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PREPARATION OF β-KETO-β-ALKANOYLOXYPHOSPHONATES, PHOSPHINE OXIDES AND SULFIDES AND THEIR APPLICATION TO THE SYNTHESIS OF NOVEL PHOSPHORYL- AND THIOPHOSPHORYLPYRAZOLES

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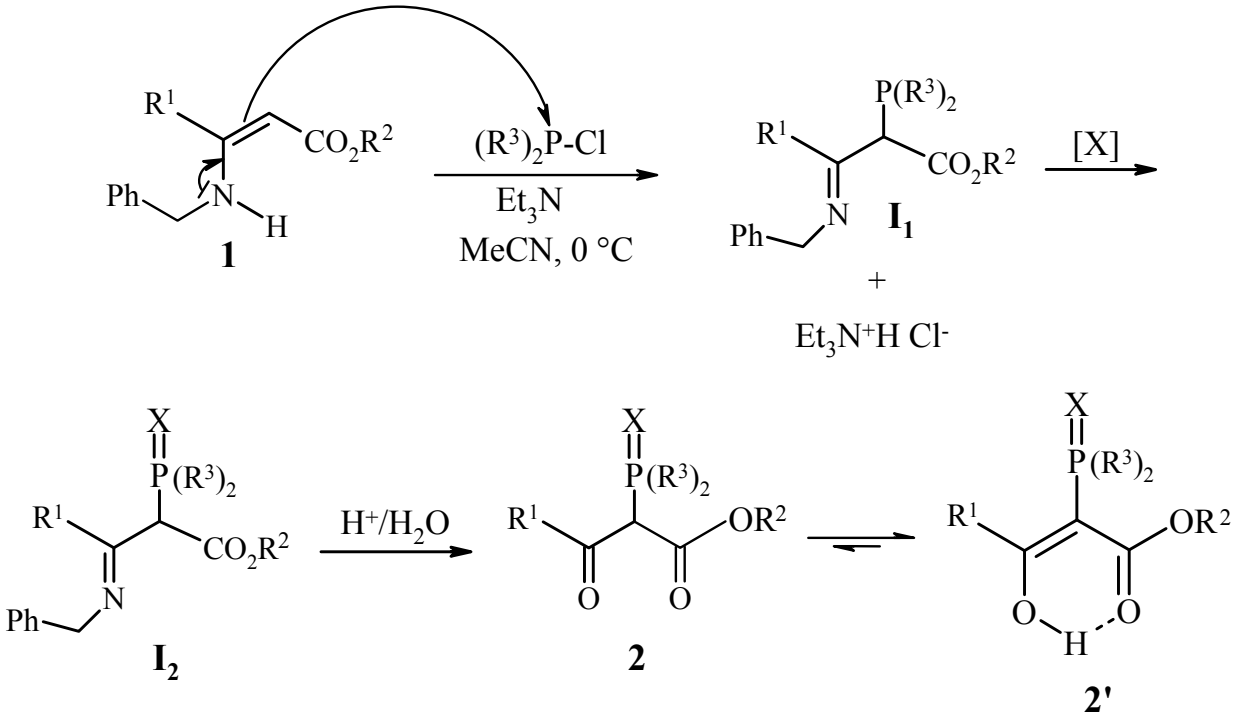
Abstract – Two synthetic methods leading to β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides **2** are reported. The first method involves the reaction of β-enaminoesters **1** with chlorophosphines and phosphites followed by oxidation or sulfurization and hydrolytic work-up. The second one utilizes the reaction of β-enaminoesters **1** with diethylchlorophosphate and thiophosphate followed by acid hydrolysis. On reaction with hydrazine derivatives, compounds **2** give the corresponding phosphoryl- and thiophosphorylpyrazoles **3**. The structures of all obtained products were confirmed by NMR (^{1}H, ^{31}P, ^{13}C) and IR spectroscopies, and by mass spectrometry.

In connection with our work on the applications of multifunctional phosphonates in heterocyclic synthesis[1-3] and pursuing our studies on the reactivity of imines and enamines with phosphorus electrophiles,[4-6] we have investigated, for the first time, the behaviour of β-enaminoesters towards chloro-phosphines, phosphates and thiophosphates, in order to obtain novel types of β-dicarbonyl compounds bearing a phosphoryl or a thiophosphoryl group. Furthermore, and in order to explore the potential of these multifunctional phosphonates and thiophosphonates in heterocyclic synthesis, we show here that their reaction with hydrazine derivatives leads to a new class of phosphoryl- and thiophosphorylpyrazoles. Our interest for these compounds is due to the well known interesting biological properties of pyrazole derivatives including anticancer,[7,8] antimicrobial,[9,10] antiviral[11] and antiinflammatory[12,13] activities. Some

of these compounds are also known for their applications in agrochemistry as herbicide[14] fungicide[15] and insecticide[16] agents.

In the first part of this work, we focused our efforts to develop new strategies for the synthesis of novel β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides. To access these compounds, we have used two different approaches. The first one (Method A) involves the reaction of β-enaminoesters **1**[17] with chlorophosphines and phosphites followed by oxidation or sulfurization and hydrolytic work-up. Experimentally, treatment of β-enaminoesters **1** with chlorophosphines and phosphites, performed in acetonitrile, at 0 °C, in the presence of an equimolar amount of triethylamine, led to the formation of the phosphine intermediate $\mathbf{I_1}$ (Scheme 1). A subsequent oxidation or sulfurization carried out, in a one pot reaction, by treating respectively with dimethyl sulfoxide (DMSO) under reflux or with elemental sulfur at 40 °C, led to the phosphorus (IV) intermediate $\mathbf{I_2}$ which, by acid hydrolysis, furnished the β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides **2** in equilibrium with their tautomeric enol forms **2'**.

The scope of the reaction was assessed with a range of substrates (Table 1) including a variety of β-enaminoesters and phosphorus (III) derivatives. All the substrates reacted in good to high yields.



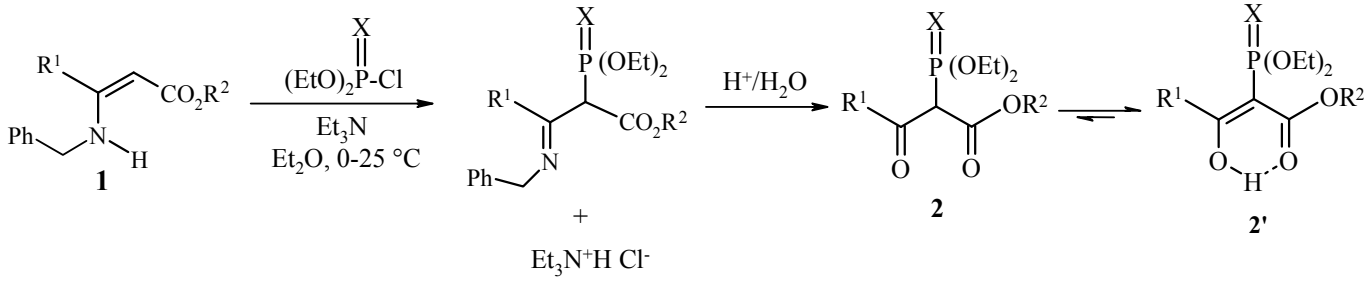
Scheme 1. Synthesis of compounds **2** (Method A)

Table 1. Substrate scope for the synthesis of compounds **2** (Method A)

Entry	R^1	R^2	R^3	X	Product	% **2**/**2'**[a]	δ ^{31}P(**2**)[b,c]	δ ^{31}P(**2'**)[b,c]	Yield (%)[d]
1	Me	Et	Ph	S	**2a** ⇌ **2'a**	19/81	71.8	71.2	84
2	Ph	Et	Ph	S	**2b** ⇌ **2'b**	11/89	71.9	71.8	76
3	Ph	Et	Ph	O	**2c** ⇌ **2'c**	35/65	27.7	21.5	71
4	Et	Me	Ph	S	**2d** ⇌ **2'd**	49/51	71.3	71.9	88
5	Me	Et	OEt	S	**2e** ⇌ **2'e**	37/63	71.4	68.2	91

[a] Determined from the ^{31}P NMR spectra.
[b] 121.5 MHz, $CDCl_3$.
[c] δ in ppm.
[d] Isolated yield

The second method (Method B) that we developed to access compounds **2** involved the reaction of β-enaminoesters **1** with diethylchlorophosphate and thiophosphate followed by acid hydrolysis. It was found that, similar to the reaction of chlorophosphines and phosphites, chlorophosphates and thiophosphates can also react with β-enaminoesters **1** in the presence of an equimolar amount of triethylamine and using diethyl ether as solvent, to afford, after acid hydrolysis, the β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides **2** in equilibrium with their tautomeric enol forms **2'** (Scheme 2). A variety of compounds **2** were obtained in good yield, by applying this strategy (Table 2).



Scheme 2. Synthesis of compounds **2** (Method B)

Table 2. Substrate scope for the synthesis of compounds **2** (Method B)

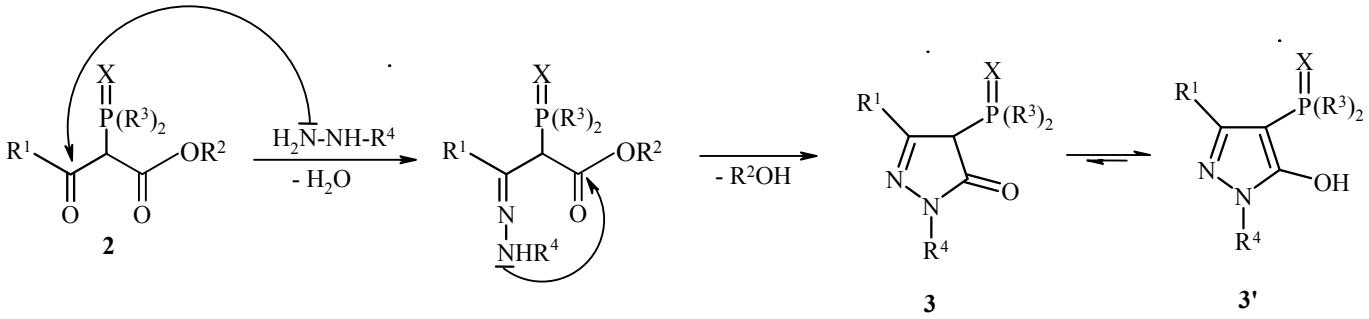
Entry	R^1	R^2	X	Product	% **2**/**2'**[a]	δ ^{31}P(**2**)[b,c]	δ ^{31}P(**2'**)[b,c]	Yield (%)[d]
1	Me	Et	S	**2e** ⇌ **2'e**	37/63	71.4	68.2	89
2	Ph	Et	S	**2f** ⇌ **2'f**	47/53	71.4	68.4	94
3	Et	Me	O	**2g** ⇌ **2'g**	26/74	21.7	16.2	72
4	Et	Me	S	**2h** ⇌ **2'h**	39/61	71.5	68.3	81

[a] Determined from the ^{31}P NMR spectra.
[b] 121.5 MHz, $CDCl_3$.
[c] δ in ppm.
[d] Isolated yield

Compounds **2** were characterized on the basis of their Infrared, NMR (^{31}P, ^{1}H, ^{13}C) and mass spectral data, which indicate that they are obtained as a tautomeric mixture of the keto and enol forms **2** and **2'**. The relative proportions of these tautomers were estimated from the ^{31}P NMR spectra where a singlet for each one is present (Tables 1 and 2). The enol form **2'** was found to be dominant probably due to conjugation and intramolecular hydrogen bonding. Indeed the infrared spectra of the synthesized compounds showed a broad band centred around 3370 cm^{-1} being characteristic of the associated O–H vibrations. This band did not disappear on dilution which confirmed the existence of an intramolecular hydrogen bond.

Being multifunctional compounds with two electrophilic centers in 1,3-positions, β-keto-β-alkanoyloxy-phosphonates, phosphine oxides and sulfides **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 phosphoryl or thiophosphoryl groups,[18] we report here our results on the reaction of compounds **2** with hydrazines which lead to a new class of phosphoryl- and thiophosphorylpyrazoles. 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 phosphoryl- and thiophosphorylpyrazoles **3** in good yields (Scheme 3). These compounds were isolated as a tautomeric mixture of the keto and enol forms **3** and **3'** as evidenced by their Infrared and NMR (^{31}P, ^{1}H, ^{13}C) spectral data. The relative proportions of these tautomers were estimated from the ^{31}P NMR

spectra where a singlet for each one is present (Tables 3). The enol form **3'** was found to be dominant probably due to aromaticity and O-H···X=P intramolecular hydrogen bonding.



Scheme 3. Synthesis of phosphoryl- and thiophosphorylpyrazoles **3**

Table 3. Substrate scope for the synthesis of compounds **3**

Entry	R^1	R^3	R^4	X	Product	% **3**/**3'**[a]	δ ^{31}P(**3**)[b,c]	δ ^{31}P(**3'**)[b,c]	Yield (%)[d]
1	Et	Ph	H	S	**3a** ⇌ **3'a**	35/65	60.9	57.2	84
2	Me	OEt	H	S	**3b** ⇌ **3'b**	24/76	62.3	64.4	86
3	Et	OEt	H	S	**3c** ⇌ **3'c**	40/60	71.3	72.6	81
4	Et	OEt	Ph	S	**3d** ⇌ **3'd**	40/60	80.1	72.0	79
5	Me	Ph	H	O	**3e** ⇌ **3'e**	29/71	20.5	20.9	90

[a] Determined from the ^{31}P NMR spectra.
[b] 121.5 MHz, $CDCl_3$.
[c] δ in ppm.
[d] Isolated yield

In summary, we successfully developed two efficient one-pot methodologies for the synthesis of β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides, which use easily made β-enaminoesters and commercially available chlorophosphines, phosphates and thiophosphates as starting materials. The obtained multifunctional phosphonates and thiophosphonates were used as efficient precursors for the straightforward preparation of novel phosphoryl- and thiophosphorylpyrazoles. Other applications of β-keto-β-alkanoyloxyphosphonates, phosphine oxides and sulfides 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-300 spectrometer. 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. 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 60 (Fluka).

General procedure for the synthesis of β-keto-β-alkanoyloxyphosphonates, phosphineoxides and sulfides 2 (Method A). To a mixture of β-enaminoester **1** (0.01 mol), triethylamine (0.012 mol) and dry MeCN (50 mL), cooled at 0 °C and maintained under a nitrogen atmosphere, was added dropwise with stirring, a solution of chlorophosphine or phosphite (0.01 mol) in dry MeCN (30 mL). Stirring at 0 °C was continued for 1 h. The reaction mixture was then treated with DMSO or sulfur as follows:

- Oxidation: DMSO (0.01 mol) was added and the mixture was heated under reflux for 2 h. After cooling, 6 M aqueous HCl solution (30 mL) was added dropwise and stirring was continued at room temperature for 12 h. The mixture was then 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 ether as eluent.

- Sulfurization: Sulfur (0.01 mol) was added and the mixture was heated at 40 °C for 30 min. After cooling, 6 M aqueous HCl solution (30 mL) was added dropwise and stirring was continued at room temperature for 12 h. The mixture was then 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 ether as eluent.

General procedure for the synthesis of β-keto-β-alkanoyloxyphosphonates, phosphineoxides and sulfides 2 (Method B). To a mixture of β-enaminoester **1** (0.01 mol), triethylamine (0.012 mol) and dry Et_2O (50 mL), cooled at 0 °C and maintained under a nitrogen atmosphere, was added dropwise with stirring, a solution of diethylchlorophosphate or thiophosphate (0.01 mol) in dry Et_2O (10 mL). Stirring was continued for 24 h at 25 °C. Then a 6 M aqueous HCl solution (30 mL) was added dropwise and stirring was continued at room temperature for an additional 12 h. The organic phase was washed with water (25 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue obtained was chromatographed on silica gel column using ether as eluent.

2a ⇌ 2'a : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2a**: δ = 1.18 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 1.75 (s, 3H, CH$_3$-C=O); 4.32 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH$_3$-C<u>H</u>$_2$-O); 4.77 (d, 1H, $^2J_{PH}$ = 24.0 Hz, CH-P); 7.03-8.28 (m, 10H, arom-H); **2'a**: δ = 1.07 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 2.14 (s, 3H, CH$_3$-C=C); 4.04 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH$_3$-C<u>H</u>$_2$-O); 7.03-8.28 (m, 10H, arom-H); 10.15 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2a**: δ = 18.6 (s, <u>C</u>H$_3$-CH$_2$-O); 30.7 (s, <u>C</u>H$_3$-C=O); 48.2 (d, $^1J_{CP}$ = 90.6 Hz, CH-P); 58.1 (s, CH$_3$-<u>C</u>H$_2$-O); 173.9 (s; O-C=O); 199.5 (s, CH$_3$-<u>C</u>=O); **2'a**: δ = 12.5 (s, <u>C</u>H$_3$-CH$_2$-O); 28.6 (s, <u>C</u>H$_3$-C=C); 59.7 (s, CH$_3$-<u>C</u>H$_2$-O); 99.3 (d, $^1J_{CP}$ = 118.5 Hz, P-<u>C</u>=C-O); 165.7 (s; O-C=O); 175.6 (s, C=<u>C</u>-OH); phenyl carbons (for **2a** and **2'a**): δ = 112.7, 115.6, 123.4, 124.3, 126.7, 127.1, 129.3, 129.5, 129.6, 129.8, 130.3, 136.1, 138.7, 139.9, 142.5, 145.1; IR (neat): $\nu_{P=S}$ = 698 cm^{-1}; $\nu_{C=O}$ (ketone) = 1642 cm^{-1}; $\nu_{C=O}$ (ester) = 1745 cm^{-1}; ν_{OH} = 3370 cm^{-1}; EI-HRMS: calculated for $C_{18}H_{19}O_3PS$, 346.0792 (M^+); found: 346.0793.

2b ⇌ 2'b : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2b** : δ = 1.27 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 3.44 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH$_3$-C<u>H</u>$_2$-O); 5.70 (d, 1H, $^2J_{PH}$ = 27.0 Hz, CH-P); 7.17-7.92 (m, 15H, arom-H); **2'b**: δ = 1.19 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 4.14 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH$_3$-C<u>H</u>$_2$-O); 7.17-7.92 (m, 15H, arom-H); 9.90 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2b** : δ = 7.0 (s, <u>C</u>H$_3$-CH$_2$-O); 42.8 (d, $^1J_{CP}$ = 129.0 Hz, CH-P); 64.1 (s, CH$_3$-<u>C</u>H$_2$-O); 169.8 (s; O-C=O); 191.1 (s, Ph-<u>C</u>=O); **2'b**: δ = 12.4 (s, <u>C</u>H$_3$-CH$_2$-O); 59.8 (s, CH$_3$-<u>C</u>H$_2$-O); 125.6 (d, $^1J_{CP}$ = 90.3 Hz, P-<u>C</u>=C-O); 166.0 (s, O-C=O); 171.6 (s, C=<u>C</u>-OH); phenyl carbons (for **2b** and **2'b**): δ = 124.4, 125.7, 126.7, 126.7, 126.9, 127.0, 127.6, 129.2, 127.6, 129.1, 129.6, 129.7, 129.9, 130.3, 131.6, 132.1, 134.3, 134.4, 134.6, 135.4, 136.0, 136.1, 138.6, 139.9; IR (neat): $\nu_{P=S}$ = 696 cm^{-1}; $\nu_{C=O}$ (ketone) = 1694 cm^{-1}; $\nu_{C=O}$ (ester) = 1748 cm^{-1}; ν_{OH} = 3384 cm^{-1}; EI-HRMS: calculated for $C_{23}H_{21}O_3PS$, 408.0949 (M^+); found: 408.0955.

2c ⇌ 2'c : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2c**: δ = 0.91 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 4.06-4.22 (m, 3H, CH$_3$-C<u>H</u>$_2$-O and CH-P); 7.13-8.77 (m, 15H, arom-H); **2'c** : δ = 1.17 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-O); 3.81 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH$_3$-C<u>H</u>$_2$-O); 7.13-8.77 (m, 15H, arom-H); 10.75 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2c**: δ = 7.1 (s, <u>C</u>H$_3$-CH$_2$-O); 41.5 (d, $^1J_{CP}$ = 80.0 Hz, CH-P); 59.7 (s, CH$_3$-<u>C</u>H$_2$-O); 169.8 (s, O-C=O); 191.1 (s, Ph-<u>C</u>=O); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2'c**: δ = 12.5 (s, <u>C</u>H$_3$-CH$_2$-O); 44.3 (s, CH$_3$-<u>C</u>H$_2$-O); 99.8 (d, $^1J_{CP}$ = 91.5 Hz, P-<u>C</u>=C-O); 166.0 (s; O-C=O); 171.6 (s, C=<u>C</u>-OH); phenyl carbons (for **2c** and **2'c**): δ = 124.4, 125.1, 125.4, 125.8, 125.9, 126.2, 126.5, 126.8, 127.0, 127.2, 127.5, 127.7, 128.1, 128.7, 129.6, 129.8, 130.6, 131.1, 131.4, 131.6, 132.2, 133.0, 135.2, 136.4; IR (neat): $\nu_{P=O}$ = 1217 cm^{-1}; $\nu_{C=O}$ (ketone) = 1690 cm^{-1}; $\nu_{C=O}$ (ester) = 1745 cm^{-1}; ν_{OH} = 3370 cm^{-1}; EI-HRMS: calculated for $C_{23}H_{21}O_4P$, 392.1177 (M^+); found: 392.1172.

2d ⇌ 2'd : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2d**: δ = 0.91 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH_2); 3.06 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$); 3.36 (s, 3H, C<u>H</u>$_3$-O); 4.49 (d, 1H, $^2J_{PH}$ = 15.0 Hz, CH-P); 7.03-7.87 (m, 10H, arom-H); **2'd**: δ = 1.00 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH_2); 2.83 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$); 3.54 (s, 3H, CH_3-O); 7.03-7.87 (m, 10H, arom-H); 10.52 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2d**: δ = 6.9 (s, <u>C</u>H$_3$-CH_2); 23.6 (s, CH_3-<u>C</u>H$_2$); 34.6 (s, <u>C</u>H$_3$-O); 45.9 (d, $^1J_{CP}$ = 118.0 Hz, CH-P); 172.5 (s; O-C=O); 207.1 (s, CH_2-<u>C</u>=O); **2'd**: δ = 10.0 (s, <u>C</u>H$_3$-CH_2); 19.5 (s, CH_3-<u>C</u>H$_2$); 24.6 (s, CH_3-O); 101.5 (d, $^1J_{CP}$ = 92.0 Hz, P-<u>C</u>=C-O); 173.8 (s; O-C=O); 179.6 (s, C=<u>C</u>-OH); phenyl carbons (for **2d** and **2'd**): δ = 124.1, 124.8, 125.9, 126.3, 127.0, 127.2, 129.0, 129.1, 129.4, 129.8, 130.0, 130.8, 130.9, 131.1, 131.6, 131.8; IR (neat): $\nu_{P=S}$ = 697 cm^{-1}; $\nu_{C=O}$ (ketone) = 1693 cm^{-1}; $\nu_{C=O}$ (ester) = 1747 cm^{-1}; ν_{OH} = 3368 cm^{-1}; EI-HRMS: calculated for $C_{18}H_{19}O_3PS$, 346.0792 (M^+); found: 346.0784.

2e ⇌ 2'e : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2e**: δ = 1.13-1.30 (m, 9H, C<u>H</u>$_3$-CH_2-O-C and C<u>H</u>$_3$-CH_2-O-P); 2.02 (s, 3H, CH_3-C=O); 3.86-4.21 (m, 6H, CH_3-C<u>H</u>$_2$-O-C and CH_3-C<u>H</u>$_2$-O-P); 4.82 (d, 1H, $^2J_{PH}$ = 27.0 Hz, CH-P); **2'e**: δ = 1.13-1.30 (m, 9H, C<u>H</u>$_3$-CH_2-O-C and C<u>H</u>$_3$-CH_2-O-P); 2.02 (s, 3H, C<u>H</u>$_3$-C=C); 3.86-4.21 (m, 6H, CH_3-C<u>H</u>$_2$-O-C and CH_3-C<u>H</u>$_2$-O-P); 10.63 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2e**: δ = 8.7 (s, <u>C</u>H$_3$-CH_2-O-C); 15.5 (d, $^3J_{CP}$ = 7.5 Hz, <u>C</u>H$_3$-CH_2-O-P); 30.8 (s, <u>C</u>H$_3$-C=O); 48.3 (d, $^1J_{CP}$ = 159.2 Hz, CH-P); 59.8 (s, CH_3-<u>C</u>H$_2$-O-C); 62.7 (d, $^2J_{CP}$ = 5.3 Hz, CH_3-<u>C</u>H$_2$-O-P); 175.3 (s, O-C=O); 200.5 (s, CH_3-<u>C</u>=O); **2'e**: δ = 14.0 (s, <u>C</u>H$_3$-CH_2-O-C); 15.8 (d, $^3J_{CP}$ = 8.3 Hz, <u>C</u>H$_3$-CH_2-O-P); 30.0 (s, <u>C</u>H$_3$-C=C); 61.1 (s, CH_3-<u>C</u>H$_2$-O-C); 66.1 (d, $^2J_{CP}$ = 7.5 Hz, CH_3-<u>C</u>H$_2$-O-P); 100.6 (d, $^1J_{CP}$ = 92.0 Hz, P-<u>C</u>=C-O); 173.7 (s; O-C=O); 177.3 (s, C=<u>C</u>-OH); IR (neat): $\nu_{P=S}$ = 706 cm^{-1}; $\nu_{C=O}$ (ketone) = 1690 cm^{-1}; $\nu_{C=O}$ (ester) = 1742 cm^{-1}; ν_{OH} = 3320 cm^{-1}; EI-HRMS: calculated for $C_{10}H_{19}O_5PS$, 282.0691 (M^+); found: 282.0693.

2f ⇌ 2'f : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2f**: δ = 1.13-1.28 (m, 9H, C<u>H</u>$_3$-CH_2-O-C and C<u>H</u>$_3$-CH_2-O-P); 3.87-4.19 (m, 7H, CH_3-C<u>H</u>$_2$-O-C, CH_3-C<u>H</u>$_2$-O-P and CH-P); 7.20-7.85 (m, 5H, arom-H); **2'f**: δ = 1.13-1.28 (m, 9H, C<u>H</u>$_3$-CH_2-O-C and C<u>H</u>$_3$-CH_2-O-P); 3.87-4.19 (m, 6H, CH_3-C<u>H</u>$_2$-O-C and CH_3-C<u>H</u>$_2$-O-P); 7.20-7.85 (m, 5H, arom-H); 12.55 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2f**: δ = 13.3 (s, <u>C</u>H$_3$-CH_2-O-C); 14.8 (d, $^3J_{CP}$ = 8.3 Hz, <u>C</u>H$_3$-CH_2-O-P); 59.8 (d, $^1J_{CP}$ = 80.0 Hz, CH-P); 60.2 (s, CH_3-<u>C</u>H$_2$-O-C); 61.8 (d, $^2J_{CP}$ = 5.3 Hz, CH_3-<u>C</u>H$_2$-O-P); 171.3 (s, O-C=O); 192.5 (s, Ph-<u>C</u>=O); **2'f**: δ = 13.0 (s, <u>C</u>H$_3$-CH_2-O-C); 14.6 (d, $^3J_{CP}$ = 9.1 Hz, <u>C</u>H$_3$-CH_2-O-P); 61.2 (s, CH_3-<u>C</u>H$_2$-O-C); 65.7 (d, $^2J_{CP}$ = 6.8 Hz, CH_3-<u>C</u>H$_2$-O-P); 126.0 (d, $^1J_{CP}$ = 117.0 Hz, P-<u>C</u>=C-O); 167.4 (s; O-C=O); 173.1 (s, C=<u>C</u>-OH); phenyl carbons (for **2f** and **2'f**): δ =127.0, 127.1, 128.1, 128.2, 129.2, 131.2, 133.0, 133.2; IR (neat): $\nu_{P=S}$ = 698 cm^{-1}; $\nu_{C=O}$ (ketone) = 1697 cm^{-1}; $\nu_{C=O}$ (ester) = 1750 cm^{-1}; ν_{OH} = 3380 cm^{-1}; EI-HRMS: calculated for $C_{15}H_{21}O_5PS$, 344.0847 (M^+); found: 344.0850.

2g ⇌ 2'g : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2g**: δ = 0.94-1.21 (m, 9H, C<u>H</u>$_3$-CH_2-C and C<u>H</u>$_3$-CH_2-O); 2.41 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$-C); 3.34 (s, 3H, CH_3-O); 3.88-3.98 (m, 4H, CH_3-C<u>H</u>$_2$-O); 4.84 (d, 1H, $^2J_{PH}$ = 24.0 Hz, CH-P); **2'g**: δ = 0.94-1.21 (m, 9H, C<u>H</u>$_3$-CH_2-C and C<u>H</u>$_3$-CH_2-O); 3.08 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$-C); 3.59 (s, 3H, CH_3-O); 3.88-3.98 (m, 4H, CH_3-C<u>H</u>$_2$-O); 11.41 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2g**: δ = 7.9 (s, <u>C</u>H_3-CH_2-C); 15.9 (d, $^3J_{CP}$ = 6.8 Hz, <u>C</u>H_3-CH_2-O); 21.3 (s, CH_3-<u>C</u>H_2-C); 47.4 (d, $^1J_{CP}$ = 165.9 Hz, CH-P); 50.7 (s, CH_3-O); 61.0 (d, $^2J_{CP}$ = 6.1 Hz, CH_3-<u>C</u>H_2-O); 167.6 (s, O-C=O); 208.7 (s, CH_2-<u>C</u>=O); **2'g**: δ = 8.6 (s, <u>C</u>H_3-CH_2-C); 11.6 (d, $^3J_{CP}$ = 6.0 Hz, <u>C</u>H_3-CH_2-O); 52.1 (s, CH_3-O); 63.4 (d, $^2J_{CP}$ = 5.3 Hz, CH_3-<u>C</u>H_2-O); 128.0 (d, $^1J_{CP}$ = 113.2 Hz, P-<u>C</u>=C-O); 162.7 (s, O-C=O); 175.4 (s, C=<u>C</u>-OH); IR (neat): $\nu_{P=O}$ = 1217 cm^{-1}; $\nu_{C=O}$ (ketone) = 1695 cm^{-1}; $\nu_{C=O}$ (ester) = 1749 cm^{-1}; ν_{OH} = 3370 cm^{-1}; EI-HRMS: calculated for $C_{10}H_{19}O_6P$, 266.0919 (M^+); found: 266.0912.

2h ⇌ 2'h: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **2h**: δ = 0.88-1.28 (m, 9H, C<u>H</u>$_3$-CH_2-C and C<u>H</u>$_3$-CH_2-O); 2.40 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$-C); 3.34 (s, 3H, CH_3-O); 4.00 (d, 1H, $^2J_{PH}$ = 12.0 Hz, CH-P); 4.09-4.21 (m, 4H, CH_3-C<u>H</u>$_2$-O); **2'h**: δ = 0.88-1.28 (m, 9H, C<u>H</u>$_3$-CH_2-C and C<u>H</u>$_3$-CH_2-O); 3.06 (q, 2H; $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$-C); 3.34 (s, 3H, CH_3-O); 4.09-4.21 (m, 4H, CH_3-C<u>H</u>$_2$-O); 15.60 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **2h**: δ = 7.4 (s, <u>C</u>H_3-CH_2-C); 15.8 (d, $^3J_{CP}$ = 8.3 Hz, <u>C</u>H_3-CH_2-O); 26.3 (s, CH_3-<u>C</u>H_2-C); 48.5 (s, CH_3-O); 44.4 (d, $^1J_{CP}$ = 167.5 Hz, CH-P); 62.7 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-<u>C</u>H_2-O); 166.4 (s, O-C=O); 208.6 (s, CH_2-<u>C</u>=O); **2'h**: δ = 8.0 (s, <u>C</u>H_3-CH_2-C); 15.5 (d, $^3J_{CP}$ = 6.8 Hz, <u>C</u>H_3-CH_2-O); 49.1 (s, CH_3-O); 66.0 (d, $^2J_{CP}$ = 6.8 Hz, CH_3-<u>C</u>H_2-O); 127.6 (d, $^1J_{CP}$ = 107.9 Hz, P-<u>C</u>=C-O); 162.7 (s, O-C=O); 175.5 (s, C=<u>C</u>-OH); IR (neat): $\nu_{P=S}$ = 696 cm^{-1}; $\nu_{C=O}$ (ketone) = 1697 cm^{-1}; $\nu_{C=O}$ (ester) = 1750 cm^{-1}; ν_{OH} = 3380 cm^{-1}; EI-HRMS: calculated for $C_{10}H_{19}O_5PS$, 282.0691 (M^+); found: 282.0687.

General procedure for the synthesis of phosphoryl- and thiophosphorylpyrazoles 3. A mixture of β-keto-β-alkanoyloxyphosphonate, phosphine oxide or sulfide **2** (0.01 mol), hydrazine derivative (0.01 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 ether as eluent.

3a ⇌ 3'a: Yellow solid; mp 212-214 °C; ^{1}H NMR (300 MHz, $CDCl_3$): **3a**: δ = 1.28 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH_2); 3.33 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$); 5.23 (br s, 1H, NH); 5.85 (s, 1H, CH-P); 7.02-7.26 (m, 10H, arom-H); **3'a**: δ = 1.11 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C<u>H</u>$_3$-CH_2); 2.46 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C<u>H</u>$_2$); 5.23 (br s, 2H, NH and OH); 7.02-7.26 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): **3a**: δ = 10.9 (s, <u>C</u>H_3-CH_2); 23.6 (s, CH_3-<u>C</u>H_2); 45.8 (s, CH-P); 163.2 (s, C=N); 175.0 (s, C=O); **3'a**: δ = 11.9 (s, <u>C</u>H_3-CH_2); 26.1 (s, CH_3-<u>C</u>H_2); 101.5 (d, $^1J_{CP}$ = 51.3 Hz, HO-C=<u>C</u>-P); 154.9 (s, C=N); 173.9 (s, C=<u>C</u>-OH); phenyl carbons (for **3a** and **3'a**): δ = 125.8, 127.2, 127.4, 128.8, 137.1; IR (neat): $\nu_{P=S}$ = 698 cm^{-1}; $\nu_{C=O}$ = 1651 cm^{-1}; ν_{OH} = 3310 cm^{-1}; ν_{NH} = 3310 cm^{-1}; EI-HRMS: calculated for $C_{17}H_{17}N_2OPS$, 328.0799 (M^+);

found: 328.0796.

3b⇌3'b: Yellow solid; mp 156-158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): **3b** : δ = 1.28 (t, 6H, $^3J_{HH}$ = 6.0 Hz, C$\underline{H}_3$-CH_2-O); 2.16 (s, 3H, CH_3-C=N); 3.98-4.16 (m, 5H, CH_3-C$\underline{H}_2$-O and CH-P); 5.19 (br s, 1H, NH); **3'b** : δ = 1.28 (t, 6H, $^3J_{HH}$ = 6.0 Hz, C$\underline{H}_3$-CH_2-O); 2.39 (s, 3H, CH_3-C=N); 3.98-4.16 (m, 4H, CH_3-C$\underline{H}_2$-O); 5.81 (br s, 1H, NH); 6,52 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **3b** : δ = 15.8 (d, $^3J_{CP}$ = 8.2 Hz, $\underline{C}H_3$-CH_2-O); 20.7 (s, $\underline{C}H_3$-C=N); 46.2 (d, $^1J_{CP}$ = 89.8 Hz, CH-P=S); 62.9 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-$\underline{C}H_2$-O); 156.0 (s, C=N); 163.3 (s, C=O); **3'b** : δ = 15.8 (d, $^3J_{CP}$ = 8.2 Hz, $\underline{C}H_3$-CH_2-O); 20.7 (s, $\underline{C}H_3$-C=N); 63.8 (d, $^2J_{CP}$ = 5.3 Hz, CH_3-$\underline{C}H_2$-O); 102.8 (d, $^1J_{CP}$ = 110.2 Hz, HO-C=$\underline{C}$-P); 155.8 (s, C=N); 168.3 (s, C=$\underline{C}$-OH); IR (neat): $\nu_{P=S}$ = 712 cm^{-1}; $\nu_{C=O}$ = 1642 cm^{-1}; ν_{OH} = 3370 cm^{-1}; ν_{NH} = 3370 cm^{-1}; EI-HRMS: calculated for $C_8H_{15}N_2O_3PS$, 250.0541 (M^+); found: 250.0540.

3c⇌3'c : Yellow solid; mp 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): **3c** : δ = 0.97-1.23 (m, 9H, C$\underline{H}_3$-CH_2-C and C$\underline{H}_3$-CH_2-O); 3.06 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C$\underline{H}_2$-C); 3.78-4.02 (m, 5H, CH_3-C$\underline{H}_2$-O and CH-P); 5.12 (br s, 1H, NH); **3'c**: δ = 0.96-1.13 (m, 9H, C$\underline{H}_3$-CH_2-C and C$\underline{H}_3$-CH_2-O); 2.32 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C$\underline{H}_2$-C); 3.78-4.02 (m, 4H, CH_3-C$\underline{H}_2$-O); 5.12 (br s, 2H, NH and OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): **3c** : δ = 10.2 (s, $\underline{C}H_3$-CH_2-C); 15.7 (d, $^3J_{CP}$ = 4.5 Hz, $\underline{C}H_3$-CH_2-O); 44.5 (s, CH_3-$\underline{C}H_2$-C); 45.2 (d, $^1J_{CP}$ = 95.8 Hz, CH-P); 62.7 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-$\underline{C}H_2$-O); 152.9 (s, C=N); 168.0 (s, C=O); **3'c**: δ = 12.1 (s, $\underline{C}H_3$-CH_2-C); 15.7 (d, $^3J_{CP}$ = 4.5 Hz, $\underline{C}H_3$-CH_2-O); 44.5 (s, CH_3-$\underline{C}H_2$-C); 63.1 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-$\underline{C}H_2$-O); 101.7 (d, $^1J_{CP}$ = 98.1 Hz, HO-C=$\underline{C}$-P); 152.3 (s, C=N); 168.0 (s, C=$\underline{C}$-OH); IR (neat): $\nu_{P=S}$ = 701 cm^{-1}; $\nu_{C=O}$ = 1652 cm^{-1}; ν_{OH} = 3365 cm^{-1}; ν_{NH} = 3365 cm^{-1}; EI-HRMS: calculated for $C_9H_{17}N_2O_3PS$, 264.0697 (M^+); found: 264.0691.

3d⇌3'd: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **3d** : δ = 0.96-1.13 (m, 9H, C$\underline{H}_3$-CH_2-C and C$\underline{H}_3$-CH_2-O); 3.07 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C$\underline{H}_2$-C); 3.80-4.01 (m, 5H, CH_3-C$\underline{H}_2$-O and CH-P); 6.69-7.89 (m, 5H, arom-H); **3'd** : δ = 0.96-1.13 (m, 9H, C$\underline{H}_3$-CH_2-C and C$\underline{H}_3$-CH_2-O); 2.77 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3-C$\underline{H}_2$-C); 3.80-4.01 (m, 4H, CH_3-C$\underline{H}_2$-O); 5.09 (br s, 1H, OH); 6.69-7.89 (m, 5H, arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): **3d** : δ = 11.8 (s, $\underline{C}H_3$-CH_2-C); 15.3 (d, $^3J_{CP}$ = 8.3 Hz, $\underline{C}H_3$-CH_2-O); 26.6 (s, CH_3-$\underline{C}H_2$-C); 45.1 (d, $^1J_{CP}$ = 94,6 Hz, CH-P); 65.8 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-$\underline{C}H_2$-O); 154.7 (s, C=N); 170.3 (s, C=O); **3'd** : δ = 12.1 (s, $\underline{C}H_3$-CH_2-C); 15.7 (d, $^3J_{CP}$ = 7.5 Hz, $\underline{C}H_3$-CH_2-O); 25.8 (s, CH_3-$\underline{C}H_2$-C); 65.8 (d, $^2J_{CP}$ = 4.5 Hz, CH_3-$\underline{C}H_2$-O); 100.0 (d, $^1J_{CP}$ = 120.0 Hz, HO-C=$\underline{C}$-P); 152.4 (s, C=N); 163.2 (s, C=$\underline{C}$-OH) ; phenyl carbons (for **3d** and **3'd)**: δ = 128.1, 128.4, 129.4, 129.5, 130.0, 131.3, 133.2, 133.7; IR (neat): $\nu_{P=S}$ = 702 cm^{-1}; $\nu_{C=O}$ = 1670 cm^{-1}; ν_{OH} = 3442 cm^{-1}; EI-HRMS: calculated for $C_{15}H_{21}N_2O_3PS$, 340.1010 (M^+); found: 340.1018.

3e ⇌ **3'e** : Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): **3e**: δ = 2.37 (s, 3H, CH_3-C=N); 3.40 (d, 1H, $^2J_{PH}$ = 15.0 Hz, CH-P); 5.29 (br s, 1H, NH); 6.93-7.57 (m, 10H, arom-H); **3'e**: δ = 2.28 (s, 3H, CH_3-C=N); 5.29 (br s, 2H, NH and OH); 6.93-7.57 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): **3e**: δ = 20.9 (s, $\underline{C}H_3$-C=N); 45.3 (d, $^1J_{CP}$ = 91.6 Hz, CH-P=O); 148.7 (s, C=N); 163.0 (s, C=O); **3'e**: δ = 21.1 (s, $\underline{C}H_3$-C=N); 103.8 (d, $^1J_{CP}$ = 98.1 Hz, HO-C=$\underline{C}$-P); 147.0 (s, C=N); 164.1 (s, C=$\underline{C}$-OH); phenyl carbons (for **3e** and **3'e)**: δ = 124.8, 125.9, 126.3, 128.6, 129.7, 131.8, 133.0, 134.8; IR (neat): $\nu_{P=O}$ = 1212 cm^{-1}; $\nu_{C=O}$ = 1644 cm^{-1}; ν_{OH} = 3354 cm^{-1}; ν_{NH} = 3354 cm^{-1}; EI-HRMS: calculated for $C_{16}H_{15}N_2O_2P$, 298.0871 (M^+); found: 298.0869.

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REFERENCES AND NOTES

1. E. Chebil, M. Chamakhi, and S. Touil, *J. Sulfur Chem.*, 2011, **32**, 249.
2. S. Touil and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.,* 1998, **134**, 493.
3. S. Touil and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.,* 1997, **131**, 183.
4. H. Slimani and S. Touil, *Phosphorus, Sulfur and Silicon Relat. Elem.*, 2011, **186**, 1655.
5. H. Slimani and S. Touil, *Tetrahedron Lett.*, 2011, **52**, 6481.
6. S. Touil and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.*, 2001, **175**, 183.
7. P.-C. Lv, H.-Q. Li, J. Sun, Y. Zhou, and H.-L. Zhu, *Bioorg. Med. Chem*., 2010, **18**, 4606.
8. R. Lin, G. Chiu, Y. Yu, P. J. Connolly, S. Li, Y. Lu, M. Adams, A. R. Fuentes-Pesquera, S. L. Emanuel, and L. M. Greenberger, *Bioorg. Med. Chem. Lett*., 2007, **17**, 4557.
9. R. Sridhar, P. J. Perumal, S. Etti, G. Shanmugam, M. N. Ponnuswamy, V. R. Prabavathy, and N. Mathivanan, *Bioorg. Med. Chem. Lett*., 2004, **14**, 6035.
10. S. Bondock, W. Fadaly, and M. A. Metwally, *Eur. J. Med. Chem*., 2010, **45**, 3692.
11. O. I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, P. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini, and A. A. Rashad, *Eur. J. Med. Chem*., 2009, **44**, 3746.
12. A. A. Bekhit, H. M. A. Ashour, Y. S. Abdel Ghany, A. D. A. Bekhit, and A. Baraka, *Eur. J. Med. Chem*., 2008, **43**, 456.
13. A. Burguete, E. Pontiki, D. Hadjipavlou-Litina, R. Villar, E. Vicente, B. Solano, S. Ancizu, S. Perez-Silanes, I. Aldanaa, and A. Monge, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6439.
14. H. J. Ma, Y. H. Li, Q. F. Zhao, T. Zhang, R. L. Xie, X. D. Mei, and J. Ning, *J. Agric. Food Chem*., 2010, **58**, 4356.
15. C. Y. Zhang, X. H. Liu, B. L. Wang, S. H. Wang, and Z. M. Li, *Chem. Biol. Drug Des*., 2010, **75**, 489.

16. R. Ohno, M. Nagaoka, K. Hirai, A. Uchida, S. Kochi, O. Yamada, and J. Tokumura, *J. Pestic. Sci.,* 2010, **35**, 15.

17. The starting β-enaminoesters **1** were prepared according to reported procedures: H. M. C. Ferraz, E. O. Oliveira, M. E. Payret-Arrua, and C. A. Brandt, *J. Org. Chem*., 1995, **60**, 7357; S. Gogoi, R. Bhuyan, and N. C. Barua, *Synth. Commun*., 2005, **35**, 2811.

18. E. Chebil and S. Touil, *Lett. Org. Chem.*, 2012, **9**, 320; L. Ben Gaied, S. Touil, and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.,* 2006, **181**, 601; N. Said, S. Touil, and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.,* 2004, **179**, 2487; S. Touil and H. Zantour, *Phosphorus, Sulfur and Silicon Relat. Elem.,* 2003, **178**, 353.