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REVIEW ARTICLE

C-Phosphorylated Azoles*

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A method of phosphorylation of heterocycles incorporating 1,3-azole moiety with phosphorus(III) halides is elaborated. As a result, previously unknown azolyldihalogenphosphines are prepared. Influence of heteroatom and quantity of nitrogen atoms in a cycle on the activity of azoles is studied. Reaction of 5-aminopyrazole derivatives with phosphorus(III) halides affords novel phosphorus-containing bi- and tricyclic fused systems.

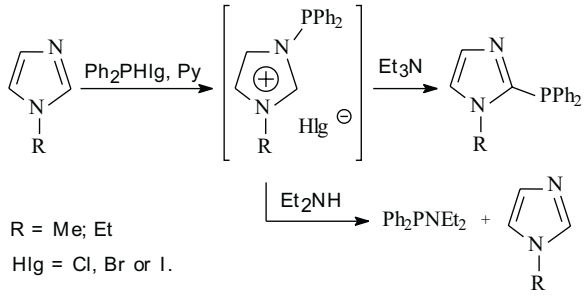
Key words: azoles, phosphorylation, phosphines, phosphonic acids, phosphorus-containing heterocycles

In the past decade, new promising types of pesticides were found among derivatives of 1,2- and 1,3-azoles. Results of investigations in this domain are summarized in Grapov's review [1]. The promising practical results boosted further growth of synthetic investigations directed at C-functionalized azoles including derivatization with various phosphorus-containing groups. It should be noted that up to 1980 the main approach to phosphorylated azoles was heterocyclization of acyclic substrates bearing phosphorus moieties. During the past two decades methods of direct introduction of phosphorus substituents at azoles by phosphorus(III) halides using lithium azoles derivatives or azoles in basic media have intensively been developed. The latter method was first developed in our laboratory approximately 8 years ago [2]. The main advantage of the method is a possibility to synthesize the key starting materials – azolylhalogenphosphines. Now we have studied phosphorylation with phosphorus(III) halides most of the azoles and established the following rules. First of all phosphorylation of the 1,3-azoles proceeds at the second position and probably in most cases begins with attacking azomethine cyclic nitrogen atom, followed by triethylamine induced migration of the phosphorus group at the 2-C atom.

Reaction between halogenodiphenylphosphines and 1-alkylimidazole in pyridine leads to the formation of imidazolium cation. ^{31}P chemical shift of the intermediate does not depend on the nature of the anion used. Moreover, upon treatment with secondary amine it decomposes giving starting imidazole and amidophosphinite. Both the facts confirm its constitution. Similar intermediates were observed in the re-

*Dedicated to Prof. Jan Michalski on the occasion of his 80th birthday.

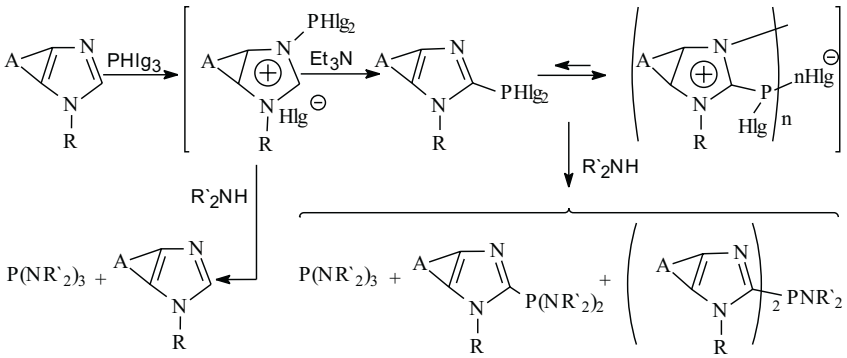
Scheme 1



action of 1-alkylimidazoles with acyl chlorides. Upon treatment with triethylamine, the intermediate transformed into phosphine probably as result of 1,2-phosphorotropic migration [3].

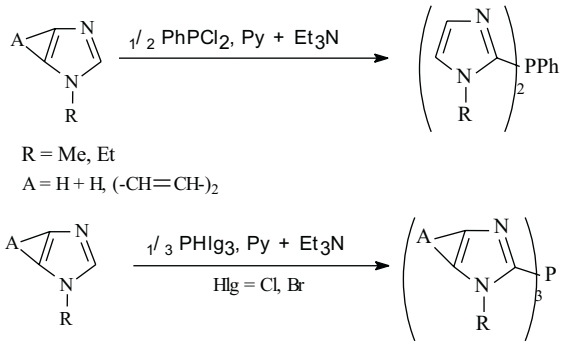
Reaction between N-alkylimidazoles and $PHal_3$ proceeds in a similar way, but due to low solubility in pyridine and other solvents, intermediate immonium salt and final dihalogenphosphine were not characterized by NMR spectra. But their structure is supported by the chemical transformation. It is suggested that dihalogenphosphines exist partially or completely as molecular associates, which are formed by intermolecular interaction between phosphorus and nitrogen atoms. But it does not hinder using them for further transformation.

Scheme 2



It is a good preparative practice to perform the phosphorylation of N-alkylimidazoles in one step, using pyridine-triethylamine mixture as a solvent. The reaction of $PhPCl_2$, PCl_3, or PBr_3 with two or three equivalents of alkylimidazoles in this medium gives tertiary phosphines in a high yield.

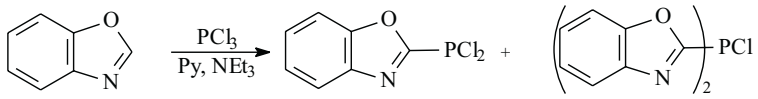
Scheme 3



A wide range of phosphorus(V) derivatives was obtained from phosphines containing imidazole moieties. At the same time it was established that phosphines undergo alkylation either at the phosphorus center or at the nitrogen atom of the heterocycle, depending on the alkylating agent. The alkylation with methyl iodide gives in most cases phosphonium salt, but hard alkylating agents such as Meerwein's salt or dimethyl sulfate lead to the products alkylated at the nitrogen atom of the cycle.

Benzoxazole like benzimidazole reacts with phosphorus trichloride at room temperature giving a mixture of dichloro- and chlorophosphines, which are separated by distillation at reduced pressure. NMR spectroscopy and its chemical transformations confirm the constitution of the dichlorophosphine.

Scheme 4



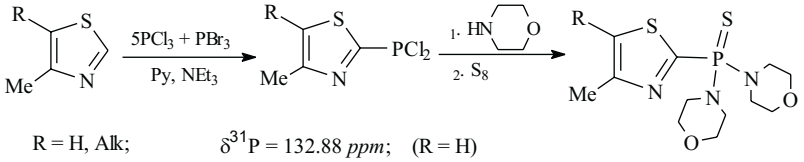
44,6 % 21,9 %

$\delta^{31}P = 118.72$ *ppm*; $\delta^{31}P = 21.7$ *ppm*;

$\delta^{13}C_{C_2} = 165$ *ppm*; $J_{PC_2} = 70.1$ *Hz*;

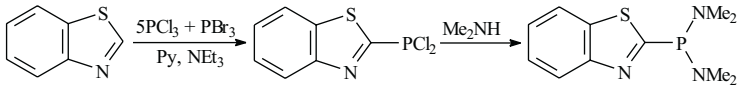
Naturally, thiazole and benzothiazole, unlike N-alkylimidazoles and benzoxazoles, turned out to be less active in reaction with phosphorus trichloride. They do not react with phosphorus trichloride and to phosphorylate them it is necessary to use a mixture of PCl_3 and PBr_3. In this case the phosphorylating agent is supposed to be $PBrCl_2$, the duration of the reaction is about 10 hrs at room temperature. Constitutions of the dichlorophosphines are confirmed by NMR spectroscopy and by their chemical transformations. Tertiary phosphine was also prepared [4].

Scheme 5



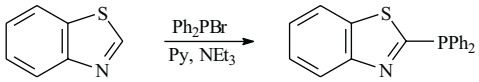
R = H, Alk; $\delta^{31}P = 132.88$ *ppm*; (R = H)

$\delta^{13}C_{C2} = 169.84$ *ppm*; $J_{PC2} = 61.1$ *Hz*;



$\delta^{31}P = 131.82$ *ppm*;

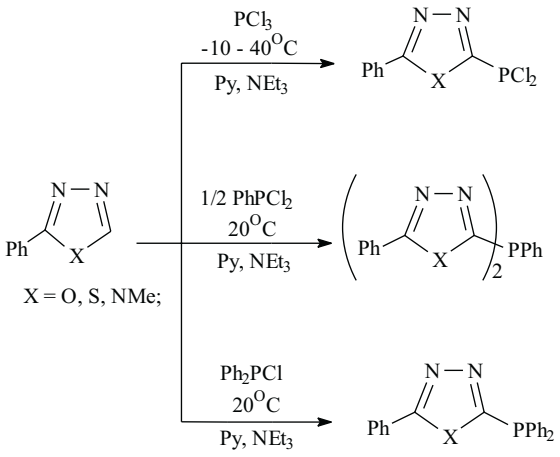
$\delta^{13}C_{C2} = 172.74$ *ppm*; $J_{PC2} = 63.5$ *Hz*;



Thus, we have found that according to their activity in reactions with phosphorus(III) halides, these heterocycles can be lined in the following order: imidazole, oxazole and thiazole.

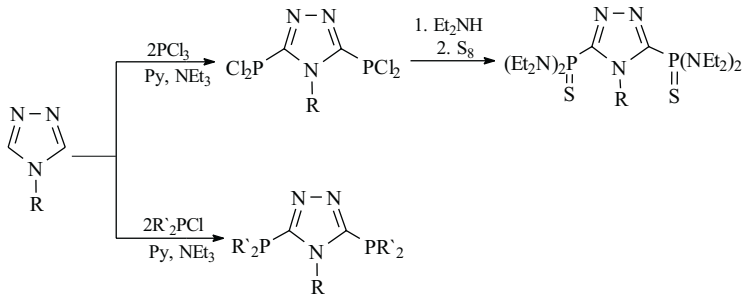
Introduction of an additional nitrogen atom into 1,3-azoles increases their activity in phosphorylation. Thus, 4-methyl-3-phenyl-1,2,4-triazole, oxadiazole and 2-phenyl-1,3,4-thiadiazole are phosphorylated with phosphorus(III) chloride even at low temperature. Less active phosphorylating agents, such as phenyldichlorophosphine and diphenylchlorophosphine, also easily react with the azoles. It should be noted that the nature of heteroatom X causes insignificant an influence on the activity of azoles [5].

Scheme 6



Upon phosphorylating triazoles, containing two identical reactive centres, use of 1:1 ratio of reagents always results in a mixture of mono- and diphosphorylated products, which were not separated. Use of twofold equivalents of phosphorylating agent affords bisphosphorylated triazoles. Electron-donating substituents R appreciably increase the reaction rate [6].

Scheme 7

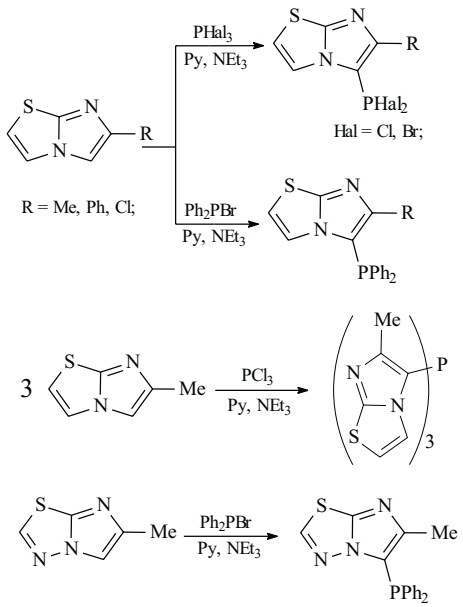


R = Ph, p-MeC$_6$H$_4$, CH$_2$Ph, -N=CH-NMe$_2$;
R` = Ph, Et$_2$N

We think that all phosphorylation reactions of 1,3-azoles giving 2-substituted products proceed by ylide-mechanism: attack initially goes at the nitrogen atom followed by migration of phosphorus group at the C-2. One should expect that in the cases, when the second position of 1,3-azoles is occupied, phosphorylation by electrophilic substitution mechanism would proceed at 5th-position. Indeed, we have found that fused heterocycles-imidazothiazoles, possessing the occupied second position, are phopshorylated at the 5th position. The rate of the reaction depends greatly on the nature of the substituent R and decreases in the following order Me > Ph > Cl. For Me derivative the reaction proceeds with such ease that three heterocycles residues can be introduced to the phosphorus atom. It is evident that imidazole moiety reacts easier than thiazole one. Phosphorylation of imidazothiazole proceeds also at the imidazole ring, despite the possibility of reaction at the thiadiazole ring by ylide mechanism.

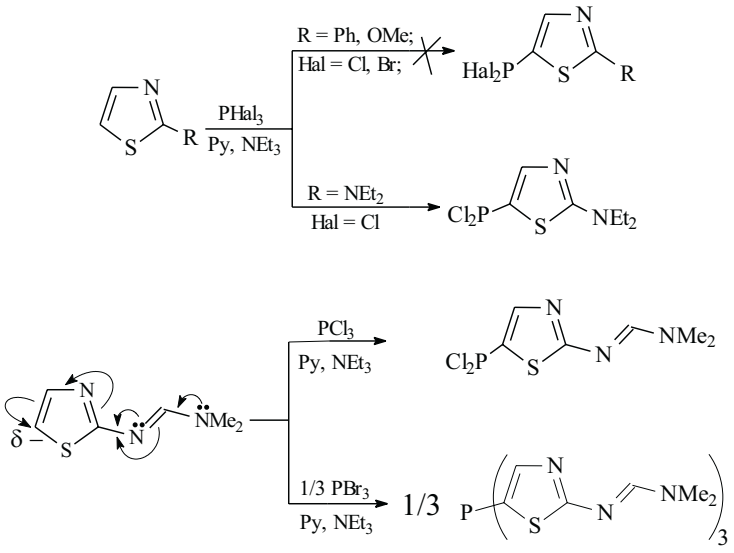
In the case of weak electron-donating substituents attached to the 2-position of thiazole ring, phosphorylation does not occur, and only for diethylamino group the phosphorylation easily proceeds at 5th position. According to quantitative data obtained by Polish scientists, dimethylformamidine group is a strong electron-donating group [7,8]. Indeed, we have established that N^1,N^1-dimethyl-N^2-2-thiazoylformamidine like 2-diethylaminothiazole is readily phosphorylated with PCl_3 at the 5th position. When PBr_3 is used, three thiazolyl substituents can be introduced at phosphorus atom [9,10]. It is only proper to note that the formamidine residue, as electron-donating substituent, can be used in phosphorylation reactions only for N-heteroarylformamidines. In the case of N-arylformamidines electron-donating properties are exhibited very weakly and phosphorylation proceeds not at aryl but at the formamidine carbon atom [11].

Scheme 8



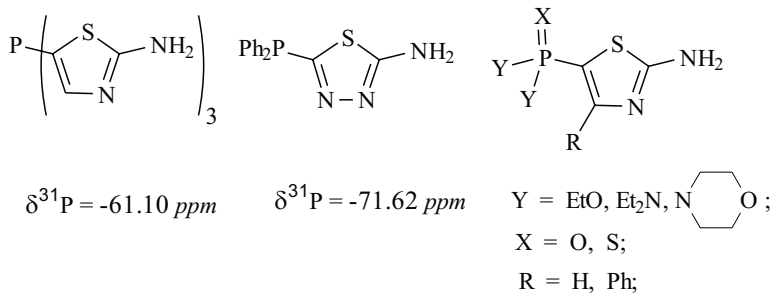
Thus, the formamidine substituent appreciably enhances the rate of phosphorylation of heterocycles. The second advantage of the reaction is that amidine protection group can be easily removed at penta- and threecovalent phosphorylated heteroaryl derivatives, thus, giving an opportunity to prepare new types of polyfunctional phosphorus derivatives, namely, tertiary aminophosphines, aminophosphonic acids. All these compounds are promising as starting reagents [9,10,12].

Scheme 9



It is clear, that in case when the amidino- and phosphorus groups occupy neighbouring positions of a heterocycle, an appropriate transformation of phosphorus-containing moiety can result in an intramolecular nucleophilic substitution reaction to produce a phosphorus-containing heterocycle. Such types of compounds have been prepared on the base of pyrazole.

Scheme 10



$\delta^{31}P = -61.10$ *ppm* $\delta^{31}P = -71.62$ *ppm* Y = EtO, Et_2N, N O ;

X = O, S;

R = H, Ph;

Dichlorophosphino- and phenylchlorophosphino- moieties were successfully introduced into 4-position of 5-pyrazolylformamidine. Note, that pyrazolylformamidine is considerably more reactive in the phosphorylation than other 5-alkyl- or 5-alkoxypyrazoles. This fact again illustrates the strong electron-donating properties of the amidine group.

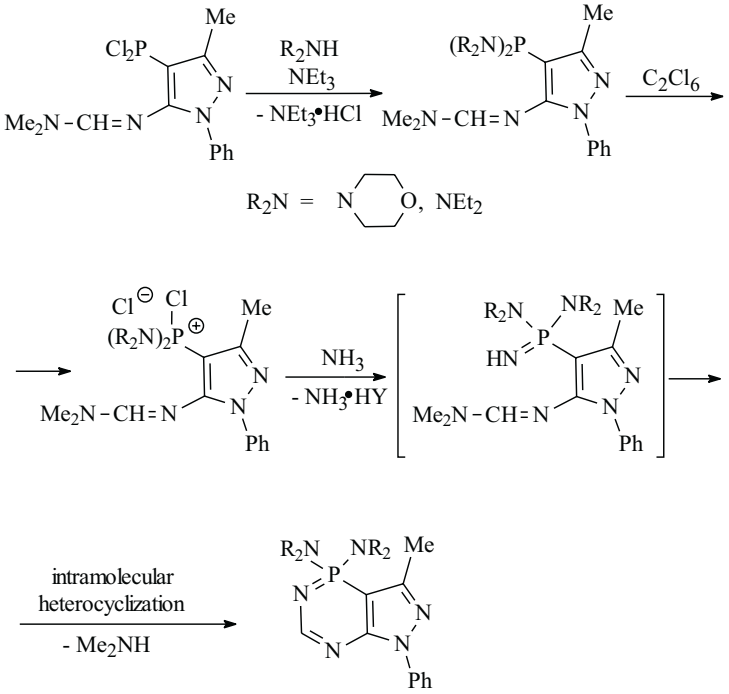
Starting from dichlorophosphine, iminoderivatives bearing a highly nucleophilic nitrogen atom are prepared in a number of simple steps. The iminoderivatives undergo intramolecular cyclization in situ, furnishing novel heterocyclic system – pyrazolodiazaphosphinine.

Analogous scheme can be used for the construction of an other new heterocyclic system. Thus, diamidophosphonite was transformed into phosphonium salts upon treatment with alkyl halides. Starting from phosphonium salt, ylides were obtained, which also undergo the further intramolecular cyclization into new heterocyclic system – pyrazoloazaphosphinines [13,14].

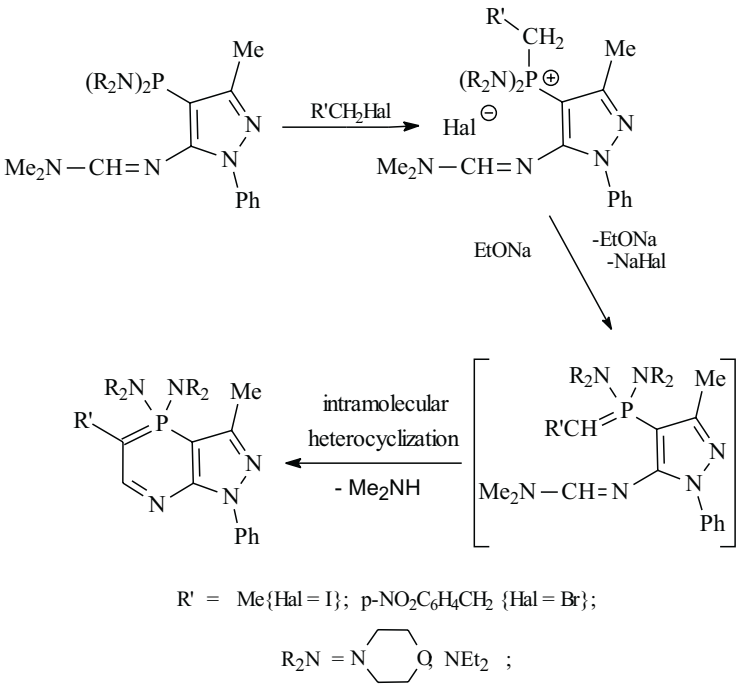
The method of synthesizing bicyclic fused phosphorus-containing heterocyclic systems, using phosphorylation of functionalized azoles with phosphorus(III) halides, has a wide range of application. Thus, we have shown that novel heterocyclic systems are formed by phosphorylating not only N-pyrazolylformamidines, but also 5-pyrazolylamides, pyrazolylureas, and pyrazolylimines [15]. Owing to weaker electron-donating properties of amide, ureido, and imine groups and, as result, weaker nucleophilicity of the 4^{th} cyclic carbon atom, it is naturally to suggest that phosphorylation of these substances begins with the functional group, what is followed by the further attack at pyrazole ring.

Thus, the first stage of phosphorylation of pyrazolylamides is supposed to proceed at the oxygen of the amide group, following by cyclization with the pyrazole carbon atom to give a six-membered ring. As a result, bicyclic system of new type –

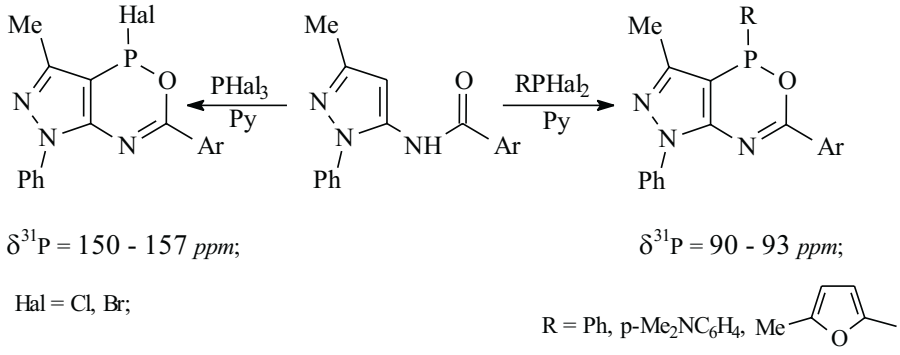
Scheme 11



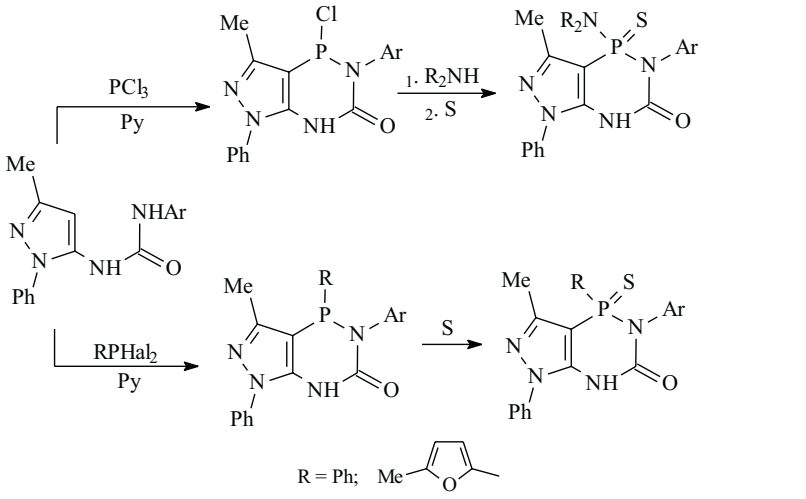
Scheme 12



Scheme 13



Scheme 14

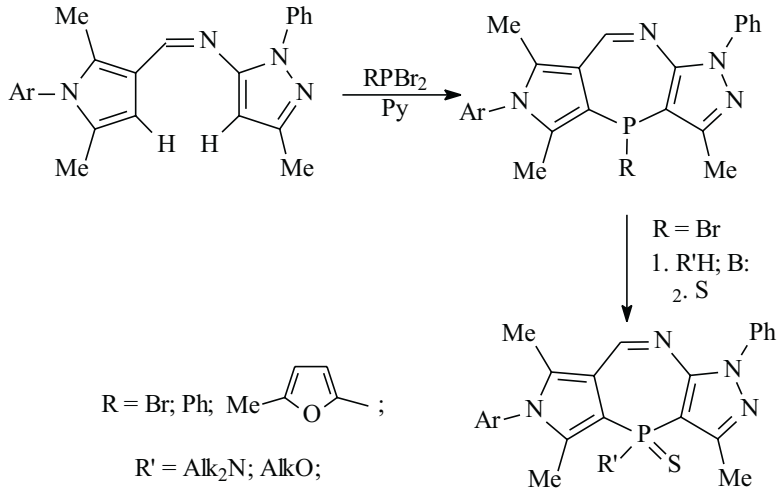


pyrazolooxaazaphosphinine is formed, whose constitution was confirmed by X-ray analysis.

Phosphorylation of 5-pyrazolylureas with phosphorus(III) halides is also accompanied by heterocyclization, but in this case the first nucleophilic center is nitrogen of ureido group. Reaction resulted in formation of pyrazolodiazaphosphinines, which were transformed into stable derivatives of pentacovalent phosphorus.

Finally, we carried out the phosphorylation of Schiff bases, in which the azomethine group connects pyrrole and pyrazole cycles. In this molecule both carbon atoms of pyrrole and pyrazole rings are nucleophilic centers. Formation of tricyclic systems, incorporating azaphosphepine cycle, comes to an end for 15–20 hrs at room temperature. Tertiary phosphines are stable solids in air. Bromophosphines were transformed into stable pentacovalent phosphorus derivatives [16].

Scheme 15



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