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Synthetic routes to 3(5)-phosphonylated pyrazoles

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This review comprehensively covers the currently available synthetic routes to 3(5)-phosphonylated pyrazoles. There are demonstrated significant advances in this field over the last 10 – 15 years caused by the use of the Bestmann – Ohira reagent [as well as (diazomethyl)phosphonates and phosphonylated hydrazonoyl halides] in reactions with diverse dipolarophiles. 1,3-Dipolar cycloaddition of diazo compounds to α,β-unsaturated phosphonates as well as intramolecular heterocyclization of (1-diazoallyl)phosphonates and (3-diazo-1-propenyl)phosphonates are discussed. Synthetic potential of cyclocondensation of organophosphorus 1,3-dielectrophilic compounds with hydrazines is shown. Ways to introduce a phosphonate group into the pyrazole ring are considered. Examples of chemical transformations of 3(5)-phosphonylated pyrazoles are reported. The bibliography includes 88 references.

Contents

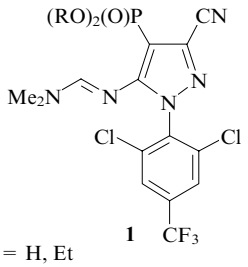
I. Introduction 667
II. Phosphonylation of the pyrazole ring 669
III. Cycloaddition of diazo compounds to α,β-unsaturated phosphonates 669
IV. Reactions of the Bestmann – Ohira reagent with various dipolarophiles 673
V. Intramolecular heterocyclization of (1-diazoallyl)phosphonates and (3-diazo-1-propenyl)phosphonates 678
VI. Cyclocondensation of 1,3-dielectrophilic compounds with hydrazines 679
VII. Reactions of 3(5)-phosphonylated pyrazoles 681

I. Introduction

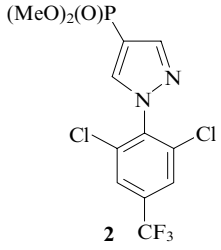
C-Phosphonylated pyrazoles, which combine two pharmacophore moieties in a molecule, are of interest, first of all, as biologically active compounds. Indeed, among compounds of this class, efficient pesticides, such as derivatives **1** (Ref. 1) and **2** (Ref. 2) have been found. The former have been patented as a means for the control of arthropods (including insects and arachnids) and helminths (including nematodes) and the latter, as an agent for protection against brown planthopper *Nilaparvata lugens*.

A mimetic of τ-phosphohistidine **3**, resistant to hydrolysis and isomerization, and its analogue **4** have been used as haptens for generation of specific antibodies.[3 – 6] In *in vitro* and *in silico* experiments, it has been shown that compound **5** inhibits the binding of phosphatidylinositol 3,4,5-triphosphate with BTK and GRP1 PH domains and Epsin 1 ENTH domain.[7, 8]

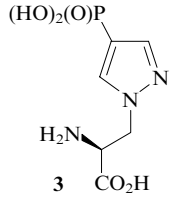
Structures 1 – 5



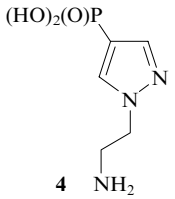
1 R = H, Et



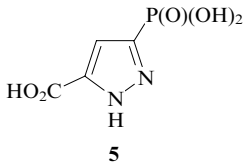
2



3



4



5

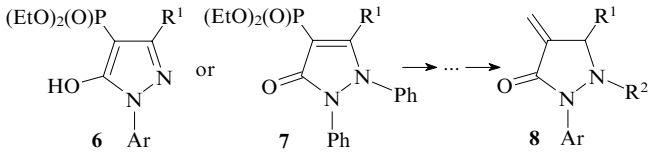
Pyrazolylphosphonates **6** and 2,3-dihydro-1*H*-pyrazolylphosphonates **7** have been used in synthesis of a series of cytostatic drugs **8** (Scheme 1); for some of these compounds (Ar = R^2 = Ph, R^1 is vinyl, Ph), the *in vitro* antitumour activity exceeding the carboplatin activity has been reported.[9]

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Current research interests of the authors: metal complex catalysis in organic and organometallic chemistry, organocatalysis, organic derivatives of lanthanides, carbanions, nucleophilic aromatic substitution, chemistry of organophosphorus compounds.

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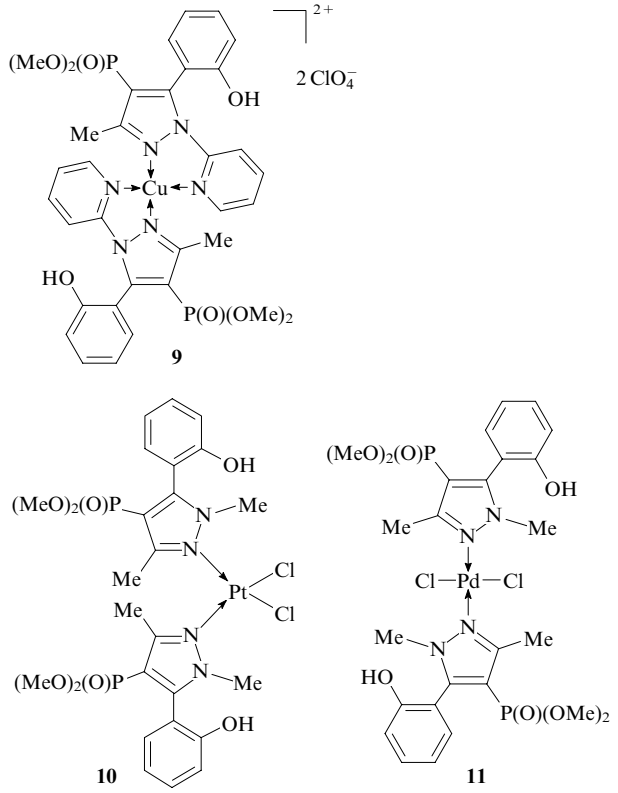
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Scheme 1



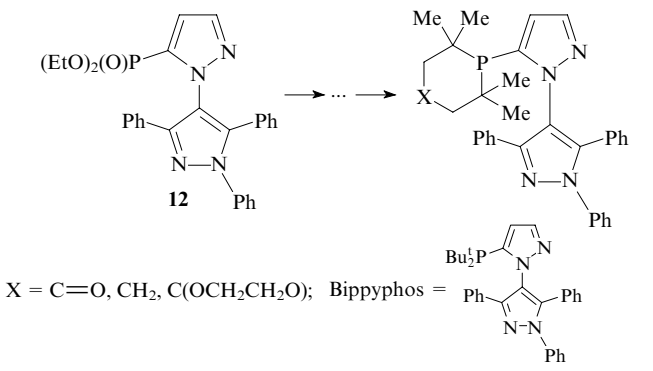
C-Phosphonylated pyrazoles are used in the chemistry of coordination compounds, especially biologically active ones. In particular, it has been demonstrated that Cu^{II} complex **9** is a biomimetic of natural antioxidants.[10] In a search for new antitumour drugs, cisplatin analogues, Pt^{II} and Pd^{II} complexes **10** and **11** have been synthesized.[11, 12]

Structures 9–11



Catalysis with pyrazolyl metal complexes is a dynamically developing field.[13–18] 5-Phosphonylated pyrazole **12** has proved to be a convenient intermediate in synthesis of Bippyphos phosphine ligands, a decent alternative to Buchwald ligands in Pd-catalyzed amination (Scheme 2).[17–19]

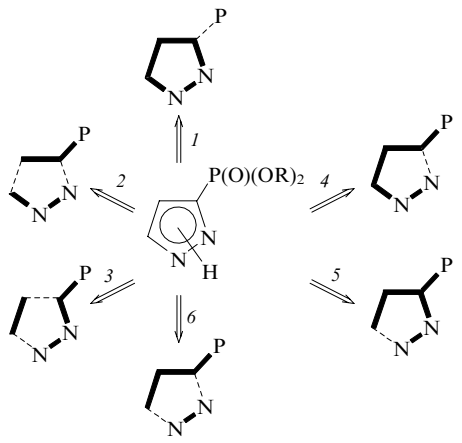
Scheme 2



An increasing interest in C-phosphonylated pyrazoles has been reflected in a number of reviews addressing methods of their synthesis;[20–24] however, they have mainly focused on 4-pyrazolylphosphonates, while 3(5)-pyrazolylphosphonates have received much less attention. This is partially due to the fact that experimental data on 3(5)-phosphonylated pyrazoles, the first representative of which was described in 1963,[25] were initially rather descriptive: their formation was merely detected when studying the reactivity of organophosphorus compounds. The development of practical procedures for the synthesis of 3(5)-pyrazolylphosphonates was started in earnest only 15 years ago. As a result, the numbers of publications devoted to different synthetic routes were distributed very unevenly over the years. Therefore, in this review, we do not restrict our consideration to the literature data reported in the last ten years, as usually; rather, to create an objective picture, we intend to examine as comprehensively as possible all available information.

The known methods of synthesis of 3(5)-phosphonylated pyrazoles can be classified on the basis of the number of C–C and/or C–heteroatom bonds forming at the key stage of synthesis (Scheme 3). First of all, this can be a C–P bond forming in the course of phosphonylation of the pyrazole ring (path *1*). Reactions of α,β-unsaturated phosphonates with diazo compounds or their synthetic equivalents lead to the formation of two bonds, C–N and C–C (path *2*). In the inverted pair, α-phosphonylated 1,3-dipoles are used (path *3*). One C–N bond is formed through the intramolecular heterocyclization of (3-diazoprop-1-enyl)-phosphonates (path *4*) or (1-diazoallyl)phosphonates (path *5*). Finally, two C–N bonds appear in the reaction of organophosphorus 1,3-dielectrophilic compounds with hydrazine (path *6*). This classification is used as a basis for presentation of the available literature data.

Scheme 3

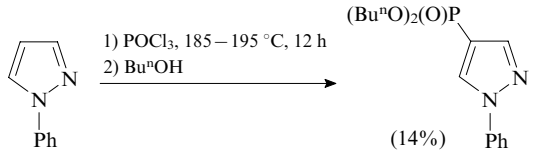


Recall that pyrazoles are characterized by annular prototropic tautomerism;[13, 26] therefore, we try to use 'neutral' presentation of structural formulas, without specifying the position of a proton. Only if the authors of an original work have argued in favour of a certain tautomeric form (based on X-ray diffraction or spectral data), we use the authors' presentation. Consideration of structural data is beyond the scope of this review.

II. Phosphonylation of the pyrazole ring

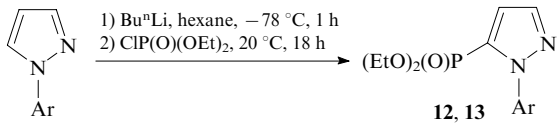
It is known that the direct phosphorylation of pyrazole gives N-phosphorylated products;[27] when the nitrogen atom is protected with an alkyl or aryl substituent, the electrophilic attack (for example, in the reaction of *N*-phenylpyrazole with $POCl_3$) occurs at the 4-position (Scheme 4).[28]

Scheme 4



The electrophilic substitution occurs at the 5-position and is considerably promoted if 5-lithium derivatives rather than N-substituted pyrazoles are used; the former are produced, for example, by metallation with n-butyllithium in synthesis of compounds **12** and **13** (Scheme 5).[19]

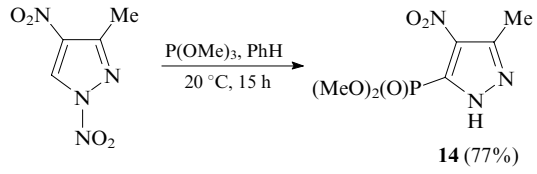
Scheme 5



Ar is 1,3,5-triphenyl-1*H*-pyrazol-4-yl (**12**, 90% yield), Ph (**13**, 79%)

Nucleophilic substitution in activated 1,4-dinitropyrazoles occurs through the *cine*-substitution mechanism and affords 5-substituted 4-nitropyrazoles. When trimethyl phosphite is used as a nucleophile, the reaction is accompanied by the Arbuzov rearrangement to give 5-dimethoxyphosphonyl-3-methyl-4-nitropyrazole (**14**) (Scheme 6).[29]

Scheme 6

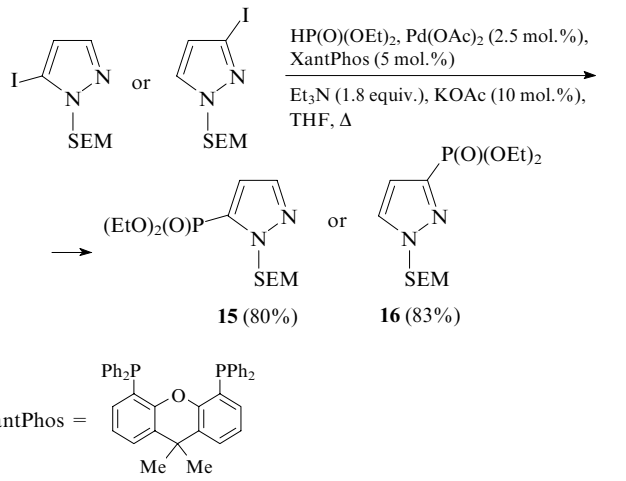


Recently, Cossy and co-workers[30] have developed a palladium-catalyzed phosphonylation of iodo- and bromo-substituted *N*-SEM-pyrazoles (SEM = $CH_2OCH_2CH_2SiMe_3$) under the Hirao reaction conditions. Diethyl phosphite readily reacts with 5- and 3-iodo-*N*-SEM-pyrazoles in the presence of 2 mol.% of the $Pd(OAc)_2$ – 2 XantPhos precatalyst, triethylamine as a base and catalytic amounts of potassium acetate (Scheme 7). The reaction leads to derivatives **15** and **16**, respectively, in good yield.

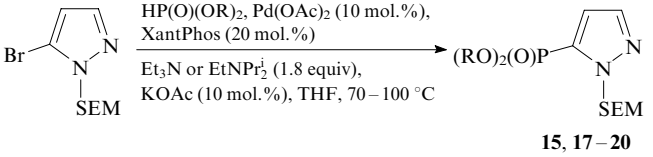
5-Bromo-*N*-SEM-pyrazole also reacts, but the loading of the precatalyst should be increased to 10 mol.% (Scheme 8). Products **15** and **17** – **20** form in moderate or good yield.

The 2-trimethylsilylethoxymethyl protective group at the nitrogen atom is removed by treatment with a trifluoroacetic acid excess in CH_2Cl_2 at room temperature

Scheme 7



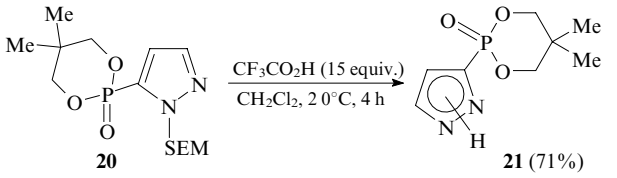
Scheme 8



Compound	$(OR)_2$	Yield (%)
15	$(OEt)_2$	75
17	$(OMe)_2$	47
18	$(OPh)_2$	46
19	$(OCH_2CF_3)_2$	40
20	$OCH_2CMe_2CH_2O$	86

(Scheme 9).[30] For example, this reaction converts compound **20** into N-unsubstituted pyrazole **21**.

Scheme 9

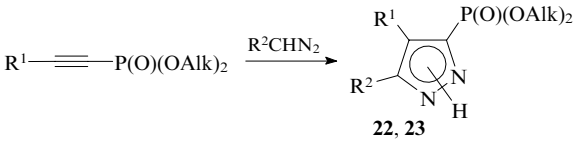


III. Cycloaddition of diazo compounds to α,β-unsaturated phosphonates

The reaction of α,β-unsaturated phosphonates with diazo compounds proceeds by the 1,3-dipolar cycloaddition mechanism through the intermediate formation of a pyrazoline ring, and its further aromatization leads to phosphonylated pyrazoles. In the reaction of ethynylphosphonates[31] with diazomethane or diazoacetic ester, as, for example, in synthesis of compounds **22** and **23** (Scheme 10), aromatization of the heterocyclic system is achieved through proton migration.[32, 33]

When an excess of diazomethane is used, the reaction is accompanied by N-methylation of the nascent pyrazole, which leads, for example, to product **24** (Scheme 11).[25] Note that it was Saunders and Simpson[25] who described

Scheme 10

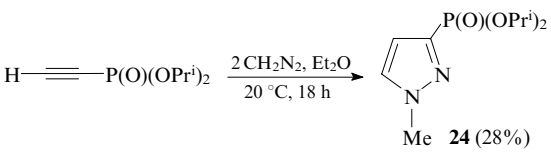


22, **23**

Compound	R^1	Alk	R^2	Yield (%)
22	$P(O)(OMe)_2$	Me	H	95
23	H	Et	CO_2Et	78

for the first time the synthesis of 3(5)-phosphonylated pyrazoles.

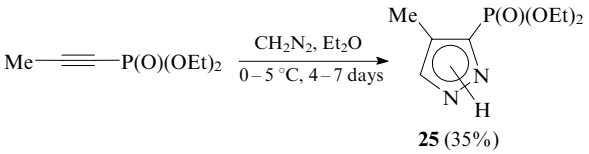
Scheme 11



24 (28%)

Complete regioselectivity of the processes is provided only by terminal or symmetric alkynes. In the general case, 1,3-dipolar cycloaddition to 2-substituted ethynylphosphonates affords a mixture of products, and the ratio between them is determined, first of all, by the electronic effect of a substituent. In particular, diazomethane reacts with an equimolar amount of diethyl 1-propynylphsphonate to give 3(5)-diethoxyphosphoryl-4-methylpyrazole (**25**) in 35% yield (Scheme 12).[34]

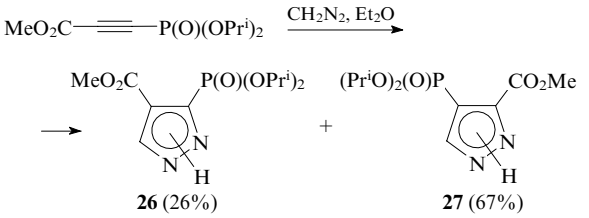
Scheme 12



25 (35%)

The presence of an additional strong electron-withdrawing group at the triple bond is responsible for the preferred formation of 4-phosphonylated pyrazoles. For example, the reaction of diazomethane with methyl 3-(diisopropoxyphosphoryl)propynoate gives a mixture of 3(5)-phosphonylated pyrazole **26** and its 4-phosphonylated isomer **27** (Scheme 13).[35]

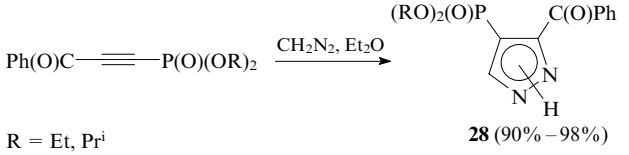
Scheme 13



26 (26%) **27** (67%)

When benzoyl is substituted for the ester moiety, 4-pyrazolylphosphonate **28** is the only product of the reaction (Scheme 14).[35]

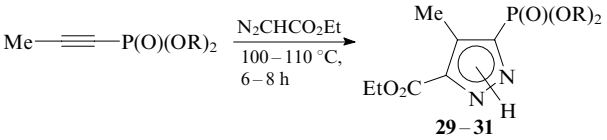
Scheme 14



28 (90%–98%)

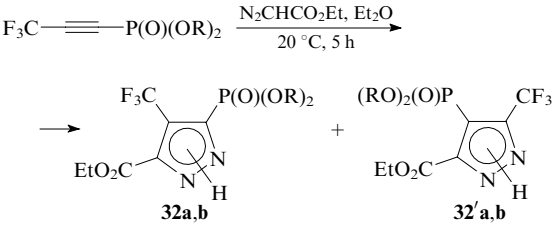
The same tendency is observed for diazoacetic ester. The reaction with 1-propynylphosphonates does not yield 4-phosphonylated pyrazole (Scheme 15).[36] Conversely, the reaction with 3,3,3-trifluoro-1-propynylphosphonates gives a mixture of 3(5)- and 4-phosphonylated pyrazoles, even if with a significant predominance of the former.[37]

Scheme 15



29–**31**

R = Et (**29**, 58% yield), Pr^n (**30**, 54%), Bu^n (**31**, 56%)

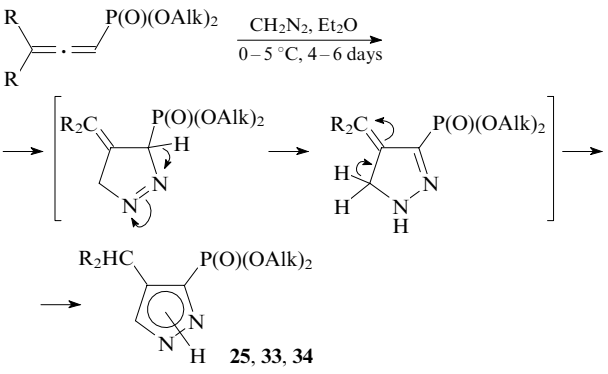


32a,**b** **32′a**,**b**

Compounds	R	Yield **32** + **32′** (%)	Ratio **32** : **32′**
32a, **32′a**	Et	89	84 : 16
32b, **32′b**	Pr^i	94	85 : 15

The reaction of diazomethane with allenylphosphonates and γ,γ-dimethylallenylphosphonates gives phosphonylated pyrazoles (Scheme 16). Due to the activating effect of the electron-withdrawing dialkoxyphosphoryl group, cycloaddition occurs at the α,β-double bond of allenylphosphonate, and aromatization of the nascent pyrazoline involves an exocyclic multiple bond.[34] 4-Methyl- or 4-isopropylpyrazol-3(5)-ylphosphonates **25**, **33** and **34** were obtained in 36%–49% yields; the products of N-methylation with diazomethane — 1,4-dimethyl- and 4-isopropyl-1-methylpyrazol-3(5)-ylphosphonates — were isolated as minor species (8%–12%).

Scheme 16



25, **33**, **34**

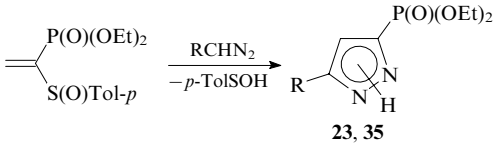
Compound	R	Alk	Yield (%)
25	H	Et	47
33	H	Bu^n	49
34	Me	Et	36

At the same time, the 1,3-dipolar cycloaddition of ethyl diazoacetate to diethyl γ,γ-dimethylallenylphosphonate

(100 °C, 16 h) affords only a mixture of isomeric 2-pyrazolines in total yield of 46%.[36]

In addition to dialkoxyphosphoryl-substituted alkynes and allenes, vinylphosphonates are also able to enter into the 1,3-dipolar cycloaddition reaction with diazo compounds. In this case, the pyrazoline intermediate is aromatized through elimination of a leaving group located, as a rule, at the α-carbon atom of the starting vinylphosphonate. When diethyl 1-(*p*-tolylsulfinyl)vinylphosphonate reacts with diazomethane and diazoacetic ester, *p*-toluenesulfenic acid is eliminated spontaneously to give corresponding 3(5)-phosphonylated pyrazoles **35** and **23** in high yield (Scheme 17).[38]

Scheme 17

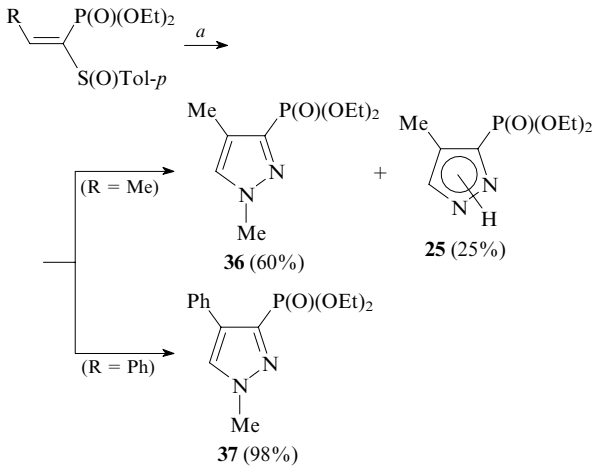


23, **35**

R = H (**35**, yield 90%), CO_2Et (**23**, 100%); *p*-Tol = 4-MeC_6H_4

The reaction of β-methyl- or β-phenyl-substituted diethyl-1-(*p*-tolylsulfinyl)vinylphosphonates with diazomethane leads mainly to N-methylated product **36** or **37**, respectively (Scheme 18). This is likely due to the reduced reactivity of these dipolarophiles so that the reaction time increases and a considerable excess of diazomethane should be used.[38]

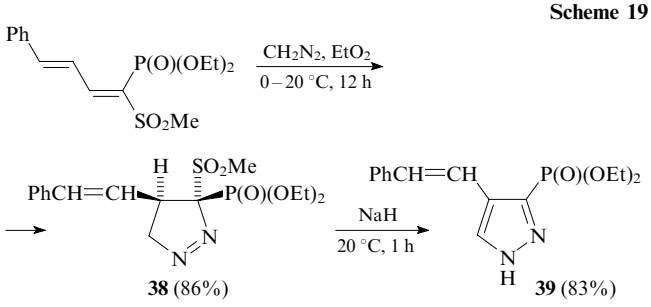
Scheme 18



R = Me, Ph; (*a*) CH_2N_2 (10 – 15 equiv.), Et_2O, 0 – 20 °C, 3 h

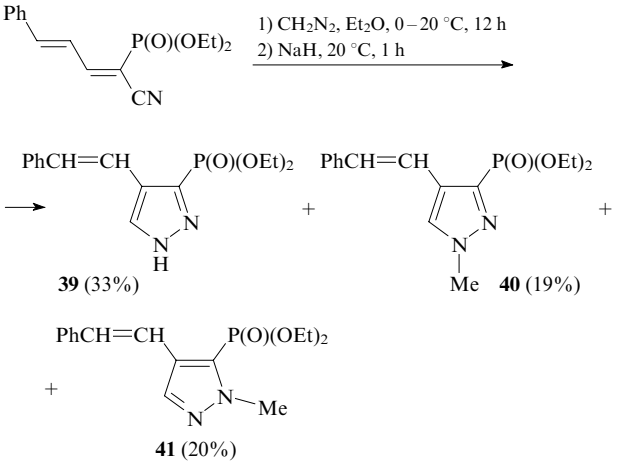
The reaction of diazomethane with β-substituted diethyl α-(methylsulfonyl)vinylphosphonate is not accompanied by spontaneous elimination of methanesulfinic acid: the reaction 'stops' at 1-pyrazoline **38**, and its aromatization to pyrazole **39** proceeds only under the action of a strong base (Scheme 19).[39]

Scheme 19



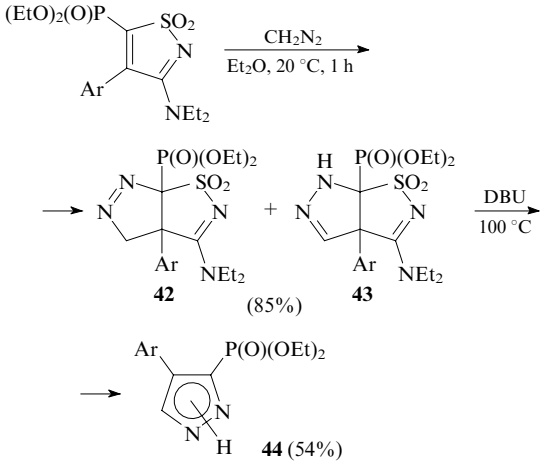
The same researchers[39] have reported that cyanide ion can be used as a leaving group. Treatment of thermally unstable diastereomeric 1-pyrazolines, synthesized *in situ* by the reaction of diazomethane with β-substituted diethyl α-(cyano)vinylphosphonate, leads to a mixture of 3(5)-phosphonylated 4-styrylpyrazole **39** and approximately equal amounts of 3- and 5-phosphonylated 1-methyl-4-styrylpyrazoles **40** and **41** (Scheme 20).

Scheme 20



The aromatization of tautomeric 1- and 2-pyrazolines **42** and **43**, synthesized by the reaction of diazomethane with diethyl [3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-1*H*-isothiazol-5-yl]phosphonate, to give pyrazole **44** is also promoted by bases [refluxing in ethanolic KOH or heating in the presence of an equimolar amount of 1,8-diazabicycloundec-7-ene (DBU) at 100 °C]. Under these conditions, the isothiazole dioxide moiety is split into SO_2 and diethylcyanamide (Scheme 21).[40]

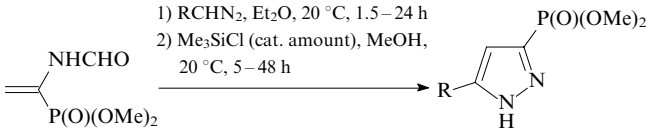
Scheme 21



Ar = 4-$MeOC_6H_4$

Pyrazolines produced by 1,3-dipolar addition of diazo compounds to dimethyl 1-formamidovinylphosphonate are aromatized in an acid medium (Scheme 22).[41,42] It has been demonstrated that the reaction is accompanied by the elimination of formamide. Products **45** – **48** are obtained in moderate to high yields.

Scheme 22

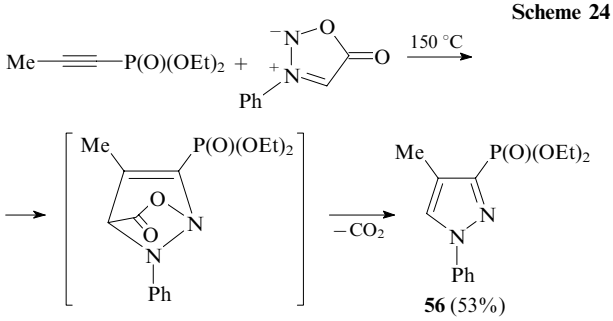


45–48

R = H (**45**, yield 61%), Me (**46**, 37%), Ph (**47**, 93%), 4-$(EtO)_2(O)PC_6H_4$ (**48**, 99%)

The formation of 3(5)-phosphonylated pyrazoles in the reaction of 2-nitrovinylphosphonate with diazo compounds, which is accompanied by the elimination of nitrous acid, is a rare example where the leaving group is located at the β-carbon atom of the starting vinylphosphonate.[43, 44] Unfortunately, this example is not very good since the presence of two strong electron-withdrawing groups in the dipolarophile (nitro- and phosphonate) leads to the non-selectivity of the 1,3-dipolar cycloaddition stage. Scheme 23 shows an approximate composition of the products of the reaction of bis(2-chloroethyl)-2-nitrovinylphosphonate with phenyldiazomethane.[43] The isomerization of the nascent 1-pyrazolines to 2-pyrazolines **49** and **50** competes with elimination of a nitrogen molecule (to give cyclopropane **51**), and aromatization of the 2-pyrazolines is accompanied not only by the elimination of nitrous acid but also by dehydrogenation leading to phosphonylated pyrazoles with and without the nitro group (**52**–**55**).

Scheme 24

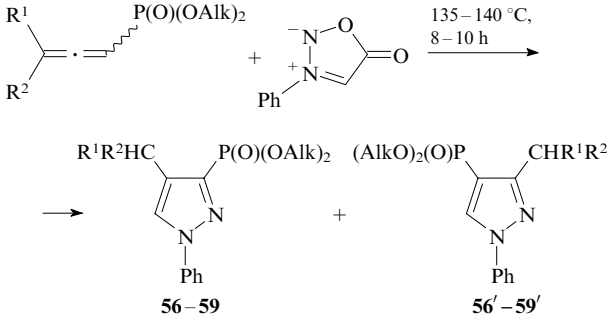


56 (53%)

In addition to diazo compounds, *N*-phenylsydnone is able to enter into the 1,3-dipolar cycloaddition with unsaturated phosphonates, and the formation of the pyrazole ring in compound **56** is accompanied by the elimination of CO_2 (Scheme 24).[45, 46]

The addition of *N*-phenylsydnone to allenylphosphonate and its γ-methyl-substituted analogues yields a mixture of two isomeric pyrazoles (compounds **56**–**59** and **56′**–**59′**, Scheme 25).[47]

Scheme 25

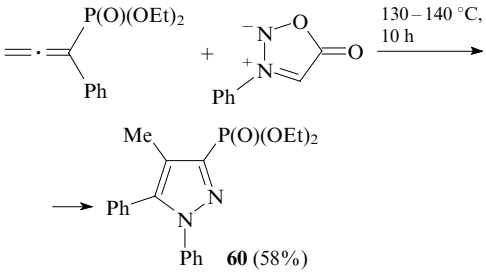


56–**59** **56′**–**59′**

Compounds	R^1	R^2	Alk	Overall yield (%)
56, **56′**	H	H	Et	65
57, **57′**	Me	H	Et	57
58, **58′**	Me	Me	Et	59
59, **59′**	Me	Me	Pr^n	42

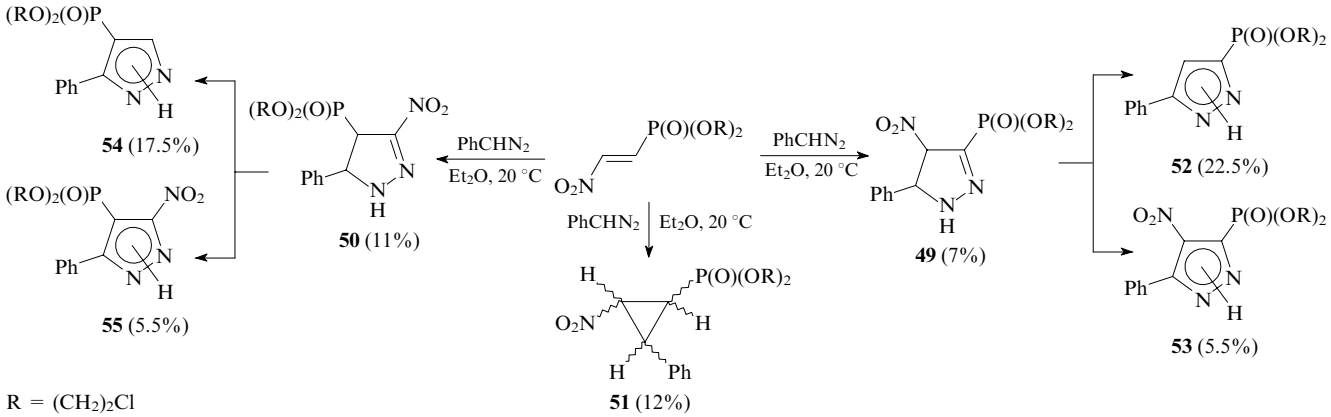
The reaction of *N*-phenylsydnone with diethyl α-phenylallenylphosphonate is accompanied by the migration of the phenyl moiety in the α-position of the dipolarophile to ultimately give 3-diethoxyphosphoryl-4-methyl-1,5-diphenylpyrazole (**60**) (Scheme 26).[48] It is worth noting that no similar migration of the vinyl moiety has been observed in the reaction of 1-vinyl-3-methylbuta-1,2-dienylphosphonates with diazomethane.[49]

Scheme 26



60 (58%)

Scheme 23

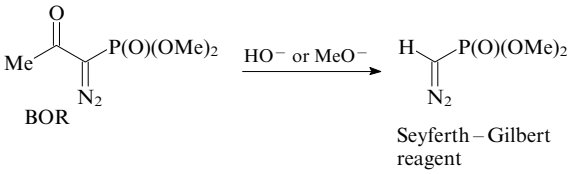


R = $(CH_2)_2Cl$

IV. Reactions of the Bestmann – Ohira reagent with various dipolarophiles

The most developed methods for synthesis of 3(5)-phosphonylated pyrazoles are based on the use of the Bestmann – Ohira reagent (BOR).[50 – 52] This reagent is known as a synthetic equivalent of (diazomethyl)phosphonate (the Seyferth – Gilbert reagent) (Scheme 27).

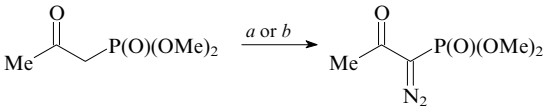
Scheme 27



The Bestmann – Ohira reagent is stable and is easily produced in one stage (Scheme 28) from commercially available 2-oxopropylphosphonate[53] [in contrast to the multistage synthesis of (diazomethyl)phosphonate[54]].

The BOR has gained popularity as an efficient reagent for conversion of aldehydes into terminal alkynes with chain elongation by one carbon atom — a convenient alternative to the Corey – Fuchs reaction. At the same time, the (diazomethyl)phosphonate anion is a 1,3-dipole and is able to enter into cycloaddition reactions with various dipolarophiles.

Scheme 28



(*a*) TsN_3, K_2CO_3, MeCN, 0 °C, 5 h (86% yield); (*b*) 1) NaH, THF, PhH, 0 – 5 °C, 1 h; 2) TsN_3, 20 °C, 2 h (80% yield); Ts = 4-$MeC_6H_4SO_2$

Namboothiri and co-workers[55, 56] were the first who demonstrated the possibility of using the BOR in synthesis of phosphonylated pyrazoles by the example of reactions with β-substituted and α,β-disubstituted conjugated nitroalkenes, as well as with 2-substituted 3-nitro-2*H*-chromenes. The reaction is carried out with a small BOR excess (1.2 equiv.) in the presence of a nucleophilic base (EtONa) in a proton-donating solvent (EtOH) (Scheme 29).† It has been noted that the yield of the product depends only slightly on the nature of the substituents at the double bond and their number.

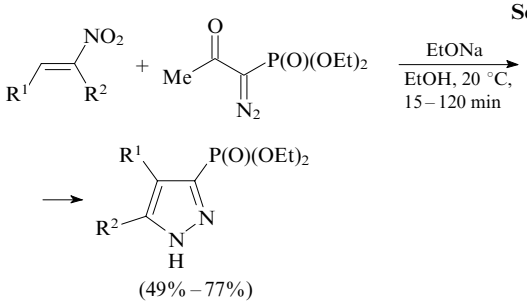
Generally, the reaction of BOR with allyl and benzyl bromides proceeds by a nucleophilic substitution mechanism and can be used as a convenient method for synthesis of α-(diazoalkyl)phosphonates; however, with (*E*)-1-(3-bromo-2-nitro-1-propenyl)-4-methoxybenzene, the BOR reacts as a 1,3-dipole with the only difference that the reaction is accompanied by solvolysis of the allyl bromine atom to give product **61** (Scheme 30).[57]

The method has been extended even to some aromatic nitro compounds, in particular, 2-nitronaphthalene and 2-methyl-6-nitroquinoline give annulated pyrazoles **62** and **63** (Scheme 31).[56] Nitrobenzene and *m*-dinitrobenzene do not enter into this reaction, presumably because of the higher degree of aromaticity.

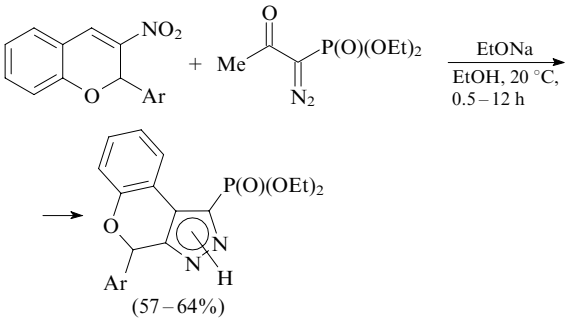
The suggested reaction mechanism (Scheme 32) involves cleavage of the BOR, as a result of the attack of the nucleophile at the carbonyl carbon atom, and the 1,3-dipolar cycloaddition of the generated diethyl 1-(diazomethyl)-phosphonate anion to a nitroalkene.[55] Stabilization of the resulting cyclic adduct **64**, leading to the formation of the pyrazole ring, can occur in two ways: either *via* protonation with subsequent base-catalyzed elimination of HNO_2 (path *a*), or *via* initial elimination of the nitro group with subsequent intramolecular proton shift (path *b*).

† The acronym BOR is also used for the corresponding diethyl ester.

Scheme 29

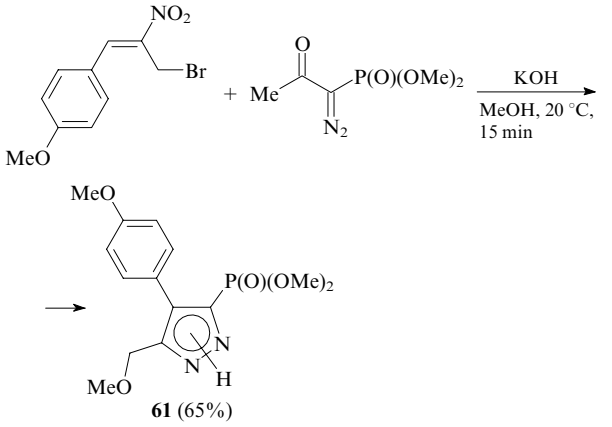


R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, benzodioxol-5-yl, 2-Fu, 2-Th, Me_2N, cyclo-C_6H_{11}, (*E*)-PhCH=CH, (*E*)-2-$MeOC_6H_4CH$=CH; R^2 = H, Me, Ph, $HOCH_2$, $Ac(CH_2)_2$, $EtO_2C(CH_2)_2$, $EtO_2CNHN(CO_2Et)$, TsNHC(Ph)H; Fu is furyl, Th is thienyl

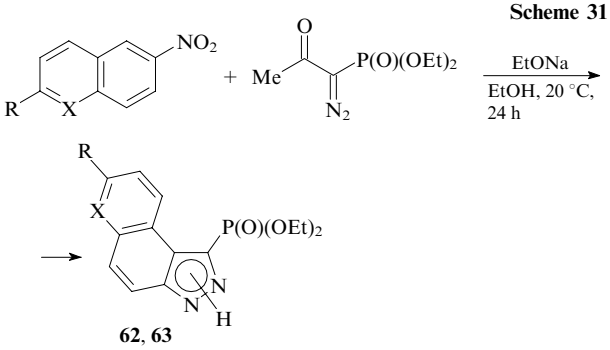


Ar = Ph, 4-$MeOC_6H_4$, 2-Th

Scheme 30



Scheme 31

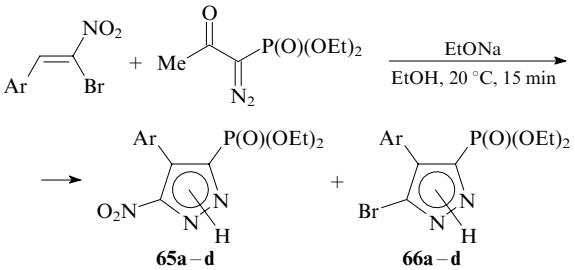


62, **63**

Compound	X	R	Yield (%)
62	CH	H	38
63	N	Me	52

It follows from Scheme 32 that if the initial nitroalkene molecule has an appropriate α-X-substituent, aromatization can be accompanied by the elimination of not only HNO_2 but also of HX. This competition is actually observed when the BOR reacts with β-aryl-α-bromo-α-nitroethenes (Scheme 33).[55,56] In the case of strong electron-donating substituents in the ring, a mixture of products **65** and **66** is formed, while in the absence of such substituents, the only product is phosphonylated nitropyrazole **65**. This is an important result in the context of the considerable synthetic potential of the nitro group and its effect on the biological activity of compounds.

Scheme 33

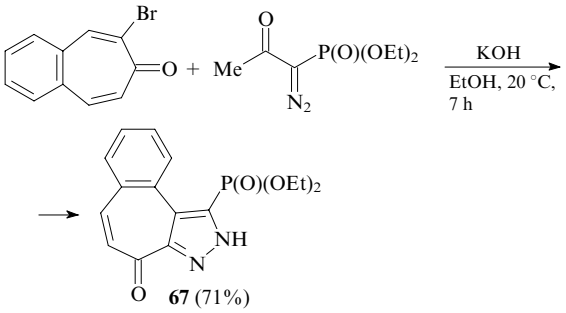


65a–d **66a–d**

Compounds	Ar	Yield **65** + **66** (%)	Ratio **65** : **66**
65a, **66a**	4-$MeOC_6H_4$	54	61 : 39
65b, **66b**	Benzodioxol-5-yl	50	52 : 48
65c, **66c**	4-ClC_6H_4	38	100 : 0
65d, **66d**	Ph	47	100 : 0

The reaction of the BOR with 2-bromobenzo[*d*]tropone is accompanied by the elimination of HBr to give tricyclic product **67** (Scheme 34).[58]

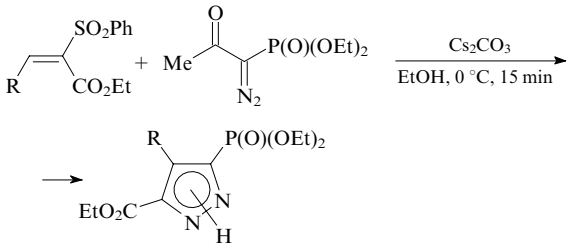
Scheme 34



67 (71%)

The sulfonyl group can also act as the leaving group (Scheme 35).[59] The reaction proceeds rapidly to give products **68**–**71** in good yield.

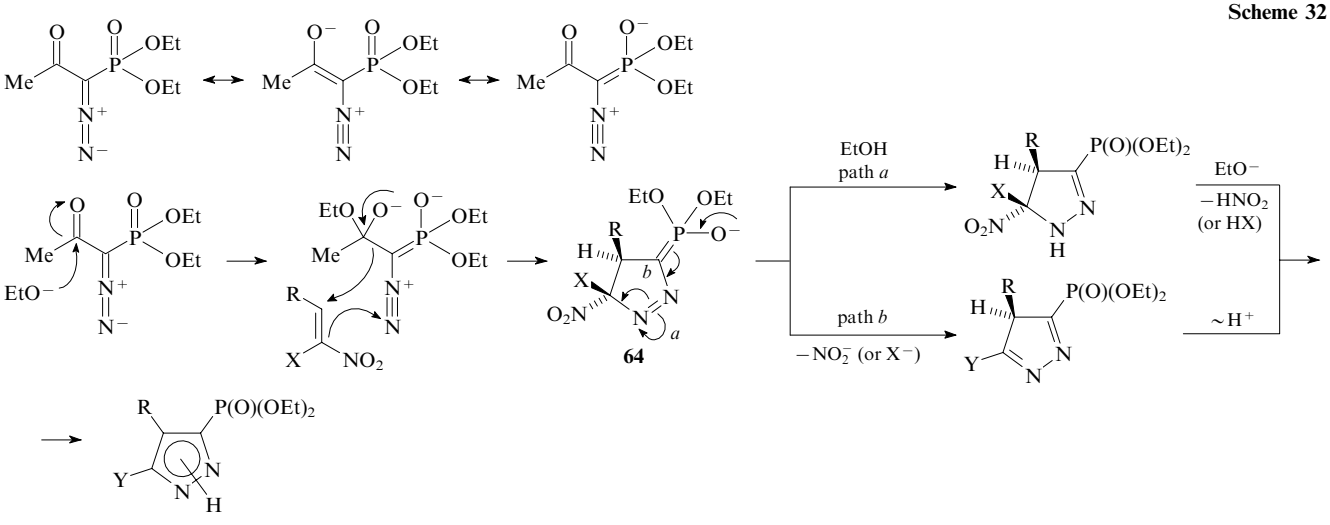
Scheme 35



68–**71**

R = cyclo-C_6H_{11} (**68**, yield 67%), 3-BrC_6H_4 (**69**, 70%), 4-$MeOC_6H_4$ (**70**, 72%), benzodioxo-5-yl (**71**, 74%)

Scheme 32



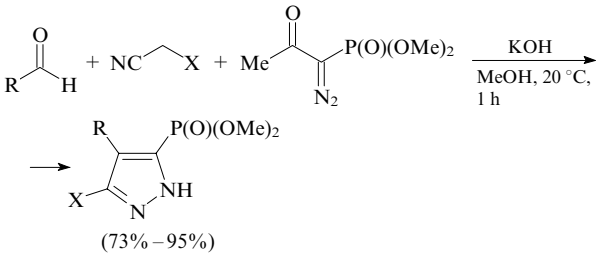
X = H, Alk, Br; Y = NO_2 or X

Smietana and co-workers [60] have suggested using, as the dipolarophile, substituted acrylonitriles readily formed *in situ* by the Knoevenagel reaction from available aldehydes (aromatic, heteroaromatic, aliphatic, or α,β-unsaturated) and malonodinitrile or its analogues of general formula XCH_2CN [X = CO_2Me, $C(O)NH_2$, C(O)NHBn] (Scheme 36). Since the Knoevenagel condensation proceeds more rapidly than the reaction of an aldehyde with the BOR, the authors have developed a three-component one-pot method of synthesis of disubstituted 3(5)-phosphonylated pyrazoles. In all cases, the reaction is accompanied by the elimination of HCN.

A series of 3-acyl-4-phenylpyrazol-5-ylphosphonates have been synthesized in high yield by the regioselective reaction of the BOR with substituted chalcones and (2*E*,4*E*)-1,5-diarylpenta-2,4-dien-1-ones (Scheme 37).[58]

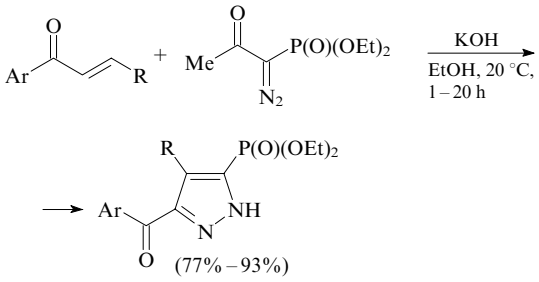
Since chalcones are the products of the Claisen – Schmidt condensation of aromatic aldehydes with methyl ketones, the above transformation can be accomplished as a two-step one-pot process (Scheme 38).[61] It is of interest to compare the time required for the synthesis by two methods. For example, it takes two days to synthesize and purify dimethyl [3-benzoyl-4-(4-bromophenyl)-1*H*-pyrazol-5-yl]phosphonate by the two-stage scheme with isolation of the intermediate chalcone, while the one-pot procedure takes 10 h, and the yield of the target product increases from 70% to 77%.

Scheme 36



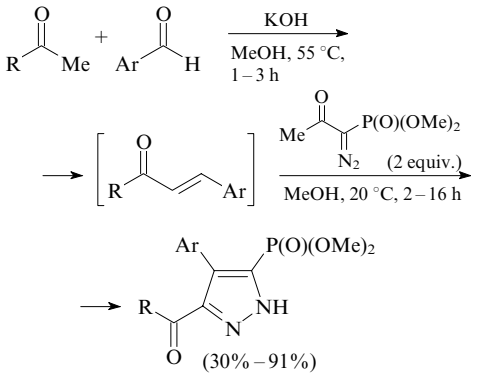
R = Ph, 4-BrC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 2-[$(HO)_2B$]C_6H_4, pyren-1-yl, 2-Th, Fc, (*E*)-$C_5H_{11}CH{=}CH$, cyclo-$C_{11}H_{21}$; X = CN, CO_2Me, $C(O)NH_2$, C(O)NHBn; Fc is ferrocenyl

Scheme 37



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4; R = Ph, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-$Me_2NC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-Th, 2-Fu, (*E*)-PhCH═CH

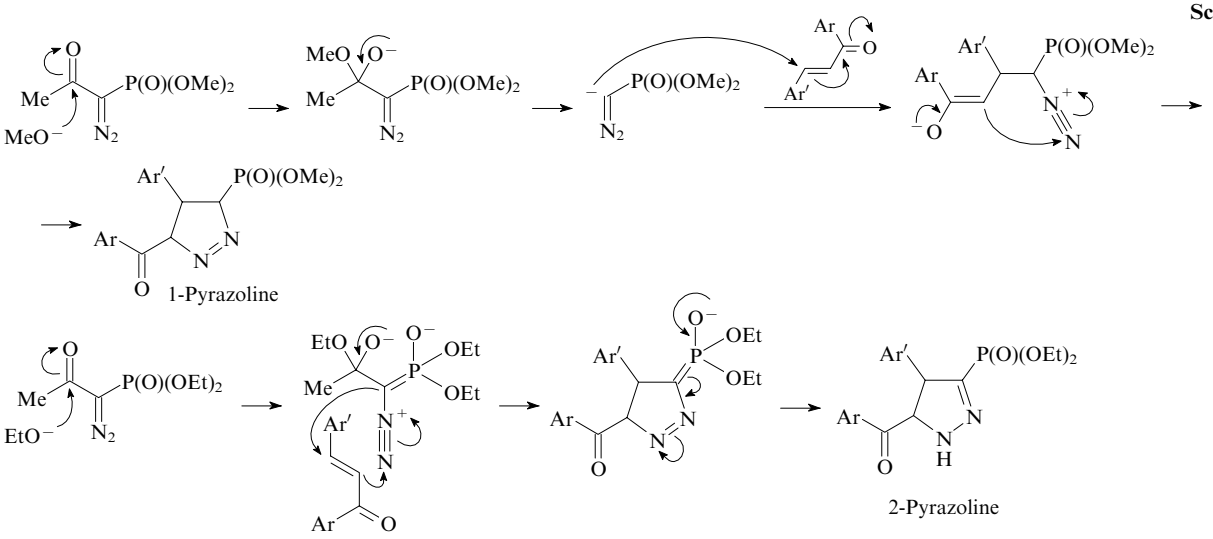
Scheme 38



R = Ph, 4-$MeOC_6H_4$, *N*-methylpyrrol-2-yl, Bu^t;
Ar = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-(HC≡C)C_6H_4, 2-Th

In general, the yields of the products are rather high. Among the limitations of the one-pot procedure, the authors note, first, that it is impossible to use acetophenones with strong electron-withdrawing substituents in the ring (for example, nitro group) since in this case the reaction is dominated by their self-condensation. Second, the yield of pyrazole decreases in the presence of *ortho*-substituents in an aromatic aldehyde, which presumably hinder the attack of the (diazomethyl)phosphonate anion. Indeed, the yield of

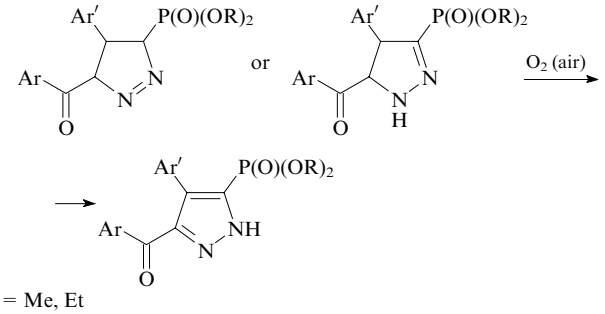
Scheme 39



phosphonylated pyrazole in the reaction of 2,4-dichlorobenzaldehyde with methyl (*N*-methylpyrrol-2-yl) ketone and the BOR is only 30%. The reaction of *o*-methoxybenzaldehyde (as distinct from *para* and *meta* isomers) with acetophenone and the BOR leads only to the corresponding substituted chalcone.

The cycloaddition mechanism has been interpreted differently. Martin *et al.*[61] assume a Michael-type addition of the (diazomethyl)phosphonate anion followed by a cyclization to give 1-pyrazoline (Scheme 39). At the same time, Verma *et al.*[58] assume a concerted mechanism (analogous to the mechanism presented in Scheme 32) leading to 2-pyrazoline.

Scheme 40

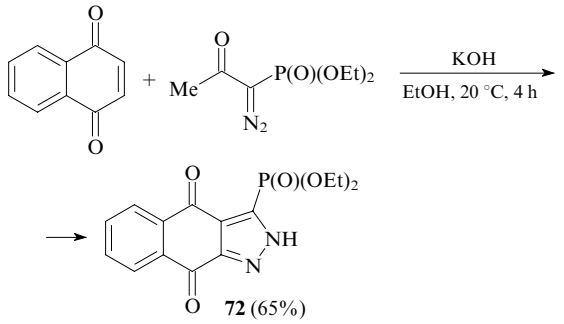


R = Me, Et

The 100% diastereoselectivity of formation of a spiroadduct when the BOR is added to (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one is evidence in favour of the second mechanism.[58] Both versions agree in that the subsequent oxidative dehydrogenation of pyrazoline to pyrazole is promoted by air oxygen during the workup of the reaction mixture and chromatographic isolation of the product (Scheme 40).

Among other dipolarophiles that react with the BOR, 1,4-naphthoquinone is noteworthy (Scheme 41); the reaction gives tricyclic compound **72**.[58]

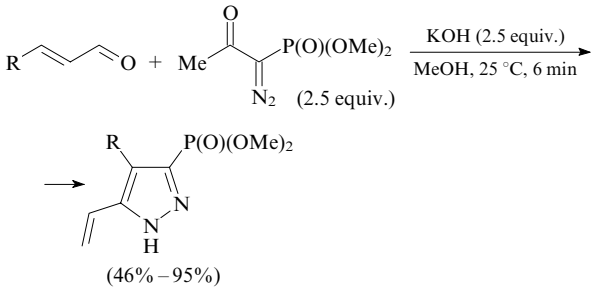
Scheme 41



The reaction of the BOR with cinnamaldehyde and its analogues has a specific feature: when an excess of the reagent (2.5 equiv.) is used, the rapid reaction leads to vinyl-substituted, rather than to formyl-substituted phosphonylated pyrazoles (Scheme 42).[62]

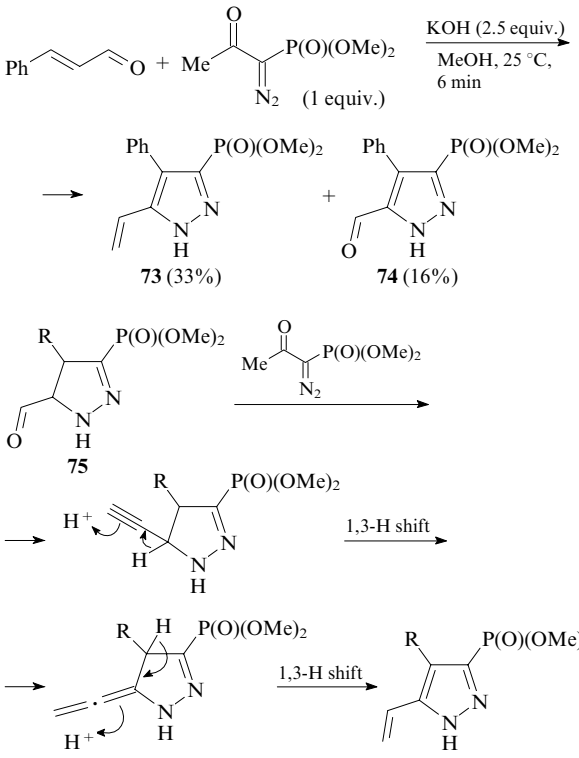
The fact that the reaction of stoichiometric amounts of the reactants leads to a mixture of vinyl- and formyl-substituted products **73** and **74** allows one to assume that formyl-substituted 2-pyrazoline **75** serves as an intermediate, which is either oxidized (as discussed above) or reacts with a BOR excess to give ethynyl-substituted 2-pyrazoline (Scheme 43). Subsequent 1,3-H shift leads to aromatization of the heterocyclic moiety.

Scheme 42



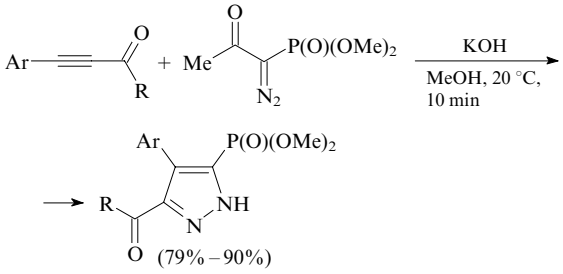
R = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-BrC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,5-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$, benzodioxol-5-yl, 1-Naph, 2-Fu, 2-Th, (*E*)-PhCH=CH, Pr^n; Naph is naphthyl

Scheme 43



In addition, activated alkynes can act as dipolarophiles in the reaction with the BOR.[63] It is evident, that oxidative aromatization is not required in this case. The reaction

Scheme 44

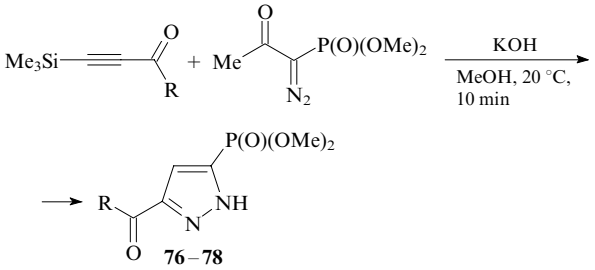


Ar = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$; R = Ph, 3-MeOC$_6$H$_4$, 2-Fu, Pr^i, Bu^i, n-C$_5$H$_{11}$, cyclo-C$_6$H$_{11}$

proceeds smoothly under mild conditions to give 4-substituted 3-acyl-5-dimethoxyphosphorylpyrazoles in high yields (Scheme 44).

3-Aroyl-5-dimethoxyphosphorylpyrazoles **76** – **78** without a substituent in the 4-position can be synthesized from 1-aryl-3-(trimethylsilyl)-2-propyn-1-ones (Scheme 45). The protective trimethylsilyl group is hydrolyzed in the course of reaction.[63]

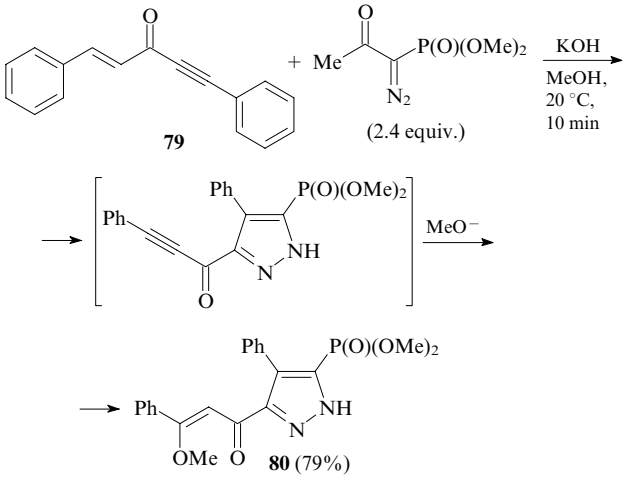
Scheme 45



R = Ph (**76**, yield 87%), 3-$MeOC_6H_4$ (**77**, 86%), 2-Fu (**78**, 84%)

The reactivities of activated double and triple bonds (with respect to the BOR) have been compared by the example of (*E*)-1,5-diphenyl-1-penten-4-yn-3-one (**79**) (Scheme 46). The structure of isolated product **80** indicates that cycloaddition occurs, first of all, at the double bond, while the triple bond acts as a Michael-type acceptor for the addition of the methoxide ion.[63]

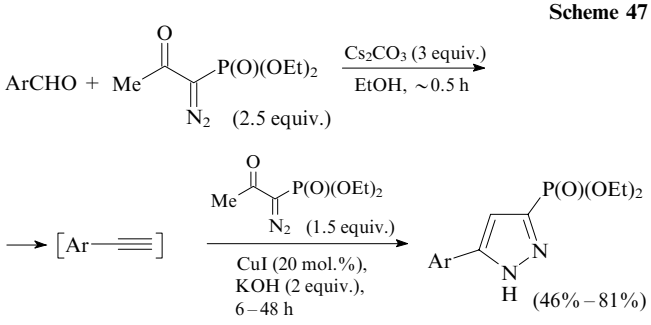
Scheme 46



Nonactivated alkynes, in particular, 4-nitrophenylacetylene, react with the BOR only in the presence of a copper catalyst.[64] Since terminal alkynes are conveniently prepared by the action of the BOR on aldehydes, a two-step one-pot method of synthesis of 5-aryl-3-diethoxyphosphorylpyrazoles directly from aromatic aldehydes has been suggested (Scheme 47). Careful optimization of synthesis conditions showed that it is expedient to use Cs_2CO_3 in ethanol as a base in the first step, while the second step requires the presence of CuI as a precatalyst and a stronger base (KOH).

Since both steps involve a nucleophilic attack of the (diazomethyl)phosphonate, a decrease in the LUMO energy of both the aldehyde and acetylene should generally have a favourable effect. Indeed, aromatic aldehydes containing strong electron-withdrawing substituents (NO_2, CF_3, F, Cl), especially in the *para*-position, react faster to give the products in higher yields. The reaction with aliphatic aldehydes and cinnamaldehyde has failed.

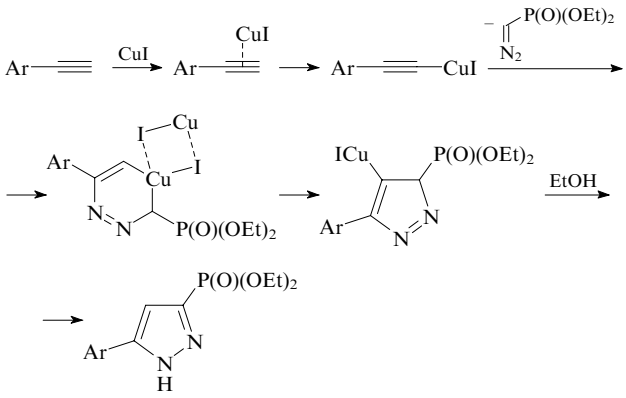
Scheme 47



Ar = Ph, 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeC_6H_4, 4-$Pr^iC_6H_4$, 3,4-$(MeO)_2C_6H_3$, benzodioxol-5-yl, 1-Naph, 2-Fu, 2-Th, 3-Th

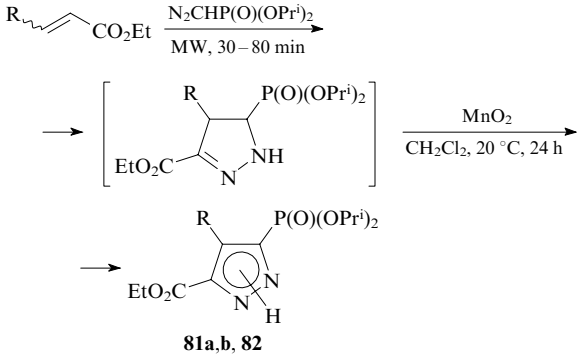
The reaction mechanism suggested by Kumar *et al.*[64] (not indisputable in detail) is based on analogy with copper-catalyzed azide – alkyne cycloaddition [65] (Scheme 48).

Scheme 48



The possibility of using (diazomethyl)phosphonate itself in synthesis of 3(5)-phosphonylated pyrazoles has been demonstrated only recently by the example of its microwave-assisted (MW) regioselective 1,3-dipolar cycloaddition to β-substituted ethyl acrylates [66] (Scheme 49). Manganese(IV) oxide was used for oxidative aromatization of cycloaddition products — 2-pyrazolines — to give target pyrazoles **81a**, **81b** and **82**.

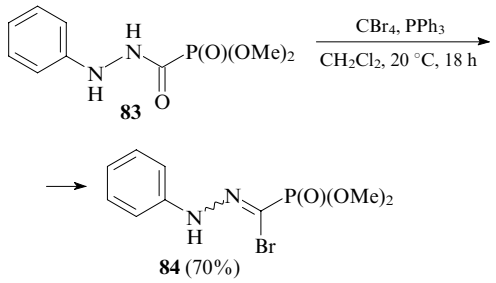
Scheme 49



R = Me (**81a**, yield 85%), Pr^n (**81b**, 82%), Ph (**82**, 72%)

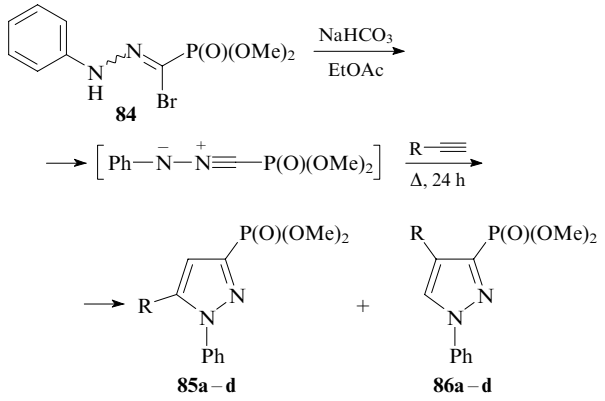
The only currently known alternative to the BOR [or (diazomethyl)phosphonate] as a source of a phosphonylated 1,3-dipole are hydrazonoyl halides, synthesized from [(2-phenylhydrazino)carbonyl]phosphonates, for example, compound **83** (Scheme 50).[67]

Scheme 50



Dimethyl [bromo(2-phenylhydrazono)methyl]phosphonate (**84**) is readily dehydrobrominated in the presence of a base to give phosphonylated nitrile imine — a 1,3-dipole that reacts with both activated and unactivated terminal acetylenes (Scheme 51). The character of the substituent at the triple bond has no essential effect on the regioselectivity of the process, and the major products (although the yields are generally low) are 5-substituted 1-phenyl-1*H*-pyrazol-3-ylphosphonates **85a–d** (along with an admixture of 4-substituted isomers **86a–d**), which can be isolated chromatographically.

Scheme 51

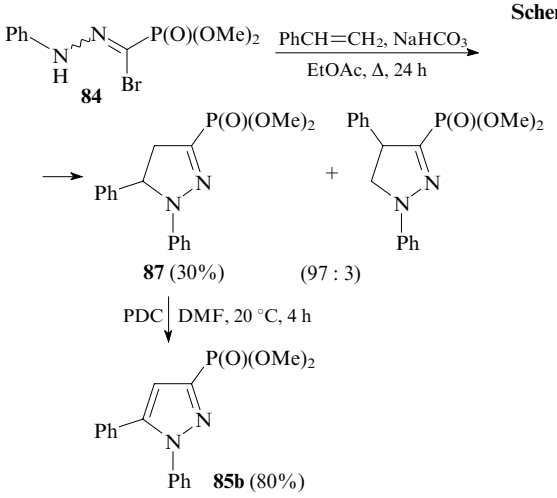


Compounds	R	Yield **85** (%)	Ratio **85** : **86**
85a, **86a**	CO_2Me	34	78 : 22
85b, **86b**	Ph	40	90 : 10
85c, **86c**	Bu^n	18	95 : 5
85d, **86d**	n-C_9H_{19}	12	81 : 19

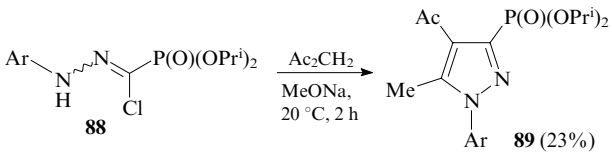
The regioselectivity is manifested to a greater extent in the reaction of phosphonylated nitrile imine with terminal alkenes leading to the predominant formation of 5-substituted 1-phenyl-4,5-dihydro-1*H*-pyrazol-3-ylphosphonates (for example, of compound **87**), which can be oxidized to the corresponding pyrazoles with pyridinium dichromate (PDC) in DMF (Scheme 52).[67]

The reaction of diisopropyl [chloro(4-nitrophenylhydrazono)methyl]phosphonate (**88**) with acetylacetone in an alkaline medium leads to 3-phosphonylated pyrazole **89** (Scheme 53).[68]

Scheme 52



Scheme 53

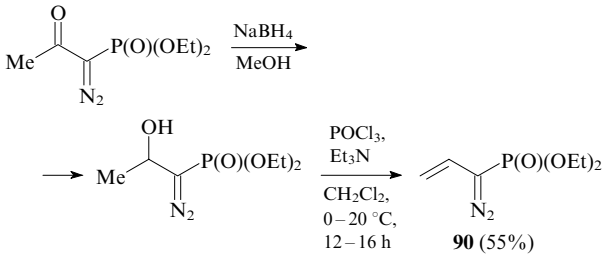


Ar = 4-$O_2NC_6H_4$

V. Intramolecular heterocyclization of (1-diazoallyl)phosphonates and (3-diazo-1-propenyl)phosphonates

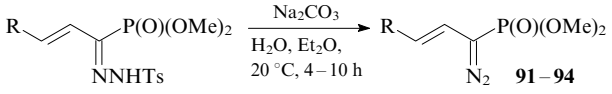
The reduction of the BOR with sodium borohydride with subsequent water elimination under the action of phosphoryl chloride in the presence of triethylamine leads to 1-diazoallylphosphonate **90** (Scheme 54).[69]

Scheme 54



Substituted (1-diazoallyl)phosphonates **91–94** are synthesized by base-induced cleavage of tosylhydrazones (Scheme 55).[70–72]

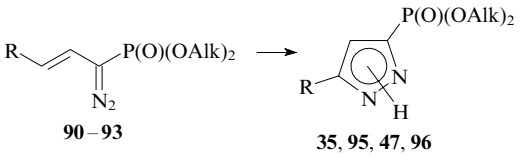
Scheme 55



R = 4-$MeOC_6H_4$ (**91**, yield 51%), Ph (**92**, 56%), (*E*)-MeCH=CH (**93**, 86%), (*E*)-PhCH=CH (**94**, 84%)

These compounds are among relatively stable (1-diazoallyl)phosphonates, which can be isolated by crystallization[70] or by chromatography.[69,71] Subsequent heterocyclization to give, for example, products **35**, **47**, **95** and **96** is carried out either on heating in benzene or toluene or at room temperature (usually in diethyl ether) in the dark (Scheme 56).[69–71]

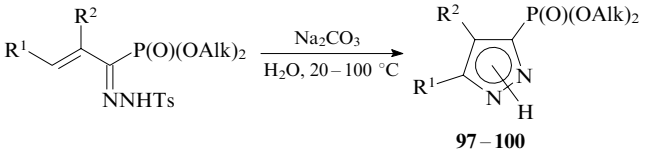
Scheme 56



Compounds	R	Alk	Yield (%)
90, **35**	H	Et	–
91, **95**	4-$MeOC_6H_4$	Me	82
92, **47**	Ph	Me	80
93, **96**	(*E*)-MeCH=CH	Me	62

In some cases, intramolecular cyclization occurs spontaneously even at the stage of synthesis of (1-diazoallyl)-phosphonate. This reaction yields, for example, pyrazoles **97** – **100** (Scheme 57).[71–73]

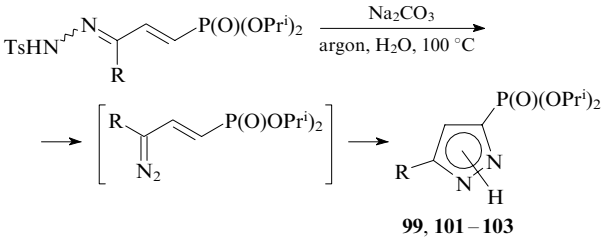
Scheme 57



Compound	R^1	R^2	Alk	Yield (%)
97	Me	Me	Me	65
98	Ph	Me	Me	86
99	Pr^i	H	Pr^i	87
100	$(CH_2)_4$		Et	52

Thermal decomposition of (3-oxo-1-alkenyl)phosphonate tosylhydrazones occurs analogously to give corresponding pyrazoles **99**, **101** – **103** (Scheme 58).[73]

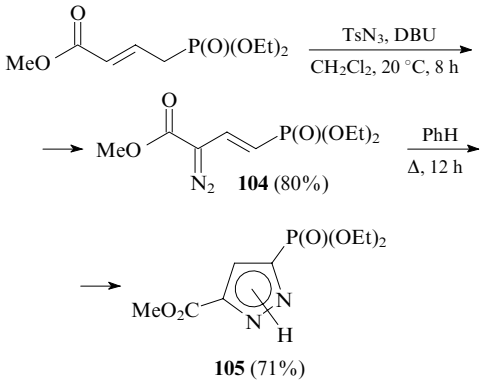
Scheme 58



R = Pr^i (**99**, 88% yield), Me (**101**, 85%), Bu^i (**102**, 85%), Ph (**103**, 75%)

Vinylphosphonate **104**, containing a diazo ester moiety in the β-position, can be obtained by the diazo transfer reaction.[74] This compound is stable on storage at – 30 °C for several months and is cyclized on heating to give pyrazole **105** (Scheme 59).

Scheme 59

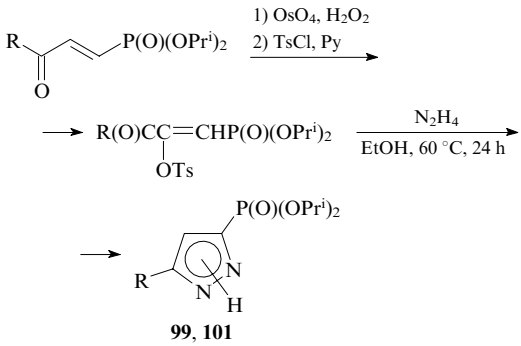


VI. Cyclocondensation of 1,3-dielectrophilic compounds with hydrazines

A classical method of formation of a pyrazole ring is through the condensation of hydrazine with 1,3-dicarbonyl compounds (the Knorr synthesis) or 1,3-dielectrophilic compounds, which are their analogues, in particular, with α,β-unsaturated carbonyl compounds containing an extra leaving group.[75–77] As applied to the synthesis of 3(5)-phosphonylated pyrazoles, this approach has been developed in several variants differing in the type of starting organophosphorus substrate, and the availability of the latter is essential in this case.

The method was pioneered by Penz and Zbiral,[78] who demonstrated that the reaction of diisopropyl (3-oxo-2-tosyloxy-1-alkenyl)phosphonates with hydrazine affords phosphonylated pyrazoles (for example, compounds **99** and **101**) in high yields (Scheme 60). The initial compounds are prepared by hydroxylation of corresponding (3-oxo-1-alkenyl)phosphonates under the action of $OsO_4 - H_2O_2$ with subsequent treatment with tosyl chlorides in pyridine.

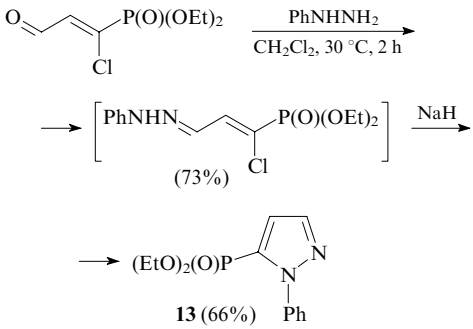
Scheme 60



R = Pr^i (**99**, yield 70%), Me (**101**, 90%); Py is pyridine

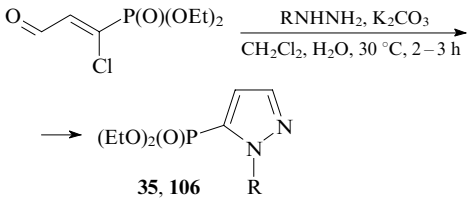
The condensation of phenylhydrazine with diethyl (3-oxo-1-chloro-1-propenyl) phosphonate leads, quite expectedly, to phenylhydrazone, which is cyclized into pyrazole **13** when sodium hydride is added to the reaction mixture (Scheme 61).[79–81]

Scheme 61



Hydrazine and methylhydrazine react analogously in the presence of potassium carbonate to give pyrazoles **35** and **106**, respectively (Scheme 62).[81]

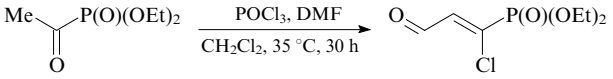
Scheme 62



R = H (**35**, yield 51%), Me (**106**, 61%)

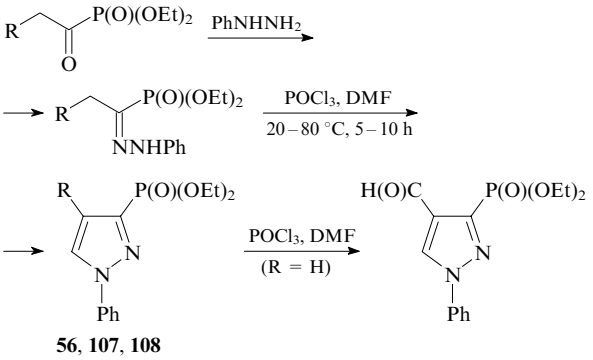
The initial compound is synthesized as a mixture of *Z*- and *E*-isomers (*Z* : *E* = 93 : 7) by the reaction of the Vilsmeier reagent with acetylphosphonate (Scheme 63).

Scheme 63



It is worth noting that the same reactants — acetylphosphonate and phenylhydrazine — can be used for synthesis of isomeric 3-phosphonylated product **107** if the steps of formylation and hydrazone formation are swapped (Scheme 64).[79, 80] The yield of the product is low (only 30%), since the reaction is hindered by further formylation of the ring; however, when propionyl- and benzoylphosphonates are used, the yields of corresponding **56** and **108** are as high as 61% and 73%.

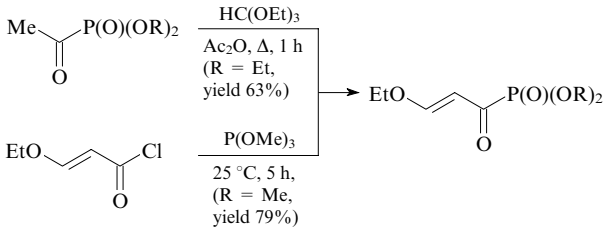
Scheme 64



R = H (**107**, yield 30%), Me (**56**, 61%), Ph (**108**, 73%)

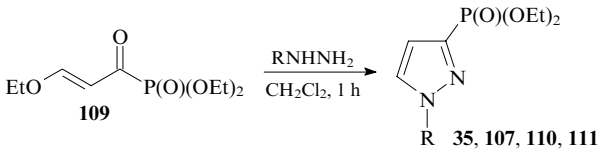
Acetylphosphonate[82] as well as (*E*)-3-ethoxyacryloyl chloride[83] have been used to produce yet another reagent in synthesis 3-phosphonylated pyrazoles (Scheme 65).

Scheme 65



(*E*)-Diethyl (3-ethoxy-2-propenoyl)phosphonate (**109**) reacts with hydrazine and alkyl(aryl) hydrazines to form N-substituted (3-pyrazolyl)phosphonates **35**, **107**, **110** and **111** in moderate yields (Scheme 66).[82]

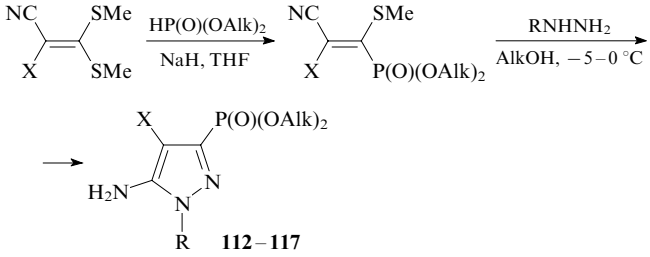
Scheme 66



R = H (**35**, 26% yield), Ph (**107**, 35%), Me (**110**, 30%), 4-MeC$_6$H$_4$ (**111**, 41%)

Lu and Yang[84] have shown that 1-methylsulfanyl-2,2-dicyano- and 1-methylsulfanyl-2-cyano-2-ethoxycarbonylvinylphosphonates can be introduced into condensation with hydrazine (Scheme 67). The yields of products **112**–**117** are nearly quantitative. The method is unique in that 3-phosphonylated pyrazoles **112**–**117** contain an amino group. The initial synthones are formed through the addition of dialkyl phosphites to α,α-dicyano- or α-cyano-α-ethoxycarbonyl ketene dithioacetals, produced in several steps from malonodinitrile or ethyl cyanoacetate, respectively.

Scheme 67

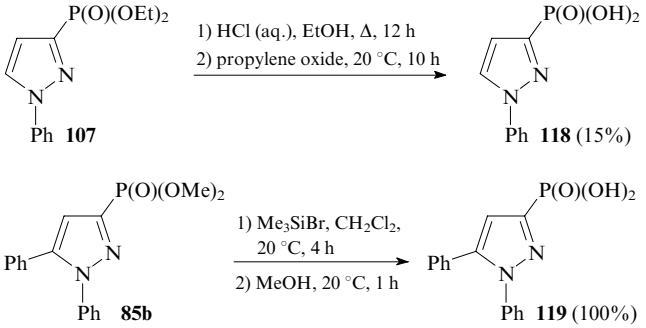


Compound	X	Alk	R	Yield (%)
112	CN	Et	H	96
113	CN	Et	Ph	94
114	CN	Pr^i	H	90
115	CN	Pr^i	Ph	89
116	CO_2Et	Et	H	95
117	CO_2Et	Et	Ph	93

VII. Reactions of 3(5)-phosphonylated pyrazoles

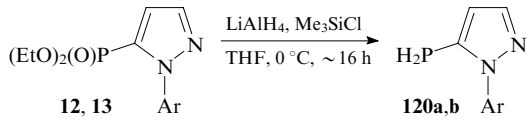
Chemical transformations of 3(5)-phosphonylated pyrazoles have been sparingly reported. We mentioned the Vilsmeier – Haack formylation of diethyl 1-phenyl-1*H*-pyrazol-3-ylphosphonate (**107**) at the 4-position (see Section VI),[79, 80] N-methylation with diazomethane (see Section III)[25, 34, 38, 39] and the possibility of removal of the SEM-protecting group at the nitrogen atom (see Section II).[30] It has been reported that a dialkoxyphosphoryl moiety of N-phenyl-substituted (3-pyrazolyl)-phosphonates is hydrolyzed in a mixture of hydrochloric acid and ethanol on heating under reflux to give product **118** in 15% yield[82] or by the McKenna method (reaction with Me_3SiBr with subsequent methanolysis)[85 – 87] affording acid **119** in quantitative yield (Scheme 68).[67]

Scheme 68



The reduction of the phosphonate group with lithium aluminiumhydride in the presence of trimethylchlorosilane leads to 5-pyrazolylphosphines — intermediates in synthesis of ligands for metal complex catalysis. For example, pyrazoles **12** and **13** are converted into phosphines **120a**,**b** (Scheme 69).[19]

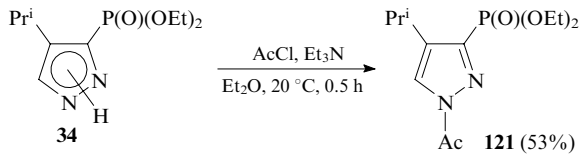
Scheme 69



Compounds	Ar	Yield **120** (%)
12, **120a**	1,3,5-triphenyl-1*H*-pyrazol-4-yl	99
13, **120b**	Ph	82

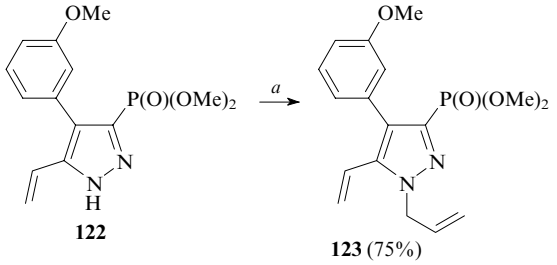
Acylation of diethyl 4-isopropyl-3-pyrazolylphosphonate (**34**) with acetyl chloride in ether leads to 1-substituted pyrazole **121** in good yield (Scheme 70).[34]

Scheme 70



N-allylation of 5-vinyl-substituted 3-pyrazolylphosphonate **122** has been described (Scheme 71).[62]

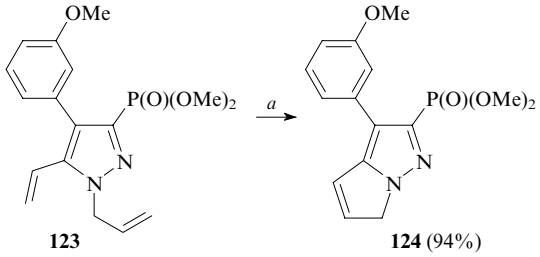
Scheme 71



(*a*) 1) NaH, THF, 0 °C, 0.5 h; 2) $CH_2{=}CHCH_2Br$, 20 °C, 14 h

Product **123** has been used in synthesis of fused pyrrolopyrazole **124** by the metathesis reaction in the presence of the second-generation Grubbs (Grubbs II[88]) catalyst (Scheme 72).[62]

Scheme 72



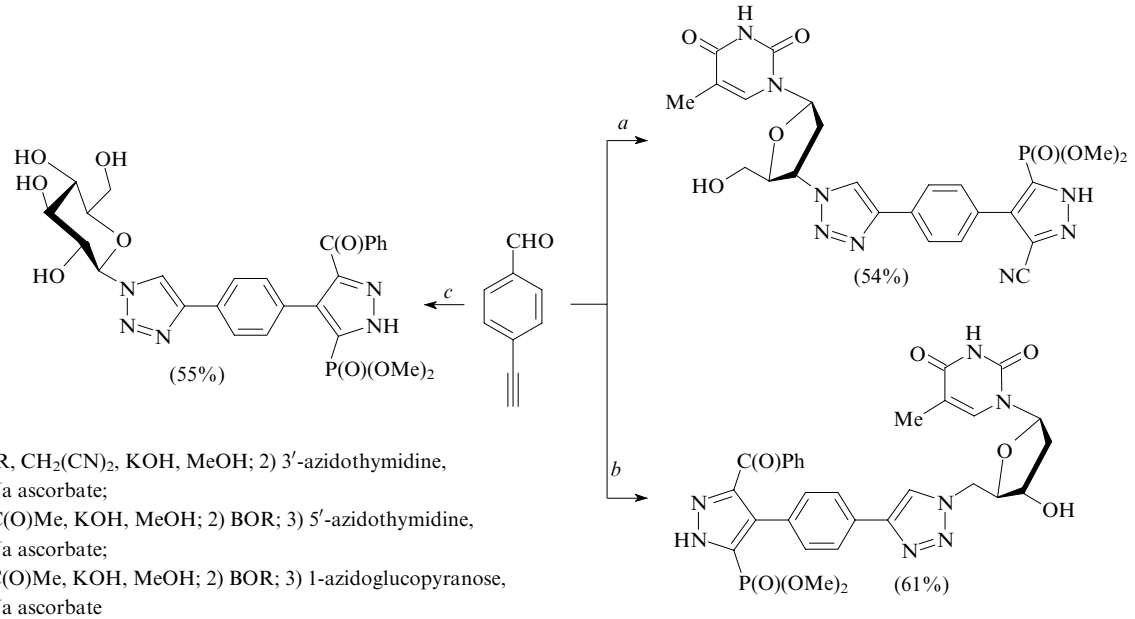
(*a*) Grubbs II (0.02 mol.%), CH_2Cl_2, 40 °C, 72 h

Finally, it has been shown that 3(5)-phosphonylated pyrazoles with an ethynyl substituent at the periphery can be involved in click chemistry reactions.[60, 61] In the known examples, the second component was a biologically significant molecule (such as a nucleoside or carbohydrate) modified with azido group (Scheme 73). The azide – alkyne cycloaddition was carried out as a step of a general one-pot process involving the synthesis of the pyrazole ring. The reaction requires using an equimolar amount of a Cu catalyst, which is explained by the authors by the possibility of competing binding of Cu^{II} ion to the pyrazole moiety.

* * *

We have performed a systematic analysis of the synthetic routes to 3(5)-phosphonylated pyrazoles with the aim to reproduce, as completely as possible, the spectrum of the currently known structures and pay some attention to the availability of the starting compounds. Information presented in this review demonstrates that various synthetic routes to 3(5)-phosphonylated pyrazoles have been developed to a different extent. Some methods are actively developed. In particular, significant progress has been made in using the Bestmann – Ohira reagent. Other approaches are still represented by a set of fragmentary experimental facts, and relevant studies are in their infancy. We hope that the data reported in this review will help organic chemists to properly assess trends in the development of different synthetic approaches and will stimulate further progress in those areas whose potential has not yet

Scheme 73



(*a*) 1) BOR, $CH_2(CN)_2$, KOH, MeOH; 2) 3′-azidothymidine, $CuSO_4$, Na ascorbate;
(*b*) 1) PhC(O)Me, KOH, MeOH; 2) BOR; 3) 5′-azidothymidine, $CuSO_4$, Na ascorbate;
(*c*) 1) PhC(O)Me, KOH, MeOH; 2) BOR; 3) 1-azidoglucopyranose, $CuSO_4$, Na ascorbate

been elucidated. Practical interest in 3(5)-phosphonylated pyrazoles, which are structural isomers of 4-pyrazolylphosphonates and phosphorus analogues of pyrazole-3(5)-carboxylates, in some areas, such as organic synthesis and medicinal and coordination chemistry, has only recently been aroused. Development of new preparative reactions should extend the range of available structures and potential fields of their application.

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