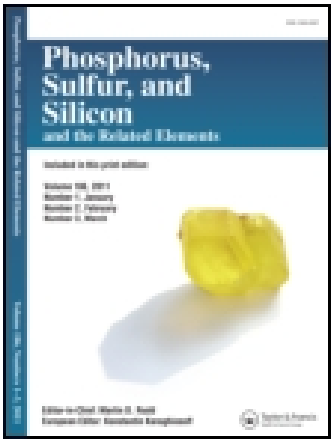


Phosphorus, Sulfur, and Silicon and the Related Elements
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# Synthesis of Some New Triphenylphosphanylidenes, Alkylphosphonates, and Heterocycles of Pyrazole Derivatives and Their Antimicrobial Activity

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# SYNTHESIS OF SOME NEW TRIPHENYLPHOSPHANYLIDENES, ALKYLPHOSPHONATES, AND HETEROCYCLES OF PYRAZOLE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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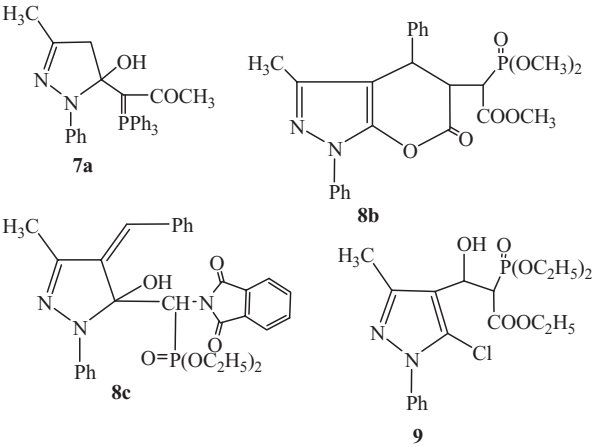
## GRAPHICAL ABSTRACT




**Abstract** *The reaction of 5(4H)-pyrazolone with phosphorus ylides afforded new triphenylphosphanylidene alkanone derivatives. Moreover, its benzylidene derivative reacted with Wittig–Horner reagents to give the corresponding dialkoxyphosphoryl, alkyl phosphonate, and heterocyclic products. Treatment of pyrazole-4-carbaldehyde with Wittig–Horner reagents and trialkyl phosphites gave the respective alkyl phosphonate adducts. Mechanisms accounting for*

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*the formation of the new products are discussed. The biological activity of some of the newly synthesized compounds was also examined.*

**Keywords** Pyrazoles; phosphorus ylides; Wittig–Horner reagents; alkyl phosphites; triphenylphosphanylidenes



## INTRODUCTION

The pyrazole ring system is frequently used in the synthesis of pharmaceuticals. A literature survey reveals that pyrazole derivatives are well known to have antibacterial,[1] antifungal,[2] antitubercular,[3] anticancer,[4] analgesic,[5] anti-inflammatory,[5] antipyretic,[6] and anticonvulsant activities.[7] In view of this, and as a continuation of our work in organophosphorus chemistry,[8–14] it was of considerable interest to synthesize new triphenylphosphanylidenes, alkyl phosphonates, and heterocycles of pyrazole derivatives to obtain potent biologically active compounds. The present study deals with the reaction of substituted pyrazole derivatives **1–3** with phosphorus ylides **4a**,**b**, Wittig–Horner reagents **5a–e**, and trialkyl phosphites **6a**,**b**.

## RESULTS AND DISCUSSION

### Chemistry

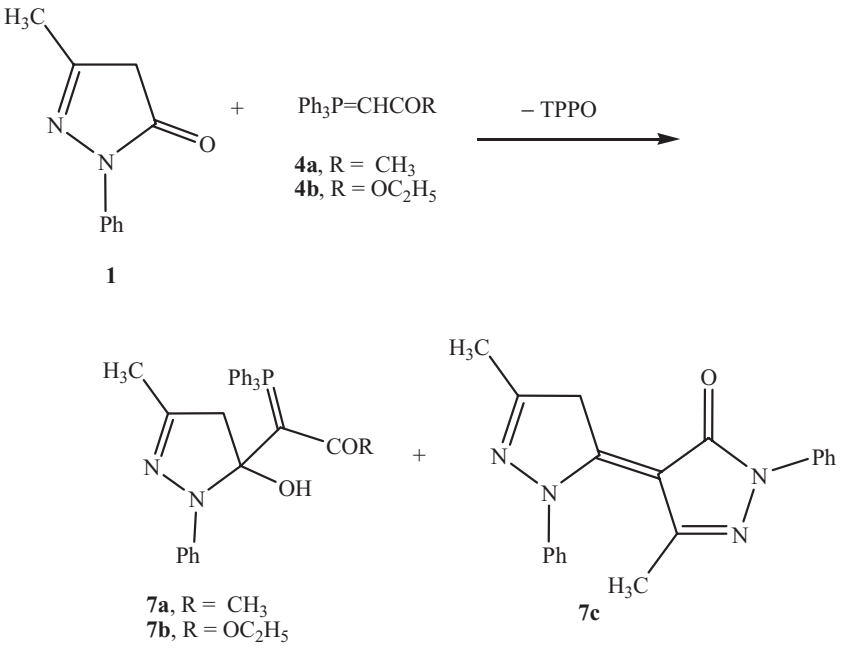
We have found that 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) reacted with 1 mol equivalent of 1-triphenylphosphoranylidene-2-propanone (**4a**) in refluxing tetrahydrofuran (THF) to give the triphenylphosphanylidene pyrazolyl pyranone **7a** (35% yield) and the dipyrazolyl ethylenic product (**7c**) (15% yield). Triphenylphosphane oxide was also isolated from the reaction medium and identified (mixed mp; mass spectral: MS) (Scheme 1).

Similarly, carbethoxymethylenetriphenylphosphorane **4b** reacted with **1** (1:1) molar ratio, in THF at r.t. for 6 h to give product **7b** (60% yield) and **7c** (15% yield). Triphenylphosphane oxide was also isolated from the reaction mixture (Scheme 1). The structures of **7a**,**b** and **7c** were deduced from correct elemental analyses, IR, $^{1}$H, $^{13}$C, $^{31}$P NMR, and MS data (*cf*. Experimental Section).

We propose the reaction course depicted in Scheme 1. The products **7a**,**b** were presumably formed through addition of alkylidene phosphoranes **4a**,**b** to the carbonyl carbon of pyrazolone **1**. Since the stabilized phosphonium ylides **4a**,**b** act as a Lewis base that facilitate also the dimerization of the starting pyrazolone **1** via dehydration process, the dimeric structure **7c** was also obtained[15] (Scheme 1).

Next, when 4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) was treated with 1 mol equivalent of triethylphosphonoacetate (**5a**) in the presence of an alcoholic sodium ethoxide solution at r.t. for 6 h, adduct **8a** was isolated in a 75% yield (Scheme 2). The structure of **8a** is deduced from its spectroscopic data (Scheme 2, Experimental Section). Similarly, compound **2** reacted with 2 mol equivalents of trimethylphosphonoacetate (**5b**) in the presence of methanolic sodium methoxide solution at the reflux temperature for 4 h to give a colorless crystalline compound assigned the pyranopyrazole structure **8b** (Scheme 2), which was established from its elemental analyses, IR, $^{1}$H, $^{13}$C, $^{31}$P NMR, and MS data (*cf*. Experimental Section).

Similarly, pyrazolone **2** reacted with one molar equivalent of diethyl(1,3-dioxoisoindolin-2-yl)methylphosphonate (**5c**) in the presence of an ethanolic sodium



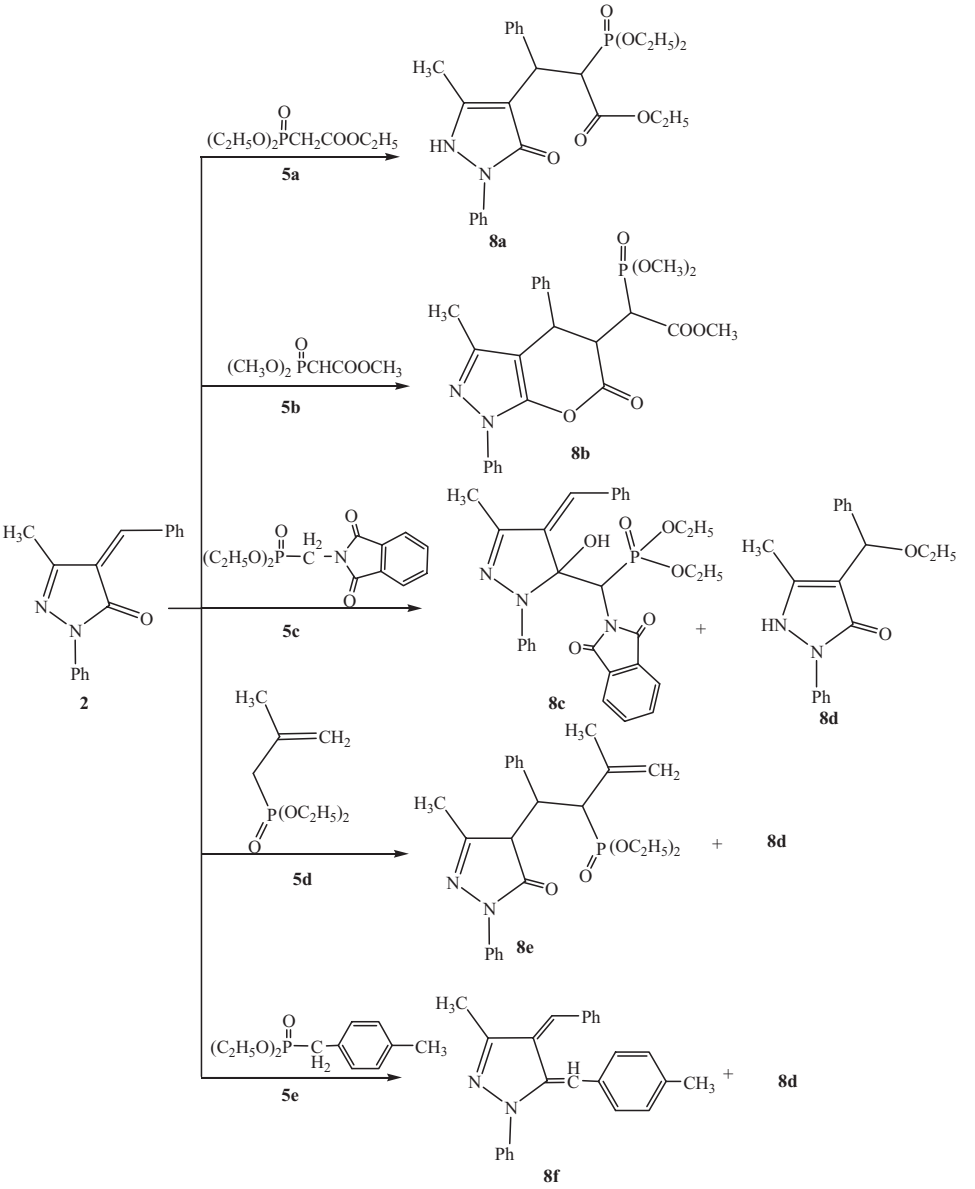

**Scheme 1**

ethoxide solution at the reflux temperature for 12 h to give two crystalline compounds assigned structures **8c**,**d** (Scheme 2), which were established on the basis of their spectral data (*cf*. Experimental Section).

Also, when pyrazolone **2** was allowed to react with 1 mol equivalent of 2-methylallylphosphonate **2d**, in the presence of an alcoholic sodium ethoxide solution, products **8e** (major) and **8d** (minor) were isolated (Scheme 2). Moreover, pyrazolone **2** reacted with one molar equivalent of **5e** in the presence of alcoholic sodium ethoxide solution for 15 h to give **8f** in a 70% yield together with **8d** (20% yield, Scheme 2). The structure of 4-benzylidene-3-methyl-5-(4-methylbenzylidene)-1-phenyl-4,5-dihydro-1*H*-pyrazole (**8f**) is assigned from its spectral data (*cf*. Experimental Section).

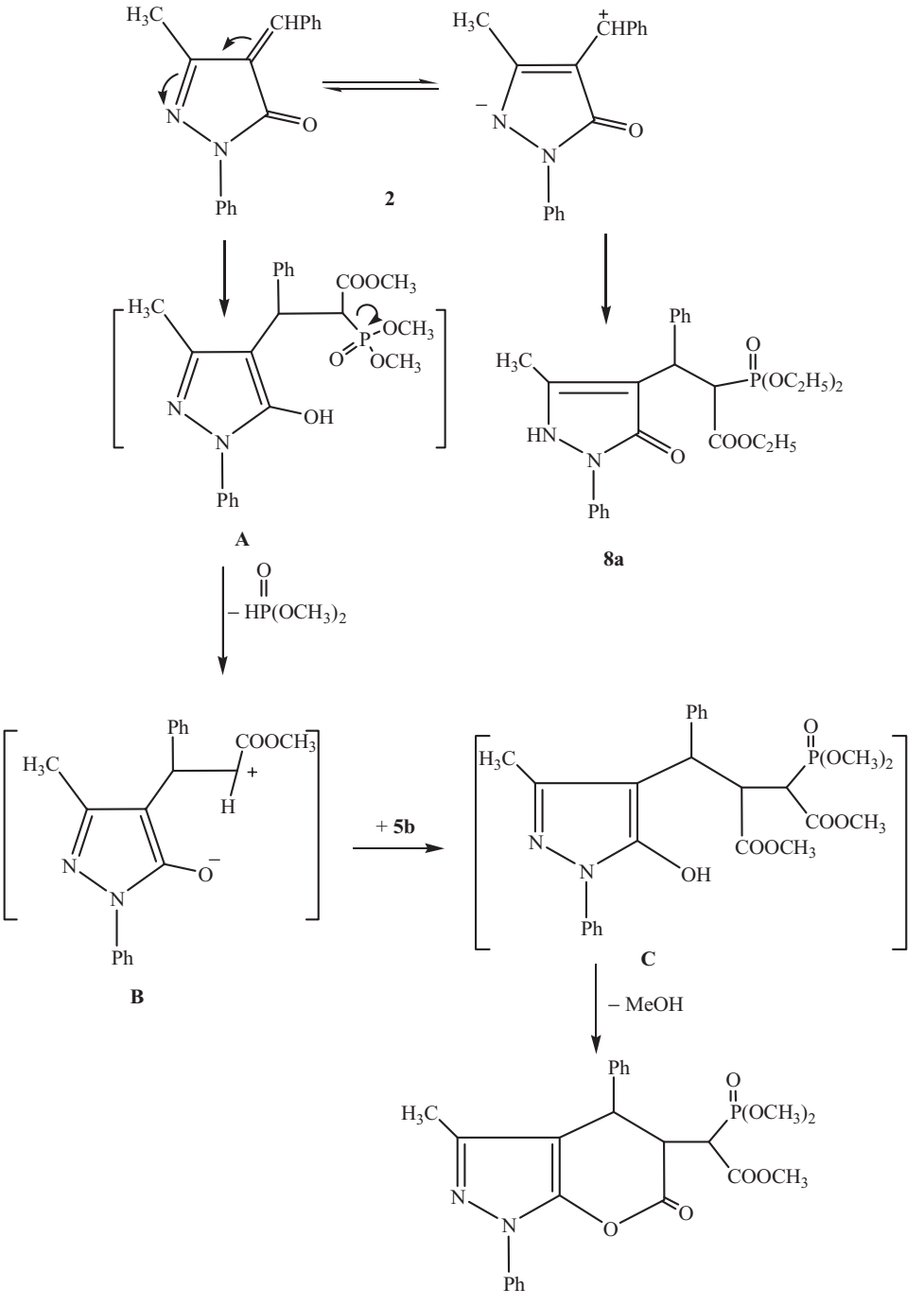
A possible explanation for the reaction course of **2** with Wittig–Horner reagents **5a**,**b** is shown in Scheme 3. Initial attack of triethylphosphonoacetate (**5a**) on the most reactive center of **2** gave the stable phosphonate product **8a**. Compound **8b** is presumably formed via intermediate **A**. Under the influence of the base present in the reaction medium, elimination of dialkyl phosphite followed by addition of another molecule of Wittig–Horner reagent **5b** together with cyclization via loss of one molecule alcohol gave the final phosphonate product **8b** (Scheme 3). The liberated dimethyl phosphite was detected in the water layer by the development of a violet color on addition of 3,5-dinitrobenzoic acid.[16]

Formation of compound **8d** can be explained by alkylation process. Since the enhanced reactivity of the phosphonate carbanions allows the $\alpha$-carbon to be elaborated by alkylation,[17,18] we suggest that the steric hindrance provided by dioxoisoindolinyl, *p*-methyl phenyl, methyl allyl groups inhibits the intramolecular displacement reaction and leads instead to the formation of **8d**. A similar alkylation was also observed in the reaction of Wittig–Horner reagents **5c–e** with pyrroles,[19] quinoneimines,[20] and nitronaphthols.[21]

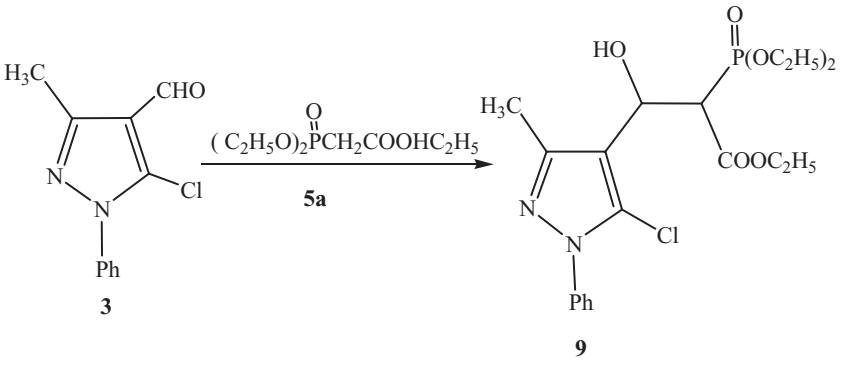



**Scheme 2**

Furthermore, this study was extended to include the behavior of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3**) toward triethylphosphonoacetate (**5a**) and trialkyl phosphites **6a**,**b** to determine the preferential site of attack. We have found that when **3** was allowed to react with one molar equivalent of triethylphosphonoacetate (**5a**) in the presence of an alcoholic sodium ethoxide solution, adduct **9** was isolated in a 75% yield (Scheme 4). The structure of ethoxyphosphono pyrazole derivative (**9**) is assigned from its spectral data (*cf*. Experimental Section).

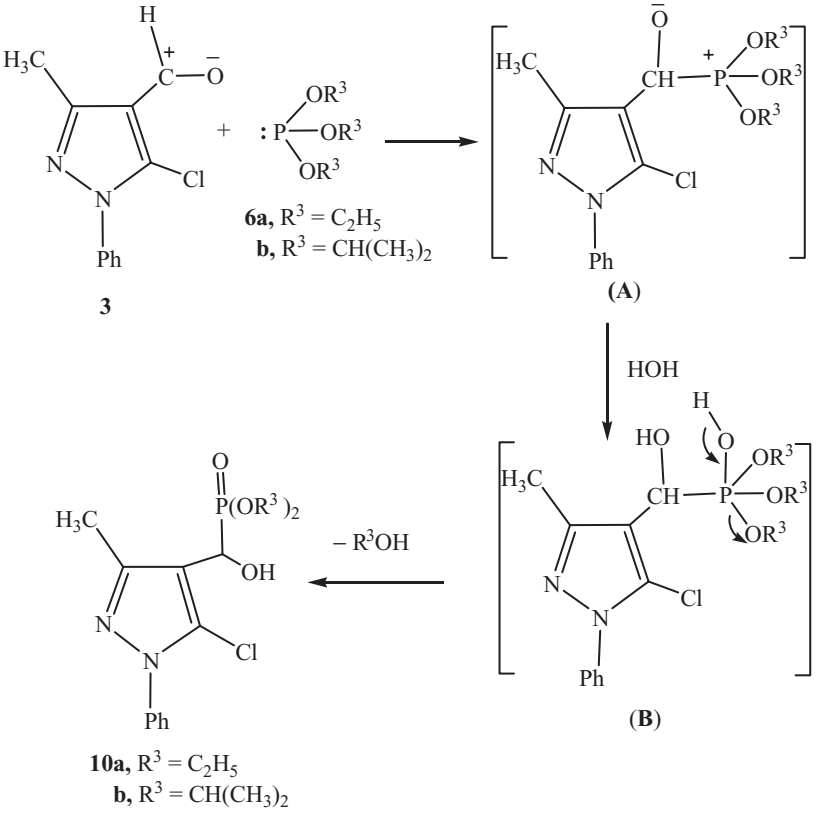



**Scheme 3**




**Scheme 4**

Also, the reaction of pyrazole-4-carbaldehyde **3** with trialkyl phosphites **6a**,**b** was also investigated. We have found that the reaction of **3** with one molar equivalent of **6a**,**b** in dry toluene at r.t. afforded products **10a**,**b** (Scheme 5). The structures of compounds **10a**,**b** were attested by their elemental analyses, IR, $^{1}H$, $^{13}C$, $^{31}P$ NMR, and MS data (*cf*. Experimental Section).




**Scheme 5**

The formation of compounds **10a**,**b** involves Michael addition[22,23] by the tertiary phosphite ester on the active carbonyl carbon in **3** to give the dipolar intermediate **A**. Addition of unavoidable moisture to intermediate **A** produces a transient intermediate **B** with pentacovalent phosphorus.[24] The latter collapses via loss of an alcohol molecule to give the dialkyl phosphonate products **10a**,**b**[25] (Scheme 5).

## BIOLOGICAL ACTIVITY

The antibacterial and antifungal activities[26–29] were carried out in the Microbial Chemistry Department, National Research Centre, Egypt, using the diffusion plate method. The obtained results are compared with the reference antibiotics that were purchased from Egyptian markets.[26–29] The obtained results revealed that the tested compounds had different antimicrobial responses.

As shown in Table S1 (Supplemental Materials, available online), compounds **7a** and **10b** are active against both Gram-positive and Gram-negative bacteria. Moreover, they have antifungal activity against the pathogen *Candida albicans*. At the same time, compound **8f** exhibited antimicrobial activity against only Gram-positive bacteria; other compounds showed antibacterial activity to different extents.

## CONCLUSION

From the results of the present investigation, it can be concluded that the reactions of pyrazolone **1** with phosphorus ylides **4** lead to different products, depending on the nature of the phosphorus ylide as well as the stability of the intermediate. Moreover, when 4-benzylidene-pyrazolone **2** was reacted with Wittig–Horner reagents **5a–c**, diethoxyphosphoryl **8a**, the cyclic dimethoxyphosphoryl **8b**, methylphosphonate **8c**, and the phosphonate product **8e** were obtained. We have noted that formation of **8a–f** depends on the nature of the phosphonate anion, the base used, as well as on the reactivity of the intermediate. Moreover, pyrazolone **3** reacted with Wittig–Horner reagents and trialkyl phosphites to give the respective alkyl phosphonate products.

Significantly, the reactions of phosphorus ylides and Wittig–Horner reagents with pyrazolone **1–3** are indicative of the broad reaction spectrum of which ylides and phosphonate anions are capable in addition to the usual olefin-forming reactions. Also, this finding which represents a new route to **8b** is a supplement to the expanded utility of reagents **5a–e** for the production of the new products.

In addition, some of the newly synthesized compounds were selected and screened for their antibacterial activity. The tested compounds **7a–c**, **8a–c**,**e**,**f**, **9**, **10b** revealed antibacterial activity to different extents.

## EXPERIMENTAL

Melting points were determined in open glass capillaries using Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infracord spectrophotometer model 157(Grating). The $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ and/or dimethyl sulfoxide (DMSO) as solvent on Joel-500 MHz spectrometer, and the chemical shifts were recorded in $\delta$ values relative to tetramethylsilane (TMS). The $^{31}P$

NMR spectra were recorded with a Varian CFT-20 (vs. external 85% $H_3PO_4$ standard). The MS were performed at 70 eV on a Shimadzu GCS-OP 1000 Ex spectrometer. Elemental analyses were performed using Elmenter Varu EL Germany Instrument. The reported yields are based upon pure materials isolated by column chromatography. Solvents were dried/purified according to the literature procedures. Starting materials were prepared according to the literature procedures.[30] Sample spectra for compounds **8a** and **10a** are shown in Figures S1–S6 (in the Supplemental Materials, available online).

### General Procedure for the Reaction of Phosphonium Ylides 4a,b with 3-Methyl-1-phenyl-5(4H)-pyrazolone (1)

One mmol of **4a** (0.31 g) or **4b** (0.34 g) and one mmol pyrazolone **1** (0.17 g) in dry THF (30 mL) were refluxed for 6 h (**4a** with **1**) or 10 h (**4b** with **1**). The reaction was preceded with thin layer chromatography (TLC). The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give **7a**,**c** or **7b**,**c**; triphenylphosphine oxide was also isolated from the reaction medium and identified (mix mp, MS).



### 1-(5-Hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-1-(triphenyl-λ$^5$-phosphanylidene)propan-2-one (7a, $C_{31}H_{29}N_2O_2P$)

Eluent: petroleum ether/ethyl acetate (65/35, *v/v*). Product **7a** was separated as pink crystals, yield 35%; mp 195–197°C; IR (KBr): $\tilde{\nu} = 3429$ (OH), 1674 (C=O), 1538 (C=N), 1482 (aryl-P), 1105 (P=C) cm$^{-1}$; $^1$H NMR (500.14 MHz, DMSO): $\delta$ = 1.65 (s, 3H, pyrazolyl-$\underline{CH_3}$), 1.84, 1.85 (d, $J_{HH}$ = 15 Hz, $^4J_{HP}$ = 4.2 Hz, 2H, $CH_2$), 2.67 (s, 3H, $COCH_3$), 6.07–7.57 (m, 20H, $H_{arom}$), 8.01 (d, $^4J_{HP}$ = 4.20 Hz, 1H, OH, exchangeable with $D_2O$) ppm; $^{13}$C NMR (125.76 MHz, DMSO): $\delta$ = 18.5, 20.5 ($2CH_3$), 44.5 (d, $^3J_{CP}$ = 8.1 Hz, $CH_2$), 71.5 (d, $^2J_{CP}$ = 28.5 Hz, cyclic C−OH), 113.5, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 133.5 (d, $J_{CP}$ = 90.2, C−P), 165.5 (C=O) ppm; $^{31}$P NMR: $\delta$ = 18.5 ppm; MS (EI, 70 eV): *m/z* (%) = 494 (5) $[M+2H]^+$, 477 (15), $[M-CH_3]^+$; Anal. for $C_{31}H_{29}N_2O_2P$ (492.2): calcd C 75.59, H 5.93, N 5.69, P 6.29; found: C 75.55, H 5.94, N 5.68, P 6.30.

### (5-Hydroxy-3-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)(triphenyl-λ$^5$-phosphanylidene)methyl propanoate (7b, $C_{32}H_{31}N_2O_3P$)

Eluent: petroleum ether/ethyl acetate (65/35, *v/v*). Product **7b** was separated as yellow crystals, yield 45%; mp 138–140°C; IR (KBr): $\tilde{\nu} = 3423$ (OH), 1641 (C=O), 1590 (C=N), 1425 (aryl-P), 1025 (P=C) cm$^{-1}$; $^1$H NMR (500.14 MHz, $CDCl_3$): $\delta$ = 0.52 (t, $J_{HH}$ = 13.8 Hz, $CH_2\underline{CH_3}$, 3H), 1.75 (d, $J_{HH}$ = 8.8 Hz, $^4J_{HP}$ = 4.23 Hz, 2H, $CH_3\underline{CH_2}$), 2.31, 2.33 (q, $J_{HH}$ = 8.8 Hz, 2H, $CH_2$), 2.65 (s, 3H, $CH_3$), 6.79–7.21 (m, 20H, $H_{arom}$), 10.06 (s, 1H, OH, exchangeable with $D_2O$) ppm; $^{13}$C NMR (125.76 MHz, $CDCl_3$): $\delta$ = 12.2 ($CH_3$), 14.8 (pyrazolyl-$\underline{CH_3}$), 29.8 ($CH_2$), 44.5, 45.6 (d, $^3J_{CP}$ = 7.20 Hz, $CH_2$), 82.5 (d, $^2J_{CP}$ = 29.1 Hz, cyclic C−OH), 103.9, 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 144.5, 145.4 (d, $J_{CP}$ = 112.5 Hz, C−P), 147.9 (C=N), 161.7 (C=O) ppm; $^{31}$P NMR: $\delta$ = 23.8 ppm; MS (EI, 70 eV): *m/z*

(%) = 524 (5) $[M+2H]^+$, 451 (35) [M−73, (OCOEt)], 262 (100) $[TPP]^+$, 174 (40), [pyrazolone]$^+$; Anal. for $C_{32}H_{31}N_2O_3P$ (522.21): calcd C 73.55, H 5.98, N 5.36, P 5.93; found: C 73.50, H 5.97, N 5.38, P 5.95.

### 5-Methyl-4-(5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-ylidene)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (7c, $C_{20}H_{20}N_4O$)

Eluent: petroleum ether/ethyl acetate (60/40, *v/v*). Product **7c** was separated as yellow crystals, yield 15%; mp 115–117°C; IR (KBr): $\tilde{\nu}$ = 1651 (C=O), 1623 (C=C), 1590 (C=N) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 2.31, 2.38 (d, $J_{HH}$ = 13.8 Hz, 2H, $CH_2$), 2.71, 2.75 (2 s, 6H, $2CH_3$), 7.13–7.93 (m, 10H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 18.5, 23.2 ($2CH_3$), 24.7 ($CH_2$), 96.8, 163.7 (C=C), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 148.1 (C=N), 166.1 (C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 334 (10) $[M+2H]^+$, 315 (15) $[M-15]^+$, 198 (75) [M−132, (PhN−N=C−$CH_3$)]$^+$; Anal. for $C_{20}H_{20}N_4O$ (332.16): calcd C 72.27, H 6.06, N 16.86; found: C 72.30, H 6.02, N 16.88.

### Reaction of 4-Benzylidene-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (2) with Trialkylphosphonoacetate (5a,b)

A solution of 1 mmol of sodium methoxide (0.54 g) or sodium ethoxide (0.68 g) in absolute alcohol (30 mL) was treated with an equimolar amount of the trialkylphosphonoacetate **5a** (0.22 mL) or **5b** (0.18 mL), and then pyrazolone **2** (1 mmol, 0.26 g) was added. The resulting reaction mixture was allowed to stir at r.t. for 6 h (**5a** with **2**) or the resulting mixture was refluxed for 4 h (**5b** with **2**) (TLC). Thence, the reaction mixture was poured onto a small amount of water, extracted with ethyl acetate; the extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual material was recrystallized from ethyl acetate to give products **8a** or **8b**.

### Ethyl 2-(Diethoxyphosphoryl)-3-(3-oxo-2-phenyl-4-methyl-2,3-dihydro-1H-pyrazol-4-yl)3-phenylpropanoate (8a, $C_{25}H_{31}N_2O_6P$)

Product **8a** was precipitated as colorless crystals, yield 80%; mp 150–152°C; IR (KBr): $\tilde{\nu}$ = 3448 (NH), 1732 (ester C=O), 1651 (C=O), 1610 (C=C), 1228 (P=O), 980 (P−O−C) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 0.80, 1.02, 1.05 (3 t, $J_{HH}$ = 13.8 Hz, 9H, $3CH_2\underline{CH_3}$,), 2.22 (s, 3H, pyrazolyl-$\underline{CH_3}$), 2.46 (t, $^2J_{HP}$ = 15.5 Hz, 1H, CH−P), 3.79, 3.88 (2 q, $J_{HH}$ = 8.8 Hz, 4H, P−(O−$CH_2$−)$_2$), 4.20 (t, $^3J_{HP}$ = 11.5 Hz, 1H, *CH*−CH−P), 4.59 (q, $J_{HH}$ = 8.8 Hz, 2H, COO−$CH_2$), 7.10−7.66 (m, 10H, $H_{arom}$), 10.95 (1H, NH, exchangeable with $D_2O$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 14.1, 14.8, 14.8 ($4CH_3$), 18.3 (CH−Ph), 40.7 (d, $J_{CP}$ = 88.2 Hz, C−P), 61.3, 62.3, 62.4 ($3CH_2$), 107.3 (cyclic *C*−CH−Ph), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 166.2 (C=O), 170.7 (ester C=O) ppm; $^{31}P$ NMR: $\delta$ = 23.0 ppm. −MS (EI, 70 eV): *m/z* (%) = 486 (65) $[M]^+$, 458 (5) $[M-28]^+$; Anal. for $C_{25}H_{31}N_2O_6P$ (486.19): calcd C 61.72, H 6.42, N 5.76, P 6.37; found: C 61.74, H 6.40, N 5.79, P 6.32.

### Methyl (dimethoxyphosphoryl)(1,4-dimethyl-3-methyl-6-oxo-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-5-yl)acetate (8b, $C_{24}H_{25}N_2O_7P$)

Product **8b** was precipitated as colorless crystals, yield 75%; mp 143−144°C; IR (KBr): $\tilde{\nu}$ = 1741 (ester C=O), 1647 (C=O), 1612 (C=C), 1547 (C=N), 1221 (P=O), 985 (P−O−C) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 2.49 (s, 3H, pyrazolyl-$\underline{CH_3}$), 2.62, 2.88 (2 d, $^3J_{HP}$ = 11.5 Hz, 6H, 2P(O)(O$\underline{CH_3}$), 3.08 (s, 3H, $COOCH_3$), 3.10 (ddd, $^3J_{HP}$ = 11.5 Hz, $J_{HH}$ = 7.8 Hz, 1H, *CH*CH−P), 3.86 (dd, $^2J_{HP}$ = 21.3 Hz, $J_{HH}$ = 7.8 Hz, 1H, CH−P), 4.23 (d, 1H, CH−Ph), 6.70–7.06 (m, 10H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 10.8 (pyrazolyl-$\underline{CH_3}$), 39.4 (d, $J_{CP}$ = 102.20, C−P), 40.1 (d, $^2J_{CP}$ = 35.37 Hz, *C*−C−P), 51.2 (d, $^3J_{CP}$ = 9.37 Hz, C−Ph), 52.3, 53.3 ($OCH_3$, $^2J_{CP}$ = 37.37 Hz), 54.4 (s, $COOCH_3$), 107.8 (cyclic *C*−C−Ph), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 153.1 (C=N), 164.7 (C=O), 168.1 (ester C=O) ppm; $^{31}P$ NMR = 29.2 ppm; MS (EI, 70 eV): *m/z* (%) = 484 (60) $[M]^+$, 363 (50), 283 (100) [pyranopyrazole]$^+$; Anal. for $C_{24}H_{25}N_2O_7P$ (484.14): calcd C 59.50, H 5.20, N 5.78, P 6.39; found: C 59.54, H 5.22, N 5.76, P 6.35.

### Reaction of 4-Benzylidene-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (2) with diethyl substituted phosphonate (5c–e)

**General procedure.** A solution of 1 mmol of sodium methoxide (0.54 g) or sodium ethoxide (0.68 g) in absolute alcohol (30 mL) was treated with an equimolar amount of the diethyl-substituted phosphonate (**5c**–**e**), and then the pyrazolone **2** (1 mmol, 0.26 g) was added. The resulting reaction mixture was allowed to heat on steam bath for 12–16 h (TLC). Thence, the reaction mixture was poured onto a small amount of water, extracted with ethyl acetate; the extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual material was chromatographed on silica gel column to give products **8c**–**f**. Compound **8d** was separated as pink crystals from all reaction mixtures.

### Diethyl (4-Benzylidene-4,5-dihydro-5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-5-yl)(1,3-dioxoisoindolin-2-yl)methylphosphonate (8c, $C_{30}H_{30}N_3O_6P$)

Eluent: petroleum ether/ethyl acetate (60/40, *v/v*). Product **8c** was separated as brown crystals, yield 35%; mp 183–185°C; IR (KBr): $\tilde{\nu}$ = 3447 (OH), 1653 (C=O), 1612 (C=C), 1555 (C=N), 1239 (P=O), 967 (P−O−C) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 1.12, 1.24 (2 t, $J_{HH}$ = 13.8 Hz, 6H, $2CH_2\underline{CH_3}$), 2.30 (s, 3H, pyrazolyl-$\underline{CH_3}$), 3.97 (d, $^2J_{HP}$ = 23.6 Hz, 1H, CH−P), 4.19, 4.63 (2 q, $J_{HH}$ = 8.8 Hz, $^3J_{HP}$ = 10.3 Hz, 4H, $\underline{CH_2}CH_3$), 5.9 (s, 1H, CH−Ph), 6.43–8.73 (m, 14H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 14.8 (s, 2(O−$CH_2$−*$CH_3$*), 18.7 (pyrazolyl-$\underline{CH_3}$), 50.2 (d, $J_{CP}$ = 133 Hz, C−P), 62.3 (d, $^2J_{CP}$ = 20.20 Hz, $2CH_2$), 75.2 (cyclic *C*−OH), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 147.5 (Ar−C), 155.6 (C=N), 167.9 (2C=O) ppm; $^{31}P$ NMR: $\delta$ = 27.4 ppm; MS (EI, 70 eV): *m/z* (%) = 561 (5) $[M+2H]^+$, 501 (35), 185 (20) [pyrazole]$^+$; Anal. for $C_{30}H_{30}N_3O_6P$ (559.19): calcd C 64.39, H 5.40, N 7.51, P 5.54; found: C 64.35, H 5.44, N 7.50, P 5.52.

### 4-(Ethoxy(phenyl)methyl)-1,2-dihydro-5-methyl-2-phenylpyrazol-3-one (8d, $C_{19}H_{20}N_2O_2$)

Eluent: petroleum ether/ethyl acetate (95/5, *v/v*). Product **8d** was separated as pink crystals, yield 20%; mp 175–176°C; IR (KBr): $\tilde{\nu} = 3442$ (NH), 1663 (C=O), 1610 (C=C) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta = 1.30$ (t, $J_{HH} = 13.8$ Hz, 3H, $CH_3$), 2.25 (s, 3H, pyrazolyl-$\underline{CH_3}$), 4.15 (q, $J_{HH} = 8.8$ Hz, 2H, $CH_2$), 5.8 (s, 1H, $\underline{CH}$−CH−Ph), 7.16–7.83 (m, 10H, $H_{arom}$), 9.01 (s, 1H, NH, exchangeable with $D_2O$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta = 15.6$ ($CH_3$), 18.3 (pyrazolyl-$\underline{CH_3}$), 65.1 ($CH_2$), 75.7 (CH−Ph), 107.7 (*C*−CH−Ph), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 150.7 (C−N), 166.2 (C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 310 (10) $[M+2H]^+$, 281 (50) $[M-29]^+$; Anal. for $C_{19}H_{20}N_2O_2$ (308.15): calcd C 74.00, H 6.54, N 9.08; found: C 74.01, H 6.55, N 9.05.

### Diethyl 1-(2,3-Dihydro-5-methyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-3-methyl-1-phenylbut-3-en-2-ylphosphonate (8e, $C_{25}H_{31}N_2O_4P$)

Eluent: petroleum ether/ethyl acetate (60/40, *v/v*). Product **8e** was separated as brown crystals, yield 55%; mp 228–230°C; IR (KBr): $\tilde{\nu}$ =1638 (C=O), 1628 (C=C), 1599 (C=N), 1244 (P=O), 963 (P−O−C) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta = 0.96$, 1.03 (2 t, $J_{HH} = 13.8$ Hz, $^4J_{HP} = 4.2$ Hz, 6H, 2O−C−*CH*$_3$), 1.11 (s, 3H, =C−*CH*$_3$), 2.04 (s, pyrazolyl-$\underline{CH_3}$), 2.84 (d, $^2J_{HP} = 28.5$ Hz, 1H, $\underline{CH}$−CH−P), 3.78 (d, $^3J_{HP} = 8.5$ Hz, 1H, *CH*−CH−P), 4.67, 4.75 (2 q, $J_{HH} = 8.8$ Hz, 4H, $CH_2$), 5.11, 5.15 (d, 2H, $=CH_2$), 6.8–7.42 (m, 10H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta = 14.8$ ($2CH_3$), 18.7 (pyrazolyl-$\underline{CH_3}$), 20.4 (d, $^2J_{CP} = 23$ Hz, CH−Ph), 23.0 (C−$CH_3$), 40.9 (d, $J_{CP} = 133$ Hz, CH−P) 151.1 (C=N), 111.0, 147.7 (C=$CH_2$), 62.7 ($2CH_2$, $^2J_{CP} = 23$ Hz), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7, 147.5 (Ar−C), 166.9 (2C=O) ppm; $^{31}P$ NMR = 22.9 ppm; MS (EI, 70 eV): *m/z* (%) = 453 (5) $[M-H]^+$, 396 (35) $[M-58]^+$; Anal. for $C_{25}H_{31}N_2O_4P$ (454.2): calcd C 66.07, H 6.87, N 6.16, P 6.81; found: C 66.07, H 6.85, N 6.19, P 6.80.

### 4-Benzylidene-3-methyl-5-(4-methylbenzylidene)-1-phenyl-4,5-dihydro-1H-pyrazole (8f, $C_{25}H_{22}N_2$)

Eluent: petroleum ether/ethyl acetate (60/40, *v/v*). Product **8f** was separated as brown crystals, yield 70%; mp 165–166°C; IR (KBr): $\tilde{\nu} = 1616$ (C=C), 1590 (C=N) $cm^{-1}$; $^1H$ NMR (500.14 MHz, DMSO): $\delta = 1.60$, 1.87 (2 s, 6H, $2CH_3$), 6.66 (s, 1H, C=CH), 7.09–8.65 (m, 14H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, DMSO): $\delta = 11.4$ (pyrazolyl-$\underline{CH_3}$), 21.07 ($CH_3$), 102.6 (CH−Ph), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 144.7 (C=N) ppm; MS (EI, 70 eV): *m/z* (%) = 350 ($M^+$, 5), 335 (M−$CH_3$, 5), 273 (M−$C_6H_5$), 100; Anal. for $C_{25}H_{22}N_2$ (350.18): calcd C 85.68, H 6.33, N 7.99; found: C 85.62, H 6.35, N 7.95.

### Reaction of 5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3) with Triethylphosphonoacetate (5b)

A solution of 1 mmol of sodium ethoxide (0.68 g) in absolute alcohol (30 mL) was treated with an equimolar amount of triethylphosphonoacetate (**5b**), and then pyrazole **3**

(1 mmol, 0.22 g) was added. The resulting reaction mixture was allowed to heat on steam bath for 12 h (TLC). The reaction mixture was poured into a small amount of water, extracted with ethyl acetate; the extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual material was recrystallized from acetone/petroleum ether to give product **9**.

### Ethyl 1-(Ethoxyphosphono)-2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-hydroxyethanoate (9, $C_{19}H_{26}ClN_2O_6P$)

Eluent: petroleum ether/acetone (85/15, *v/v*). Product **9** was separated as colorless crystals, yield 75%; mp 210–212°C; IR (KBr): $\tilde{\nu}$ = 3248 (OH), 1732 (ester C=O), 1226 (P=O), 1610 (C=C), 1554 (C=N), 959 (P−O−C), 763 (C−Cl) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 0.83, 1.25, 1.29 (3 t, $J_{HH}$ = 13.8 Hz, 9H, $3CH_3$), 2.60 (s, 3H, pyrazolyl-$\underline{CH_3}$), 3.60, 3.62 (dd, $^2J_{HP}$ = 23 Hz, $J_{HH}$ = 8.6 Hz, 1H, CH−P), 3.62, 4.07, 4.11 (3 q, $J_{HH}$ = 8.8 Hz, 6H, $3CH_2$), 5.42, 5.50 (d, $^3J_{HP}$ = 9.6 Hz, 1H, *CH*−CH−P), 6.46 (1H, OH, exchangeable with $D_2O$), 6.64–8.09 (m, 5H, $H_{arom}$), ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 14.3, 20.1, 31.8 ($4CH_3$), 40.2 (C−OH), 56.2 (d, C−P, $J_{CP}$ = 88.2 Hz), 60.5, 62.3 ($3CH_2$), 107.2, 107.4 (cyclic *C*−CH−OH, $^3J_{CP}$ = 10.38 Hz), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 153.1 (C=N), 168.4 (ester C=O) ppm; $^{31}P$ NMR: $\delta$ = 26.29 ppm; MS (EI, 70 eV): *m/z* (%) = 446 (5) $[M+H]^+$, 400 (5) $[M-45, (OEt)]^+$; Anal. for $C_{19}H_{26}ClN_2O_6P$ (445.12): calcd C 51.30, H 5.89, Cl 7.97, N 6.30, P 6.96; found: C 51.35, H 5.87, Cl 7.94, N 6.32, P 6.97.

### Reaction of 5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3) with Trialkylphosphite (6a,b)

A mixture of **3** (1 mmol, **0.22 g**) and **6a** (1 mmol, 0.16 mL) **or 6b** (1 mmol, 0.20 mL) in dry toluene (30 mL) was stirred for 7 h (**3** with **6a**) or 10 h (**3** with **6b**) (TLC). The volatile materials were evaporated under reduced pressure. The residue was chromatographed on silica gel column to give products **10a**,**b** together with unchanged pyrazole-4-carbaldehyde **3** (ca, 10%).

### Diethyl (5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)(hydroxy) methylphosphonate (10a, $C_{15}H_{20}ClN_2O_4P$)

Eluent: petroleum ether/acetone (75/25, *v/v*). Product **10a** was separated as colorless crystals, yield 45%; mp 188–190°C; IR (KBr): $\tilde{\nu}$ = 3282 (OH), 1596 (C=C), 1550 (C=N), 1240 (P=O), 969 (P−O−C), 725 (C−Cl) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta$ = 1.22, 1.27 (2 t, $J_{HH}$ = 13.8 Hz, 6H, $2CH_2\underline{CH_3}$), 2.00 (1H, OH, exchangeable with $D_2O$), 2.41 (pyrazolyl-$\underline{CH_3}$), 4.12, 4.14 (2 q, $J_{HH}$ = 8.8 Hz, 4H, $2\underline{CH_2}CH_3$), 5.06 (d, $^2J_{HP}$ = 25.6 Hz, 1H, CH−P), 7.41–7.46 (m, 5H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta$ = 11.3 (pyrazolyl-$\underline{CH_3}$), 14.8 ($2CH_3$), 53.8 (d, $J_{CP}$ = 88.20, C−P), 62.6 ($CH_2$), 119.6, 128.0 (cyclic C=C), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 133.5, 144.7 (Ar−C), 152.3 (C=N) ppm; $^{31}P$ NMR: $\delta$ = 20.7 ppm; MS (EI, 70 eV): *m/z* (%) = 358 (5) $[M]^+$, 343 (60) $[M-CH_3]^+$, 221 (45) $[M-137, P(O)(OC_2H_5)_2]^+$; Anal. for $C_{15}H_{20}ClN_2O_4P$ (358.780): calcd C 50.22, H 5.62, Cl 9.88, N 7.81, P 8.63; found: C 50.23, H 5.60, Cl 9.88, N 7.85, P 8.65.

### Dipropan-2-yl [(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)(hydroxy) methyl] phosphonate (10b, $C_{17}H_{24}ClN_2O_4P$)

Eluent: petroleum ether/acetone (75/25, *v/v*). Product **10b** was separated as golden brown crystals, yield 45%; mp 178–180°C; IR (KBr): $\tilde{\nu} = 3282$ (OH), 1555 (C=N), 1236 (P=O), 952 (P−O−C), 730 (C−Cl) $cm^{-1}$; $^1H$ NMR (500.14 MHz, $CDCl_3$): $\delta = 0.99$, 1.27 (2 d, 12H, $4CH_3$), 2.05–2.17 (2 septets, 2H, 2 isopropyl-CH), 2.46 (s, 3H, pyrazolyl-$CH_3$), 4.41 (d, $^2J_{HP} = 30.6$ Hz, 1H, CH−P), 4.71 (1H, OH, exchangeable with $D_2O$), 7.02–7.97 (m, 5H, $H_{arom}$) ppm; $^{13}C$ NMR (125.76 MHz, $CDCl_3$): $\delta = 11.3$ (pyrazolyl-$CH_3$), 24.8 ($4CH_3$), 54.5 (d, $J_{CP} = 90.20$, C−P), 72.6 (2CH), 119.6, 128.0 (cyclic C=C), 112.4, 114.3, 114.7, 117.0, 119.3, 120.5, 121.2, 124.7, 128.8, 129.2, 129.6, 133.1, 144.7 (Ar−C), 147.3 (C=N) ppm; $^{31}P$ NMR: $\delta = 25.1$ ppm; MS (EI, 70 eV): *m/z* (%) = 386 (5) $[M]^+$, 221 (25) $[M-165, P(O)(OCH(CH_3)_2)_2]^+$; Anal. for $C_{17}H_{24}ClN_2O_4P$ (387.12): calcd C 52.79, H 6.25, Cl 9.17, N 7.24, P 8.01; found: C 52.80, H 6.22, Cl 9.15, N 7.25, P 8.04.

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