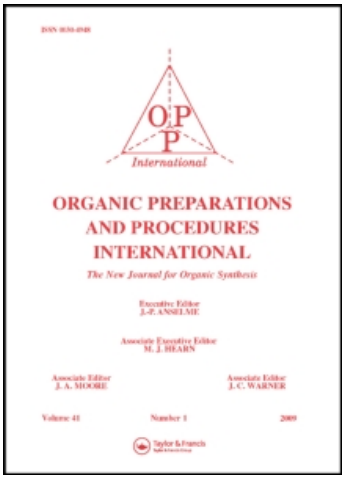

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Shoji Eguchi[a]; Yuji Matsushita[a]; Keizo Yamashita[a]
[a] Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Nagoya, Japan

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THE AZA-WITTIG REACTION IN HETEROCYCLIC SYNTHESIS. A REVIEW

Shoji Eguchi,* Yuji Matsushita and Keizo Yamashita

Institute of Applied Organic Chemistry, Faculty of Engineering
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, JAPAN

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INTRODUCTION

Phosphazo compounds containing a nitrogen-phosphorus double bond (phospha-λ^5-azenes) are called iminophosphoranes and were first prepared *via* the reaction of tertiary phosphines with organic azides (the so-called Staudinger reaction) by Staudinger and Meyer more than seventy years ago.[1] In 1950, Kirsanov prepared these phosphazo compounds by reaction of phosphorus pentachloride with amines.[2] To date, various types of iminophosphoranes have been prepared and the related chemistry involving mechanistic and structural studies, synthesis and reactions of their derivatives and their synthetic applications has been developed.[3] Their reaction with aldehydes or ketones affords the corresponding imines (the Wittig imination or aza-Wittig reaction).[4] However, in contrast to the Wittig olefination with phosphoranes (the Wittig reaction),[5] synthetic applications of the aza-Wittig reaction, in particular to heterocyclic synthesis, have been neglected until the intramolecular version drew the attention of synthetic chemists. During the last several years, extensive studies have been reported on heterocyclic synthesis by utilizing aza-Wittig reaction. This review will focus on recent synthetic applications of the aza-Wittig reaction, with emphasis on nitrogen heterocycles.[6]

I. GENERATION AND REACTIVITY OF IMINOPHOSPHORANES

The simplest, cleanest generation of iminophosphoranes involves reaction of organic azides with tervalent phosphines (the Staudinger reaction, Eq. 1).[1] The reaction generally proceeds at room

$$R'N_3 + R_3P \longrightarrow \left[R_3P{=}N{-}N{=}NR'\right] \longrightarrow R_3P{=}NR' + N_2 \qquad (1)$$

temperature *via* the unstable phosphazide which loses nitrogen to afford the corresponding aza ylide (iminophosphorane).[7,8] The iminophosphoranes are isolable compounds[3] but they are often used without isolation for further conversions. The second method uses the Kirsanov reaction, i. e., amination of phosphorus pentachloride or other polyhalophosphorus(V) compounds with amines (Eq. 2).[2]

$$R'NH_2 + R_3PCl_2 \longrightarrow R_3P{=}NR' + 2\ HCl \quad (2)$$

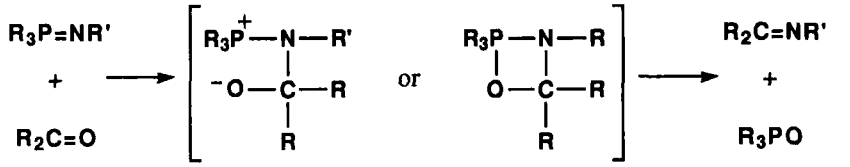
While this method is useful for iminophosphoranes from stable aliphatic and aromatic amines, it is not applicable for N-vinyliminophosphoranes[6e] because of the instability of the corresponding amines. Some other novel methods, e. g., reactions of ylides with Schiff bases[9] and nitriles[10] have been reported (Eq. 3). A redox-condensation reaction of amides, triphenylphosphine and diethyl

$$\begin{aligned} R'N{=}CHR' + R_3P{=}CHR &\longrightarrow R_3P{=}NR' + RCH{=}CHR \\ R'CN + R_3P{=}CHR &\longrightarrow R_3P{=}N{-}CR'{=}CHR \end{aligned} \quad (3)$$

azodicarboxylate affords directly N-acyliminophosphoranes (Eq. 4).[11] This method can be applied also to the synthesis of N-sulfonyl- and N-phosphinyliminophosphoranes.

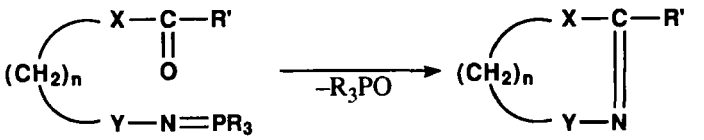
$$R'CONH_2 + R_3P + EtO_2CN{=}NCO_2Et \longrightarrow R_3P{=}NCOR' + (EtO_2CNH)_2 \quad (4)$$

Iminophosphoranes as aza-ylides react both at the nitrogen (strongly nucleophilic) and the phosphorus (available vacant 3d-orbitals) atoms.[3,6] Therefore, derivatives of an iminophosphorane can be prepared with relative ease, in particular by using N-trimethylsilyl and/or P-alkoxy iminophosphoranes. However, one of the most fascinating reactions for heterocyclic synthesis is the imination of carbonyl compounds (Eq. 5).



(5)

The intramolecular version (Eq. 6) has drawn considerable attention recently because of its



(6)

high potential in heterocyclic synthesis. The reactivity towards cyclization of the intramolecular aza-Wittig reaction is controlled by the following factors.

a) Chain length (product ring-size and ring strain): generally 5, 6, or 7-membered cyclic imines can be obtained by this reaction but 3- and 4-membered rings cannot because of excessive strain of the corresponding intermediate oxazaphosphetanes.[12]

b) The reactivity of the carbonyl group: in general, only aldehydes and ketones are sufficiently reactive for intermolecular reactions but ester,[12,13] amide,[14] and imide[15] carbonyls are also reactive in

the intramolecular case, at least for 5-membered ring formation.

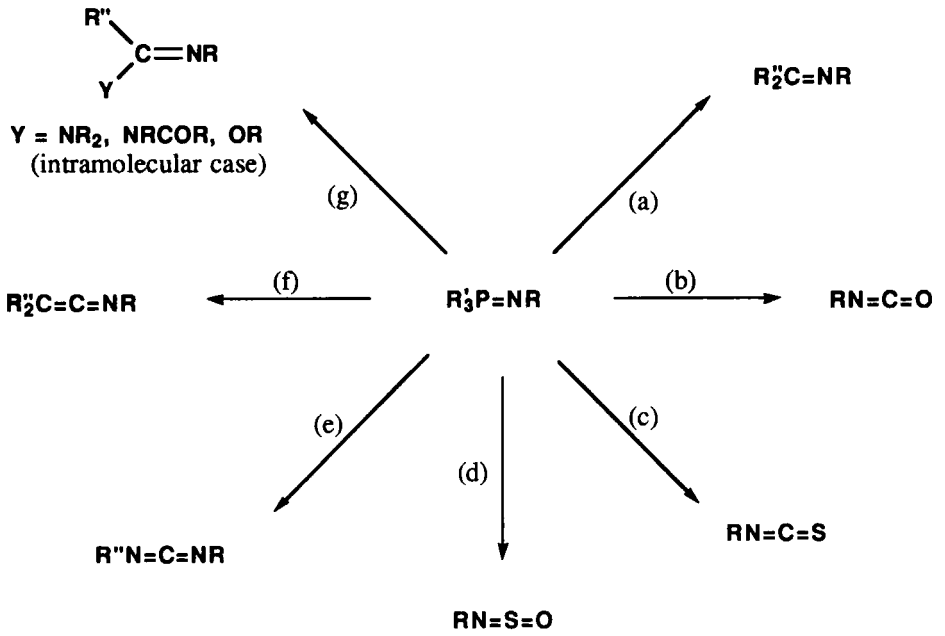
c) Substituent groups on N and P: for Y = alkyl and aryl groups, Wittig-imination occurs but for the case of Y = acyl, the corresponding nitriles are produced[16] except for one example.[17] The substituent R' on P has a considerable effect on the reactivity but the higher reactivity of tributylphosphine, for example, does not always result in better yields for heterocyclic synthesis (as discussed in section III).

A multinuclear NMR study of the structure and properties of iminophosphoranes, in particular, the effect of substituents on the dπ-pπ bonding, has been reported also recently by Pomerantz *et al.*[18] Some examples of general synthetic application are discussed in section II.

II. SYNTHETIC APPLICATIONS OF IMINOPHOSPHORANES

The Wittig imination of carbonyl compounds with iminophosphoranes is one of the most useful reactions for the synthesis of nitrogen containing functionalities (Scheme 1). As mentioned in

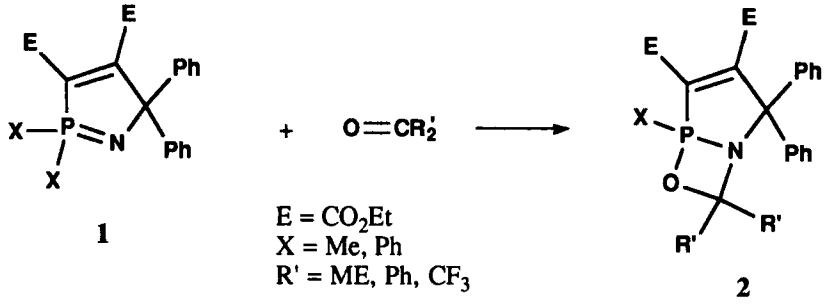
Scheme 1



a) R''_2CO b) CO_2 c) CS_2 d) SO_2 e) R''_2NCO or R''NCS f) $R''_2C{=}C{=}O$ g) R''COY

section I, aldehydes and ketones are reactive in intermolecular reactions but esters, amides and imides are only reactive for some intramolecular cases. However, carbon dioxide, ketenes, isocyanates, carbon disulfide, isothiocyanates and sulfur dioxide are reactive even in intermolecular reactions, providing convenient routes to various heterocumulenes (Scheme 1). Schmidpeter and Criegern[19] first demonstrated that an intermediate oxazaphosphetane was formed in the aza-Wittig

reaction by isolation of the corresponding [2+2] cycloadduct **2** using the 5-membered iminophosphorane **1** (Eq. 7). Recently, Barluenga *et al.*[20] devised a one-pot synthesis of 2-vinyl-1-azadienes[3]



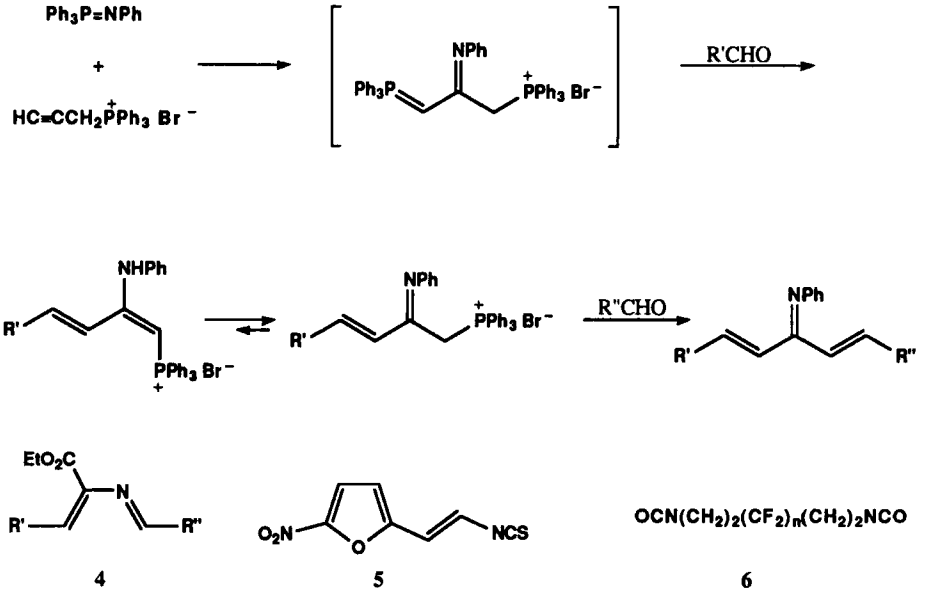
1

E = CO_2Et
X = Me, Ph
R' = ME, Ph, CF_3

2

(7)

starting with an iminophosphorane and propargylphosphonium bromide (Eq. 8). The use of N-vinyliminophosphoranes in the aza-Wittig reaction provides a convenient and direct route to 2-aza-1,3-dienes **4**.[21] The aza-Wittig reaction was recently applied to the synthesis of N-(silylmethyl)imines,



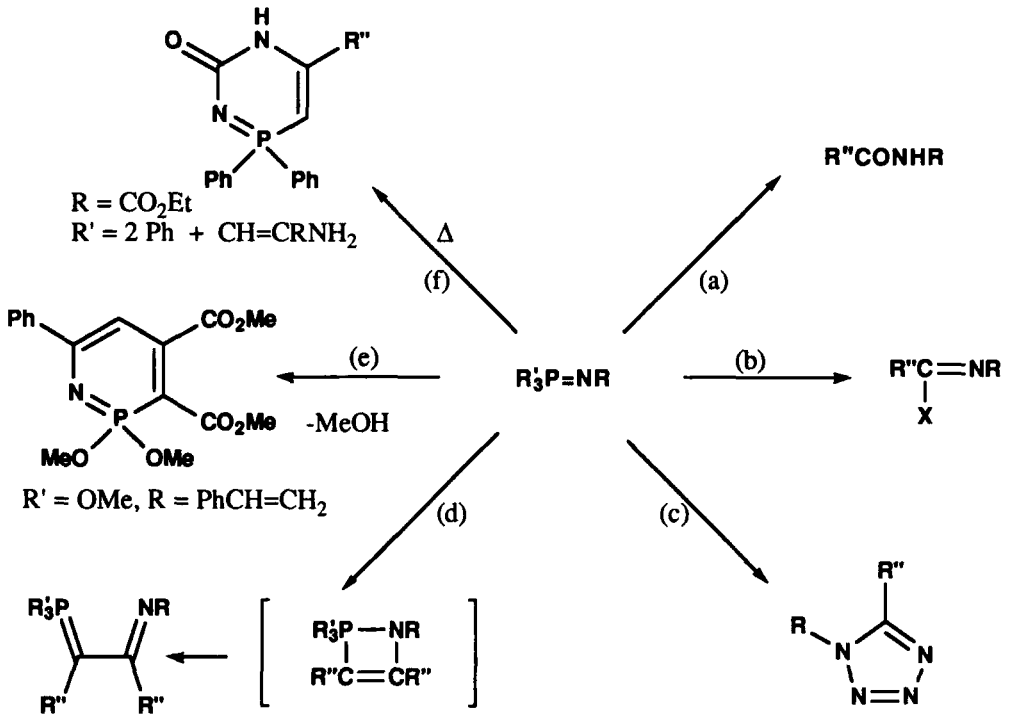
(8)

4 **5** **6**

heterocumulenes,[22] and also antibacterial 5-nitro-2-furylvinylene isothiocyanate **5**.[23] However, the fluorinated diisocyanate **6** was obtained only in low yield *via* the aza-Wittig route.[24] Successful application of the above heterocumulene synthesis to preparation of heterocycles will be discussed in section IV.

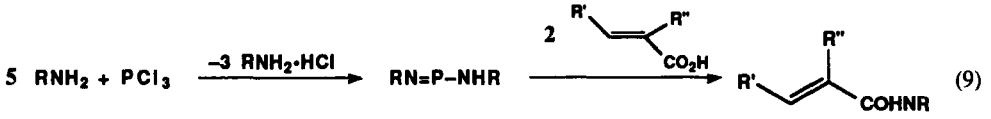
Other useful synthetic reactions with iminophosphoranes are summarized in Schemes 2 and 3. Thus, reaction with a carboxylic acid produces the corresponding amide (**a** in Scheme 2). This reaction was utilized as a one-pot synthesis of amides from carboxylic acids with organic azides or

Scheme 2



a) $R''CO_2H$ b) R"COX c) R"COCl, NaN_3 d) R"C≡CR"[2+2] e) DMAD [4+2] f) Neat

with amines in the presence of a tertiary phosphine or phosphonium bromide.[25a] A new 2-alkenamide synthesis has been developed recently by this type of reaction (Eq. 9).[25b] The reaction with an acid halide affords an imidoyl halide (**b**).[26] This reaction has been used for the synthesis of

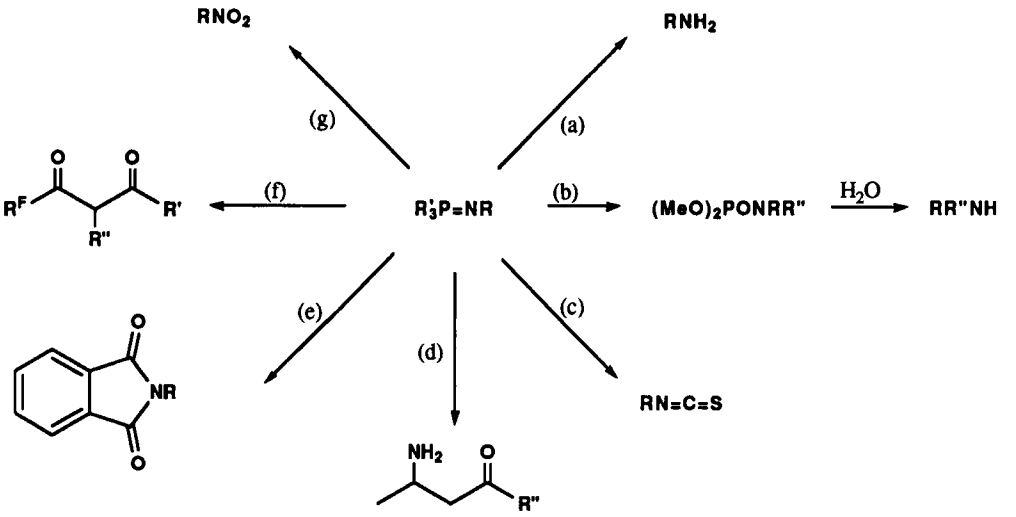


(9)

1-substituted 2-azadienes[27] and also for the preparation of tetrazoles (**c**).[28] The reaction with DMAD gives the corresponding β-iminophosphonium ylide *via* [2+2] cycloaddition (**d**) rather than Michael addition.[29] However, the reaction of N-vinyliminophosphorane with DMAD affords the corresponding 1,2-azaphosphorine *via* [4+2] cycloaddition (**e**).[30] P-β-Enaminoiminophosphoranes were converted to novel 2-oxo-1,3,4-diaza-λ^5-phosphinines on heating (**f**).[31]

Iminophosphoranes are versatile reagents for synthesis of amines and their derivatives (Scheme 3). Simple hydrolysis of iminophosphoranes or N-alkylphosphoroamidates, obtainable after alkylation of alkoxyiminophosphoranes gives the corresponding amines (**a** and **b**). These methods

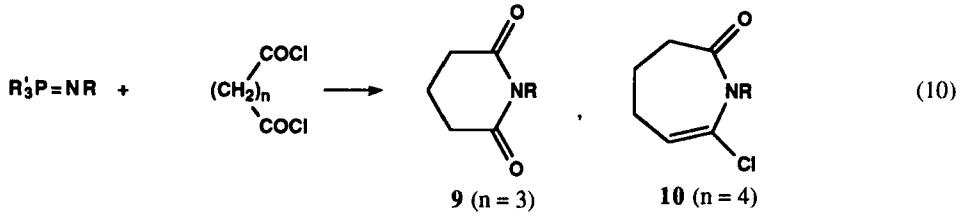
Scheme 3



a) H_2O b) R"I (R' = OMe) c) R"MgBr or R"Li (R = 1-benzotriazolyl) d) $R"COCH_2COMe$ (R = $SiMe_3$) e) phthalic anhydride f) H_2O ($R = R^FC=C(R")COR'$)

were applied recently to the synthesis of alkylpolyamines **7**[32] and vicinal diamines **8**.[33] A novel

synthesis of amines has been devised recently by Katritzky *et al.* utilizing N-benzotriazolylmethylliminophosphorane (**c**).[34] Reaction of N-trimethylsilyliminophosphorane with β-dicarbonyl compounds affords enamine derivatives (**d**).[35] The reaction with anhydrides gives the corresponding imides (**e**).[36] The reaction with diacyl chlorides has been reported recently to afford the corresponding imides (n = 2, 3) and azepine derivatives (n = 4) such as **9** and **10** respectively (Eq. 10).[37]

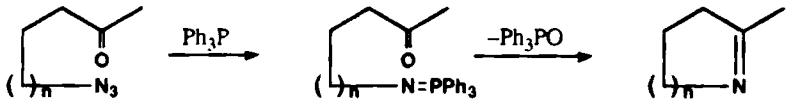


(10)

Hydrolysis of N-vinyliminophosphoranes has been applied also to the synthesis of 3-perfluoroalkyl-1,3-dicarbonyl compounds (**f**).[38] A new synthesis of nitro compounds *via* iminophosphoranes was devised by Corey *et al.*, and this method was utilized for the synthesis of nitro sugar derivatives (**g** in Scheme 3).[39]

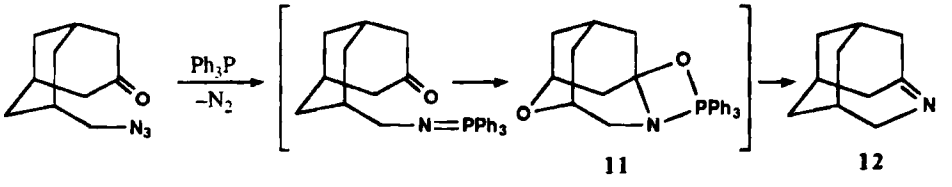
III. HETEROCYCLIC SYNTHESIS *via* INTRAMOLECULAR AZA-WITTIG REACTIONS

Application of aza-Wittig reactions to heterocyclic synthesis has drawn considerable attention from synthetic chemists only after the synthesis of simple 5-7 membered cyclic imines by Lambert, Vaultier and Carrié was reported in 1982 (Eq. 11).[40] This imine route has been applied



(11)

successfully to the synthesis of strained bridgehead imines such as 4-azahomoadamant-3-ene **12** and 4-azahomobrend-3-enes **13** by our group (Eq. 12).[17] The oxazaphosphetane **11** was observable by



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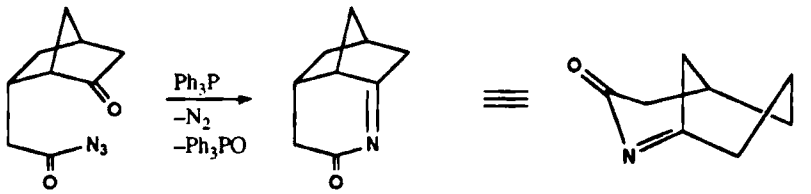
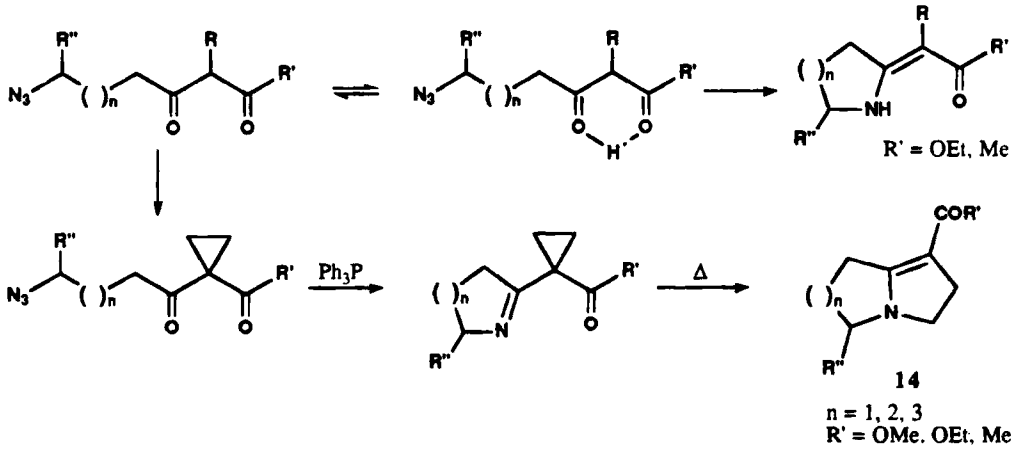
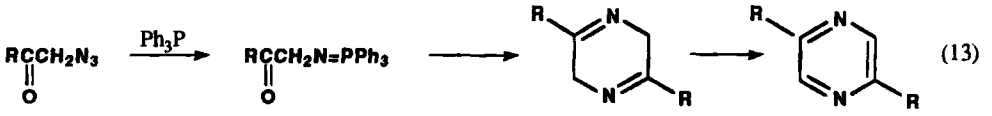


NMR spectroscopy because of its kinetic stability. Carrié *et al.* extended the intramolecular aza-Wittig reaction to the synthesis of vinylogous urethanes and amides (Scheme 4).[41a] Combination of this imination and cyclopropyl rearrangement provided a new synthesis of the pyrrolizidine skeleton

Scheme 4

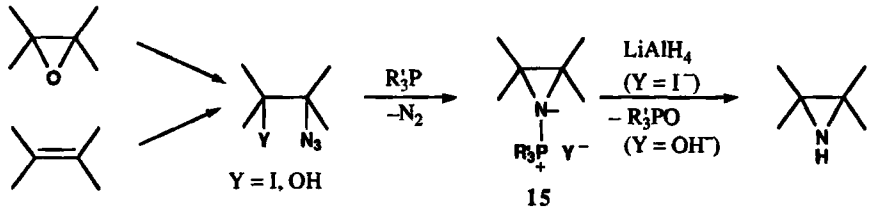


14 (n = 1).[41b] However, application of this intramolecular imination to 1-azetine synthesis (for n = 0 case of Eq. 11) gave only trace amounts of the corresponding azetidine derivatives after $LiAlH_4$ reduction.[12] The formation of pyrazine but not of 1-azirine from the reaction of α-azidoketones with Ph_3P is also well known (Eq. 13).[42] However, it should be noted that the reaction of 2-iodo- or



(13)

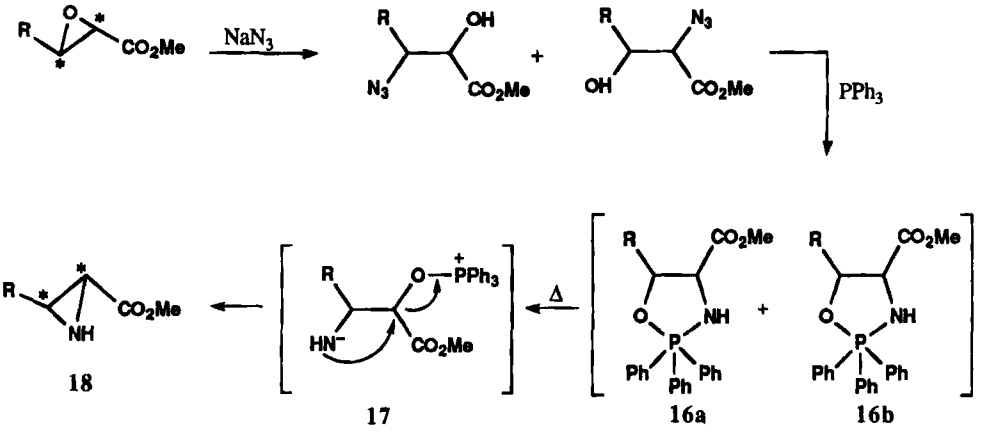
2-hydroxyazides with phosphorus(III) compounds is known as an important synthetic route to aziridines (Eq. 14).[43,44] Optically active 1H-aziridine-2-carboxylic esters have been prepared by



(14)

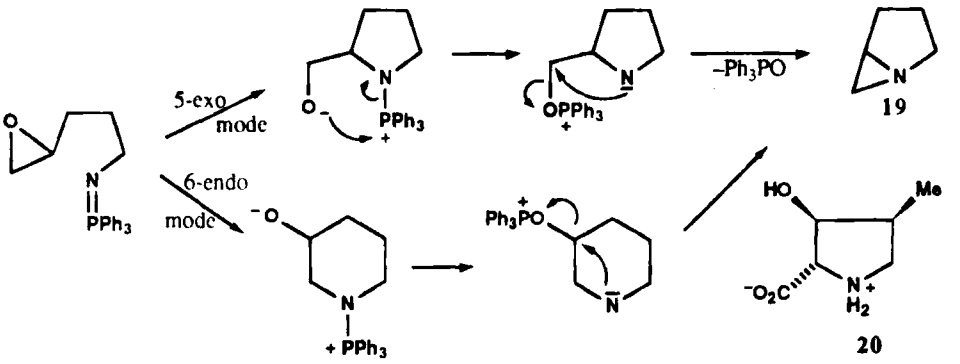
Zwanenburg *et al.* using the type of pathway summarized in Scheme 5.[45] The intermediate

Scheme 5

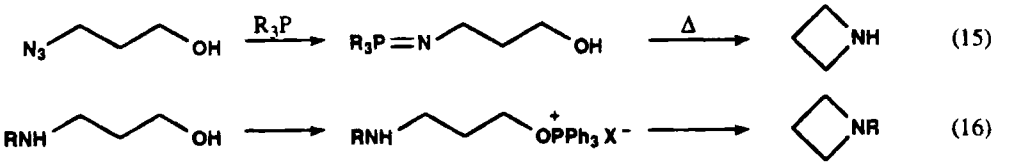


oxazaphospholidines **16a,b** were isolated and characterized by X-ray diffraction analysis and the stereospecific formation of **18** was explained *via* initial N-P bond cleavage of **16**, followed by intramolecular S_N2 displacement of the Ph_3PO group. Furthermore, Mulzer *et al.* have devised a novel synthesis of hydroxylated 1-azabicyclo[3.1.0]hexanes by stereo- and regiocontrolled Staudinger aminocyclization (Scheme 6).[46] Treatment of an ω-epoxyazide with Ph_3P affords the corresponding iminophosphorane. The strongly nucleophilic nitrogen[47] opens the epoxide either in a 5-*exo*- or a 6-*endo* fashion[48] to generate the corresponding betaines which undergo an N-O migration

Scheme 6

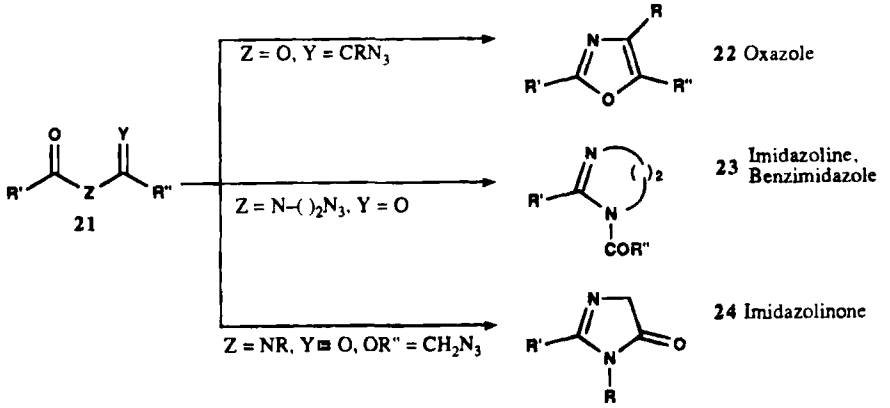


of the phosphorus group to give the Mitsunobu type betaines.[49] The S_N2 displacement of Ph_3PO as in **17** of Scheme 5 affords the bicyclic aziridine **19**. The 5-*exo* mode is postulated as the more likely process from the known examples.[50] Mulzer *et al.* have applied this novel method to the synthesis of (2S,3S,4S)-3-hydroxy-4-methylproline (HMP) **20**, a non-proteinogenic amino acid found in the cyclopeptides echinocandin **B-D**.[51] Azetidines have also been similarly prepared (Eq. 15 and 16).[52,53] The latter route (Eq. 16) using PPh_3-CBr_4 or PPh_3-DADC (Mitsunobu reaction)[49] is useful for the formation of N-substituted azetidines.



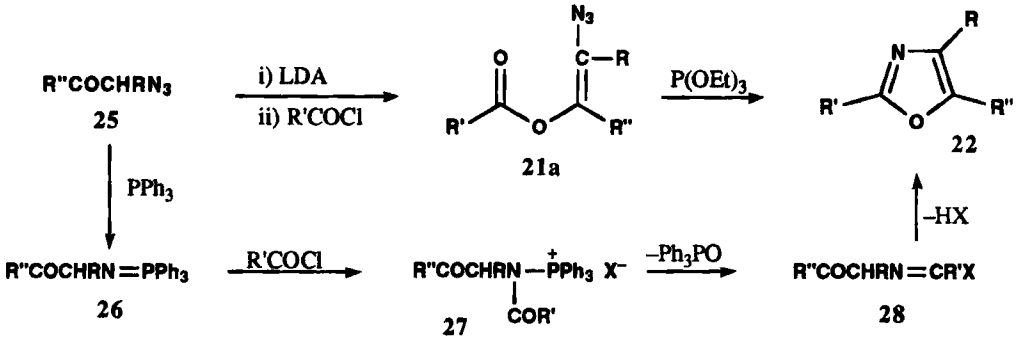
The intramolecular aza-Wittig reaction is very useful for the synthesis of 5- and 6-membered nitrogen heterocycles. For example, oxazole **22**,[54,55] imidazoline **23**,[15] benzimidazole,[15a,56] and imidazolinone **24**[57] can be obtained in good yield from appropriate azido derivatives **21** (Scheme 7). In our

Scheme 7



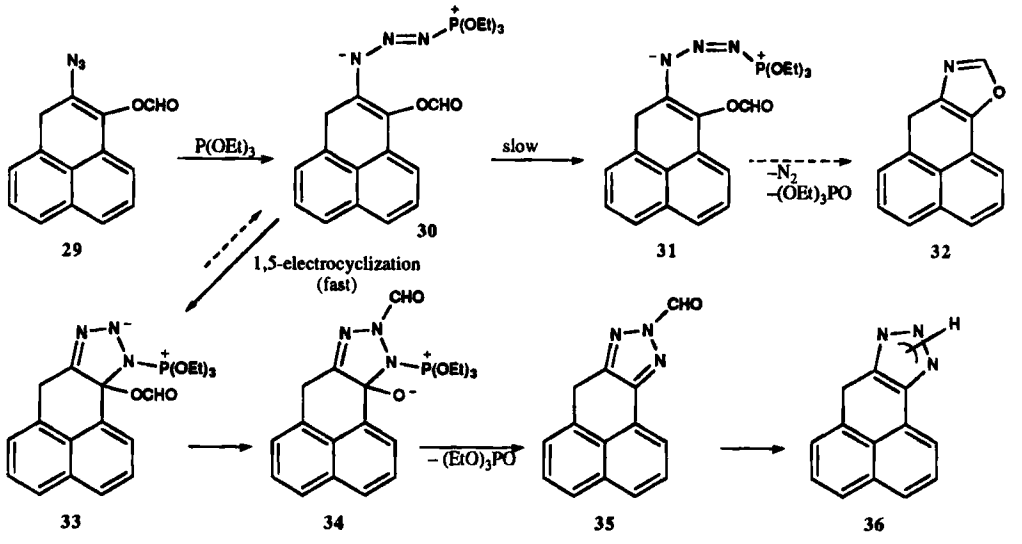
oxazole synthesis,[54a] α-azido ketone **25** was enol acylated to **21a** which gave oxazole 22 on treatment with triethyl phosphite (Scheme 8). In the Zbiral synthesis,[55] **25** was treated with triphenylphosphine first and the then produced iminophosphorane **26** was acylated to **27** which gave oxazole **22** *via* **28**

Scheme 8



(Scheme 8). The former route involves less side-reactions and gives better yields. However, it should be mentioned here that this oxazole synthesis is not successful for 2-unsubstituted oxazoles. Freeman, Szmuszkovicz *et al.*[58] have found very recently that reaction of β-azidoformate **29** with triethylphosphite gives 1H-1,2,3-triazole **36** *via* **35** rather than oxazole 32 (Scheme 9).[56]

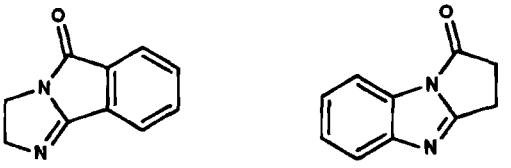
Scheme 9



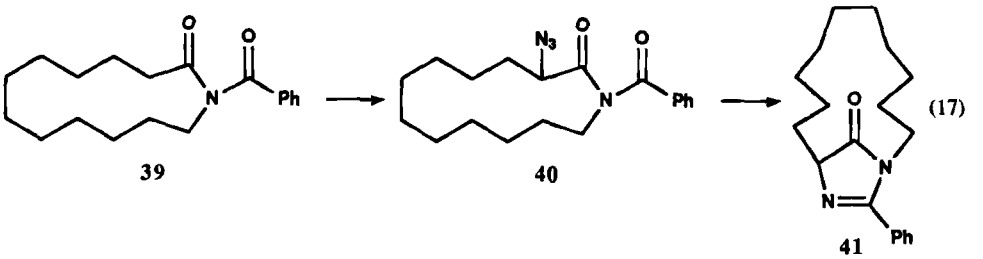
In this case, the *cis* phosphazide **31**, a possible intermediate to the iminophosphorane, seems to be much more hindered sterically than the *trans* form **30**, and hence, a competitive 1,5-electrocyclization of **30** occurs exclusively to give **33** which can be converted to **35** *via* **34**.

Cyclization at imide carbonyl provides a facile route to imidazoline **37**[15b] and benzimidazole

38.[56] In the imidazolinone synthesis,[57] the use of lactams as starting materials provides a convenient route to fused and bridged types of imidazolinones such as **41** (Eq. 17).



37 **38**

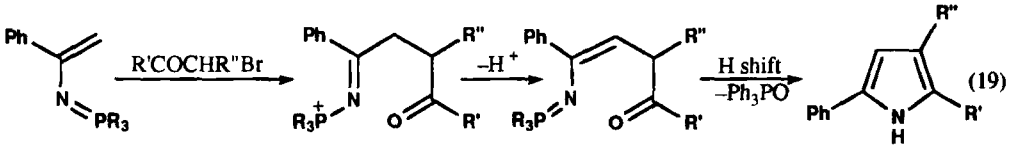


39 **40** **41** (17)

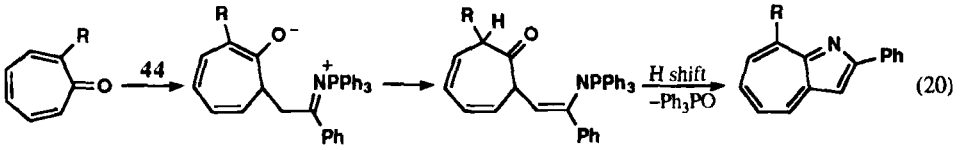
Pyrrole synthesis by aza-Wittig reaction has been reported also. Thus, the intramolecular aza-Wittig reaction of azido ester **42** gave 2-methoxypyrroles **43** (Eq. 18).[59] A more general route to

42 **43** (18)

pyrroles has been reported by Nitta *et al.*[60] Thus, the reaction of N-vinyliminophosphorane **44** with α-bromoketones yields pyrroles **47** *via* the intramolecular aza-Wittig reaction of **46** derived from the initial adduct **45** (Eq. 19). The reaction of **44** with tropone provided a facile route to 1-azaazulenes **50** (Eq. 20).[61]



44 **45** **46** **47** (19)



48 **49** **50** (20)

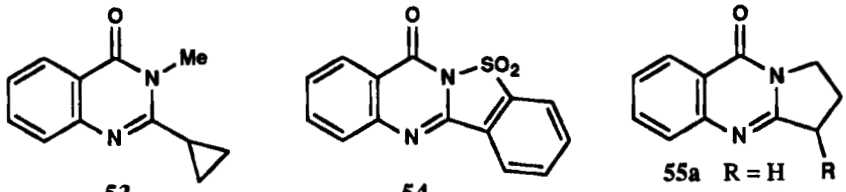
The intramolecular aza-Wittig cyclization also provides an excellent route to 6-membered nitrogen heterocycles. For example, we have developed a facile and mild route to quinazolinone **52**

(Eq. 21).[57,62a] This route is useful for the synthesis of quinazolinones such as **53** having acid-labile

(21)

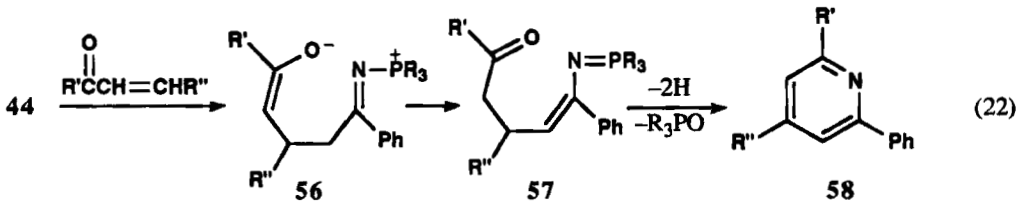
51 **52**

substituents and also for quinazoline alkaloids such as deoxyvasicinone **55a**[57] and vasicinone **55b**.[62b] A hetero-ring fused quinazolinone **54** has been obtained by the same route.[56]



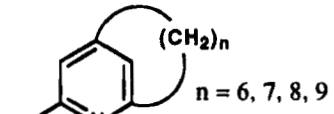
53 **54** **55a** R = H **55b** R = OH

The synthesis of pyridines has also been developed by using N-vinyliminophosphorane **44**. The reaction of **44** with enones affords pyridine **58** *via* **56** and **57** (Eq. 22).[63] This approach has been shown to be useful for the [n](2,4)pyridinophane ring system **59**.[64] The reaction of cycloheptatrienyl-



(22)

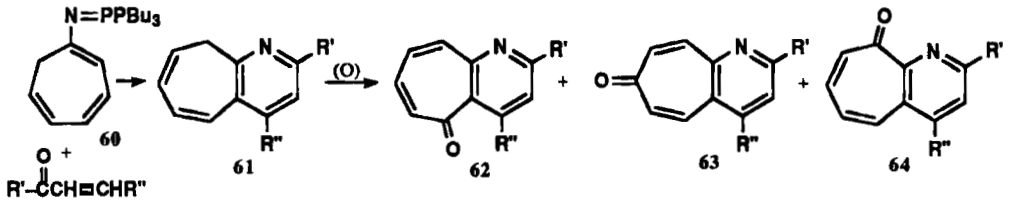
56 **57** **58**



59

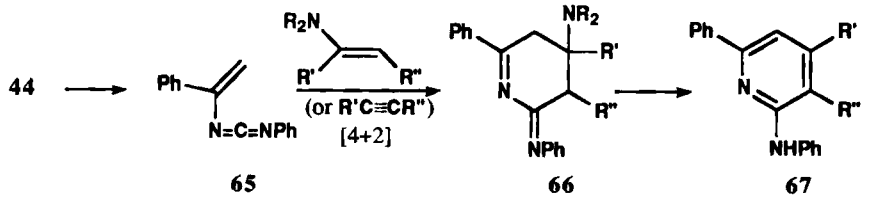
iminophosphorane **60** with enones affords 9H-cyclohepta[b]pyridine derivatives **61** which were oxidized to the corresponding pyridotropones **62-64** (Scheme 10).[65] The cycloaddition of conjugated

Scheme 10



60 **61** **62** **63** **64**

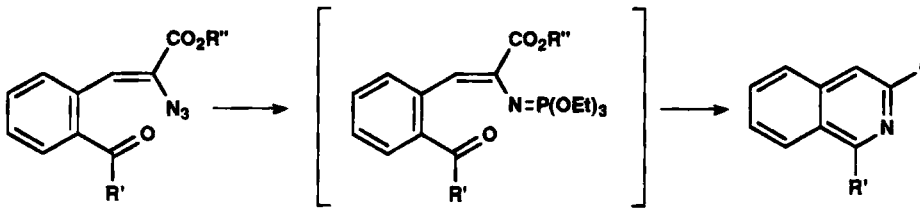
carbodiimides **65**, derived from **44**, with enamines and acetylenes is also reported to afford 2-aminopyridine derivatives **67** (Eq. 23).[66] The electrocyclization of conjugated carbodiimides also



(23)

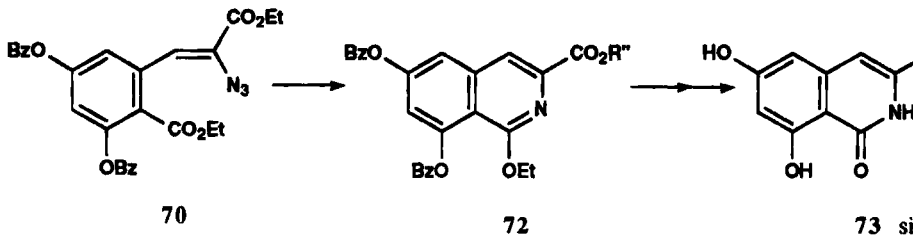
provides a facile route for pyridine derivatives (see section IV).

The Saunders' synthesis of 2-substituted quinolines from *o*-azidocinnamate and triethyl phosphite under irradiation belongs now to an earlier example of heterocyclic synthesis by aza-Wittig reaction.[3, 67] Recently, Rees' group has devised a short synthesis of isoquinolines **70** using the azide **68** utilizing intramolecular aza-Wittig reaction (Eq. 24)[68] and applied this method successfully to



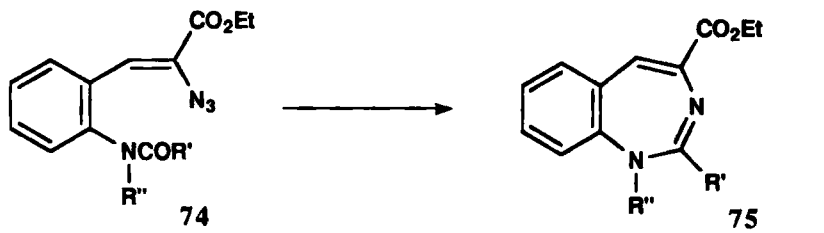
(24)

synthesis of the isoquinolone alkaloid siamine **73** (Eq. 25).[69]

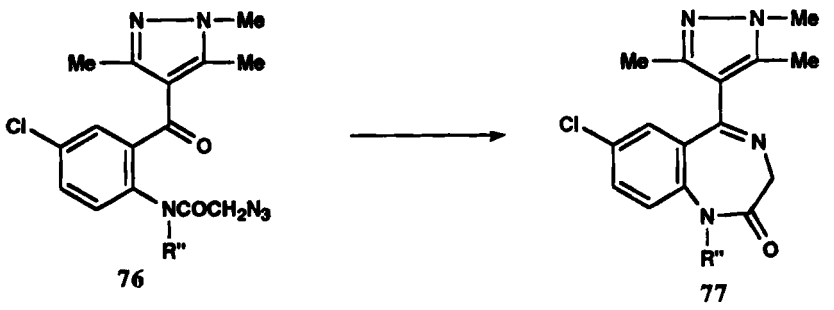


(25)

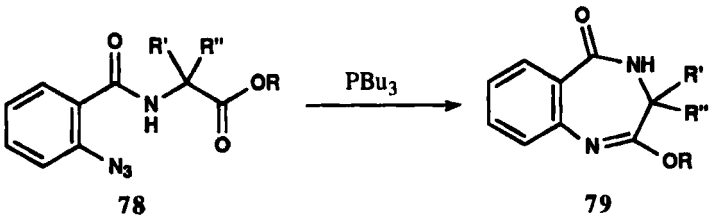
7-Membered nitrogen heterocycles such as benzo-1,3-diazepines **75**[70] and benzo-1,4-diazepines **77**[71] and **79**[72] have been synthesized recently utilizing the intramolecular aza-Wittig reaction (Eq. 26-28). Only one example of cyclization to an 8-membered ring by intramolecular



(26)

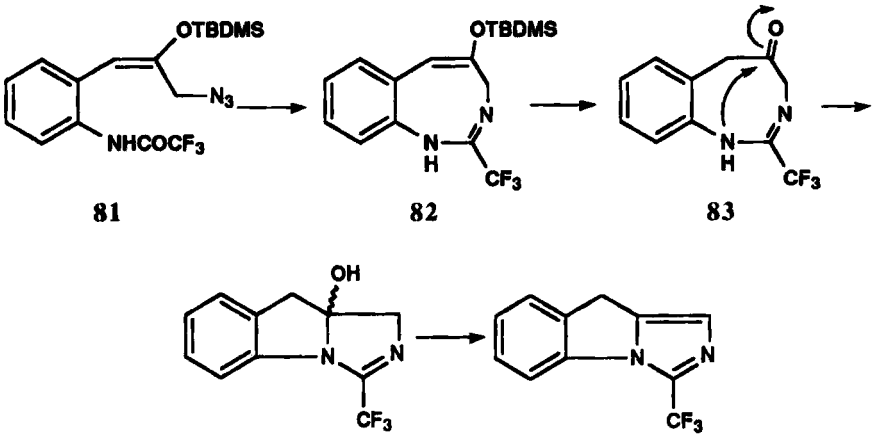


(27)



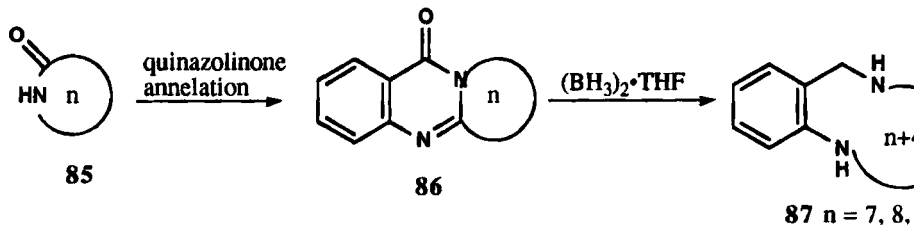
(28)

aza-Wittig reaction seems to have been reported. However, the initial 1,3-benzodiazocine product **81** was not isolable and the imidazoindole derivative **84** was obtained instead as shown in Eq. 29.[73]



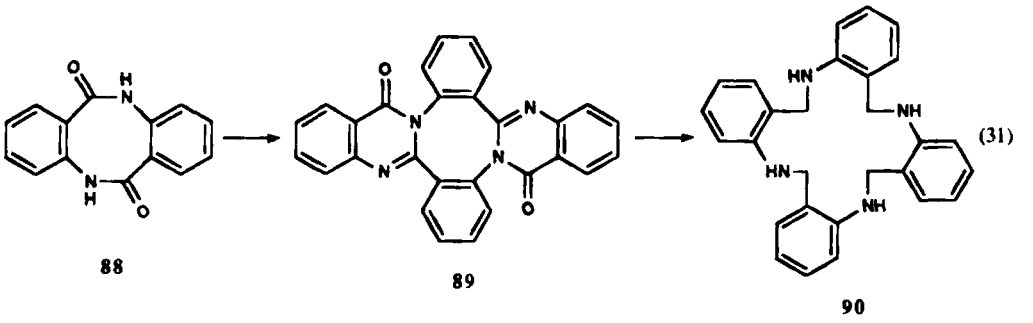
(29)

The direct synthesis of macrocyclic nitrogen heterocycles by the intramolecular aza-Wittig reaction has not yet appeared, but a novel ring-expansion route to such heterocycles starting from fused quinazolinones **86** (readily obtainable by intramolecular aza-Wittig reaction) has been developed recently by us (Eq. 30).[74] Quinazolinone annelation of lactam **85** affords fused quinazolinone



(30)

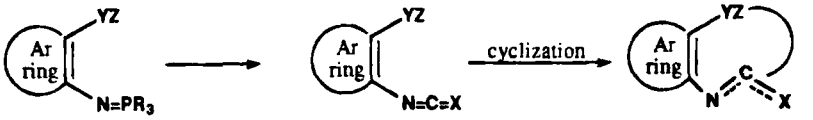
86 which undergoes reductive ring-enlargement on treatment with borane to give macrocyclic 1,5-diamine **87** in good yield. Application of this method to the synthesis of 1,5,9,13-tetraaza-2,3;6,7;10,11;14,15-tetrabenzocyclohexadecane **88** was successful as well.[75]



88 **89** **90** (31)

IV. HETEROCYCLIC SYNTHESIS *via* TANDEM AZA-WITTIG REACTION AND CYCLIZATION REACTIONS

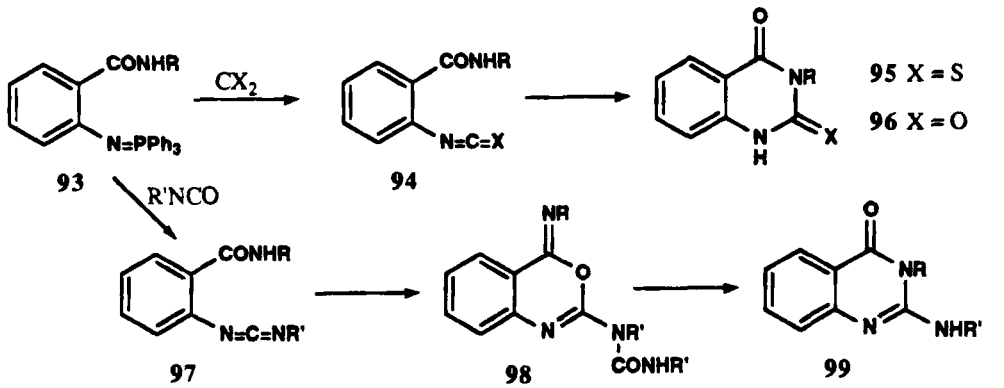
Heterocyclic synthesis *via* tandem aza-Wittig reaction and cyclizations (Eq. 32) is one of the



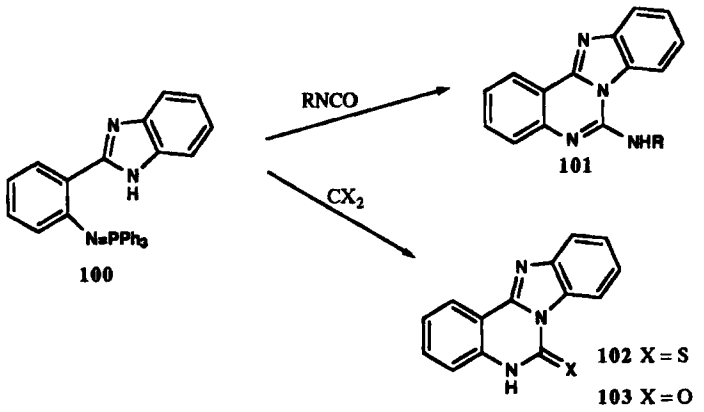
91 **92** YZ = CONHR, CH_2OH, heterocycles, etc (32)

most rapidly expanding fields in heterocyclic chemistry. This methodology was first applied successfully for the synthesis of quinazoline derivatives by Molina *et al.*[76] In the synthesis of 4(3H)-quinazolinones, heterocumulenes, generated *in situ via* the aza-Wittig reaction, cyclized to an *o*-amido group to afford quinazolinones **95**, **96**, and **99** (Scheme 11). Similarly, benzimidazo[1,2-c]quinazolines **101-103** (Scheme 12), quinazolino[3,2-a]quinazolines **107** (Scheme 13), and benzothiazolo[3,2-c]quinazolines **112** (Scheme 14) have been synthesized.[76] However, the cyclization of **113** and **114** to **115** was not successful (Scheme 14). Thus, tandem aza-Wittig/heterocumulene mediated annulation provides an

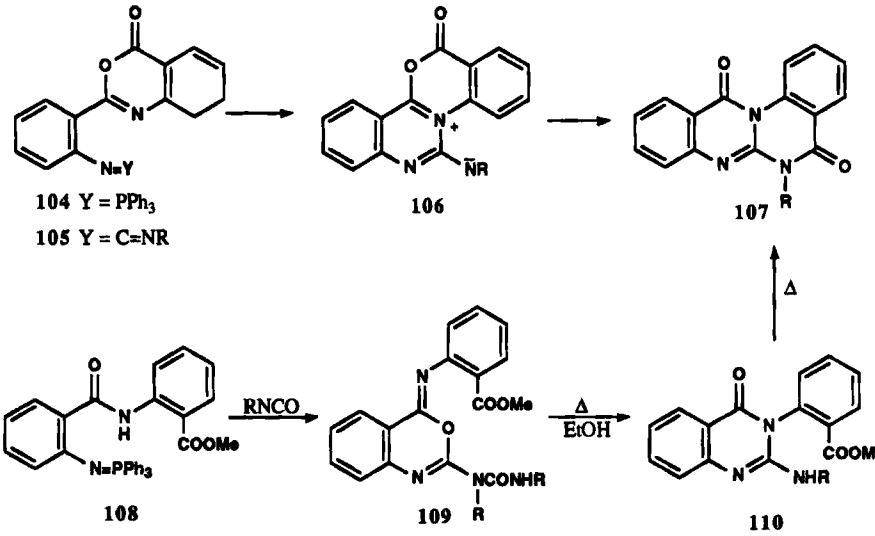
Scheme 11



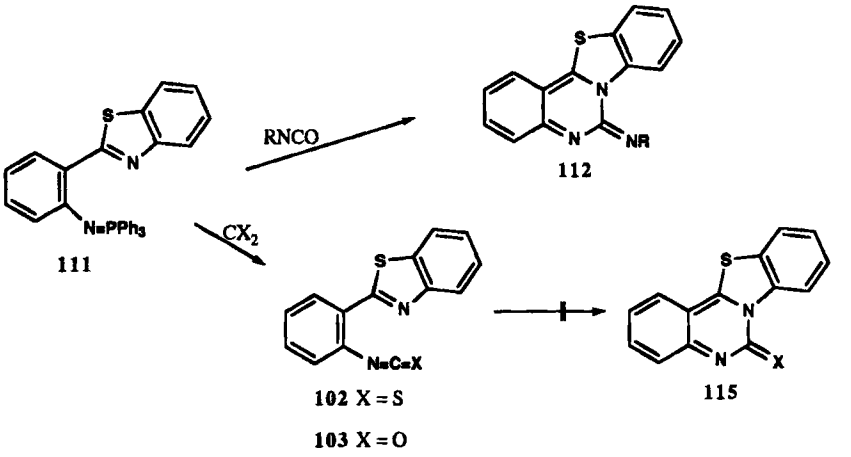
Scheme 12



Scheme 13

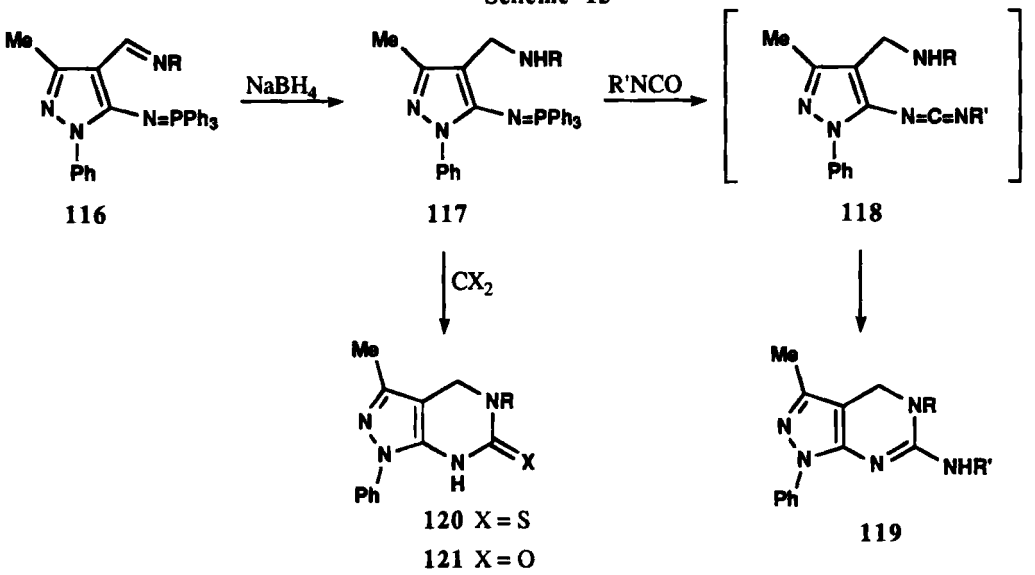


Scheme 14



efficient route to a variety of fused quinazolines. The same principle was also applied by Molina *et al.*[77,78] for the synthesis of 4,5-dihydropyrazolo[3,4-d]pyrimidine derivatives **119-121** (Scheme 15) and indolo[1,2-c]quinazoline derivatives **123-125** (Scheme 16).

Scheme 15

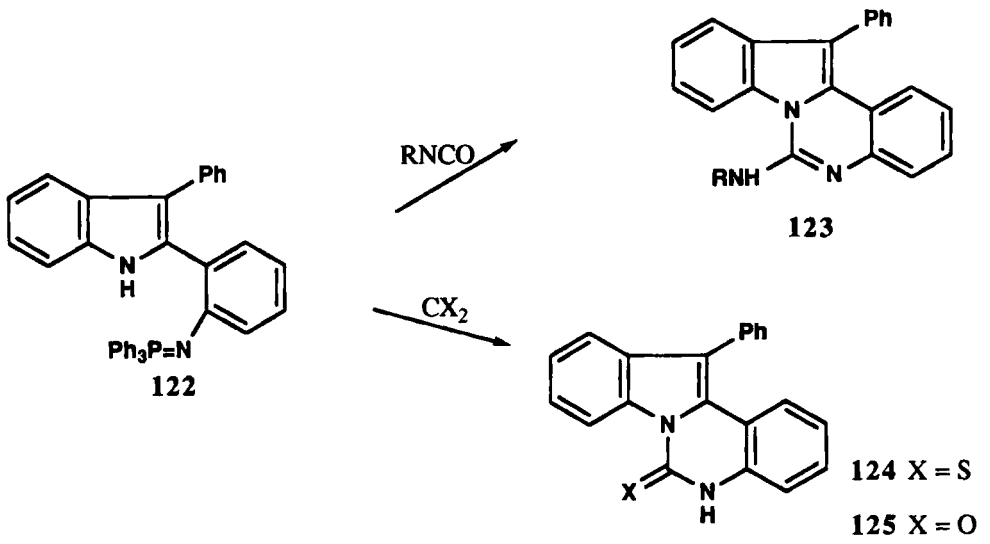


116 **117** **118**

120 X = S
121 X = O

119

Scheme 16



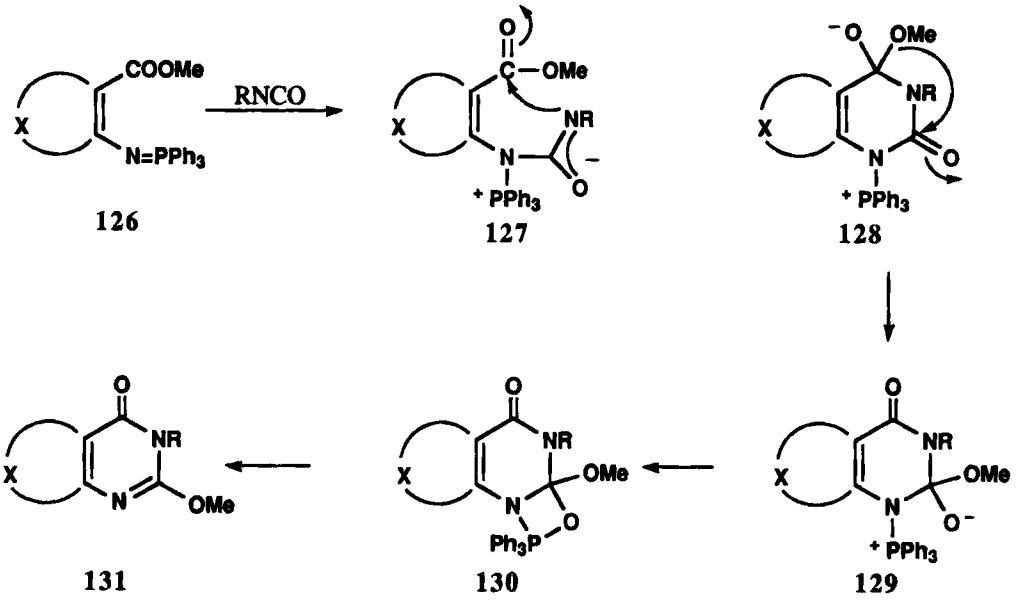
122

123

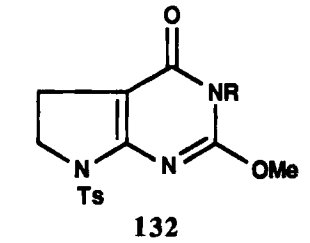
124 X = S
125 X = O

A novel route to fused pyrimidines **131** has been developed recently by Wamhoff *et al.*[79] *via* heterocyclization of an intermediate zwitterion to an ester group (see **127**, Scheme 17). The reaction

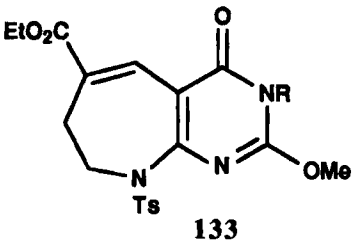
Scheme 17



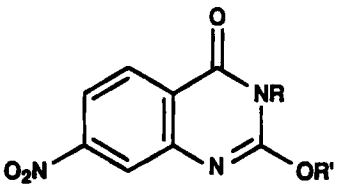
involves 1,3-migration of an alkoxy group, followed by elimination of triphenylphosphine oxide. Novel fused pyrimidines **132-135** were prepared by this method.[79]



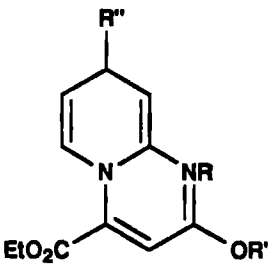
132



133



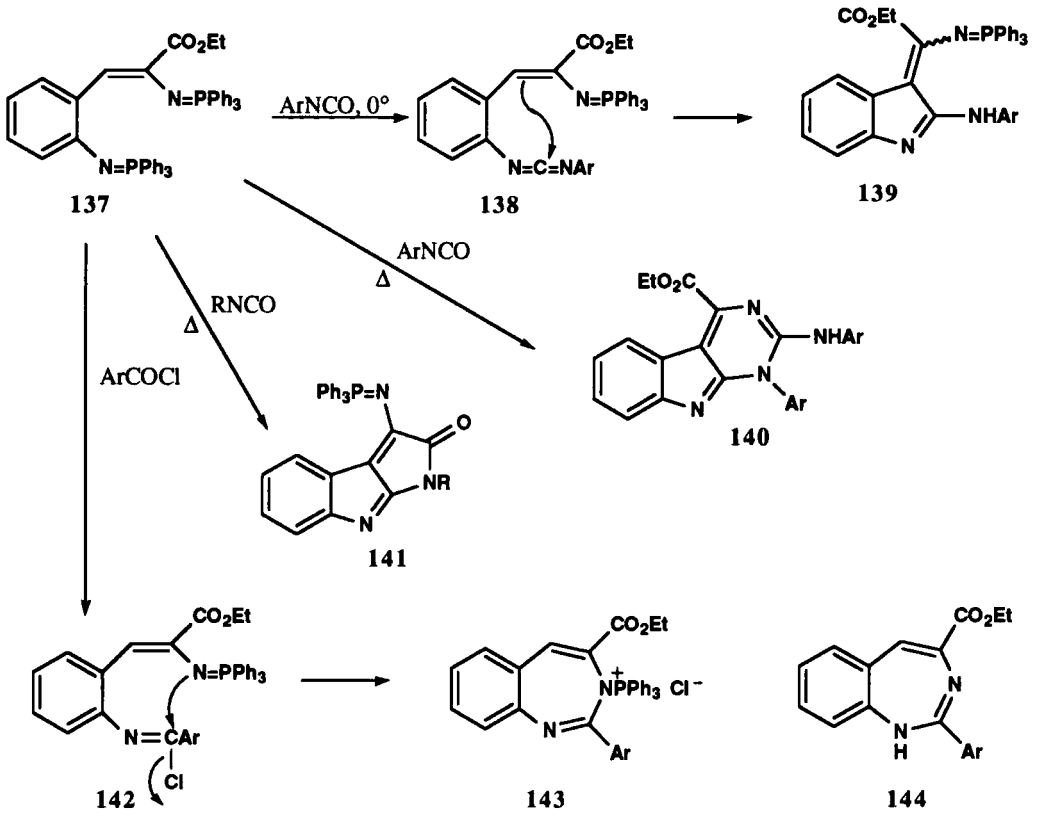
124



135

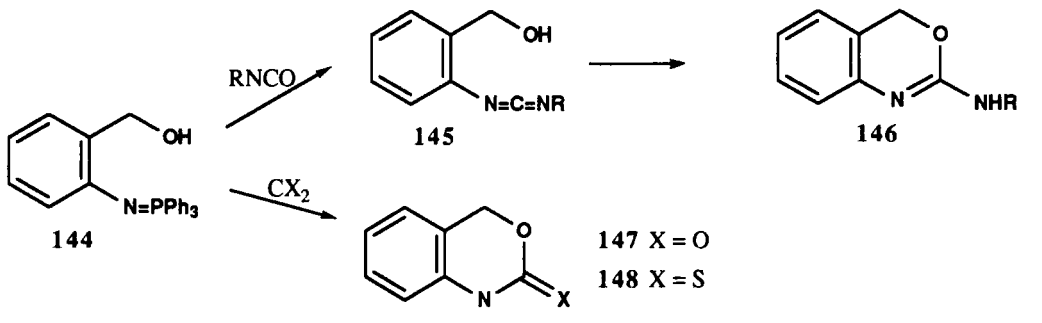
A tandem aza-Wittig/cyclization process using *bis*iminophosphoranes **137** provides short routes to indolenines **139-141** and benzodiazepine derivatives **144** as summarized in Scheme18.[80]

Scheme 18

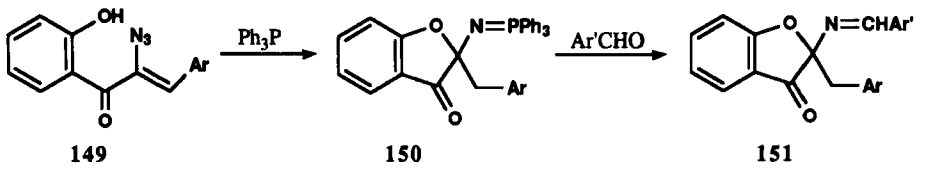


Cyclization *via* hydroxyl group trapping of a heterocumulene was also utilized for the synthesis of 4H-3,1-benzoxazine derivatives **146-148** (Scheme 19). However, *o*-hydroxybenzoylvinyl

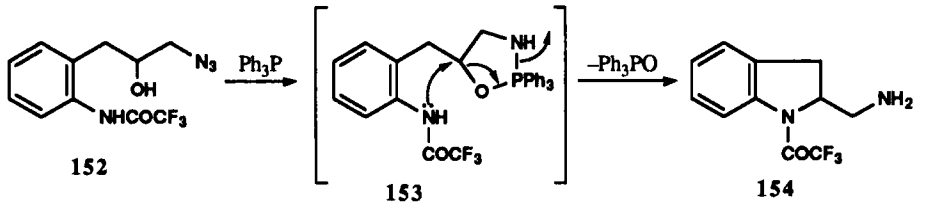
Scheme 19



azide **149** is reported to cyclize *via* conjugate addition to afford 3(2H)-benzofuranone derivatives **150** and **151** (Eq. 33).[81] The Staudinger reaction of 3-(*o*-trifluoro-acetylaminophenyl)-2-hydroxypropylazide **152** is also known to afford indoline derivative **154**, presumably *via* **153** (Eq. 34).[73]



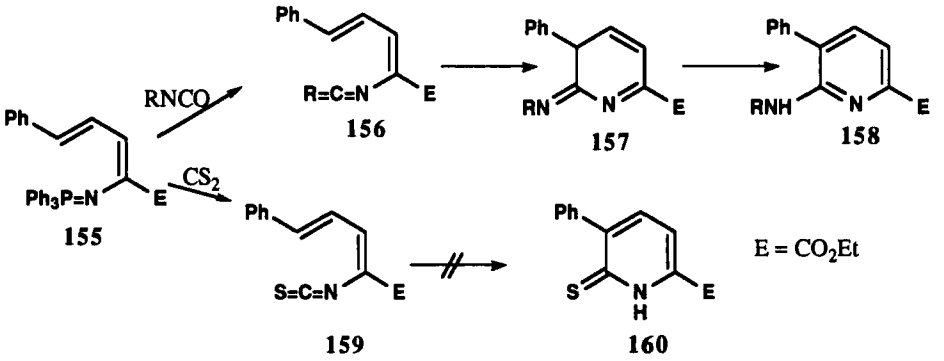
149 150 151 (33)



152 153 154 (34)

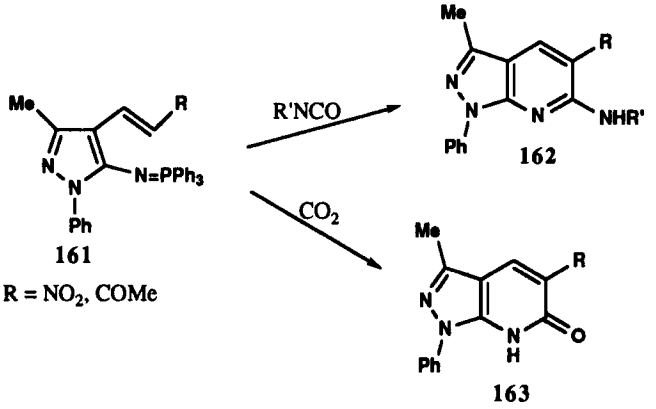
The tandem aza-Wittig/electrocyclization method developed by the Molina group has been shown to be useful for the synthesis of 2-aminopyridine derivatives **158** (Scheme 20).[82] This same

Scheme 20

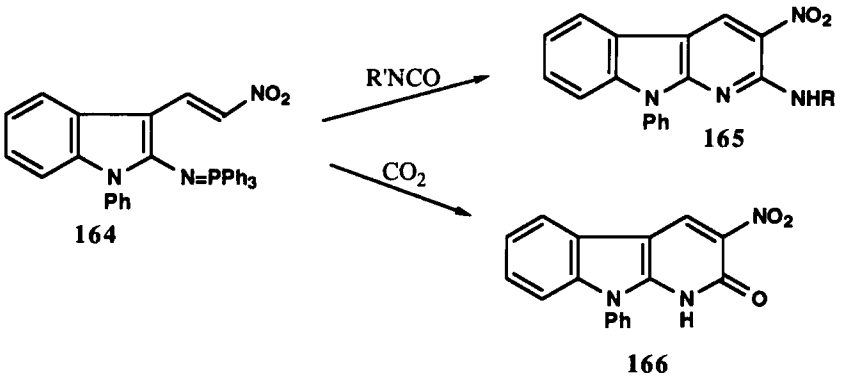


pyridine annulation strategy was used for the preparation of the pyridine ring in fused heterocycles containing pyrazoles (Scheme 21),[82b] indoles (Scheme 22 and 23),[83, 78] and pyrimidines (Eq. 35).[84]

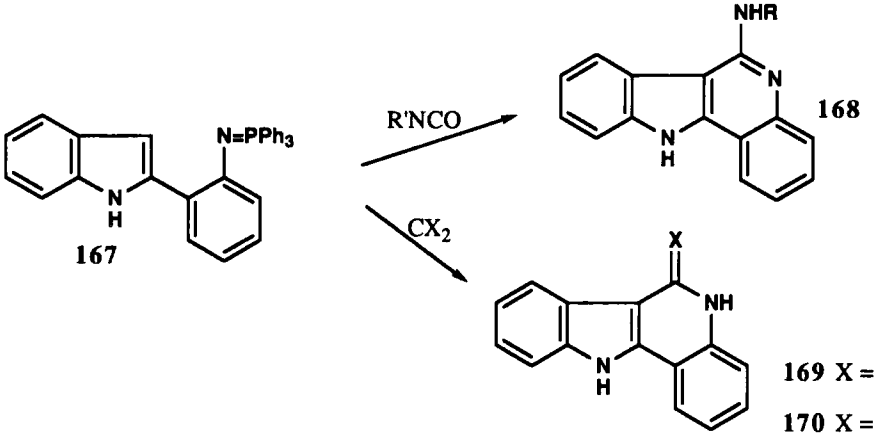
Scheme 21

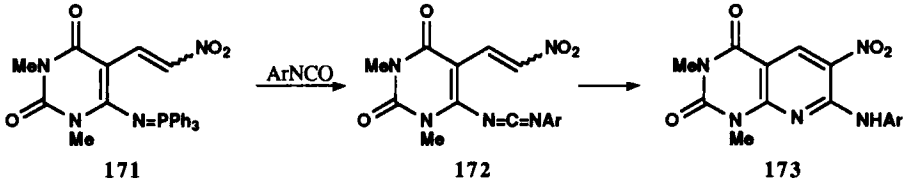


Scheme 22



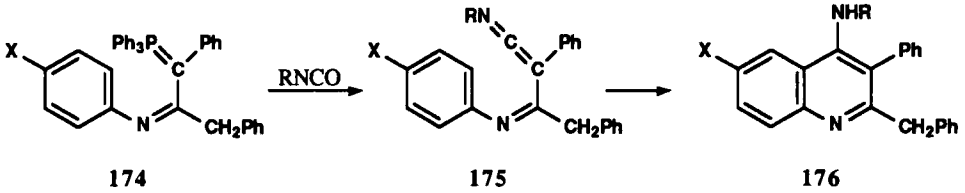
Scheme 23





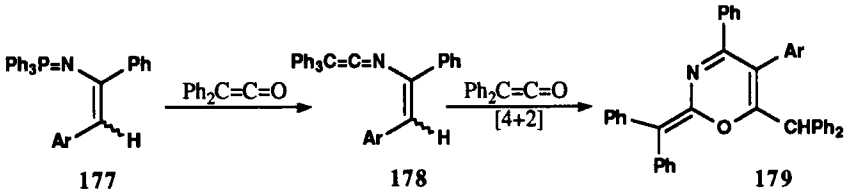
(35)

Electrocyclization of conjugated keteneimines **175** derived from **174** by Wittig-type reaction is also a convenient route to 4-aminoquinoline derivatives **176** (Eq. 36).[85] However, the reaction of vinyliminophosphorane **177** with diphenylketene afforded 2H-1,3-oxazine **179** by a [4+2] cycloaddition of



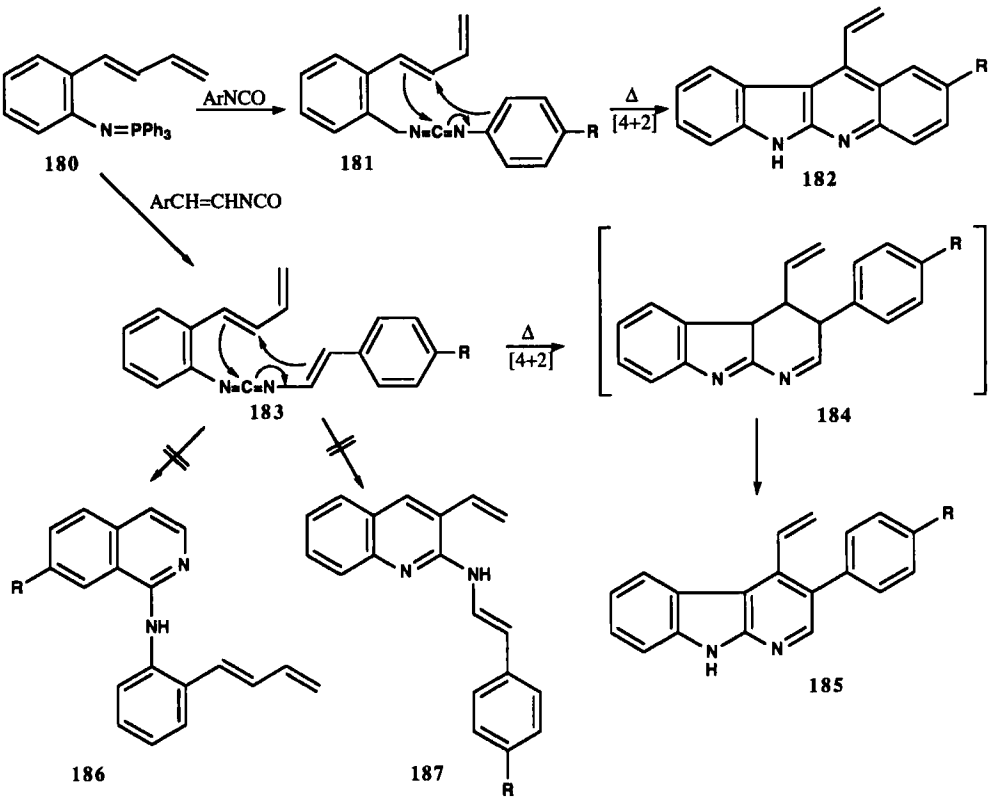
(36)

178 and the ketene, no electrocyclization product being detected (Eq. 36).[85,86] An intramolecular [4+2] cycloaddition process was also favored for *o*-butadienylphenylcarbodiimide **181** derived from **180**, affording tetracyclic quinindolines **182** in moderate yield (Scheme 24).[87] Analogously,



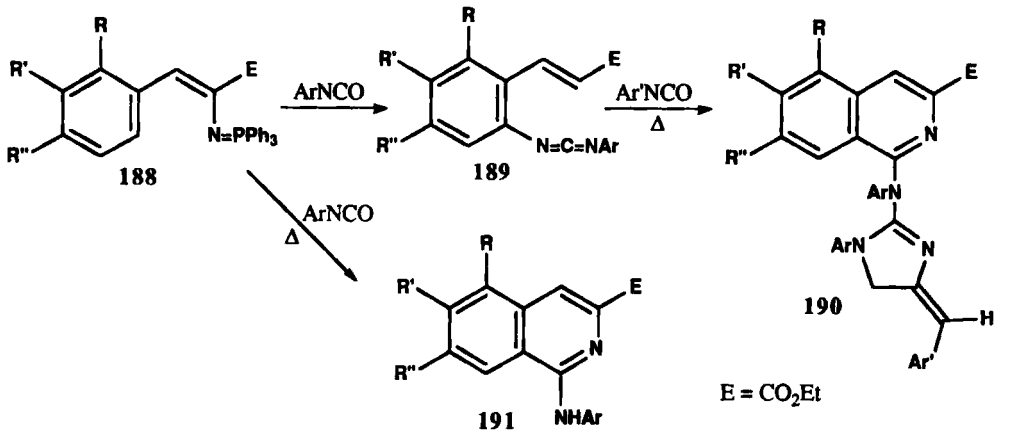
(37)

Scheme 24



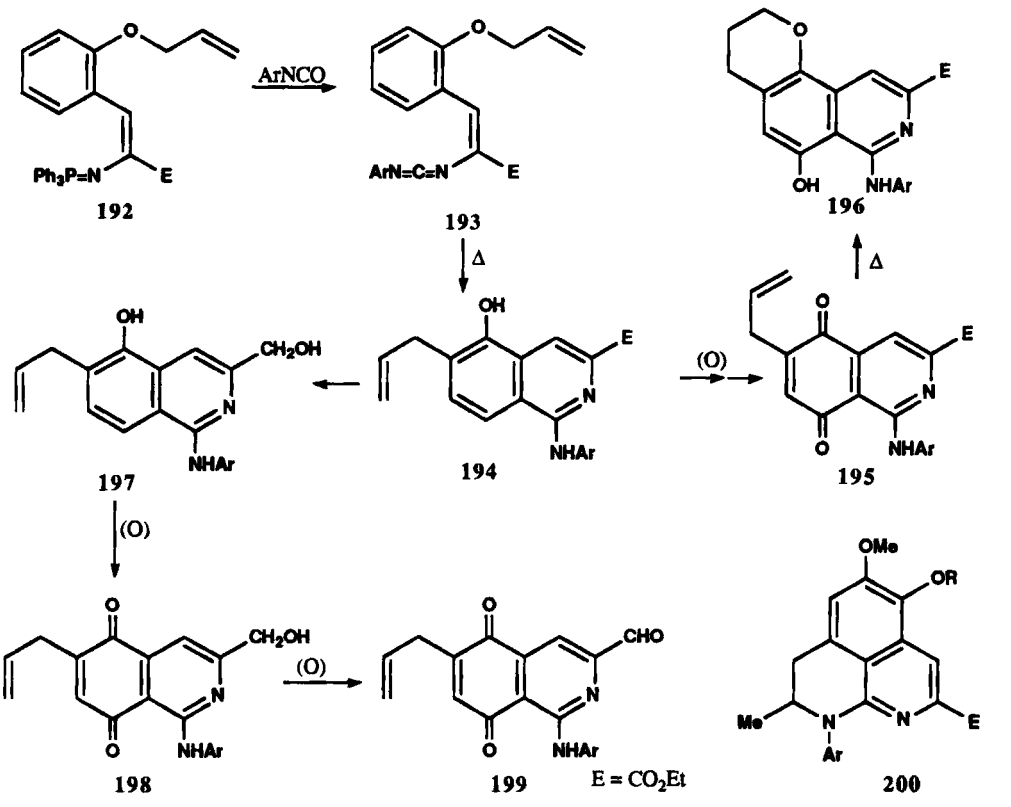
the more conjugated carbodiimide **183** also gave tricyclic pyrido[2,3-b]indoles **185** *via* the intramolecular [4+2] process and oxidative aromatization on heating, but no isoquinolines **186** or quinolines **187**, the expected products from electrocyclization process were detected (Scheme 24).[87] Selectively functionalized isoquinoline derivatives **190** and **191** can be synthesized by electrocyclization of β-arylvinylcarbodiimides **189**, derived from iminophosphoranes **188**, in a stepwise- or one-pot procedure (Scheme 25).[88] Tandem electrocyclization/Claisen rearrangement of *o*-allyloxy-styrylcarbodiimide **193**, derived from iminophosphorane **192**, provided the selectively

Scheme 25



functionalized isoquinoline **194** which was converted to the novel 2H-pyrano[2,3-f]isoquinoline **196** *via* 5,8-isoquinolinequinone allide **195** (Scheme 26).[89] The isoquinoline **194** was also converted to

Scheme 26

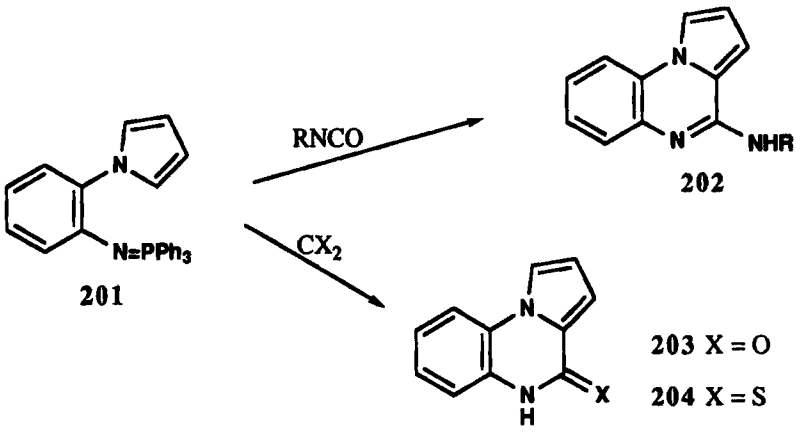


3-formyl-5,8-isoquinolinequinone **199** *via* **197** and **198** (Scheme 26).[89] Furthermore, novel 1,9-diaza-

phenalene derivatives **200** were also prepared by a consecutive electrocyclization/Claisen rearrangement/intramolecular amination process by the same workers.[89]

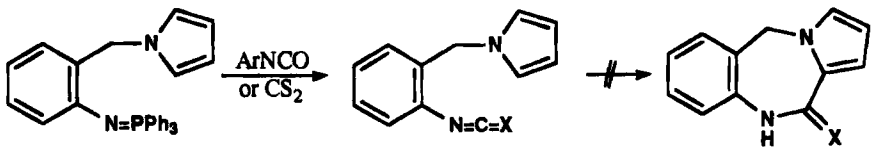
Pyrrolo[1,2-a]quinoxaline derivatives **202-204** were obtainable by a tandem aza-Wittig/electrocyclization process from N-(*o*-1-pyrrolyl)phenyliminophosphorane **201** (Scheme 27).[78,80]

Scheme 27



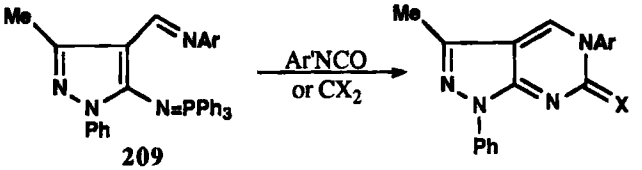
201 **202**

However, attempted cyclization of the *o*-[(1-pyrrolyl)methyl]phenylheterocumulenes **206** and **207** to the 7-membered ring compounds **208**, *via* electrophilic substitution was not successful (Eq. 38).[78]



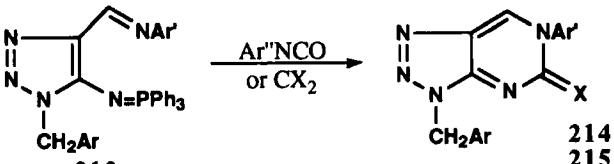
205 **206** X = NAr, **207** X = S **208** (38)

A variety of fused pyrimidine derivatives also are readily synthesized by the aza-Wittig/electrocyclization process as demonstrated by the synthesis of pyrazolo[3,4-d]- (**210-212**), 1,2,3-triazolo[4,5-d]- (**214-216**) and thiazolo[4,5-d]pyrimidines (**218-220**) (Eq. 39-41).[91] Molina's group has extended this tandem aza-Wittig/electrocyclization methodology to synthesis of imidazo[5,1-f][1,2,4]triazine derivatives **223** from **221** (Eq. 42).[92]



209 (39)

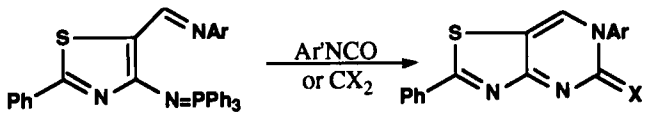
210 X = NAr'
211 X = O
212 X = S



213

214 X = NAr''
215 X = O
216 X = S

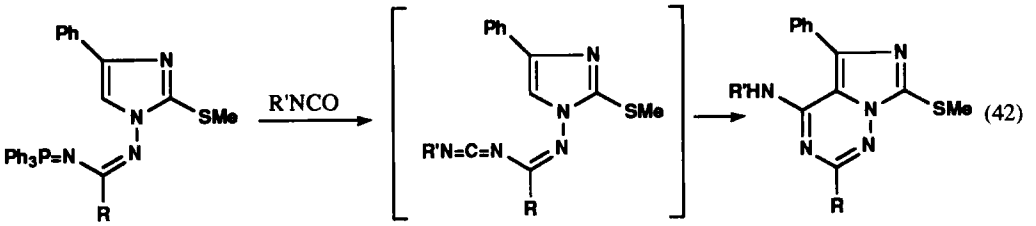
(40)



217

218 X = NAr'
219 X = O
220 X = S

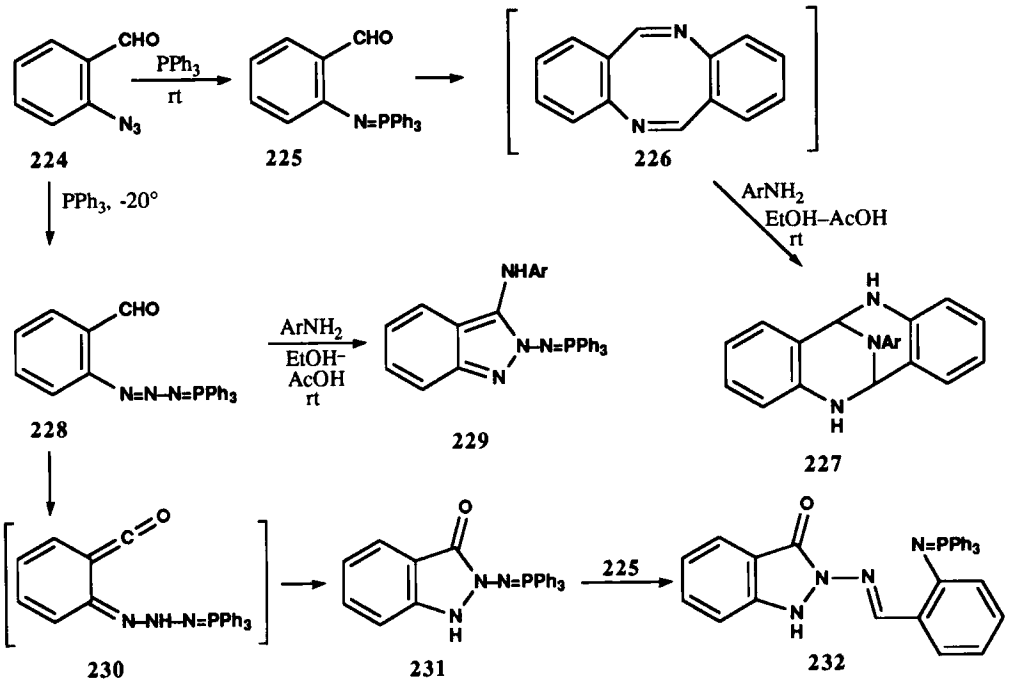
(41)



221 222 223

(42)

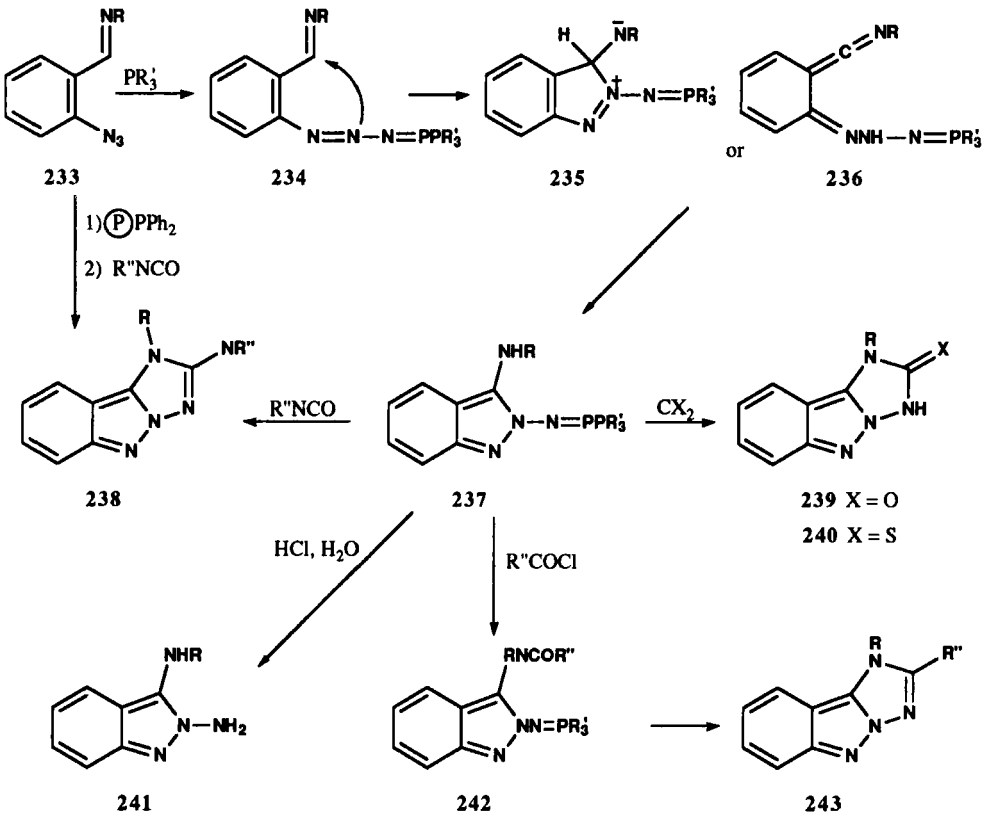
Scheme 28



224 225 226 227 228 229 230 231 232

Recently, the same group has isolated the unstable phosphazide intermediate **228** from the reaction of *o*-azidobenzaldehyde **224** with triphenylphosphine (TPP) at -20° (Scheme 28).[93] The Staudinger reaction of **224** with TPP at 0° gave the known *o*-(triphenylphosphoranylidene)amino-benzaldehyde **225**[94, 95] and iminophosphorane **232**. The formation of the latter could be explained by heterocyclization of **228** to iminophosphorane **231**, presumably *via* **230**, followed by further reaction with **225**. In the presence of aromatic amines, **228** afforded the interesting indazolyliminophospho-ranes **229** in high yield. In contrast, iminophosphorane **225** affords the triazabicyclo[3.3.1]nonane system **227** in the presence of aromatic amines, presumably *via* **226**. These results, in particular the electrocyclization of phosphazide **228** and the 1,5-electrocyclization of **30** (Scheme 9)[58] discussed in section III, demonstrate the considerable potential of the Staudinger reaction for heterocyclic synthesis. Molina *et al.* have developed a new synthesis of 2-amino-3-(alkyl(aryl)amino)-2H-inda-zoles **241** and 1H-1,2,4-triazolo[2,3-b]indazole derivatives **238-240** and **243** (Scheme 29).[96] The key reaction in these syntheses is an intramolecular trapping of phosphazide **234** by an imine function *via*

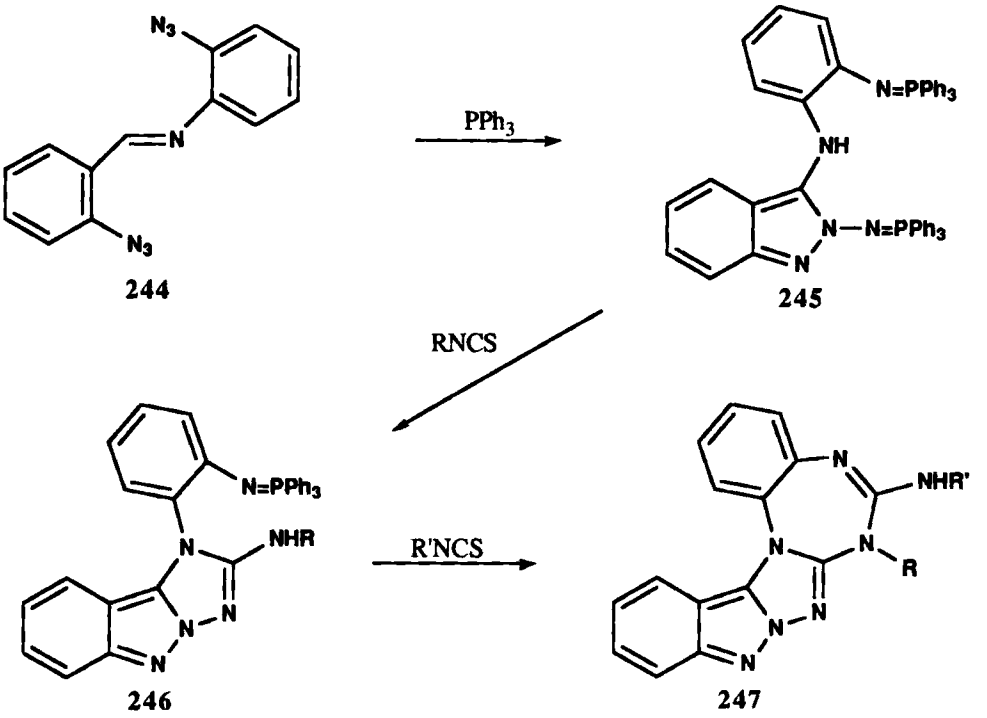
Scheme 29



235 or **236** to afford **237**. Application of the tandem aza-Wittig/heterocyclization method to **237** provides an efficient route to 1,2,4-triazolo[2,3-b]indazole derivatives. A one-pot procedure to **238** has

also been devised using a polymeric phosphine reagent (Scheme 29). The novel fused-[1,3,5]benzotriazepines **247** were also synthesized recently by a consecutive phosphazide trapping/aza-Wittig reaction/heterocyclization process starting from bisazide **244** (Scheme 30).[97]

Scheme 30



244 245 246 247

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