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A Regioselective Synthesis of 5-Pyrazolones and Pyrazoles from Phosphazenes derived from Hydrazines and Acetylenic Esters

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Abstract: Efficient and regioselective syntheses of 1-phenyl-5-pyrazolones substituted with a phosphoranylidene group in the 3-position and of 3-alkoxycarbonyl-5-methoxy-1-phenyl pyrazoles are described. The key step is the formation of functionalized hydrazones by [2+2] cycloaddition reaction of phosphazenes derived from hydrazines with acetylenic esters. Subsequent cyclization of these compounds with butyl lithium affords substituted 5-pyrazolones, while their heating with acetonitrile leads to the formation of 3-alkoxycarbonyl-5-methoxy-1-phenyl pyrazoles in a regioselective fashion.

Keywords: 5-pyrazolones, pyrazoles, hydrazines, acetylenic esters, phosphazenes.

Pyrazole and pyrazolone ring systems represent an important class of compounds[1] not only for their theoretical interest but also for their biological activities and because they can constitute the skeleton of dyestuffs and polymers. Likewise, 3-alkoxycarbonyl pyrazoles are important intermediates in the preparation of agrochemicals,[2] and have had applications in drug synthesis as antihyperglycemic[3a] and antitumor agents,[3b] angiotensin antagonists[3c] and for the preparation of combinatorial libraries.[3d] 1-Phenyl pyrazolone derivatives have interesting pharmacological properties as analgesic,[4a] antipyretic,[4b] and antiinflamatory agents,[4c] and solid-phase synthesis of these compounds has been recently developed.[4d,e] Furthermore, it is known that the phosphor substituents regulate important biological functions,[5] and that molecular modifications of pyrazole rings introducing organo phosphorus functionalities can lead to very interesting and useful agrochemical[6a-d] products such as insecticides[6e-g] and herbicides.[6h]

A wide range of procedures for the synthesis of pyrazoles[1,7] has been reported. However, pyrazoles directly substituted with phosphorus containing functional groups have received much less attention,[7a,8]

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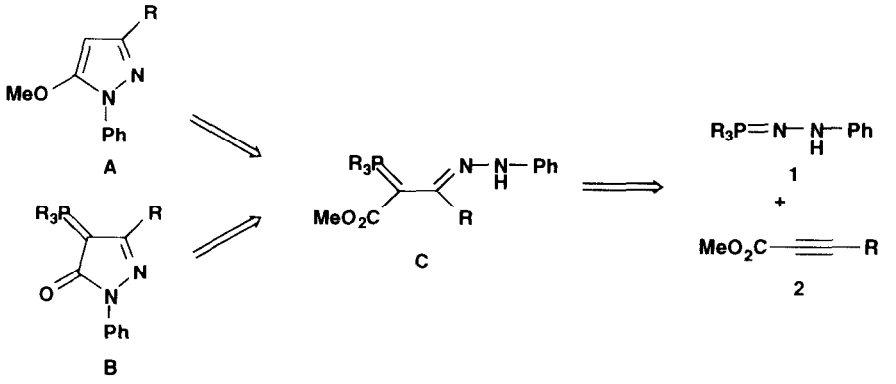
probably owing to the lack of general methods for their synthesis.[1,7] In connection with our interest in the synthesis of five[9] and six[10] membered nitrogen heterocycles we have used β-functionalized phosphorylated compounds as synthetic intermediates in the synthesis of acyclic derivatives such as oximes,[11a] allylamines,[11b] hydrazones[11c] and β-aminofunctionalized compounds[11d] as well as pyridines[12a] and phosphorus containing heterocycles.[12b-e] We have described the synthesis of 4-aminopyrazoles[9c] derived from phosphine oxides, and easily prepared from β-hydrazono phosphine oxides. Here we aim to extend the synthetic use of functionalized hydrazones **I** in the preparation of substituted 3-alkoxycarbonyl pyrazoles **A** and of 1-phenyl-5-pyrazolones **B** containing a phosphoranylidene group in the 4-position. Retrosynthetically, heterocycles **A** and **B** could be prepared from hydrazones **I**. Hydrazones derived from β-phosphonium salts have been prepared by reaction of azoalkenes with phosphines[13] or by 1,3-cycloaddition reaction[14] of phosphorus ylides to nitrilimines. We envisaged the preparation of hydrazones **I** by [2+2] cycloaddition reaction of phosphazenes derived from hydrazines **1** with acetylenic esters **2** (Scheme 1). This strategy involving the reaction of phosphazenes derived from imines or enamines and acetylenic esters has been previously used for the preparation of a wide range of acyclic[15a,b] and cyclic derivatives.[15c-e]

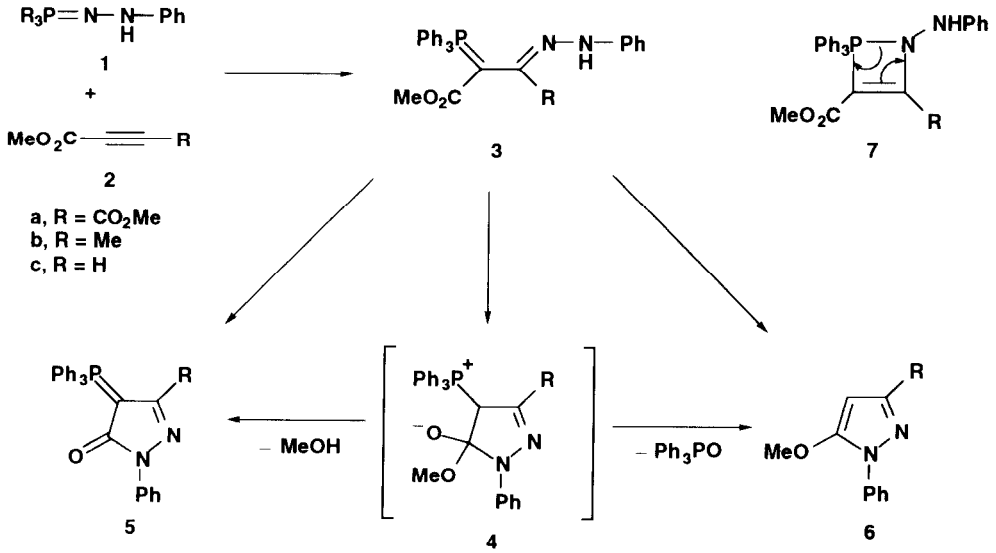


Scheme 1

RESULTS AND DISCUSSION

Due to the interest in these compounds as agrochemicals[2,6] and in medicinal chemistry,[3,4] the preparation of arylpyrazole and arylpyrazolone derivatives containing a carboxylic ester at position 3 was first explored from phosphazenes derived from phenyl hydrazine **1** and dimethyl acetylenedicarboxylate **2a** (DMAD, R= CO_2Me). But when DMAD **2a** (R = CO_2Me) was added to phosphazene derived from phenylhydrazine **1**[16] in THF at room temperature, the conjugated ylide **3a** was not isolated and a mixture of the phosphoranylidene 5-pyrazolone **5a** and substituted pyrazole **6a** (Scheme 2) was obtained instead. Both heterocycles **5a** and **6a** were separated by flash column chromatography and spectroscopic data were in agreement with assigned structures. Mass spectrometry gives the molecular ion peak for the 5-pyrazolone **5a** (*m/z*, 478, 24%) as well as for the pyrazole **6a** (*m/z*, 232, 54%). In the ^{31}P-NMR a signal is observed at δ_P = 11.9 ppm for pyrazolone **5a** containing a triphenylphosphonium substituent in the 4 position, while there is not an absorption for the

pyrazole **6a**. ^{13}C-NMR of pyrazolone **5a** showed a well resolved doublet at 63.8 ppm ($^{1}J_{PC}$ = 132.4 Hz) for the ylidene carbon attached to the phosphorus, and the vinylic carbon at 4-position of the pyrazole **6a** appeared as a singlet at 87.9 ppm. Formation of both heterocycles **5a** and **6a** could be explained through formation of hydrazone **3a** and subsequent cyclisation to give substituted pyrazoline **4**. The elimination of methanol could give pyrazolone **5a**, while the loss of phosphine oxide may lead to the formation of pyrazole **6a**, in a similar way to that previously described for the formation of pyrazoles from nitrilimines and phosphorus ylides.[14]



Scheme 2

These results prompted us to control the reaction conditions of the process with the aim of isolating the functionalized hydrazones **3** and of using them as intermediates for the preparation of pyrazolones **5** or pyrazoles **6** in a regioselective fashion. The reaction of the phosphazene **1** and DMAD **2a** was performed in a more polar solvent (acetonitrile) at room temperature, and conjugated hydrazone **3a** was isolated in excellent yield (Table 1). The structure of adduct **3a** is supported by the spectroscopic data. Mass spectrometry of **3a** gives the molecular ion peak (*m/z*, 511, 2%) and the ^{31}P-NMR spectrum of this compound **3a** showed absorption at δ_P = 17.6 ppm. Formation of this compound **3a**, by analogy with simple phosphazenes,[15] could be explained through [2+2] cycloaddition of the phosphazene linkage of **1** to the carbon-carbon triple bond of acetylenic ester **2a** followed by an electrocyclic ring opening of the unstable phosphor heterocycle **7**.

The isolation of hydrazone **3a** allowed us to explore the regioselective synthesis of pyrazolones **5** and pyrazoles **6**. The reaction of functionalized hydrazone **3a** in refluxing ethanol yielded a mixture of the heterocycles **5a** and **6a** in a 35:65 ratio. But the treatment of conjugated ylide **3a** with butyllithium in THF at 0°C gave, regioselectively, the phosphoranylidene 5-pyrazolone **5a** (Scheme 2, Table 1). However, conjugated hydrazone **3a**, heated in acetonitrile, afforded the pyrazole **6a** in a regioselective fashion (Scheme 2, Table 1).

Table 1. Preparation of conjugated hydrazones **3**, pyrazolones **5** and pyrazoles **6**.

Compound	R	Conditions	Yield (%)	m.p. (°C)
3a	CO_2Me	CH_3CN, rt	80	138-139 (dec)
3c	H	THF, rt	70	153-154 (dec)
5a	CO_2Me	THF, 0°C → rt	70	270-271 (dec)
5b	Me	CH_3CN, rt	28[a]	220-221 (dec)
5c	H	EtOH, reflux	75	238-239 (dec)
6a	CO_2Me	CH_3CN, reflux	90	82-83
6b	Me	CH_3CN, rt	31[a]	oil
6c	H	CH_3CN, reflux	70	oil

[a]Obtained as a mixture of **5b** and **6b**.

The scope of this reaction was not limited to pyrazolone **5a** and pyrazole derivatives **6a** (R = CO_2Me). The reaction of phosphazene **1** with methyl butynoate **2b** (R = CH_3) in acetonitrile at room temperature led to the formation of a mixture of the pyrazolone **5b** and the pyrazole **6b** (Scheme 2). These heterocyles were separated by flash column chromatography. The treatment of phosphazene **1** with methyl propiolate **2c** (R = H) in THF at room temperature gave the conjugated ylide **3c** in a good yield (Scheme 2, Table 1). The spectroscopic data were consistent with the ylide **3c**. The ^{1}H-NMR spectrum showed the methinic proton at 5.93 ppm as a doublet ($^3J_{PH}$ = 6.4 Hz), while in the ^{13}C-NMR the quaternary carbon attached to the phosphorus gave a well resolved doublet at 52.1 ppm ($^1J_{PC}$ = 111.8 Hz)). Heating conjugated ylide **3c** in ethanol gave the phosphoranylidene 5-pyrazolone **5c** with only traces of the pyrazole **6c** (Scheme 2, Table 1), while conjugated hydrazone **3c** heated in acetonitrile, afforded as sole product the pyrazole **6c** in a regioselective fashion (Scheme 2, Table 1).

In conclusion, we describe here an easy and efficient method for the regioselective synthesis of 5-pyrazolones substituted with a phosphoranylidene group **5** in the 4-position and 3-alkoxycarbonyl pyrazoles **6** from readily available starting materials such as phosphazenes derived from phenylhydrazine and acetylenic esters under mild reaction conditions.

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EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. Analytical TLC was performed on 0.25mm silica gel plates (Merck). Visualization was accomplished by UV light and iodine. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5); *n*-hexane and diethyl ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3). All

solvents used in reactions were freshly distilled from appropriate drying agents before use: acetonitrile (P_2O_5); THF (sodium benzophenone ketyl). All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Mass spectra were obtained on a Hewlett Packard 5890 spectrometer. Infrared spectra were taken on a Nicolet IRFT Magna 550 spectrometer. ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solution. ^{13}C-NMR spectra were recorded at 75 MHz with chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solution. ^{31}P-NMR spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. R_f values are taken using ethyl acetate as an eluting system. Elemental analyses were performed in a Leco CHNS-932 instrument. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet) or m (multiplet). Coupling constants, J, are reported in Hertz. Infrared spectra (IR) were obtained as neat liquids, or as solids in KBr. Peaks are reported in cm^{-1}. Mass spectra (EI) were obtained with a ionization voltage of 70 eV. Data are reported in the form m/z (intensity relative to base = 100). Phosphazene **1** was synthesized as described in the literature.[16]

Reaction of phosphazene (1) with dimethyl acetylenedicarboxylate in acetonitrile. Preparation of 2,3-bis(methoxycarbonyl)-1,1,1-triphenyl-4-phenylamino-4-aza-1-phosphabuta-1,3-diene (3a). To a solution of the phosphazene **1**[17] (5 mmol) dissolved in acetonitrile (10 ml) dimethyl acetylendicarboxylate (0.71 g, 5 mmol) was added. The mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The crude reaction was treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated, giving the ylide **3a** (2.04 g, 80%) as a yellow solid, which was recrystallized from dichloromethane/hexane. Data for **3a**: mp 138-139°C (dec); *^{1}H-NMR* (300 MHz) 3.37 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 7.17-7.19 (m, 5H, arom), 7.36-7.69 (m, 15H, arom), 9.08 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) 51.3 (d, $^1J_{PC}$ = 115.9 Hz, C=P), 51.6 (OCH_3), 51.8 (OCH_3), 113.9-133.8 (C-arom), 166.9 (C=O), 169.0 (C=O) ppm; *^{31}P-NMR* (120 MHz) 17.6 ppm; *IR (KBr)* 1696, 1685 cm^{-1}; *MS* (EI) 511 (M^+, 2). Anal. Calcd for $C_{30}H_{27}N_2O_4P$: C, 70.59; H, 5.29; N, 5.49. Found: C, 70.63; H, 5.25; N, 5.45.

Reaction of phosphazene (1) with dimethyl acetylenedicarboxylate in THF. Preparation of 3-methoxycarbonyl-1-phenyl-4-triphenylphosphorylidene-5-pyrazolone (5a) and 5-methoxy-3-methoxycarbonyl-1-phenylpyrazole (6a). To a solution of the phosphazene **1**[16] (5 mmol) in THF (10 ml) dimethyl acetylenedicarboxylate (0.71 g, 5 mmol) was added. The mixture was stirred at room temperature for 12 h and then diluted with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated, giving a mixture of pyrazolone **5a** (0.84g, 35%) and pyrazole **6a** (0.37g, 32%) as white solids, which were separated by flash column chromatogaphy, using ether/hexane as eluent. Data for **5a**: mp 270-271°C (dec); *^{1}H-NMR* (300 MHz) 3.45 (s, 3H, OCH_3), 7.08-7.35 (m, 5H, arom), 7.49-8.04 (m, 15H, arom) ppm; *^{13}C-NMR* (75 MHz) 51.8 (OCH_3), 63.8 (d, $^1J_{PC}$ = 132.4 Hz, C=P), 121.0-139.8 (C-arom), 142.5 (d, $^2J_{PC}$ = 9.1 Hz, C=N), 162.7 (COO), 166.7 (d, $^2J_{PC}$ = 19.1 Hz, C=O) ppm; *^{31}P-NMR* (120 MHz) 11.9 ppm; *IR (KBr)* 1727 cm^{-1}; *MS* (EI) 478 (M^+, 24). Anal. Calcd for $C_{29}H_{23}N_2O_3P$: C, 72.80; H, 4.81; N, 5.86. Found: C, 72.85; H, 4.79; N, 5.88. Data for **6a**: mp 82-83°C; *^{1}H-NMR* (300 MHz) 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.17 (s, 1H, CH=), 7.27-7.65 (m, 5H, arom) ppm; *^{13}C-NMR* (75 MHz) 52.1 (OCH_3), 59.2 (OCH_3), 87.9 (CH=), 123.0-137.8 (C-arom), 142.5 (C=N), 155.8 (C=), 162.7 (COO) ppm; *IR (KBr)* 1719 cm^{-1}; *MS* (EI) 232 (M^+, 54). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 62.01; H, 5.12; N, 12.09.

Addition of BuLi to the ylide (3a). Preparation of pyrazoline (5a). To a solution of ylide **3a** (1.02 g, 2 mmol) in THF (10 ml) at 0°C BuLi 6N (1.38 ml, 2.2 mmol) was added dropwise. The mixture was stirred

at room temperature and after 1 h the solvent was evaporated under reduced pressure and the crude was treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated, giving pyrazolone **5a** (0.67g, 70%) as a pale yellow solid, which was purified by crystallization from ethyl ether. Data for **5a** are same as described above.

Reflux of ylide (3a) in acetonitrile. Preparation of pyrazole (6a). A solution of ylide **3a** (1.02 g, 2 mmol) in acetonitrile (10 ml) was heated at reflux for 12 h. Evaporation of the solvent under reduced pressure gave triphenylphosphine oxide and pyrazole **6a** (0.42g, 90%), which was purified by flash column chromatography on silica gel, using ether/hexane as eluent. Data for **6a** are same as described above.

Preparation of 3-methyl-1-phenyl-4-triphenylphosphorylidene-5-pyrazolone (5b) and 5-methoxy-3-methyl-1-phenylpyrazole (6b). To a solution of phosphazene **1**[17] (5 mmol) dissolved in acetonitrile (10 ml) was added methyl 2-butynoate (0.49 g, 5 mmol). The mixture was stirred at room temperature for 6 h and the solvent was evaporated under reduced pressure. The crude reaction was treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated, giving a mixture of pyrazolone **5b** (0.61g, 28%) and pyrazole **6b** (0.29g, 31%) as white solids, which were separated and purified by flash column chromatography on silica gel, using ether/hexane as eluent. Data for **5b**: mp 220-221°C (dec); *^{1}H-NMR* (300 MHz) 1.43 (s, 3H, CH_3), 7.04-7.48 (m, 5H, arom), 7.52-8.11 (15H, arom) ppm; *^{13}C-NMR* (75 MHz) 15.9 (CH_3), 65.8 (d, $^1J_{PC}$ = 130.3 Hz, C=P), 119.0-140.4 (C-arom), 149.3 (d, $^2J_{PC}$ = 12.5 Hz, C=), 166.9 (d, $^2J_{PC}$ = 18.5 Hz, C=O) ppm; *^{31}P-NMR* (120 MHz) 10.6 ppm; *IR (KBr)* 1640 cm^{-1}; *MS* (EI) 434 (M^+, 95). Anal. Calcd for $C_{28}H_{23}N_2OP$: C, 77.42; H, 5.30; N, 6.45. Found: C, 77.38; H, 5.33; N, 6.49. Data for **6b**: Rf (0.75); *^{1}H-NMR* (300 MHz) 2.20 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.40 (s, 1H, CH=), 7.11-7.60 (m, 5H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.4 (CH_3), 58.6 (OCH_3), 85.7 (CH=), 121.7-138.5 (C-arom), 148.6 (C=N), 155.7 (C=) ppm; *IR (KBr)* 1606 cm^{-1}; *MS* (EI) 188 (M^+, 58). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.43; N, 14.89. Found: C, 70.28; H, 6.35; N, 14.87.

Preparation of 2-methoxycarbonyl-1,1,1-triphenyl-4-phenylamino-4-aza-1-phosphabuta-1,3-diene (3c). To a solution of phosphazene **1**[16] (5 mmol) in THF (10 ml) methyl propiolate (0.42 g, 5 mmol) was added. The mixture was stirred at room temperature and after 12 h the insoluble solid in THF was filtered. Then the solid was dissolved in dichloromethane (25 ml), water (20 ml) was added and the organic layer was separated. The evaporation of the solvent gave ylide **3c** (1.58g, 70%) as a white solid, which was purified by recrystallization from THF/hexane. Data for **3c**: mp 153-154°C (dec); *^{1}H-NMR* (300 MHz) 3.10 (s, 3H, OCH_3), 5.93 (d, $^3J_{PH}$ = 6.4 Hz, 1H, CH), 6.63-7.15 (m, 5H, arom), 7.40-7.63 (m, 15H, arom), 9.66 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) 49.8 (OCH_3), 52.1 (d, $^1J_{PC}$ = 111.8 Hz, C=P), 112-133.8 (C-arom), 134.7 (d, $^2J_{PC}$ = 17.6 Hz, CH=), 147.6 (C-arom), 167.0 (d, $^2J_{PC}$ = 11.1 Hz, C=O) ppm; *^{31}P-NMR* (120 MHz) 23.0 ppm; *IR (KBr)* 1630 cm^{-1}; *MS* (EI) 452 (M^+, 4). Anal. Calcd for $C_{28}H_{25}N_2O_2P$: C, 74.34; H, 5.53; N, 6.19. Found: C, 74.30; H, 5.56; N, 6.21.

Preparation of 1-phenyl-4-triphenylphosphorylidene-5-pyrazolone (5c). A solution of ylide **3c** (0.90 g, 2 mmol) in ethanol (10 ml) was heated at reflux for 10 h. Evaporation of the solvent gave pyrazolone **5c** (0.63, 75%) as a pale green solid, which was purified by recrystallization from ethyl acetate. Data for **5c**: mp 238-239°C (dec); *^{1}H-NMR* (300 MHz) 6.90 (s, 1H, CH=), 7.01-7.33 (m, 5H, arom), 7.48-8.09 (m, 15H, arom) ppm; *^{13}C-NMR* (75 MHz) 68.5 (d, $^1J_{PC}$ = 131.4 Hz, C=P), 119.5-140.8 (C-arom), 142.6 (d, $^2J_{PC}$ = 13.6 Hz, CH=), 166.9 (d, $^2J_{PC}$ = 18.1 Hz, C=O) ppm; *^{31}P-NMR* (120 MHz) 12.6 ppm; *IR (KBr)* 1624 cm^{-1}; *MS* (EI) 420 (M^+, 15). Anal. Calcd for $C_{27}H_{21}N_2OP$: C, 77.14; H, 5.00; N, 6.67. Found: C, 77.19; H, 5.06; N, 6.69.

Preparation of 5-methoxy-1-phenylpyrazole (6c). A solution of the ylide **3c** (0.90 g, 2 mmol) in acetonitrile (10 ml) was heated at reflux for 12 h. Evaporation of the solvent under reduced pressure gave triphenylphosphine oxide and the pyrazole **6c** (0.24g, 70%), which was purified by flash column chromatography on silica gel, using ether/hexane as eluent. The pyrazole **6c** was obtained as an oil. Data for **6c**: Rf (0.76); *^{1}H-NMR* (300 MHz) 3.81 (s, 3H, OCH_3), 5.56 (d, $^3J_{HH}$ = 1.8 Hz, 1H, CH=), 7.30-7.64 (m, 6H, arom, CH=N) ppm; *^{13}C-NMR* (75 MHz) 59.0 (OCH_3), 85.9 (CH=), 122.2-138.8 (C-arom), 139.8 (CH=N), 155.7 (C=) ppm; *IR (KBr)* 1602 cm^{-1}; *MS* (EI) 174 (M^+, 93). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.09. Found: C, 68.93; H, 5.79; N, 16.05.

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17. Phosphazene **1** was prepared as Ref. 16 in THF, the solvent was evaporated under inert atmosphere without isolation, acetonitrile was then added and the solution was used "in situ" for the next step.