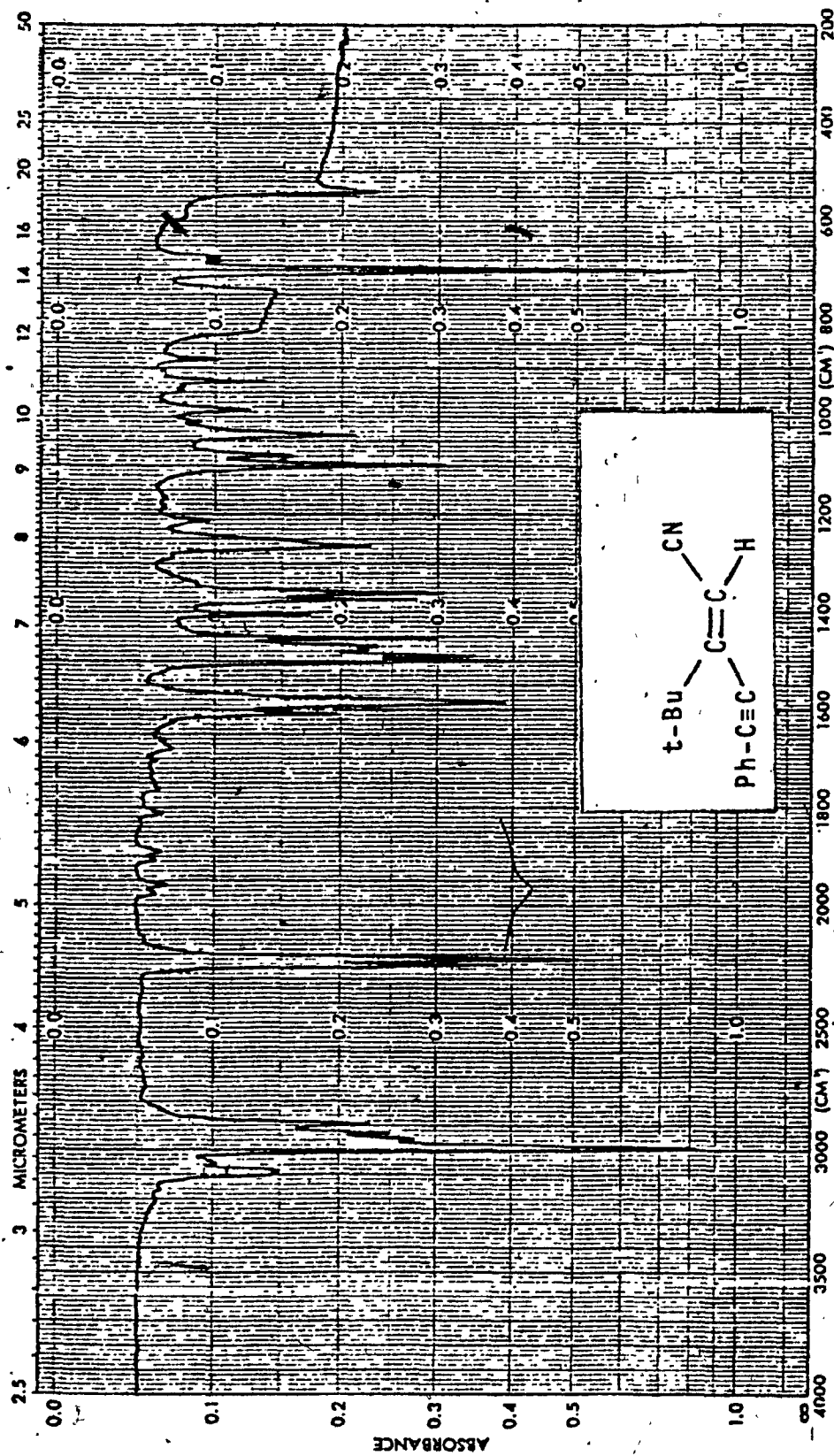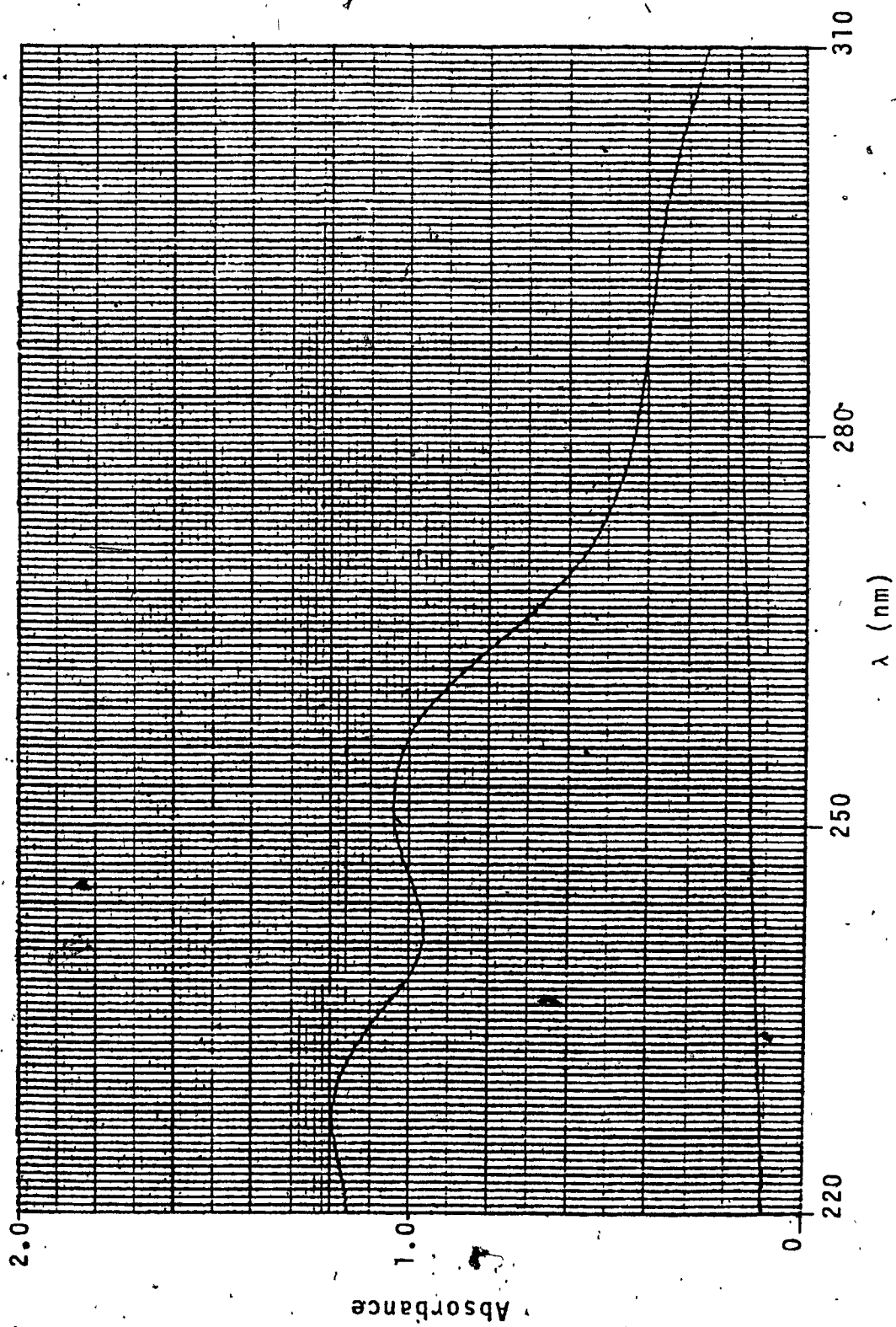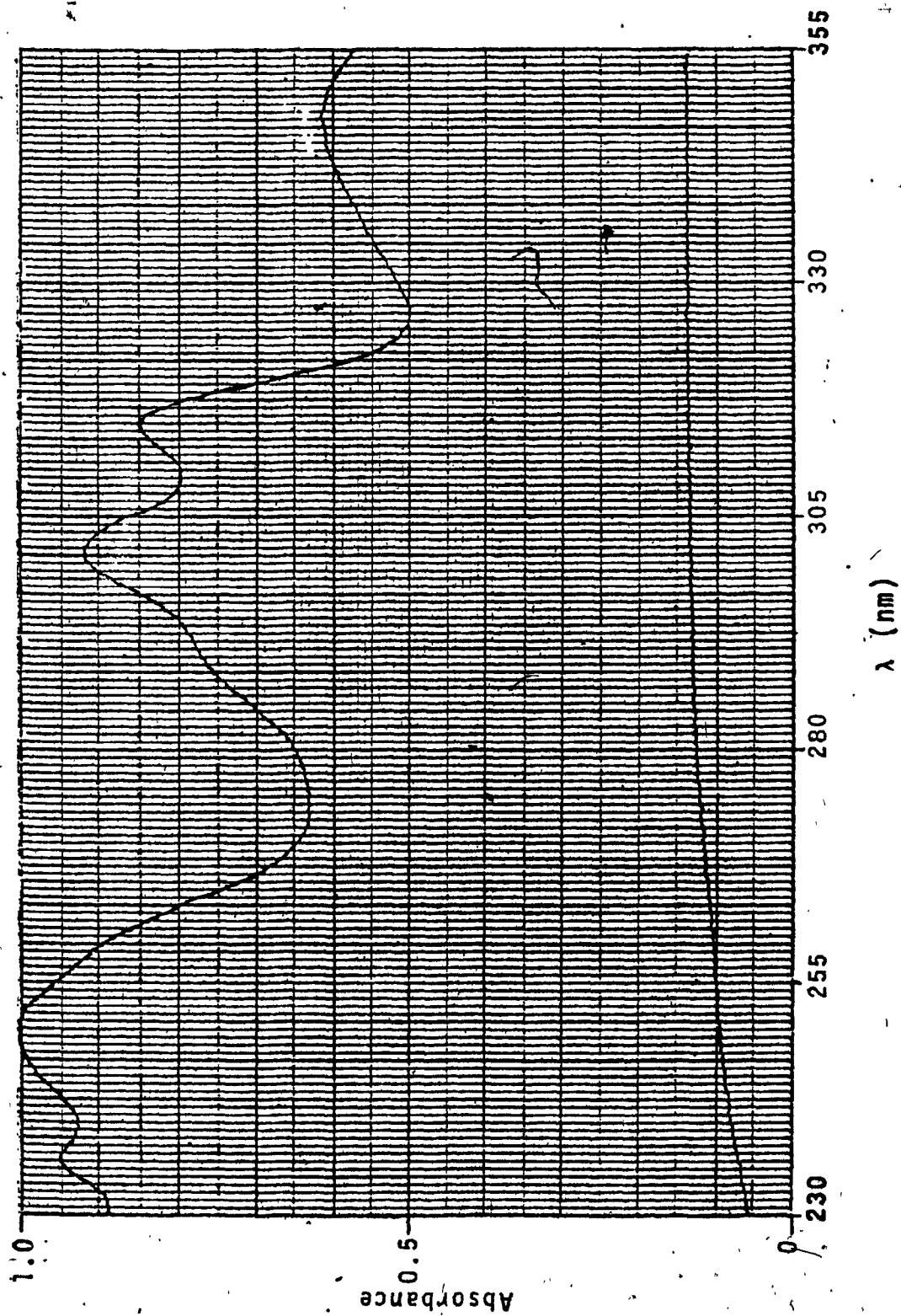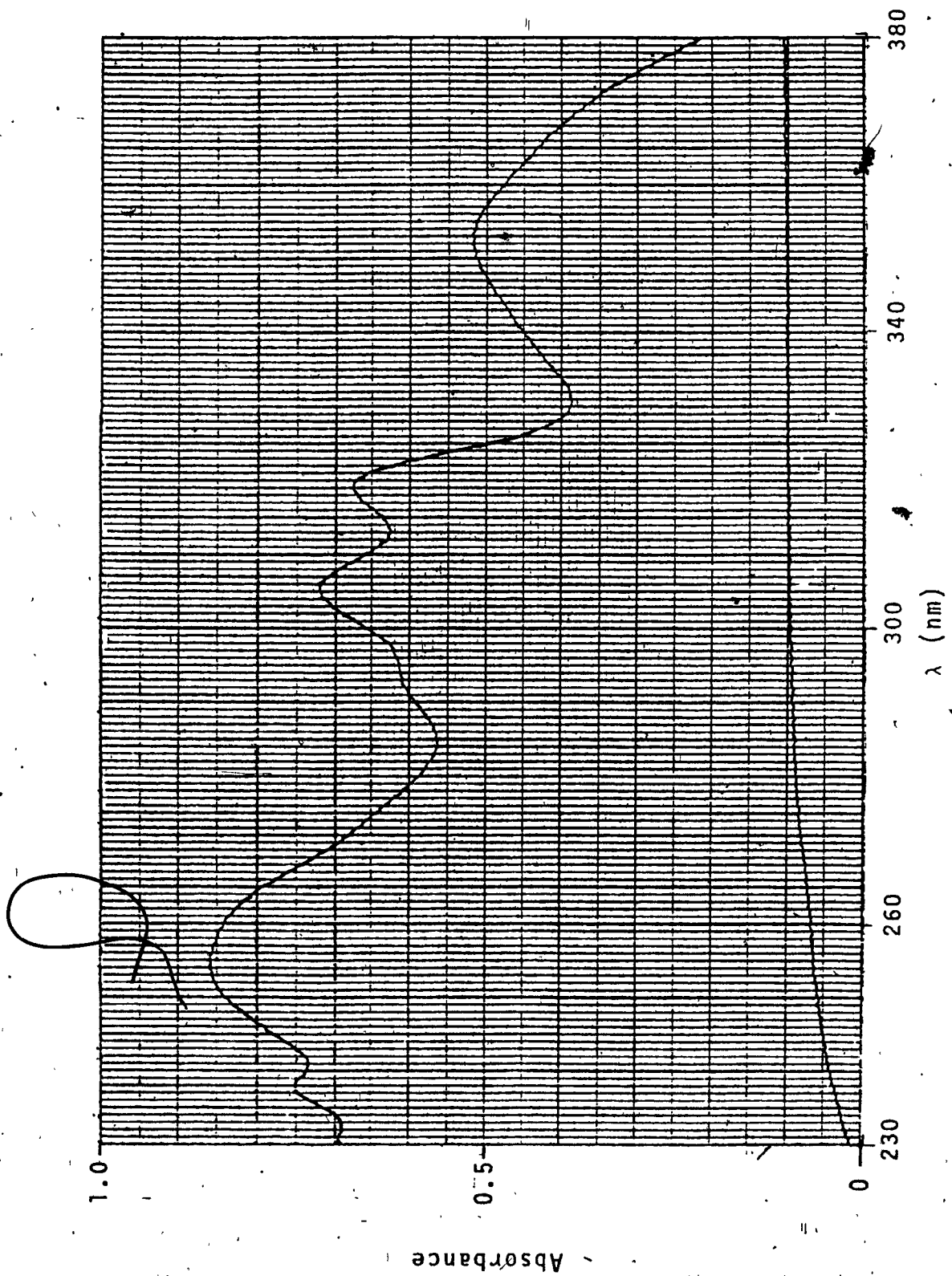
UV Spectrum of 4-benzoyl-2-cyano-3,5-dimethylbiphenyl

UV Spectrum of 8-methyl-3,6-diphenylisocoumarin

UV Spectrum of 8-ethyl-5-methyl-3,6-diphenylisocoumarin

VITA

The author was born in Alwaye, India. He obtained his Bachelors Degree from the University of Kerala, India in 1966. He finished his graduate studies in chemistry at the University of Saugar, India and obtained his Master of Science Degree in 1968. He worked as a lecturer in chemistry in St. Mary's College, S. Battery, India until 1974. He started his graduate studies in Concordia University in 1976 and expects to obtain his M.Sc. in 1980.