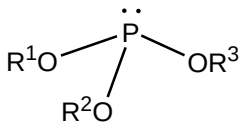
Introduction

It is evident that compounds of phosphorus display vital role in the living processes. Our interest in the field of organophosphorus chemistry led us to study the preparation of organophosphorus compounds for their increasing importance in industry and biology. Organophosphorus compounds occupy a fascinating niche at the interface between chemistry and biology together with industry. They can be obtained by reaction of organophosphorus reagents (eg. Alkyl phosphites and Wittig Reagents) with the active centers in certain organic molecules (eg. α,β-unsaturated carbonyls).[1]

The popularity of organophosphorus compounds, in general, originates from their simplicity, ease access and reactivity. In general, they decompose into non hazardous metabolites in living tissues and don't accumulate in vertebrate organs. This is also the main reason for the great concern oldly forwarded to insecticides and fungicides and presently forwarded to drugs based on OP-compounds. Many of these compounds are used mainly as drugs for the treatment of heart diseases, osteoporosis, convulsion and others. They can be used too in industry as anti-scaling agents for the treatment of cooling water circuits. They are also mixed with other materials in blends used as bactericides and fungicides.[1-5]

1. Alkyl Phosphites (Phosphite Esters)

The phosphite molecule **1** is polyatomic with a phosphorus central atom. Its geometry is trigonal pyramidal. The term phosphite is sometimes used to mean phosphite ester, an organophosphorus compound with the formula $P(OR)_3$.



The structure of a typical phosphite molecule

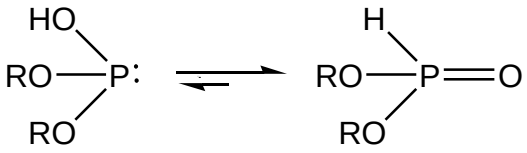
1a: R^1 = H, R^2 = R^3 = alkyl
b: R^1 = R^2 = R^3 = alkyl

The conjugate acid of the phosphite molecule is phosphorous acid (H_3PO_3). Other names for this acid are orthophosphorous acid and dihydroxyphosphine oxide. Phosphorous acid is diprotic, since the hydrogen bonded directly to the central

phosphorus atom is not ionizable. Thus, a more logical chemical formula for phosphorous acid is $H(O)P(OH)_2$.[2,3]

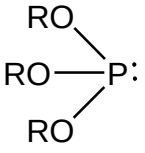
The alkyl esters of phosphorous acid are classified into three groups :

primary [$ROP(OH)_2$], secondary[$(RO)_2P$-OH] **1**a and tertiary [$(RO)_3P$] **1**b esters. The latter two groups are the most important and active ones due to their high reactivity and varying characteristics. Their reactivity is due to the presence of lone pair of electrons on the phosphorus atom that facilitates donation of electrons to a substrate to form σ or π-bond. Trialkyl esters are highly nucleophilic than dialkyl esters i.e. reacting rapidly with electron deficient centers by donation of electrons to the substrate. This is apparently due to the presence of the phosphorus atom in the tri- rather in the pentavalent state i.e. the phosphorus atom carries a lone pair of electrons.[4,5]



Dialkyl phosphites

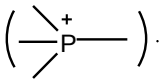
1a

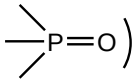
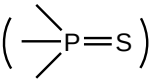
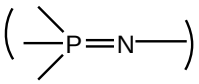


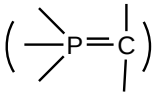
Trialkyl phosphites

1b

Trialkyl phosphites also possess strong nucleophilic characters and their reactions with different substrates lead mainly to three types of products:

a) Quaternary phosphonium compounds  .

b) Phosphoryl  , thiophosphoryl  , phosphite imine 

and phosphite methylene  compounds.

c) 5-, or 6- Coordinate structures

Active principles based on OP-compounds can be classified into the following three main groups according to the environment of the phosphorus atom in their molecules:

1) Phosphates [$(RO)_2P(O)$-O-, R = H or alkyl] which incorporate a *phosphorus-to-oxygen* bond in their molecules.

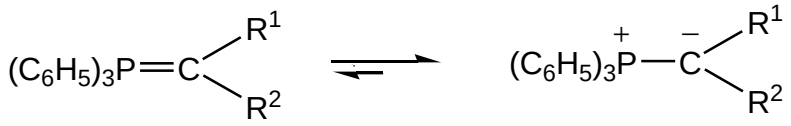
2) Phosphonates [$(RO)_2P(O)$-C-, R = H or alkyl] which incorporate a *phosphorus-to-carbon* bond in their molecules.

3) Trisaminophosphines [$(NR_2)_3P=X$] and phosphoramidates [$(RO)_2P(X)$-N-, R = H or alkyl, X = O or S] which incorporate *phosphorus-to-nitrogen* bond in their molecules.[4,5]

2. Phosphorus Ylides (Wittig Reagents)

An ylid or ylide (US) **2** is a neutral molecule with positive and negative charges on adjacent atoms. Ylides appear in organic chemistry as reagents or reactive intermediates .[6, 7]

An yilde is accompanied to some extent by its double bond resonance structure :



Phosphorane form **2** Ylide form

Where R^1 and R^2 = H or alkyl groups and their substituents

Since the phosphorus atom is in the third row of the periodic table, it has low energy d-orbitals that allow it to expand its octet, and form 4-membered ring transition-states and intermediate structures.[8]

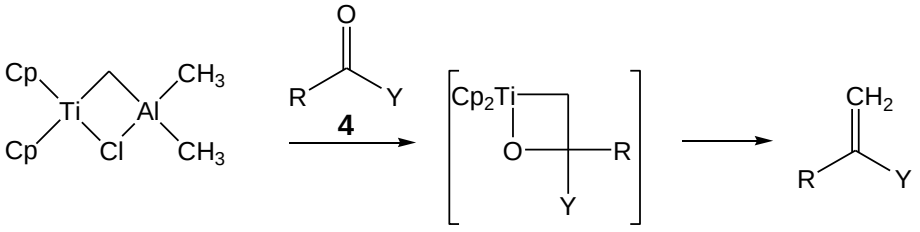
The reactivity of phosphorus ylides varies according to the substituents attached to the carbon end of the dipole. In $Ph_3P^+—C^-HR$, electron withdrawing groups such as $R=CO_2Et$ lead to delocalization of the carbon anionic charge with subsequent loss of carbanionic (and hence ylidic) reactivity. They are called stable ylides and they are stable against atmospheric oxygen and water. In contrast, unstable reactive ylides possess no stabilizing α-substituents, they carry electron-donating groups on their anionic center (such as an alkyl group) which leads to strong nucleophilic carbon and hence an increase in reactivity. They must be handled under an inert gas. Most synthetic applications of yildes couple with subsequent loss of triphenylphosphine or its oxide, both of which are good leaving groups.[9-12]

Ylide types:

- The most common ylides are phosphonium ylides. They are used in the Wittig reactions for double bond creation from carbonyl groups. The positive charge

in the Wittig reagents is carried by a phosphorus atom with three phenyl substituents and one bond to carbon bearing a negative charge and two substituents commonly alkyl groups. Ylides can be "stabilized" or "non-stabilized". Non-stabilized ylides react readily with both aldehydes and ketones whereas stabilized ylides react only with aldehydes.

- Other common ylides include sulfonium ylides and sulfoxonium ylides.
- Certain nitrogen-based ylides also exist such as azomethine ylides. These compounds can be invisioned as iminium cations placed next to a carbanion. These ylides can be generated by condensation of an α-amino acid with an aldehyde.
- Iminophosphoranes (also called: phosphazides) with the general structure R_3P^+-N^- R are intermediates in the Staudinger reaction.[13]
- The active form of Tebbe's reagent **3** is often considered as titanium ylide. Like the Wittig reagent, it is able to replace the oxygen atom on carbonyl groups with a methylene group. Compared with the Wittig reagent, it has more functional group tolerance.[13]

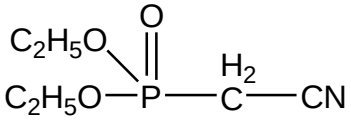


3 **5** **6**

Y = H, R, OR, NR_2

Cp = cyclopentenyl (C_5H_5)

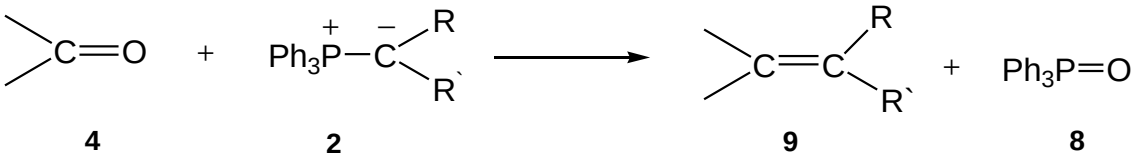
- Horner-Wadsworth-Emmons ylide e.g. cyanomethylphosphonic acid diethyl ester **7**.[14]



7

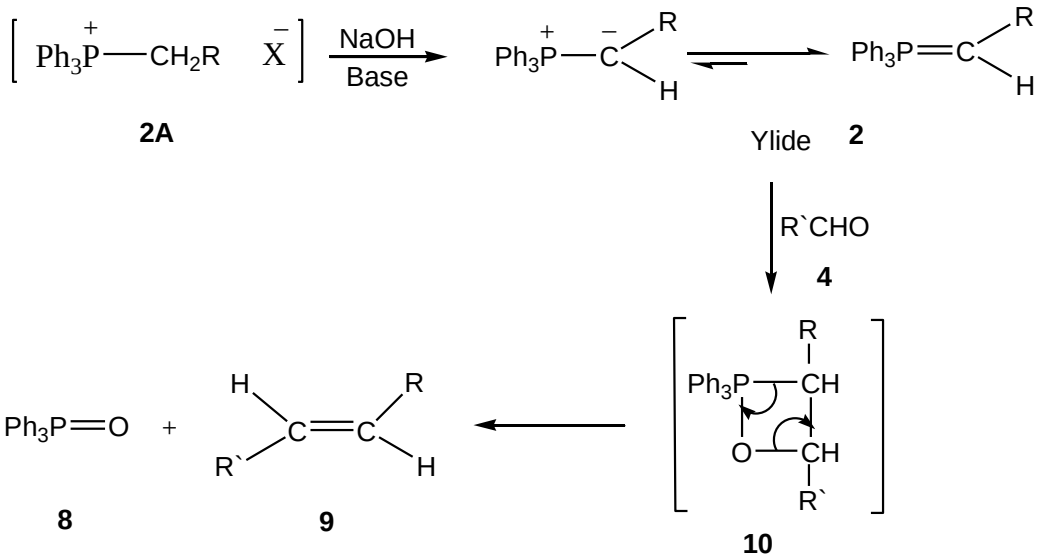
Wittig reaction

The Wittig reaction is a chemical reaction of an aldehyde or ketone **4** with triphenylphosphonium ylide **2** to give an alkene **9** and triphenylphosphine oxide **8**.[15-17]



4 **2** **9** **8**

Only the Wittig reaction provides a single alkene with the double bond in a known position with no ambiguity, by reaction of aldehyde or ketone with the ylide generated by deprotonation of a phosphonium salt obtained by the reaction of triphenylphosphine with alkyl halide using a strong base such as NaOH.[15]



2A Ylide **2** **4** **8** **9** **10**

The geometry of the resulting alkene depends on the reactivity of the ylide. If R is Ph, then the ylide is stabilized and is not as reactive as when R is alkyl. Stabilized phosphorus ylides lead to olefins with excellent *E* selectivity. They contain groups that can stabilize the negative charge on phosphonate carbanion carbon e.g. Ph_3P=CH-COOR and Ph_3P=CH-Ph. These are less reactive than simple ylides, and so they usually fail to react with ketones. There can be a problem with sterically hindered ketones, where the reaction may be slow and give poor yield particularly with stabilized ylides and in such cases the Horner-Wadsworth-Emmons (HWE) reaction (using phosphonate esters) is preferred. The non-stabilized reactive ylides lead to rapid reaction and *Z* alkenes. [17-19]

The mechanism of the Wittig reaction is commonly expressed in two steps:

1. Nucleophilic addition of phosphorus ylide to the carbonyl compound to give a betaine species.
2. Irreversible decomposition of the betaine to form alkene and phosphine oxide.[20-23]

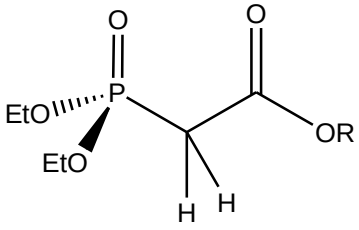
The reaction mechanism of Wittig-Horner reaction is similar to the mechanism of Wittig reaction.[24, 25]

Wittig reactions are synthetically useful because they are:

- Regioselective.
- Stereoselective (the preferred *E* stereoisomer is the major product). [24, 25]

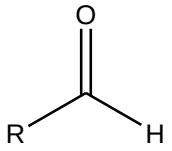
Horner-Wadsworth-Emmons reaction

In 1958, Horner published a modified Wittig reaction using phosphonate-stabilized carbanions.[26] Wadsworth and Emmons further defined the reaction. The Horner-Wadsworth-Emmons (HWE) reaction is a method by which an enone **12** can be formed. There are two components to this reaction: a phosphonate **11** and an aldehyde **4**.



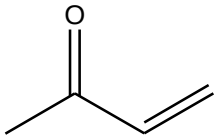
A phosphonate

11



An aldehyde

4



An enone

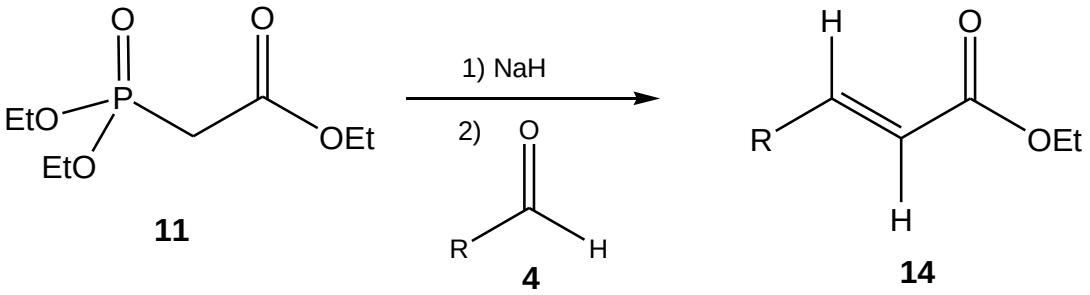
12

The most common reagents used in this reaction are LiCl and a base such as DBU(1,8-diazabicyclo[5,4,0]undec-7-ene) or DIPEA (diisopropylethylamine). LiCl is used because lithium cations form a tight complex **13** with the anion derived from phosphonate **11**. [27,28]

11 **13**

The complex that is formed is stable which increases the acidity of the original phosphonate. The HWE is often used to create an enone (a molecule with a double bond conjugated to a carbonyl group) especially with molecules that contain a base-sensitive substrate or reagent.[26-28]

The Horner-Wadsworth-Emmons (HWE) reaction is thus the chemical reaction of stabilized phosphonate carbaniones with aldehydes (or ketones) to produce predominantly *E* alkenes **14**. [26-28]



In contrast to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbaniones are more nucleophilic and more basic. Likewise, phosphonate-stabilized carbanions can be alkylated unlike phosphonium ylides. [29,30]

Stereoselectivity

The Horner-Wadsworth-Emmons reaction favours the formation of *E* alkenes. In general, the more equilibration amongst intermediates, the higher the selectivity for *E* alkene formation. Aromatic aldehydes produce almost exclusively *E* alkenes. In case that *Z* alkenes from aromatic aldehydes are needed the **Still modification** can be used. [31, 32]

Still modification

Still and Gennari have developed conditions that give *Z* alkenes with excellent stereoselectivity. Using phosphonates with electron-withdrawing groups together with strongly dissociating conditions, nearly exclusive *Z* alkene production can be achieved.[31, 32]

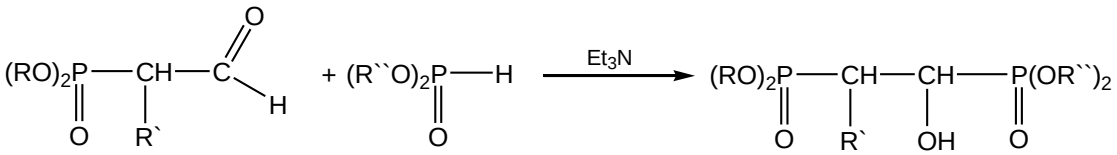
I- Reactions of Alkyl Phosphites with Aldehydes and Imines:

In view of the high reactivity of the formyl group, aldehydes may be considered as suitable starting materials for the synthesis of a wide variety of organophosphorus compounds. [33,34]

The vast majority of methods for the preparation of compounds with a C-P bond are based on the interaction of phosphorus (III) acid esters with electrophilic agents. [35]

1- Reaction of Dialkyl Phosphites with Aldehydes:

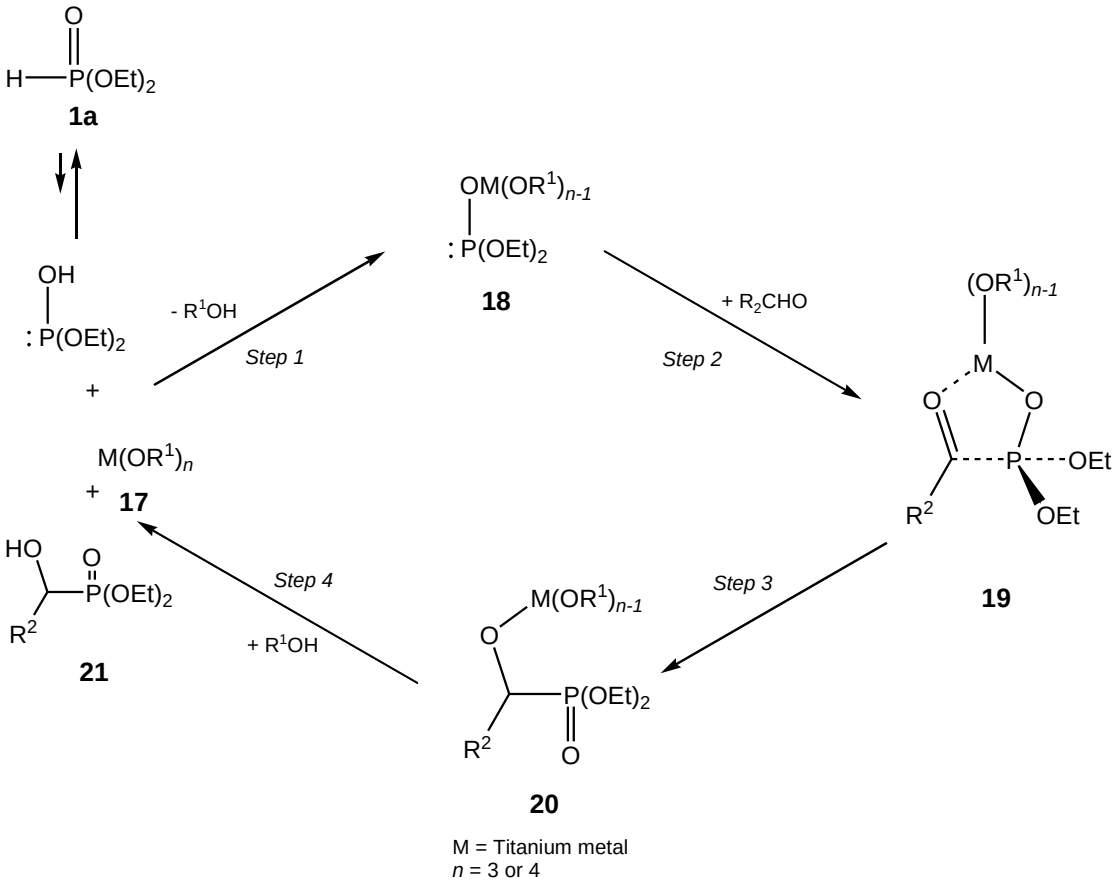
1) Phosphorylated aldehydes **15** lead to new possibilities in the synthesis of substituted ethylenediphosphonates **16** by their familiar reactions with dialkyl phosphites . [35]



15 **1a** **16**

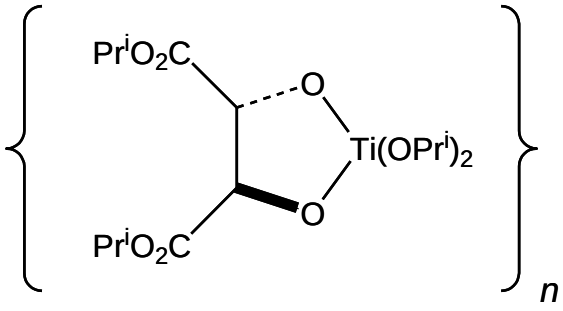
R, R`, R`` = alkyl groups

2) The transition-metal catalysts **17** such as titanium alkoxides act as weak bases and are available as activators of diethyl phosphite **1a** through a ligand-exchange reaction. The resulting organometallic phosphorus species **18** add to aldehydes to form α-hydroxy phosphonates **21** *via* a transition state such as **19.** [36] **(Scheme 1)**

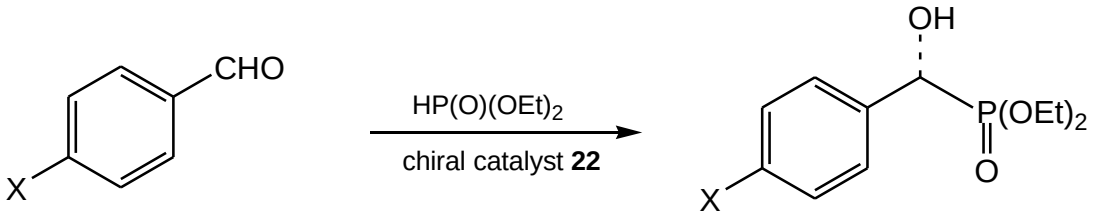


Scheme 1

The Pudovik reaction of benzaldehyde as well as *para*-substituted benzaldehyde **23** with diethyl phosphite were carried out in the presence of a catalytic amount of the chiral catalyst; tartrate modified titanium (IV) alkoxide **22** in several kinds of solvents. [36]



Tartrate modified titanium(IV) alkoxide **22**

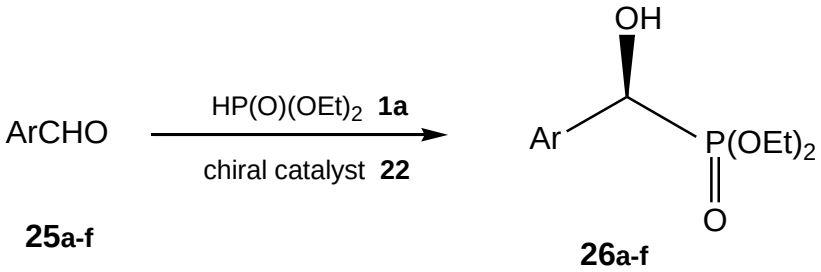


23

X = H, Cl, OMe

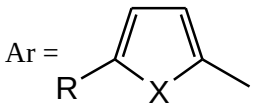
24

Pudovik reaction of heteroaromatic aldehydes **25** having either a thiophene or furan nucleus were catalyzed for the synthesis of α-hydroxyphosphonates **26** by reaction with diethyl phosphite **1a**.[36]



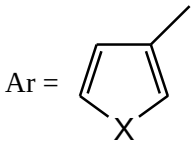
25a-f

26a-f



a, R = H, X = O; b, R = Me, X = O

c, R = H, X = S; d, R = Me, X = S



e, X = O; f, X = S

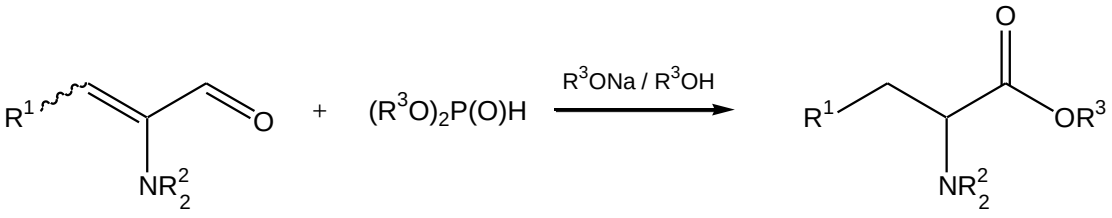
This work is important for synthesis of asymmetric α-hydroxyphosphonates. When dialkyl phosphites $(RO)_2P(O)H$ (R= Me, Et) react with aliphatic and aromatic aldehydes R^1CHO (R^1= Me, Ph, 1-naphthyl, 2-tolyl) in presence of NaOH, the corresponding phosphonates $(RO)_2P(O)CH(OH)R^1$ were obtained in excellent yields under optimum conditions.[37,38]

3) N,N-Disubstituted α-formyl enamines are compounds of particular interest. Two important features characterize this type of compounds;

a) They can be treated either as α,β-unsaturated carbonyl systems with a tertiary amino function or as α-formyl enamines to give surprising and unexpected reactions.

b) In view of the presence of the tertiary amino-group and of the double bond at the α-position of the carbonyl function, these derivatives can readily provide access to various biologically important products and natural analogues. [39]

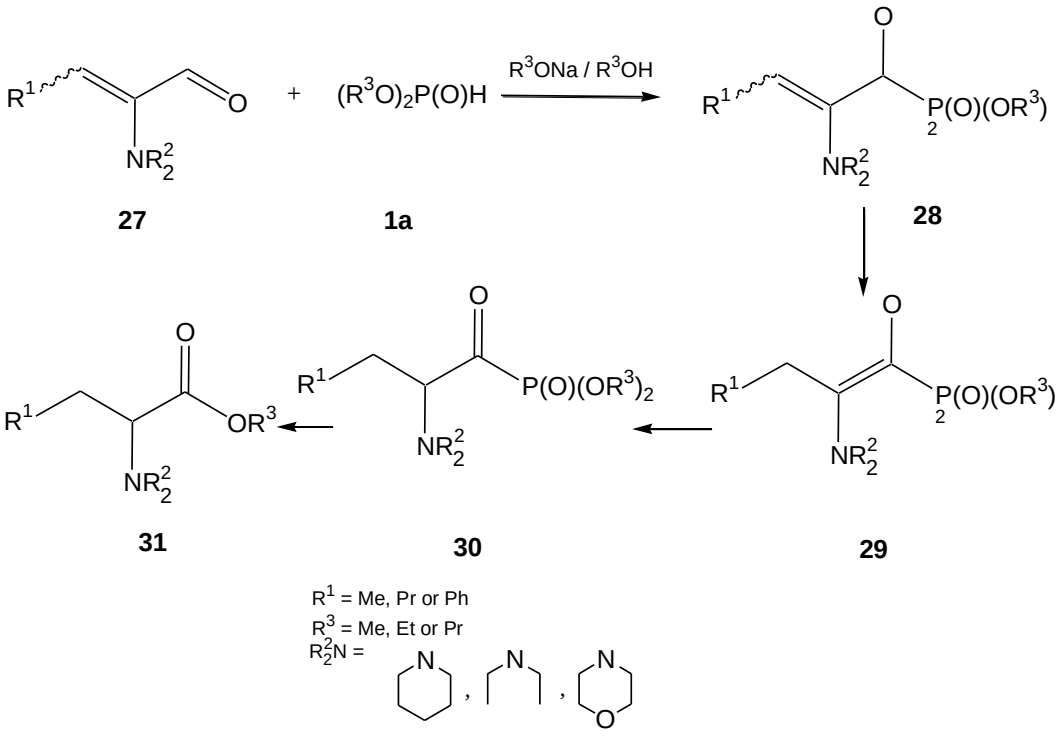
α-Formyl enamines **27** under the action of dialkyl phosphites **1a** undergo an unusual transformation leading to tertiary α-amino esters **31**.[39]



27 **1a** **31**

R^1 = Me, Pr or Ph
N_2R^2 = $N(CH_2)_5$, NEt_2 or $N(CH_2CH_2)_2O$
R^3 = Me, Et or Pr

A likely mechanism for the formation of the esters is presented in **Scheme 2**:

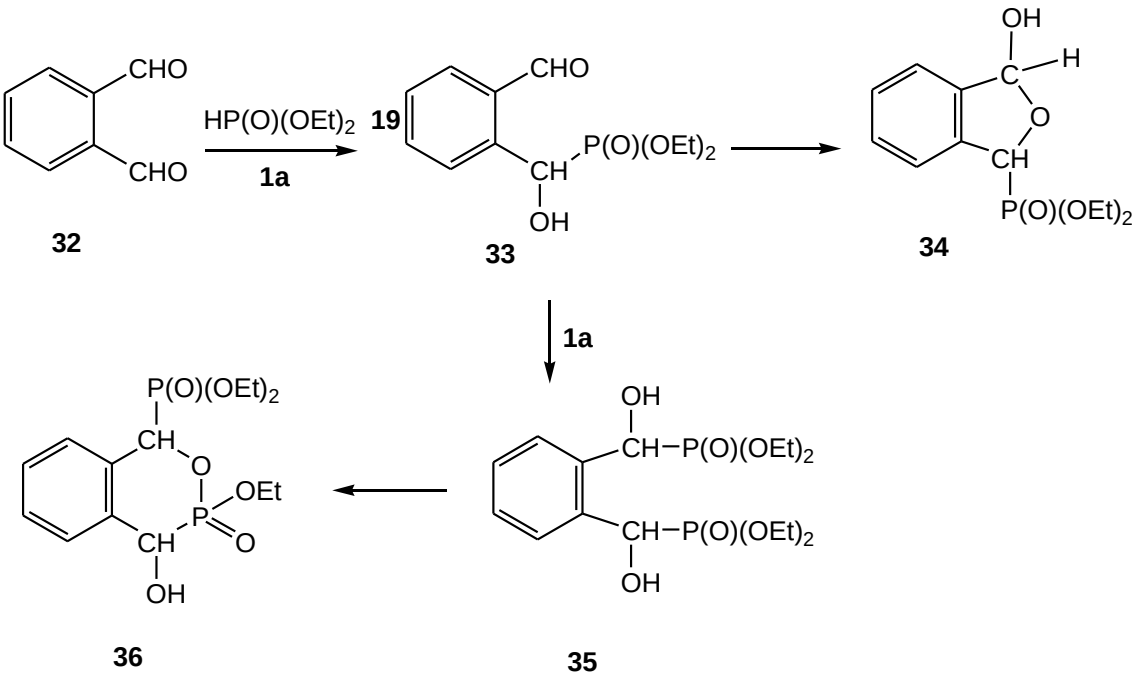


27 **1a** **28** **29** **30** **31**

R^1 = Me, Pr or Ph
R^3 = Me, Et or Pr
R^2_2N =

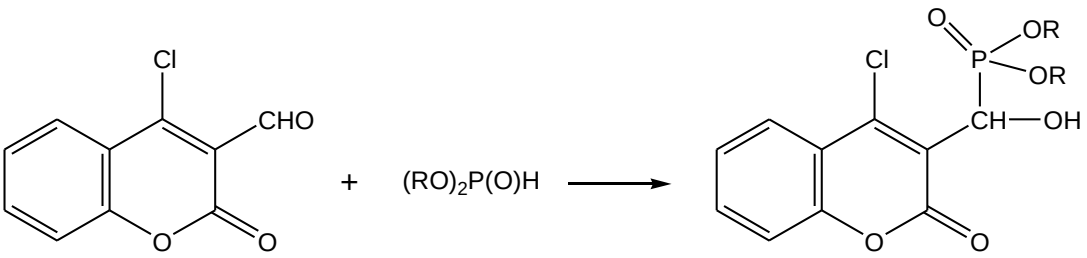
Scheme 2

4) The reaction of o-phthalaldehyde **32** with diethyl phosphite leads to the bishydroxy bisphosphonate **35** which undergoes intramolecular rearrangement to give the cyclic phosphorane **36.** [40] **(Scheme 3)**



Scheme 3

5) 4-Chlorocoumarin-3-carboxaldehyde **37** produces its respective 1:1 phosphonate adduct **38** upon reaction with the appropriate dialkyl phosphite **1a**.[41]

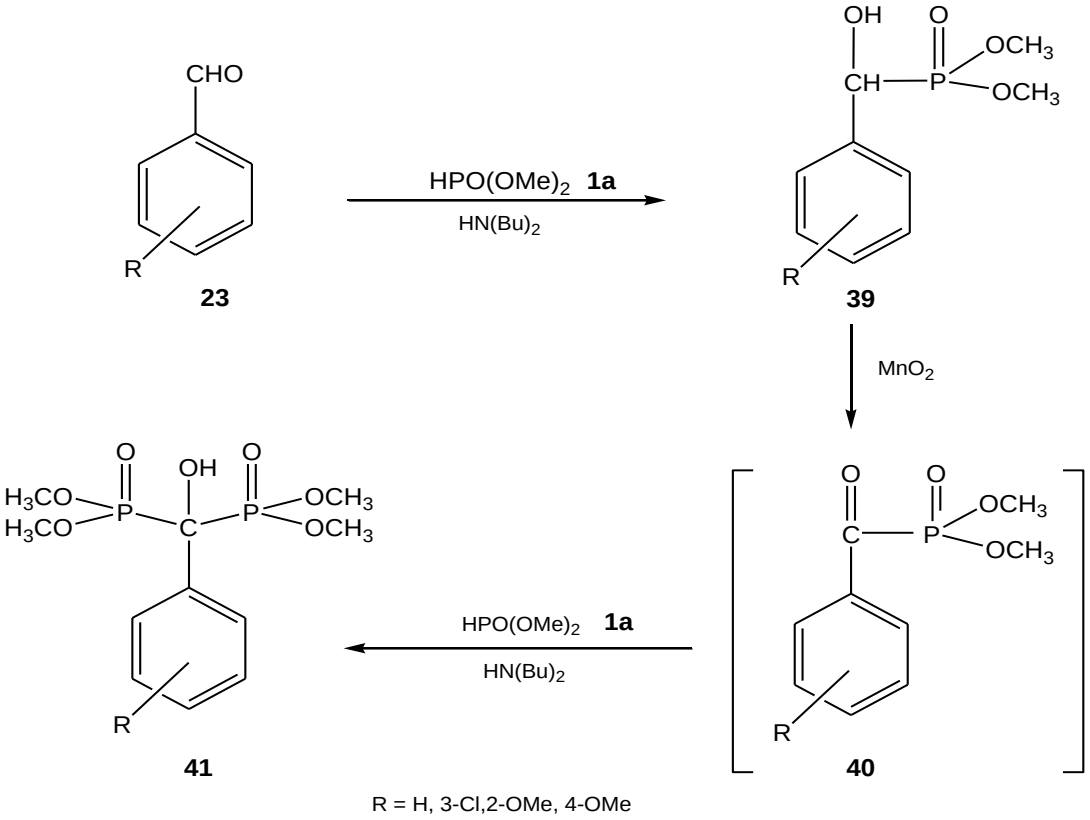


R = CH_3, C_2H_5, C_3H_7-i

6) Bisphosphonates (BPs) as stable analogues of pyrophosphates, contain two phosphonate groups attached to a single carbon atom forming a "P-C-P" structures that are completely resistant to enzymatic hydrolysis. The 1-hydroxymethylene-1,1-bisphosphonates(HMBP) are the most effective compounds for treatment of a number of diseases.[42] Several methods have been reported for the synthesis of HMBP.

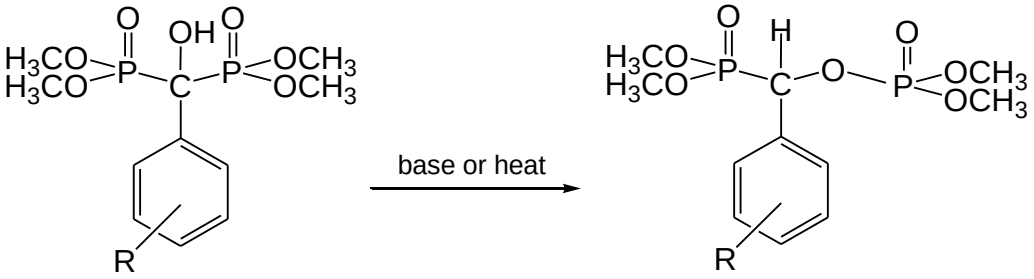
However, the common method that involves the reaction of a carboxylic acid and phosphorus trichloride was limited only to the compounds with alkyl substituents, not allowing the synthesis of aromatic analogues. [42]

Recently, there has been considerable interest in aromatic BPs because of their novel biological properties as anti-inflammatory, anti-neoplastic and lipid lowering agents. α-Hydroxyphosphonate **39** can be easily obtained by the addition of dimethyl phosphite **1a** to aldehydes **23** in the presence of a catalytic amount of di-n-butylamine based on Pudovik reaction.[42] **(Scheme 4)**



Scheme 4

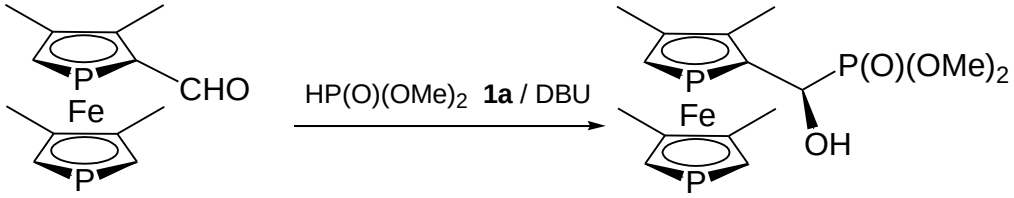
Bisphosphonate **41** is not stable thermally or under basic conditions due to its rearrangement to the phosphonophosphate **42**. The addition of dimethyl phosphite was strongly exothermic, so it was necessary to work at -5°C for a good result.[42]



41 **42**

7) During recent years there has been a growing interest in the stereoselective synthesis of α-hydroxyphosphonates due to their biological activity and wide application in synthesis of other functionalized phosphonates. Biological activity of numerous ferrocene derivatives was documented. Racemic ferrocenyl α-hydroxyphosphonates are accessible by the addition of dialkyl phosphites to ferrocenecarboxaldehyde.[43]

Addition of dimethyl phosphite **1a** to racemic 3,3\',4,4\'-tetramethyl-1,1\'-diphosphaferrocene-2-carboxaldehyde **43** gives almost exclusively one diastereomer of the corresponding α-hydroxyphosphonate **44**. [43]



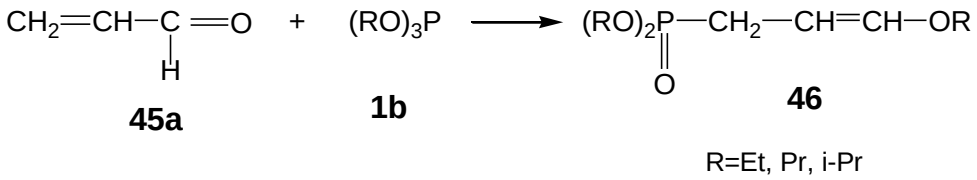
43 **44**

(Only one enantiomer of **44** is shown)

The results obtained in this work show that addition of a dialkyl phosphite to **43** proceeds in a highly diastereoselective manner.[43]

2-Reaction of Trialkyl Phosphites with Aldehydes:

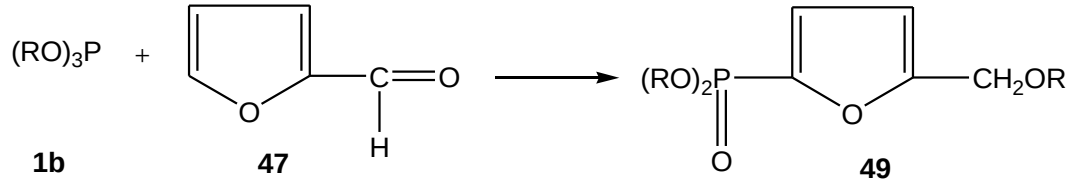
1) Kamai and Kukhtin showed that phosphorus triesters **1b** add to the α, β–unsaturated aldehyde **45a** (acrolein) with formation of phosphonic esters **46**.[44]



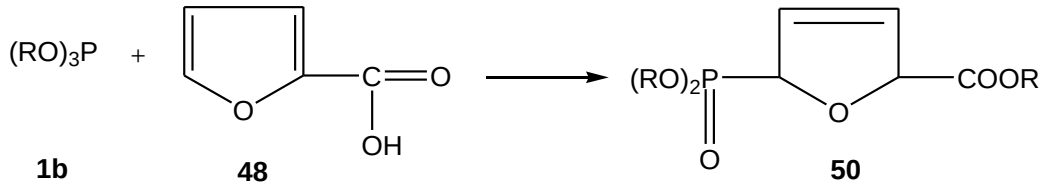
45a **1b** **46**

R=Et, Pr, i-Pr

It may be supposed that conjugated systems containing many double bonds will also be capable of this sort of addition reaction. Such systems are found in the aldehydes **47** and acids **48** of the furan series. When trialkyl phosphites add to these compounds, substituted furyl-phosphonic ethers and acids **49, 50** are respectively obtained.[44]

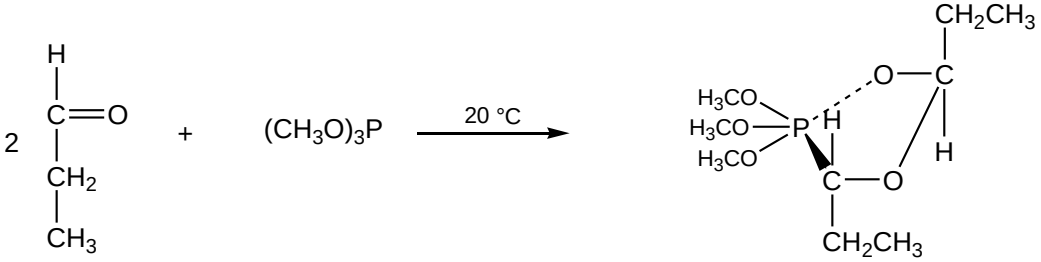


1b **47** **49**



1b **48** **50**

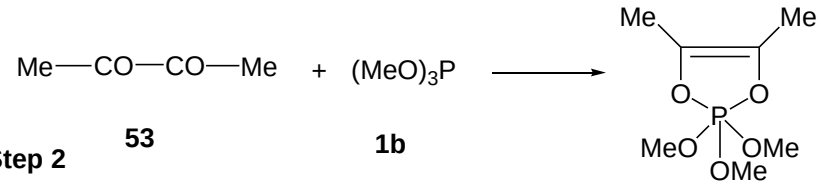
2) The reaction of 2 moles of anhydrous propionaldehyde **51** with 1 mole of trimethyl phosphite **1b** at 20°C yields 2:1 adduct **52** based on the reacted phosphite.[45]



51 **1b** **52a**, *E*
b, *Z*

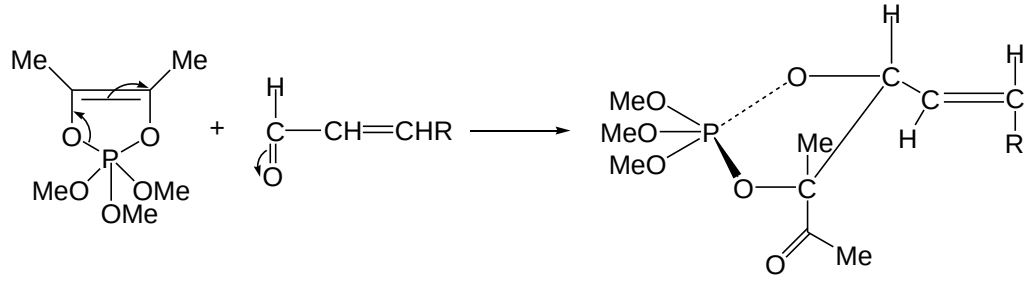
3) The condensation of biacetyl Me-CO.CO-Me **53** with acrolein CH_2=CH-CHO **45a** and /or crotonaldehyde Me-CH=CH-CHO **45b** in presence of trimethyl phosphite $(MeO)_3P$ **1b** takes place in 2 steps to give phospholene **54** and phospholane **55** adducts . [46]

Step 1



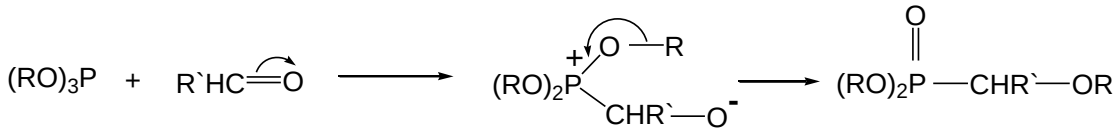
53 **1b** **54**

Step 2



54 **45a** R = H
45b R = Me **55**

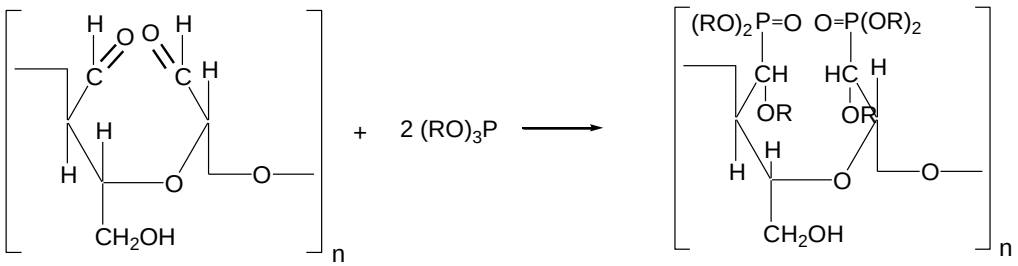
4) Phosphorus-containing derivatives of cellulose were produced in earlier work by the Arbuzov reaction of trialkyl phosphites **1b** with desoxychloro- and tosylated cellulose, the former played the part of the alkyl halide normally employed in the Arbuzov rearrangement. Trialkyl phosphites are also known to react with aldehydes **56** to give α-alkoxyalkyl phosphonates **58**. [47]



1b **56** **57** **58**

R = Me, Et, i-Pr
R`HCO = aldehyde- containing cellulose

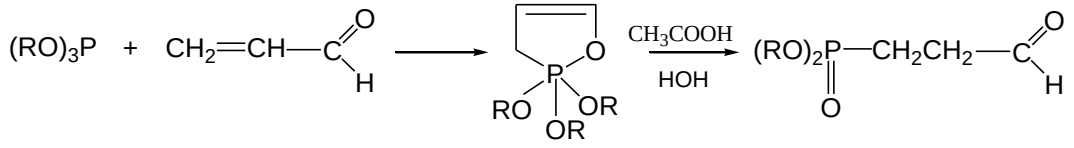
The pentavalent phosphorus compounds with a C-P bond in the cellulose macromolecule **60** were produced by reaction of cellulose dialdehyde **59** with trialkyl phosphites. [47]



59 **1b** **60**

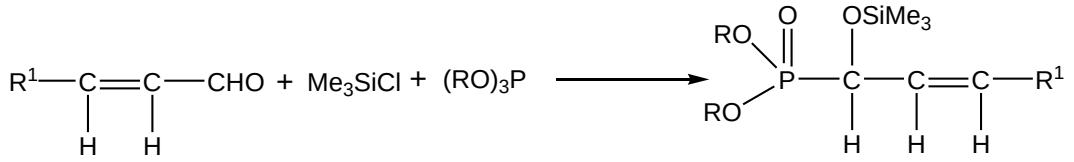
R = Me, Et or i-Pr
n = 5-10 under the experimental conditions

5) Phosphorylated aldehydes can be obtained by reaction of aldehydes with trialkyl phosphites. The synthesis of aldehydes from compounds of the oxaphosphorane type can be achieved as a result of the interaction of trialkyl phosphites with α,β-unsaturated carbonyl compounds e.g. **45a**. Treatment of the oxaphosphorane **61** with acetic acid yields phosphonopropionaldehyde **62**.[35]



1b **45a** **61** **62**

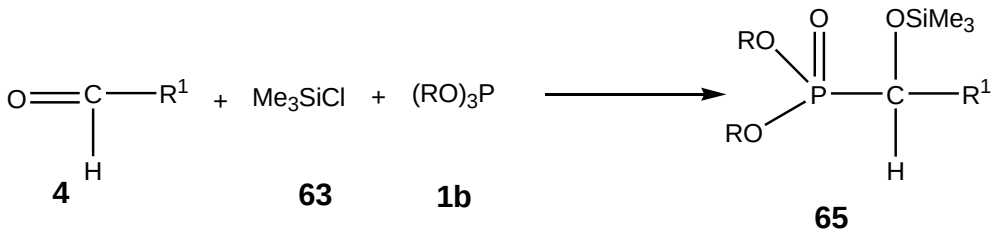
6) Derivatives of (trimethylsilyloxy)alkylphosphonates **64** were synthesized by the reaction of trialkyl phosphites **1b**, trimethylchlorosilane **63** and aldehydes **45** in one-pot reaction.[48]



45 **63** **1b** **64**

R= Me, Et
R^1= H, Me, Ph

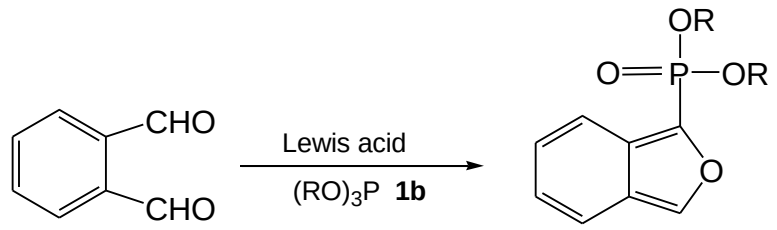
Dialkyl-1-(trimethylsilyloxy)alkylphosphonates **65** were also prepared with the same procedure.[49]



4 **63** **1b** **65**

R= Me, Et
R^1= alkyl, aryl and substituted aryl

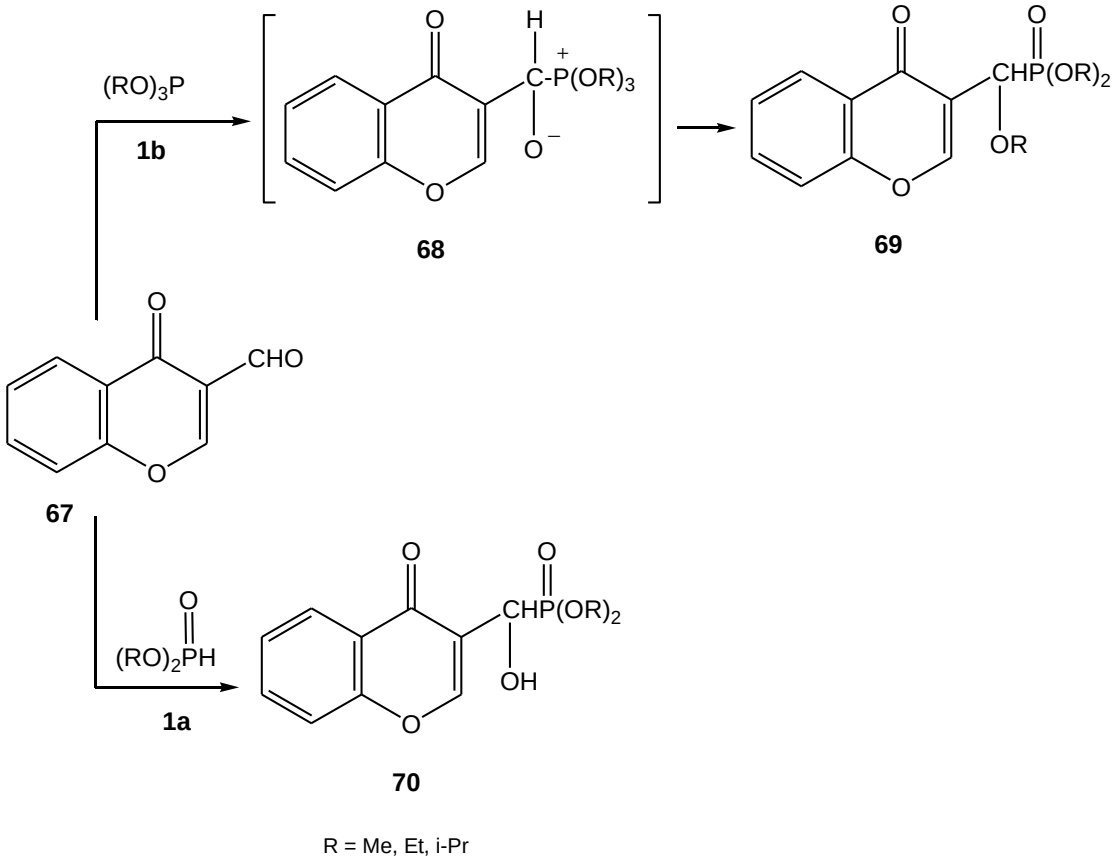
7) Reaction of *o*-phthalaldehyde **32** with trialkyl phosphites led to the novel formation of 1-dialkoxyphosphorylisobenzofurans **66**.[50]



32 **66**

R = Me, Et, i-Pr

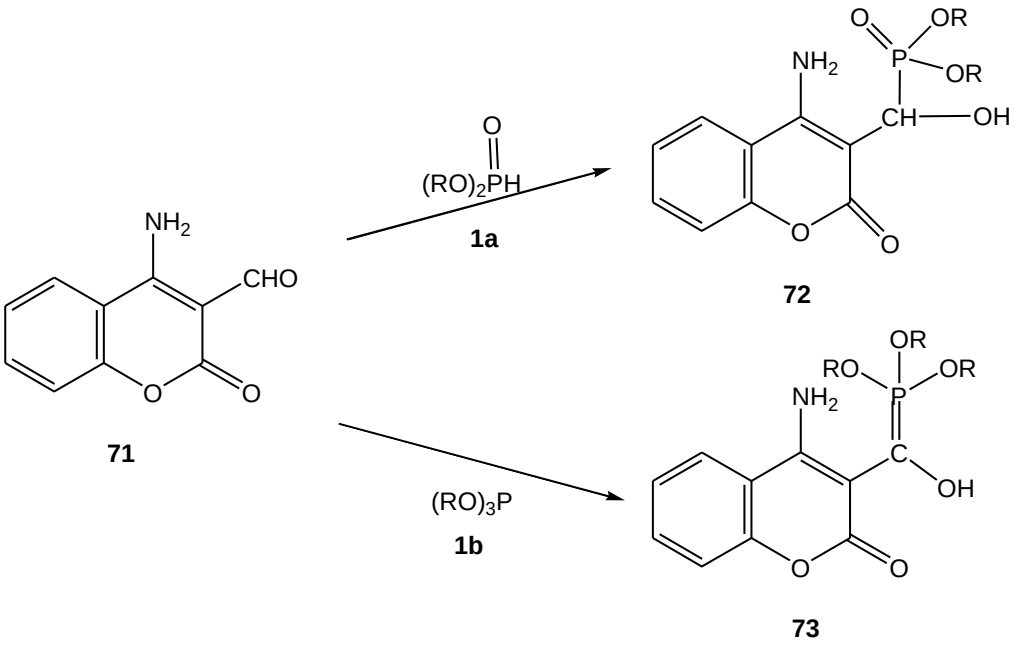
8) Trialkyl and dialkyl phosphites attack the aldehydic carbonyl-carbon of chromone-3-carboxaldehyde **67** yielding the corresponding α-alkoxy-, **69** and α-hydroxyphosphonates **70.** [51] **(Scheme 5)**



R = Me, Et, i-Pr

Scheme 5

9) The reaction of 4-aminocoumarin-3-carboxaldehyde **71** with dialkyl phosphites leads to the corresponding phosphonates **72** while its reaction with trialkyl phosphites leads to the corresponding methylene phosphites **73**. Both reactions take place in absence of solvent at 100 °C and by addition on the aldehydic group.[52]



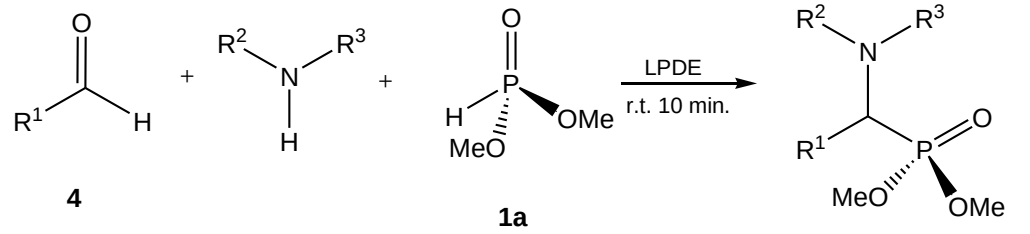
R = Me, Et, i-Pr

3- One Pot Three Component Reactions:

The one pot reactions of aldehydes with amines and alkyl phosphites by using a catalyst are considered as simple and efficient methods for preparation of α-amino-phosphonates under relatively mild conditions.[53]

1) α-Aminophosphonic acids and their diesters exhibit a wide range of biological activities. A general method for one pot α-aminoalkylation of aldehydes in a solution of lithium perchlorate/diethylether LPDE using dimethyl phosphite as a nucleophile, is reported. [54]

The α-aminophosphonates **75** were prepared by stirring a mixture of aldehydes **4**, amines e.g. diethyl and dibenzyl amines **74** and dimethyl phosphite **1a** in LPDE. Aliphatic aldehydes as well as aromatic aldehydes gave α-aminophosphonates in excellent yields.[54]



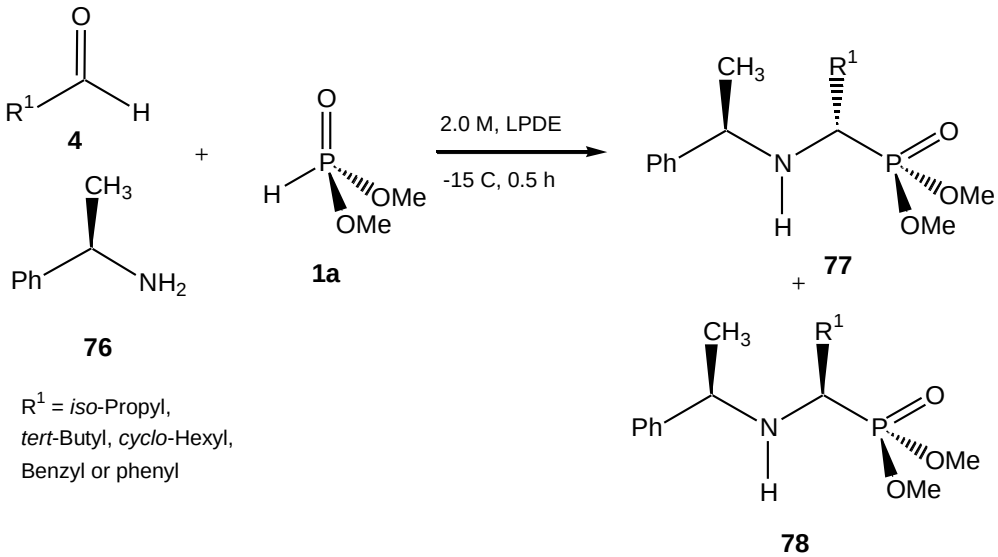
4 **1a**

R^1 = alkyl or aryl

74a, $R^2 = R^3$ = Ethyl
b, $R^2 = R^3$ = Benzyl

75a, $R^2 = R^3$ = Ethyl
b, $R^2 = R^3$ = Benzyl

One pot reaction of aliphatic aldehydes **4**, 1-phenylethylamine **76** and dimethyl phosphites **1a** afforded mixtures of diastereomers with one diastereomer predominating and purification by HPLC provided **77** and **78** in a useable scale. The configurations of the major and minor diastereomeric products were determined by ^{1}H-NMR spectra.[54]

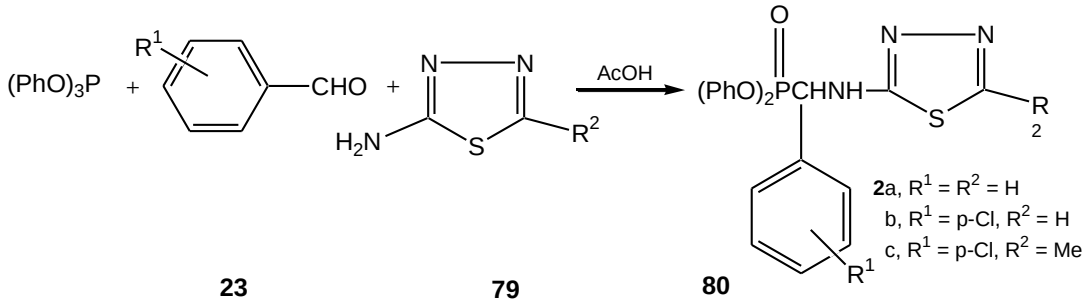


4 **76** **1a**

R^1 = *iso*-Propyl, *tert*-Butyl, *cyclo*-Hexyl, Benzyl or phenyl

77 **78**

2) Little attention has been paid to the synthesis of α-aminophosphonates bearing N-heterocycles such as 1,3,4-thiadiazole and oxadiazole derivatives for their fundamental significance as raw materials for medical and agricultural chemicals. However, a series of *O,O*-diphenyl-1-(5-alkyl-1,3,4-thiadiazol-2-yl)aminoarylmethyl-phosphonates **80** were synthesized by the three-component condensation reactions of 2-amino-5-alkyl-1,3,4-thiadiazoles **79** with triphenyl phosphite and aromatic aldehydes **23** in acetic acid.[55]

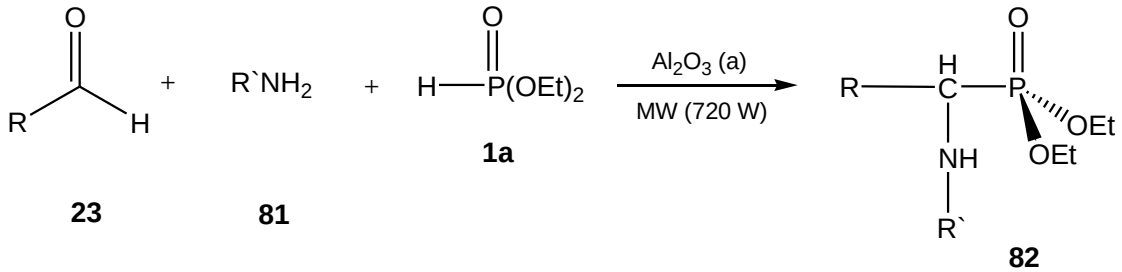


23 **79** **80**

3) α-Aminoalkyl phosphonates have received an increasing amount of attention since they are key substrates in the synthesis of phosphonopeptides.[56]

A simple, efficient and general method has been developed for the synthesis of α -aminoalkyl phosphonates through a one-pot reaction of aldehydes with amines in the presence of acidic alumina under solvent-free conditions using microwave irradiation.[56] The Kabachnik–Fields synthesis of α -aminoalkyl phosphonates, catalyzed by a base or an acid, is the most convenient. The key step in the Kabachnik–Fields synthesis of α -aminoalkyl phosphonates **82** is the nucleophilic addition of aniline and/or its derivatives **81** to aromatic aldehydes **23** followed by the addition of a dialkyl or diaryl phosphite to the resulting imine.[56]

.

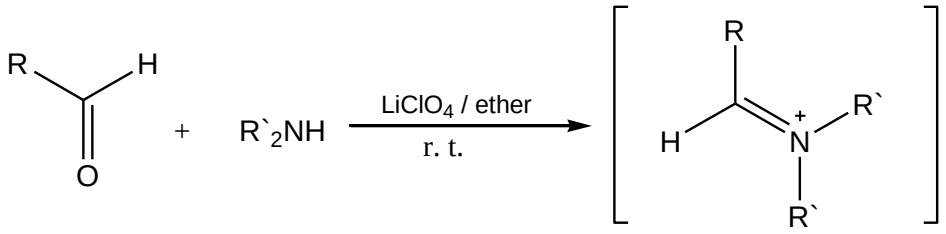


23 **81** **1a** **82**

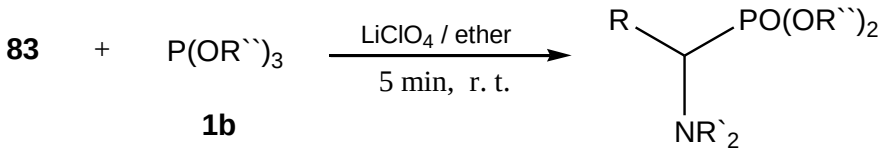
R = C_6H_5- , m-$NO_2C_6H_4$-, $HOCH_2CH_2$-
R` = C_6H_5-, p-$CH_3C_6H_4$-, p-$NO_2C_6H_4$-

A wide range of aldehydes and amines was converted into the corresponding 1-aminophosphonates using this reaction procedure.[56]

4) A very mild, efficient and simple method for the synthesis of tertiary α-amino-phosphonates in high yields is reported by reaction of an aldehyde, a secondary amine and a trialkyl phosphite in ethereal solution of lithium perchlorate/diethylether LPDE, at ambient temperature. A direct one pot synthesis of tertiary α-aminophosphonates **84** has been reported *via* the reaction of aromatic aldehydes **23** with amines **74** and trialkyl phosphites. It is a general method for the aminoalkylation of aldehydes with different nucleophiles. [57] **(Scheme 6)**

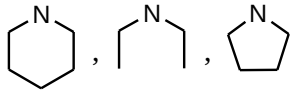


23 **74** **83**



1b **84**

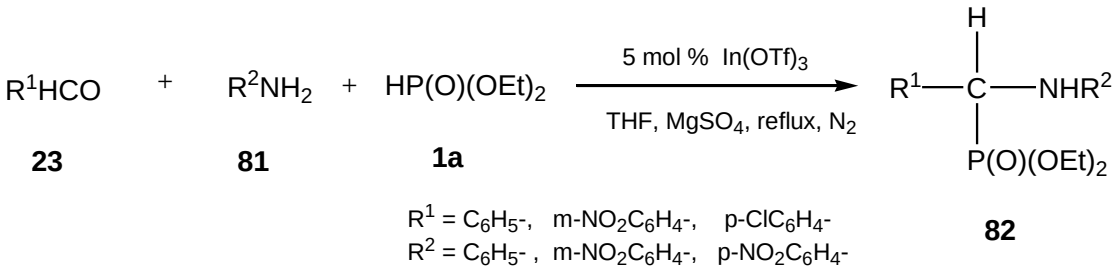
R =C_6H_5-, 2,4-$Cl_2C_6H_3$-, o-$MeOC_6H_4$-
R`` = Me or Et
R`$_2$N =



Scheme 6

5) A new efficient one-pot synthesis of α-aminophosphonates derived from nitro-substituted anilines, aldehydes and diethyl phosphite has been carried out by employing 5 mol % indium trifluoromethanesulfonate $In(OTf)_3$.[58] The method is equally effective for the generation of α-aminophosphonates from various carbonyl compounds and other amines. Thus, reaction of diethyl phosphite **1a** with *in situ* generated imines (from benzaldehyde or its derivatives **23** and aniline, *m*- or *p*-nitroaniline **81)** in refluxing THF using $MgSO_4$ as the internal desiccant in the

presence of a catalytic amount of $In(OTf)_3$ afforded the corresponding α-amino-phosphonates **82** in very good yields.[58]



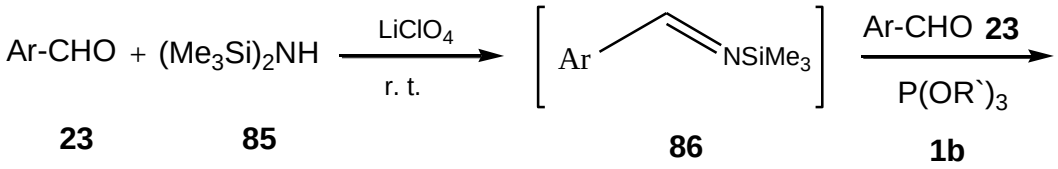
23 **81** **1a**

R^1 = C_6H_5-, m-$NO_2C_6H_4$-, p-ClC_6H_4-
R^2 = C_6H_5- , m-$NO_2C_6H_4$-, p-$NO_2C_6H_4$-

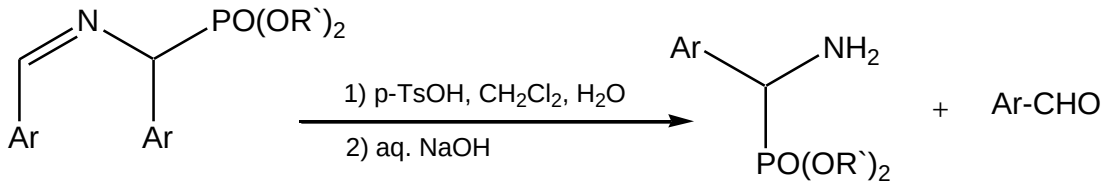
82

Aliphatic aldehydes require longer reaction times compared to those of their aromatic counterparts.[58]

6) A successful one pot three-component reaction of an aldehyde **23**, hexamethyl-disilazane (HMDS) **85** and a trialkyl phosphite **1b** is an attractive approach for the synthesis of primary α-aminophosphonates **88** under solvent-free conditions. The reaction proceeds *via* an imine as an intermediate. In the presence of trialkyl phosphite, the imine is converted to **87**, which gives α-aminophosphonate **88** after hydrolysis.[59] **(Scheme 7)**



23 **85** **86** **1b**



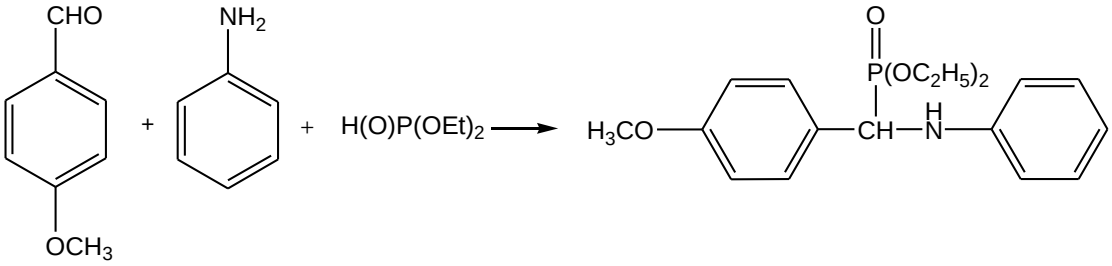
87

Ar = C_6H_5-, p-MeC_6H_4-, m-$NO_2C_6H_4$-, p-ClC_6H_4-,
R` = Me or Et

88

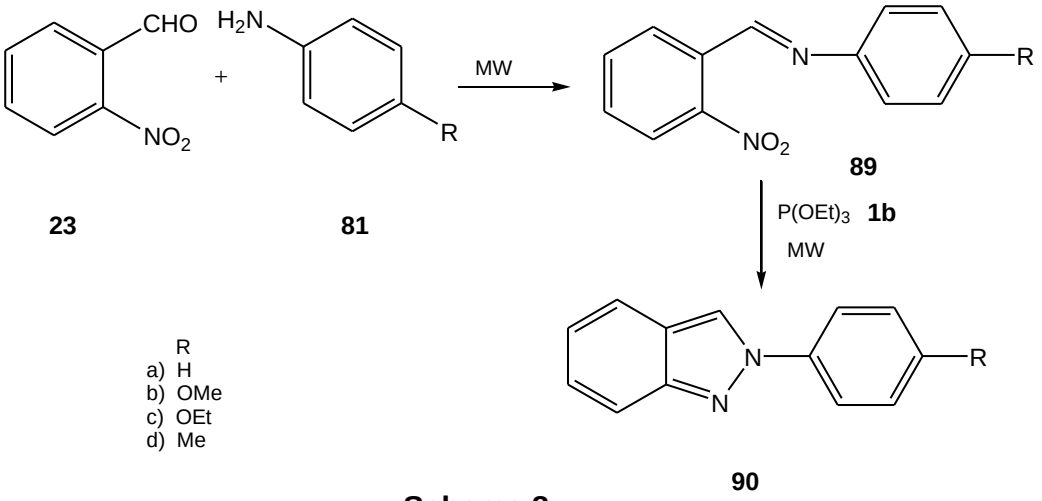
Scheme 7

7) A mixture of *p*-methoxybenzaldehyde **23**, aniline **81** and diethyl phosphite **1a** absorbed on silica gel was irradiated for 15 min giving the corresponding α-amino-phosphonate **82**.[60]



23 **81** **1a** **82**

8) The synthesis of 2-arylindazoles **90** occurs on two steps. The first step was the preparation of a Schiff base **89** from *o*-nitrobenzaldehyde **23** and aniline and/or its derivatives **81**. The second step was the reaction of the Schiff base with excess triethyl phosphite. These steps have been greatly shortened and improved by using microwave irradiation.[61] **(Scheme 8)**

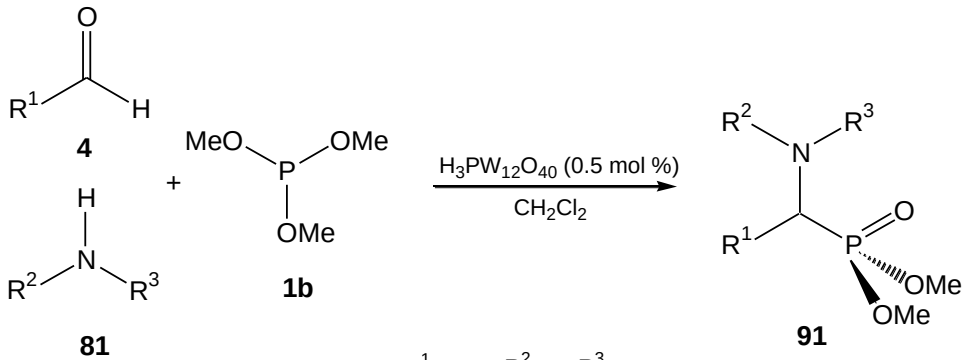


23 **81** **90**

Scheme 8

9) The nucleophilic addition reaction of phosphites with imines is one of the most convenient methods, which is usually promoted by bases, or Lewis acids like $SnCl_4$, $ZnCl_2$ and $MgBr_2$ for the synthesis of α-aminophosphonate derivatives.

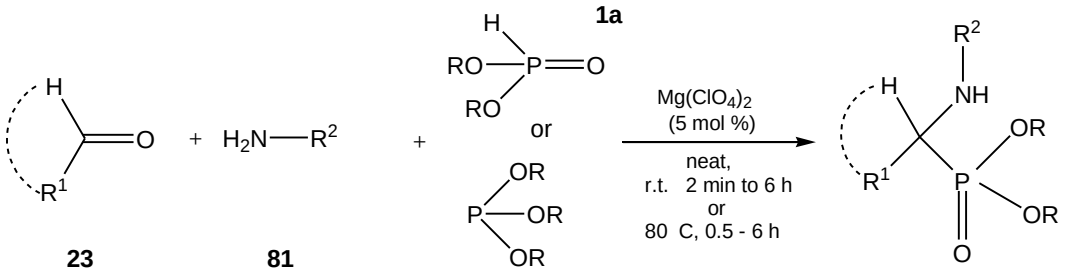
The reaction between trimethyl phosphite and *in situ* generated imine (from benzaldehyde , aniline and their derivatives **23, 81**) in DCM (dichloromethane) in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ (0.5 mol%) gives the desired amino-phosphonates **91**.[62]



	R^1	R^2	R^3
a	*tert*-Butyl	H	Phenyl
b	*n*-Pentyl	H	Phenyl
c	4-Pyridyl	H	Phenyl
d	Phenyl	H	Benzyl

Not only benzaldehyde but also electron deficient aromatic aldehydes react with aromatic as well as aliphatic amines and phosphites to give the corresponding α-aminophosphonates in high yields.[62]

10) A three-component reaction of an amine **81**, an aldehyde **23** and a di-/trialkyl phosphite (Kabachnik-Fields reaction) takes place in one pot under solvent-free conditions to afford the corresponding α-aminophosphonates **82** in high yields and short times. Magnesium perchlorate is reported as an extremely efficient catalyst for the synthesis of α-aminophosphonates.[63] The α-aminophosphonate moiety is a versatile and promising pharmacophore due to the broad spectrum of biological activity exhibited by compounds bearing this structural unit. [63]



R = Me, Et

$R^1 = R^2 = C_6H_5$- , p-$MeOC_6H_4$- , p-$NO_2C_6H_4$- , p-ClC_6H_4-

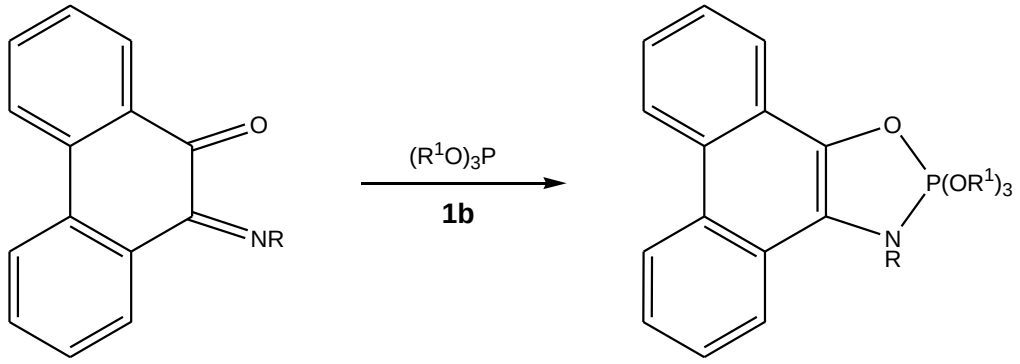
The formation of α-aminophosphonate from the reaction of an aldehyde, an amine and a phosphite involves thus a two-step process:

i) The nucleophilic addition of the amine to the carbonyl group forming an imine.

ii) The nuceophilic addition of the phosphite to the imine.[63]

4- Reaction of Di- and Trialkyl Phosphites with Imines:

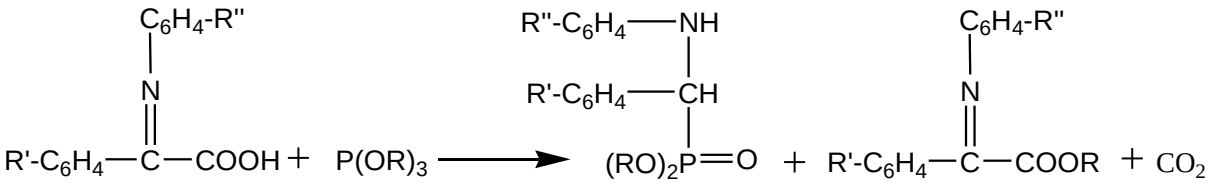
1) Addition reaction of trialkyl phosphites on phenanthrenequinone monoimine **92** in boiling benzene, results in the formation of oxazaphosphole adducts **93**. Pyrolysis of **93** regenerates the starting quinone monoimine .[64]



92 **93**

R = H, R^1 = Me, Et, i-Pr

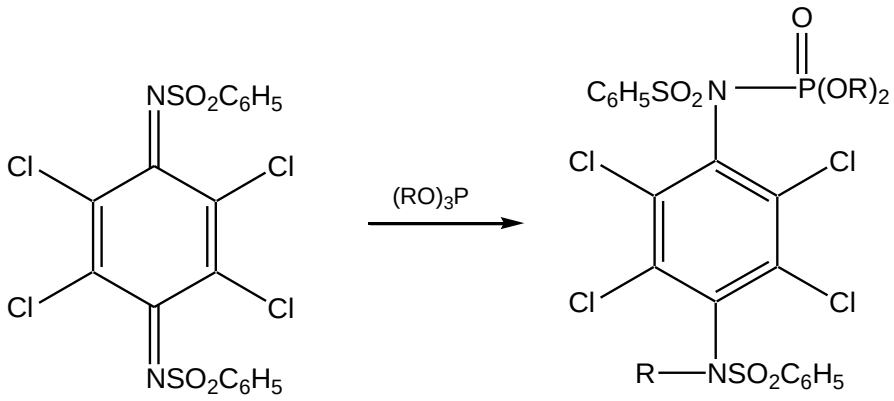
3) Reaction of trialkyl phosphites with N-phenylbenzimidoyl formic acid **94** gives phosphonates **82**. These phosphite esters also, cause alkylation of acid **94** to give the respective esters.[65]



94 **82**

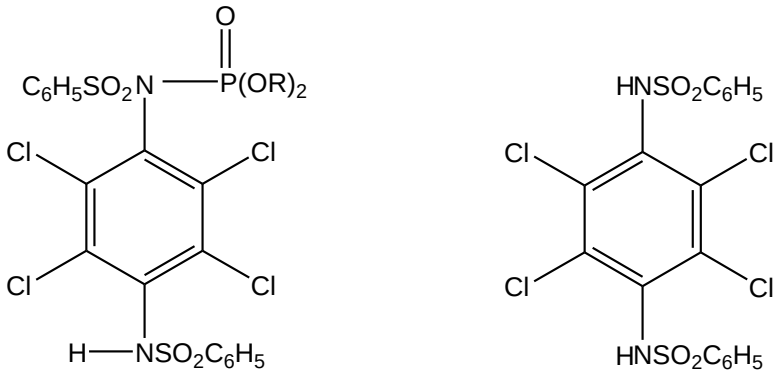
R = Me or Et
R' = R'' = H

3) Tetrachloro-p-quinone dibenzenesulfonimide **95** reacts with trimethyl or triethyl phosphite at room temperature in dry aprotic solvents e.g dioxane, benzene, acetonitrile or dimethylformamide to give the corresponding 1:1 adducts **96**. [66]



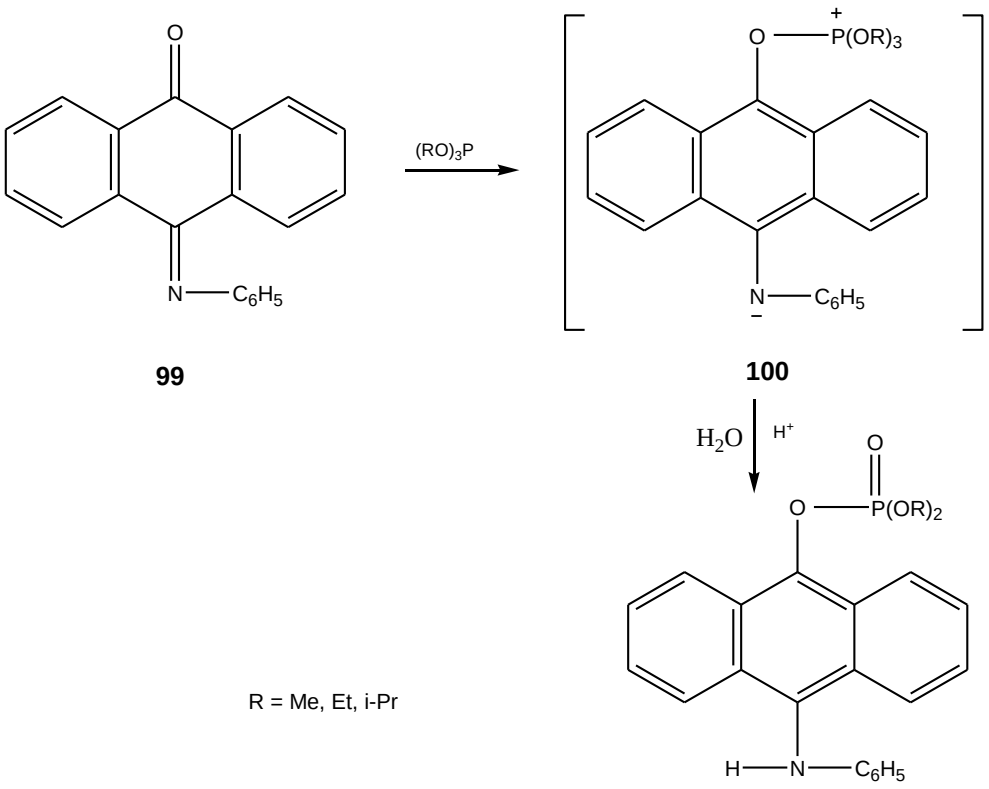
95 R = Me or Et **96**

When the reaction was carried out in dioxane-water or benzene-water mixture, **97** and **98** were isolated together with the main product **96**. On the other hand, in protic solvents such as acetic acid or ethanol, compound **98** represented the sole reaction product.[66]



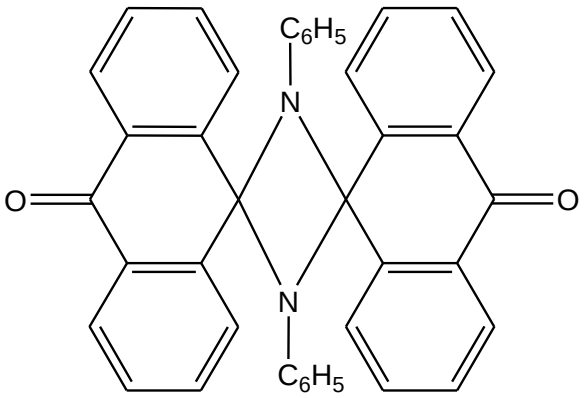
97 R = Me or Et **98**

4) The reaction of anthraquinonemonoanil **99** with trialkyl phosphites in presence of acetic acid (or in dry benzene to which controlled amounts of water are added) proceeds with formation of the corresponding, dialkyl (10-anilino-9-anthryl) phosphates **101**.[67,68] **(Scheme 9)**



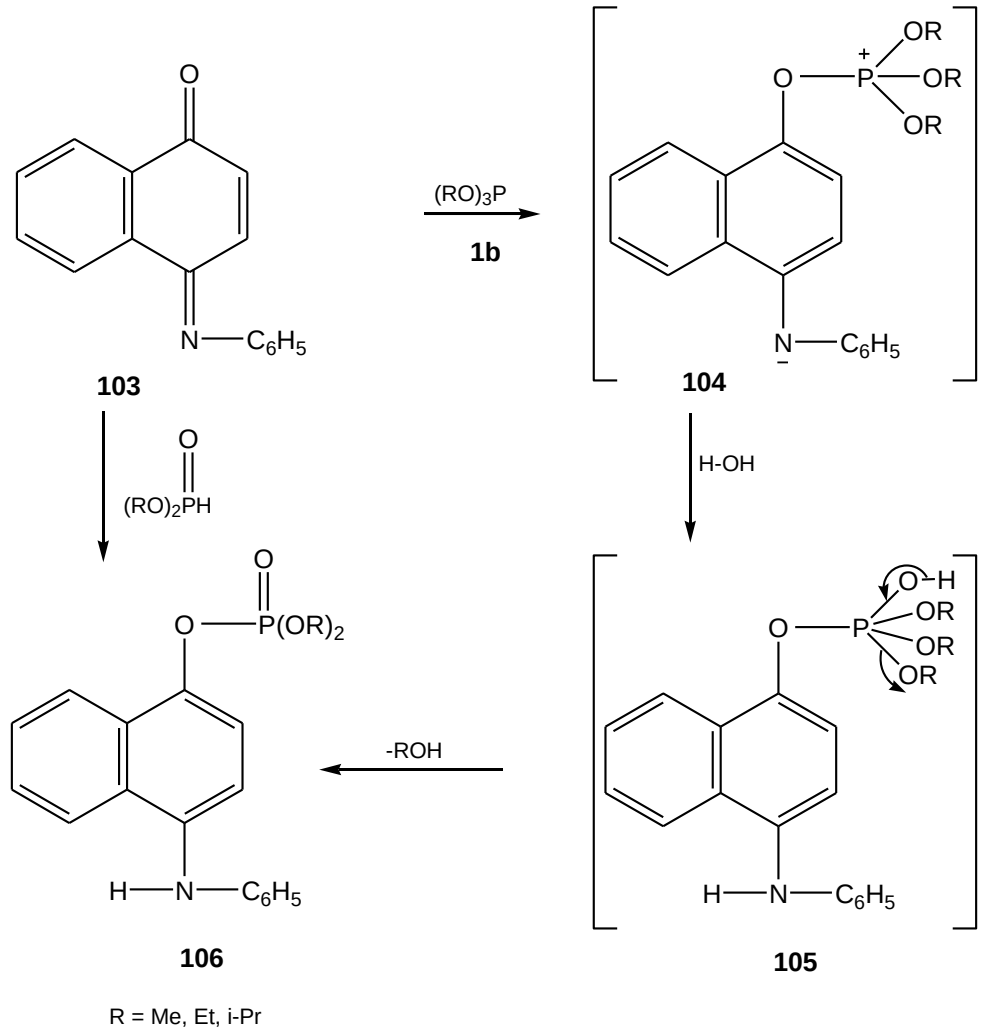
Scheme 9

The same phosphates were obtained by heating anil **99** with dimethyl-, diethyl- and/or diisopropyl phosphites, respectively at 100°C in the presence of a base (piperidine). When the latter reaction was done in absence of a base, a dimeric substance devoid of phosphorus (**102)** was isolated.[68]



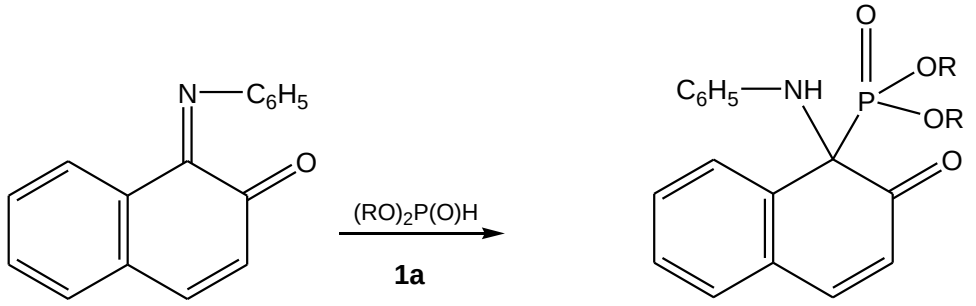
102

5) The reaction of *p*-naphthoquinonemonoanil **103** with alkyl phosphites gives the dialkyl (4-anilino-1-naphthyl) phosphate products **106**.[68]



R = Me, Et, i-Pr

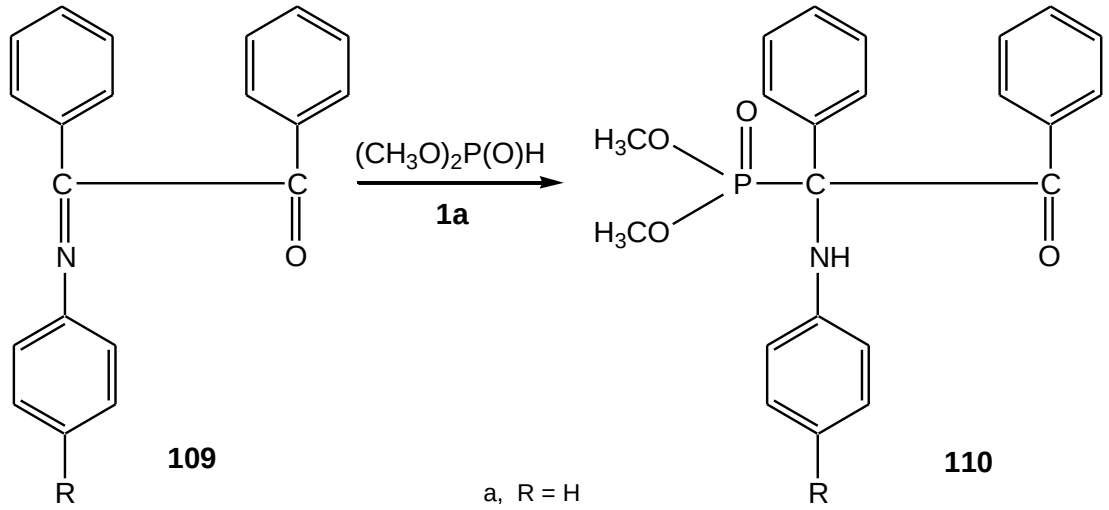
6) The reaction of *o*-naphthoquinonemonoanil **107** with dimethyl or diethyl phosphite produces crystalline 1:1 adducts formulated as dialkyl (1-anilino-1,2-dihydro-2-oxo-1-naphthyl) phosphonates **108**.[69]



107

108 a, R = Me
b, R = Et

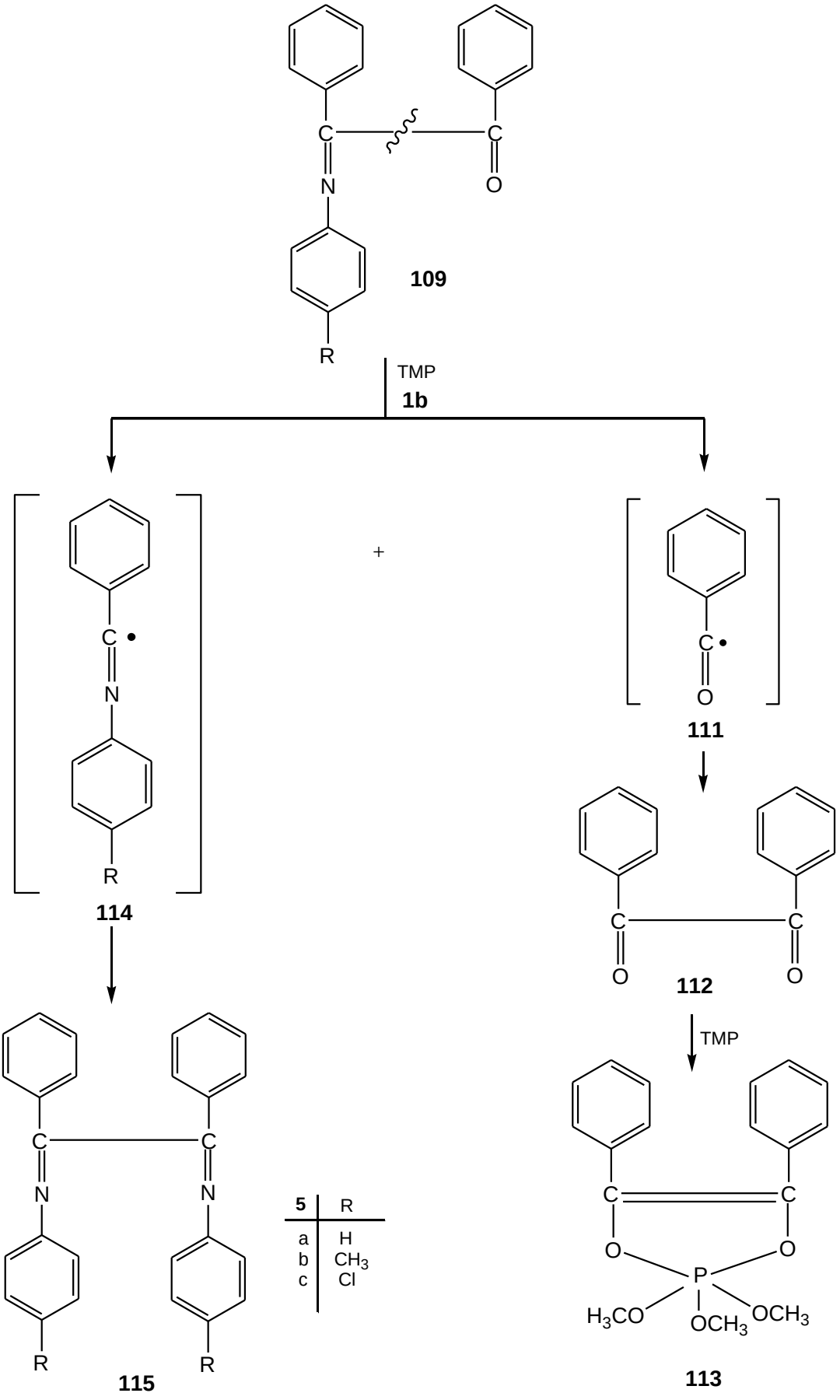
7) Benzil monoanils **109** react with dimethyl phosphite to give 1:1 adducts formulated as dimethyl(α-arylamino-α-phenylphenacyl) phosphonates **110**.[69]



109 **110**

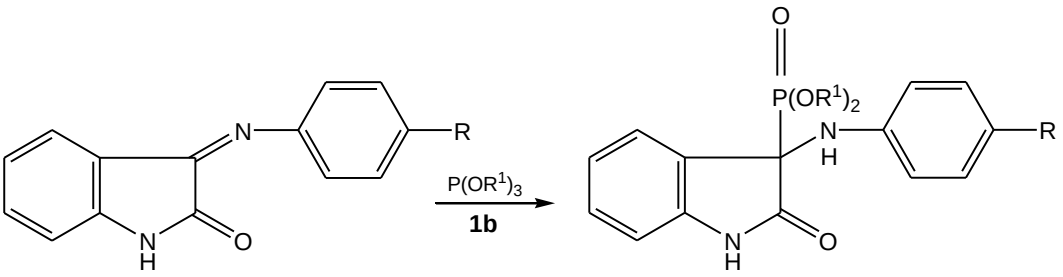
a, R = H
b, R = CH_3
c, R = Cl

Trimethyl phosphite reacts with benzil monoanils **109a-c** in dry benzene to give the respective dianils **115a-c** together with 4,5-diphenyl-2,2,2-trimethoxy-l,3,2,dioxa-phospholene **113** in each reaction.[70] **(Scheme10)**



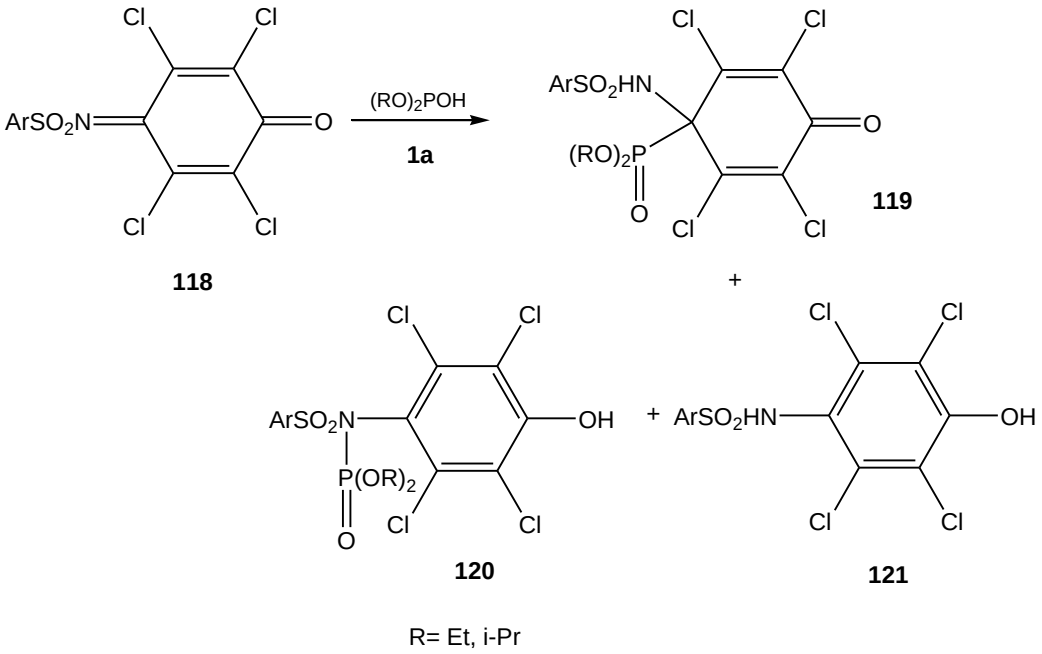
Scheme 10

8) Iminoxindoles **116** react with trialkyl phosphites, in the presence of water or acetic acid to give indolylphosphonates **117**.[71]



116 R = H, Cl, Me; R^1 =Me, Et, i-Pr **117**

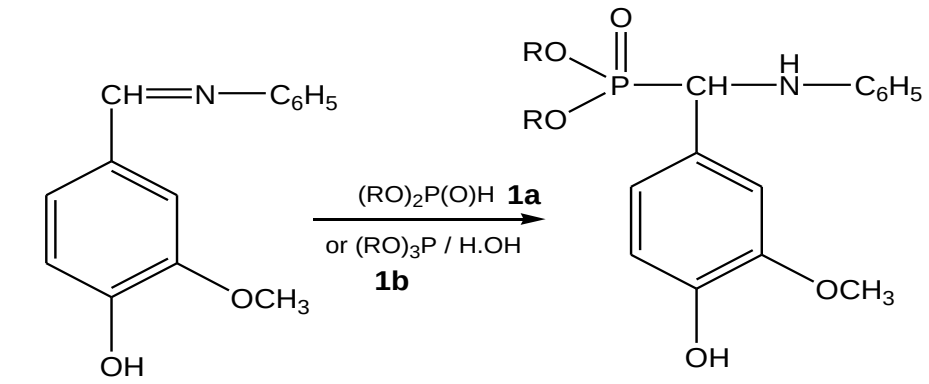
9) Reaction of arylsulfonyl benzoquinonemonoimines **118** with dialkyl phosphites (R= Et, i-Pr) gives quinolides **119** (Ar= 4-MeC_6H_4-), **120** (Ar=C_6H_5-, 4-MeC_6H_4-) , alongwith **121** (Ar= C_6H_5-, 4-MeC_6H_4-).[72]



R= Et, i-Pr

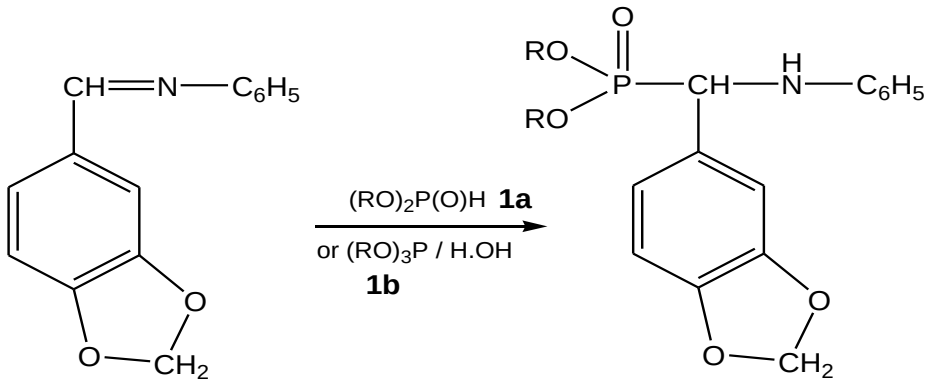
10) Reactions of vanillin-anil (4-hydroxy-3-methoxybenzylideneaniline) **122** and piperonal-anil (3,4-methylenedioxybenzylideneaniline) **124** with trimethyl or triethyl phosphite proceed only when a few drops of water are introduced in the reaction medium and give the corresponding phosphonates **123** ,**125**.[73]

The same phosphonate products are equally produced upon reacting anils **122** and **124** with dimethyl or diethyl phosphite, respectively.[73]



122

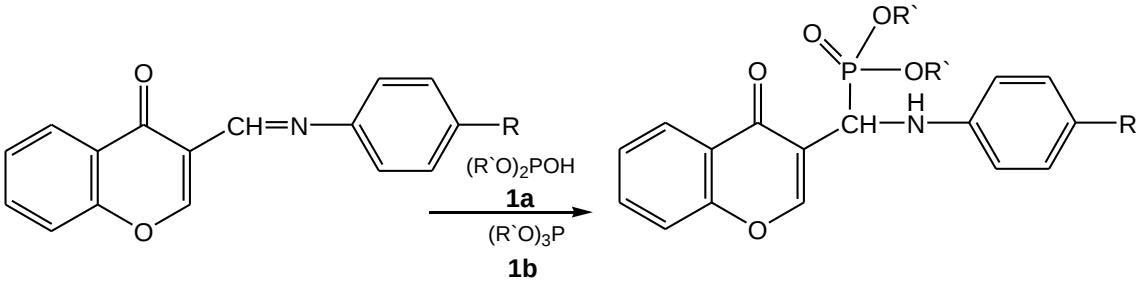
123 a, R = Me
b, R =Et



124

125 a, R = Me
b, R = Et

11) 3-(Aryliminomethyl)chromones **126** produce the respective phosphonates **127** upon reaction with the appropriate dialkyl phosphite and/or trialkyl phosphite.[74]

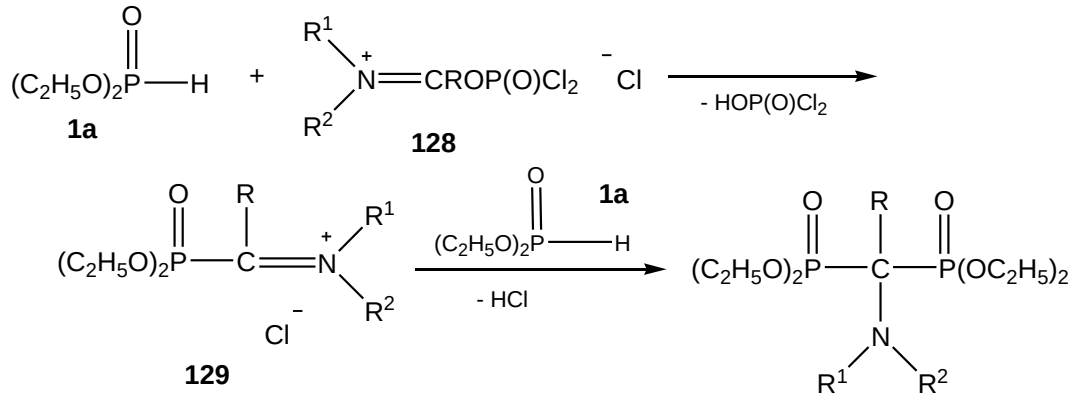


126

R = Cl, OMe
R`= Me, Et, i-Pr

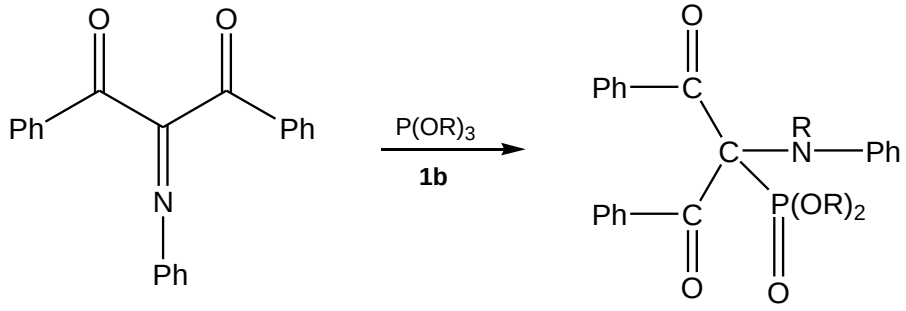
127

12) Reaction of diethyl phosphite with Vilsmeier reagents $RCONR^1R^2/POCl_3$ **128**, afford various alkyl(aminosubstituted)methylenediphosphonates **130** which are important as pesticidal phosphonates.[75]



R = C_2H_5, C_6H_5
$R^1 + R^2 = (CH_2)_5$, $(CH_2\text{-}CH_2)$

13) Trialkyl phosphites react with 1,3-diphenyl-2-(phenylimino)-1,3-propanedione **131** to give the respective phosphonate products **132**.[76]

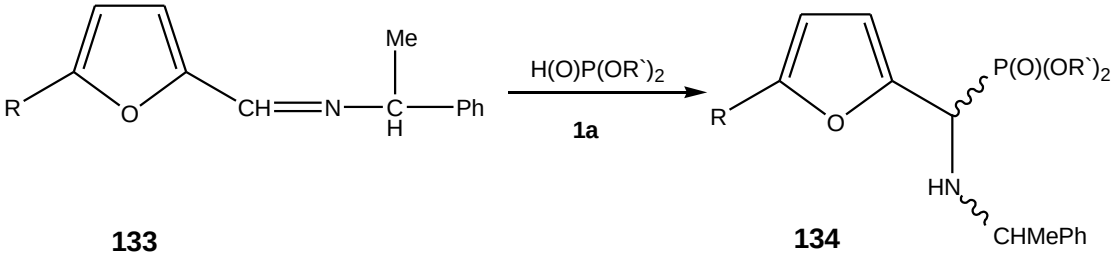


131

132

R = Me, Et, i-Pr

14) The reaction of N-furfurylidene α-methylbenzylamine **133** with dialkyl phosphites results in the formation of diastereomeric pairs of dialkyl (2-furyl)-N-(methyl)benzyl-aminophosphonates **134**.[77]

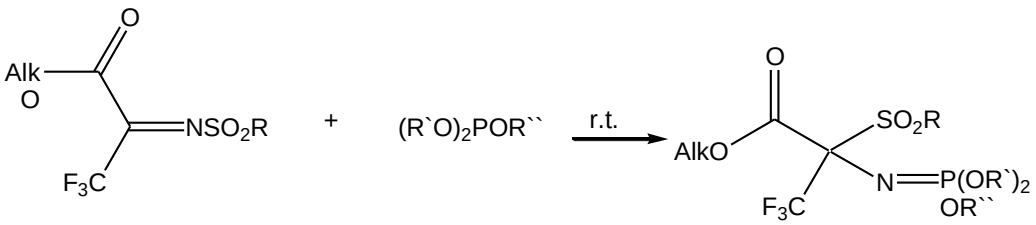


133

134

R = H, CH_2OH
R` = C_2H_5, CH_2Ph

15) The interaction of sulfonylimine **135a** with triisopropyl phosphite **1b** results in the formation of iminophosphorane **136a**.[78]

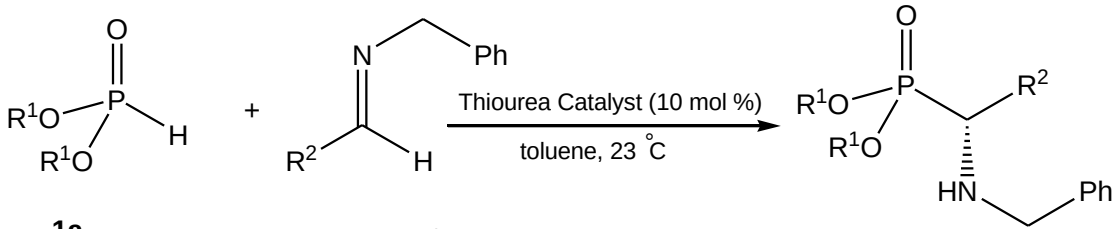


135 **1b** **136**a-f

	R	R` = R``	Alk
a	4-$MeOC_6H_4$-	i-Pr	Me
b	4-$MeOC_6H_4$-	Et	Me
c	4-MeC_6H_4-	Et	Me
d	4-ClC_6H_4-	Et	Me
e	4-MeC_6H_4-	Ph	Me
f	4-ClC_6H_4-	Ph	Me

The reaction of imines **135e**,**f** with the less nucleophilic triphenyl phosphite $(PhO)_3P$ proceeds much more slowly.[78]

16) Chiral ureas and thioureas have recently emerged as highly enantioselective catalysts for the addition of carbon nucleophiles to active π-systems. Experimets with phosphorus-based nucleophiles revealed that the thiourea catalyst promotes the addition of dialkyl phosphite **1a** to aryl imine **137** in an enantioselective but poor reaction rate.[79]



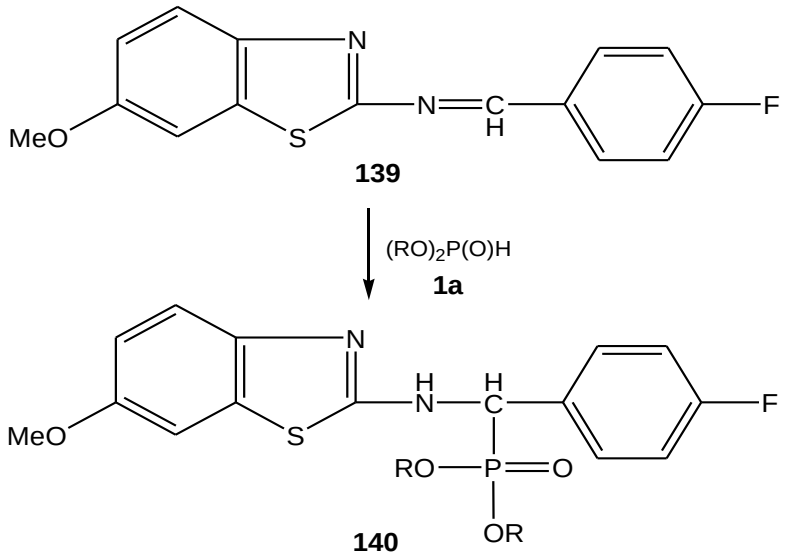
1a

137a, R^2 = Ph
b, R^2 = 3-pentyl

138

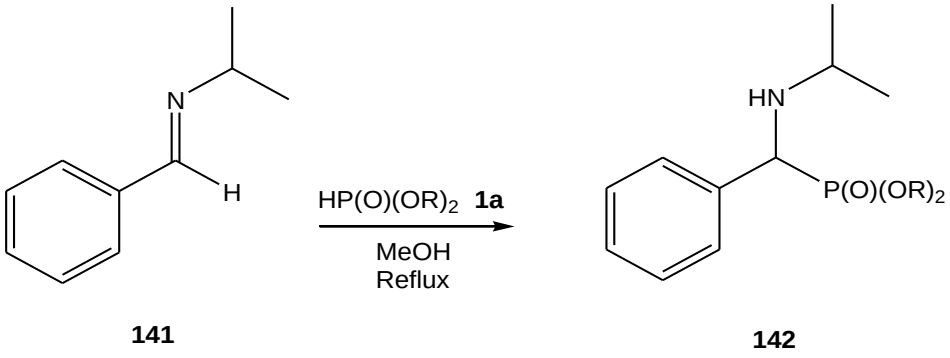
R^1= Me, Ph, *o*-$NO_2C_6H_4$ -

17) Some novel *O,O*-dialkyl-α-(6-methoxybenzothiazol-2-ylamino)-4-fluorophenyl-phosphonates **140** have been synthesized through the reaction of Schiff base **139** with dialkyl phosphites **1a**.[80]



R = CH_3, C_2H_5, C_3H_7, C_3H_7-i, C_4H_9, C_4H_9-i

18) The synthesis of α-aminophosphonates **142** has been recently adjusted for use in microreactor systems. The reaction of imine **141** with dialkyl phosphites in different solvents was optimized, to give the final products.[81]

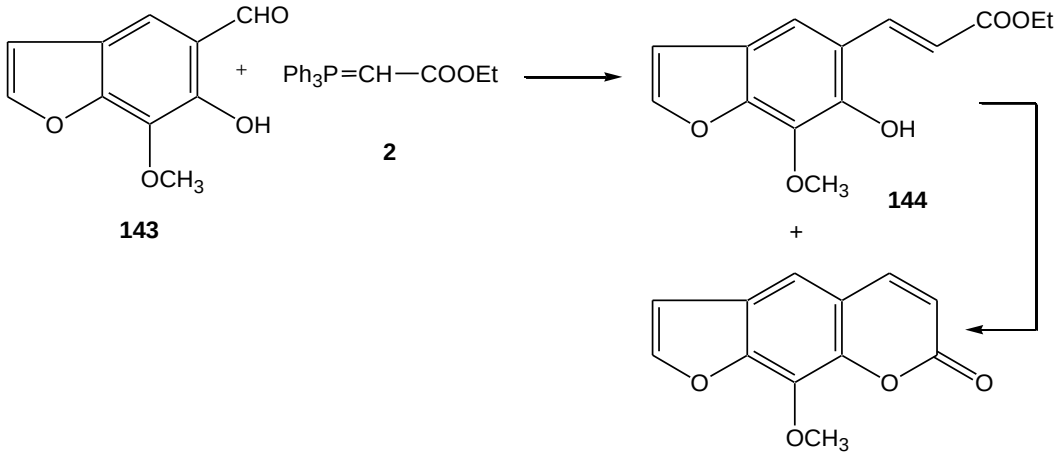


R =Me, Et, i-Pr

II- Reactions of Wittig Reagents with Aldehydes and Imines :

1- Reaction of Wittig Reagents with Aldehydes:

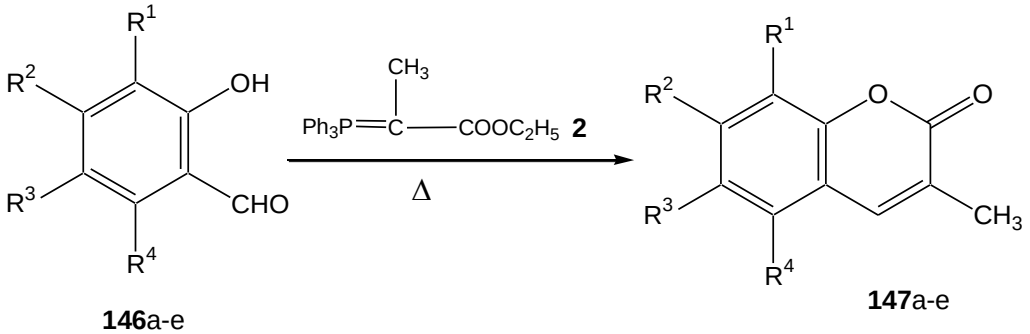
1) The reaction of 6-hydroxy-7-methoxybenzofuran-5-carboxaldehyde **143** with carbethoxymethylenetriphenylphosphorane **2** provides the *E* ester **144** and methoxsalen **145**. The Wittig reaction requires two equivalents of the phosphorane to complete the reaction .[82] **(Scheme 11)**



143

Scheme 11

2) The synthesis of 3-methylcoumarins **147** involves condensation of *o*-hydroxybenzaldehydes **146a-e** with triphenyl-α-ethoxycarbonylpropylidenephosphorane **2**. Using this method, several 3-methylcoumarins and 3-methylbenzocoumarins have been synthesized.[83] 2-Hydroxy-3-methoxybenzaldehyde **146b** gives the uncyclized ester **148b** which is cyclized to coumarin **147b**. 2-Hydroxy-3-naphthaldehyde **146e** gives the uncyclized ester **149** alongwith the coumarin **147e**. Ester **149** undergoes ready cyclization to **147e** on exposure to sunlight in benzene solution.[83]



146a-e

147a-e

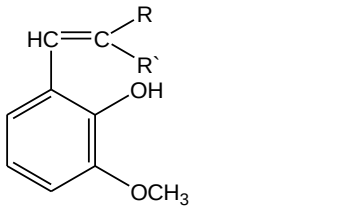
a, $R^1 = R^2 = R^3 = R^4 = H$

b, $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$

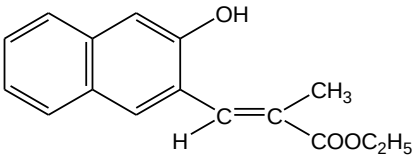
c, $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$

d, $R^1 = R^4 = H$ $R^2 = OCH3$, $R^3 = CH_3$

e, $R^1 = R^4 = H$ $R^2 + R^3 = (\bar{C}H=CH-CH=CH-)$

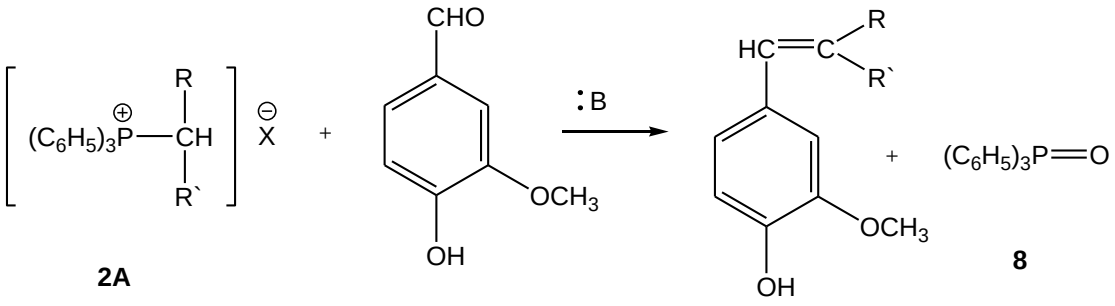


148a, R = H, R` = CH_2—CH═CH_2
b, R = CH_3; R` = $COOC_2H_5$
c, R = $COOC_2H_5$; R` = CH_2—CH═CH_2



149

3) The carbonyl group in vanillin **150** interacts with a variety of alkyltriphenyl-phosphonium halides (Wittig reagents) **2A** to give the respective α-alkyl styrene derivatives **151a-c** and triphenylphosphine oxide **8**.[84-88]



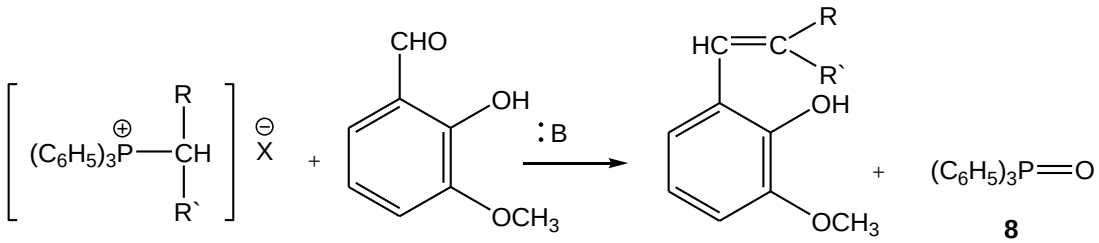
2A

150

151a, R = H, R` = n-C_3H_7
b, R = R` = CH_3
c, R = H; R` = $COOCH_2$—C(=CH_2)—CH_3

8

Similarly, α-substituted- **148a** and α,α-disubstituted- **148b,c** styrenes are prepared by reacting *ortho* vanillin **146** with the appropriate Wittig reagent.[83, 89]



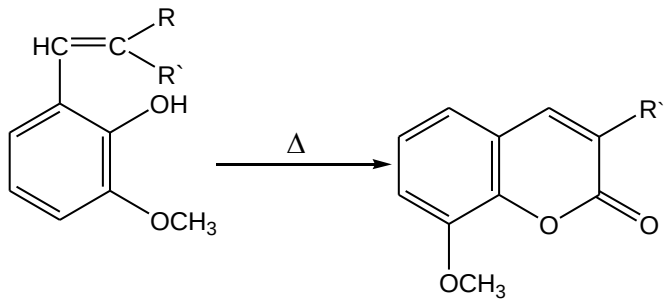
2A

146b

148a, R = H, R` = CH_2—CH═CH_2
b, R = CH_3; R` = $COOC_2H_5$
c, R = $COOC_2H_5$; R` = CH_2—CH═CH_2

8

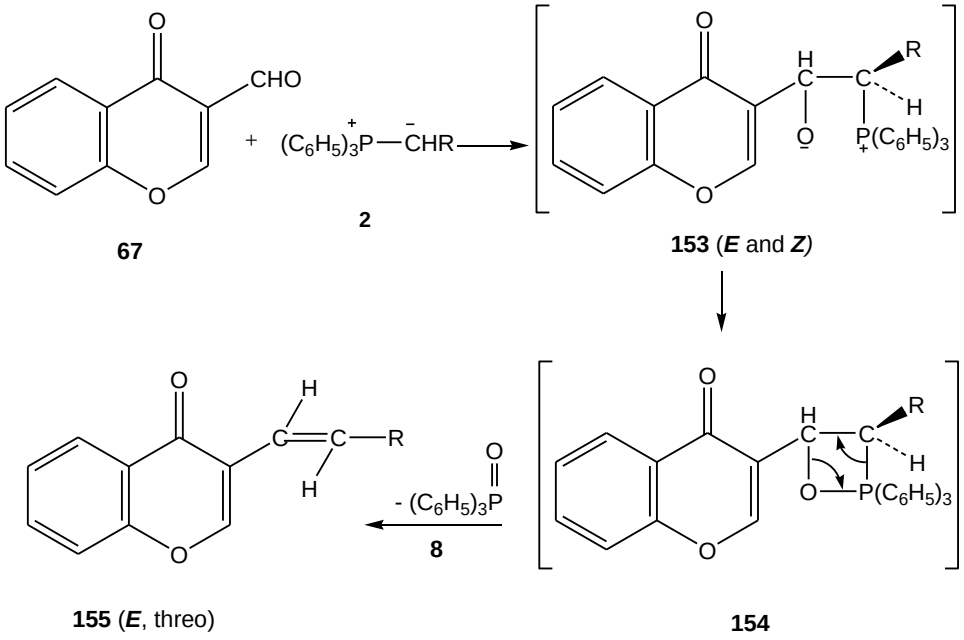
Cyclization of compounds **148b,c** *via* removal of ethanol represents a convenient approach for producing substituted coumarins, namely 3-methyl-8-methoxycoumarin **152b** [88] and 3-allyl-8-methoxycoumarin **152c**, respectively.[89]



148 b, R = $COOC_2H_5$ R` = CH_3
c, R = $COOC_2H_5$; R` = CH_2—CH═CH_2

152 b, R` = CH_3
c, R` = CH_2—CH═CH_2

4) The reaction of chromone-3-carboxaldehyde **67** with ylidenetriphenylphosphoranes **2** proceeds according to the Wittig reaction mechanism to give the respective ethylenes **155** .[51] **(Scheme 12)**



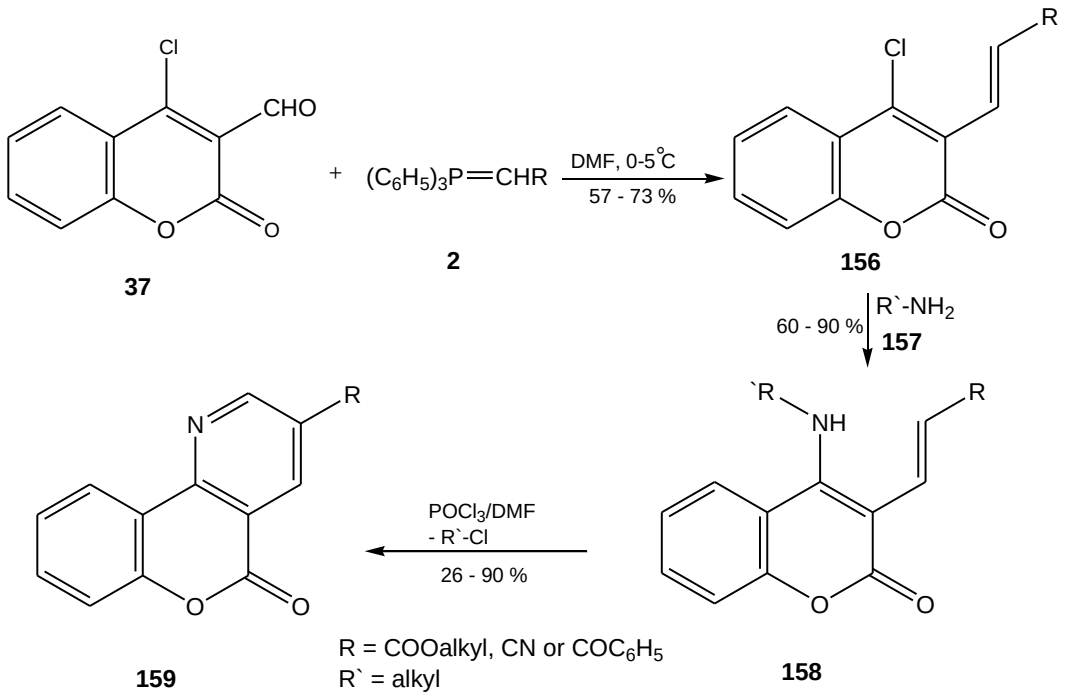
67 **2** **153** (***E*** and ***Z***)

155 (***E***, threo) **154**

R= $COOCH_3$, $COOC_2H_5$, COC_6H_5

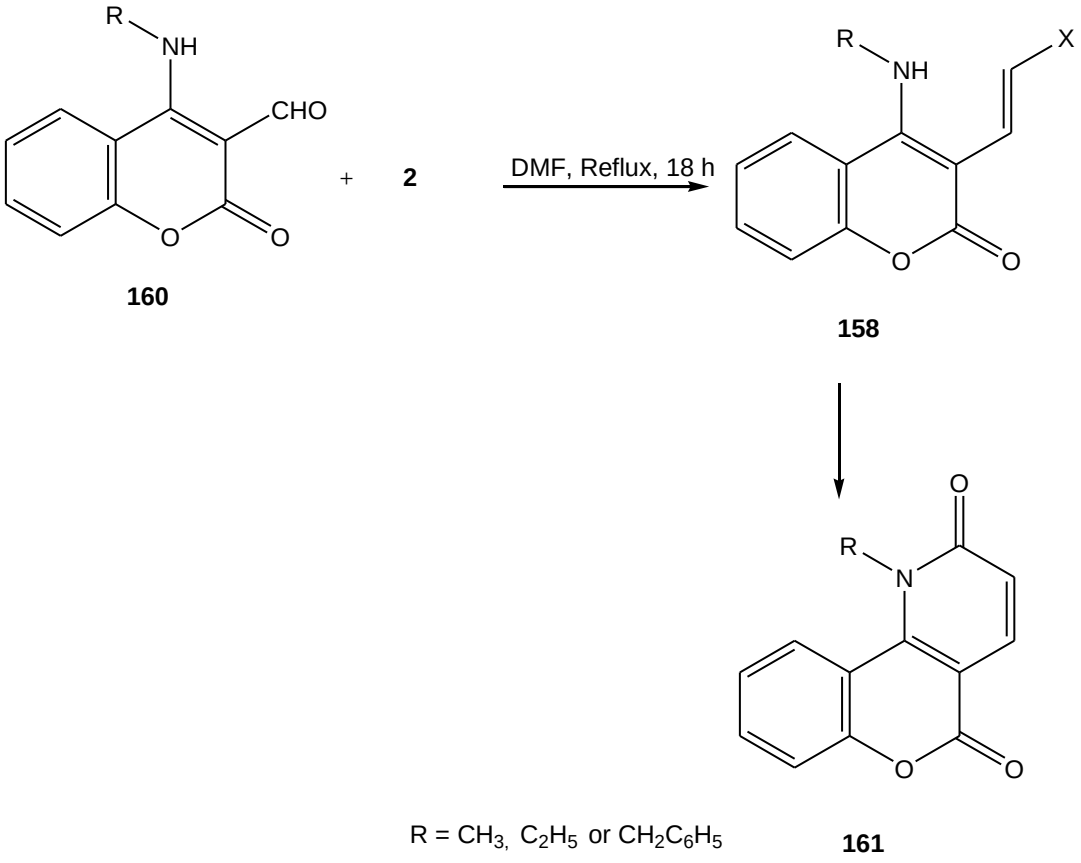
Scheme 12

5) Starting from 4-chlorocoumarin-3-carboxaldehyde **37** and ylidenetriphenyl-phosphoranes **2** the 3-substituted[1]benzopyrano[3,4-*b*]pyridine-5-ones **159** are synthesized *via* a three-step sequence. The intermediate 4-alkylamino-3-vinylcoumarins **158** are prepared by the reaction of 4-chloro-3-vinylcoumarins **156** with primary aliphatic amines **157**. The coumarin derivatives **158** undergo unusual pyridine ring closure under Vilsmeier conditions to form the benzopyrano[4,3-*b*]pyridines **159**. [90] **(Scheme 13)**



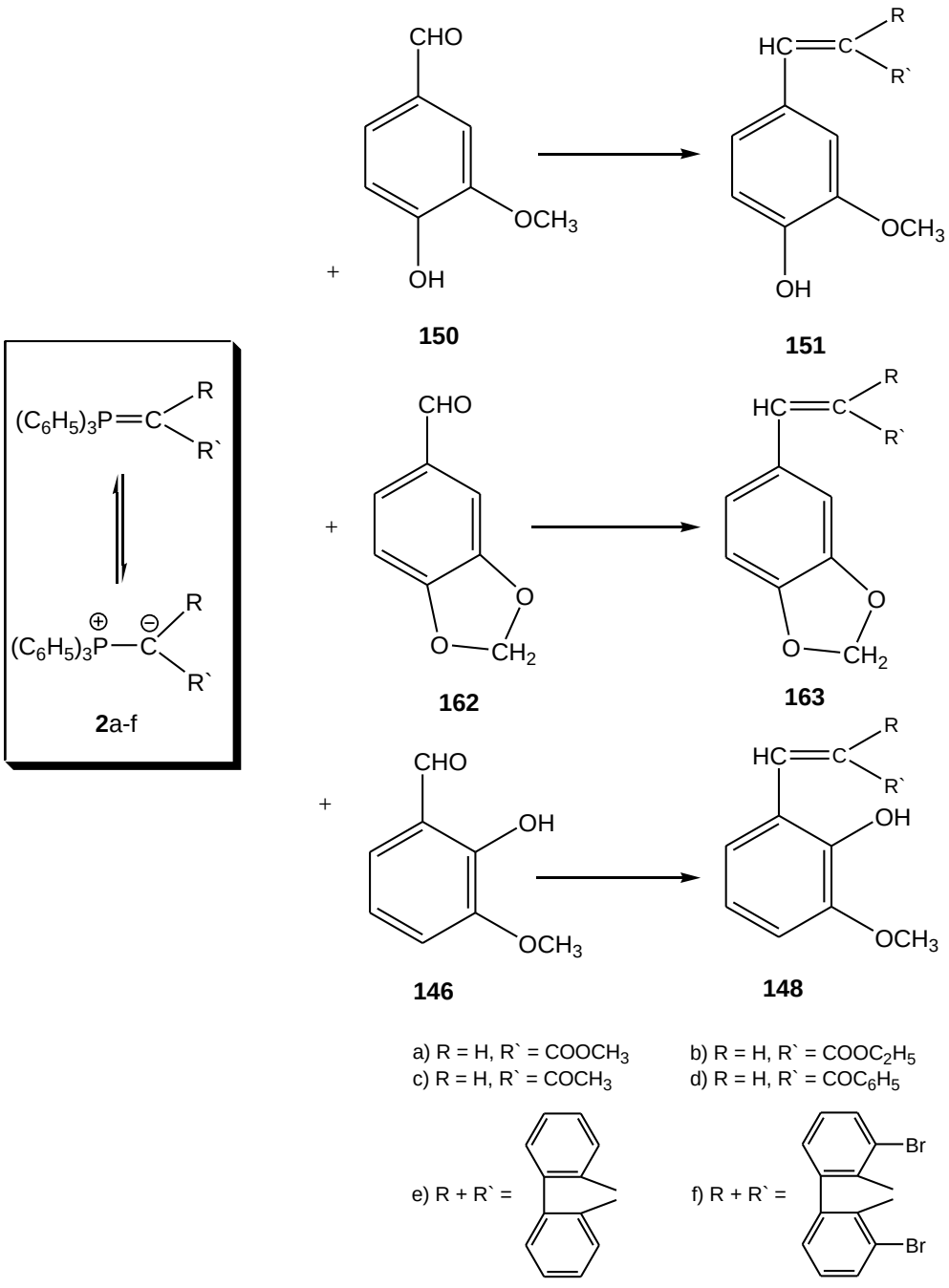
Scheme 13

When the α-aminoaldehydes **160** were treated with Wittig reagents **2** the fused *N*-alkyl-2-(1H)-pyridinones **161** could be obtained.[90] **(Scheme 14)**

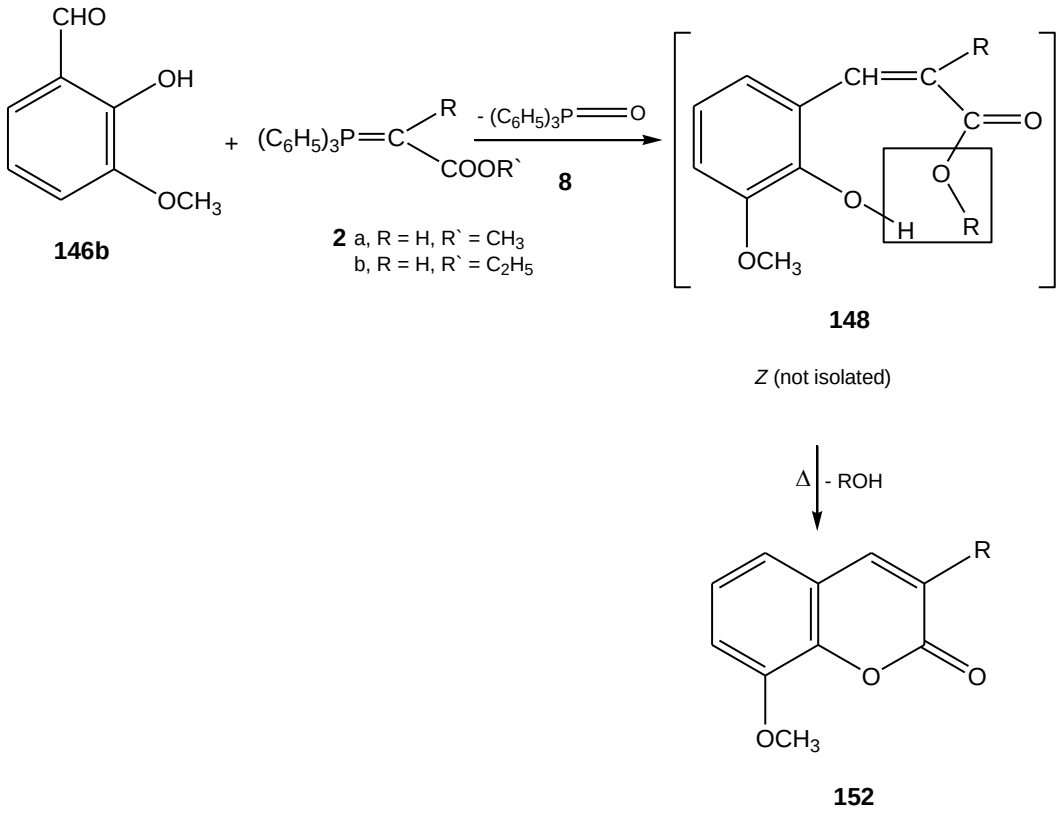


Scheme 14

6) Vanillin **150** and piperonal **162** react with ylidenetriphenylphosphoranes **2a-f** in boiling toluene following the Wittig mechanism to give ethylenes **151a-f** and **163a-f** respectively. Similarly, ethylenes **148c-f** were produced when *ortho*-vanillin **146b** was allowed to react with **2c-f**. The reaction of aldehyde **146** with the P-ylides **2a,b** yielded the Wittig products **148a,b** and 8-methoxycoumarin **152**. Triphenylphosphine oxide (TPPO) **8** was isolated and identified in all cases.[91] **(Schemes 15, 16)**

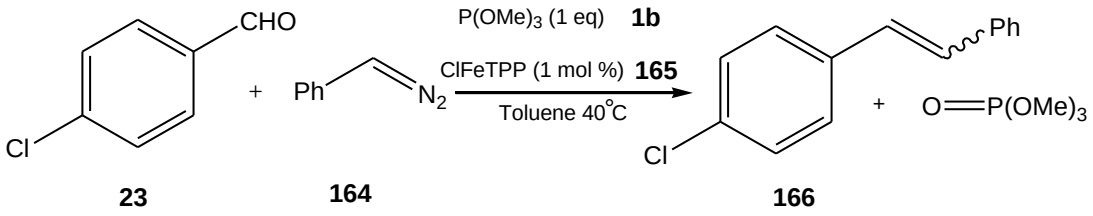


Scheme 15

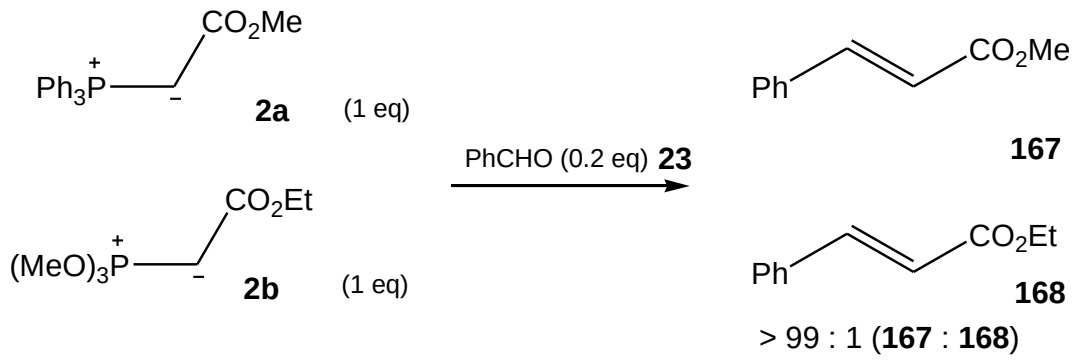


Scheme 16

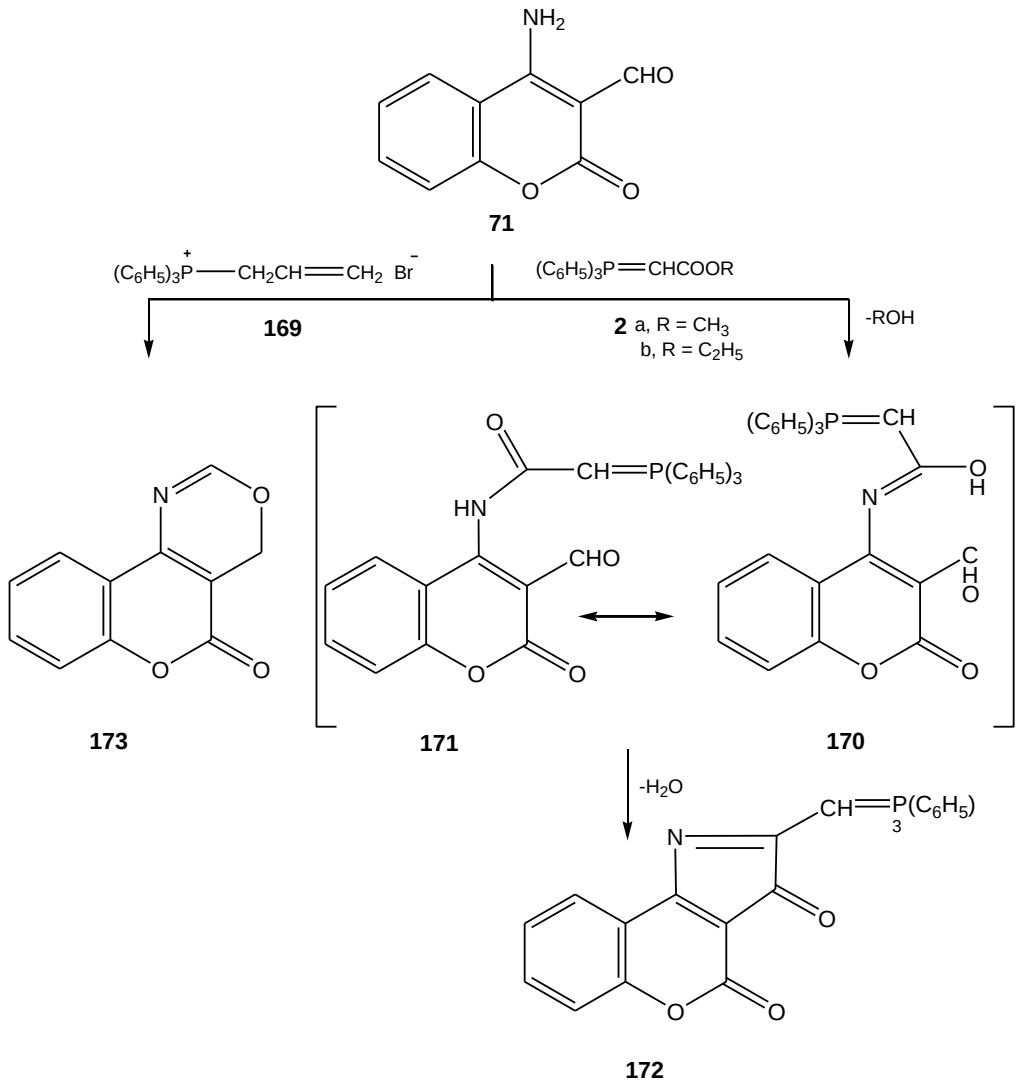
7) Slow addition of phenyldiazomethane **164** to a toluene solution of $(MeO)_3P$ **1b**, *p*-chlorobenzaldehyde **23** and catalytic amounts of *meso*-tetraphenylporphyrin iron chloride (ClFeTPP) **165** resulted in the formation of the corresponding alkenes **166** with an *E/Z* selectivity. The alkenes formed from the non-stabilized phosphoranes were predominantly *Z*, while the alkene from the stabilized phosphorane was *E*.[92,93]



Ylide **2b** is substantially less hindered than ylide **2a** and on the basis of steric effects, would be expected to be the more reactive. To test the differences in reactivity, a competition experiment between the stabilized ylides **2a** and **2b** was conducted. This experiment only gave olefin **167**, indicating that the more hindered ylide **2a** is substantially more reactive than the alkoxy-substituted ylide **2b**. There is a very significant electronic effect resulting in stabilization of the alkoxy-substituted ylide. [92, 93]

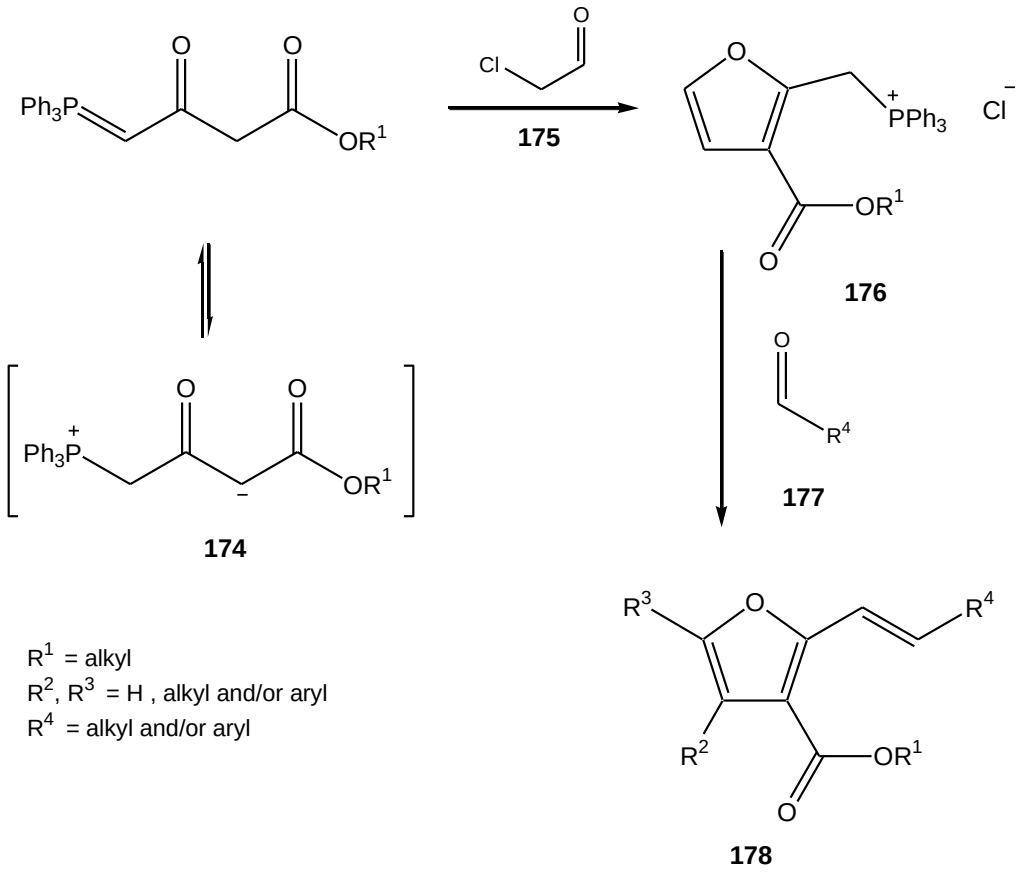


8) The reaction of 4-aminocoumarin-3-carboxaldehyde **71** with different types of phosphorus ylides such as stabilized carbmethoxy- **2a** (or carbethoxytriphenylphosphorane **2b**) led to the formation of phosphoranylidene **172** while reaction of the same compound with allyltriphenylphosphonium bromide **169** led to the cyclized product **173**.[52] **(Scheme 17)**



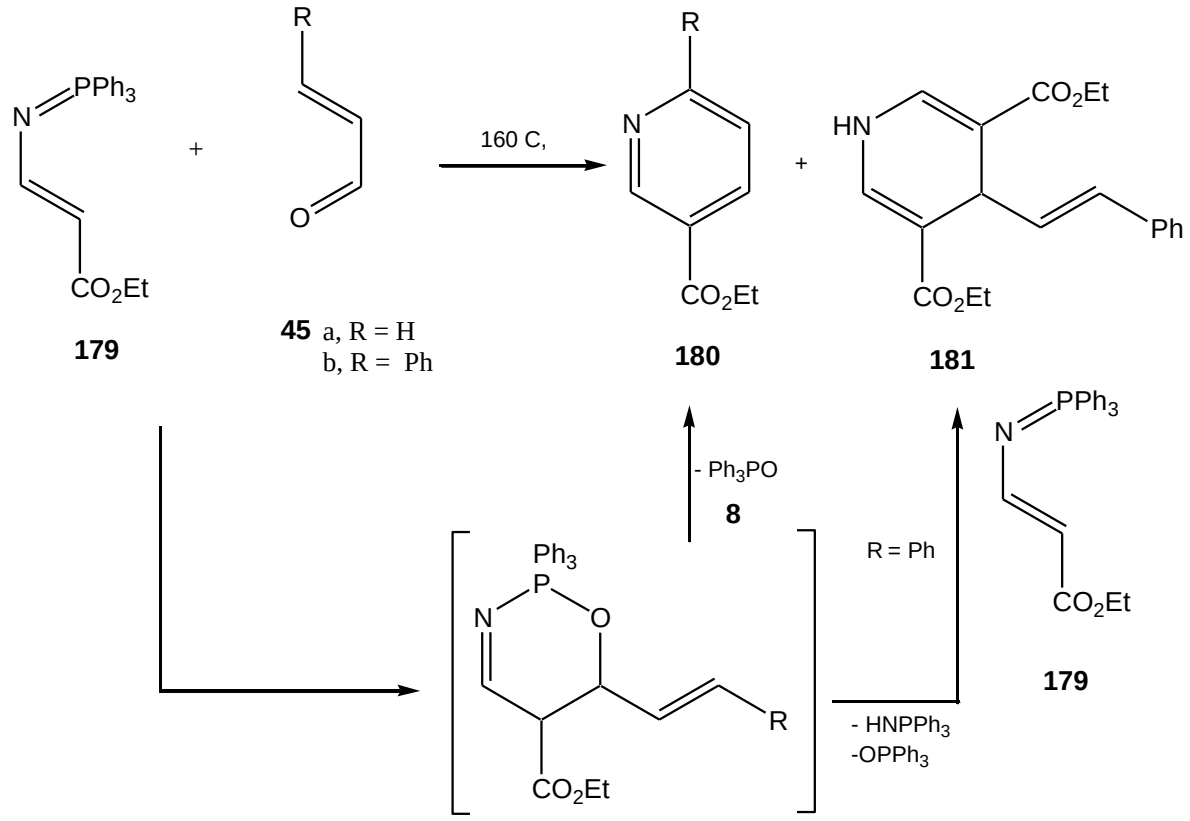
Scheme 17

9) The synthesis of 2-alkenyl-3-(alkoxycarbonyl) furans by cyclo-condensation of (2,4-dioxobutylidene)phosphoranes **174** with chloracetaldehyde **175** gives 3-alkoxycarbonyl-2-furylmethyltriphenylphosphonium chloride **176** which undergoes Wittig reaction with various aliphatic and aromatic aldehydes **177** to afford 2-alkenyl-3-(alkoxycarbonyl)furans of type **178**.[94]



10) Aza-Wittig reaction of N-vinylic phosphazenes, derived from diphenylmethylphosphine or from trimethylphosphine with α,β-unsaturated aldehydes leads to the formation of 3-azatrienes.[95]

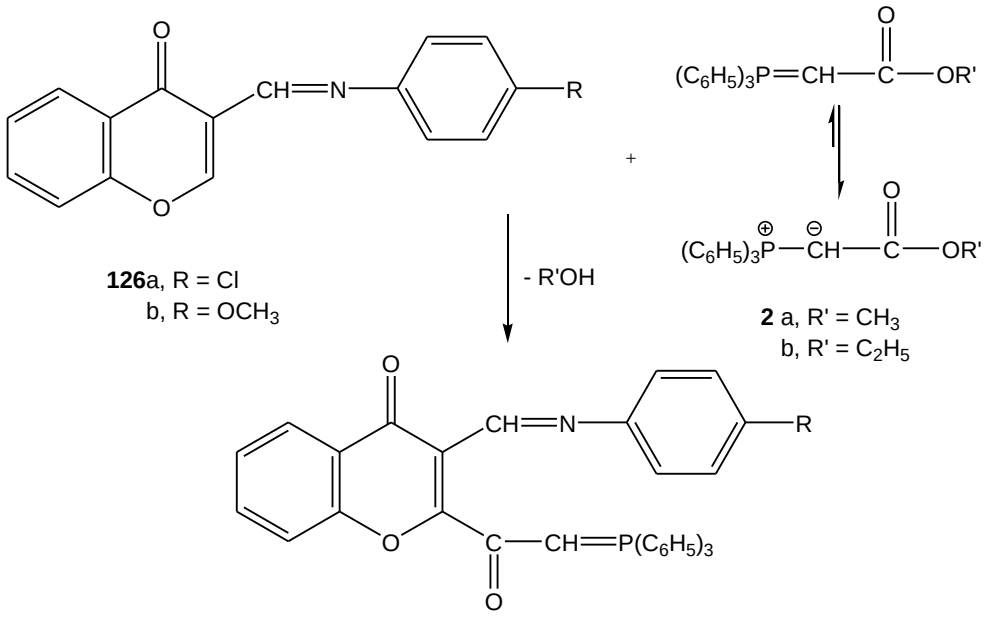
Scheme 18 shows the reaction of N-vinylic phosphazene **179** derived from triphenylphosphine with acrolein **45a** and cinnamaldehyde **45b** to give pyridines **180** and dihydropyridine **181**. [95] **(Scheme 18)**


PPh3
N
CO2Et
179
+
R
O
45 a, R = H
b, R = Ph
160 C,
R
N
CO2Et
180
+
HN
CO2Et
Ph
CO2Et
181
- Ph3PO
8
Ph3
P
N
O
R
CO2Et
1,2,5-oxaazaphosphorane
182
R = Ph
- HNPPh3
-OPPh3
PPh3
N
CO2Et
179

Scheme 18

2- Reaction of Wittig Reagents with Imines:

1) New complex yildenetriphenylphosphoranes **183** were obtained directly *via* condensing arlyimines **126** with the resonance stabilized methylenetriphenyl-phosphoranes **2a,b**.[74]

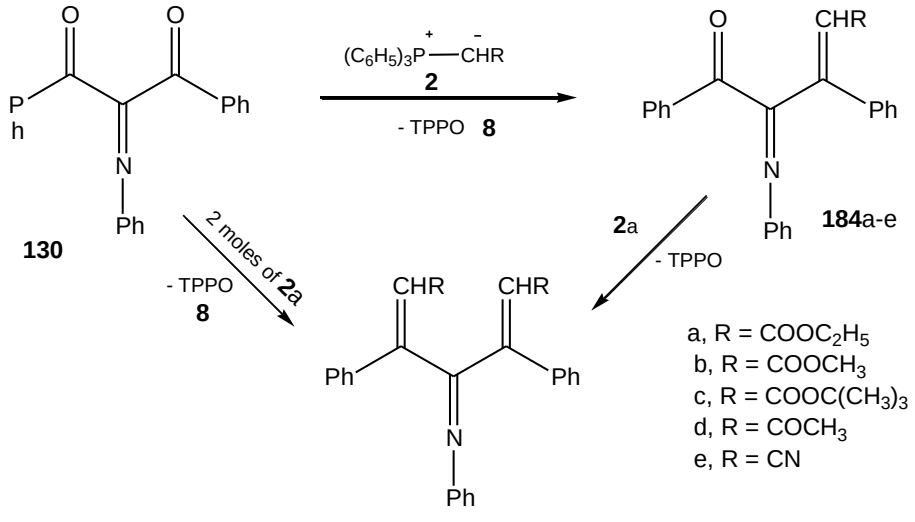


126a, R = Cl
b, R = OCH_3

2 a, R' = CH_3
b, R' = C_2H_5

183a, R = Cl
b, R = OCH_3

2) The olefinic compounds **184** and **185** were isolated from the reaction of 1,3-diphenyl-2-(phenylimino)-1,3-propanedione **130** with Wittig reagents **2**.[76] **(Scheme 19)**



130

184a-e

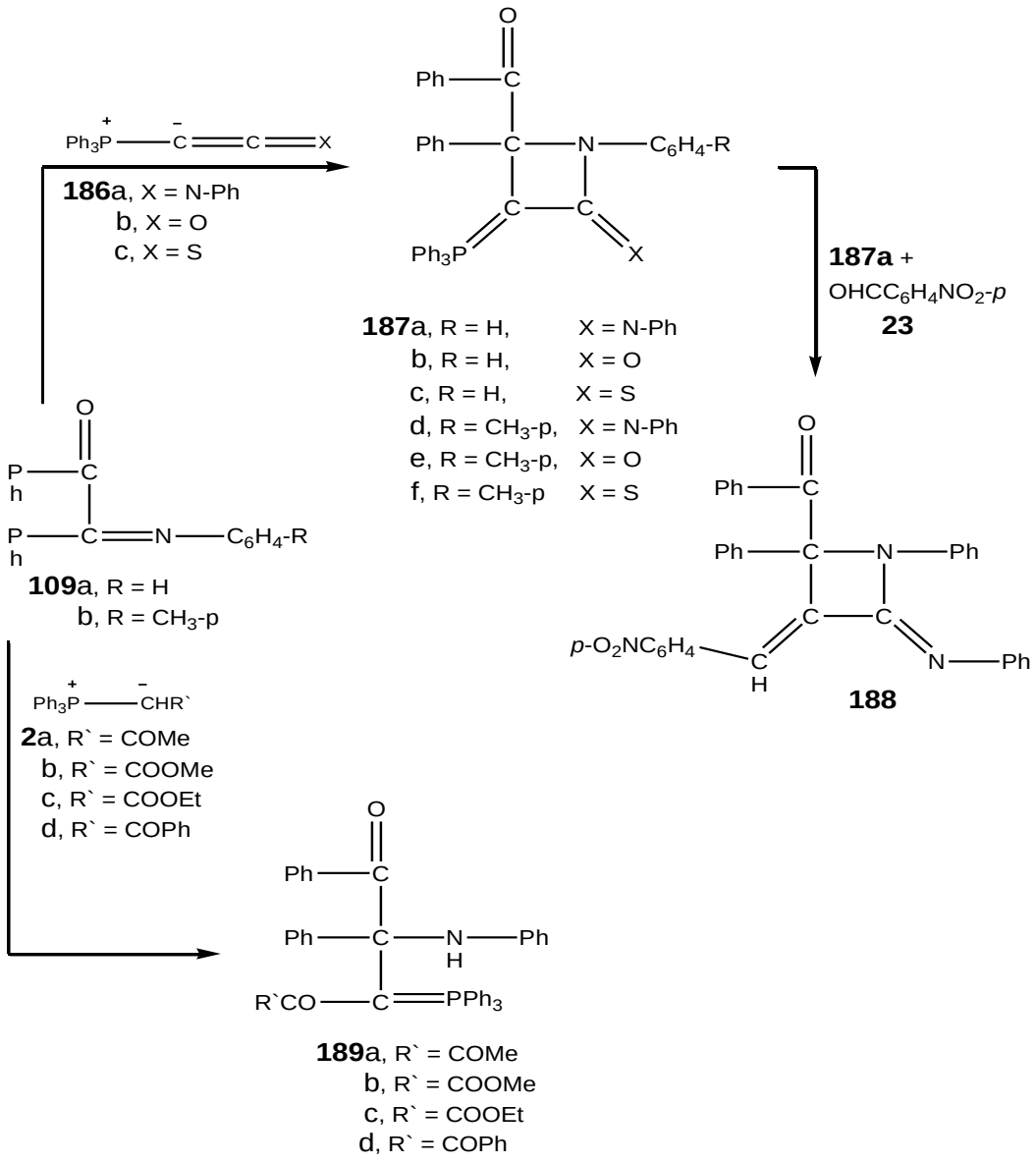
a, R = $COOC_2H_5$
b, R = $COOCH_3$
c, R = $COOC(CH_3)_3$
d, R = $COCH_3$
e, R = CN

185a, R = $COOC_2H_5$

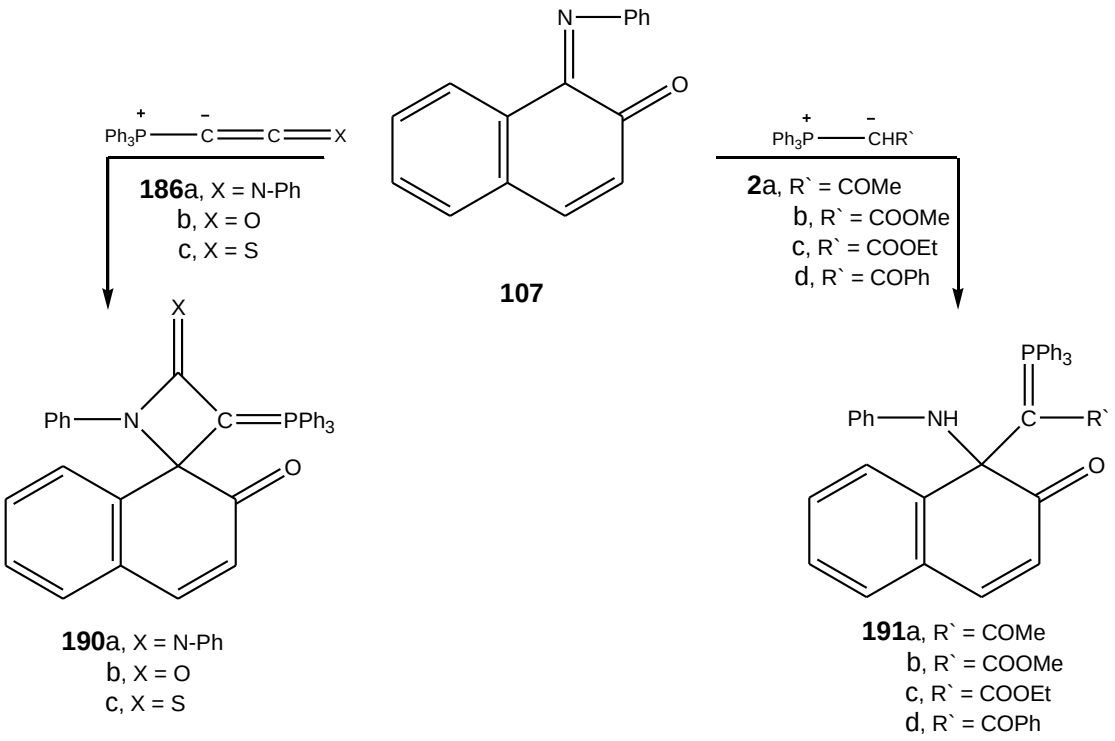
Scheme 19

3) The active phosphacumulene ylides, namely N-phenylimino- **186a**, 2-oxo- **186b** or 2 thioxovinylidenetriphenylphosphoranes **186c**, react with monoanils of benzil- **109 a,b**, o-naphthoquinone- **107**, or indane 1,2,3-triketone **192**, to give the phenylimino- (**187a,d, 190a, 193a**), oxo- (**187b,e, 190b, 193b**) or thioxoazetidinones (**187c,f, 190c, 193c**) respectively.

On the other hand, monoanils **109a,b**, **107** and **192** can be converted by the stabilized alkylidenetriphenylphosphoranes **2a–d**, namely acetylmethylene- **2a**, methoxycarbonylmethylene- **2b**, ethoxycarbonylmethylene- **2c**, and benzoylmethylenetriphenylphosphorane **2d**, into the respective phosphoranylidenes (**189a–d**, **191a–d**, **194a–d**) .[96] **(Schemes 20, 21, 22)**



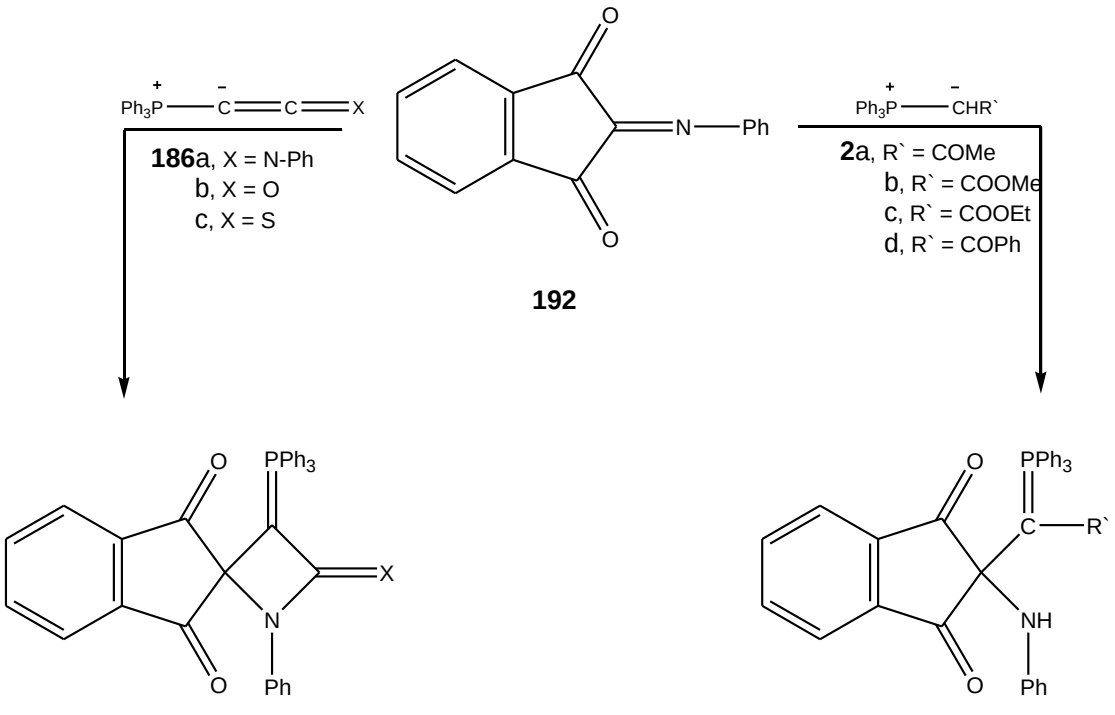
Scheme 20



190a, X = N-Ph
b, X = O
c, X = S

191a, R` = COMe
b, R` = COOMe
c, R` = COOEt
d, R` = COPh

Scheme 21



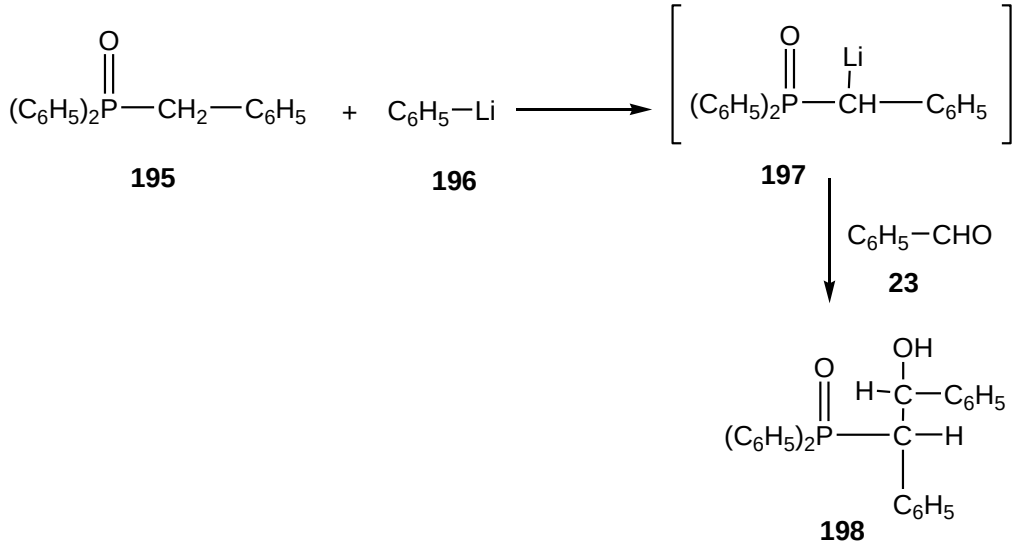
193a, X = N-Ph
b, X = O
c, X = S

194a, R` = COMe
b, R` = COOMe
c, R` = COOEt
d, R` = COPh

Scheme 22

3-Reaction of Horner -Wadsworth-Emmons Reagents with Aldehydes

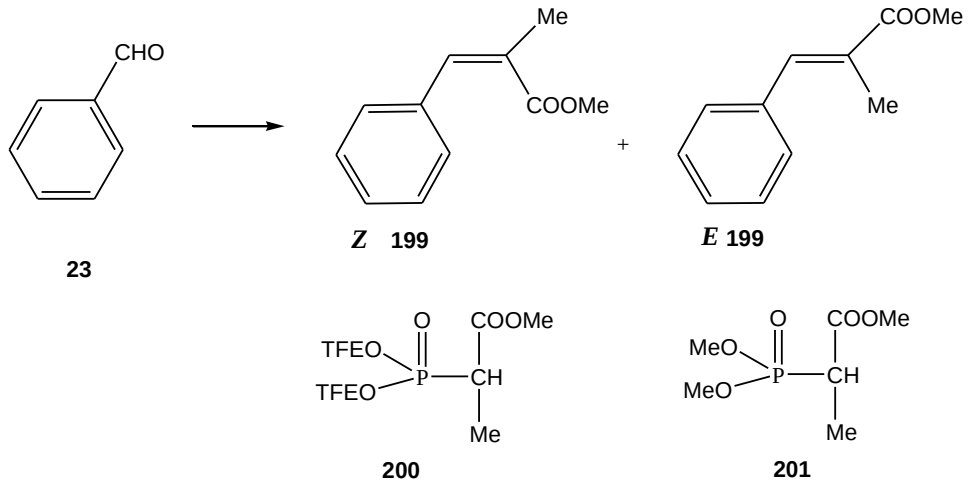
1) The reaction of diphenyl benzylphosphine oxide **195** with phenyl lithium **196** produces the corresponding lithium salt **197** which upon interaction with benzaldehyde **23** produces (β-hydroxy,α,β-diphenylethyl)diphenyl phosphine oxide **198**.[97]



195 **196** **197** **23** **198**

2) The Horner-Wadsworth-Emmons (HWE) reaction is a classical method for the preparation of unsaturated esters. Phosphonoester reagents yield *Z* α,β-unsaturated esters stereoselectively and in high yield from aliphatic and aromatic aldehydes. [31]

The almost stereoexclusive conversions of benzaldehyde **23** to a *Z* cinnamate with methyl trifluoroethylphosphonoester **200** and to an *E* cinnamate with methyl trimethylphosphono-acetate **201** represent the only known direct route from aromatic aldehydes to pure *Z* disubstituted cinnamic esters.[31]

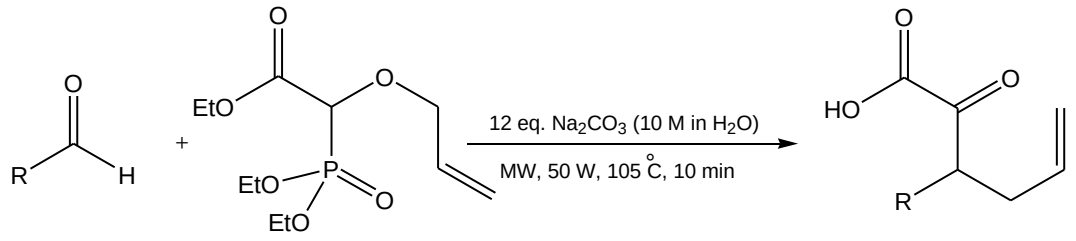


23 ***Z*** **199** ***E*** **199**

200 **201**

TFE = trifluoroethyl

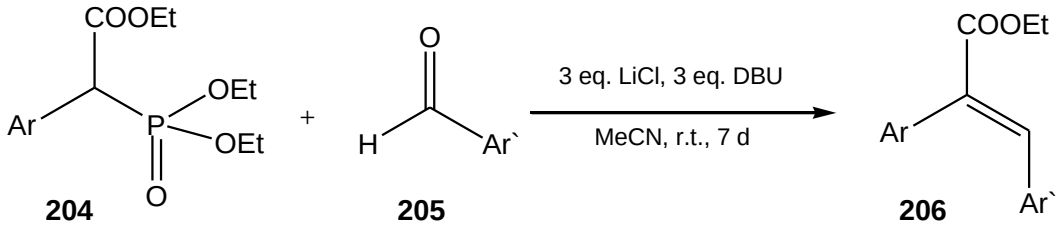
3) The conversion of aldehydes into β-substituted-2-oxohex-5-enoic acids **203** occurs by a three-step, one pot method. The optimized sequence is carried out in water with microwave irradiation and involves sequential Horner-Wadsworth-Emmons (HWE) olefination by the application of the phosphonate reagent **202**.[98]



23 **202** **203**

R = , , Br

4) 2-Aryl-substituted phosphono-acetates **204** can be readily synthesized from the respective arenes. Succeeding Horner-Wadsworth-Emmons olefinations provide the 2-aryl cinnamic acid esters **206** stereoselectively.[99]



204 **205** **206**

Ar = , ,

Ar` = , ,