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SYNTHESIS OF γ-KETO-δ-ALKENYL-PHOSPHONATES AND PHOSPHINE OXIDES AS PRECURSORS OF NOVEL PHOSPHONO-PYRAZOLINE AND PYRAZOLE DERIVATIVES

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Abstract – Herein we report the synthesis of γ-keto-δ-alkenyl-phosphonates and phosphine oxides by two versions of strategy (a) which involves the addition of dialkyl phosphites to α,α'-diarylideneketones, and by strategy (b) which utilizes the reaction of *P*-chlorodiphenylphosphine with diarylidene ketones in acetic acid. On reaction with hydrazine derivatives, γ-keto-δ-alkenyl-phosphonates and phosphine oxides give 3-phosphonoethylpyrazoline derivatives which can be converted into the corresponding aromatic pyrazoles by oxidative dehydrogenation, using sodium nitrite as oxidizing agent.

INTRODUCTION

From last few decades, a considerable amount of attention has been focused on the synthesis of γ-ketophosphonates owing to their promising applications as antihypertensive,[1] herbicide or fungicide agents,[2] some are also medicinally important as inhibitors of matrix-metalloprotease[3] and kininogenase.[4] On the other hand, γ-ketophosphonates and their derivatives are recognized as key intermediates for the synthesis of biologically active natural compounds such as methylenomycin B which belongs to the family of cyclopentanoid antibiotics.[5]

The introduction of an alkene functionality on γ-ketophosphonates, leading to the corresponding enone phosphonates, may be very interesting for the enhancement of the biological properties of these molecules (due to the presence of the enone pharmacophore),[6-8] and for synthetic transformations leading to heterocyclic phosphonates which are known to exhibit a variety of pharmacological properties.[9]

In the last few years, it was shown that the reaction of α,α'-diarylideneketones with dialkyl phosphites or *P*-chlorodiphenylphosphine can lead to γ-keto-δ-alkenyl-phosphonate and phosphine oxide derivatives.[10-12] The scope of these reactions is however limited and only a few of the desired products

have been synthesized from these strategies, in moderate yields, long reaction times, and sometimes using the hazardous benzene as solvent. Therefore, additional synthetic protocols are required to obtain a wider variety of compounds belonging to this class, in higher yields and greener conditions.

On the other hand, and in order to explore the potential of these multifunctional phosphonates in heterocyclic synthesis, we show here that their reaction with hydrazine derivatives leads to a new class of phosphonopyrazolines[13] which can be converted into the corresponding aromatic pyrazoles by oxidative dehydrogenation, using sodium nitrite as oxidizing agent. Our interest for these compounds is due to the well known interesting biological properties of pyrazoline and pyrazole derivatives including anticancer,[14] antiviral,[15] antimicrobial,[16] anti-inflammatory,[17] analgesic[18] and cardiovascular[19] activities. Some 3-phosphonopyrazoline derivatives were also proposed, in recent years, as potent and selective NMDA receptor antagonists with good neuroprotective and anticonvulsant activities.[20]

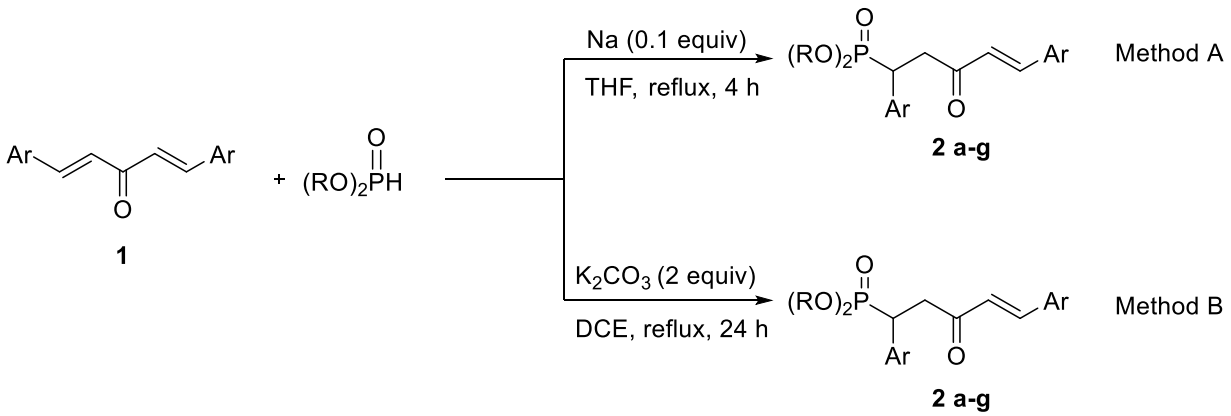
RESULTS AND DISCUSSION

In the continuation of our studies on the preparation and potential synthetic applications of multifunctional phosphonates,[21-25] we report in the present investigation, three convenient and efficient methods for the synthesis of γ-keto-δ-alkenyl-phosphonates and phosphine oxides from easily accessible α,α'-diarylideneketones and commercially available dialkyl phosphites or *P*-chlorodiphenylphosphine. By comparison with the existing strategies,[10-12] our synthetic protocols have the advantages of generality, good yields and shorter reaction times. Furthermore, they avoid the use of the hazardous benzene as solvent.

For the synthesis of γ-keto-δ-alkenylphosphonates **2a-g**, we have used two versions of strategy (a) which involves the addition of dialkyl phosphites to α,α'-diarylideneketones **1** (Table 1). In the first version (Method A), the reaction was performed in refluxing THF for 4 h, in the presence of a catalytic amount of sodium. The scope of the reaction was assessed with a range of diarylideneketones **1** and dialkyl phosphites. All the substrates reacted to afford the desired γ-keto-δ-alkenylphosphonates **2a-g** in 52-66% yields (Table 1). These compounds were isolated as a single *E*-diastereoisomer as evidenced by the absence of signal doubling in the ^{31}P, ^{13}C and ^{1}H NMR spectra. The *E* configuration was assigned on the basis of $^{3}J_{H\text{-}C=C\text{-}H}$ coupling constant values (15–18 Hz).

Better results were obtained when performing the reaction in refluxing 1,2-dichloroethane (DCE) for 24 h, in the presence of potassium carbonate (Method B). The isolated yield of the reaction ranges, in this case, from 74 to 83% (Table 1).

Table 1. Synthesis of γ-keto-δ-alkenylphosphonates **2a-g** from diarylideneketones **1** and dialkyl phosphites: Strategy (a)

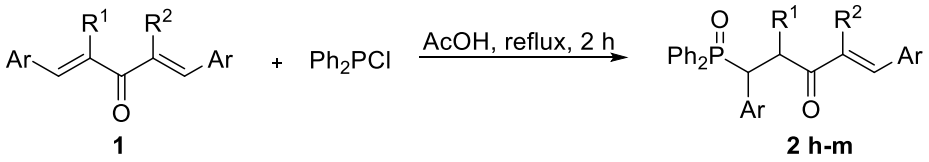


Entry	Ar	R	Product	Yield (%)[a] Method A	Method B
1	Ph	Et	**2a**	62	88
2	*p*-ClC_6H_4	Et	**2b**	54	80
3		Et	**2c**	66	83
4		Et	**2d**	63	79
5	*p*-ClC_6H_4	Me	**2e**	52	77
6	Ph	Me	**2f**	58	82
7	*p*-MeC_6H_4	Me	**2g**	55	81

[a]Isolated yield.

The second approach [strategy (b)] that we developed to access γ-keto-δ-alkenylphosphine oxides **2h-m**, involves a Conant-type reaction[5,26,27] between α,α'-diarylideneketones **1** and *P*-chlorodiphenylphosphine. The reaction was performed in refluxing acetic acid, for 2 h. The isolated yield in compounds **2h-m** ranges from 68 to 90% (Table 2). We shall note here that, similar to compounds **2a-g**, ketones **2h**, **k-m** were obtained as a single *E*-diastereoisomer. However, cyclic compounds **2i**, **j**, presenting two stereocenters, were obtained as a mixture of two unseparable diastereoisomers in an approximate 3:2 ratio. The diastereoisomeric ratio was determined from the ^{31}P NMR spectra where a singlet for each isomer is present.

Table 2. Synthesis of γ-keto-δ-alkenylphosphine oxides **2h-m** from diarylideneketones **1** and *P*-chlorodiphenylphosphine: Strategy (b)



1 **2 h-m**

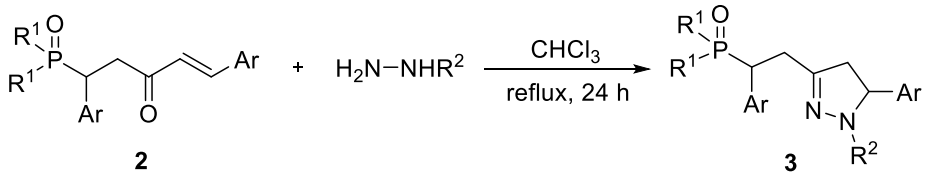
Entry	Ar	R^1	R^2	Product	Yield (%)[a]
1	Ph	H	H	**2h**	81
2	Ph	$(CH_2)_2$		**2i**	90
3	Ph	$(CH_2)_3$		**2j**	68
4		H	H	**2k**	78
5		H	H	**2l**	76
6	*p*-$MeOC_6H_4$	H	H	**2m**	73

[a]Isolated yield.

Being multifunctional compounds with two electrophilic centers in 1,3-positions, γ-keto-δ-alkenyl-phosphonates and phosphine oxides **2** can undergo cyclization reactions with binucleophilic agents leading to various heterocyclic systems. With this in mind and pursuing our research program regarding the synthesis of novel heterocyclic compounds bearing a phosphoryl group,[21-25] we report here our results on the reaction of compounds **2** with hydrazines which lead to a new class of phosphonopyrazolines. Thus, treatment of compounds **2** with an equimolar amount of hydrazine derivative, using chloroform as solvent and heating the mixture under reflux for 24 h gives the 3-phosphonoethylpyrazolines **3** in good to excellent yields (Table 3). These compounds, presenting two stereocenters, were isolated as a mixture of two unseparable diastereoisomers in an approximate 7:3 ratio, as evidenced by their NMR spectral data. The relative proportions of these diastereoisomers were estimated from the ^{31}P NMR spectra where a singlet for each one is present (Table 3).

In the next part of this work, we focused our efforts on the conversion of compounds **3** into the corresponding aromatic pyrazoles, by oxidative dehydrogenation. The reaction was initially tested with several oxidizing agents such as potassium permanganate, O_2/activated carbon and DDQ, but this left the starting materials intact. A great improvement was observed when using sodium nitrite as oxidizing agent. Indeed, the reaction of 3-phosphonoethylpyrazolines **3** with an equimolar amount of sodium nitrite, performed in refluxing chloroform for 6 h, led to the formation of 3-phosphonoethylpyrazoles **4a-d** in 53-68% yields (Table 4).

Table 3. Synthesis of 3-phosphonoethylpyrazolines **3**

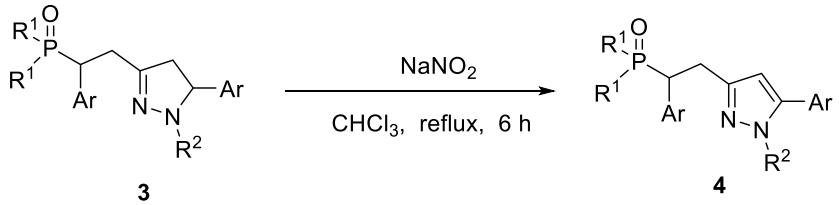


2 **3**

Entry	Ar	R^1	R^2	Product	% (major/minor)[a]	Yield (%)[b]
1	Ph	Ph	H	**3a**	70/30	93
2		Ph	H	**3b**	69/31	74
3	Ph	EtO	H	**3c**	65/35	86
4	Ph	Ph	Ph	**3d**	71/29	66
5		Ph	H	**3e**	82/18	78
6	*p*-$MeOC_6H_4$	Ph	Ph	**3f**	73/27	67
7	Ph	MeO	Ph	**3g**	62/38	76
8	Ph	MeO	H	**3h**	58/42	81
9	Ph	MeO	Me	**3i**	72/28	79
10		Ph	Me	**3j**	56/44	88

[a]Determined by ^{31}P NMR at 121.5 MHz, $CDCl_3$.
[b]Isolated yield.

Table 4. Synthesis of 3-phosphonoethylpyrazoles **4**



3 **4**

Entry	Ar	R^1	R^2	Product	Yield (%)[a]
1	Ph	EtO	H	**4a**	68
2	Ph	MeO	Me	**4b**	62
3	Ph	Ph	H	**4c**	56
4		Ph	Me	**4d**	53

[a]Isolated yield.

CONCLUSION

In summary, we successfully developed three efficient and simple methodologies for the synthesis of γ-keto-δ-alkenyl-phosphonates and phosphine oxides, from easily accessible α,α'-diarylideneketones and commercially available dialkyl phosphites or *P*-chlorodiphenylphosphine as starting materials. The obtained multifunctional phosphonates and phosphine oxides were used as efficient precursors for the straightforward preparation of novel phosphono- pyrazoline and pyrazole derivatives. Other applications of γ-keto-δ-alkenyl-phosphonates and phosphine oxides in heterocyclic synthesis are ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded with $CDCl_3$ as the solvent, on a Bruker AC-300 spectrometer operating at 300.1 MHz for ^{1}H, 121.5 MHz for ^{31}P and 75.5 MHz for ^{13}C. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P NMR. The coupling constants are reported in Hz. For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet and br s: broad singlet. Mass spectra were determined on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel (Fluka).

Synthesis of α,α'-diarylideneketones 1

The starting diarylideneketones **1** were prepared according to the reported procedure.[28]

General procedure for the synthesis of γ-keto-δ-alkenylphosphonates 2a-g

Method A: To a solution of dialkyl phosphite (0.01 mol) in anhydrous tetrahydrofuran (30 mL), maintained under a nitrogen atmosphere, sodium (0.02 g) was added and the mixture was stirred at room temperature until complete dissolution of sodium. Diarylideneketone **1** (0.01 mol) was then added and the mixture heated under reflux for 4 h. After cooling, the reaction mixture was diluted with water (50 mL) and extracted with $CHCl_3$ (2 × 25 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The obtained residue was chromatographed on a silica gel column using a mixture of Et_2O and hexane 9:1 as an eluent.

Method B: A mixture of dialkyl phosphite (0.01 mol), diarylideneketone **1** (0.01 mol) and potassium carbonate (0.02 mol), in CH_2Cl_2 (30 mL), was heated under reflux for 24 h. The solvent was then

removed under reduced pressure. The obtained residue was diluted with $CHCl_3$ (60 mL) and washed with water (2 × 30 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude obtained was chromatographed on a silica gel column using a mixture of Et_2O and hexane 9:1 as an eluent.

*(E)-Diethyl 3-oxo-1,5-diphenylpent-4-enylphosphonate (**2a**).* White solid; mp 180-182 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 28.4; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 1.28 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 2.90-3.27 (m, 2H, P-CH-C*H*$_2$); 3.59-3.75 (m, 1H, P-C*H*); 3.83-4.09 (m, 4H, 2 C*H*$_2$O); 6,63-7.56 (AB system, J_{AB} = 18.0 Hz, 2H, C*H*=C*H*); 7.04-7.49 (m, 10H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.2 (d, $^3J_{CP}$ = 6.0 Hz, *C*H$_3$-CH$_2$); 16.4 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$-CH$_2$); 39.0 (d, $^1J_{CP}$ = 144.1 Hz, P-*C*H); 40.9 (s, P-CH-*C*H$_2$); 61.9 (d, $^2J_{CP}$ = 6.8 Hz, *C*H$_2$O); 62.8 (d, $^2J_{CP}$ = 6.5 Hz, *C*H$_2$O); 143.1 (s, O=C-*C*H=CH); 196.1 (d, $^3J_{CP}$ = 14.4 Hz, *C*=O); Ar-C and O=C-CH=*C*H: δ = 125.88, 127.21, 128.29, 128.44, 128.88, 129.58, 130.46, 134.23, 134.75, 135.40, 135.97; IR (neat): $\nu_{P=O}$ = 1240 cm^{-1}; $\nu_{C=C}$ = 1617 cm^{-1}; $\nu_{C=O}$ = 1663 cm^{-1}; EI-HRMS: calculated for $C_{21}H_{25}O_4P$, 372.1490 (M^+); found: 372.1479.

*(E)-Diethyl 1,5-bis(4-chlorophenyl)-3-oxopent-4-enylphosphonate (**2b**).* White solid; mp 110-112 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 28.1; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.11 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 1.27 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 2.93-3.25 (m, 2H, P-CH-C*H*$_2$); 3.47-3.57 (m, 1H, P-C*H*); 3.68-4.11 (m, 4H, 2 C*H*$_2$O); 6.65-7.47 (AB system, J_{AB} = 15.0 Hz, 2H, C*H*=C*H*); 7.06-7.42 (m, 8H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.2 (d, $^3J_{CP}$ = 4.5 Hz, *C*H$_3$-CH$_2$); 16.3 (d, $^3J_{CP}$ = 5.3 Hz, *C*H$_3$-CH$_2$); 38.3 (d, $^1J_{CP}$ = 141.1 Hz, P-*C*H); 41.0 (s, P-CH-*C*H$_2$); 62.2 (d, $^2J_{CP}$ = 6.8 Hz, *C*H$_2$O); 62.8 (d, $^2J_{CP}$ = 5.3 Hz, *C*H$_2$O); 141.7 (s, O=C-*C*H=CH); 195.6 (d, $^3J_{CP}$ = 15.1 Hz, *C*=O); Ar-C and O=C-CH=*C*H: δ = 126.15, 128.57, 129.56, 130.26, 131.29, 132.42, 133.03, 134.36, 134.75, 136.48; IR (neat): $\nu_{P=O}$ = 1218 cm^{-1}; $\nu_{C=C}$ = 1610 cm^{-1}; $\nu_{C=O}$ = 1681 cm^{-1}; EI-HRMS: calculated for $C_{21}H_{23}Cl_2O_4P$, 440.0711 (M^+); found: 440.0702.

*(E)-Diethyl 3-oxo-1,5-di(thiophen-2-yl)pent-4-enylphosphonate (**2c**).* Brown solid; mp 132-134 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 26.3; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 1.22 (t, 3H, $^3J_{HH}$ = 9.0 Hz, C*H*$_3$-CH$_2$); 3.19-3.24 (m, 2H, P-CH-C*H*$_2$); 3.80-3.95 (m, 1H, P-C*H*); 3.92-4.03 (m, 4H, 2 C*H*$_2$O); 6,39-7.57 (AB system, 2H, J_{AB} = 15,0 Hz, C*H*=C*H*); 6.74-7.28 (m, 6H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.1 (d, $^3J_{CP}$ = 6.0 Hz, *C*H$_3$-CH$_2$); 16.2 (d, $^3J_{CP}$ = 6.0 Hz, *C*H$_3$-CH$_2$); 39.3 (d, $^1J_{CP}$ = 146.4 Hz, P-*C*H); 42.1 (s, P-CH-*C*H$_2$); 62.6 (d, $^2J_{CP}$ = 7.5 Hz, O*C*H$_2$); 63.4 (d, $^2J_{CP}$ = 7.5 Hz, O*C*H$_2$); 139.6 (s, O=C-*C*H=CH); 195.2 (d, $^3J_{CP}$ = 14.3 Hz, *C*=O); Ar-C and O=C-CH=*C*H:

δ = 124.39, 124.73, 126.83, 128.32, 129.22, 131.98, 135.87, 137.02, 137.14, 137.63, 137.74; IR (neat): $\nu_{P=O}$ = 1238 cm^{-1}; $\nu_{C=C}$ = 1603 cm^{-1}; $\nu_{C=O}$ = 1672 cm^{-1}; EI-HRMS: calculated for $C_{17}H_{21}O_4PS_2$, 384.0619 (M^+); found: 384.0602.

*(E)-Diethyl 1,5-di(furan-2-yl)-3-oxopent-4-enylphosphonate (**2d**)*. Yellow oil; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 25.9; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.10 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 1.26 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C*H*$_3$-CH$_2$); 2.91-3.14 (m, 2H, P-CH-C*H*$_2$); 3.54-3.78 (m, 1H, P-C*H*); 3.92-4.29 (m, 4H, 2 C*H*$_2$O); 6.92-7.48 (AB system, J_{AB} = 15.6 Hz, 2H, C*H*=C*H*); 6.65-7.32 (m, 6H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.3 (d, $^3J_{CP}$ = 6.5 Hz, *C*H$_3$-CH$_2$); 16.4 (d, $^3J_{CP}$ = 6.5 Hz, *C*H$_3$-CH$_2$); 33.2 (d, $^1J_{CP}$ = 144.5 Hz, P-*C*H); 43.5 (s, P-CH-*C*H$_2$); 62.5 (d, $^2J_{CP}$ = 7.5 Hz, *C*H$_2$O); 62.9 (d, $^2J_{CP}$ = 7.5 Hz, *C*H$_2$O); 144.9 (s, O=C-*C*H=CH); 195.7 (d, $^3J_{CP}$ = 14.5 Hz, *C*=O); Ar-C and O=C-CH=*C*H: δ = 108.06, 112.55, 112.64, 115.90, 123.20, 129.41, 141.86, 145.19, 149.19, 151.53; IR (neat): $\nu_{P=O}$ = 1242 cm^{-1}; $\nu_{C=C}$ = 1620 cm^{-1}; $\nu_{C=O}$ = 1692 cm^{-1}; EI-HRMS: calculated for $C_{17}H_{21}O_6P$, 352.1076 (M^+); found: 352.1023.

*(E)-Dimethyl 1,5-bis(4-chlorophenyl)-3-oxopent-4-enylphosphonate (**2e**)*. White solid; mp 154-156 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 28.8; ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.20-3.34 (m, 2H, P-CH-C*H*$_2$); 3.40 (d, 3H, $^3J_{HP}$ = 10.6 Hz, C*H*$_3$O); 3.57 (d, 3H, $^3J_{HP}$ = 10.8 Hz, C*H*$_3$O); 3.71-3.88 (m, 1H, P-C*H*); 6.72-7.86 (AB system, J_{AB} = 16.5 Hz, 2H, C*H*=C*H*); 6.86-7.88 (m, 8H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.8 (d, $^1J_{CP}$ = 155.5 Hz, P-*C*H); 43.2 (s, P-CH-*C*H$_2$); 52.9 (d, $^2J_{CP}$ = 7.2 Hz, *C*H$_3$O); 53.8 (d, $^2J_{CP}$ = 7.2 Hz, *C*H$_3$O); 142.1 (s, O=C-*C*H=CH); 195.5 (d, $^3J_{CP}$ = 15.1 Hz, *C*=O); Ar-C and O=C-CH=*C*H: δ = 125.67, 125.94, 128.71, 128.75, 128.78, 129.21, 129.51, 130.11, 130.25, 130.34, 130.41, 130.50, 131.24; IR (neat): $\nu_{P=O}$ = 1255 cm^{-1}; $\nu_{C=C}$ = 1618 cm^{-1}; $\nu_{C=O}$ = 1687 cm^{-1}; EI-HRMS: calculated for $C_{19}H_{19}Cl_2O_4P$, 412.0398 (M^+); found: 412.0366.

*(E)-Dimethyl 3-oxo-1,5-diphenylpent-4-enylphosphonate (**2f**)*. White solid; mp 167-169 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 28.8; ^1H NMR ($CDCl_3$): δ = 2.81-3.24 (m, 2H, P-CH-C*H*$_2$); 3.35 (d, 3H, $^3J_{HP}$ = 10.5 Hz, C*H*$_3$O); 3.59 (d, 3H, $^3J_{HP}$ = 10.7 Hz, C*H*$_3$O); 3.82-4.04 (m, 1H, P-C*H*); 6.65-7.52 (AB system, J_{AB} = 16.0 Hz, 2H, C*H*=C*H*); 6.93-7.49 (m, 10H, arom-*H*); ^{13}C NMR ($CDCl_3$): δ = 40.4 (d, $^1J_{CP}$ = 127.9 Hz, P-*C*H); 43.2 (s, P-CH-*C*H$_2$); 51.9 (t, $^2J_{CP}$ = 6.8 Hz, O*C*H$_3$); 52.7 (d, $^2J_{CP}$ = 6.8 Hz, O*C*H$_3$); 143.3 (s, O=C-*C*H=CH); 196.1 (d, $^3J_{CP}$ = 15.1 Hz, *C*=O); Ar-C and O=C-CH=*C*H: 125.10, 125.80, 127.44, 128.75, 128.95, 129.21, 130.51, 131.18, 134.74, 135.59, 135.68; IR (neat): $\nu_{P=O}$ = 1254 cm^{-1}; $\nu_{C=C}$ = 1624 cm^{-1}; $\nu_{C=O}$ = 1662 cm^{-1}; EI-HRMS: calculated for $C_{19}H_{21}O_4P$, 344.1177 (M^+); found: 344.1187.

*(E)-Dimethyl 3-oxo-1,5-di-p-tolylpent-4-enylphosphonate (**2g**)*. Yellow solid; mp 111-113 °C; ^{31}P NMR

($CDCl_3$, 121.5 MHz): δ (ppm) = 30.4; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.15 (s, 3H, C*H*$_3$); 2.32 (s, 3H, C*H*$_3$); 2.78-3.14 (m, 2H, P-CH-C*H*$_2$); 3.38 (d, 3H, $^3J_{HP}$ = 10.6 Hz, C*H*$_3$O); 3.60 (d, 3H, $^3J_{HP}$ = 10.7 Hz, C*H*$_3$O); 3.78-3.92 (m, 1H, P-C*H*); 6.51-7.58 (AB system, J_{AB} = 16.2 Hz, 2H, C*H*=C*H*); 6.81-7.49 (m, 8H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 21.06 (s, *C*H$_3$-C$_6$H$_4$); 21.49 (s, *C*H$_3$-C$_6$H$_4$); 39.0 (d, $^1J_{CP}$ = 130.5 Hz, P-*C*H); 43.3 (s, P-CH-*C*H$_2$); 53.4 (d, $^2J_{CP}$ = 4.5 Hz, *C*H$_3$O); 53.6 (d, $^2J_{CP}$ = 6.8 Hz, *C*H$_3$O); 143.3 (s, O=C-*C*H=CH); 196.2 (d, $^3J_{CP}$ = 15.1 Hz, *C*=O); Ar-C and O=C-CH=*C*H: δ = 124.60, 126.01, 128.40, 128.72, 128.87, 129.27, 129.70, 131.92, 132.02, 132.55, 136.89, 137.00, 140.93; IR (neat): $\nu_{P=O}$ = 1255 cm^{-1}; $\nu_{C=C}$ = 1616 cm^{-1}; $\nu_{C=O}$ = 1687 cm^{-1}; EI-HRMS: calculated for $C_{21}H_{25}O_4P$, 372.1490 (M^+); found: 372.1471.

General procedure for the synthesis of γ-keto-δ-alkenylphosphine oxides 2h-m

A mixture of diarylideneketone **1** (0.022 mol) in glacial acetic acid (20 mL), was added dropwise with stirring to *P*-chlorodiphenylphosphine (0.02 mol), under a nitrogen atmosphere. Distilled water (0.2 mL) was then added and the mixture heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was diluted with water (60 mL) and extracted with an equal volume of $CHCl_3$. The organic phase obtained was washed with a saturated aqueous solution of $NaHCO_3$ (60 mL), dried over Na_2SO_4 and concentrated under vacuum. The obtained residue was chromatographed on a silica gel column using Et_2O as an eluent.

*(E)-5-(Diphenylphosphoryl)-1,5-diphenylpent-1-en-3-one (**2h**).* White solid; mp 216-218 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 34.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.09-3.75 (m, 2H, P-CH-C*H*$_2$); 4.36-4.43 (m, 1H, P-C*H*); 6.54-7.83 (AB system, J_{AB} = 16.2 Hz, 2H, C*H*=C*H*); 6.98-8.03 (m, 20H, arom-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.2 (d, $^1J_{CP}$ = 68.7 Hz, P-*C*H); 43.3 (s, P-CH-*C*H$_2$); 143.4 (s, O=C-*C*H=CH); 196.6 (d, $^3J_{CP}$ = 13.6 Hz, *C*=O); Ar-C and O=C-CH=*C*H): δ = 126.02, 126.97, 127.08, 127.97, 128.13, 128.26, 128.72, 128.88, 129.30, 129.50, 129.76, 129.84, 130.61, 130.89, 131.11, 131.24, 131.30, 131.36, 131.40, 131.99, 132.29, 134.15, 135.84, 135.91; IR (neat): $\nu_{P=O}$ = 1188 cm^{-1}; $\nu_{C=C}$ = 1617 cm^{-1};$\nu_{C=O}$ = 1695 cm^{-1}; EI-HRMS: calculated for $C_{29}H_{25}O_2P$, 436.1592 (M^+); found: 436.1591.

*2-Benzylidene-5-[(diphenylphosphoryl)(phenyl)methyl]cyclopentanone (**2i**).* White solid; mp 84-86 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 33.6 (s, 78%, maj); 34.4 (s, 22%, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.87-3.51 (m, 5H, cyclic-*H*); 4.41-4.45 (m, 1H, P-C*H*); 6.83-8.04 (m, 21H, arom-*H* and C=C*H*-C$_6$H$_5$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 30.0 (s, *C*H$_2$-CH-C=O, min); 31.1 (s, *C*H$_2$-CH-C=O, maj); 33.3 (s, *C*H$_2$-C-C=O, min); 36.7 (s, *C*H$_2$-C-C=O, maj); 44.4 (d, $^1J_{CP}$ = 72.5 Hz, P-*C*H); 45.4 (s, P-CH-*C*H); 144.6 (s, O=C-*C*=CH); 160.1 (s, O=C-C=*C*H); 208.8 (d, $^3J_{CP}$ = 14.3 Hz, *C*=O); Ar-*C*: 126.10,

126.30, 127.08, 127.31, 128.23, 128.30, 128.34, 128.38, 128.44, 128.63, 128.89, 128.96, 129.04, 129.97, 130.81, 130.93, 130.95, 130.98, 131.06, 131.10, 131.30, 131.33, 131.85, 132.23, 132.84, 132.88, 133.01, 133.13, 138.44; IR (neat): $\nu_{P=O}$ = 1188 cm^{-1}; $\nu_{C=C}$ = 1619 cm^{-1}; $\nu_{C=O}$ = 1706 cm^{-1}; EI-HRMS: calculated for $C_{31}H_{27}O_2P$, 462.1749 (M^+); found: 462.1726.

*2-Benzylidene-6-[(diphenylphosphoryl)(phenyl)methyl]cyclohexanone (**2j**).* White solid; mp 200-202 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz, $CDCl_3$): δ (ppm): δ = 35.7 (s, 59%, maj); 35.5 (s, 41%, min); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.03-3.43 (m, 7H, cyclic-*H*); 4.86-4.93 (m, 1H, P-C*H*); 7.10-7.61 (m, 21H, arom-*H* and C=C*H*-C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 21.1 (s, CH_2-*C*H_2-CH_2, min); 23.2 (s, CH_2-*C*H_2-CH_2, maj); 26.5 (s, *C*H_2-CH-C=O, min); 28.7 (s, *C*H_2-CH-C=O, maj); 30.9 (s, *C*H_2-C-C=O, maj); 35.7 (s, *C*H_2-C-C=O, min); 42.4 (d, $^1J_{CP}$ = 73.2 Hz, P-*C*H); 47.5 (s, P-CH-*C*H, min); 50.5 (s, P-CH-*C*H, maj); 139.3 (s, O=C-*C*=CH); 147.0 (s, O=C-C=*C*H); 200.3 (d, $^3J_{CP}$ = 13.7 Hz, *C*=O); Ar-*C*: 126.00, 127.07, 128.01, 128.08, 128.24, 128.29, 128.43, 128.65, 128.89, 129.04, 130.09, 130.21, 130.69, 130.75, 130.81, 130.86, 130.89, 130.93, 131.01, 131.04, 131.13, 131.37, 131.54, 131.66, 131.77, 132.96, 133.71, 134.06, 134.11, 135.38, 136.29, 136.83, 138.66; IR (neat): $\nu_{P=O}$ = 1178 cm^{-1}; $\nu_{C=C}$ = 1614 cm^{-1}; $\nu_{C=O}$ = 1678 cm^{-1}; EI-HRMS: calculated for $C_{32}H_{29}O_2P$, 476.1905 (M^+); found: 476.1887.

*(E)-5-(Diphenylphosphoryl)-1,5-di(thiophen-2-yl)pent-1-en-3-one (**2k**).* Dark green solid; mp 120-122 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 33.2; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.99-3.60 (m, 2H, P-CH-C*H*$_2$); 4.71-4.77 (m, 1H, P-C*H*); 6.79-7.84 (AB system, J_{AB} = 15.0 Hz, 2H, C*H*=C*H*); 6.77-7.98 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 37.10 (d, $^1J_{CP}$ = 70.9 Hz, P-*C*H); 41.2 (s, P-CH-*C*H_2); 140.2 (s, O=C-*C*H=CH); 195.6 (d, $^3J_{CP}$ = 12.8 Hz, *C*=O); Ar-C and O=C-CH=*C*H): 124.33, 124.48, 124.86, 126.68, 127.30, 127.39, 128.24, 128.30, 128.83, 128.98, 129.32, 130.30, 130.90, 131.02, 131.15, 131.27, 131.61, 131.83, 132.02, 132.10, 132.13, 135.53, 136.04, 137.33, 139.38; IR (neat): $\nu_{P=O}$ = 1233 cm^{-1}; $\nu_{C=C}$ = 1611 cm^{-1}; $\nu_{C=O}$ = 1657 cm^{-1}; EI-HRMS: calculated for $C_{25}H_{21}O_2PS_2$, 448.0721 (M^+); found: 448.0736.

*(E)-5-(Diphenylphosphoryl)-1,5-di(furan-2-yl)pent-1-en-3-one (**2l**).* Beige solid; mp 182-184 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 32.5; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.53-3.54 (m, 2H, P-CH-C*H*$_2$); 4.33-4.42 (m, 1H, P-C*H*); 7.06-7.88 (AB system, J_{AB} = 15.2 Hz, 2H; C*H*=C*H*); 7.15-7.90 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 40.1 (d, $^1J_{CP}$ = 69.5 Hz, P-*C*H); 41.3 (s, P-CH-*C*H_2); 148.3 (s, O=C-*C*H=CH); 203.9 (d, $^3J_{CP}$ = 12.1 Hz, *C*=O); Ar-*C* and O=C-CH=*C*H: 108.67, 108.75, 108.83, 110.75, 128.17, 128.32, 128.67, 128.70, 128.83, 128.92, 129.32, 129.63, 130.05, 130.66, 131.21, 131.28, 131.33, 131.40, 131.94, 132.17, 141.71, 141.76, 141.82; IR (neat): $\nu_{P=O}$ = 1191 cm^{-1}; $\nu_{C=C}$ = 1615

cm^{-1}; $\nu_{C=O}$ = 1694 cm^{-1}; EI-HRMS: calculated for $C_{25}H_{21}O_4P$, 416.1177 (M^+); found: 416.1191.

*(E)-5-(Diphenylphosphoryl)-1,5-bis(4-methoxyphenyl)pent-1-en-3-one (**2m**)*. Bright yellow solid; mp 162-164 °C; ^{31}P NMR: ($CDCl_3$, 121.5 MHz): δ (ppm) = 34.4; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.93-3.49 (m, 2H, P-CH-C*H*$_2$); 3.74 (s, 3H, OC*H*$_3$); 3.82 (s, 3H, OC*H*$_3$); 4.32-4.45 (m, 1H, P-C*H*); 6.34-7.33 (AB system, J_{AB} = 16.2 Hz, 2H, C*H*=C*H*); 7.08-7.93 (m, 18H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.3 (d, $^1J_{CP}$ = 69.9 Hz, P-*C*H); 43.4 (s, P-CH-*C*H$_2$); 55.1 (s, OCH$_3$); 55.4 (s, OCH$_3$); 143.3 (s, O=C-*C*H=CH); 158.6 (s, CH$_3$O−*C*H); 161.7 (s, CH$_3$O−*C*H); 196.7 (d, $^3J_{CP}$ = 13.4 Hz, *C*=O); Ar-*C* and O=C-CH=*C*H): δ = 113.75, 114.40, 123.95, 126.82, 127.67, 127.99, 128.14, 128.36, 128.72, 128.83, 128.98, 130.07, 130.38, 130.68, 130.78, 130.98, 131.03, 131.17, 131.34, 131.93, 132.22, 132.47, 142.69; IR (neat): $\nu_{P=O}$ = 1200 cm^{-1}; $\nu_{C=C}$ = 1608 cm^{-1}; $\nu_{C=O}$ = 1696 cm^{-1}; EI-HRMS: calculated for $C_{31}H_{29}O_4P$, 496.1803 (M^+); found: 496.1772.

General procedure for the synthesis of 3-phosphonoethylpyrazolines 3a-j

A mixture of γ-keto-δ-alkenyl-phosphonate or phosphine oxide **2** (0.01 mol), hydrazine derivative (0.011 mol) and dry $CHCl_3$ (30 mL), was heated under reflux for 24 h. The reaction mixture was then concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using a mixture of Et_2O and hexane 7:3 as an eluent.

*3-[2-(Diphenylphosphoryl)-2-phenylethyl]-5-phenyl-4,5-dihydro-1H-pyrazole (**3a**)*. White solid; mp 148-150 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 33.1 (s, maj); 33.2 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.12-3.19 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-NH); 3.97-4.18 (m, 1H, P-C*H*); 4.37-4.45 (m, 1H, C*H*-NH); 4.82 (br s, 1H, N*H*); 6.80-8.02 (m, 20H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 30.2 (s, P-CH-*C*H$_2$); 44.3 (d, $^1J_{CP}$ = 61.1 Hz, P-*C*H, maj); 44.4 (d, $^1J_{CP}$ = 46.8 Hz, P-*C*H, min); 44.7 (s, *C*H$_2$-CH-NH); 57.6 (s, CH$_2$-*C*H-NH, min); 63.5 (s, CH$_2$-*C*H-NH, maj); 152.4 (d, $^3J_{CP}$ = 9.8 Hz, *C*=N, min); 152.6 (d, $^3J_{CP}$ = 9.8 Hz, *C*=N, maj); Ar-*C*: δ = 125.44, 125.84, 125.95, 126.98, 127.30, 127.89, 128.04, 128.17, 128.38, 128.51, 128.71, 128.79, 128.86, 129.18, 129.50, 129.69, 129.84, 129.91, 130.54, 130.82, 130.94, 131.00, 131.18, 131.30, 131.87, 132.07, 135.16, 135.42, 135.49, 142.76, 142.84, 143.37; IR (neat): $\nu_{P=O}$ = 1183 cm^{-1}; ν_{NH} = 3400 cm^{-1}; $\nu_{C=N}$ = 1605 cm^{-1}; EI-HRMS: calculated for $C_{29}H_{27}N_2OP$, 450.1861 (M^+); found: 450.1850.

*3-[2-(Diphenylphosphoryl)-2-(thiophen-2-yl)ethyl]-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole (**3b**)*. Light brown solid; mp 166-168 °C; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 32.3 (s, maj); 32.5 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.19-2.9 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-NH); 3.35 (br s, 1H,

N*H*, maj); 4.12-4.27 (m, 1H, P-C*H*, maj); 4.29-4.37 (m, 1H, P-C*H*, min); 4.61-4.69 (m, 1H, C*H*-NH, min); 4.79-4.98 (m, 1H, C*H*-NH, maj); 5.65 (br s, 1H, N*H*, min); 6.54-7.87 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 31.7 (s, P-CH-*C*H_2, min); 36.5 (s, P-CH-*C*H_2, maj); 39.9 (d, $^1J_{CP}$ = 68.7 Hz, P-*C*H, maj); 40.3 (d, $^1J_{CP}$ = 61.1 Hz, P-*C*H, min); 44.6 (s, *C*H_2-CH-NH, maj); 44.7 (s, *C*H_2-CH-NH, min); 59.3 (s, CH_2-*C*H-NH, min); 61.3 (s, CH_2-*C*H-NH, maj); 152.8 (d, $^3J_{CP}$ = 7.5 Hz, *C*=N, maj); 152.9 (d, $^3J_{CP}$ = 4.5 Hz, *C*=N, min); Ar-*C*: δ = 124.07, 124.11, 124.21, 124.30, 124.34, 124.40, 124.83, 124.87, 124.90, 124.94, 125.32, 126.70, 126.78, 127.60, 127.68, 127.78, 128.10, 128.26, 128.83, 128.98, 130.37, 131.02, 131.14, 131.29, 131.40, 131.66, 132.11, 137.18, 145.70, 145.78, 145.95, 146.07, 146.12; IR (neat): $\nu_{P=O}$ = 1165 cm^{-1}; ν_{NH} = 3405 cm^{-1}; $\nu_{C=N}$ = 1593 cm^{-1}; EI-HRMS: calculated for $C_{25}H_{23}N_2OPS_2$, 462.0989 (M^+); found: 462.1058.

*Diethyl 1-phenyl-2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)ethylphosphonate (**3c**).* White oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 27.3 (s, maj); 27.4 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.74-1.42 (m, 6H, C*H*$_3$-CH_2); 2.24-3.09 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-NH); 3.12-3.61 (m, 1H, P-C*H*); 3.68-4.06 (m, 4H, 2 C*H*$_2$O); 4.37-4.51 (m, 1H, C*H*-NH); 5.56 (br s, 1H, N*H*); 6.81-7.55 (m, 10H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.2 (d, $^3J_{CP}$ = 7.0 Hz, *C*H_3-CH_2); 15.4 (d, $^3J_{CP}$ = 4.5 Hz, *C*H_3-CH_2); 35.7 (s, P-CH-*C*H_2, min); 38.7 (s, P-CH-*C*H_2, maj); 39.9 (d, $^1J_{CP}$ = 146.4 Hz, P-*C*H, maj); 41.4 (d, $^1J_{CP}$ = 138.1 Hz, P-*C*H, min); 43.2 (s, *C*H_2-CH-NH); 61.0 (d, $^2J_{CP}$ = 7.0 Hz, *C*H_2O, min); 61.5 (d, $^2J_{CP}$ = 6.0 Hz, *C*H_2O, maj); 61.8 (d, $^2J_{CP}$ = 7.0 Hz, *C*H_2O, min); 62.5 (d, $^2J_{CP}$ = 6.0 Hz, *C*H_2O, maj); 63.1 (s, CH_2-*C*H-NH, min); 63.3 (s, CH_2-*C*H-NH, maj); 152.1 (d, $^3J_{CP}$ = 7.8 Hz, *C*=N, min); 152.2 (d, $^3J_{CP}$ = 6.2 Hz, *C*=N, maj); Ar-*C*: δ = 124.27, 124.44, 124.94, 125.01, 125.69, 126.03, 126.37, 126.41, 127.18, 127.45, 127.48, 127.60, 127.64, 127.98, 128.29, 128.37, 128.45, 134.01, 134.68, 135.11; IR (neat): $\nu_{P=O}$ = 1170 cm^{-1}; ν_{NH} = 3305 cm^{-1}; $\nu_{C=N}$ = 1628 cm^{-1}; EI-HRMS: calculated for $C_{21}H_{27}N_2O_3P$, 386.1759 (M^+); found: 386.1772.

*3-[2-(Diphenylphosphoryl)-2-phenylethyl]-1,5-diphenyl-4,5-dihydro-1H-pyrazole (**3d**).* Dark brown solid; mp 118-120 °C; ^{31}P NMR: δ = 32.9 (s, maj); 33.1 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.57-3.69 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-N-C_6H_5); 3.92-4.18 (m, 1H, P-C*H*, min); 4.21-4.33 (m, 1H, P-C*H*, maj); 4.68-4.79 (m, 1H, C*H*-N-C_6H_5); 6.61-8.11 (m, 25H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 32.6 (s, P-CH-*C*H_2, maj); 36.8 (s, P-CH-*C*H_2, min); 41.2 (d, $^1J_{CP}$ = 78.3 Hz, P-*C*H, min); 42.4 (d, $^1J_{CP}$ = 67.3 Hz, P-*C*H, maj); 43.1 (s, *C*H_2-CH-N-C_6H_5, min); 44.9 (s, *C*H_2-CH-N-C_6H_5, maj); 64.3 (s, CH_2-*C*H-N-C_6H_5, maj); 64.5 (s, CH_2-*C*H-N-C_6H_5, min); 148.6 (d, $^3J_{CP}$ = 7.2 Hz, *C*=N, maj); 150.3 (d, $^3J_{CP}$ = 6.0 Hz, *C*=N, min); Ar-*C*: δ = 119.41, 125.02, 125.66, 126.89, 126.93, 127.15, 127.22, 127.80, 127.83, 127.89, 127.94, 127.98, 128.05, 128.09, 128.14, 128.20, 128.46, 128.63, 128.69, 128.74, 128.84, 128.88, 128.98, 129.06, 129.14, 129.23, 129.31, 129.44, 129.51, 129.80, 129.87, 129.91, 129.96, 130.76, 130.82, 130.88, 130.94,

130.99, 131.02, 131.13, 131.22, 131.25, 131.30, 131.37, 131.41, 131.57, 131.68, 131.92; 132.11; 132.15; 142.28; 145.47; IR (neat): $\nu_{P=O}$ = 1167 cm^{-1}; $\nu_{C=N}$ = 1630 cm^{-1}; EI-HRMS: calculated for $C_{35}H_{31}N_2OP$, 526.2174 (M^+); found: 526.2117.

*3-[2-(Diphenylphosphoryl)-2-(furan-2-yl)ethyl]-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole (**3e**).* Brown solid; mp 130-132 °C; ^{31}P NMR: δ = 32.5 (s, maj); 32.9 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.51-3.47 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-NH); 3.61 (br s, 1H, N*H*); 3.97-4.38 (m, 1H, P-C*H*, maj); 4.62-4.90 (m, 1H, P-C*H*, min); 5.24-5.81 (m, 1H, C*H*-NH); 6.62-7.93 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 36.2 (s, P-CH-*C*H$_2$, maj); 37.1 (s, P-CH-*C*H$_2$, min); 41.6 (d, $^1J_{CP}$ = 72.6 Hz, P-*C*H, min); 42.8 (d, $^1J_{CP}$ = 52.3 Hz, P-*C*H, maj); 43.5 (s, HN-CH-*C*H$_2$, maj); 44.1 (s, HN-CH-*C*H$_2$, min); 53.9 (s, HN-*C*H-CH$_2$, min); 61.9 (s, HN-*C*H-CH$_2$, maj); 154.1 (d, $^3J_{CP}$ = 9.0 Hz, *C*=N); Ar-*C*: δ = 123.65, 124.53, 124.88, 125.11, 125.14, 126.57, 126.77, 126.88, 127.13, 127.21, 127.68, 127.76, 128.10, 128.12, 128.26, 128.28, 128.31, 128.40, 128.43, 128.50, 128.59, 128.83, 128.85, 128.88, 128.98, 129.04, 129.77, 129.98, 130.96, 131.11, 131.25, 131.28, 131.32, 131.37, 131.39, 131.50, 131.73, 131.92, 132.08, 132.17, 135.09, 135.44; IR (neat): $\nu_{P=O}$ = 1230 cm^{-1}; ν_{NH} = 3320 cm^{-1}; $\nu_{C=N}$ = 1634 cm^{-1}; EI-HRMS: calculated for $C_{25}H_{23}N_2O_3P$, 430.1446 (M^+); found: 430.1401.

*3-[2-(Diphenylphosphoryl)-2-(4-methoxyphenyl)ethyl]-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3f**).* Brown solid; mp 100-102 °C; ^{31}P NMR: δ = 33.6 (s, maj); 33.8 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.38-3.81 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-N-C_6H_5); 3.57 (s, 3H, OC*H*$_3$, min); 3.59 (s, 3H, OC*H*$_3$, min); 3.60 (s, 3H, OC*H*$_3$, maj); 3.64 (s, 3H, OC*H*$_3$, maj); 4.19-4.48 (m, 1H, P-C*H*); 4.54-4.76 (m, 1H, C*H*-N-C_6H_5); 6.57-7.98 (m, 23H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 29.6 (s, P-CH-*C*H$_2$, min); 35.9 (s, P-CH-*C*H$_2$, maj); 39.1 (d, $^1J_{CP}$ = 78.7 Hz, P-*C*H, maj); 40.3 (d, $^1J_{CP}$ = 70.0 Hz, P-*C*H, min); 42.4 (s, *C*H$_2$-CH-N-C_6H_5, min); 45.6 (s, *C*H$_2$-CH-N-C_6H_5, maj); 53.8 (s, O*C*H$_3$, min); 53.9 (s, O*C*H$_3$, maj); 54.0 (s, O*C*H$_3$, min); 54.1 (s, O*C*H$_3$, maj); 56.2 (s, CH$_2$-*C*H-N-C_6H_5, maj); 62.7 (s, CH$_2$-*C*H-N-C_6H_5, min); 157.5 (d, $^3J_{CP}$ = 9.8 Hz, *C*=N); 157.8 (s, *C*-OCH$_3$); 172.4 (s, *C*-OCH$_3$); Ar-*C*: δ = 111.80, 111.92, 111.99, 112.05, 112.21, 112.26, 112.32, 112.45, 112.55, 112.70, 113.09, 113.20, 117.48, 117.55, 118.41, 124.17, 125.87, 125.92, 126.20, 126.73, 127.04, 127.08, 127.19, 127.30, 127.53, 127.71, 127.77, 127.82, 127.88, 127.92, 128.85, 129.23, 129.53, 129.61, 129.84, 129.90, 129.96, 130.03, 130.09, 130.14, 130.34, 130.45, 130.99, 131.16, 133.43, 133.54, 133.83, 134.78, 144.54, 144.76, 144.96; IR (neat): $\nu_{P=O}$ = 1207 cm^{-1}; $\nu_{C=N}$ = 1632 cm^{-1}; EI-HRMS: calculated for $C_{37}H_{35}N_2O_3P$, 586.2385 (M^+); found: 586.2331.

*Dimethyl 2-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-1-phenylethylphosphonate (**3g**).* Yellow oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 29.1 (s, maj); 29.6 (s, min); ^{1}H NMR ($CDCl_3$, 300 MHz): δ =

2.68-3.46 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-N-C$_6$H$_5$); 3.49-3.52 (m, 6H, 2 C*H*$_3$O); 3.56-3.69 (m, 1H, P-C*H*); 4.18-4.45 (m, 1H, C*H*-N-C$_6$H$_5$); 6.92-7.45 (m, 15H, arom-*H*); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 36.1 (s, P-CH-*C*H$_2$, min); 36.3 (s, P-CH-*C*H$_2$, maj); 42.7 (d, $^1J_{CP}$ = 157.7 Hz, P-*C*H); 44.2 (s, *C*H$_2$-CH-N-C$_6$H$_5$); 53.5 (d, $^2J_{CP}$ = 6.5 Hz, *C*H$_3$O); 53.6 (d, $^2J_{CP}$ = 6.5 Hz, *C*H$_3$O); 63.8 (s, CH$_2$-*C*H-N-C$_6$H$_5$); 149.6 (d, $^3J_{CP}$ = 7.3 Hz, *C*=N); Ar-*C*: δ = 112.63, 112.94, 113.09, 113.18, 113.25, 118.58, 118.61, 119.25, 121.60, 128.33, 128.78, 128.94, 129.15, 129.45, 132.64, 136.63, 142.47, 142.84, 144.11, 145.57; IR (neat): $\nu_{P=O}$ = 1197 cm^{-1}; $\nu_{C=N}$ = 1622 cm^{-1}; EI-HRMS: calculated for $C_{25}H_{27}N_2O_3P$, 434.1759 (M^+); found: 434.1695.

*Dimethyl 1-phenyl-2-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)ethylphosphonate (**3h**).* Yellow oil; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ (ppm) = 29.7 (s, min); 29.9 (s, maj); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.07-2.85 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-NH); 2.90-3.16 (m, 1H, P-C*H*); 3.14-3.71 (m, 6H, 2 C*H*$_3$O); 4.27-4.56 (m, 1H, C*H*-NH); 5.43 (br s, 1H, N*H*); 6.82-7.38 (m, 10H, arom-*H*); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 35.6 (s, P-CH-*C*H$_2$, maj); 38.5 (s, P-CH-*C*H$_2$, min); 39.4 (d, $^1J_{CP}$ = 104.1 Hz, P-*C*H, min); 40.7 (d, $^1J_{CP}$ = 165.3 Hz, P-*C*H, maj); 42.1 (s, *C*H$_2$-CH-NH, min); 42.8 (s, *C*H$_2$-CH-NH, maj); 52.5 (d, $^2J_{CP}$ = 6.3 Hz, *C*H$_3$O); 52.8 (d, $^2J_{CP}$ = 6.3 Hz, *C*H$_3$O); 62.3 (s, CH$_2$-*C*H-NH, min); 62.7 (s, CH$_2$-*C*H-NH, maj); 151.0 (d, $^3J_{CP}$ = 14.3 Hz, *C*=N, min); 151.2 (d, $^3J_{CP}$ = 13.6 Hz, *C*=N, maj); Ar-*C*: δ = 124.93, 125.01, 125.44, 125.58, 126.45, 126.55, 126.70, 127.10, 127.32, 127.59, 127.62, 127.66, 127.80, 127.86, 128.19, 128.27, 128.36, 132.17, 141.76; IR (neat): $\nu_{P=O}$ = 1200 cm^{-1}; ν_{NH} = 3408 cm^{-1}, $\nu_{C=N}$ = 1618 cm^{-1}; EI-HRMS: calculated for $C_{19}H_{23}N_2O_3P$, 358.1446 (M^+); found: 358.1433.

*Dimethyl 2-(1-methyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1-phenylethylphosphonate (**3i**).* Brown oil; ^{31}P NMR (CDCl$_3$, 121.5 MHz): δ (ppm) = 29.3 (s, min); 29.7 (s, maj); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.09-2.96 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-N-CH$_3$); 2.94 (s, 3H, N-C*H*$_3$); 3.46-3.64 (m, 6H, 2 C*H*$_3$O); 3.53-3.55 (m, 1H, P-C*H*); 3.90-4.06 (m, 1H, C*H*-N-CH$_3$); 6.63-7.97 (m, 10H, arom-*H*); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 36.2 (s, N-*C*H$_3$); 36.6 (s, P-CH-*C*H$_2$, min); 38.2 (s, P-CH-*C*H$_2$, maj); 41.0 (d, $^1J_{CP}$ = 146.4 Hz, P-*C*H); 45.5 (s, *C*H$_2$-CH-N-CH$_3$, maj); 45.6 (s, *C*H$_2$-CH-N-CH$_3$, min); 52.2 (d, $^2J_{CP}$ = 6.8 Hz, O*C*H$_3$, min); 52.5 (d, $^2J_{CP}$ = 6.8 Hz, O*C*H$_3$, maj); 53.4 (d, $^2J_{CP}$ = 7.3 Hz, O*C*H$_3$, maj); 53.8 (d, $^2J_{CP}$ = 7.3 Hz, O*C*H$_3$, min); 66.7 (s, CH$_2$-*C*H-N-CH$_3$, min); 68.0 (s, CH$_2$-*C*H-N-CH$_3$, maj); 150.8 (d, $^3J_{CP}$ = 14.3 Hz, C=N, maj); 152.2 (d, $^3J_{CP}$ = 14.3 Hz, C=N, min); Ar-*C*: δ = 125.17, 126.26, 126.83, 127.30, 127.65, 128.13, 128.40, 128.60, 128.80, 129.09, 129.28, 129.56, 129.64, 130.06, 132.53, 140.07, 142.87, 143.09, IR (neat): $\nu_{P=O}$ = 1192 cm^{-1}; $\nu_{C=N}$ = 1616 cm^{-1}; EI-HRMS: calculated for $C_{20}H_{25}N_2O_3P$, 372.1603 (M^+); found: 372.1606.

3-*[2-Diphenylphosphoryl]-2-(thiophen-2-yl)ethyl]-1-methyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole* ***(3j)***. Light brown oil; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 32.1 (s, min); 32.4 (s, maj); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09-3.05 (m, 4H, P-CH-C*H*$_2$ and C*H*$_2$-CH-N-CH$_3$); 2.91 (s, 3H, N-C*H*$_3$, min); 2.98 (s, 3H, N-C*H*$_3$, maj); 3.75-3.83 (m, 1H, P-C*H*, maj); 3.96-4.06 (m, 1H, P-C*H*, min); 4.15-4.23 (m, 1H, C*H*-N-CH$_3$, min); 4.27-4.37 (m, 1H, C*H*-N-CH$_3$, maj); 6.55-7.92 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 36.1 (s, P-CH-*C*H$_2$, min); 36.5 (s, P-CH-*C*H$_2$, maj); 37.9 (s, N-*C*H$_3$); 39.4 (d, $^{1}J_{CP}$ = 68.7 Hz, P-*C*H, min); 41.1 (d, $^{1}J_{CP}$ = 71.7 Hz, P-*C*H, maj); 44.0 (s, *C*H$_2$-CH-N-CH$_3$, maj); 44.2 (s, *C*H$_2$-CH-N-CH$_3$, min); 68.8 (s, CH$_2$-*C*H-N-CH$_3$, min); 68.9 (s, CH$_2$-*C*H-N-CH$_3$, maj); 151.7 (d, $^{3}J_{CP}$ = 14.3 Hz, *C*=N, maj); 152.1 (d, $^{3}J_{CP}$ = 14.3 Hz, *C*=N, min); Ar-*C*: δ = 120.38, 124.41, 124.82, 124.90, 125.05, 125.09, 125.48, 125.52, 125.61, 126.60, 126.64, 126.75, 126.89, 126.92, 127.15, 127.19, 127.27, 127.40, 127.54, 127.62, 127.71, 128.12, 128.23, 128.28, 128.39, 128.70, 128.84, 128.99, 130.39, 130.90, 131.00, 131.08, 131.23, 131.30, 131.46, 131.66, 132.09, 132.12, 132.45, 137.02, 137.11, 142.86, 143.70; IR (neat): $\nu_{P=O}$ = 1171 cm^{-1}; $\nu_{C=N}$ = 1596 cm^{-1}; EI-HRMS: calculated for $C_{26}H_{25}N_2OPS_2$, 476.1146 (M^+); found: 476.1138.

General procedure for the synthesis of 3-phosphonoethylpyrazoles 4a-d

A mixture of 3-phosphonoethylpyrazoline **3** (1 mmol), sodium nitrite (1.1 mmol) and dry $CHCl_3$ (10 mL), was heated under reflux for 6 h. After cooling, the reaction mixture was washed with water (2 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using Et_2O as an eluent.

Diethyl (1-phenyl-2-(5-phenyl-1H-pyrazol-3-yl)ethyl)phosphonate ***(4a)***. White solid; mp 140-142 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 27.6; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (t, 3H, $^{3}J_{HH}$ = 5.5 Hz C*H*$_3$-CH$_2$); 1.35 (t, 3H, $^{3}J_{HH}$ = 5.1 Hz C*H*$_3$-CH$_2$); 2.28-2.88 (m, 2H, P-CH-C*H*$_2$); 3.09-3.41 (m, 1H, P-C*H*); 3.65-3.99 (m, 4H, 2 C*H*$_2$O); 5.61 (br s, 1H, N*H*); 6.12 (s, 1H, C*H*=C-NH); 6.83-7.90 (m, 10H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.1 (d, $^{3}J_{CP}$ = 7.0 Hz, *C*H$_3$-CH$_2$); 15.3 (d, $^{3}J_{CP}$ = 5.5 Hz, *C*H$_3$-CH$_2$); 35.9 (s, P-CH-*C*H$_2$); 41.2 (d, $^{1}J_{CP}$ = 139.0 Hz, P-*C*H); 61.0 (d, $^{2}J_{CP}$ = 7.0 Hz, *C*H$_2$O); 61.5 (d, $^{2}J_{CP}$ = 7.0 Hz, *C*H$_2$O); 100.1 (s, *C*H=C-NH); 142.1 (s, CH=*C*-NH); 150.8 (s, *C*=N); Ar-*C*: 125.93, 126.01, 126.57, 127.32, 128.45, 128.70, 129.28, 135.23, 135.44; IR (Neat): $\nu_{P=O}$ = 1179 cm^{-1}; ν_{NH} = 3355 cm^{-1}; $\nu_{C=N}$ = 1613 cm^{-1}; EI-HRMS: calculated for $C_{21}H_{27}N_2O_3P$, 384.1603 (M^+); found: 384.1601.

Dimethyl (2-(1-methyl-5-phenyl-1H-pyrazol-3-yl)-1-phenylethyl)phosphonate ***(4b)***. Brown oil; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 29.8; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.42-2.73 (m, 2H, P-CH-C*H*$_2$); 3.37 (s, 3H, N-C*H*$_3$); 3.48 (d, 3H, $^{3}J_{PH}$ = 8.7 Hz, C*H*$_3$O); 3.35 (d, 3H, $^{3}J_{PH}$ = 7.1 Hz, C*H*$_3$O); 3.53-3.55 (m,

1H, P-C*H*); 6.02 (s, 1H, C*H*=C-N-Me); 6.46-7.74 (m, 10H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 31.1 (s, P-CH-*C*H_2); 37.1 (s, N-*C*H_3); 42.1 (d, $^1J_{CP}$ = 137.7 Hz, P-*C*H); 52.1 (d, $^2J_{CP}$ = 7.1 Hz, O*C*H_3); 53.6 (d, $^2J_{CP}$ = 7.1 Hz, O*C*H_3); 102.4 (s, *C*H=C-NH); 143.8 (s, CH=*C*-N-Me); 149.8 (s, *C*=N); Ar-*C*: δ = 125.60, 126.48, 127.56, 128.30, 128.53, 129.17, 129.47, 132.75; 133.39; IR (Neat): $\nu_{P=O}$ = 1199 cm^{-1}; $\nu_{C=N}$ = 1612 cm^{-1}; EI-HRMS: calculated for $C_{20}H_{23}N_2O_3P$, 370.1446 (M^+); found: 370.1410.

*Diphenyl-(1-phenyl-2-(5-phenyl-1H-pyrazol-3-yl)ethyl)phosphine oxide (**4c**)*. White solid; mp 108-110 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 33.6; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.91-3.16 (m, 2H, P-CH-C*H*$_2$); 3.85-4.06 (m, 1H, P-C*H*); 5.95 (s, 1H, C*H*=C-NH); 6.40-7.92 (m, 20H, arom-*H*); 6.99 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 28.5 (s, P-CH-*C*H_2); 40.0 (d, $^1J_{CP}$ = 68.7 Hz, P-*C*H); 101.1 (s, *C*H=C-NH); 142.5 (s, CH=*C*-NH); 144.4 (s, *C*=N); Ar-*C*: δ = 124.46, 126.08, 126.47, 126.91, 127.07, 127.22, 127.48, 127.60, 127.75, 127.87, 128.44, 128.51, 128.73, 128.80, 129.77, 129.83, 129.94, 130.06, 130.17, 130.28, 130.71, 130.93; IR (neat): $\nu_{P=O}$ = 1191 cm^{-1}; ν_{NH} = 3388 cm^{-1}; $\nu_{C=N}$ = 1601 cm^{-1}; EI-HRMS: calculated for $C_{29}H_{25}N_2OP$, 448.1704 (M^+); found: 448.1653.

*Diphenyl-(2-(1-methyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-1-(thiophen-2-yl)ethyl)phosphine oxide (**4d**)*. Dark green oil; ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ (ppm) = 31.8; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.88-3.17 (m, 2H, P-CH-C*H*$_2$); 3.37 (s, 3H, N-C*H*$_3$); 3.94-4.11 (m, 1H, P-C*H*); 5.95 (s, 1H, C*H*=C-N-Me); 6.72-7.84 (m, 16H, arom-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 32.0 (s, P-CH-*C*H_2); 38.0 (s, N-*C*H_3); 40.4 (d, $^1J_{CP}$ = 68.2 Hz, P-*C*H); 102.2 (s, *C*H=C-NH); 142.8 (s, CH=*C*-N-Me); 143.7 (s, *C*=N); Ar-*C*: δ = 120.79, 124.93, 125.08, 125.61, 126.55, 126.68, 127.12, 127.48, 127.60, 127.70, 128.12, 128.23, 128.97, 130.26, 130.90, 131.73, 132.08, 136.84, 137.11, 138.0; IR (neat): $\nu_{P=O}$ = 1188 cm^{-1}; $\nu_{C=N}$ = 1592 cm^{-1}; EI-HRMS: calculated for $C_{26}H_{23}N_2OPS2$, 474.0989 (M^+); found: 474.0965.

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