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REACTION OF LAWESSON'S REAGENT WITH γ -PHOSPHONYL- OXIMES: SYNTHESIS OF NOVEL 1,2,5-OXAZAPHOSPHOLINE DERIVATIVES

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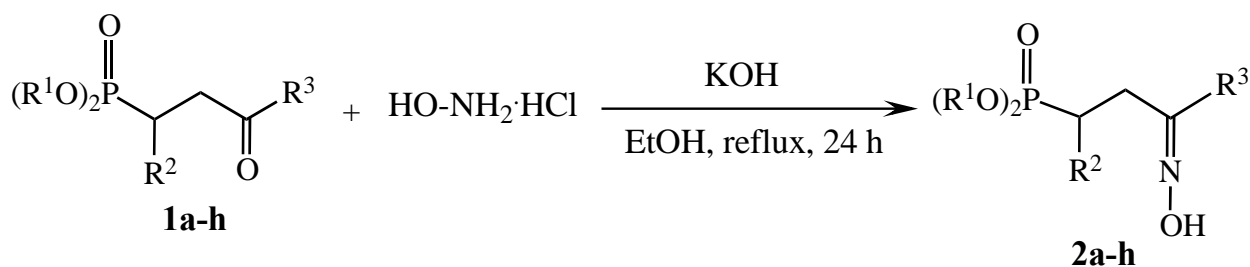
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Abstract – The reaction of γ -phosphonyloximes with Lawesson's reagent leads to a variety of new 1,2,5-oxazaphospholine derivatives. The reaction shows complete regioselectivity and gives a mixture of two diastereoisomers. The steric factors influencing the regioselectivity of the reaction are discussed and a mechanism accounting for the formation of the new compounds is proposed.

The use of 2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide [Lawesson's reagent (LR)] in heterocyclic synthesis has been well documented.¹⁻³ One of its important applications involves the synthesis of five-membered phosphorus-containing heterocycles by reaction with hydrazones and oximes.⁴⁻⁷ In this area, we have previously shown that phosphoryl- and esterhydrazones react with LR to give 1,2,3-diazaphospholine or pyrazole derivatives.⁸⁻¹⁰ We report, in the present investigation, the extension of this reaction to γ -phosphonyloximes. Our main objective here was to study the reactivity of carbons at the α and α' positions relative to the C=N double bond, and to access a variety of novel 1,2,5-oxazaphospholine derivatives, substituted in positions 3 or 4 by an ethyl- or a methylthiophosphoryl group.

We shall note here that oxazaphospholine derivatives are known for their useful biological properties ranging from antifungal to antibacterial activities.⁷

The starting γ -ketophosphonates **1a-h** were easily prepared according to reported procedures.^{11,12} It was found that reaction of these compounds with hydroxylamine hydrochloride, performed in refluxing ethanol, for 24 h, in the presence of an equimolar amount of potassium hydroxide, led to γ -phosphonyloximes **2a-h** (Scheme 1). The isolated yield of the reaction ranges from 56 to 92% (Table 1).



Scheme 1. Synthesis of γ -phosphonyloximes **2**

Compounds **2a-h** were characterized on the basis of their IR, NMR (^1H , ^{31}P , ^{13}C) and mass spectral data, which indicate that they are obtained as a mixture of *Z* and *E* isomers. Their relative proportions were estimated from the ^{31}P NMR spectra where a singlet for each isomer is present (Table 1). The *Z* and *E* configurations were attributed on the basis of the ^{13}C chemical shifts of carbons in α position with respect to the $\text{C}=\text{N}$ double bond. Indeed, according to some literature data¹³⁻¹⁶ concerning the stereochemistry of imines, hydrazones and oximes, the carbon adjacent to the $\text{C}=\text{N}$ double bond resonates at higher field if it is in *syn* position to the group on the nitrogen atom (OH in our case).

Table 1. Substrate scope for the synthesis of compounds **2**

Entry	R ¹	R ²	R ³	Product	Yield ^a (%)	$\delta^{31}\text{P}$ (<i>Z</i>) ^{b,c}	$\delta^{31}\text{P}$ (<i>E</i>)	% <i>Z</i> ^d	% <i>E</i> ^d
1	Et		Me	2a	92	25.1	25.8	30	70
2	Et		Me	2b	84	26.0	25.8	36	64
3	Et	Ph	Me	2c	84	27.9	28.1	31	69
4	Et	Ph	Ph	2d	71	28.3	28.1	23	77
5	Me		Me	2e	83	27.8	27.3	32	68
6	Me		Me	2f	58	28.6	28.8	42	58
7	Me	Ph	Me	2g	56	29.3	30.5	34	66
8	Me	Ph	Ph	2h	77	29.9	30.1	44	56

^a Isolated yield.

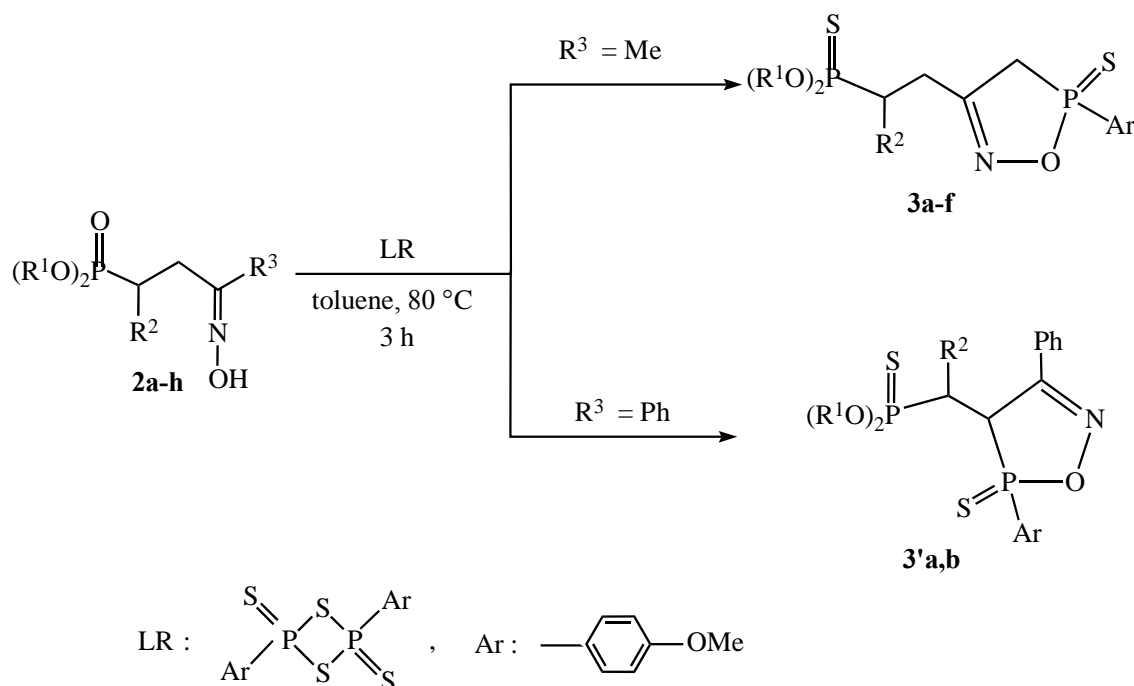
^b 121.5 MHz, CDCl_3 .

^c δ in ppm.

^d Determined from the ^{31}P NMR spectra.

With these oxime derivatives in hand, we next focused our efforts to investigate their behaviour towards Lawesson's reagent. Thus, treatment of compounds **2a-h** with an equimolar amount of LR, performed in toluene, at 80 °C, for 3 h, led according to the nature of substituent R³ in α position with respect to the $\text{C}=\text{N}$ double bond, either to the 3-(thiophosphonoethyl)-1,2,5-oxazaphospholines **3a-f** (R³ = Me), or to the

4-(thiophosphonomethyl)-1,2,5-oxazaphospholines **3'a,b** ($R^3 = \text{Ph}$) (Scheme 2). These compounds were obtained as a mixture of two unseparable diastereoisomers in an approximate 3:2 ratio and good yields (Table 2).



Scheme 2. Synthesis of 1,2,5-oxazaphospholines **3** and **3'**

Table 2. Substrate scope for the synthesis of compounds **3** and **3'**

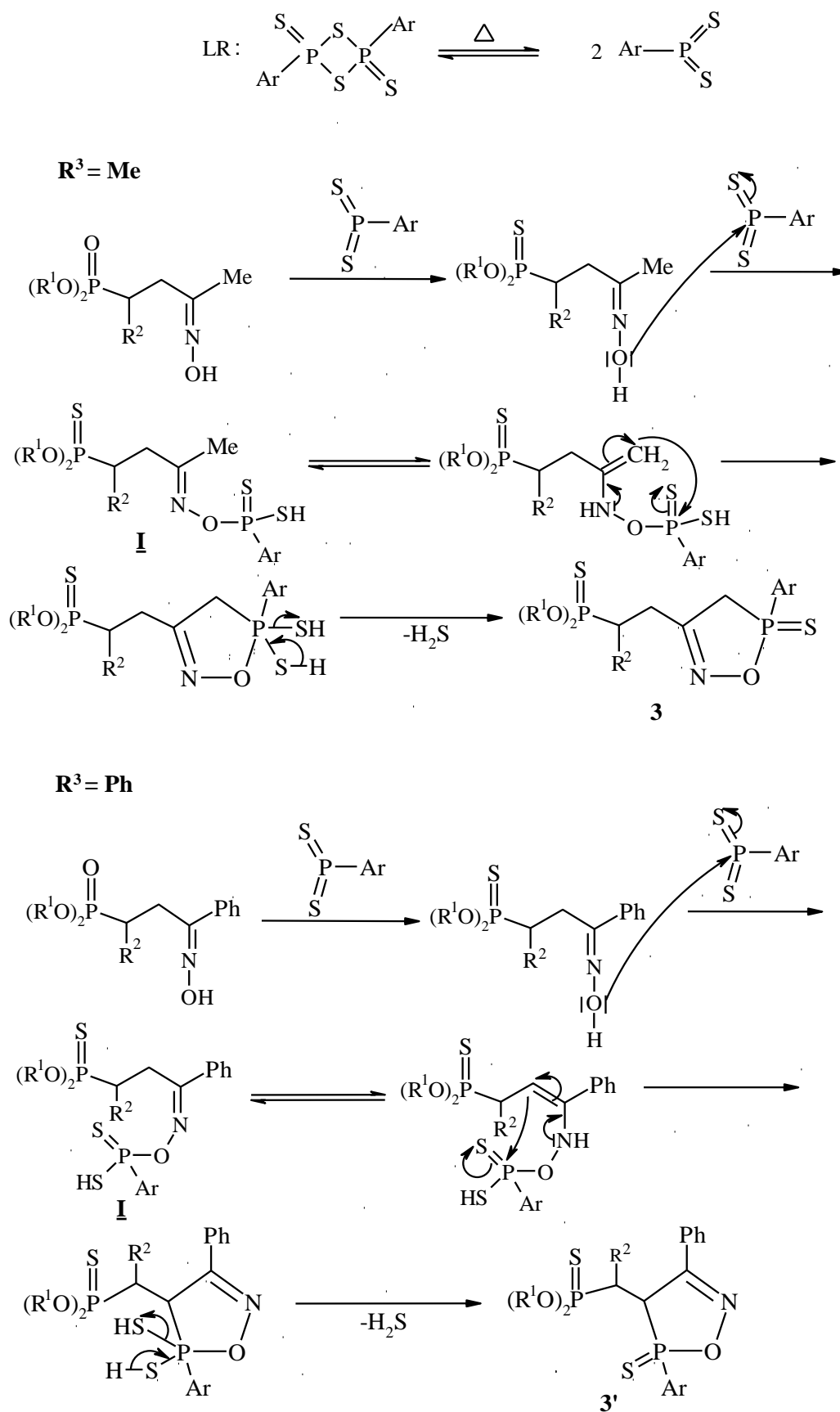
Entry	R ¹	R ²	R ³	Product	Yield ^a (%)	$\delta^{31}\text{P}_{\text{maj}}$ ^{b,c}	$\delta^{31}\text{P}_{\text{min}}$	% (maj/min) ^d
1	Et		Me	3a	83	89.6, 91.4	89.5, 90.2	62/38
2	Et		Me	3b	79	79.8, 80.7	79.5, 80.5	51/49
3	Et	Ph	Me	3c	86	89.7, 91.5	89.6, 90.3	58/42
4	Me		Me	3d	77	93.7, 97.1	91.0, 95.9	53/47
5	Me		Me	3e	68	83.4, 97.6	83.0, 96.9	56/44
6	Me	Ph	Me	3f	74	91.0, 95.8	90.7, 94.0	75/25
7	Et	Ph	Ph	3'a	81	89.6, 91.4	89.4, 90.2	66/34
8	Me	Ph	Ph	3'b	73	94.9, 97.2	94.2, 95.4	56/44

^a Isolated yield.

^b 121.5 MHz, CDCl₃.

^c δ in ppm.

^d Determined from the ³¹P NMR spectra.



Scheme 3. Proposed mechanism for the synthesis of compounds **3** and **3'**

A plausible mechanism for the formation of compounds **3** and **3'** is depicted in Scheme 3. It is believed that the reaction begins with a thionation of the phosphoryl group. Subsequent nucleophilic attack by the oxygen of the oxime group on the second monomer of LR, leads to intermediate **I**. This undergoes intramolecular cyclization, through its enamine tautomer, via a second nucleophilic attack at the phosphorus atom, by one of the carbons at the α or α' positions relative to the C=N double bond.

The orientation of the reaction towards the formation of oxazaphospholines **3** or **3'** depends essentially on the reactivity of carbons at the α and α' positions relative to the C=N double bond. Indeed, for γ -phosphonyloximes having a -CH₂-C(=N-OH)-Me moiety, where a mixture of **3** and **3'** regioisomers is possible, the reaction was found to be completely regioselective and took place exclusively on the side of the methyl group, thereby providing the least substituted oxazaphospholine **3** (Scheme 2). These results strongly suggest that the reaction is subject to steric control and takes place mainly at the less hindered α -carbon relative to the C=N double bond, which corresponds to the most reactive enamine form.

In conclusion, a simple and efficient methodology has been developed for the synthesis of novel 1,2,5-oxazaphospholine derivatives, from easily made γ -phosphonyloximes and commercially available Lawesson's reagent. Further studies on the bioactivity of the synthesized compounds are currently under way in our laboratory.

EXPERIMENTAL

¹H, ³¹P and ¹³C NMR spectra were recorded with CDCl₃ as the solvent, on a Bruker AC-300 spectrometer operating at 300.1MHz for ¹H, 121.5MHz for ³¹P and 75.5MHz for ¹³C. The chemical shifts are reported in ppm relative to TMS (internal reference) for ¹H and ¹³C NMR and relative to 85% H₃PO₄ (external reference) for ³¹P NMR. The coupling constants are reported in Hz. For the ¹H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, m: multiplet. Mass spectra were determined on a VOYAGER DE STR spectrometer under MALDI ionization 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 γ -phosphonyloximes **2**

To a mixture of hydroxylamine hydrochloride (0.01 mol), potassium hydroxide (0.01 mol) and dry EtOH (30 mL), was added dropwise with stirring, at 25 °C, a solution of γ -ketophosphonate **1** (0.01 mol) in dry EtOH (20 mL). The reaction mixture was then heated under reflux for 24 h. After cooling, the solvent was removed under reduced pressure. The obtained residue was diluted with CHCl₃ (40 mL) and washed with water (2 x 20 mL). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The obtained crude product was washed with petroleum ether.

Diethyl 1-furyl-3-(hydroxyimino)butylphosphonate (2a). Brown solid; mp 90-92 °C; ^1H NMR: δ = 1.17-1.23 (m, 6H, 2 $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 1.50 (s, 3H, $\text{CH}_3\text{-C=N}$, *E*); 1.92 (s, 3H, $\text{CH}_3\text{-C=N}$, *Z*); 2.66-3.35 (m, 2H, $\text{CH}_2\text{-C=N}$); 3.51-3.64 (m, 1H, CH-P); 3.73-4.03 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 6.11-7.30 (m, 3H, arom-H); 9.87 (br s, 1H, OH); ^{13}C NMR: δ = 16.1 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 16.2 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 20.1 (s, $\underline{\text{CH}}_3\text{-C=N}$, *E*); 24.2 (s, $\underline{\text{CH}}_3\text{-C=N}$, *Z*); 34.1 (s, $\underline{\text{CH}}_2\text{-C=N}$, *Z*); 34.2 (s, $\underline{\text{CH}}_2\text{-C=N}$, *E*); 34.6 (d, $^1J_{\text{CP}} = 143.4$, CH-P, *Z*); 35.5 (d, $^1J_{\text{CP}} = 143.4$, CH-P, *E*); 62.4 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.7 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-CH}_2\text{-O}$); 153.6 (d, $^3J_{\text{CP}} = 15.1$, C=N, *Z*); 153.8 (d, $^3J_{\text{CP}} = 15.1$, C=N, *E*); aryl carbons: 108.3, 109.4, 110.1, 110.6, 110.7, 119.7, 123.4, 124.7, 140.9, 141.1, 141.7, 141.8; IR (neat): $\nu_{\text{P=O}} = 1234\text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1660\text{ cm}^{-1}$; $\nu_{\text{OH}} = 3281\text{ cm}^{-1}$; MALDI-MS: $m/z = 290.024$ ($[\text{M}+\text{H}]^+$).

Diethyl 3-(hydroxyimino)-1-thienylbutylphosphonate (2b). Brown solid; mp 84-86 °C; ^1H NMR: δ = 1.10-1.30 (m, 6H, 2 $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 1.52 (s, 3H, $\text{CH}_3\text{-C=N}$, *Z*); 1.68 (s, 3H, $\text{CH}_3\text{-C=N}$, *E*); 2.70-3.15 (m, 2H, $\text{CH}_2\text{-C=N}$); 3.71-3.82 (m, 1H, CH-P); 3.93-4.13 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 6.61-7.20 (m, 3H, arom-H); 9.60 (br s, 1H, OH); ^{13}C NMR: δ = 16.1 (d, $^3J_{\text{CP}} = 6.8$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 16.3 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 20.2 (s, $\underline{\text{CH}}_3\text{-C=N}$, *E*); 20.9 (s, $\underline{\text{CH}}_3\text{-C=N}$, *Z*); 31.2 (s, $\underline{\text{CH}}_2\text{-C=N}$, *Z*); 35.5 (d, $^1J_{\text{CP}} = 142.6$, CH-P, *Z*); 36.8 (d, $^1J_{\text{CP}} = 143.4$, CH-P, *E*); 37.1 (s, $\underline{\text{CH}}_2\text{-C=N}$, *E*); 62.5 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 63.0 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 153.8 (d, $^3J_{\text{CP}} = 15.8$, C=N, *E*); 154.8 (d, $^3J_{\text{CP}} = 14.3$, C=N, *Z*); aryl carbons: 123.9, 124.3, 124.7, 125.1, 126.1, 126.9, 127.0, 128.9, 130.4, 137.3, 143.1, 144.9; IR (neat): $\nu_{\text{P=O}} = 1237\text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1666\text{ cm}^{-1}$; $\nu_{\text{OH}} = 3291\text{ cm}^{-1}$; MALDI-MS: $m/z = 306.002$ ($[\text{M}+\text{H}]^+$).

Diethyl 3-(hydroxyimino)-1-phenylbutylphosphonate (2c). Yellow solid; mp 96-98 °C; ^1H NMR: δ = 1.10-1.23 (m, 6H, 2 $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 1.44 (s, 3H, $\text{CH}_3\text{-C=N}$, *Z*); 1.64 (s, 3H, $\text{CH}_3\text{-C=N}$, *E*); 2.72-3.03 (m, 2H, $\text{CH}_2\text{-C=N}$); 3.29-3.60 (m, 1H, CH-P); 3.63-4.10 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 7.12-7.30 (m, 5H, arom-H); 8.36 (br s, 1H, OH); ^{13}C NMR: δ = 16.2 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 16.3 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 20.8 (s, $\underline{\text{CH}}_3\text{-C=N}$, *E*); 22.6 (s, $\underline{\text{CH}}_3\text{-C=N}$, *Z*); 29.5 (s, $\underline{\text{CH}}_2\text{-C=N}$, *Z*); 35.8 (s, $\underline{\text{CH}}_2\text{-C=N}$, *E*); 40.2 (d, $^1J_{\text{CP}} = 138.1$, CH-P, *Z*); 41.6 (d, $^1J_{\text{CP}} = 138.9$, CH-P, *E*); 62.0 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.9 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-CH}_2\text{-O}$); 154.5 (d, $^3J_{\text{CP}} = 15.8$, C=N, *E*); 155.3 (d, $^3J_{\text{CP}} = 15.1$, C=N, *Z*); phenyl carbons: 120.1, 120.4, 127.2, 127.3, 128.4, 129.2, 129.3, 130.6, 132.8, 134.9, 135.1, 135.3; IR (neat): $\nu_{\text{P=O}} = 1238\text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1654\text{ cm}^{-1}$; $\nu_{\text{OH}} = 3286\text{ cm}^{-1}$; MALDI-MS: $m/z = 300.022$ ($[\text{M}+\text{H}]^+$).

Diethyl 3-(hydroxyimino)-1,3-diphenylpropylphosphonate (2d). Yellow solid; mp 104-106 °C; ^1H NMR: δ = 1.19-1.24 (m, 6H, 2 $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 2.81-3.13 (m, 2H, $\text{CH}_2\text{-C=N}$); 3.31-3.57 (m, 1H, CH-P); 3.60-4.07 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 7.00-7.80 (m, 10H, arom-H); 10.20 (br s, 1H, OH); ^{13}C NMR: δ = 16.2 (d, $^3J_{\text{CP}} = 5.3$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 16.3 (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$); 32.3 (s, $\underline{\text{CH}}_2\text{-C=N}$, *Z*); 35.0 (s, $\underline{\text{CH}}_2\text{-C=N}$, *E*); 40.0 (d, $^1J_{\text{CP}} = 139.6$, CH-P, *Z*); 40.9 (d, $^1J_{\text{CP}} = 139.6$, CH-P, *E*); 62.2 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 63.0 (d, $^2J_{\text{CP}} =$

6.8, CH₃-CH₂-O); 154.2 (d, ³J_{CP} = 15.1, C=N, Z); 156.1 (d, ³J_{CP} = 15.1, C=N, E); phenyl carbons: 125.6, 125.9, 126.5, 126.6, 126.8, 126.9, 127.2, 127.3, 127.7, 128.4, 128.9, 129.5, 129.7, 130.2, 131.5, 131.9, 133.3, 135.1, 136.6, 141.5; IR (neat): ν_{P=O} = 1236 cm⁻¹; ν_{C=N} = 1640 cm⁻¹; ν_{OH} = 3275 cm⁻¹; MALDI-MS: *m/z* = 362.058 ([M+H]⁺).

Dimethyl 1-furyl-3-(hydroxyimino)butylphosphonate (2e). Brown oil; ¹H NMR: δ = 1.92 (s, 3H, CH₃-C=N, E); 2.13 (s, 3H, CH₃-C=N, Z); 2.43-2.86 (m, 2H, CH₂-C=N); 3.38-3.61 (m, 1H, CH-P); 3.63 (d, 6H, ³J_{HP} = 6.0, 2 CH₃-O, E); 3.67 (d, 6H, ³J_{HP} = 6.0, 2 CH₃-O, Z); 6.13-7.36 (m, 3H, arom-H); 9.62 (br s, 1H, OH); ¹³C NMR: δ = 26.7 (s, CH₃-C=N, E); 28.8 (s, CH₃-C=N, Z); 33.3 (s, CH₂-C=N, Z); 40.6 (s, CH₂-C=N, E); 41.0 (d, ¹J_{CP} = 135.7, CH-P, Z); 44.2 (d, ¹J_{CP} = 135.7, CH-P, E); 53.2 (d, ²J_{CP} = 6.0, CH₃-O, Z); 53.6 (d, ²J_{CP} = 6.0, CH₃-O, E); 153.8 (d, ³J_{CP} = 15.1, C=N, Z); 154.6 (d, ³J_{CP} = 15.8, C=N, E); aryl carbons: 110.9, 111.6, 118.6, 123.3, 128.5, 129.0, 132.1, 133.7, 139.9, 140.1, 141.7, 141.8; IR (neat): ν_{P=O} = 1244 cm⁻¹; ν_{C=N} = 1656 cm⁻¹; ν_{OH} = 3290 cm⁻¹; MALDI-MS: *m/z* = 262.009 ([M+H]⁺).

Dimethyl 3-(hydroxyimino)-1-thienylbutylphosphonate (2f). Red oil; ¹H NMR: δ = 1.90 (s, 3H, CH₃-C=N, Z); 2.05 (s, 3H, CH₃-C=N, E); 2.43-3.16 (m, 2H, CH₂-C=N); 3.58-3.62 (m, 1H, CH-P); 3.66 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, Z); 3.77 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, E); 6.73-7.26 (m, 3H, arom-H); 8.52 (br s, 1H, OH); ¹³C NMR: δ = 30.0 (s, CH₃-C=N, E); 31.0 (s, CH₃-C=N, Z); 37.0 (s, CH₂-C=N, Z); 37.8 (s, CH₂-C=N, E); 39.0 (d, ¹J_{CP} = 108.7, CH-P, Z); 45.9 (d, ¹J_{CP} = 108.7, CH-P, E); 54.4 (d, ²J_{CP} = 6.0, CH₃-O, E); 54.7 (d, ²J_{CP} = 6.0, CH₃-O, Z); 157.0 (d, ³J_{CP} = 12.8, C=N, E); 157.4 (d, ³J_{CP} = 12.8, C=N, Z); aryl carbons: 113.2, 123.3, 124.5, 125.4, 126.9, 127.0, 127.3, 128.6, 130.9, 134.5, 136.1, 141.7; IR (neat): ν_{P=O} = 1264 cm⁻¹; ν_{C=N} = 1666 cm⁻¹; ν_{OH} = 3294 cm⁻¹; MALDI-MS: *m/z* = 277.949 ([M+H]⁺).

Dimethyl 3-(hydroxyimino)-1-phenylbutylphosphonate (2g). Yellow oil; ¹H NMR: δ = 1.59 (s, 3H, CH₃-C=N, E); 1.77 (s, 3H, CH₃-C=N, Z); 2.33-2.86 (m, 2H, CH₂-C=N); 3.28-3.36 (m, 1H, CH-P); 3.30 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, Z); 3.50 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, E); 7.03-7.56 (m, 5H, arom-H); 8.00 (br s, 1H, OH); ¹³C NMR: δ = 19.2 (s, CH₃-C=N, E); 20.8 (s, CH₃-C=N, Z); 30.5 (s, CH₂-C=N, Z); 33.7 (s, CH₂-C=N, E); 36.6 (d, ¹J_{CP} = 135.8, CH-P, E); 41.5 (d, ¹J_{CP} = 123.0, CH-P, Z); 53.3 (d, ²J_{CP} = 6.0, CH₃-O, Z); 53.6 (d, ²J_{CP} = 6.0, CH₃-O, E); 154.7 (d, ³J_{CP} = 15.8, C=N, E); 155.5 (d, ³J_{CP} = 15.8, C=N, Z); phenyl carbons: 125.7, 128.1, 128.4, 129.0, 129.2, 129.5, 130.0, 131.0, 132.3, 133.6, 134.7, 141.0; IR (neat): ν_{P=O} = 1230 cm⁻¹; ν_{C=N} = 1661 cm⁻¹; ν_{OH} = 3311 cm⁻¹; MALDI-MS: *m/z* = 271.984 ([M+H]⁺).

Dimethyl 3-(hydroxyimino)-1,3-diphenylpropylphosphonate (2h). Yellow oil; ¹H NMR: δ = 3.13-3.36 (m, 2H, CH₂-C=N); 3.48-3.56 (m, 1H, CH-P); 3.60 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, Z); 3.82 (d, 6H, ³J_{HP} = 9.0, 2 CH₃-O, E); 7.33-7.86 (m, 10H, arom-H); 9.46 (br s, 1H, OH); ¹³C NMR: δ = 30.4 (s, CH₂-C=N, Z); 32.5

(s, $\underline{\text{C}}\text{H}_2\text{-C=N}$, *E*); 33.9 (d, $^1J_{\text{CP}} = 133.6$, CH-P, *E*); 40.6 (d, $^1J_{\text{CP}} = 133.0$, CH-P, *Z*); 56.5 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-O}$, *E*); 56.6 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-O}$, *Z*); 157.7 (d, $^3J_{\text{CP}} = 14.3$, C=N, *E*); 158.8 (d, $^3J_{\text{CP}} = 14.3$, C=N, *Z*); phenyl carbons: 126.0, 126.7, 127.2, 127.8, 128.3, 128.7, 129.1, 129.8, 130.5, 131.3, 131.8, 132.5, 133.3, 134.1, 135.0, 136.0, 136.8, 137.0, 141.2, 141.7; IR (neat): $\nu_{\text{P=O}} = 1239 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1663 \text{ cm}^{-1}$; $\nu_{\text{OH}} = 3281 \text{ cm}^{-1}$; MALDI-MS: $m/z = 334.009$ ($[\text{M}+\text{H}]^+$).

General procedure for the synthesis of 1,2,5-oxazaphospholines 3 and 3'

A mixture of γ -phosphonyloxime **2** (0.01 mol), LR (0.01 mol) and dry toluene (20 mL) was heated at 80 °C with stirring for 3 h. After cooling, the mixture was filtered and the filtrate was concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using Et₂O as the eluent.

Diethyl 1-furyl-2-[-5-(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-yl]ethylphosphonothioate (3a). Brown oil; $^1\text{H NMR}$: $\delta = 1.16\text{-}1.38$ (m, 6H, 2 $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 2.19-2.66 (m, 2H, $\text{CH}_2\text{-C=N}$); 2.75-2.92 (m, 3H, $\text{CH}_2\text{-P(S)}$, CH-P(S)); 3.74 (s, 3H, O-CH₃, maj); 3.76 (s, 3H, O-CH₃, min); 3.80-4.32 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 7.78-8.20 (m, 7H, arom-H); $^{13}\text{C NMR}$: $\delta = 14.5$ (d, $^3J_{\text{CP}} = 6.0$, $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 14.9 (d, $^3J_{\text{CP}} = 6.8$, $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 27.2 (s, $\underline{\text{C}}\text{H}_2\text{-C=N}$, min); 27.8 (s, $\underline{\text{C}}\text{H}_2\text{-C=N}$, maj); 29.6 (d, $^1J_{\text{CP}} = 141.9$, CH-P, min); 30.2 (d, $^1J_{\text{CP}} = 139.6$, CH-P, maj); 31.8 (d, $^1J_{\text{CP}} = 116.2$, $\text{CH}_2\text{-P}$, min); 31.9 (d, $^1J_{\text{CP}} = 120.8$, $\text{CH}_2\text{-P}$, maj); 54.5 (s, $\text{CH}_3\text{-O}$, min); 54.6 (s, $\text{CH}_3\text{-O}$, maj); 61.0 (d, $^2J_{\text{CP}} = 6.0$, $\text{CH}_3\text{-CH}_2\text{-O}$); 61.3 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 161.8 (d, $^4J_{\text{CP}} = 3.0$, $\text{CH}_3\text{-O-C=C}$, maj); 162.1 (d, $^4J_{\text{CP}} = 3.0$, $\text{CH}_3\text{-O-C=C}$, min); 163.2 (d, $^3J_{\text{CP}} = 10.6$, C=N, maj); 163.3 (d, $^3J_{\text{CP}} = 12.1$, C=N, min); aryl carbons: 112.9, 113.0, 113.1, 113.2, 113.3, 120.4, 120.5, 124.8, 124.9, 125.0, 125.1, 125.7, 126.0, 126.3, 127.2, 131.7, 131.9, 132.3, 132.4, 132.5, 132.6, 132.7, 132.8, 132.9, 133.1, 133.1, 133.4, 133.6; IR (neat): $\nu_{\text{P=S}} = 692 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1580 \text{ cm}^{-1}$; MALDI-MS: $m/z = 474.149$ ($[\text{M}+\text{H}]^+$).

Diethyl 2-[-5-(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-yl]-1-thienylethylphosphonothioate (3b). Brown oil; $^1\text{H NMR}$: $\delta = 1.20\text{-}1.41$ (t, 6H, 2 $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 2.24-2.71 (m, 2H, $\text{CH}_2\text{-C=N}$); 2.80-2.97 (m, 3H, $\text{CH}_2\text{-P(S)}$, CH-P(S)); 3.78 (s, 3H, O-CH₃, maj); 3.79 (s, 3H, O-CH₃, min); 4.01-4.38 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 6.78-8.05 (m, 7H, arom-H); $^{13}\text{C NMR}$: $\delta = 15.5$ (d, $^3J_{\text{CP}} = 5.3$, $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 16.0 (d, $^3J_{\text{CP}} = 7.5$, $\underline{\text{C}}\text{H}_3\text{-CH}_2\text{-O}$); 29.0 (d, $^1J_{\text{CP}} = 132.0$, CH-P); 29.5 (s, $\underline{\text{C}}\text{H}_2\text{-C=N}$, maj); 31.9 (s, $\underline{\text{C}}\text{H}_2\text{-C=N}$, min); 32.0 (d, $^1J_{\text{CP}} = 123.0$, $\text{CH}_2\text{-P}$, min); 32.7 (d, $^1J_{\text{CP}} = 123.0$, $\text{CH}_2\text{-P}$, maj); 55.3 (s, $\text{CH}_3\text{-O}$, min); 55.4 (s, $\text{CH}_3\text{-O}$, maj); 61.9 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.0 (d, $^2J_{\text{CP}} = 6.0$, $\text{CH}_3\text{-CH}_2\text{-O}$); 162.7 (d, $^4J_{\text{CP}} = 3.0$, $\text{CH}_3\text{-O-C=C}$); 163.0 (d, $^3J_{\text{CP}} = 13.6$, C=N); aryl carbons: 113.7, 125.4, 127.1, 127.4, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 128.6, 128.9, 129.0, 129.4, 129.8, 130.1, 130.9, 131.0, 131.1, 131.2, 131.3, 131.4, 131.5, 131.8, 131.9, 132.0, 132.1, 133.6; IR (neat): $\nu_{\text{P=S}} = 699 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1584 \text{ cm}^{-1}$; MALDI-MS: $m/z =$

490.217 ([M+H]⁺).

Diethyl 2-[(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-yl]-1-phenylethylphosphonothioate (3c). Yellow oil; ¹H NMR: δ = 1.13-1.41 (t, 6H, 2 CH₃-CH₂-O); 2.19-2.71 (m, 2H, CH₂-C=N); 2.80-2.93 (m, 3H, CH₂-P(S), CH-P(S)); 3.78 (s, 3H, O-CH₃, maj); 3.79 (s, 3H, O-CH₃, min); 4.01-4.37 (m, 4H, 2 CH₃-CH₂-O); 6.74-7.90 (m, 9H, arom-H); ¹³C NMR: δ = 14.3 (d, ³J_{CP} = 6.0, CH₃-CH₂-O); 15.6 (d, ³J_{CP} = 5.3, CH₃-CH₂-O); 28.2 (s, CH₂-C=N, min); 28.3 (s, CH₂-C=N, maj); 30.6 (d, ¹J_{CP} = 141.9, CH-P, maj); 32.8 (d, ¹J_{CP} = 118.5, CH₂-P, min); 32.9 (d, ¹J_{CP} = 119.2, CH₂-P, maj); 34.0 (d, ¹J_{CP} = 136.4, CH-P, min); 55.5 (s, CH₃-O, min); 55.6 (s, CH₃-O, maj); 62.3 (d, ²J_{CP} = 6.0, CH₃-CH₂-O); 62.5 (d, ²J_{CP} = 6.8, CH₃-CH₂-O); 163.1 (d, ⁴J_{CP} = 3.8, CH₃-O-C=C, maj); 163.2 (d, ⁴J_{CP} = 3.8, CH₃-O-C=C, min); 164.0 (d, ³J_{CP} = 12.1, C=N, min); 164.1 (d, ³J_{CP} = 11.3, C=N, maj); phenyl carbons: 113.9, 114.0, 114.1, 124.2, 124.4, 124.7, 124.9, 125.2, 125.6, 125.8, 125.9, 126.4, 127.6, 128.2, 128.4, 128.5, 129.4, 130.1, 131.7, 132.6, 132.8, 132.9, 133.4, 133.5, 133.6, 133.7, 133.8, 136.5; IR (neat): ν_{P=S} = 697 cm⁻¹; ν_{C=N} = 1579 cm⁻¹; MALDI-MS: m/z = 484.138 ([M+H]⁺).

Dimethyl 1-furyl-2-[-5-(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-ylethyl]phosphonothioate (3d). Brown oil; ¹H NMR: δ = 2.60-2.75 (m, 2H, CH₂-C=N); 3.31-3.37 (m, 3H, CH₂-P(S), CH-P(S)); 3.58 (d, 3H, ³J_{PH} = 9.0, CH₃-O-P); 3.60 (d, 3H, ³J_{PH} = 9.0, CH₃-O-P); 3.68 (s, 3H, O-CH₃, maj); 3.69 (s, 3H, O-CH₃, min); 6.12-7.89 (m, 7H, arom-H); ¹³C NMR: δ = 32.9 (d, ¹J_{CP} = 143.3, CH-P); 33.8 (s, CH₂-C=N, min); 34.0 (s, CH₂-C=N, maj); 39.3 (d, ¹J_{CP} = 128.3, CH₂-P, min); 39.4 (d, ¹J_{CP} = 120.8, CH₂-P, maj); 51.9 (d, ²J_{CP} = 6.0, CH₃-O-P); 52.0 (d, ²J_{CP} = 6.0, CH₃-O-P); 55.6 (s, CH₃-O, min); 55.7 (s, CH₃-O, maj); 162.8 (d, ⁴J_{CP} = 3.0, CH₃-O-C=C, min); 163.0 (d, ⁴J_{CP} = 3.0, CH₃-O-C=C, maj); 164.2 (d, ³J_{CP} = 12.1, C=N, maj); 164.8 (d, ³J_{CP} = 12.1, C=N, min); aryl carbons: 111.4, 113.8, 113.9, 114.1, 114.3, 114.4, 118.5, 118.8, 125.3, 126.6, 128.3, 129.1, 132.6, 132.9, 133.0, 133.1, 133.3, 133.6, 133.7, 133.9, 134.0, 134.1, 134.4, 134.6, 140.9, 141.0, 142.0, 142.1; IR (neat): ν_{P=S} = 692 cm⁻¹; ν_{C=N} = 1585 cm⁻¹; MALDI-MS: m/z = 446.102 ([M+H]⁺).

Dimethyl 2-[-5-(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-yl]-1-thienylethylphosphonothioate (3e). Brown oil; ¹H NMR: δ = 2.40-3.05 (m, 2H, CH₂-C=N); 3.71-3.78 (m, 3H, CH₂-P(S), CH-P(S)); 3.73 (d, 3H, ³J_{PH} = 9.0, CH₃-O-P); 3.76 (d, 3H, ³J_{PH} = 9.0, CH₃-O-P); 3.82 (s, 3H, O-CH₃); 6.80-8.05 (m, 7H, arom-H); ¹³C NMR: δ = 29.6 (s, CH₂-C=N, maj); 31.8 (s, CH₂-C=N, min); 41.2 (d, ¹J_{CP} = 129.0, CH₂-P, min); 43.2 (d, ¹J_{CP} = 144.9, CH-P); 44.6 (d, ¹J_{CP} = 121.6, CH₂-P, maj); 51.3 (d, ²J_{CP} = 6.8, CH₃-O-P); 52.0 (d, ²J_{CP} = 6.0, CH₃-O-P); 55.3 (s, CH₃-O, min); 55.4 (s, CH₃-O, maj); 162.9 (d, ⁴J_{CP} = 3.0, CH₃-O-C=C); 163.4 (d, ³J_{CP} = 14.9, C=N); aryl carbons: 113.8, 113.9, 114.0, 122.7, 123.2, 123.4, 123.7,

123.9, 124.2, 124.3, 124.7, 125.2, 125.8, 126.4, 126.7, 127.0, 127.3, 127.7, 128.1, 129.0, 130.4, 132.5, 132.7, 133.2, 133.5, 137.7, 143.7, 143.8; IR (neat): $\nu_{\text{P=S}} = 700 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1572 \text{ cm}^{-1}$; MALDI-MS: $m/z = 462, 164$ ($[\text{M}+\text{H}]^+$).

Dimethyl 2-[(4-methoxyphenyl)-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-3-yl]-1-phenylethylphosphonothioate (3f). Yellow oil; $^1\text{H NMR}$: $\delta = 3.28\text{--}3.35$ (m, 2H, $\text{CH}_2\text{-C=N}$); $3.58\text{--}3.70$ (m, 3H, $\text{CH}_2\text{-P(S)}$, CH-P(S)); 3.62 (d, 3H, $^3J_{\text{PH}} = 9.0$, $\text{CH}_3\text{-O-P}$); 3.64 (d, 3H, $^3J_{\text{PH}} = 9.0$, $\text{CH}_3\text{-O-P}$); 3.65 (s, 3H, O-CH_3 , maj); 3.66 (s, 3H, O-CH_3 , min); $6.80\text{--}7.87$ (m, 9H, arom-H); $^{13}\text{C NMR}$: $\delta = 29.8$ (s, $\text{CH}_2\text{-C=N}$, min); 30.1 (d, $^1J_{\text{CP}} = 143.4$, CH-P , min); 30.6 (d, $^1J_{\text{CP}} = 143.4$, CH-P , maj); 30.7 (d, $^1J_{\text{CP}} = 120.8$, $\text{CH}_2\text{-P}$, maj); 31.6 (s, $\text{CH}_2\text{-C=N}$, maj); 34.0 (d, $^1J_{\text{CP}} = 113.2$, $\text{CH}_2\text{-P}$, min); 51.9 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-O-P}$); 52.1 (d, $^2J_{\text{CP}} = 7.5$, $\text{CH}_3\text{-O-P}$); 55.5 (s, $\text{CH}_3\text{-O}$, min); 55.7 (s, $\text{CH}_3\text{-O}$, maj); 162.8 (d, $^4J_{\text{CP}} = 3.0$, $\text{CH}_3\text{-O-C=C}$, min); 163.1 (d, $^4J_{\text{CP}} = 3.8$, $\text{CH}_3\text{-O-C=C}$, maj); 164.3 (d, $^3J_{\text{CP}} = 9.1$, C=N); phenyl carbons: 114.2, 114.4, 125.4, 125.9, 126.5, 126.6, 127.6, 127.7, 127.9, 128.5, 128.6, 128.7, 129.1, 130.0, 130.3, 130.9, 132.7, 132.8, 133.1, 133.4, 133.6, 133.9, 134.1, 134.2, 134.4, 134.6, 136.4, 136.5; IR (neat): $\nu_{\text{P=S}} = 700 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1576 \text{ cm}^{-1}$; MALDI-MS: $m/z = 456.122$ ($[\text{M}+\text{H}]^+$).

Diethyl [5-(4-methoxyphenyl)-3-phenyl-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-4-yl]phenylmethylphosphonothioate (3'a). Red oil; $^1\text{H NMR}$: $\delta = 1.03\text{--}1.31$ (m, 6H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); $2.55\text{--}3.61$ (m, 2H, 2 CH-P(S)); 3.64 (s, 3H, O-CH_3 , min); 3.65 (s, 3H, O-CH_3 , maj); $3.84\text{--}4.20$ (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); $6.78\text{--}7.95$ (m, 14H, arom-H); $^{13}\text{C NMR}$: $\delta = 15.7$ (d, $^3J_{\text{CP}} = 5.3$, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.7 (d, $^3J_{\text{CP}} = 5.3$, $\text{CH}_3\text{-CH}_2\text{-O}$); 29.2 (d, $^1J_{\text{CP}} = 141.1$, CH-P-O , maj); 30.7 (d, $^1J_{\text{CP}} = 141.9$, CH-P-O , min); 32.5 (d, $^1J_{\text{CP}} = 129.2$, CH-P-C=C , min); 32.9 (d, $^1J_{\text{CP}} = 116.2$, CH-P-C=C , maj); 55.5 (s, $\text{CH}_3\text{-O}$, min); 55.6 (s, $\text{CH}_3\text{-O}$, maj); 62.1 (d, $^2J_{\text{CP}} = 6.0$, $\text{CH}_3\text{-CH}_2\text{-O}$); 63.1 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-CH}_2\text{-O}$); 162.8 (d, $^4J_{\text{CP}} = 3.3$, $\text{CH}_3\text{-O-C=C}$, maj); 162.9 (d, $^4J_{\text{CP}} = 3.0$, $\text{CH}_3\text{-O-C=C}$, min); 163.1 (d, $^3J_{\text{CP}} = 18.6$, C=N , maj); 163.4 (d, $^3J_{\text{CP}} = 14.0$, C=N , min); phenyl carbons: 114.1, 114.2, 125.9, 126.0, 126.8, 126.9, 127.4, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 129.2, 129.6, 130.8, 133.4, 133.5, 133.6, 133.8, 134.2, 134.9; IR (neat): $\nu_{\text{P=S}} = 699 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1585 \text{ cm}^{-1}$; MALDI-MS: $m/z = 546.130$ ($[\text{M}+\text{H}]^+$).

Dimethyl [5-(4-methoxyphenyl)-3-phenyl-5-sulfido-4,5-dihydro-1,2,5-oxazaphosphol-4-yl]phenylmethylphosphonothioate (3'b). Red oil; $^1\text{H NMR}$: $\delta = 3.32\text{--}3.60$ (m, 2H, 2 CH-P(S)); 3.82 (d, 3H, $^3J_{\text{PH}} = 9.0$, $\text{CH}_3\text{-O-P}$); 3.84 (d, 3H, $^3J_{\text{PH}} = 9.0$, $\text{CH}_3\text{-O-P}$); 3.86 (s, 3H, O-CH_3 , min); 3.87 (s, 3H, O-CH_3 , maj); $7.04\text{--}8.26$ (m, 14H, arom-H); $^{13}\text{C NMR}$: $\delta = 31.0$ (d, $^1J_{\text{CP}} = 110.2$, CH-P-C=C , maj); 31.6 (d, $^1J_{\text{CP}} = 103.3$, CH-P-C=C , min); 35.4 (d, $^1J_{\text{CP}} = 114.0$, CH-P-O); 55.6 (s, $\text{CH}_3\text{-O}$, min); 55.7 (s, $\text{CH}_3\text{-O}$, maj); 51.9 (d, $^2J_{\text{CP}} = 6.8$, $\text{CH}_3\text{-O-P}$); 52.0 (d, $^2J_{\text{CP}} = 6.0$, $\text{CH}_3\text{-O-P}$); 162.7 (d, $^4J_{\text{CP}} = 2.3$, $\text{CH}_3\text{-O-C=C}$); 163.2 (d, $^3J_{\text{CP}} = 12.8$, C=N); phenyl carbons: 114.4, 114.5, 126.0, 126.1, 126.3, 126.7, 126.9, 127.0, 127.5, 127.7, 127.8,

128.0, 128.6, 128.7, 128.8, 128.9, 129.4, 129.5, 129.7, 130.4, 130.9, 132.9, 133.2, 133.7, 134.2, 141.2; IR (neat): $\nu_{\text{P=S}} = 700 \text{ cm}^{-1}$; $\nu_{\text{C=N}} = 1579 \text{ cm}^{-1}$; MALDI-MS: $m/z = 518, 106$ ($[\text{M}+\text{H}]^+$).

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