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SIMPLE AND EFFICIENT SYNTHESIS OF PHOSPHORYLATED THIENOPYRIDONES FROM 2-AMINOTHIOPHENE-3-CARBOXYLATES AND β-PHOSPHONYLKETONES

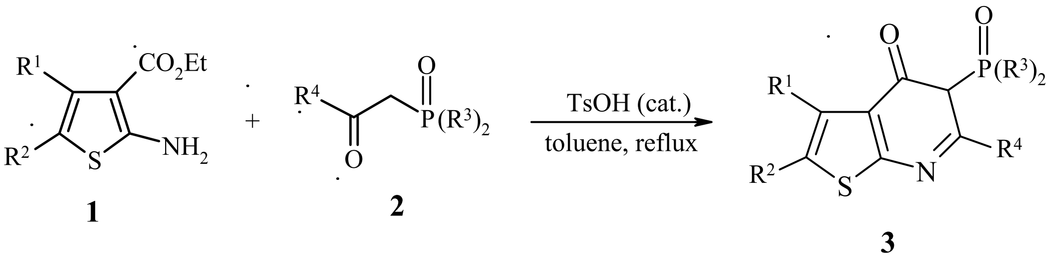
Khaoula Khalladi and Soufiane Touil*

Laboratory of Heteroatom Organic Chemistry, Department of Chemistry, Faculty of Sciences of Bizerta, University of Carthage, 7021-Jarzouna, Tunisia; E-mail: soufiane.touil@fsb.rnu.tn

Abstract – Herein, we report an efficient and straightforward synthesis of the new 5-phosphonothieno[2,3-*b*]pyridin-4(5*H*)-ones, via the *p*-toluenesulfonic acid catalyzed reaction of ethyl 2-aminothiophene-3-carboxylates with β-phosphonylketones. To the best of our knowledge, this is the first synthesis of thienopyridone derivatives bearing a phosphonate or a phosphine oxide group.

In connection with our work on the synthesis of new phosphorylated heterocycles with possible biological properties[1-3] and pursuing our studies on the reactivity and potential synthetic applications of 2-aminothiophenes,[4-6] we have investigated, for the first time, the behaviour of ethyl 2-aminothiophene-3-carboxylates towards β-ketophosphonates and phosphine oxides, in order to obtain novel types of thienopyridones bearing a phosphoryl group. Our interest for these compounds is due to the well known interesting biological properties of thienopyridone derivatives including antibacterial[7-10] and antitumor[7] activities. Some thienopyridones have been also reported to directly activate the AMP-activated protein kinase (AMPK) which is a key regulator of cellular and systemic energy metabolism and is an attractive drug target for treatment of metabolic diseases, particularly obesity and type 2 diabetes.[11] Furthermore, it is known that phosphorus substituents regulate important biological functions[12] and the introduction of organophosphorus functionalities in the thienopyridone core could improve the biological activity of such compounds.

The starting ethyl 2-aminothiophene-3-carboxylates **1**[13] and β-phosphonylketones **2**[14] were easily prepared according to the reported procedures. It was found that the condensation of thiophenes **1** with ketones **2**, performed in refluxing toluene, for 24 h, in the presence of a catalytic amount of *p*-toluenesulfonic acid, led to the formation of 5-phosphonothieno[2,3-*b*]pyridin-4(5*H*)-ones **3** (Scheme 1). In order to demonstrate the efficiency and generality of this protocol, we examined the reactions of various ethyl 2-aminothiophene-3-carboxylates and β-phosphonylketones (Table 1). All substrates react to give the corresponding phosphonothienopyridones in good to excellent yields.



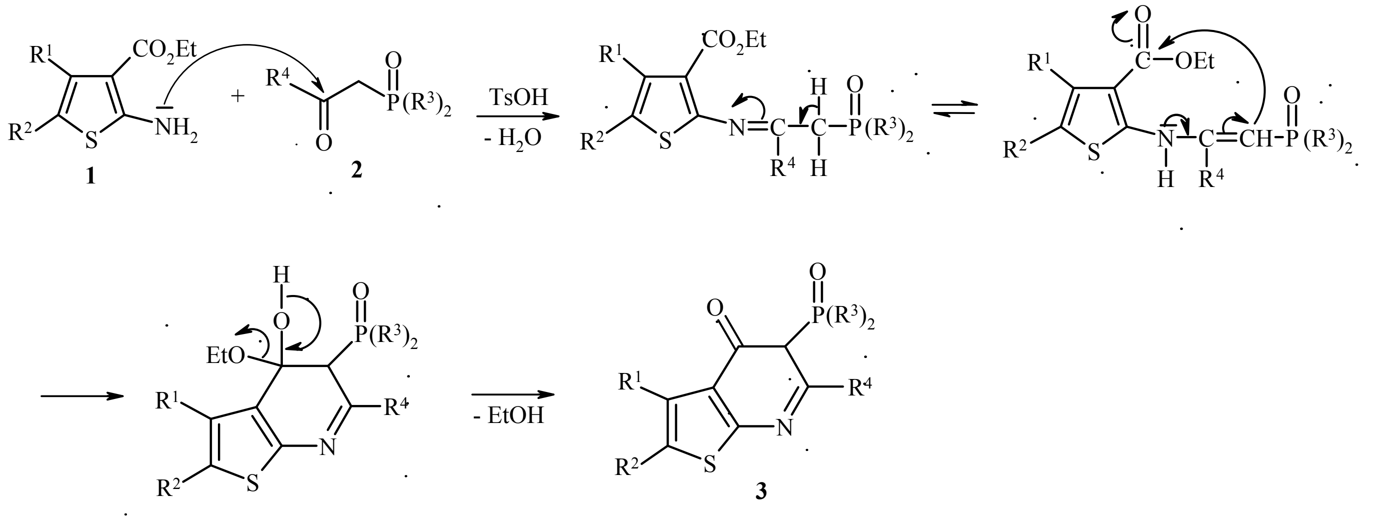
Scheme 1. Synthesis of 5-phosphonothieno[2,3-*b*]pyridin-4(5*H*)-ones **3**

Table 1. Substrate scope studies

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)[a]
1	$(CH_2)_3$		OEt	Ph	**3a**	96
2	$(CH_2)_3$		OMe	Ph	**3b**	89
3	$(CH_2)_4$		Ph	Ph	**3c**	59
4	$(CH_2)_4$		OEt	Me	**3d**	56
5	$(CH_2)_4$		OMe	Ph	**3e**	53
6	Ph-CH_2	Ph	OMe	Ph	**3f**	92
7	Ph-CH_2	Ph	OEt	Me	**3g**	74
8	Ph-CH_2	Ph	OMe	Me	**3h**	94
9	Ph	H	OEt	Me	**3i**	78
10	Me	Ph-CH_2	OEt	Ph	**3j**	68
11	Me	Ph	OEt	Ph	**3k**	88
12	Me	iPr	Ph	Ph	**3l**	86
13	Me	Me	OMe	Me	**3m**	73
14	Me	H	OEt	Me	**3n**	81

[a] Isolated yield.

A plausible mechanism for the formation of compounds **3** is depicted in Scheme 2. The transformation is believed to proceed via a nucleophilic attack of the amino group on the β-phosphonylketone, giving rise to an imine intermediate. A subsequent intramolecular cyclization through the nucleophilic attack of the enamine tautomer on the ester group, leads to the final products **3.**



Scheme 2. Proposed mechanism for the synthesis of compounds **3**

The structures of phosphonothienopyridones **3** were established through their IR, NMR (^{1}H, ^{31}P, ^{13}C) and mass spectral data. The IR spectra revealed the presence of absorption bands towards 1250 and 1680 cm^{-1} corresponding respectively to the P=O and C=O vibrators. The ^{1}H NMR spectra showed, in particular, a doublet in the region included between 3 and 4 ppm, ascribable to the CH-P=O proton. Such a doublet is characteristic for the coupling with phosphorus with a $^2J_{PH}$ coupling constant of about 12-24 Hz. The alkoxy groups on the phosphorus atom showed a signal doubling indicating that they are not magnetically equivalent, probably due to the neighboring asymmetric carbon. The ^{31}P NMR shift recorded for compounds **3** was $\delta = 20\text{-}27$ ppm which is consistent with the phosphonate and phosphine oxide chemical shift values. The ^{13}C NMR spectra display the characteristic signals of all carbons and particularly those corresponding to the heterocyclic ring. Of particular note is the CH-P=O carbon that resonates as a doublet ($^1J_{CP}$ = 58.1-147.9 Hz) around 40 ppm. We also observed a doublet ($^2J_{CP}$ = 6-7 Hz) near 200 ppm corresponding to the keto carbon. The structures of the compounds **3** were supported additionally by the mass spectra which showed the correct molecular ion peaks.

In conclusion, a simple and efficient methodology has been developed for the synthesis of

5-phosphonothieno[2,3-*b*]pyridin-4(5*H*)-ones, from easily made ethyl 2-aminothiophene-3-carboxylates and β-phosphonylketones. To the best of our knowledge, this is the first synthesis of thienopyridone derivatives bearing a phosphonate or a phosphine oxide group. Further studies on the bioactivity of the synthesized compounds are currently under way in our laboratory.

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, quint: quintet, 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 5-phosphonothieno[2,3-*b*]pyridin-4(5*H*)-ones 3. A mixture of ethyl 2-aminothiophene-3-carboxylate **1** (0.005 mol), β-phosphonylketone **2** (0.005 mol) and TsOH (0.1 g) in dry toluene (25 mL), was heated at reflux, with Dean-Stark separation of water, for 24 h. The reaction mixture was then cooled and extracted with a saturated aqueous sodium bicarbonate solution (30 mL) then with water (2 x 30 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on a silica gel column using Et_2O as eluent.

3a: Light brown solid; mp 194-196 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.1$ ppm; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.16$ (t, 3H, $^3J_{HH} = 6.0$ Hz, $C\underline{H}_3$-CH_2-O); 1.20 (t, 3H, $^3J_{HH} = 6.0$ Hz, $C\underline{H}_3$-CH_2-O); 1.68-2.71 (m, 6H, cyclic H); 3.52 (d, 1H, $^2J_{PH} = 18.0$ Hz, CH-P); 4.01 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, CH_3-$C\underline{H}_2$-O); 4.10 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, CH_3-$C\underline{H}_2$-O); 7.03-7.91 (m, 5H, arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.5$ (d, $^3J_{CP} = 6.0$ Hz, $\underline{C}H_3$-CH_2-O); 15.2 (d, $^3J_{CP} = 6.8$ Hz, $\underline{C}H_3$-CH_2-O); 26.2 (s, $\underline{C}H_2$-CH_2-C=C-S); 27.8 (s, $\underline{C}H_2$-C=C-S); 29.8 (s, $\underline{C}H_2$-$(CH_2)_2$-C=C-S); 37.4 (d, $^1J_{CP} = 129.8$ Hz, $\underline{C}$H-P=O); 61.6 (d, $^2J_{CP} = 6.8$ Hz, CH_3-$\underline{C}H_2$-O); 62.6 (d, $^2J_{CP} = 6.0$ Hz, CH_3-$\underline{C}H_2$-O); 128.8 (s, CH_2-$\underline{C}$=C-S); 132.0 (s, CH_2-$\underline{C}$-S); 141.6 (s, $\underline{C}$=C-S); 164.5 (d, $^2J_{CP} = 23.4$ Hz, $\underline{C}$=N); 165.8 (s, N-$\underline{C}$-S); 190.9 (d, $^2J_{CP} = 6.8$ Hz, $\underline{C}$=O); Phenyl carbons: 124.3, 127.3, 133.3, 136.8; IR (neat): $\nu_{P=O} = 1264$ cm^{-1}; $\nu_{C=O} = 1686$ cm^{-1}; MALDI-MS: *m/z* 404.069 ($[M+H]^+$).

3b: Light brown solid; mp 219-221 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 23.3$ ppm; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$-2.74 (m, 6H, cyclic H); 3.86 (d, 3H, $^3J_{PH} = 9.0$ Hz, O-CH_3); 3.90 (d, 3H, $^3J_{PH} = 9.0$ Hz, O-CH$_3$); 3.96 (d, 1H, $^2J_{PH}$ = 12.0 Hz, CH-P); 7.36-8.24 (m, 5H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 26.6 (s, $\underline{C}$H$_2$-CH$_2$-C=C-S); 30.4 (s, $\underline{C}$H$_2$-C=C-S); 36.1 (s, $\underline{C}$H$_2$-(CH$_2$)$_2$-C=C-S); 44.4 (d, $^1J_{CP}$ = 147.9 Hz, $\underline{C}$H-P=O); 53.1 (d, $^2J_{CP}$ = 6.0 Hz, $\underline{C}$H$_3$-O); 59.7 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$H$_3$-O); 129.5 (s, CH$_2$-$\underline{C}$=C-S); 133.9 (s, CH$_2$-$\underline{C}$-S); 144.9 (s, $\underline{C}$=C-S); 164.3 (d, $^2J_{CP}$ = 24.2 Hz, $\underline{C}$=N); 166.1 (s, N-$\underline{C}$-S); 191.9 (d, $^2J_{CP}$ = 6.0 Hz, $\underline{C}$=O); Phenyl carbons: 125.1, 127.3, 130.8, 138.0; IR (neat): $\nu_{P=O}$ = 1272 cm^{-1}; $\nu_{C=O}$ = 1690 cm^{-1}; MALDI-MS: *m/z* 376.032 ([M+H]$^+$).

3c: Light brown solid; mp 121-122 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 26.4 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.38-2.53 (m, 8H, cyclic H); 3.95 (d, 1H, $^2J_{PH}$ = 21.0 Hz, CH-P); 6.61-7.65 (m, 15H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 21.4 (s, $\underline{C}$H$_2$-CH$_2$-CH$_2$-C=C-S); 22.9 (s, $\underline{C}$H$_2$-CH$_2$-C=C-S); 24.3 (s, $\underline{C}$H$_2$-C=C-S); 24.5 (s, $\underline{C}$H$_2$-(CH$_2$)$_3$-C=C-S); 42.9 (d, $^1J_{CP}$ = 58.1 Hz, $\underline{C}$H-P=O); 128.2 (s, $\underline{C}$=C-S); 130.0 (s, CH$_2$-$\underline{C}$-S); 152.0 (s, CH$_2$-$\underline{C}$=C-S); 162.9 (d, $^2J_{CP}$ = 18.9 Hz, $\underline{C}$=N); 166.1 (s, N-$\underline{C}$-S); 192.6 (d, $^2J_{CP}$ = 6.0 Hz, $\underline{C}$=O); Phenyl carbons: 124.0, 125.3, 128.4, 128.6, 129.0, 129.5, 130.8, 131.1, 134.0, 131.7, 136.4, 137.6; IR (neat): $\nu_{P=O}$ = 1278 cm^{-1}; $\nu_{C=O}$ = 1682 cm^{-1}; MALDI-MS: *m/z* 482.045 ([M+H]$^+$).

3d: Light brown solid; mp 85-87 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 23.6 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.21 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C$\underline{H}_3$-CH$_2$-O); 1.26 (t, 3H, $^3J_{HH}$ = 6.0 Hz, C$\underline{H}_3$-CH$_2$-O); 1.64-2.69 (m, 8H, cyclic H); 2.23 (s, 3H, CH$_3$-C=N); 3.38 (d, 1H, $^2J_{PH}$ = 21.0 Hz, CH-P); 4.02 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH$_3$-C$\underline{H}_2$-O); 4.08 (quint, 2H, $^3J_{\ HH}$ = $^3J_{PH}$ = 6.0 Hz, CH$_3$-C$\underline{H}_2$-O); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 14.6 (d, $^3J_{CP}$ = 6.0 Hz, $\underline{C}$H$_3$-CH$_2$-O); 16.2 (d, $^3J_{CP}$ = 6.0 Hz, $\underline{C}$H$_3$-CH$_2$-O); 21.3 (s, $\underline{C}$H$_3$-C=N); 21.7 (s, $\underline{C}$H$_2$-CH$_2$-CH$_2$-C=C-S); 22.8 (s, $\underline{C}$H$_2$-CH$_2$-C=C-S); 22.2 (s, $\underline{C}$H$_2$-C=C-S); 24.4 (s, $\underline{C}$H$_2$-(CH$_2$)$_3$-C=C-S); 43.7 (d, $^1J_{CP}$ = 129.1 Hz, $\underline{C}$H-P=O); 59.1 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$-$\underline{C}$H$_2$-O); 62.4 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$-$\underline{C}$H$_2$-O); 125.9 (s, CH$_2$-$\underline{C}$=C-S); 132.8 (s, CH$_2$-$\underline{C}$-S); 141.5 (s, $\underline{C}$=C-S); 160.8 (d, $^2J_{CP}$ = 25.7 Hz, $\underline{C}$=N); 165.8 (s, N-$\underline{C}$-S); 190.4 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$=O); IR (neat): $\nu_{P=O}$ = 1258 cm^{-1}; $\nu_{C=O}$ = 1667 cm^{-1}; MALDI-MS: *m/z* 355.961 ([M+H]$^+$).

3e: Light brown solid; mp 101-103 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 23.2 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.59-2.56 (m, 8H, cyclic H); 3.47 (d, 3H, $^3J_{PH}$ = 9.0 Hz, O-CH$_3$); 3.55 (d, 3H, $^3J_{PH}$ = 9.0 Hz, O-CH$_3$); 3.88 (d, 1H, $^2J_{PH}$ = 24.0 Hz, CH-P); 6.88-7.94 (m, 5H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 22.8 (s, $\underline{C}$H$_2$-CH$_2$-CH$_2$-C=C-S); 23.2 (s, $\underline{C}$H$_2$-CH$_2$-C=C-S); 24.5(s, $\underline{C}$H$_2$-C=C-S); 26.9 (s, $\underline{C}$H$_2$-(CH$_2$)$_3$-C=C-S); 37.0 (d, $^1J_{CP}$ = 113.2 Hz, $\underline{C}$H-P=O); 53.1 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$H$_3$-O); 59.2 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$H$_3$-O); 128.2 (s, CH$_2$-$\underline{C}$=C-S); 128.6 (s, CH$_2$-$\underline{C}$-S); 141.0 (s, $\underline{C}$=C-S); 161.1 (d, $^2J_{CP}$ = 27.2 Hz, $\underline{C}$=N); 165.9 (s, N-$\underline{C}$-S); 191.9 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$=O); Phenyl carbons: 125.2, 127.5, 129.8, 139.6; IR (neat): $\nu_{P=O}$ = 1272 cm^{-1}; $\nu_{C=O}$ = 1669 cm^{-1}; MALDI-MS: *m/z* 390.032 ([M+H]$^+$).

3f: Light brown solid; mp 179-181°C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 23.1 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.59 (d, 3H, $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, O-CH$_3$); 3.62 (d, 3H, $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, O-CH$_3$); 4.03 (s, 2H, CH$_2$-Ph); 4.06 (d, 1H, $^{2}J_{\mathrm{PH}}$ = 12.0 Hz, CH-P); 6.98-7.85 (m, 15H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 30.8 (s, Ph-$\underline{\mathrm{C}}$H$_2$-C=C-S); 37.3 (d, $^{1}J_{\mathrm{CP}}$ = 131.3 Hz, $\underline{\mathrm{C}}$H-P=O); 53.2 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$H$_3$-O); 59.3 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$H$_3$-O); 129.9 (s, CH$_2$-$\underline{\mathrm{C}}$=C-S); 133.0 (s, Ph-$\underline{\mathrm{C}}$-S); 144.9 (s, $\underline{\mathrm{C}}$=C-S); 165.5 (d, $^{2}J_{\mathrm{CP}}$ = 25.7 Hz, $\underline{\mathrm{C}}$=N); 168.9 (s, N-$\underline{\mathrm{C}}$-S); 191.6 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons: 125.3, 126.1, 126.4, 127.1, 127.6, 128.2, 128.6, 128.8, 133.7, 135.7, 142.5, 143.0; IR (neat): $\nu_{\mathrm{P=O}}$ = 1267 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1682 cm^{-1}; MALDI-MS: *m/z* 502.082 ([M+H]$^{+}$).

3g: Light brown solid; mp 134-136 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 21.2 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.80 (t, 3H, $^{3}J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 1.20 (t, 3H, $^{3}J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 2.15 (s, 3H, CH$_3$-C=N); 3.66 (d, 1H, $^{2}J_{\mathrm{PH}}$ = 21.0 Hz, CH-P); 3.90 (quint, 2H, $^{3}J_{\mathrm{HH}}$ = $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 4.01 (quint, 2H, $^{3}J_{\mathrm{HH}}$ = $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 4.05 (s, 2H, CH$_2$-Ph); 6.99-7.66 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 16.2 (d, $^{3}J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 16.3 (d, $^{3}J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 27.1 (s, $\underline{\mathrm{C}}$H$_3$-C=N); 31.7 (s, $\underline{\mathrm{C}}$H$_2$-Ph); 43.8 (d, $^{1}J_{\mathrm{CP}}$ = 116.3 Hz, $\underline{\mathrm{C}}$H-P=O); 59.3 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 62.9 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 129.3 (s, CH$_2$-$\underline{\mathrm{C}}$=C-S); 133.3 (s, Ph-$\underline{\mathrm{C}}$-S); 144.7 (s, $\underline{\mathrm{C}}$=C-S); 163.8 (d, $^{2}J_{\mathrm{CP}}$ = 18.9 Hz, $\underline{\mathrm{C}}$=N); 166.0 (s, N-$\underline{\mathrm{C}}$-S); 205.2 (d, $^{2}J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons: 125.4, 127.0, 127.8, 128.1, 128.7, 129.9, 132.4, 134.1; IR (neat): $\nu_{\mathrm{P=O}}$ = 1271 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1674 cm^{-1}; MALDI-MS: *m/z* 468.028 ([M+H]$^{+}$).

3h: Light brown solid; mp 112-114 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 23.7 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.09 (s, 3H, CH$_3$-C=N); 3.47 (d, 3H, $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, O-CH$_3$); 3.57 (d, 3H, $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, O-CH$_3$); 3.64 (s, 2H, CH$_2$-Ph); 4.03 (d, 1H, $^{2}J_{\mathrm{PH}}$ = 18.0 Hz, CH-P); 6.52-7.92 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 27.2 (s, $\underline{\mathrm{C}}$H$_3$-C=N); 31.5 (s, $\underline{\mathrm{C}}$H$_2$-Ph); 42.3 (d, $^{1}J_{\mathrm{CP}}$ = 141.1 Hz, $\underline{\mathrm{C}}$H-P=O); 56.5 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$H$_3$-O); 59.4 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$H$_3$-O); 129.6 (s, CH$_2$-$\underline{\mathrm{C}}$=C-S); 132.6 (s, Ph-$\underline{\mathrm{C}}$-S); 145.0 (s, $\underline{\mathrm{C}}$=C-S); 165.1 (d, $^{2}J_{\mathrm{CP}}$ = 29.4 Hz, $\underline{\mathrm{C}}$=N); 166.5 (s, N-$\underline{\mathrm{C}}$-S); 205.9 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons: 125.3, 127.7, 128.4, 129.1, 129.7, 132.6, 134.1, 142.1; IR (neat): $\nu_{\mathrm{P=O}}$ = 1271 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1669 cm^{-1}; MALDI-MS: *m/z* 440.078 ([M+H]$^{+}$).

3i: Light brown solid; mp 110-112 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 24.4 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.16 (t, 3H, $^{3}J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 1.22 (t, 3H, $^{3}J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 2.48 (s, 3H, CH$_3$-C=N); 3.36 (d, 1H, $^{2}J_{\mathrm{PH}}$ = 21.0 Hz, CH-P); 3.99 (quint, 2H, $^{3}J_{\mathrm{HH}}$ = $^{3}J_{\mathrm{PH}}$ = 6.0 Hz; CH$_3$-C$\underline{\mathrm{H}}_2$-O); 4.06 (quint, 2H, $^{3}J_{\mathrm{HH}}$ = $^{3}J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 7.21-7.85 (m, 6H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 14.3 (d, $^{3}J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 16.1 (d, $^{3}J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 26.5 (s, $\underline{\mathrm{C}}$H$_3$-C=N); 42.9 (d, $^{1}J_{\mathrm{CP}}$ = 132.1 Hz, $\underline{\mathrm{C}}$H-P=O); 64.7 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 66.7 (d, $^{2}J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 133.1

(s, H-$\underline{\mathrm{C}}$-S); 136.9 (s, Ph-$\underline{\mathrm{C}}$=C-S); 144.7 (s, $\underline{\mathrm{C}}$=C-S); 161.8 (d, $^2J_{\mathrm{CP}}$ = 25.7 Hz, $\underline{\mathrm{C}}$=N); 163.0 (s, N-$\underline{\mathrm{C}}$-S); 198.2 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons: 125.9, 128.4, 133.1, 140.4; IR (neat): $\nu_{\mathrm{P=O}}$ = 1273 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1693 cm^{-1}; MALDI-MS: *m/z* 378.017 ([M+H]$^+$).

3j: Light brown solid; mp 119-121 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 22.3 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.07 (t, 3H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 1.18 (t, 3H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 2.32 (s, 3H, CH$_3$-C=C); 3.43 (d, 1H, $^2J_{\mathrm{PH}}$ = 21.0 Hz, CH-P); 3.68 (s, 2H, CH$_2$-Ph); 3.92 (quint, 2H, $^3J_{\mathrm{HH}}$ = $^3J_{\mathrm{PH}}$= 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 4.07 (quint, 2H, $^3J_{\mathrm{HH}}$ = $^3J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 6.89-7.88 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 14.5 (d, $^3J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 16.2 (d, $^3J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 21.4 (s, $\underline{\mathrm{C}}$H$_3$-C=C); 33.0 (s, Ph-$\underline{\mathrm{C}}$H$_2$); 38.4 (d, $^1J_{\mathrm{CP}}$ = 129.8 Hz, $\underline{\mathrm{C}}$H-P=O); 59.1 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 62.4 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 128.0 (s, CH$_3$-$\underline{\mathrm{C}}$=C-S); 130.9 (s, CH$_2$-$\underline{\mathrm{C}}$-S); 140.4 (s, $\underline{\mathrm{C}}$=C-S); 162.8 (d, $^2J_{\mathrm{CP}}$ = 19.6 Hz, $\underline{\mathrm{C}}$=N); 166.6 (s, N-$\underline{\mathrm{C}}$-S); 191.3 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons: 125.3, 126.2, 127.7, 128.3, 129.0, 133.0, 136.6, 139.8; IR (neat): $\nu_{\mathrm{P=O}}$ = 1269 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1693 cm^{-1}; MALDI-MS: *m/z* 468.097 ([M+H]$^+$).

3k: Light brown solid; mp 249-251 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 22.2 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.11 (t, 3H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 1.18 (t, 3H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, C$\underline{\mathrm{H}}_3$-CH$_2$-O); 2.40 (s, 3H, CH$_3$-C=C); 3.49 (d, 1H, $^2J_{\mathrm{PH}}$ = 24.0 Hz, CH-P); 3.99 (quint, 2H, $^3J_{\mathrm{HH}}$ = $^3J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 4.13 (quint, 2H, $^3J_{\mathrm{HH}}$ = $^3J_{\mathrm{PH}}$ = 6.0 Hz, CH$_3$-C$\underline{\mathrm{H}}_2$-O); 6.98-7.87 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 14.4 (d, $^3J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 16.3 (d, $^3J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$H$_3$-CH$_2$-O); 27.0 (s, $\underline{\mathrm{C}}$H$_3$-C=C); 38.6 (d, $^1J_{\mathrm{CP}}$ = 129.1 Hz, $\underline{\mathrm{C}}$H-P=O); 59.3 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 62.5 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, CH$_3$-$\underline{\mathrm{C}}$H$_2$-O); 129.0 (s, CH$_3$-$\underline{\mathrm{C}}$=C-S); 134.3 (s, CH$_3$-C=$\underline{\mathrm{C}}$-S); 137.7 (s, $\underline{\mathrm{C}}$=C-S); 163.4 (d, $^2J_{\mathrm{CP}}$ = 19.8 Hz, $\underline{\mathrm{C}}$=N); 166.2 (s, N-$\underline{\mathrm{C}}$-S); 191.8 (d, $^2J_{\mathrm{CP}}$ = 6.8 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons : 125.3, 126.9, 128.3, 129.0, 132.4, 133.6, 136.5, 137.4; IR (neat): $\nu_{\mathrm{P=O}}$ = 1270 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1692 cm^{-1}; MALDI-MS: *m/z* 454.015 ([M+H]$^+$).

3l: Light brown solid; mp 128-130 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 27.6 ppm; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.18 (d, 6H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, ((C$\underline{\mathrm{H}_3}$)$_2$CH); 2.23 (s, 3H, CH$_3$-C=C); 3.75 (sept, 1H, $^3J_{\mathrm{H\text{-}H}}$ = 6.0 Hz, ((CH$_3$)$_2$C$\underline{\mathrm{H}}$); 4.06 (d, 1H, $^2J_{\mathrm{PH}}$ = 24.0 Hz, CH-P); 7.04-7.87 (m, 15H, arom-H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 13.3 (s, $\underline{\mathrm{C}}$H$_3$-C=C); 18.7 (s, ($\underline{\mathrm{C}}$H$_3$)$_2$CH); 21.3 (s, (CH$_3$)$_2$$\underline{\mathrm{C}}$H); 41.9 (d, $^1J_{\mathrm{CP}}$ = 59.6 Hz, $\underline{\mathrm{C}}$H-P=O); 128.8 (s, CH$_3$-$\underline{\mathrm{C}}$=C-S); 131.5 (s, CH-$\underline{\mathrm{C}}$-S); 135.9 (s, $\underline{\mathrm{C}}$=C-S); 162.0 (d, $^2J_{\mathrm{CP}}$ = 23.4 Hz, $\underline{\mathrm{C}}$=N); 163.5 (s, N-$\underline{\mathrm{C}}$-S); 191.8 (d, $^2J_{\mathrm{CP}}$ = 6.0 Hz, $\underline{\mathrm{C}}$=O); Phenyl carbons : 124.3, 127.2, 127.5, 127.9, 128.2, 130.0, 130.3, 130.7, 131.1, 132.1, 132.6, 136.8; IR (neat): $\nu_{\mathrm{P=O}}$ = 1280 cm^{-1}; $\nu_{\mathrm{C=O}}$ = 1684 cm^{-1}; MALDI-MS: *m/z* 484.066 ([M+H]$^+$).

3m: Light brown solid; mp 94-96 °C; ^{31}P NMR (121.5 MHz, CDCl$_3$): δ = 24.3 ppm; ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 2.01 (s, 3H, CH_3-C=C); 2.05 (s, 3H, CH_3-C=N); 2.82 (s, 3H, CH_3-C-S); 3.65 (d, 3H, $^3J_{PH}$ = 6.0 Hz, O-CH_3); 3.69 (d, 3H, $^3J_{PH}$ = 6.0 Hz, O-CH_3); 3.04 (d, 1H, $^2J_{PH}$ = 24.0 Hz, CH-P); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (s, $\underline{C}H_3$-C-S); 14.6 (s, $\underline{C}H_3$-C=C-S); 22.7 (s, $\underline{C}H_3$-C=N); 41.8 (d, $^1J_{CP}$ = 129.1 Hz, $\underline{C}$H-P=O); 52.6 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}H_3$-O); 59.3 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}H_3$-O); 124.3 (s, CH_3-$\underline{C}$=C-S); 130.3 (s, CH_3-$\underline{C}$-S); 144.8 (s, $\underline{C}$=C-S); 165.5 (d, $^2J_{CP}$ = 23.4 Hz, $\underline{C}$=N); 166.0 (s, N-$\underline{C}$-S); 199.8 (d, $^2J_{CP}$ = 6.8 Hz, $\underline{C}$=O); IR (neat): $\nu_{P=O}$ = 1271 cm^{-1}; $\nu_{C=O}$ = 1668 cm^{-1}; MALDI-MS: *m/z* 302.025 ([M+H]$^+$).

3n: Light brown solid; mp 84-86 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.8 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 3H, $^3J_{H-H}$ = 6.0 Hz, $C\underline{H}_3$-CH_2-O); 1.29 (t, 3H, $^3J_{H-H}$ = 6.0 Hz, $C\underline{H}_3$-CH_2-O); 2.24 (s, 3H, CH_3-C=C); 2.36 (s, 3H, CH_3-C=N); 3.05 (d, 1H, $^2J_{PH}$ = 18.0 Hz, CH-P); 4.04 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$C\underline{H}_2$-O); 4.18 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$C\underline{H}_2$-O); 7.36 (s, 1H, C=CH-S); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.1 (d, $^3J_{CP}$ = 6.8 Hz, $\underline{C}H_3$-CH_2-O); 15.3 (d, $^3J_{CP}$ = 6.0 Hz, $\underline{C}H_3$-CH_2-O); 23.7 (s, $\underline{C}H_3$-C=C); 30.3 (s, $\underline{C}H_3$-C=N); 42.1 (d, $^1J_{CP}$ = 127.6 Hz, $\underline{C}$H-P=O); 58.6 (d, $^2J_{CP}$ = 6.8 Hz, CH_3-$\underline{C}H_2$-O); 61.5 (d, $^2J_{CP}$ = 6.8 Hz, CH_3-$\underline{C}H_2$-O); 127.8 (s, CH_3-$\underline{C}$=C-S); 134.2 (s, CH_3-C=$\underline{C}$-S); 139.0 (s, $\underline{C}$=C-S); 164.8 (d, $^2J_{CP}$ = 24.1 Hz, $\underline{C}$=N); 168.3 (s, N-$\underline{C}$-S); 198.9 (d, $^2J_{CP}$ = 6.0 Hz, $\underline{C}$=O); IR (neat): $\nu_{P=O}$ = 1268 cm^{-1}; $\nu_{C=O}$ = 1674 cm^{-1}; MALDI-MS: *m/z* 316.047 ([M+H]$^+$).

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