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Synthesis of heterocycles by the aza-Wittig reaction

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ABSTRACT. **This review is devoted to the synthesis of *N*-heterocyclics by the interaction of phosphazo groups (either preformed or prepared *in situ*) with carbonyl or thiocarbonyl groups. Examples are presented systematically only for syntheses by an intramolecular aza-Wittig reaction or where the latter is incorporated in a multi-step route. The feasibility of preparing various types of heterocycle by this method has been examined.**

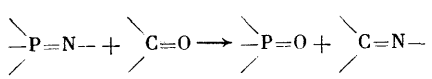
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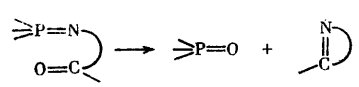
I. Introduction

Phosphazo compounds (phosphine imines) can react with carbonyl compounds in the same manner as phosphonium ylids, i.e. as aza-analogues of the latter. The reaction is thus analogous to the Wittig synthesis,[1] the end product being the corresponding imine.



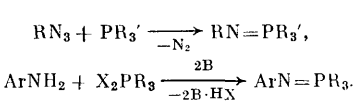
Because of this analogy, it is generally referred to nowadays as the aza-Wittig reaction, although, in fact, it was first discussed by Staudinger and Meyer[2] independently of the work of Wittig.

If the phosphazo and carbonyl groups are in the same molecule, intramolecular condensation can take place to give a nitrogen-containing heterocycle:



Many types of five-, six- and unusual seven-membered *N*-heterocylics, including natural products and their analogues, have been prepared by this route, notably in the last two decades. However, up to now, there has been no systematic survey of literature data on this reaction, except in Zbiral's review[3] of 1974, in which there is a small section on the synthesis of heterocyclics with phosphine imines.

The mild conditions of the cyclisation and the ready availability of the starting materials are normally considered as the principal advantages of the aza-Wittig synthesis. Azides and aromatic amines are very often used as precursors of phosphazo compounds, the first being converted into the latter by treatment with the corresponding phosphine or phosphite, while aromatic amines afford phosphazo compounds by treatment with dihalogenotriorganophosphoranes in the presence of base:

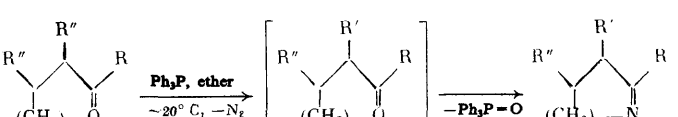


In many cases, reaction can be undertaken with *in situ*-generated phosphazo compounds.

II. Syntheses by aza-Wittig reaction

1. Cyclisation of phosphazoketones and phosphazoaldehydes

Ketones and aldehydes are normally used as the carbonyl function in the aza-Wittig reaction. Reaction with phosphazo groups proceeds under comparatively mild conditions—in many instances at room temperature. Notably, this reaction has been applied with readily available ω-azidoketones, from which five-, six-, and seven-membered cyclic imines (I) can be obtained. Such compounds are intermediates for alkaloids. There are a number of advantages of this method over other known procedures. For example, as reaction can be conducted in non-aqueous media under non-reductive conditions, the method can be applied to ring systems with substituents which are sensitive to reductants and water.[4,5]

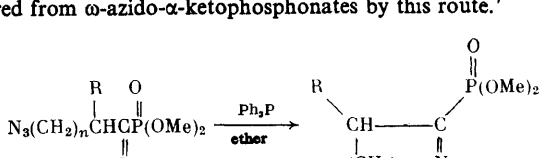


(I), 60–92%

$n = 1–3$; R, R′, R″ = H, Me, Et, PhS, 4-BrC$_6$H$_4$.

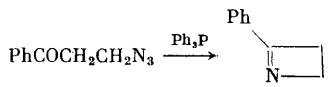
The synthesis of 1-pyrrolines (I, n = 1) by the aza-Wittig reaction has already been discussed.[6]

2-Phosphonyl-Δ^1-pyrrolines and -Δ^1-piperideines have been prepared from ω-azido-α-ketophosphonates by this route.[7]

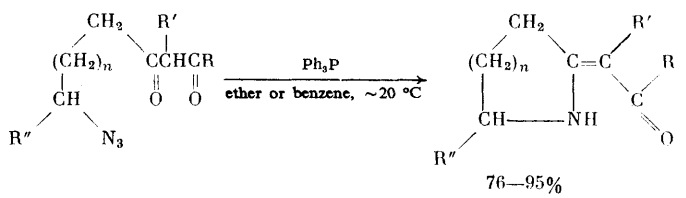


n=2,3; R=H, Me, allyl.

Azetines cannot be obtained by the aza-Wittig reaction in preparative yield.[8] Thus, 4-azidobutan-2-one and methyl 3-azidopropionate do not cyclise on treatment with triphenylphosphine, even under harsh conditions. However, it is possible to prepare 2-phenyl-1-azetine in very low yield by reaction of β-azidopropiophenone with triphenylphosphine.



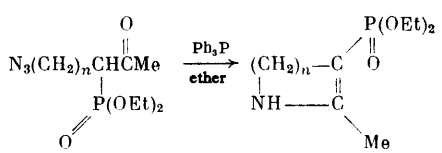
The reaction of ω-azido-β-diketones or ω-azido-β-ketoesters with triphenylphosphine is accompanied by migration of a labile hydrogen atom from carbon to nitrogen to provide heterocyclics with an exocyclic double bond. Such products, obtainable in quantitative yield, may be regarded as vinylogous amides or urethans.[6,7,9]



$n = 1-3$

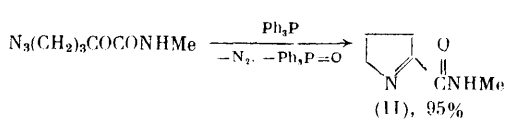
Attempts to prepare eight-membered heterocycles in this way failed when the starting materials were heated in toluene.[9]

Transfer of hydrogen from carbon to nitrogen also takes place on intramolecular aza-Wittig cyclisation of ω-azido-α-(diethoxyphosphinyl)ketones, there affording 3-diethoxyphosphinyl-2-pyrrolines and -2-piperideines in ~75% yield.[6]

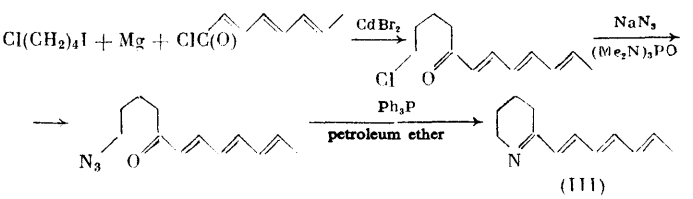


$n = 2, 3$

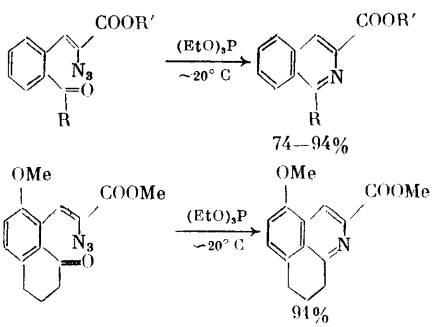
The amide (II) is obtained in high yield by interaction of *N*-methyl-5-azido-2-ketovaleramide with triphenylphosphine in benzene. It is reported that this method is suitable for preparing the relatively inaccessible 1,2-dehydroproline system. However, it is not possible to prepare seven-membered heterocyclics by such ring closure of ketoamides.[10]



The method has also been applied in the final step of a multistage route to the alkaloid nigrifactine (III), which possesses high physiological activity. The intermediate chloro- and azido-ketones, with four double bonds in conjugation, and nigrifactine itself, are all very unstable and are isolated in low yield.[11]

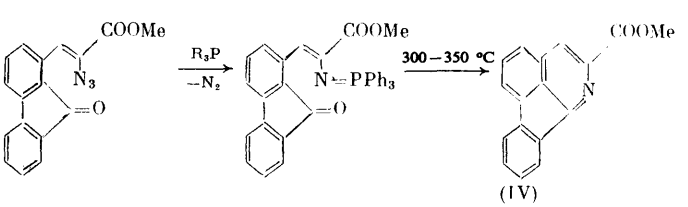


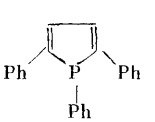
Intramolecular aza-Wittig reaction with *o*-carbonyl-substituted α-azidocinnamates and analogous 1-tetralone derivatives readily cyclise at room temperature to isoquinolines without isolation of intermediate phosphazo compounds.



R = H, Me, Ph; R′ = Me, Et.

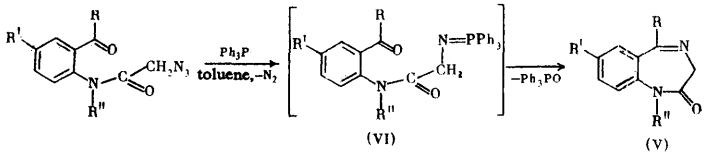
The phosphazo compounds obtained from fluorenone and triphenylphosphine or triethyl phosphite do not cyclise on heating in xylene; however, the azafluoranthene (IV) is obtained at 300–350 °C in 12 and 19% yield, respectively. The product can be obtained in somewhat higher yield (34%) by cyclisation of the phosphazo compound obtained by reaction of the starting azide with 1,2,5-triphenylphosphole (see p. 152). In this case reaction is complete within two minutes at 300 °C.[12,13]



R = Ph, EtO or R$_3$P = 

Benzodiazepine derivatives, including the psychotherapeutic drugs diazepam and nitrazepam (Va, b),[14] as well as the analogues (Vc–e),[15] have also been prepared by intramolecular aza-Wittig reaction. The intermediate phosphazo compound (VIe), formed by reaction of triphenylphosphine with 2-(azidoacetylamino)4-chlorobenzophenone, is stable at room temperature and may be isolated as

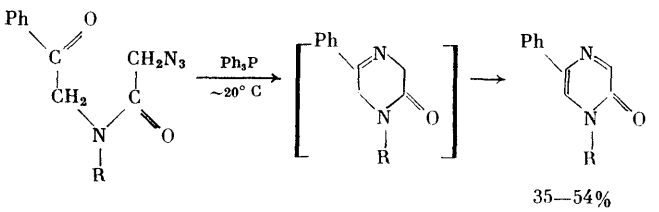
the hydrochloride; on heating in toluene it is converted into the corresponding benzodiazepine (Ve) in 80% yield.[15]



(VI) (V)

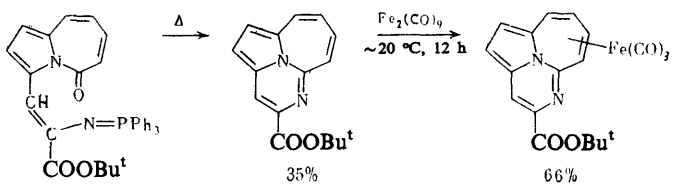
	a	b	c	d	e
R	Ph	Ph	H	Ph	Ph
R′	Cl	NO_2H	H	Cl	
R″	Me	H	H	Me	H

The analogous cyclisation of azidoacetyl(phenacyl)amines leads to 2-pyrazinones, even on conducting the reaction under argon, rather than the corresponding dihydro derivatives as would have been anticipated for an intramolecular aza-Wittig reaction.[15]



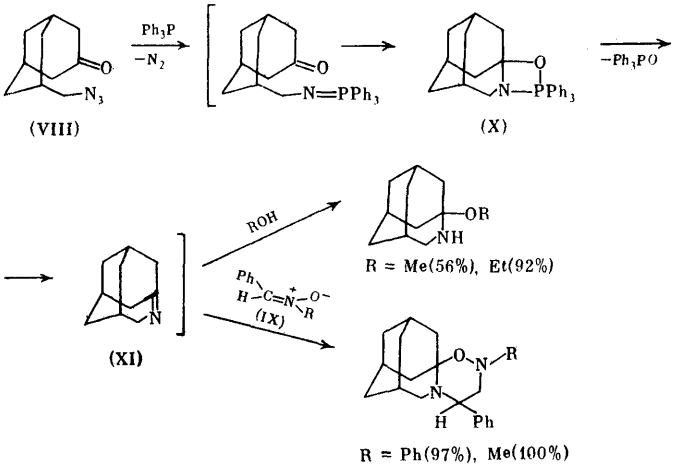
35—54%

The tricyclic system, 5,9-diazabenz[*c*,*d*]azulene, is formed by heating the phosphazo compound (VII) in toluene. The product is very unstable, but may be characterised as an iron tricabornyl complex.[16]



(VII) 35% 66%

Similarly, heating 3-azidomethylbicyclo[3.3.1]nonan-7-one (VIII) with triphenylphosphine in alcoholic media gave alkoxy-4-azahomoadamantanes, while reaction with triphenylphosphine and nitrones (IX) in benzene afforded compounds having the oxadiazinohomodamantane skeleton. By following the reaction of azide (VIII) with triphenylphosphine in deuteriochloroform with the aid of ^{1}H- and ^{13}C-NMR spectroscopy, it was shown that the conversion of the intermediate phosphazo compound into the oxazaphosphetane (X) is a rapid process by virtue of a favourable entropy factor, while the cleavage of (X) to the highly strained imine (XI) is slow. As a consequence, it is possible to characterise compound (X) spectroscopically.

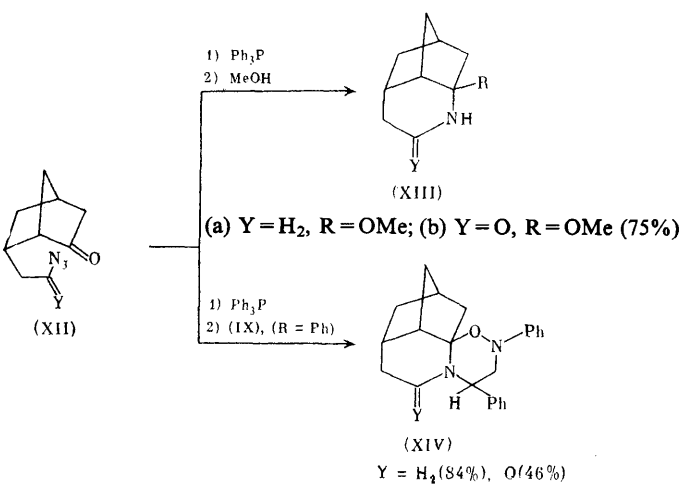


(VIII) (X) (XI)

R = Me(56%), Et(92%)

R = Ph(97%), Me(100%)

Azide (XII) affords 4-aza-4-homobrendane derivatives (XIII, XIV) in high yield with the same reagents under the same conditions. The unstable aminoacetal (XIIIa) was reduced with $LiAlH_4$ to the stable imine (XIII; Y = H_2, R = H) in 87% yield.[17]



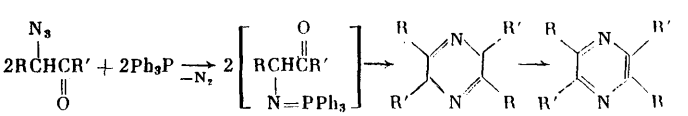
(XII) (XIII)

(a) Y = H_2, R = OMe; (b) Y = O, R = OMe (75%)

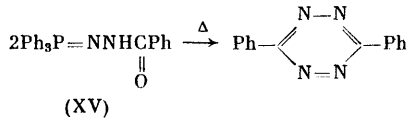
(XIV)

Y = H_2(84%), O(46%)

A number of heterocyclic systems has been obtained by double aza-Wittig reaction. Thus, pyrazine derivatives can be prepared conveniently by reaction of α-azidoketones with triphenylphosphine. In this case, two molecules of phosphazo compound, formed in the initial step of the reaction, participate in a "head-to-tail" double aza-Wittig coupling providing dihydropyrazines which undergo dehydrogenation to pyrazines during the reaction.[18]

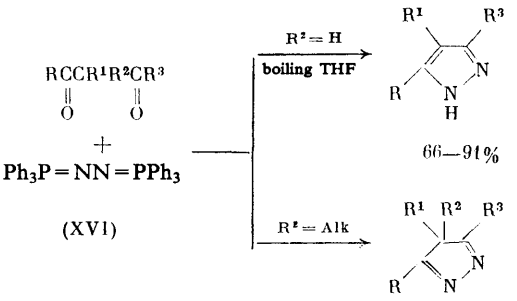


A similar sequence is involved in the preparation of 2,6-diphenyl-*s*-tetrazine from phosphazo compound (XV).[19]



(XV)

An original method has also been reported for the preparation of pyrazoles by condensation of β-ketones with phosphazine (XVI).[20] If there is one hydrogen atom on the α-carbon atom of the β-diketone, the reaction provides 1*H*-pyrazoles, but if the α-carbon is disubstituted by alkyl groups a double aza-Wittig reaction takes place to give 4*H*-pyrazoles.



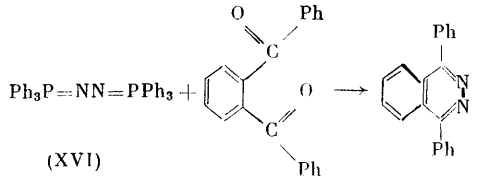
(XVI)

66—91%

R = Me, Ph; R^1 = H, Me; R^2 = H, Me; R^3 = Me, Ph.

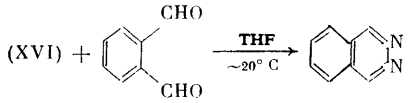
R = R^1 = R^2 = R^3 = Me, 38,4%

Treatment of *o*-dibenzoylbenzene with phosphazine (XVI) affords 1,4-diphenylphthalazine,[20] while *o*-phthalaldehyde gives phthalazine itself.[21]



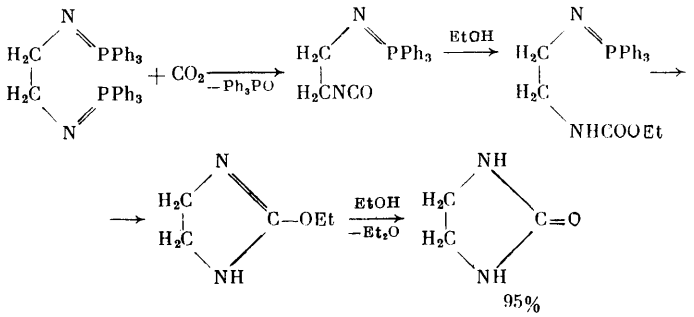
(XVI)

55%



77%

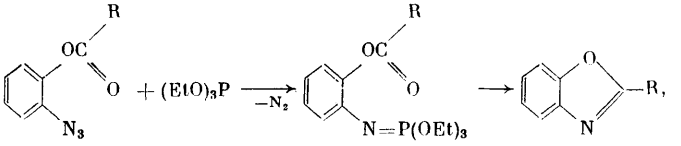
An excellent yield of 2-imidazolidone was obtained by passing carbon dioxide into an alcoholic solution of 1,2-*bis*(triphenylphosphazo)ethane. It is likely that reaction proceeds via isocyanate and urethan intermediates.[20]



95%

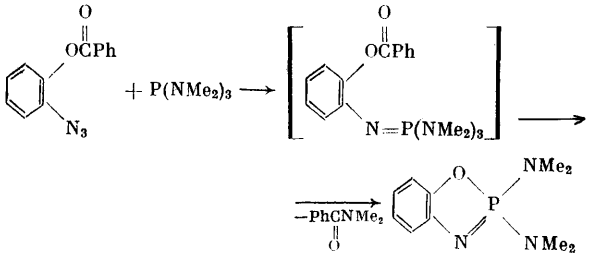
2. Cyclisation of phosphazoesters (of carboxylic acids)

The intramolecular condensation of phosphazo groups with esters requires somewhat harsher conditions than the condensation with ketones. Thus, cyclisation of the phosphazo compounds obtained by the exothermic reaction of *o*-acoxyazides with triethyl phosphite proceeds by prolonged heating in cyclohexane to give 2-substituted benzoxazoles.[22]

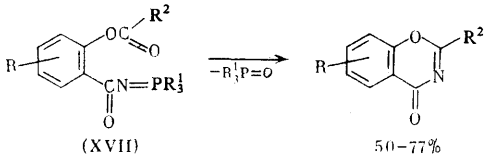


R = Me (69%), Ph (71%).

Interestingly, heating *o*-azidophenyl benzoate with hexamethylphosphorous triamide in cyclohexane for 24 h is accompanied by evolution of *N,N*-dimethylbenzamide, rather than hexamethylphosphoramide, to give 1,3,2-benzoxazaphosphole derivatives.[23]



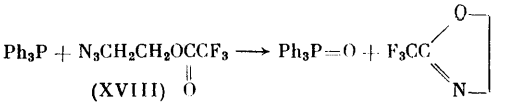
With salicyclic acid derivatives (XVII), intramolecular aza-Wittig reaction proceeds at room temperature in toluene, or on heating in a mixture of acetone and petroleum spirit, to give 4*H*-1,3-benzoxazin-4-ones, including the previously unknown 2-alkoxy derivatives.[24,25]



(XVII)

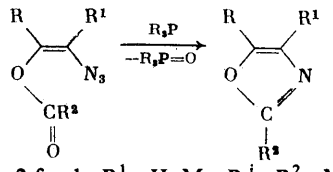
50—77%

At the same time, the azidoester (XVIII) reacts immediately with triphenylphosphine in the cold to give a high yield of 2-trifluoromethyl-2-oxazoline.[26]



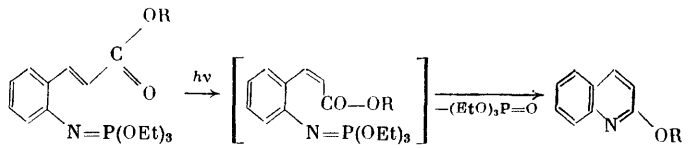
80%

The cyclisation of β-acoxyvinyl azides with trivalent phosphorus compounds (preferably triethyl phosphite) provides a suitable method of preparing oxazoles, which are used not only as blocking groups, but also as intermediates and as key components of alkaloids and macrocyclic antibiotics.[27]



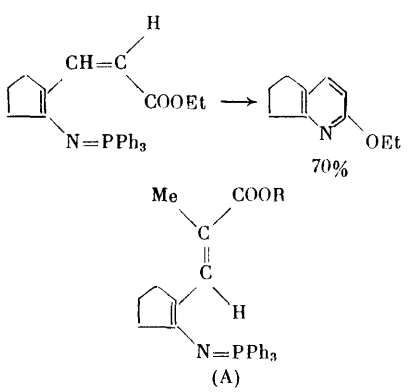
R = Ar, 2-furyl; R^1 = H, Me, Pr^i; R^2 = Me, Et, cyclopropyl, 2-furyl, 3-pyridyl.

Heating is not necessary for the cyclisation of *o*-phosphazocinnamic acids and their esters. Reaction takes place on irradiation (365 nm) for 30 minutes to give a high yield of 2-hydroxy-, 2-alkoxy- or 2-phenoxy-quinolines, probably as a result of an initial *trans*→*cis*-isomerisation.[28]

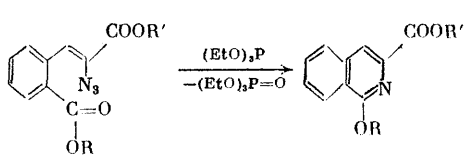


R = H, Me, C_6H_{11}(>75%), Ph(95%).

By studying the analogous cyclisation of 3-(2-triphenylphosphazocyclopent-1-enyl)-acrylates and -methacrylates, it was found that the ethyl acrylates react under harsh conditions (at 207 °C in boiling tetralin) to give a high yield of 2-ethoxycyclopenteno[*b*]pyridine. The corresponding methacrylate derivative did not cyclise under these conditions, probably as a result of the steric repulsion between the methyl and the phosphazo group. This stabilises the structure in the (*E*)-form (A) which is unfavourable for cyclisation.[29]

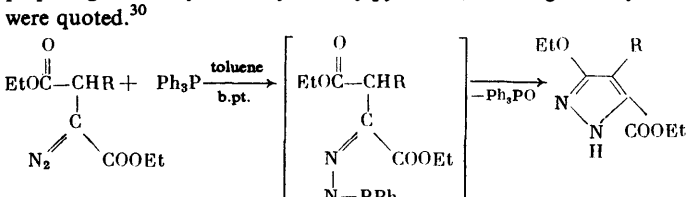


α-Azido-*o*-carboxy- and α-azido-*o*-carbethoxycinnamates react with triethyl phosphite at 20–50 °C to give the corresponding esters of 1-hydroxy- or 1-ethoxy-isoquinoline-3-carboxylic acid esters.[12]



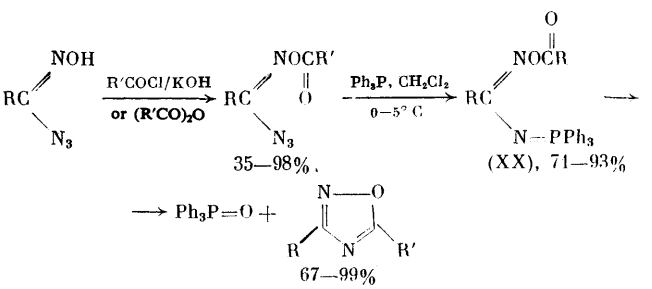
70—90%

The reaction of β-diazoesters with triphenylphosphine in heated toluene may be used for the preparation of 3-ethoxypyrazoles. The phosphazine (XIX) is an intermediate in this conversion. The authors of this work consider this to be a general method of preparing 3-ethoxy-5-ethoxycarbonylpyrazoles, although no yields were quoted.[30]



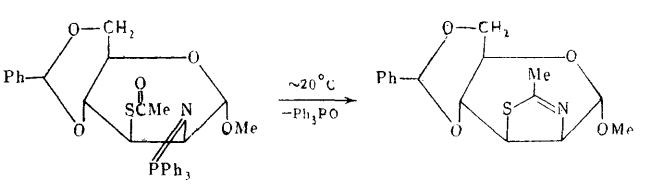
R = H, NHCOOEt. (XIX)

The carbonyl group of *O*-acyloximes may also participate in the aza-Wittig reaction. This has been incorporated as the final step in a convenient synthesis of 3,5-disubstituted 1,2,4-oxadiazoles, based on acylation of 1,1-azido-oximes, treatment of the intermediate with triphenylphosphine, and then heating the resulting phosphazo compound in toluene.[31] It was not possible to prepare 5-alkylamino-1,2,4-oxadiazoles by this route because the intermediate 1,1-phosphazo-oxime carbamates (XX, R′ = MeNH, EtNH) give a complex mixture of compounds on heating in toluene.



R = Ar; R′ = Me, EtO, Ar.

Ring closure of acetylthio compounds to give acid-resistant thiazole derivatives can be achieved by condensation with a neighbouring phosphazo group. This has been adapted for the protection of the 2-aminomercaptan function in the synthesis of thiosugars with potential biological activity. The phosphazo compound (XXI), obtained from the corresponding azidodeoxy-mannose derivative, has been shown to be stable in ether but is immediately converted into the thiazoline (XXII) on dissolution in chloroform.[32]



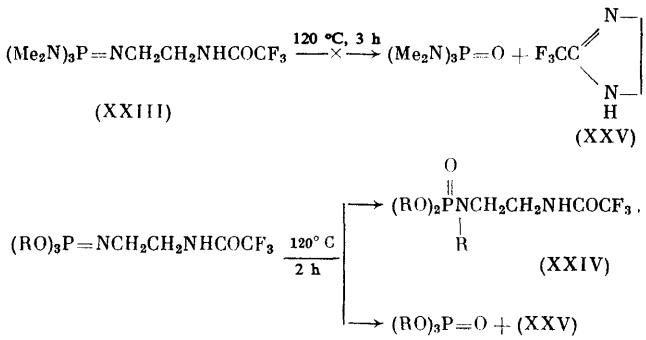
(XXI) (XXII)

3. Cyclisation of phosphazoamides

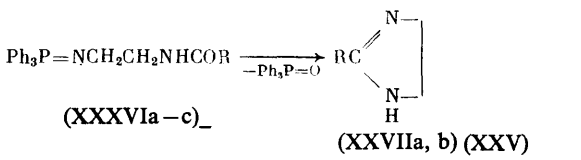
As the electrophilicity of the amide carbonyl group is lower than that of the ester group, phosphazo compounds generally do not react with carboxylic acid amides unless the amide group is activated by an additional acceptor group (see, for example, Ref. 33).

In those instances where intramolecular aza-Wittig reaction does take place with amides, the readiness to cyclise depends largely on the nature of the substituents on the phosphorus and amide nitrogen atoms. Thus, it has been found that phosphazo compound (XXIII) with dimethylamino groups on the phosphorous atom do not react,[34] while the analogues *N*-(trialkoxyphosphazoethyl) amides, based on trifluoroacetic acid, are converted to trialkyl phosphate and 2-trifluoromethyl-2-imidazoline (XXV), in addition to amide (XXIV) derived via imine-amide rearrangement. The more facile the

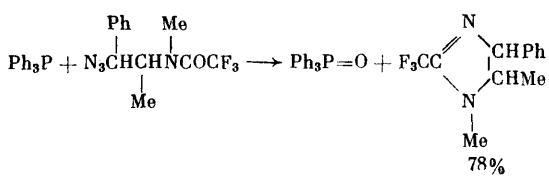
rearrangement into amide (XXIV), the lower the yield of imidazoline (XXV), being 1–1.5% for R = Et, and 27% for R = Bu.[35]



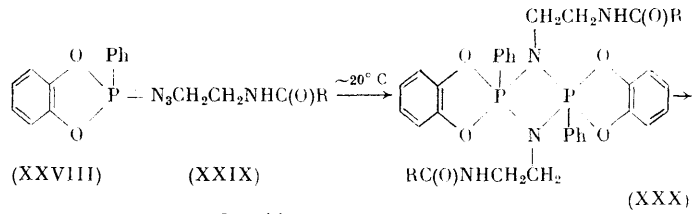
The tendency of phosphazoamides to cyclise is greater for compounds with a phenyl group on the phosphorus atom. Heating such compounds affords a high yield of imidazolines substituted in the 2-position by alkyl or aryl groups. Thus, triphenylphosphazo compounds (XXVI) based on acetamide and benzamide are converted into triphenylphosphine oxide and the corresponding 2-imidazoline (XXVIIa, b) at 180 °C; similarly, the trifluoroacetamide derivative (XXVIc) provides the imidazoline (XXV) at 120 °C, the yield of the three products being 72%, 91% and 80%, respectively.



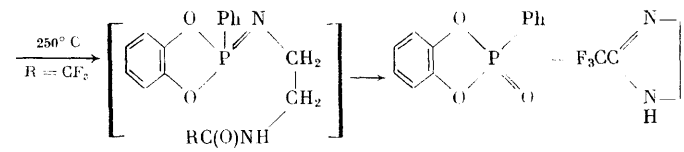
Substituted imidazolines are formed more readily by using phosphazo compounds derived from azidoamides with substituents on the chain linking the two reactive functions. Thus, in the reaction of triphenylphosphine with the azide obtained from racemic pseudoephedrine cyclisation to 4,5-disubstituted 2-imidazolines can be effected, even at room temperature, with associated cleavage of triphenylphosphine oxide. The intermediate phosphazo compound cannot be isolated.[26]



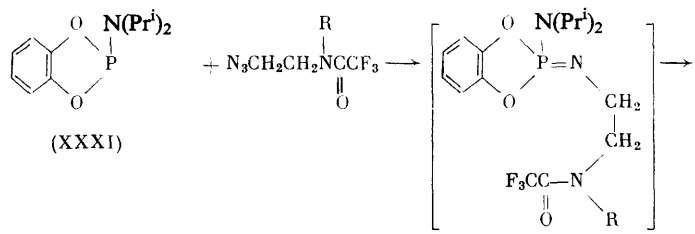
Phosphazo compounds derived from cyclic phosphorus(III) acid esters exhibit a noticeably different mode of cyclisation. Thus, interaction of the cyclic phosphonite (XXVIII) with azides (XXIX) affords exclusively the corresponding dimeric phosphazo compound (XXX), which may be converted to 2-imidazolines on heating to 250 °C, as exemplified below with (XXXc). It is possible that reaction is facilitated via initial thermal cleavage to a monomeric phosphazo compound.[26]



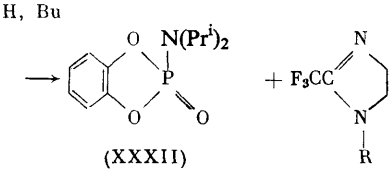
R = Me (a), Ph (b), CF_3 (c)



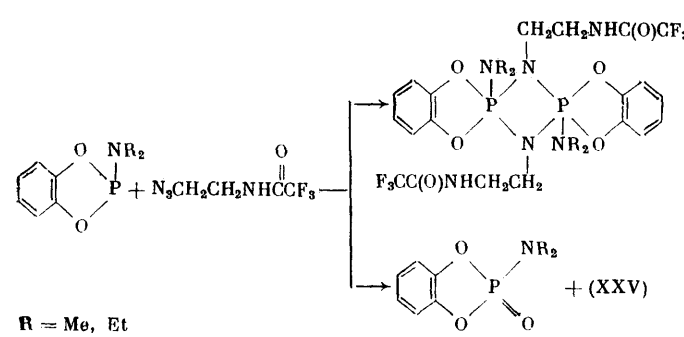
On the other hand, treatment of the pyrocatechol amidophosphite (XXXI) with azide (XXIXc) and its *N*-butyl derivative, even at 80 °C, affords the P-oxide (XXXII) and imidazolines (XXV) and (XXXIII), respectively. An intermediate situation obtains with the dimethylamino- and diethylamino-analogues of (XXXI). In each case, the interaction with azidoamide (XXIXc) proceeds with the simultaneous formation of a phosphazo compound and a mixture of imidazoline (XXV) and the corresponding catechol dialkylamidophosphate.[34,35]



R = H, Bu

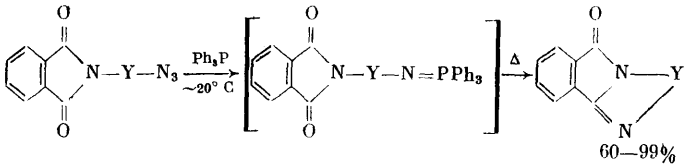


(XXV): R = H (97%); (XXXIII): R = Bu (91%).

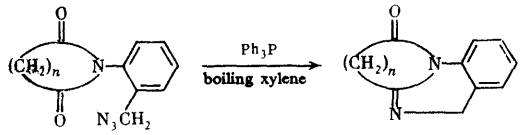


R = Me, Et

One of the carbonyl groups of cyclic imides (phthalimides, succinimides, glutarimides) participates in the aza-Wittig reaction by heating the appropriate phosphazo compounds in toluene or xylene. Five-, six- and seven-membered 1,3-diazaheterocyclics are thereby obtained.[36]



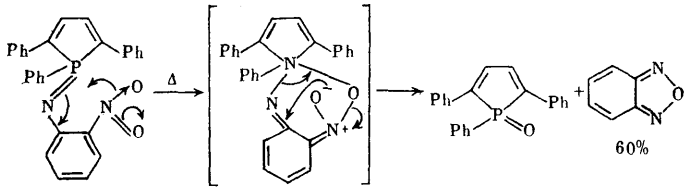
Y = $(CH_2)_n$ (n = 2—4), o-$CH_2C_6H_4$, o-$CH_2C_6H_4CH_2$



n = 2,3 92%

4. Cyclisation of nitrophosphazo compounds

On heating the *o*-nitrophosphazobenzene (XXXIV), derived from 1,2,5-triphenylphosphole, in mesitylene, aza-Wittig ring closure takes place with participation of the nitro group to give benzofurazan in 60% yield. The nature of the substituent on the phosphorus atom has a marked effect on the course of this reaction. Thus, the analogous phosphazo compound derived from triphenylphosphine and triethyl phosphite do not undergo ring closure, while the trichlorophosphazo analogue affords benzofurazan in the same way.[37]

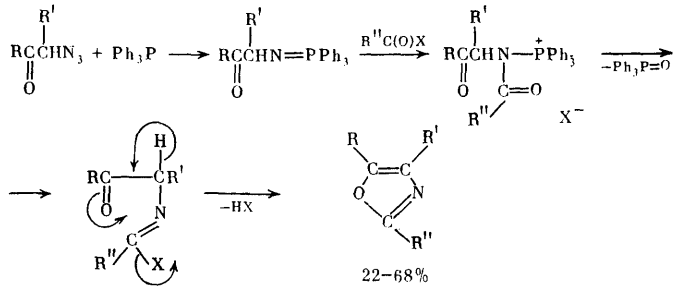


(XXXIV)

III. Syntheses where the aza-Wittig reaction is included in a multi-step route

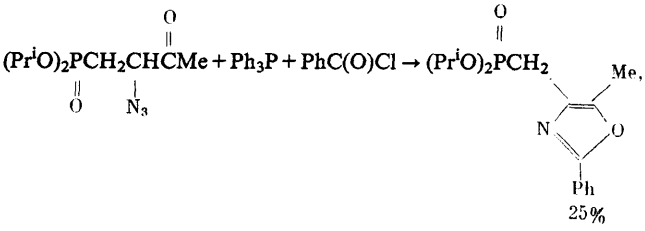
1. Acylation and aza-Wittig reaction

Oxazoles with a wide variety of substituents may be obtained by three-component reaction of triphenylphosphine, acyl halides, and α-azidoketones possessing an α-hydrogen atom. The synthesis, which takes place at room temperature, involves an initial Staudinger reaction, followed by acylation of the *in situ*-formed phosphazo compound, and aza-Wittig cyclisation of the resulting β-ketoimidoyl halide with liberation of triphenylphosphine oxide.[38]

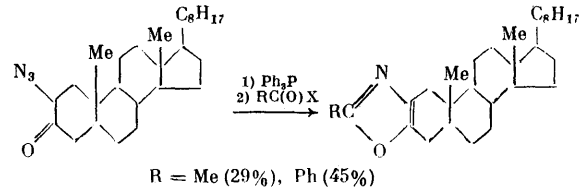


Although hydrogen halide is formed in the last step of the reaction, no additional base is required to trap it. This is possibly why 1.5—2 equivalents of triphenylphosphine are required, and may explain the moderate yield of oxazole.

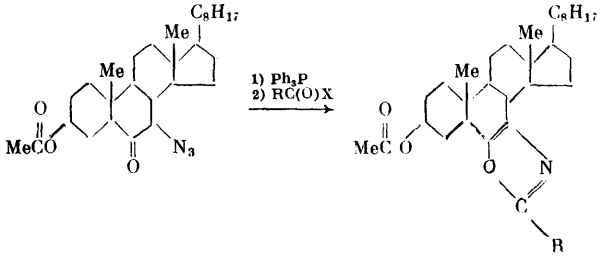
The same reaction has been applied for the preparation of phosphorylated oxazoles.[39]



It has also been adapted for annelation of the oxazole ring to the steroid skeleton for the synthesis of cholest-2-eno[2,3-*d*]oxazoles and cholest-6-eno[7,6-*d*]oxazoles.[40]



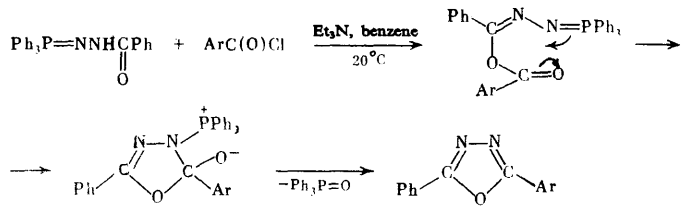
R = Me (29%), Ph (45%)



R = Me (29%), Ph (21%), $PhCH_2$ (36%), EtOOC (42%).

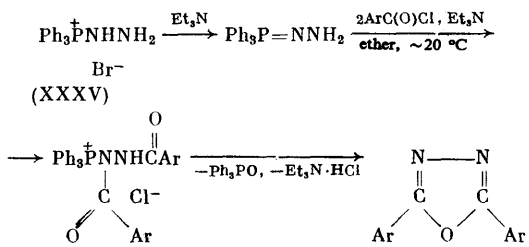
Extension of this reaction to phosphazo compounds having an acylamino group on the imine nitrogen leads to an effective mixture of preparing 1,3,4-oxadiazoles. In this case, reaction is carried out in

the presence of base (butyllithium[3] or triethylamine[19]), and the yield exceeds 90% in certain cases.

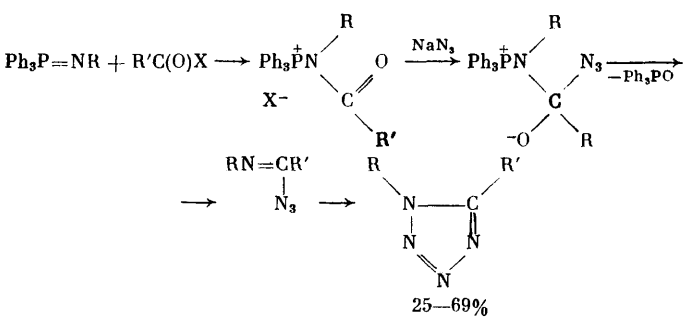


Ar = Ph, $4\text{-}O_2NC_6H_4$, $3,5\text{-}(O_2N)_2C_6H_3$, $4\text{-}BrC_6H_4$.

In a similar way, symmetrically substituted 1,3,4-oxadiazoles are obtained by treatment of phosphonium salts (XXXV) with an excess of triethylamine and two equivalents of aroyl halide.[19]



Tetrazoles may be obtained by interaction of phosphazo compounds with acyl halides and sodium azide under mild conditions (in benzene at room temperature). In certain cases, acyl azides may be used efficiently in place of the acyl halide and NaN_3.

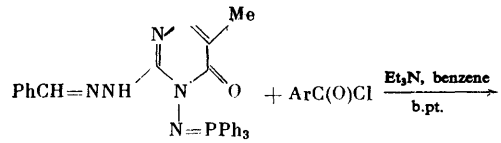


25—69%

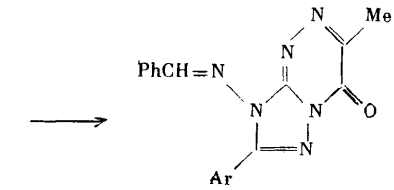
R = Ar, 2-pyridyl, R′ = Alk, alkenyl, alkadienyl.

Under these conditions, trifluoroacetic acid derivatives are converted to acylic imidoyl azides which exist in equilibrium with the corresponding tetrazole. Phosphazo compounds with trimethylsilyl, *tert*-butyl and methoxymethyl groups do not form tetrazoles as reaction proceeds by another pathway.[41]

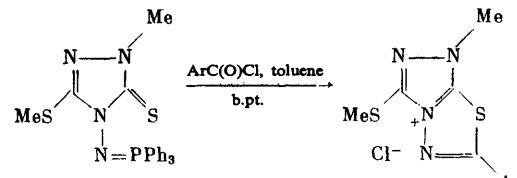
N-Phosphazohetaryls with adjacent benzylidenehydrazino, thione or aldimine groups undergo ring closure with acyl chlorides to give bicyclic systems. Thus, heating triazine (XXXVI) with aromatic aroyl chlorides and triethylamine in benzene affords 1,2,4-triazolo-[5,1-c][1,2,4]triazines,[42] while heating triazole (XXXVII) with acyl chlorides in toluene gives 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazolium salts;[43] the interaction of pyrazoles (XXXVIII) with aroyl chlorides yields pyrazolo[5,4-*d*]pyrimidinium fluoroborates at room temperature.[44]



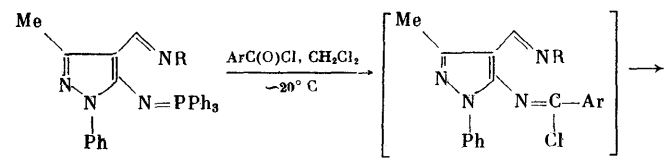
(XXXVI)



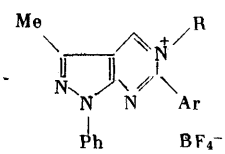
68—80%



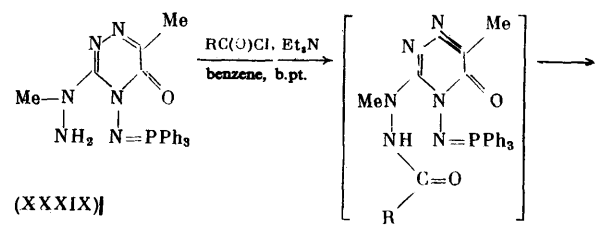
(XXXVII) 48—67%



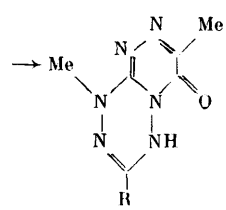
(XXXVIII)



In a similar way, the 4-triphenylphosphazo-3-(1-methylhydrazino)-1,2,4-triazine (XXXIX) with acyl chlorides yields the corresponding *N*-condensed 1,2,4,5-tetrazine derivatives on heating in benzene containing triethylamine.



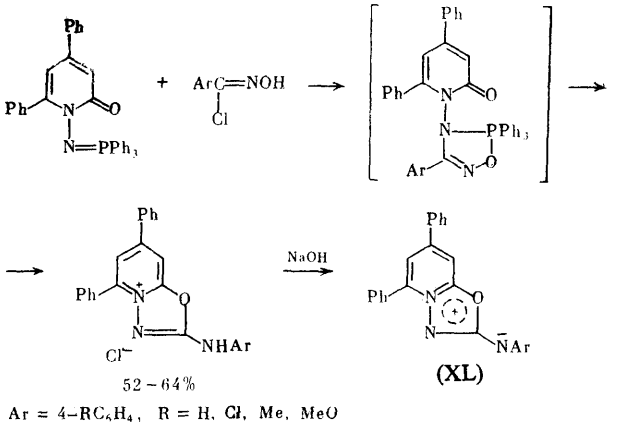
(XXXIX)



37—64%

An intermediate acylhydrazine has been isolated by acylation of the triazine (XXXIX) at room temperature.[45]

The interaction of 1-triphenylphosphazo-4,6-diphenyl-2-pyridone with 1,1-oximinochlorides on heating in benzene is accompanied by C→N-aryl migration to give 1,3,4-oxadiazolo[3,2-*a*]pyridinium chlorides in moderate yield. The structure of the product has been confirmed by its dehydrochlorination to the mesoionic heterocycle (XL) which has been prepared by an independent route.[46]

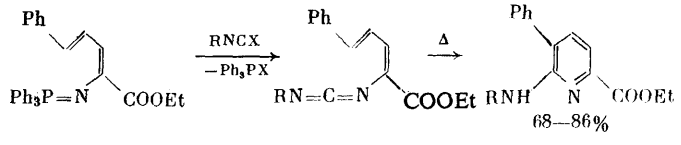


Ar = 4-RC$_6$H$_4$, R = H, Cl, Me, MeO

2. Aza-Wittig reaction and cyclisation

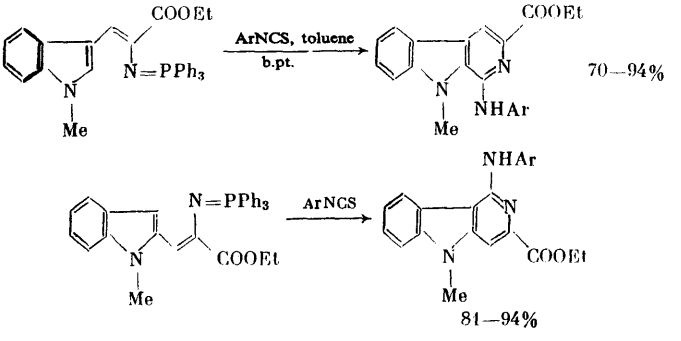
The commonest sequence of this type comprises the interaction of phosphazo compounds with heterocumulenes, such as isocyanates and isothiocyanates. Reaction proceeds via ring closure of an intermediate carbodiimide which, in most cases, is not isolated.

Pyridine derivatives were the first to be prepared by this route, involving ring closure of unsaturated carbodiimides. The preparation of 6-arylaminopicolinic acid esters illustrates the methodology. Here, the phosphazo compound interacts with alkyl or aryl isocyanates or isothiocyanates in toluene at room temperature to give the corresponding carbodiimide which cyclises on heating in the same solvent. The intermediate carbodiimides can be isolated as oils following column chromatography.[47,48]

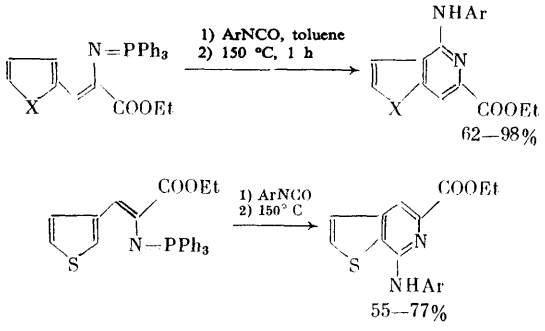


R = Et, Bu^t, Ph, Ar; X = O, S.

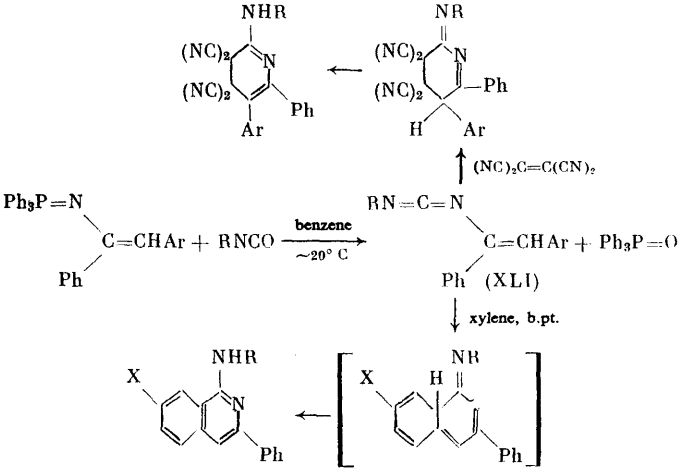
Derivatives of β- and γ-carbolines have been prepared similarly:[49]



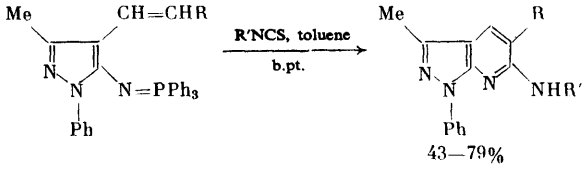
The method has also been applied to the synthesis of thieno- and furo-[3,2-*c*]pyridines as well as thieno[2,3-*c*]pyridines.[50,51]



1-Arylaminoisoquinolines have been synthesised by high-temperature ring closure of unsaturated carbodiimides (XLI), obtainable from the corresponding phosphazo compound and isocyanate. [4+2]-Cycloaddition of this enecarbodiimide to tetracyanoethylene leads to tetrahydro- or dihydro-pyridines, depending on the nature of the substituent.[52]

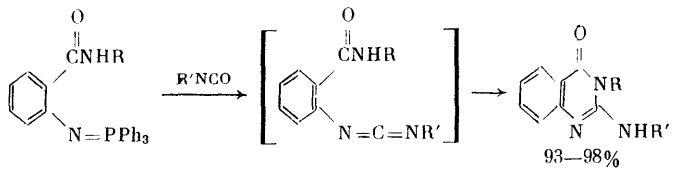


The carbodiimide group can also interact with a neighbouring carbon-carbon double bond activated by a strong electron-accepting group. This is exemplified by the synthesis of 6-aminopyrazolo-[3,4-*b*]pyridines, formed by annelation of the pyridine ring onto a pyrazole derivative.[53]

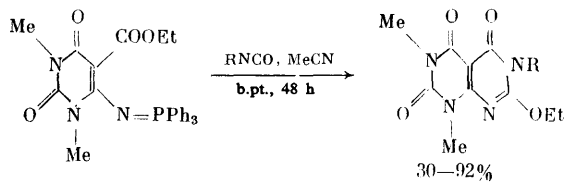


R = MeCO, NO_2; R' = Me, allyl, Ar.

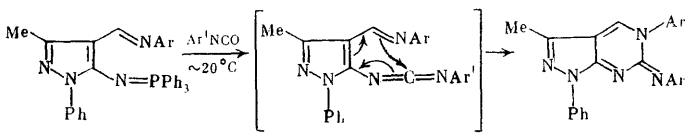
Quinazoline derivatives have been prepared in almost quantitative yield by reaction of *o*-phosphazobenzamides with isocyanates. This is the first example of an intramolecular addition of an amide group to a carbodiimide. The intermediate formation of a carbodiimide is confirmed both by its isolation in the case of *N,N*-disubstituted amides and by the formation of *o*-ureidobenzonitriles by reaction of *N,N*-unsubstituted benzamides.[54]

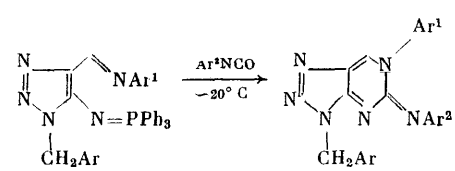


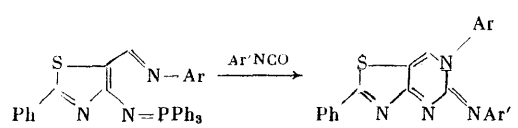
Annelation of the pyrimidine ring can be achieved by cyclisation of a carbodiimidoheterocycle having an *o*-substituted carbethoxy group. Reaction proceeds in refluxing acetonitrile without isolation of the carbodiimide. The resulting pyrimido[4,5-*d*]pyrimidines display a variety of physiological activities.[51]



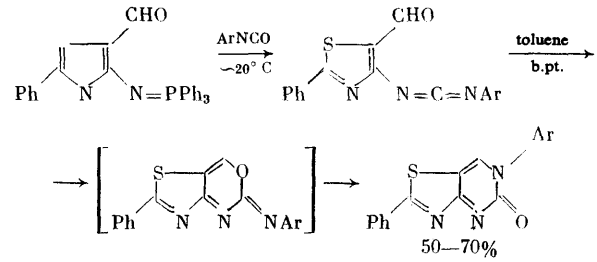
Similarly, annelation of the pyrimidine ring to pyrazole, triazole and thiazole derivatives can be achieved, even at room temperature, by ring closure of carbodiimides with neighbouring aldimine groups. In this way, pyrazolo[5,4-*d*]pyrimidines, 1,2,3-triazolo[5,4-*d*]pyrimidines and thiazolo[4,5-*d*]pyrimidines, having an arylimino group in the 2-position of the pyrimidine ring, have been prepared in high yield,[44,55]



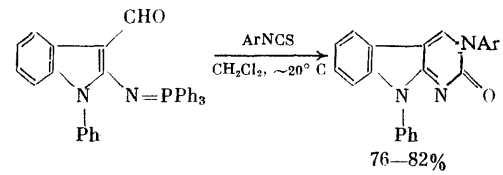




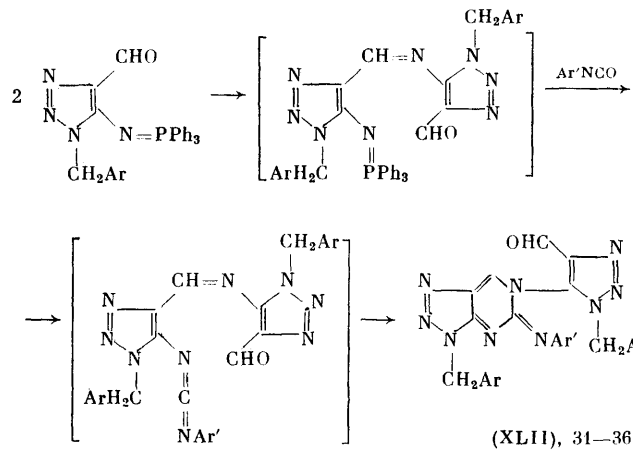
Carbodiimides have also been prepared by interaction of 2-phenyl-4-triphenylphosphazothiazole-5-carboxaldehyde with aryl isocyanates at room temperature. However, the subsequent ring closure to thiazolo[4,5-*d*]pyrimidin-5-ones requires heating in toluene, and is evidently associated with Dimroth rearrangement of the intermediate thiazolo[4,5-*d*]-1,3-oxazines.[44]



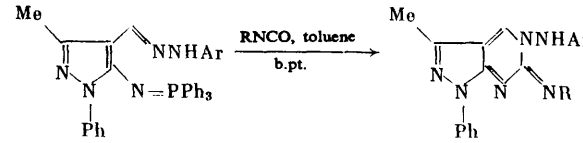
Dimroth rearrangement is also evident in the reaction of a 2-phosphazoindole-3-carboxaldehyde with aryl isothiocyanates, providing pyrimido[4,5-*b*]indoles in methylene chloride at room temperature.[49]



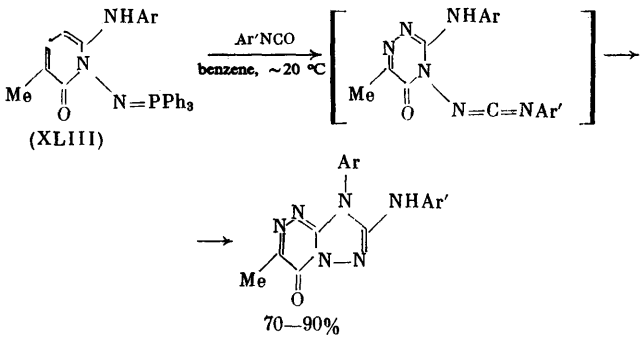
There is no reaction between 5-triphenylphosphazo-1,2,3-triazole-4-carboxaldehydes and aryl isocyanates at room temperature, while heating in toluene affords a more complex product (XLII). Formation of the latter can be explained by an initial aza-Wittig reaction involving the phosphazo group of one molecule with the aldehyde group of a second molecule; the aryl isocyanate then condenses with the remaining phosphazo group, and the intermediate carbodiimide cyclises as before.



Aryl isocyanates react readily on heating with 4-hydrazono-5-phosphazopyrazoles in toluene to give pyrazolo[5,4-*d*]pyrimidines having an arylamino group on a nitrogen atom of the pyrimidine ring.[44]



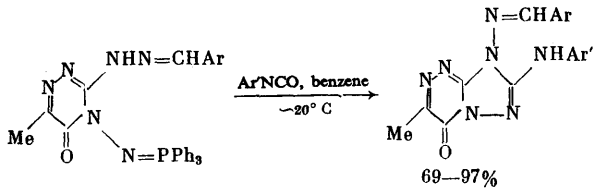
Annelation of the 1,2,4-triazole ring can be achieved by interaction of aryl isocyanates with hetaryls having a phosphazo group on an endocyclic nitrogen atom and an adjacent *o*-arylamino functionality. Thus, 1,2,4-triazolo[5,1-*c*]-1,2,4-triazines are obtainable in high yield by reaction of aryl isocyanates with phosphazotriazines (XLIII), even at room temeprature.[56]



(XLIII)

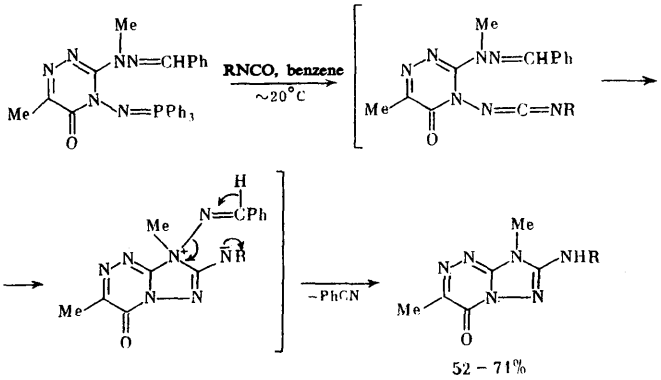
70—90%

The reaction also proceeds smoothly on replacing the arylamino group in the starting phosphazo compound by a benzylidenehydrazino group. In this case, the method provides 1,2,4-triazolo-[5,1-*c*][1,2,4]triazines having a benzylideneamino group on the triazole ring.



69—97%

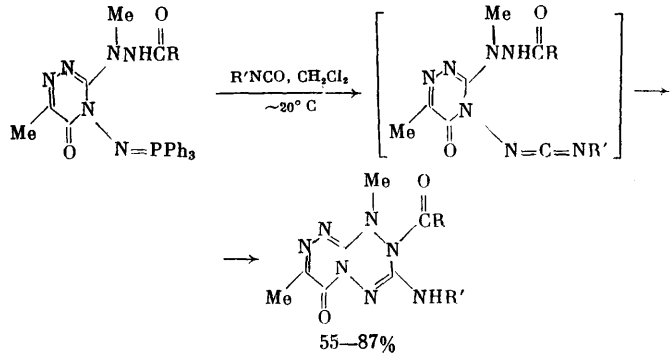
Reaction with the *N*-methylbenzylidenehydrazino analogue of the above phosphazo compound also proceeds under mild conditions, but in this case the benzylideneamino group is eliminated as benzonitrile.[57]



52 - 71%

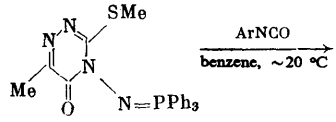
R = Me, Et, Pr, Pr^i, cyclo-C_6H_{11}, $PhCH_2$, allyl.

Molina et al. have reported what in their view is the first example of ring closure of a carbodiimide with a hydrazide group. Thus, 1,2,4-triazino[4,3-*b*]-1,2,4,5-tetrazines have been obtained by reaction of aryl isocyanates with 1,2,4-triazines having a phosphazo group at the 4-position and an acylhydrazino group at the 3-position.[57]

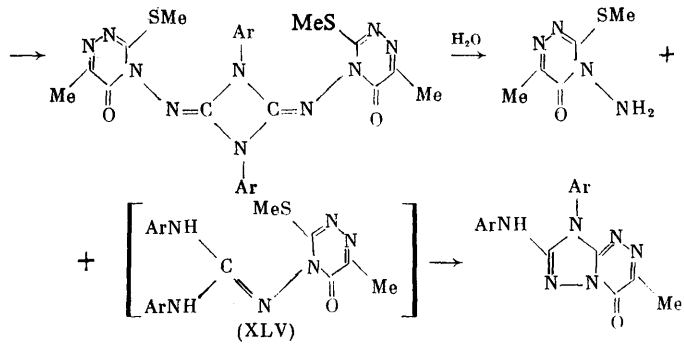


55—87%

On the other hand, the 2-methylthio analogue (XLIV) reacts quite differently. Treatment with aryl isocyanates at room temperature affords a stable carbodiimide dimer, which can be converted to 1,2,4-triazole[5,1-*c*][1,2,4]triazines by prolonged heating in 85% aq. ethanol. It is likely that reaction proceeds via a guanidine intermediate (XLV).[42]

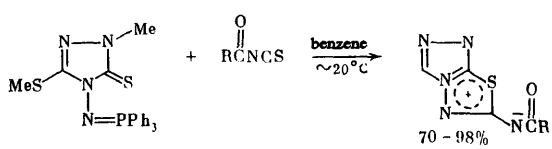


(XLIV)

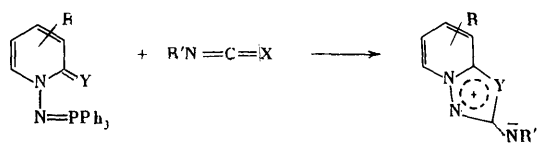


(XLV)

Fusion of a ring onto an *N*-phosphazohetaryl is also possible by reaction of the intermediate carbodiimide with a neighbouring oxo or thioxo group. However, in such cases mesoionic bicyclic systems are formed. Thus, 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazolium-6-aminides[43] are obtained by interaction of 4-triphenylphosphazo-1,2,4-triazoline-3-thiones with acyl isothiocyanates at room temperature, while salts (XLVI) are formed by reaction of 1-phosphazo-2-pyridones and -2-pyridinethiones with isocynates and isothiocyanates under the same conditions.[46,58,59]

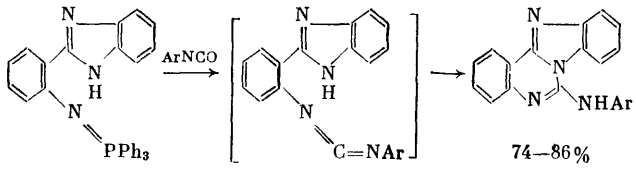


70 - 98%



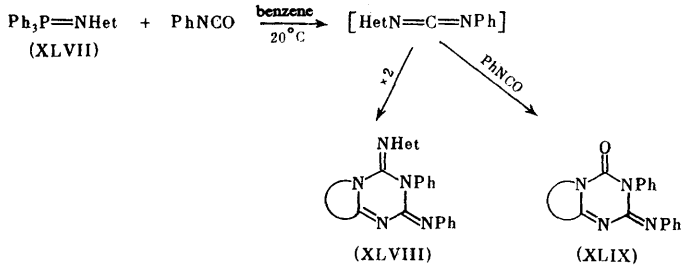
X, Y = O or S.

Ring closure of the carbodiimide function with an imino group can also take place, as in the synthesis of benzimidazo[1,2-*c*]-quinazolines from 2-(*o*-phosphazophenyl)benzimidazoles.[54]



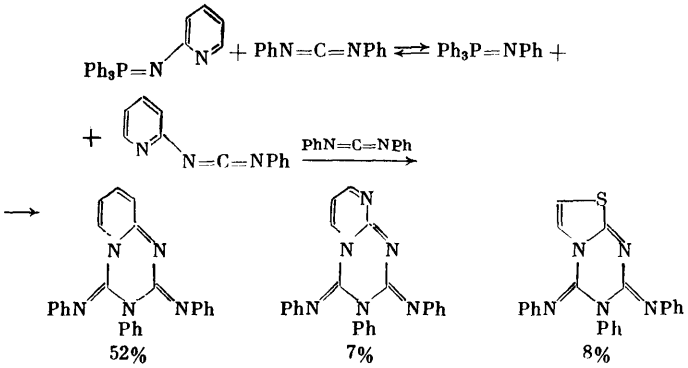
2-Triphenylphosphazohetaryls (XLVII) without an associated functionality react with phenyl isocyanate via intermediate carbodiimides to give either the corresponding carbodiimide dimers (XLVIII) or the bicyclic compound (XLIX), formed by cycloaddition of the carbodiimide with a second isocyanate molecule. In each case, reaction provides an *N*-condensed 1,3,5-triazine system. The proportion of the two products depends on the order of addition of the reactants: by addition of the phosphazo compound (XLVII) to phenyl isocyanate only compound (XLIX) is formed, whereas gradual addition of the isocyanate to the phosphazo compound normally affords a mixture of both products; the phosphazo-quinoline derivative is an exception in that only the product of type (XLIX) is obtained under the latter conditions.

The interaction of phosphazo compound (XLVII) with phenyl isothiocyanate requires a higher temperature than the corresponding reaction with phenyl isocyanate, and the reaction time is much longer. It leads primarily to the product of type (XLVIII).[60]

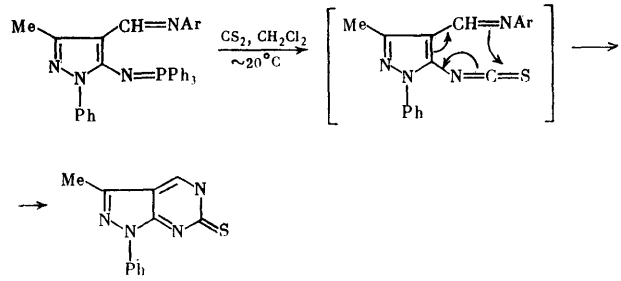


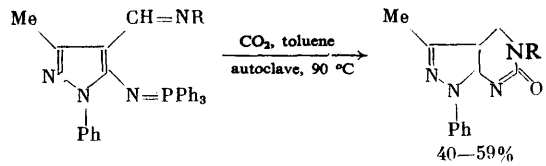
Het = 2-pyridyl, 2-quinolyl, 2-pyrimidyl, 2-thiazolyl

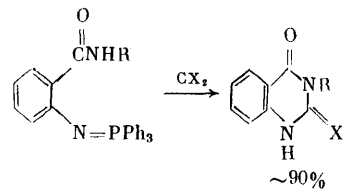
Phosphazohetaryls react with diphenylcarbodiimide on heating in benzene. As with phenyl isocyanate, the reactants condense in 1:2 proportion, affording again a condensed 1,3,5-triazine system with two phenylimino groups. The yield of the pyrido[1,2-*a*]-[1,3,5]triazine analogue, from 2-(triphenylphosphazo)pyridine and diphenylcarbodiimide, is respectable (52%), but normally the yield is poor, as in the case of the pyrimidino- and thiazolo-analogues (7–8%), because of the susceptibility of the carbodiimide to polymerisation.[61]



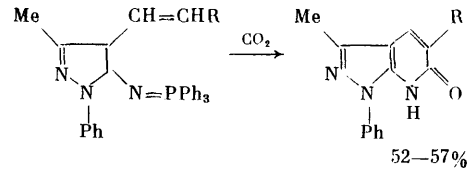
A variety of condensed ring systems have been secured by reaction of carbon dioxide or carbon disulphide with phosphazo compounds via intramolecular condensation of the resulting isocyanates or isothiocyanates with neighbouring aldimine,[44,45] amide or imine groups,[54] as well as with electron-deficient carbon-carbon double bonds.[53] Bicyclic α-oxo- or α-thioxo-*N*-heterocyclics are thereby obtained, for example:



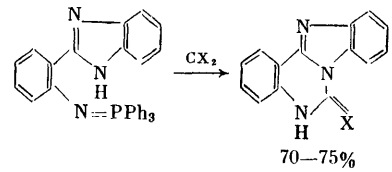




X = O, S,

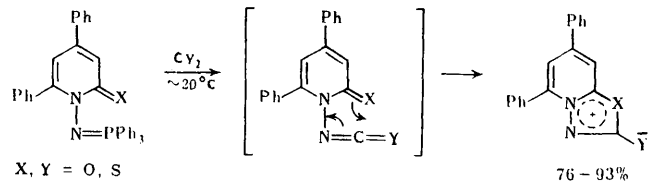


R = MeC(O), NO_2

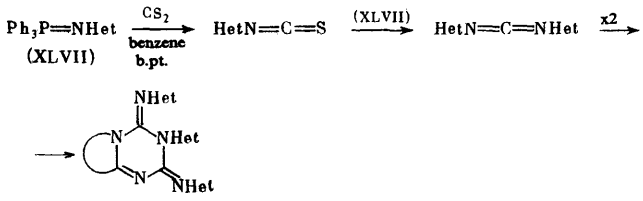


X = O, S.

Mesoionic bicycles are formed by interaction of *N*-phosphazo-α-oxo- or *N*-phosphazo-α-thioxo-*N*-heterocyclics with carbon dioxide or carbon disulphide.[58,59]

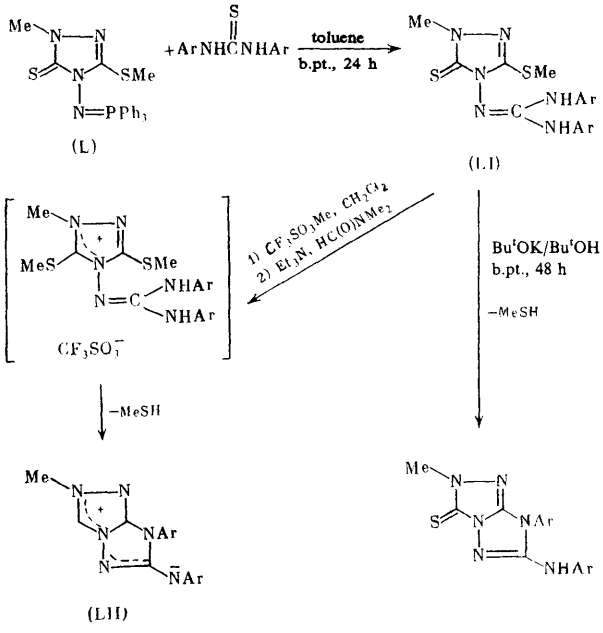


In the absence of a neighbouring functionality, the isothiocynates, obtained as intermediates by reaction of 2-triphenylphosphazohetaryls with carbon disulphide, condense with a second molecule of the phosphazo compound to give the corresponding *N,N'-bis*(hetaryl)carbodiimides which cyclodimerise as shown below.[60]

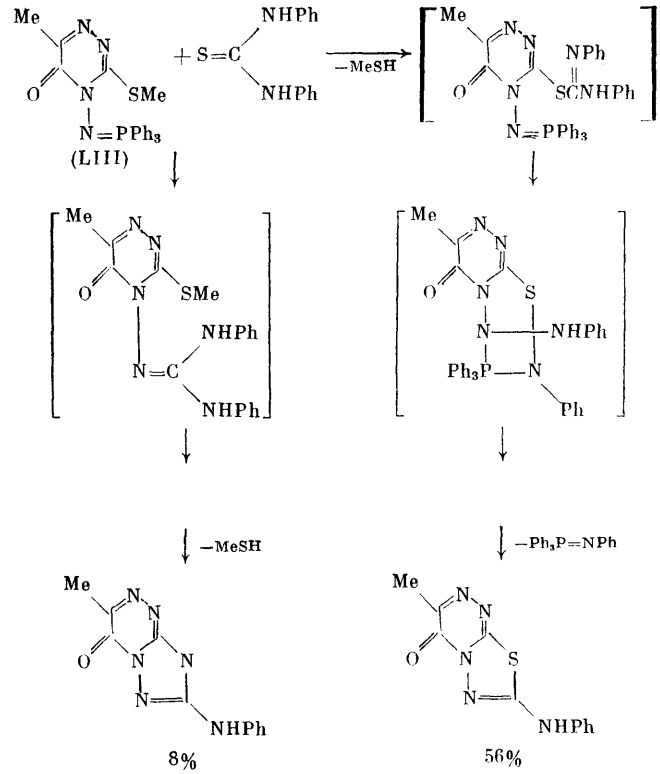


Het = 2-pyridyl, 2-thiazolyl, 2-quinolyl, 2-benzothiazolyl

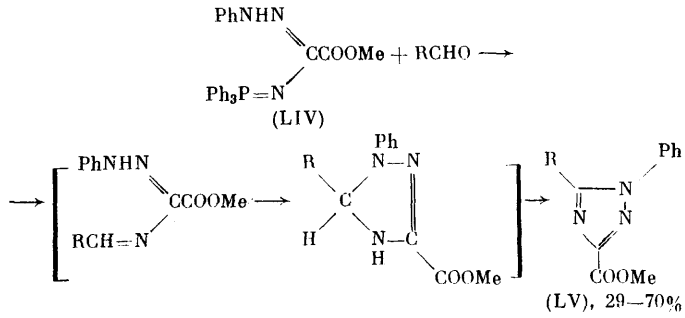
Ring closure to bicyclics can also be achieved by aza-Wittig reaction of phosphazohetaryls with *N,N'*-diarylthioureas. Thus, heating the latter with methylthio-substituted phosphazo compound (L) in toluene affords the guanidine derivative (LI) which cyclises to 1,2,4-triazolo[4,3-*b*]-1,2,4-triazoles in strongly basic media. However, treatment of the guanidine (LI) with methyl triflate followed by triethylamine in dimethylformamide provides the bicyclic betaine (LII).[62]



Two reactions take place in parallel on heating the related 4-phosphazo-1,2,4-triazine (LIII) with *N,N'*-diphenylthiourea in benzene: a small amount of 1,2,4-triazolo[5,1-*c*]-1,2,4-triazine is formed by the same route as shown above for the reaction with (L); however, the principal product is a fused thiadiazole—a 1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazine derivative—formed by condensation of the thiourea with the methylthio group of (LIII) followed by intramolecular condensation of the intermediate isothiourea with the phosphazo group.[42]



5-Substituted monocyclic 1,2,4-triazoles (LV), including derivatives with heterocyclic residues, may be prepared from phosphazohydrazones (LIV) and the appropriate aldehyde in benzene or toluene. Such products have potential pharmacological activity. It is suggested that the intermediate triazolines are oxidised in the last step of the reaction by atmospheric oxygen.[63]

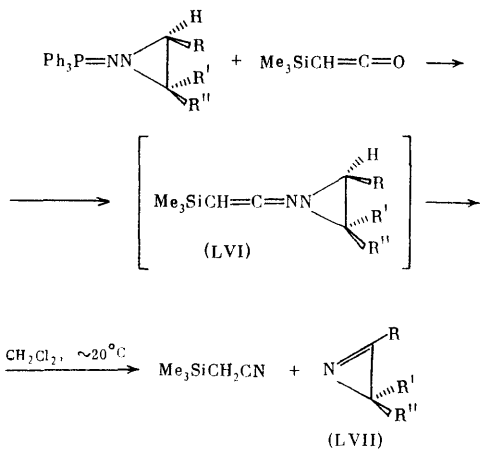


R = H, Me, Pr^i, 4-$O_2NC_6H_4$, 4-pyridyl, 2-furyl, 2-pyrrolyl.

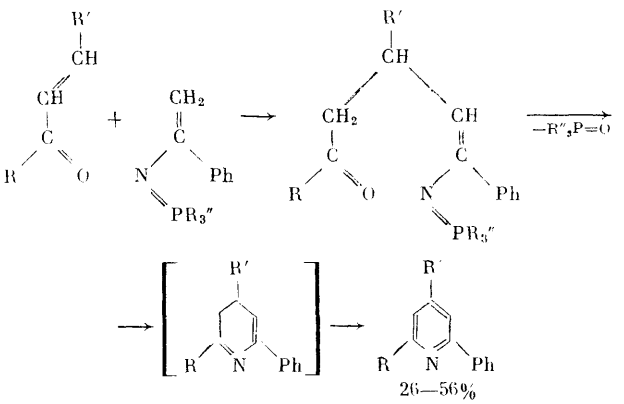
3. Other syntheses incorporating an aza-Wittig reaction

N-(1-Aziridinyl)trimethylsilylketenimines (LVI), obtained by aza-Wittig reaction from *N*-(triphenylphosphazo)aziridines and trimethylsilylketene, may be converted to 2*H*-azirines (LVII) by

elimination of trimethylsilylacetonitrile. The facility of this process depends on the nature of the substituents on the ring and their relative stereochemistry: the *cis*-2,3-diphenyl derivative (LVI, R = R″ = Ph, R′ = H) decomposes at room temperature to give azirine (LVII, R = R′ = Ph; R″ = H) in 70% yield (half-life 15 min), while the *trans*-isomer affords only 25% of this product with a half-life of 24 h.[64]

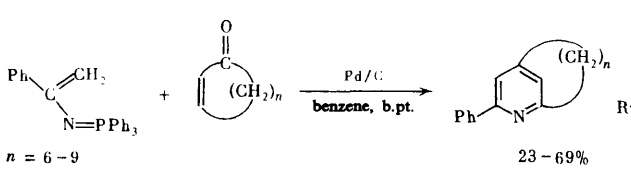


It is considered that the formation of 2-phenylpyridines from α-phosphazostyrenes and α,β-unsaturated ketones involves an initial Michael addition followed by an intramolecular aza-Wittig reaction. Evidently, reaction proceeds via oxidation of the intermediate dihydropyridines.[65,66]

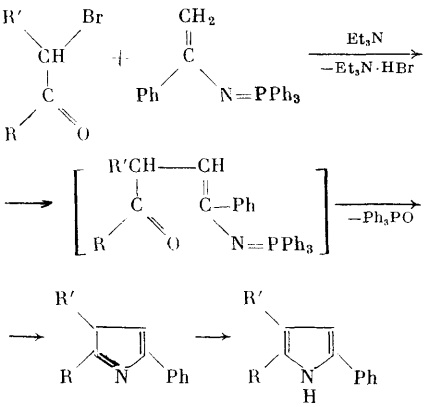


R = Me, Ph; R′ = H, Me, Ph; R″ = Ph, Bu.

[*n*](2,4)Pyridinophanes have been prepared similarly from cyclic α,β-unsaturated ketones with 9 – 12 carbon atoms.[67]

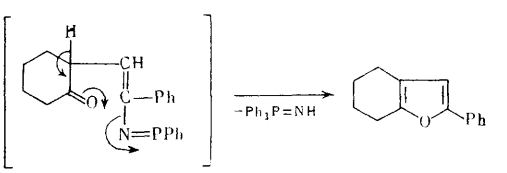


The synthesis of 2-phenylpyrroles from α-phosphazostyrenes and α-bromoketones in the presence of triethylamine is also thought to involve an initial carbon-carbon bond formation, followed thereafter by intramolecular aza-Wittig reaction.[65,68]

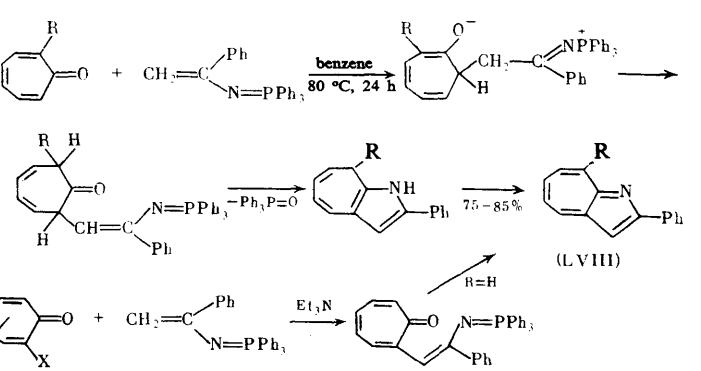


R = Ar, Me; R′ = H, Me, Ph or R + R′ = $(CH_2)_n$ (*n* = 4,5).

The same reaction with 2-bromocyclohexanone proceeds similarly to give the anticipated 2-phenyltetrahydroindole in 20% yield, together with 12% of 2-phenyl-4,5-tetramethylenefuran. The latter arises by ring closure of the intermediate γ-phosphazoketone with elimination of triphenylphosphine imine.[68]

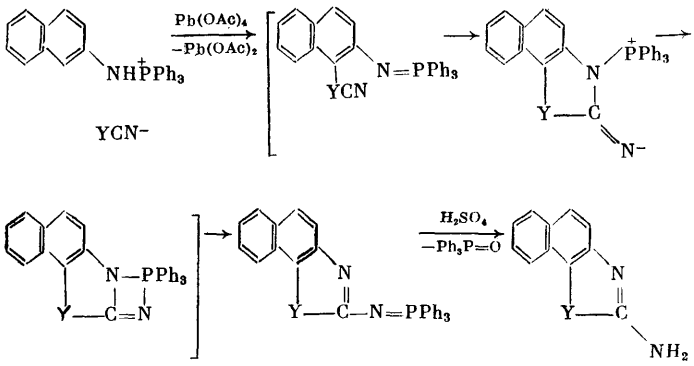


Two methods of preparing 2-phenyl-1-azaazulenes from α-phosphazostryenes have been reported. In a two-step procedure, 2-substituted tropones condense with an α-phosphazostyrene on heating in benzene to give 2-phenyl-8*H*-cycloheptanopyrroles, which are oxidised with nickel peroxide or manganese dioxide to give (LVIII). However, treatment of 2-halogenotropones with an α-phosphazostyrene in the presence of triethylamine leads to the 2-phenyl-1-azaazulenes (LVIII) in one step.[69,70]



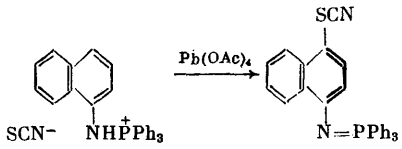
2,7-Diobromo-, 2,4,7-tribromo- and 2,3,5,7-tetrachloro-tropones react similarly to give the corresponding 1-azaazulenes in low yield.[70]

It is likely that oxidation of (2-naphthylamino)triphenylphosphonium thiocyanate and selenocyanate with lead tetraacetate also proceeds through an intermediate phosphazo compound. The interaction involves incorporation of the pseudohalide ion in the 1-position of the naphthalene ring, followed by a rather unusual cyclisation, which can be considered as an aza-Wittig reaction with participation of the cyano group; this is accompanied by an *N*-triphenylphosphino group migration. 2-Triphenylphosphazonaphtho[2,1-*d*]-thiazole and -selenazole are thereby obtained in 60–70% yield, and may be converted to the corresponding 2-aminoderivatives in 70–80% yield on hydrolytic cleavage.[71]

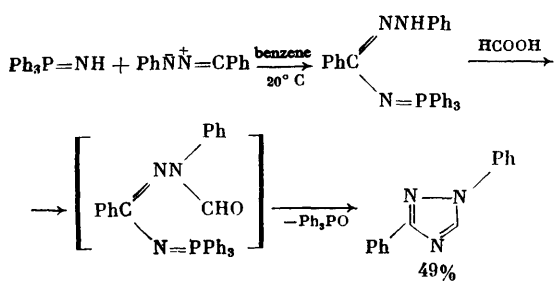


Y = S, Se

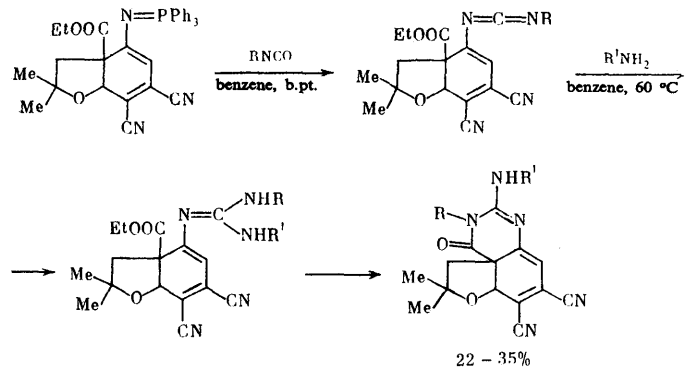
The suggested formation of a 1-thiocyano-2-phosphazonaphthalene in the first stage of the reaction was confirmed by the fact that similar oxidation of 1-naphthylaminotriphenylphosphonium thiocyanate, in which the 1-position is occupied, results in incorporation of the thiocyano group at the *para*-position to give 4-thiocyanato-1-triphenylphosphazonaphthalene in 65% yield.[71]



1,3-Diphenyl-1,2,4-triazole may be prepared via addition of triphenylphosphine imine to the 1,3-dipole, diphenylnitrilimine, followed by cyclisation of the resulting phosphazohydrazone on treatment with formic acid. It is most likely that ring closure proceeds by intramolecular aza-Wittig reaction after *N*-formylation of the intermediate hydrazone.[72]



The pyrimidine ring can be obtained via ring closure of an intermediate carbodiimide having a neighbouring carbalkoxy group, as shown below.



In the presence of an amine, reaction is complicated by formation of an intermediate guanidine, which condenses with the carbalkoxy group to give a low yield of furo[3,2-*e*]quinazolines.[73]

As is apparent from the data which has been collected, many types of N-heterocycle can be synthesised by the aza-Wittig reaction. These range from simple monocyclic compounds to complex polycyclic systems. The phosphazo groups—one of the components of this reaction—is readily prepared, notably from azides, and is resistant to a wide range of reagents. It can thus be retained while adjacent functionalities are manipulated, and then undergo intramolecular condensation as required to give heterocyclic compounds with a variety of different substituents.

In many cases, the resulting compounds are physiologically active or are of potential value as intermediates in the synthesis of physiologically active compounds including analogues of natural products.

A whole range of polycyclic compounds is available for the first time, and for many syntheses the aza-Wittig route is clearly more advantageous than alternative methods. The structures of the new heterocyclic compounds have been established, in most cases, by spectral data, by independent syntheses, and/or by studying their chemical properties.

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