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An Efficient and General Strategy for the Synthesis of 4-Phosphorylated Pyrazoles from β-Hydrazono Phosphine Oxides.

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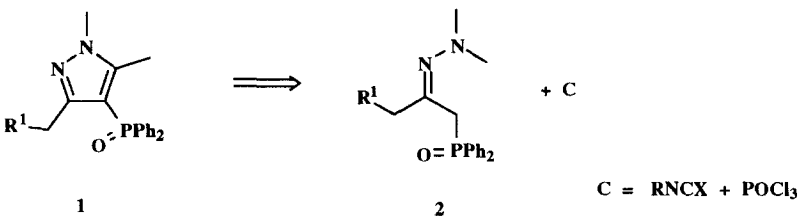
Abstract: A simple and efficient synthesis of aminopyrazoles substituted with a phosphino oxide and sulphide groups in the 4-position **1** is described. The key step is a regioselective addition of lithiated β-hydrazonophosphine oxides **2** to isocyanates and isothiocyanates to give functionalized amides **3** and **7**. Subsequent cyclization of **3** with phosphorus oxychloride in the presence of triethylamine afforded pyrazoles derived from phosphine oxides **1** and phosphine sulphides **8**. Substituted heterocycles **1** can also be obtained in "one pot" reaction from phosphine oxides **2** when these compounds are metallated followed by addition of isocyanates and phosphorus oxychloride.

Pyrazole ring systems represent an important class of compounds[1] not only for their theoretical interest but also for their biological activities and that they can constitute the skeleton of dyestuffs and polymers. Likewise, 4-substituted pyrazoles are inhibitors of alcohol dehydrogenase (ADH), have interesting pharmacological properties and have had applications in drug synthesis.[2] Furthermore, it is known that the phosphoryl group regulates important biological functions,[3] and that molecular modifications of pyrazole rings introducing organo phosphorus functionalities can lead to very interesting and useful agrochemical[4-6] products such as insecticides[7] and herbicides.[8]

A wide range of procedures for the synthesis of pyrazoles[1,9] has been reported. However, pyrazoles directly substituted with phosphorus containing functional groups have received much less attention, probably owing to the lack of general methods for the synthesis of these compounds.[1,9] Pyrazoles of this type such as dihalophosphine-pyrazoles[10a] as well as pyrazoles derived from phosphonates,[10b] phosphinates[10c] and phosphonium salts[9a,10d] have been reported in recent years. We, however, are interested in the synthesis of five[11] and six[12] membered phosphorylated nitrogen heterocycles, and we have even used β-functionalized

phosphonium salts, phosphine oxides and phosphonates as synthetic intermediates in the preparation of allylamines,[13a] divinyl imines,[13b] 2-aminodienes,[13c] 2-azadienes[13d] and phosphorus containing heterocycles.[14] In this context, we have recently described the synthesis of β-hydrazono phosphine oxides[15] **2** and the use of these compounds as homologation reagents of carbonyl compounds into unsaturated hydrazones with the introduction of two additional carbon atoms in the resulting chain.

Continuing with our interest in the reactivity of functionalized phosphorus derivatives and in the preparation of phosphorylated heterocycles, here we aim to extend the synthetic use of functionalized hydrazones **2** in the preparation of substituted pyrazole compounds **1** containing phosphino oxide and sulphide groups in the 4-position. Retrosynthetically, we envisaged obtaining pyrazoles **1** by insertion of a carbon atom between the nitrogen and the C-α-carbon atom of the hydrazone **2**. (Scheme 1). A combination of isocyanates or isothiocyanates and phosphorus oxychloride was used as synthetic equivalents of the additional carbon atom shown in Scheme 1.The key step in this synthetic methodology involves the regioselective reaction of the carbanion derived from hydrazone **2** with isocyanates or isothiocyanates. It is know that, for the formation of carbon-carbon bonds, an important methodology has been developed making use of carbanions derived from hydrazones,[16] which leads to very successful applications in the enantioselective synthesis of oxosulfones,[17a] pheromones,[17b] the potassium channel opener RP66471[17c] and natural products such as the ionophore antibiotic indanomycin,[18a] the sex pheromone serricornin,[18b] and the sesquiterpene (+)-eremophilinolide.[18c] This strategy is especially useful in organic synthesis taking into account: the reactivity of the intermediate azaallyl anions, the control over stereochemistry of electrophilic substitution step afforded by the nitrogen substituent, and the considerable control of regiochemistry which can be reached using hydrazone. Furthermore, in our case, the presence of an anion stabilizing group such as phosphine oxide **2** could control the deprotonation at the internal less-substituted carbon in a regioselective fashion and therefore the carbon-carbon bond formation through this position.



1 **2**

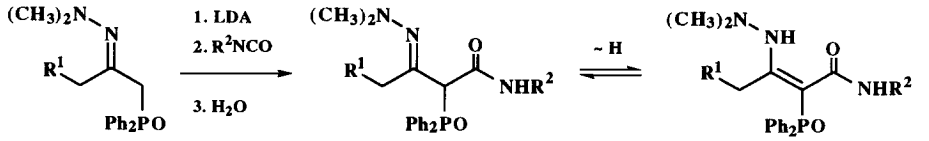
Scheme 1

RESULTS AND DISCUSSION

Reaction of hydrazone carbanions derived from phosphine oxide **2** with isocyanates.

Hydrazones **2** were treated with lithium diisopropylamide (LDA) in tetrahydrofuran followed by addition of isocyanates (TLC control) and aqueous work-up giving functionalized phosphine oxides **3/3'** in high yield. (See Table 1). Compounds **3/3'** were characterized on the basis of their spectroscopic data, which indicate that they were isolated as a mixture of the hydrazono **3** and the enehydrazino **3'** tautomers, although, for our purposes, the separation of both isomers was not necessary for subsequent reactions. Thus, the *^{31}P-NMR*

spectrum of the mixture **3/3'a** showed two different absorptions at δ_P = 30.8 and 37.1 ppm in an approximate isomer ratio 56 / 44 as evidenced by the relative peak areas for each salt, in which the high-field chemical shift corresponds to compound **3a**. Further examination of the ^1H and ^{13}C-*NMR* is consistent with the hydrazine **3a** and enehydrazine **3'a**. In the ^1H-*NMR* spectrum of **3a**, the methyl groups gave singlets at δ_H = 1.72 and 2.54 ppm and the methine proton resonated at δ_H = 4.49 ppm as a well resolved doublet ($^2J_{PH}$ = 12.9 Hz), while the ^{13}C-*NMR* showed an absorption at δ_C = 59.0 ($^1J_{PC}$ = 52.4 Hz) assignable to the methine carbon. Conversely, the enehydrazine **3'a** showed clearly different absorptions, namely signals for the methyl groups at δ_H = 2.07 and 2.38 ppm, while in the ^{13}C-*NMR* spectrum the absorption of the carbon bonded to phosphorus was shifted to lower field (δ_C = 79.8 ppm) with a higher value of phosphorus-carbon coupling constant ($^1J_{PC}$ = 114.2 Hz) relative to those of the hydrazono compound **3a** and supporting the proposed structure of the tautomer **3'a**.



2 3 3'

Scheme 2

Table 1. Functionalized phosphine oxide derivatives **3/3'** and **7** obtained.

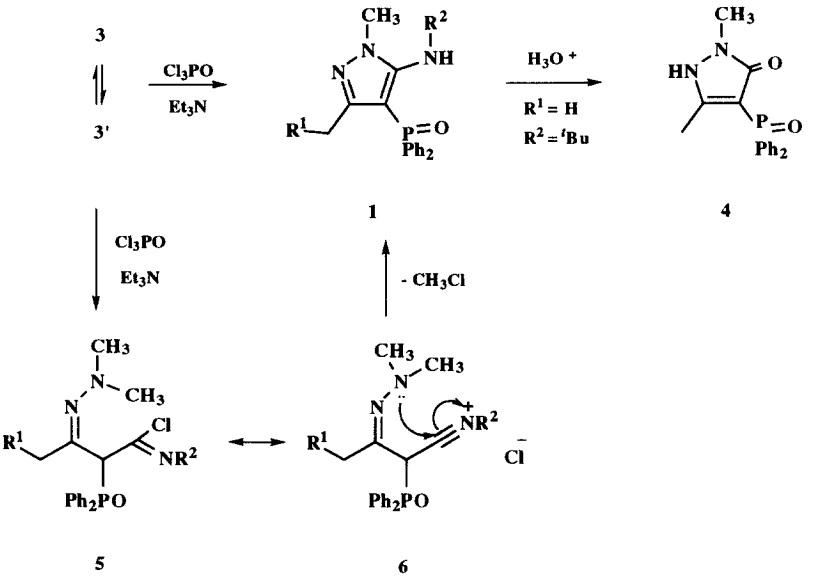
Compound	R^1	R^2	Yield (%)[a]	Ratio (3 : 3')[b]	m.p.(°C)
3/3'a	H	Ph	92	56 : 44	162-163
3/3'b	H	^{t}Bu	79	95 : 5	189-190
3/3'c	H	Et	82	83 : 17	200-201
3/3'd	H	C_6H_{11}	88	90 : 10	179-180
3/3'e	H	*p*-MePh	90	63 : 37	186-187
3/3'f	Me	^{t}Bu	86	72 : 28	114-115
3/3'g	Me	Ph	78	62 : 38	139-140
3/3'h	Me	Et	79	81 : 19	158-159
7a	H	Ph	87	100 : 0	151-152
7b	H	Et	75	100 : 0	168-170
7c	H	*p*-MePh	81	100 : 0	148-149

[a] Yield of isolated product **3/3'** and **7** based on **2**. [b] *Hydrazono / enehydrazino* ratio determined by ^{31}P-*NMR*.

Preparation of substituted pyrazoles **1** from phosphine oxide derivatives **3/3'**.

Functionalized aminoadducts **3/3'** are useful intermediates in organic synthesis and provide an easy and efficient access to pyrazoles substituted with a phosphine oxide group **1**, which otherwise are not readily available. Treatment of compounds **3/3'** with phosphorus oxychloride in the presence of triethylamine led to

the formation of aminopyrazolyl-phosphine oxides **1** (see Scheme 3) in excellent yields (Table 2). Spectroscopic data were in agreement with the assigned structure. Mass spectrometry of **1a** showed the molecular ion peak (*m/z* 387, 81%), while both methyl groups gave ^1H resonances at δ_H = 1.83 and 3.48 ppm



Scheme 3

Table 2. Pyrazoles **1**, **4** and **8** obtained.

Compound	R^1	R^2	Yield (%)	m.p.(°C)
1a	H	Ph	91[a]	204-205
1b	H	^{t}Bu	87[a]	oil[c]
1c	H	Et	89[a] (71)[b]	95-96
1d	H	C_6H_{11}	90[a]	oil[c]
1e	H	*p*-MePh	86[a]	208-209
1f	Me	Ph	84[a]	191-192
1g	Me	Et	79[a]	74-75
4	H	^{t}Bu	89[a]	180-181
8a	H	Et	79[c]	129-130
8b	H	Ph	83[c]	223-225

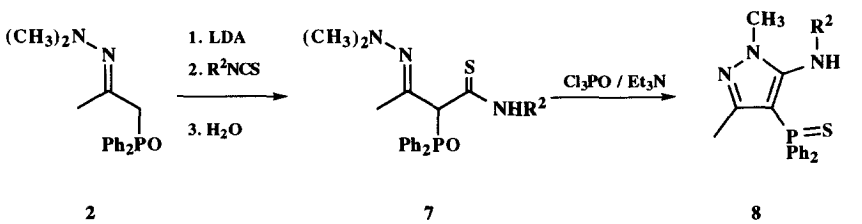
[a] Yield of isolated product **1** based on **3/3'**. [b] Yield of isolated product **1** in "one pot" reaction from **2**. [c] Purified by flash chromatography. [c] Yield of isolated products **8** based on **7**.

as singlets. Phosphorylated pyrazole **1** underwent amino cleavage by acid hydrolysis with 2N ClH to give the corresponding pyrazoline-5-one substituted with a phosphine oxide group **4**. The formation of pyrazoles **1** can be assumed to proceed *via* intramolecular cyclisation of imidoyl chlorides **5** or nitrilium ions **6** formed by the reaction of functionalized amides **3/3'** with phosphorus oxychloride in a similar way to that previously reported in the synthesis of 3-aminobenzofurane[19a] and isoquinolines[19b] from amides.

From a preparative point of view it is noteworthy that the synthesis of phosphorylated pyrazoles **1** does not require the isolation and purification of functionalized phosphine oxides **3/3'** and they can be obtained in "one pot" reaction from β-hydrazono phosphine oxides **2** when these compounds are directly metalled with LDA in THF with subsequent addition of isocyanates, phosphorus oxychloride and aqueous work-up.

Synthesis of pyrazoles derived from phosphine sulphides **8**.

This methodology used for the preparation of pyrazoles **1** can also be applied to the synthesis of pyrazoles derived from phosphine sulphides **8** when isothiocyanates are used instead of isocyanates. Metallation of β-hydrazono phosphine oxides **2** with LDA in tetrahydrofuran followed by addition of isothiocyanates (TLC control) and aqueous work-up afforded the thioamide derived from β-hydrazono phosphine oxides **7**, instead of the mixture of both the hydrazono and the enehydrazino compounds **3/3'** such as had been obtained in the case of isocyanates. Treatment of thioamides **7** with phosphorus oxychloride in the presence of triethylamine gave aminopyrazolyl phosphine sulphides **8** (Scheme 4). Formation of pyrazoles **8** could be explained by a similar process to that mentioned in Scheme 3, although with a spontaneous exchange of oxygen for sulphur, with transformation of phosphine oxide into the phosphine sulphide group, caused by the reaction condition.



2 **7** **8**

Scheme 4

In summary, we describe a new strategy for an easy and efficient method for synthesis of pyrazoles substituted with a phosphine oxide **1** and phosphine sulphide **8** group in 4-position from readily available starting materials and under mild reaction conditions. These phosphorylated pyrazoles **1** and **8** could be intermediates in the synthesis of biologically active compounds and of useful agrochemicals with insecticidal and herbicidal activity.[4-8]

ACKNOWLEDGEMENTS

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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); 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: THF (sodium benzophenone ketyl); $CHCl_3$ (P_2O_5). All other reagents were recystallized 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 Unity Plus 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solutions. *^{13}C-NMR* spectra were recorded at 75 MHz with chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solutions. *^{31}P-NMR* spectra were recorded at 150 MHz with 85% phosphoric acid as an external reference. Elemental analyses were performed in a Perkin Elmer Model 240 instrument. Chemical shifs are given in ppm *(δ)*; multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet) q (quadruplet) 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). All reactions were performed in oven (125°C) or flame-dried glassware under an inert atmosphere of dry N_2.

General procedure for the reaction of hydrazone carbanions derived from phosphine oxide 2 with isocyanates or isothiocyanates. A dry flask, 100-mL, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged 5 mmol of lithium diisopropylamide (LDA) and 45 mL of THF. The temperature was allowed to descend to - 78 °C and a solution 1.5 g (5 mmol) of β-*N,N*-dimethylhydrazonopropyldiphenylphophine oxide **2**[15] in 40 mL of THF was then added. The mixture was allowed to stir for 1 h. A solution 5 mmol of isocyanate or isothiocyanate in 10 mL of THF was added at -78 °C. The mixture was stirred until TLC indicated the disappearance of compound **2** (~ 3 h). The mixture was diluted with 50 mL water and extracted with CH_2Cl_2. The CH_2Cl_2 layers were washed with water. The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by recrystallization from CH_2Cl_2 / hexane.

1-Phenylamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (3a) and 1-phenylamide-2-(*N,N*-dimethylhydrazino)prop-1-enyldiphenylphosphine oxide (3'a). 1920 mg (92 %) of **3a/3'a** as a white solid. Data for **3a/3'a**: mp 162-163 °C; *^{1}H-NMR* (300 MHz) **3a**: 1.72 (s, 3H, CH_3), 2.54 (s, 6H, CH_3N), 4.49 (d, 1H, $^2J_{PH}$ = 12.9 Hz, CH), 7.25-7.86 (m, 15H, arom), 9.62 (s, 1H, NH). **3'a**: 2.07 (s, 3H, CH_3), 2.38 (s, 6H, CH_3N), 7.25-7.86 (m, 15H, arom), 8.73 (s, 1H, NH), 10.34 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) **3a**: 20.2 (CH_3), 47.1 (CH_3N), 59.3 (d,$^1J_{PC}$ = 52.4 Hz, CH), 119.9-139.3 (C-arom), 160.2 (d, $^2J_{PC}$ = 7.5 Hz), 163.0 (d, $^2J_{PC}$ = 3.0 Hz). **3'a**: 19.7 (d, $^3J_{PC}$ = 5.5 Hz, CH_3), 48.3 (CH_3N), 79.8 (d, $^1J_{PC}$ = 114.2 Hz, =C), 119.9-139.3 (C-arom), 167.4 (d, $^2J_{PC}$ = 16.7 Hz), 170.6 (d, $^2J_{PC}$ = 11.1 Hz) ppm; *^{31}P-NMR* (150 MHz) **3a**: 30.8 (56 %), **3'a**: 37.1 (44 %) ppm; *IR (KBr)* 3250, 3194, 1683, 1552, 1439, 1332, 1177 cm^{-1}; *MS* (70 eV) 419 (M^+, 5). Anal. Calcd for $C_{24}H_{26}N_3O_2P$: C, 68.71; H, 6.25; N, 10.02. Found: C, 68.50; H, 6.26; N, 9.99.

1-^{t}Butylamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (3b) and 1-^{t}Butylamide-2-(*N,N*-dimethylhydrazino)prop-1-enyldiphenylphosphine oxide (3'b). 1580 mg (79 %) of **3b/3'b** as a white solid. Data for **3b/3'b**: mp 189-190 °C; *^{1}H-NMR* (300 MHz) **3b**: 1.16 (s, 9H, CH_3), 2.03 (s, 3H, CH_3), 2.27 (s, 6H, CH_3N), 4.25 (d, 1H, $^2J_{PH}$ = 11.7 Hz, CH), 7.26-7.91 (m, 11H, arom and NH). **3'b**: 1.05 (s, 9H, CH_3), 1.67 (s, 3H, CH_3), 2.48 (s, 6H, CH_3N), 7.26-7.91 (m, 12H, arom and NH) ppm; *^{13}C-NMR* (75 MHz) **3b**: 19.0 (CH_3), 28.3 (CH_3), 46.8 (CH_3N), 51.4 (C), 59.1 (d, $^1J_{PC}$ = 54.9 Hz, CH), 128.3-132.1 (C-arom), 160.1, 163.6 ppm; *^{31}P-NMR* (150 MHz) **3b**: 30.7 (95 %), **3'b**: 35.7 (5 %) ppm; *IR (KBr)* 3281, 1671, 1549, 1190 cm^{-1}; *MS* (70 eV) 399 (M^+, 3). Anal. Calcd for $C_{22}H_{30}N_3O_2P$: C, 66.13; H, 7.57; N, 10.52. Found: C, 66.30; H, 7.54; N, 10.56.

1-Ethylamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (3c) and 1-ethylamide-2-(*N,N*-dimethylhydrazino)prop-1-enyldiphenylphosphine oxide (3'c). 1520 mg (82 %) of **3c/3'c** as a white solid. Data for **3c/3'c**: mp 200-201 °C; *^{1}H-NMR* (300 MHz) **3c**: 0.94-1.06 (m, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.26 (s, 6H, CH_3N), 3.08-3.28 (m, 2H, CH_2), 4.35 (d, $^2J_{PH}$ = 10.8 Hz, 1H, CH), 7.26-8.08 (m, 10H, arom), 8.60 (s, 1H, NH). **3'c**: 0.94-1.06 (m, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.50 (s, 6H, CH_3N), 3.08-3.28 (m, 2H, CH_2), 7.26-8.08 (m, 10H, arom), 8.08 (s, 1H, NH), 9.21 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) **3c**: 14.3 (CH_3), 14.4 (CH_3), 34.6 (CH_2), 46.7 (CH_3N), 58.1 (d, $^1J_{PC}$ = 54.8 Hz, CH), 128.3-136.5 (C-arom), 159.7 (d, $^2J_{PC}$ = 7.1 Hz), 164.5 (d, $^2J_{PC}$ = 13.0 Hz). **3'c**: 14.4 (CH_3), 18.8 (CH_3), 34.0 (CH_2), 48.1 (CH_3N), 128.3-136.5 (C-arom), 166.1 (d, $^2J_{PC}$ = 17.1 Hz), 171.4 (d, $^2J_{PC}$ = 11.6 Hz) ppm; *^{31}P-NMR* (150 MHz) **3c**: 30.6 (83 %), **3'c**: 34.8 (17 %) ppm; *IR (KBr)* 3240, 1690, 1665, 1562, 1443, 1197 cm^{-1}; *MS* (70 eV) 371 (M^+, 38). Anal. Calcd for $C_{20}H_{26}N_3O_2P$: C, 64.66; H, 7.06; N, 11.32. Found: C, 64.81; H, 7.04; N, 11.35.

1-Cyclohexylamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (3d) and 1-cyclohexylamide-2-(*N,N*-dimethylhydrazino)prop-1-enyldiphenylphosphine oxide (3'd). 1870 mg (88 %) of **3d/3'd** as a white solid. Data for **3d/3'd**: mp 179-180 °C; *^{1}H-NMR* (300 MHz) **3d**: 0.90-1.77 (m, 10H, CH_2), 2.03 (s, 3H, CH_3), 2.27 (s, 6H, CH_3N), 3.62 (m, 1H, CH), 4.34 (d, $^2J_{PH}$ = 11.1 Hz, 1H, CH), 7.26-7.90 (m, 11H, arom and NH). **3'd**: 0.90-1.77 (m, 10H, CH_2), 1.66 (s, 3H, CH_3), 2.50 (s, 6H, CH_3N), 3.62 (m, 1H, CH), 7.26-7.90 (m, 12H, arom and NH) ppm; *^{13}C-NMR* (75 MHz) **3d**: 18.9 (CH_3), 24.3 (CH_2), 24.3 (CH_2), 25.5 (CH_2), 32.1 (CH_2), 32.4 (CH_2), 46.8 (CH_3N), 48.3 (CH), 58.2 (d, $^1J_{PC}$ = 53.5 Hz, CH), 128.4-132.2 (C-arom), 159.9, 163.7 ppm; *^{31}P-NMR* (150 MHz) **3d**: 30.5 (90 %), **3'd**: 33.1 (10 %)

ppm; *IR* (*KBr*) 3254, 1669, 1558, 1439, 1190 cm^{-1}; *MS* (70 eV) 425 (M^+, 21). Anal. Calcd for $C_{24}H_{32}N_3O_2P$: C, 67.73; H, 7.58; N, 9.88. Found: C, 67.51; H, 7.60; N, 9.85.

1-*p*-Tolylamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (3e) and 1-*p*-tolylamide-2-(*N,N*-dimethylhydrazino)prop-1-enyldiphenylphosphine oxide (3'e). 1950 mg (90 %) of **3e/3'e** as a white solid. Data for **3e/3'e**: mp 186-187 °C; *^{1}H-NMR* (300 MHz) **3e**: 1.70 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.51 (s, 6H, CH_3N), 4.49 (d, 1H, $^2J_{PH}$ = 12.9 Hz, CH), 7.02-7.89 (m, 14H, arom). 9.75 (s, 1H, NH). **3'e**: 2.06 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.34 (s, 6H, CH_3N), 7.02-7.89 (m, 14H, arom), 8.79 (s, 1H, NH), 10.25 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) **3e**: 19.9 (CH_3), 20.9 (CH_3), 46.9 (CH_3N), 58.9 (d, $^1J_{PC}$ = 52.3 Hz, CH), 119.9-136.5 (C-arom), 160.0 (d, $^2J_{PC}$ = 7.1 Hz), 162.7 (d, $^2J_{PC}$ = 3.0 Hz). **3'e**: 19.5 (CH_3), 20.9 (CH_3), 48.1 (CH_3N), 78.9 (d, $^1J_{PC}$ = 114.8 Hz, =C), 119.9-136.5 (C-arom), 167.1 (d, $^2J_{PC}$ = 17.4 Hz), 170.2 (d, $^2J_{PC}$ = 11.1 Hz) ppm; *^{31}P-NMR* (150 MHz) **3e**: 30.6 (63 %), **3'e**: 36.7 (37 %) ppm; *IR* (*KBr*) 3235, 3181, 1680, 1519, 1438, 1176 cm^{-1}; *MS* (70 eV) 433 (M^+, 29). Anal. Calcd for $C_{25}H_{28}N_3O_2P$: C, 69.25; H, 6.51; N, 9.70. Found: C, 69.04; H, 6.49; N, 9.73.

1-^{t}Butylamide-2-(*N,N*-dimethylhydrazono)butyldiphenylphosphine oxide (3f) and 1-^{t}Butylamide-2-(*N,N*-dimethylhydrazino)but-1-enyldiphenylphosphine oxide (3'f). 1780 mg (86 %) of **3f/3'f** as a white solid. Data for **3f/3'f**: mp 114-115 °C; *^{1}H-NMR* (300 MHz) **3f**: 0.95-1.06 (m, 3H, CH_3), 1.11 (s, 9H, CH_3), 2.33 (s, 6H, CH_3), 2.54-2.70 (m, 2H, CH_2), 4.33 (d, 1H, $^2J_{PH}$ = 14.0 Hz, CH), 7.26-8.04 (m, 11H, arom and NH). **3'f**: 0.95-1.06 (m, 3H, CH_3), 1.22 (s, 9H, CH_3), 2.08-2.17 (m, 2H, CH_2), 2.50 (s, 6H, CH_3N), 7.26-8.04 (m, 12H, arom and NH) ppm; *^{13}C-NMR* (75 MHz) **3f**: 10.4 (CH_3), 25.8 (CH_2), 28.2 (CH_3), 47.5 (CH_3N), 51.3 (C), 56.0 (d, $^1J_{PC}$ = 53.9 Hz, CH), 128.0-132.3 (C-arom), 162.9, 166.7 ppm; *^{31}P-NMR* (150 MHz) **3f**: 30.7 (72 %), **3'f**: 37.1 (28 %) ppm; *IR* (*KBr*) 3293, 1674, 1438, 1185 cm^{-1}; *MS* (70 eV) 413 (M^+, 3). Anal. Calcd for $C_{23}H_{33}N_3O_2P$: C, 66.79; H, 7.81; N, 10.17. Found: C, 67.01; H, 7.83; N, 10.14.

1-Phenylamide-2-(*N,N*-dimethylhydrazono)butyldiphenylphosphine oxide (3g) and 1-phenylamide-2-(*N,N*-dimethylhydrazino)but-1-enyldiphenylphosphine oxide (3'g). 1690 mg (78 %) of **3g/3'g** as a white solid. Data for **3g/3'g**: mp 139-140 °C; *^{1}H-NMR* (300 MHz) **3g**: 1.05 (t, 3H, $^3J_{HH}$ = 7.7 Hz, CH_3), 2.15-2.24 (m, 2H, CH_2), 2.58 (s, 6H, CH_3N), 4.59 (d, 1H, $^2J_{PH}$ = 14.5 Hz, CH), 6.98-8.00 (m, 15H, arom), 9,42 (s, 1H, NH). **3'g**: 0.97 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3), 2.42 (s, 6H, CH_3N), 2.59-2.65 (m, 2H, CH_2), 6.98-8.00 (m, 15H, arom), 8.80 (s, 1H, NH), 10.25 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) **3g**: 11.3 (CH_3), 26.3 (CH_2), 48.6 (CH_3N), 55.7 (d,$^1J_{PC}$ = 53.4 Hz, CH), 119.7-139.2 (C-arom), 162.9, 166.3. **3'g**: 19.7 (CH_3), 26.6 (CH_2), 47.7 (CH_3N), 119.7-139.2 (C-arom), 170.5, 172.2 (d, $^2J_{PC}$ = 17.5 Hz) ppm; *^{31}P-NMR* (150 MHz) **3g**: 30.2 (62 %), **3'g**: 37.1 (38 %) ppm; *IR* (*KBr*) 3248, 3194, 1682, 1550, 1440, 1335, 1174 cm^{-1}; *MS* (70 eV) 433 (M^+, 8). Anal. Calcd for $C_{25}H_{28}N_3O_2P$: C, 69.25; H, 6.51; N, 9.70. Found: C, 69.06; H, 6.53; N, 9.67.

1-Ethylamide-2-(*N,N*-dimethylhydrazono)butyldiphenylphosphine oxide (3h) and 1-ethylamide-2-(*N,N*-dimethylhydrazino)but-1-enyldiphenylphosphine oxide (3'h). 1520 mg (79 %) of **3h/3'h** as a white solid. Data for **3h/3'h**: mp 158-159 °C; *^{1}H-NMR* (300 MHz) **3h**: 0.89-1.06 (m, 6H, CH_3), 2.08-2.32 (m, 2H, CH_2), 2.33 (s, 6H, CH_3N), 3.15-3.21 (m, 2H, CH_2), 4.42 (d, $^2J_{PH}$ = 13.0 Hz, 1H, CH), 7.26-7.98 (m, 10H, arom), 9.05 (s, 1H, NH). **3'h**: 0.89-1.06 (m, 6H, CH_3), 2.53 (s, 6H, CH_3N), 2.54-2.75 (m, 2H, CH_2), 3.03-3.13 (m, 2H, CH_2), 7.26-7.98 (m, 10H, arom), 8.09 (s, 1H, NH), 9.37 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) **3h**: 10.4 (CH_3), 14.2 (CH_3), 25.8 (CH_2), 34.6 (CH_2), 48.7 (CH_3N), 55.0 (d, $^1J_{PC}$ = 54.4 Hz, CH), 128.0-136.7 (C-arom), 164.7, 166.3 (d, $^2J_{PC}$ = 7.5 Hz). **3'h**: 11.4 (CH_3), 14.4 (CH_3), 26.0 (CH_2), 34.1 (CH_2), 47.4 (CH_3N), 128.0-136.7 (C-arom), 170.9, 171.6 (d, $^2J_{PC}$ = 11.7 Hz) ppm; *^{31}P-NMR* (150 MHz) **3h**: 30.6 (83 %), **3'h**: 34.8 (17 %) ppm; *IR* (*KBr*) 3234, 1664, 1561, 1443, 1324, 1196 cm^{-1}; *MS* (70 eV) 385 (M^+, 23). Anal. Calcd for $C_{21}H_{28}N_3O_2P$: C, 65.42; H, 7.33; N, 10.91. Found: C, 65.21; H, 7.35; N, 10.87.

1-Phenylthioamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (7a). 1890 mg (87 %) of **7a** as a white solid. Data for **7a**: mp 151-152 °C; *^{1}H-NMR* (300 MHz) 1.99 (s, 3H, CH_3), 2.35 (s, 6H, CH_3N), 5.10 (d, 1H, $^2J_{PH}$ = 9.3 Hz, CH), 7.26-7.97 (m, 15H, arom), 9.31 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) 19.6 (CH_3), 46.9 (CH_3N), 66.5 (d, $^1J_{PC}$ = 50.1 Hz, CH), 122.7-139.1 (C-arom), 159.9 (C=N), 190.2 (C=S) ppm; *^{31}P-NMR* (150 MHz) 30.8 ppm; *IR* (*KBr*) 3112, 1611, 1440, 1400, 1189 cm^{-1}; *MS* (70 eV) 435 (M^+, 1). Anal. Calcd for $C_{24}H_{26}N_3OPS$: C, 66.22; H, 6.02; N, 9.65. Found: C, 66.02; H, 6.04; N, 9.62.

1-Ethylthioamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (7b). 1450 mg (75 %) of **7b** as a white solid. Data for **7b**: mp 168-169 °C; *^{1}H-NMR* (300 MHz) 1.15 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3), 1.90 (s, 3H, CH_3), 2.25 (s, 6H, CH_3N), 3.50-3.65 (m, 2H, CH_2), 4.98 (d, 1H, $^2J_{PH}$ = 8.3 Hz, CH), 7.26-7.91 (m, 10H, arom), 10.02 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) 12.7 (CH_3), 18.9 (CH_3), 41.4 (CH_2), 46.7 (CH_3N), 64.2 (d, $^1J_{PC}$ = 51.2 Hz, CH), 128.3-132.4 (C-arom), 159.4 (C=N), 189.8 (C=S) ppm; *^{31}P-NMR* (150 MHz) 30.9 ppm; *IR* (*KBr*) 3203, 1570, 1436, 1182, 1164 cm^{-1}; *MS* (70 eV) 387 (M^+, 3). Anal. Calcd for $C_{20}H_{26}N_3OPS$: C, 62.03; H, 6.77; N, 10.85. Found: C, 61.84; H, 6.79; N, 10.82.

1-*p*-Tolylthioamide-2-(*N,N*-dimethylhydrazono)propyldiphenylphosphine oxide (7c). 1820 mg (81 %) of **7c** as a white solid. Data for **7c**: mp 148-149 °C; *^{1}H-NMR* (300 MHz) 1.98 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.33 (s, 6H, CH_3N), 5.08 (d, 1H, $^2J_{PH}$ = 9.2 Hz, CH), 7.11-7.96 (m, 14H, arom), 9.41 (s, 1H, NH) ppm; *^{13}C-NMR* (75 MHz) 19.6 (CH_3), 21.2 (CH_3), 46.9 (CH_3N), 66.3 (d, $^1J_{PC}$ = 49.7 Hz, CH), 122.7-136.7 (C-arom), 160.0 (C=N), 189.9 (C=S) ppm; *^{31}P-NMR* (150 MHz) 31.0 ppm; *IR* (*KBr*) 3161, 1589, 1437, 1378, 1174 cm^{-1}; *MS* (70 eV) 449 (M^+, 3). Anal. Calcd for $C_{25}H_{28}N_3OPS$: C, 66.83; H, 6.28; N, 9.35. Found: C, 67.00; H, 6.26; N, 9.32.

General procedure for the preparation of the phosphorylated pyrazoles 1 and 8. A dry flask, 100-mL, 3-necked, fitted with a reflux condenser, gas inlet, dropping funnel, and magnetic stirrer, was charged (5 mmol) of amide **3/3'** or thioamide **7**, 0.83 mL (6 mmol) of triethylamine and 30 mL of THF. A solution 0.47 mL (5 mmol) of phosphorus oxychloride and 20 mL of THF was added over 5 min. The mixture was stirred and refluxed until *TLC* indicated the disappearance of the compound **3/3'** or **7** (~ 2 days). The mixture was diluted with 30 mL water and extracted with CH_2Cl_2 (3 x 15 mL). The CH_2Cl_2 layers were washed with water. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated the crude product was purified by flash-chromatography. Pyrazoles **1** can also be obtained in "one pot" reaction: 1.5 g (5 mmol) of β-*N,N*-dimethylhydrazonopropyldiphenylphophine oxide **2** in 40 mL of THF was metallated with LDA (5 mmol) at -78°C. The mixture was allowed to stir for 1 h. A solution 5 mmol of isocyanate in 10 mL of THF was added at -78 °C. The mixture was stirred for 2 h, and a solution of 0.47 mL (5 mmol) of phosphorus oxychloride and 20 mL of THF was added. The pyrazole **1** was purified as described above.

4-Diphenylphosphoryl-1,3-dimethyl-5-phenylaminopyrazole (1a). 1760 mg (91 %) of **1a** as a white solid. Data for **1a**: mp 204-205 °C; *^{1}H-NMR* (300 MHz) 1.83 (s, 3H, CH_3), 3.48 (s, 3H, CH_3N), 6.52-7.67 (m, 16H, arom and NH) ppm; *^{13}C-NMR* (75 MHz) 14.5 (CH_3), 36.0 (CH_3N), 97.3 (d, $^1J_{PC}$ = 134.5 Hz, C=), 116.9-131.9 (C-arom), 131.3 (d, $^1J_{PC}$ = 108.3 Hz, C-ipso), 143.2 (C-arom), 148.1 (d, $^2J_{PC}$ = 14.5 Hz), 150.0 (d, $^2J_{PC}$ = 10.4 Hz) ppm; *^{31}P-NMR* (150 MHz) 24.0 ppm; *IR (KBr)* 3215, 1605, 1541, 1500, 1441, 1170 cm^{-1}; *MS* (70 eV) 387 (M^+, 81). Anal. Calcd for $C_{23}H_{22}N_3OP$: C, 71.29; H, 5.73; N, 10.85. Found: C, 71.09; H, 5.71; N, 10.88.

5-^{t}Butylamino-4-diphenylphosphoryl-1,3-dimethylpyrazole (1b). 1600 mg (87 %) of **1b** as a yellow oil (R_f =, hexane). Data for **1b**: *^{1}H-NMR* (300 MHz) 0.89 (s, 9H, CH_3), 1.44 (s, 3H, CH_3), 3.52 (s, 3H, CH_3N), 4.88 (s, 1H, NH), 7.21-7.48 (m, 10H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.4 (CH_3), 30.1 (CH_3), 36.3 (CH_3N), 56.0 (C), 97.4 (d, $^1J_{PC}$ = 127.6 Hz, C=), 128.2-131.7 (C-arom), 133.6 (d, $^1J_{PC}$ = 108.5 Hz, C-ipso), 148.9 (C-arom), 148.1 (d, $^2J_{PC}$ = 12.1 Hz), 153.8 (d, $^2J_{PC}$ = 15.5 Hz) ppm; *^{31}P-NMR* (150 MHz) 26.0 ppm; *IR (KBr)* cm^{-1}; *MS* (70 eV) 367 (M^+, 20). Anal. Calcd for $C_{21}H_{26}N_3OP$: C, 68.63; H, 7.14; N, 11.44. Found: C, 68.41; H, 7.16; N, 11.41.

4-Diphenylphosphoryl-1,3-dimethyl-5-ethylaminopyrazole (1c). 1500 mg (89 %) of **1c** as a white solid and 1200 mg (71 %) in "one pot" reaction. Data for **1c**: mp 95-96 °C; *^{1}H-NMR* (300 MHz) 1.06 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.07 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 3.69 (s, 3H, CH_3N), 5.58 (s, 1H, NH), 7.26-7.70 (m, 10H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.5 (CH_3), 15.6 (CH_3), 35.9 (CH_3N), 42.5 (CH_2), 92.0 (d, $^1J_{PC}$ = 132.0 Hz, C=), 128.4-131.8 (C-arom), 133.8 (d, $^1J_{PC}$ = 108.1 Hz, C-ipso), 148.8 (d, $^2J_{PC}$ = 14.8 Hz), 155.8 (d, $^2J_{PC}$ = 10.1 Hz) ppm; *^{31}P-NMR* (150 MHz) 26.1 ppm; *IR (KBr)* 3280, 1555, 1527, 1436, 1408, 1167 cm^{-1}; *MS* (70 eV) 339 (M^+, 59). Anal. Calcd for $C_{19}H_{22}N_3OP$: C, 67.23; H, 6.54; N, 12.39. Found: C, 67.38; H, 6.52; N, 12.35.

5-Cyclohexylamino-4-diphenylphosphoryl-1,3-dimethylpyrazole (1d). 1770 mg (90 %) of **1d** as a yellow oil (R_f=, hexane). Data for **1d**: *^{1}H-NMR* (300 MHz) 1.13-1.79 (m, 10H, CH_2), 1.65 (s, 3H, CH_3), 3.00 (m, 1H, CH), 3.66 (s, 3H, CH_3N), 5.70 (1H, s, NH), 7.40-7.69 (m, 10H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.4 (CH_3), 24.7 (CH_2), 25.3 (CH_2), 33.6 (CH_2), 35.9 (CH_3N), 55.7 (CH), 92.1 (d, $^1J_{PC}$ = 130.0 Hz, C=), 128.3-131.8 (C-arom), 132.3 (d, $^1J_{PC}$ = 108.2 Hz, C-ipso), 148.4 (d, $^2J_{PC}$ = 11.9 Hz), 154.7 (d, $^2J_{PC}$ = 15.4 Hz) ppm; *^{31}P-NMR* (150 MHz) 26.6 ppm; *IR (KBr)* 3275, 2933, 1738, 1551, 1045 cm^{-1}; *MS* (70 eV) 393 (M^+, 37). Anal. Calcd for $C_{23}H_{28}N_3OP$: C, 70.19; H, 7.18; N, 10.68. Found: C, 70.33; H, 7.15; N, 10.64.

4-Diphenylphosphoryl-1,3-dimethyl-5-*p*-tolylaminopyrazole (1e). 1720 mg (86 %) of **1e** as a white solid. Data for **1e**: mp 208-209 °C; *^{1}H-NMR* (300 MHz) 1.81 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.46 (s, 3H, CH_3N), 6.91 (s, 1H, NH), 6.48-7.68 (m, 14H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.5 (CH_3), 20.6 (CH_3), 36.1 (CH_3N), 96.2 (d, $^1J_{PC}$ = 132.3 Hz, C=), 117.6-131.9 (C-arom), 133.2 (d, $^1J_{PC}$ = 108.6 Hz, C-ipso), 140.6 (C-arom), 148.9 (d, $^2J_{PC}$ = 15.6 Hz), 149.8 (d, $^2J_{PC}$ = 10.0 Hz) ppm; *^{31}P-NMR* (150 MHz) 24.6 ppm; *IR (KBr)* 3207, 1553, 1520, 1438, 1165 cm^{-1}; *MS* (70 eV) 401 (M^+, 100). Anal. Calcd for $C_{24}H_{24}N_3OP$: C, 71.79; H, 6.03; N, 10.47. Found: C, 71.56; H, 6.05; N, 10.43.

4-Diphenylphosphoryl-3-ethyl-5-phenylamino-1-methylpyrazole (1f). 1680 mg (84 %) of **1f** as a white solid. Data for **1f**: mp 191-193 °C; *^{1}H-NMR* (300 MHz) 0.90 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.86 (s, 1H, NH), 2.15 (q, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 3.46 (s, 3H, CH_3N), 6.44-7.62 (m, 16H, arom) ppm; *^{13}C-NMR* (75 MHz) 12.9 (CH_3), 22.1 (CH_2), 36.4 (CH_3N), 96.7 (d, $^1J_{PC}$ = 126.9 Hz, C=), 117.1-143.4 (C-arom), 134.8 (d, $^1J_{PC}$ = 108.7 Hz, C-ipso), 143.4 (C-arom), 147.9 (d, $^2J_{PC}$ = 15.6 Hz), 155.6 (d, $^2J_{PC}$ = 10.1 Hz) ppm; *^{31}P-NMR* (150 MHz) 24.6 ppm; *IR (KBr)* 3200, 3172, 2966, 1605, 1549, 1499, 1443, 1166 cm^{-1}; *MS* (70 eV) 401 (M^+, 100). Anal. Calcd for $C_{24}H_{24}N_3OP$: C, 71.79; H, 6.03; N, 10.47. Found: C, 71.64; H, 6.05; N, 10.44.

4-Diphenylphosphoryl-3-ethyl-5-ethylamino-1-methylpyrazole (1g). 1390 mg (79 %) of **1g** as a white solid. Data for **1g**: mp 74-75 °C; *^{1}H-NMR* (300 MHz) 0.77 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 0.99 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.95 (q, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 2.98 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 3.65 (s, 3H, CH_3N), 5.41 (s, 1H, NH), 7.21-7.64 (m, 10H, arom) ppm; *^{13}C-NMR* (75 MHz) 12.4 (CH_3), 15.5 (CH_3), 21.7 (CH_2), 35.9 (CH_3N), 42.6 (CH_2), 91.2 (d, $^1J_{PC}$ = 129.2 Hz, C=), 128.3-132.2 (C-arom), 133.8 (d, $^1J_{PC}$ = 107.6 Hz, C-ipso), 153.9 (d, $^2J_{PC}$ = 11.6 Hz), 155.2 (d, $^2J_{PC}$ = 15.5 Hz) ppm; *^{31}P-NMR* (150 MHz) 25.8 ppm; *IR (KBr)* 3448, 3353, 2974, 1533, 1125 cm^{-1}; *MS* (70 eV) 353 (M^+, 75). Anal. Calcd for $C_{20}H_{24}N_3OP$: C, 67.97; H, 6.85; N, 11.89. Found: C, 67.83; H, 6.87; N, 11.86.

4-Diphenylphosphoryl-1,3-dimethyl-3-pyrazolin-5-one (4). 1380 mg (89 %) of **4** as a white solid. Data for **4**: mp 180-181 °C; *^{1}H-NMR* (300 MHz) 1.66 (s, 3H, CH_3), 3.56 (s, 3H, CH_3N), 5.07 (s, 1H, NH), 7.26-7.70 (m, 10H, arom) ppm;

^{13}C-NMR (75 MHz) 14.7 (CH_3), 34.0 (CH_3N), 87.0 (d, $^1J_{PC}$ = 131.4 Hz, C=), 128.4-132.6 (C-arom), 134.2 (d, $^1J_{PC}$ = 108.3 Hz, C-ipso), 148.8 (d, $^2J_{PC}$ = 11.1 Hz), 153.3 (d, $^2J_{PC}$ = 14.1 Hz) ppm; *^{31}P-NMR* (150 MHz) 26.6 ppm; *IR (KBr)* 3389, 3180, 3149, 1646, 1535, 1521, 1155, 1123 cm^{-1}; *MS* (70 eV) 312 (M^+, 18). Anal. Calcd for $C_{17}H_{17}N_2O_2P$: C, 65.36; H, 5.49; N, 8.97. Found: C, 65.16; H, 5.50; N, 8.95.

4-Diphenylthiophosphoryl-1,3-dimethyl-5-ethylaminopyrazole (8a). 1400 mg (79 %) of **8a** as a white solid. Data for **8a**: mp 129-130 °C; *^1H-NMR* (300 MHz) 0.97 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.45 (s, 3H, CH_3), 2.94 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 3.62 (s, 3H, CH_3N), 5.67 (s, 1H, NH), 7.33-7.69 (m, 10H, arom) ppm; *^{13}C-NMR* (75 MHz) 14.5 (CH_3), 15.3 (CH_3), 35.6 (CH_3N), 42.6 (CH_2), 90.6 (d, $^1J_{PC}$ = 110.8 Hz, C=), 128.3-131.6 (C-arom), 133.9 (d, $^1J_{PC}$ = 89.6 Hz, C-ipso), 148.7 (d, $^2J_{PC}$ = 8.5 Hz), 154.7 (d, $^2J_{PC}$ = 19.1 Hz) ppm; *^{31}P-NMR* (150 MHz) 29.7 ppm; *IR (KBr)* 3238, 1547, 1435, 1398, 1103, 712, 639 cm^{-1}; *MS* (70 eV) 355 (M^+, 62). Anal. Calcd for $C_{19}H_{22}N_3PS$: C, 64.20; H, 6.24; N, 11.82. Found: C, 64.07; H, 6.22; N, 11.84.

4-Diphenylthiophosphoryl-1,3-dimethyl-5-phenylaminopyrazole (8b). 1670 mg (83 %) of **8b** as a yellow solid. Data for **8b**: mp 223-225 °C; *^1H-NMR* (300 MHz) 1.63 (s, 3H, CH_3), 3.27 (s, 3H, CH_3N), 6.55-7.80 (m, 16H, arom and NH) ppm; *^{13}C-NMR* (75 MHz) 16.8 (CH_3), 51.6 (CH_3N), 72.0 (d, $^1J_{PC}$ = 115.8 Hz, C=), 116.3-131.6 (C-arom), 134.4 (d, $^1J_{PC}$ = 88.6 Hz, C-ipso), 146.9 (C-arom), 163.5 (d, $^2J_{PC}$ = 19.2 Hz), 177.0 (d, $^2J_{PC}$ = 13.1 Hz) ppm; *^{31}P-NMR* (150 MHz) 27.0 ppm; *IR (KBr)* 3248, 1600, 1532, 1437, 1095, 749, 713, 692, 535 cm^{-1}; *MS* (70 eV) 403 (M^+, 100). Anal. Calcd for $C_{23}H_{22}N_3PS$: C, 68.47; H, 5.49; N, 10.41. Found: C, 68.38; H, 5.51; N, 10.40.

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