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Novel aminophosphonothiophene derivatives from β-keto-δ-carbethoxyphosphonates and phosphineoxides

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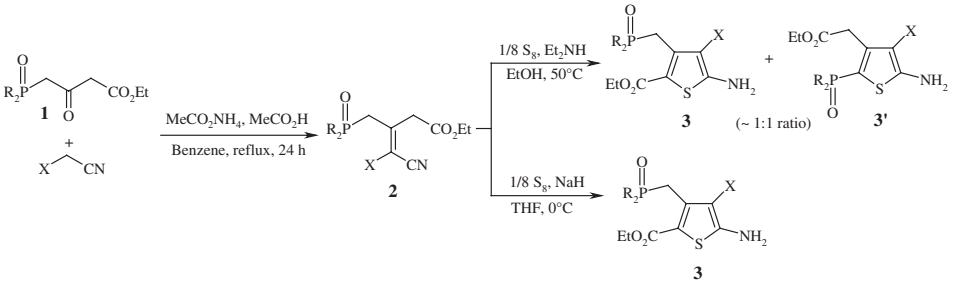
The reaction of β-keto-δ-carbethoxyphosphonates and phosphineoxides with active methylene nitriles leads to the corresponding phosphonoalkylidenes. Treatment of these compounds with sulfur, under the classical Gewald reaction conditions, gives a ca. 1:1 mixture of novel aminophosphonothiophene derivatives **3** and **3′**. In order to improve the regioselectivity of the reaction, novel conditions have been developed for the Gewald condensation, in which we used an inorganic base NaH in THF as the solvent. These conditions afforded exclusively the **3**-regioisomer in good yield.



Keywords: thiophenes; aminophosphonothiophenes; ketophosphonates; Gewald reaction; regioselectivity

1. Introduction

Thiophene derivatives prepared via the Gewald reaction (*1–4*) recently have seen increasing interest due to the utility of these heterocycles as starting points for the synthesis of a variety of agrochemicals (*4*, *5*), dyes (*6*) and pharmacologically active compounds. For instance, it has recently been reported that these thiophene scaffolds are valuable intermediates in the synthesis of inhibitors of the phosphatase PTP1B (*7*), kainate receptor subtype GluR6 (*8*), human leukocyte elastase (*9*), adenosine receptor A_3 (*10*) and multitargeted kinase (*11*). In this area, we

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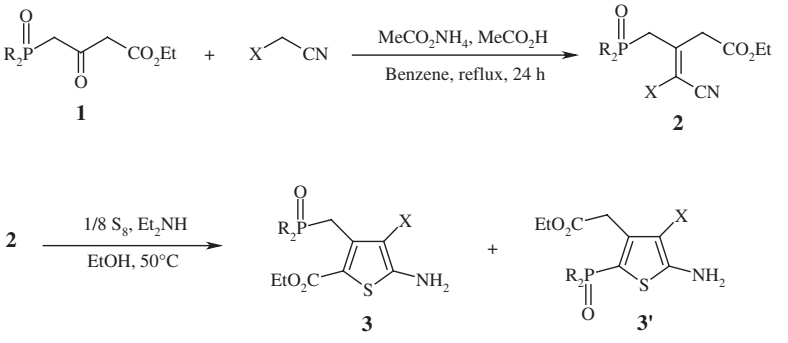
have previously shown that α, β and γ-ketophosphonates undergo Gewald condensation to give aminophosphonothiophene derivatives (*12–15*). We report in the present investigation the extension of this reaction to the β-keto-δ-carbethoxyphosphonates and phosphineoxides **1** (*16*). Our ultimate aim here was to compare the reactivity of carbons in the α, α′ positions with the keto function in order to obtain more precise information about the regioselectivity of the Gewald reaction and to access new aminophosphonothiophene derivatives bearing the ethoxycarbonyl group.

2. Results and discussion

The condensation of compounds **1** with active methylene nitriles performed in refluxing benzene for 24 h, in the presence of catalytic amounts of ammonium acetate and acetic acid, leads to the phosphonoalkylidenes **2** in 60–90% yield. Treatment of alkylidenes **2** with an equimolar quantity of sulfur, under the classical Gewald reaction conditions (Method A), that is, using a catalytic amount of diethylamine in ethanol as solvent and heating the solution at 50°C for 24–48 h, gives a mixture of two aminophosphonothiophenes **3** and **3′** (Scheme 1) in an approximate 1:1 ratio and a combined yield of 55–87% (Table 1).



3, 3′	a	b	c	d	e		f	g
R	Ph	EtO	MeO	Ph	EtO	R_2P		
X	CN	CN	CN	CO_2Et	CO_2Et	X	CN	CN

Scheme 1. Synthesis of aminophosphonothiophenes **3** and **3′** (Method A).

Mechanistically (*12–15*), it is clear that deprotonation of **2** with diethylamine produces an equilibrium mixture of α- and γ-anions which react with sulfur leading to thiophenes **3** and **3′** (Scheme 2).

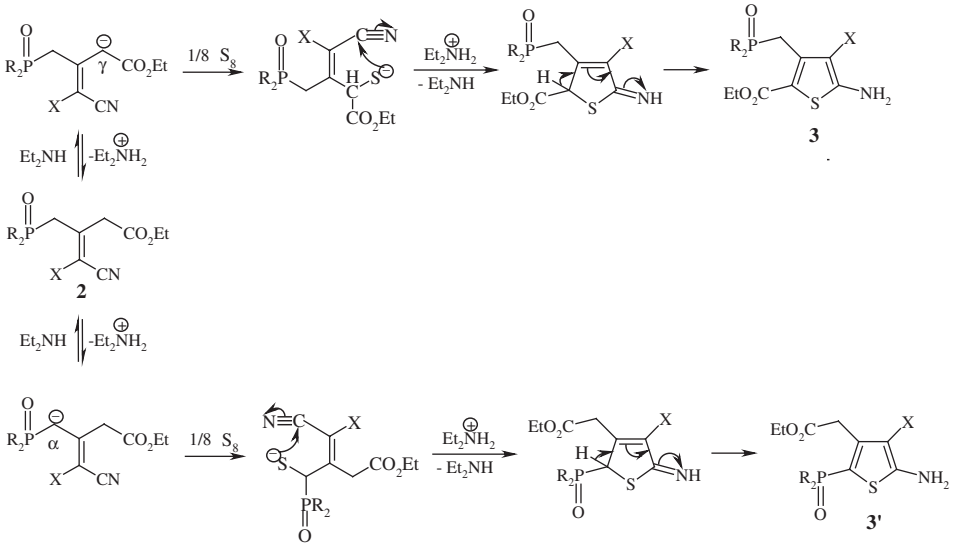
2.1. *Regioselective synthesis of aminophosphonothiophenes 3 (Method B)*

With the aim to improve the regioselectivity of the reaction, we first carried out a theoretical AM1 calculation with Gaussian 03 program, in order to compare the acidity of hydrogens at the α, α′ positions to the C=C double bond in alkylidenes **2**. The results suggest that the hydrogens at the α position to the ethoxycarbonyl group are the most acidic (Scheme 3).

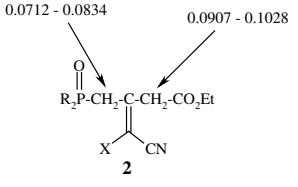
Table 1. Synthesis of aminophosphonothiophenes **3** and **3′**.

Entry	Method	Products	% **3**/**3′**	Reaction time (h)[a]	Yield (%)[b]
1	A	**3a** + **3′a**	44/56	24	87
2	A	**3b** + **3′b**	52/48	24	68
3	A	**3c** + **3′c**	55/45	24	72
4	A	**3d** + **3′d**	59/41	24	79
5	A	**3e** + **3′e**	56/44	24	55
6	A	**3f** + **3′f**	53/47	48	68
7	A	**3g** + **3′g**	52/48	48	57
8	B	**3a**	–	3	81
9	B	**3b**	–	3	70
10	B	**3c**	–	3	76
11	B	**3d**	–	3	72
12	B	**3e**	–	3	63
13	B	**3f**	–	3	75
14	B	**3g**	–	3	78

Notes: [a]The progress of the reactions was monitored by TLC; [b]Yield of isolated products.



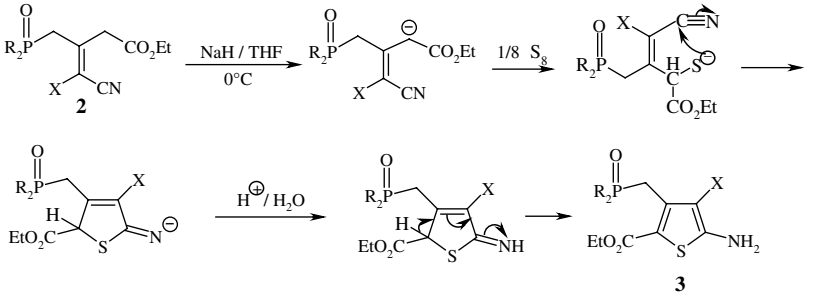
Scheme 2. Reaction mechanism (Method A).



Scheme 3. Calculated Mulliken charges of hydrogen at α, α′ positions to the C=C double bond in alkylidenes **2**.

On the basis of these results, we surmised that kinetic control of the reaction using a strong base such as NaH, at lower temperature, could allow us to abstract selectively the more acidic hydrogen at the α position to the ethoxycarbonyl group, leading regioselectively to compounds **3**.

Experimentally, the reaction of alkylidenes **2** with sulfur at 0°C, using an equimolar amount of NaH in THF as solvent, and stirring the solution at the same temperature for 3 h leads regioselectively to aminophosphonothiophenes **3** in good yield (Scheme 4).



	3a	**3b**	**3c**	**3d**	**3e**		**3f**	**3g**
R	Ph	EtO	MeO	Ph	EtO	R_2P		
X	CN	CN	CN	CO_2Et	CO_2Et	X	CN	CN

Scheme 4. Regioselective synthesis of aminophosphonothiophenes **3** (Method B).

The formation of compounds **3** and **3′** was confirmed by IR, NMR (^1H, ^{31}P, ^{13}C) and mass spectral data. We observed, in particular, the appearance of broad singlets at 5–6 ppm, corresponding to the protons of NH_2 groups. For compounds **3**, we observed a doublet at 3.5–4.5 ppm, ascribable to the CH_2–P=O protons. Such a doublet is characteristic of the coupling with phosphorus with a $^2J_{PH}$ coupling constant of about 10–15 Hz. As for compounds **3′**, we notice the absence of the signal assignable to the CH_2–P=O protons and the presence of a singlet (in some cases a doublet with a small $^4J_{PH}$ coupling constant) towards 3.8 ppm corresponding to the methylene at the α position to the ethoxycarbonyl group.

Other evidence of structure for aminophosphonothiophenes **3** and **3′** is provided by ^{13}C NMR. Indeed, we find the signals of all carbons and particularly those corresponding to the thiophene ring.

3. Experimental section

^1H, ^{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 ^1H and ^{13}C NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P NMR. The coupling constants are reported in hertz. For the ^1H NMR, the multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qp, quintet; m, multiplet.

Mass spectra were determined on a Micromass Quatro-ultima Pt (triple quadrupole) spectrometer, under electrospray ionization (ESI) conditions. IR spectra were recorded on a Perkin Elmer Paragon 1000 PC spectrometer. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

3.1. *Synthesis of phosphonoalkylidene intermediates 2*

A mixture of β-keto-δ-carbethoxyphosphonate or phosphineoxide **1** (0.01 mol), active methylene nitrile (0.01 mol), ammonium acetate (0.15 g) and acetic acid (0.2 ml) in dry benzene (25 ml) was heated at reflux, with Dean-Stark separation of water, for 24 h. The mixture was then cooled, diluted with water (30 ml) and extracted with $CHCl_3$ (2 × 25 ml). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was recrystallized from a mixture of toluene, hexane and ether.

3.2. *Synthesis of aminophosphonothiophenes 3 and 3′ (Method A)*

To a mixture of phosphonoalkylidene **2** (0.01 mol) and sulfur (0.011 mol) in ethanol (30 ml), a solution of diethylamine (1 ml) in ethanol (5 ml) was added dropwise with stirring. The reaction mixture was then stirred at 50°C for 24–48 h (Table 1). The ethanol was removed under reduced pressure and then $CHCl_3$ (100 ml) was added. The organic phase was washed with 5% aqueous HCl solution (2 × 50 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was chromatographed on a silica gel column using a mixture of ether and ethanol 98:2 as the eluent.

3.3. *Regioselective synthesis of aminophosphonothiophenes 3 (Method B)*

To a mixture of phosphonoalkylidene **2** (0.01 mol), sulfur (0.011 mol) and THF (30 ml), cooled at 0°C and maintained under a nitrogen atmosphere, a suspension of NaH (0.01 mol) in THF (5 ml) was added dropwise with stirring. The reaction mixture was then stirred at 0°C for 3 h. A 5% aqueous HCl solution (30 ml) was added and stirring was continued for 15 min. The mixture was then extracted with $CHCl_3$ (2 × 30 ml). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was chromatographed on a silica gel column using a mixture of ether and ethanol 98:2 as the eluent.

3a: m.p. = 185°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.1 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t; 3H; $^3J_{HH}$ = 7.2 Hz; C<u>H</u>$_3$–CH_2–O); 4.02 (q; 2H; $^3J_{HH}$ = 7.2 Hz; CH_3–C<u>H</u>$_2$–O); 4.26 (d; 2H; $^2J_{PH}$ = 13.5 Hz; CH_2–P); 6.12 (broad s; 2H; NH_2); 7.26–7.80 (m; 10H; arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ(J_{CP}): 12.4 (CH_3); 30.1 (62.4 Hz; CH_2–P); 58.3 (CH_3–<u>C</u>H_2–O); 87.9 (12.0 Hz; <u>C</u>–CN); 113.0 (CN); 129.9 (EtO_2C–<u>C</u>–S); 137.5 (9.3 Hz; <u>C</u>–CH_2–P); 141.9 (C–NH_2); 166.4 (C = O); Phenyl carbons: 126.8, 126.9, 129.6, 129.7, 130.1, 131.3, 132.0; IR (neat): ν_{NH_2} = 3305–3412 cm^{-1}; ν_{CN} = 2220 cm^{-1}; $\nu_{C=O}$ = 1728 cm^{-1}; $\nu_{P=O}$ = 1264 cm^{-1}; ESI-MS: m/z = 411.414($[M + H]^+$).

3b: Oil, ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.8 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–1.36 (m; 9H; 3 C<u>H</u>$_3$–CH_2–O); 3.99–4.19 (m; 8H; 3 CH_3–C<u>H</u>$_2$–O and CH_2–P); 5.76 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 13.2 (<u>C</u>H_3–CH_2–O); 15.1 (3.8 Hz; <u>C</u>H_3–CH_2–O–P); 32.0 (168.3 Hz; CH_2–P); 60.4 (CH_3–<u>C</u>H_2–O); 61.7 (4.5 Hz; CH_3–<u>C</u>H_2–O–P); 90.7 (<u>C</u>–CN); 114.3 (CN); 124.5 (EtO_2C–<u>C</u>–S); 129.5 (5.3 Hz; <u>C</u>–CH_2–P); 156.9 (C–NH_2); 164.0 (C = O); IR (neat): ν_{NH_2} = 3200–3310 cm^{-1}; ν_{CN} = 2225 cm^{-1}; $\nu_{C=O}$ = 1720 cm^{-1}; $\nu_{P=O}$ = 1260 cm^{-1}; ESI-MS: m/z = 347.329($[M + H]^+$).

3c: Oil, ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 31.3 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t; 3H; $^3J_{HH}$ = 9.0 Hz; C<u>H</u>$_3$–CH_2–O); 3.85 (d; 6H; $^2J_{PH}$ = 3 Hz ; 2 CH_3–O); 4.05 (d; 2H; $^2J_{PH}$ = 9.0 Hz; CH_2–P); 4.24 (q; 2H; $^3J_{HH}$ = 9.0 Hz; CH_3–C<u>H</u>$_2$–O); 6.15 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 12.7 (<u>C</u>H_3–CH_2–O); 29.8 (166.0 Hz; CH_2–P); 58.8 (9.8 Hz; CH_3–O); 67.8 (CH_3–<u>C</u>H_2–O); 90.7 (<u>C</u>–CN); 111.1 (CN); 129.6 (EtO_2C–<u>C</u>–S); 136.7 (<u>C</u>–CH_2–P); 151.9 (C–NH_2); 164.5 (C = O); IR (neat): ν_{NH_2} = 3285–3400 cm^{-1}; ν_{CN} = 2215 cm^{-1}; $\nu_{C=O}$ = 1710 cm^{-1}; $\nu_{P=O}$ = 1270 cm^{-1}; ESI-MS: m/z = 319.277($[M + H]^+$).

3d: Oil, ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.1 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.29 (m; 6H; 2 C<u>H</u>$_3$–CH_2–O); 3.14–4.31 (m; 4H; 2 CH_3–C<u>H</u>$_2$–O); 3.59 (d; 2H; $^2J_{PH}$ = 12.0 Hz; CH_2–P); 6.45 (broad s; 2H; NH_2); 7.21–7.83 (m; 10H; arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 11.9 (<u>C</u>$H_3CH_2O_2C$); 13.2 (<u>C</u>$H_3CH_2O_2C$–C–S); 40.9 (83.0 Hz; CH_2–P); 58.6 (CH_3–<u>C</u>H_2–O_2C); 58.9 (CH_3<u>C</u>H_2O_2C–C–S); 127.2 (<u>C</u>–CO_2Et); 130.5 (11.3 Hz; <u>C</u>–CH_2–P); 131.9 (S–<u>C</u>–CO_2Et); 161.0 (C–NH_2); 165.1 (<u>C</u>O_2Et); 165.9 (S–C–<u>C</u>O_2Et); Phenyl carbons: 127.4, 127.8, 127.90, 127.94, 130.1, 130.3, 130.4; IR (neat): ν_{NH_2} = 3320–3410 cm^{-1}; ν_{CN} = 2215 cm^{-1}; $\nu_{C=O}$ = 1728 cm^{-1}; $\nu_{P=O}$ = 1265 cm^{-1}; ESI-MS: m/z = 458.462([M + H]$^+$).

3e: Oil, ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 28.1 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–1,28 (m; 12H; 4 C<u>H</u>$_3$–CH_2–O); 4.15–4.56 (m; 10H; 4 CH_3–C<u>H</u>$_2$–O and CH_2–P); 6.85 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 14.7 (<u>C</u>$H_3CH_2O_2C$–CH_2); 14.2 (<u>C</u>H_3–CH_2–O–C); 15.1 (6.8 Hz; <u>C</u>H_3–CH_2–O–P); 30.2 (126.0 Hz; CH_2–P); 60.7 (CH_3<u>C</u>H_2O_2C); 62.1 (CH_3<u>C</u>H_2O_2C–C–S); 62.6 (6.0 Hz; CH_3–<u>C</u>H_2–O–P); 119.2 (<u>C</u>–CO_2Et); 121.3 (EtO_2C–<u>C</u>–S); 129.6 (<u>C</u>–CH_2–P); 139.6 (7.5 Hz; C–NH_2); 163.0 (<u>C</u>O_2Et); 167.8 (S–C–<u>C</u>O_2Et); IR (neat): ν_{NH_2} = 3350–3463 cm^{-1}; ν_{CN} = 2214 cm^{-1}; $\nu_{C=O}$ = 1730 cm^{-1}; $\nu_{P=O}$ = 1267 cm^{-1}; ESI-MS: m/z = 394.379([M + H]$^+$).

3f: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = −7.5 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t; 3H; $^3J_{HH}$ = 6.0 Hz; C<u>H</u>$_3$–CH_2–O); 3.46–4.71 (m; 8H; CH_3–C<u>H</u>$_2$–O, –O–C<u>H</u>$_2$–C<u>H</u>$_2$–O– and CH_2–P); 5.32 (broad s; 2H; N<u>H</u>$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 13.0 (CH_3); 32.1 (174,3 Hz; CH_2–P); 63.8 (6.8 Hz; –O–<u>C</u>H_2–<u>C</u>H_2–O); 64.4 (CH_3–<u>C</u>H_2–O); 97.5 (<u>C</u>–CN); 105.7 (CN); 124.5 (<u>C</u>–CO_2Et); 134.8 (<u>C</u>–CH_2–P); 161.8 (C–NH_2); 178.5 (C = O); IR (neat): ν_{NH_2} = 3300–3410 cm^{-1}; ν_{CN} = 2220 cm^{-1}; $\nu_{C=O}$ = 1725 cm^{-1}; $\nu_{P=O}$ = 1270 cm^{-1}; ESI-MS: m/z = 317.241([M + H]$^+$).

3g: m.p. = 88°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = −8.8 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t; 3H; $^3J_{HH}$ = 3.0 Hz; C<u>H</u>$_3$–CH_2–O); 2.16 (s; 6H; 2 CH_3); 3.95(d; 4H; $^3J_{PH}$ = 12.0 Hz; 2 C<u>H</u>$_2$–O–P); 4.05–4.12 (m; 4H; CH_3–C<u>H</u>$_2$–O and CH_2–P); 5.27 (broad s; 2H;NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 17.4 (<u>C</u>$H_3CH_2O_2C$); 21.8 (2 CH_3): 28.6 (Me_2<u>C</u>); 41.2 (129.8 Hz; CH_2–P); 56.9 (CH_3–<u>C</u>H_2–O); 59.1 (6.0 Hz; 2 <u>C</u>H_2–O–P); 92.8 (C–CN); 109.0 (CN); 114.8 (<u>C</u>–CO_2Et); 132.0 (<u>C</u>–CH_2–P); 141.1 (C–NH_2); 161.7 (C = O); IR (neat): ν_{NH_2} = 3245–3360 cm^{-1}; ν_{CN} = 2226 cm^{-1}; $\nu_{C=O}$ = 1730 cm^{-1}; $\nu_{P=O}$ = 1260 cm^{-1}; ESI-MS: m/z = 359.328 ([M + H]$^+$).

3′a: m.p. = 176°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 20.1 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t; 3H; $^3J_{HH}$ = 7.2 Hz; C<u>H</u>$_3$–CH_2–O); 3.83 (d; 2H; $^4J_{PH}$ = 0.7 Hz; C<u>H</u>$_2$–CO_2Et); 3.98 (q; 2H; $^3J_{HH}$ = 7.2 Hz; CH_3–C<u>H</u>$_2$–O); 5.51 (broad s; 2H; NH_2); 6.95–7.72 (m; 10H; arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 12.2 (CH_3); 32.1 (23.1 Hz; <u>C</u>H_2–CO_2Et); 58.8 (CH_3–<u>C</u>H_2–O); 88.3 (2.6 Hz; <u>C</u>–CN); 106.9 (117.9 Hz; P–C–S); 112.9 (CN); 142.0 (7.8 Hz; <u>C</u>–CH_2–CO_2Et); 159.3 (2.5 Hz; C–NH_2); 166.6 (7.1 Hz; C = O); Phenyl carbons: 126.5, 126.6, 129.2, 129.3, 129.5, 130.0, 130.5; IR (neat): ν_{NH_2} = 3280–3396 cm^{-1}; ν_{CN} = 2216 cm^{-1}; $\nu_{C=O}$ = 1737 cm^{-1}; $\nu_{P=O}$ = 1250 cm^{-1}; ESI-MS: m/z = 411.421([M + H]$^+$).

3′b: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 19.6 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–1.36 (m; 9H; 3 C<u>H</u>$_3$–CH_2–O); 3.82 (s; 2H; C<u>H</u>$_2$–CO_2Et); 3.99–4.19 (m; 6H; 3 CH_3–C<u>H</u>$_2$–O); 5.76 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 14.2 (<u>C</u>H_3–CH_2–O–C); 15.2 (3.8 Hz; <u>C</u>H_3–CH_2–O–P); 26.4 (23.4 Hz; <u>C</u>H_2–CO_2Et); 60.1 (CH_3–<u>C</u>H_2–O); 62.8 (6.0 Hz; CH_3–<u>C</u>H_2–O–P); 90.9 (<u>C</u>–CN); 104.0 (158.5 Hz; P–C–S); 114.3 (CN); 139.7 (7.5 Hz; <u>C</u>–CH_2–CO_2Et); 157.0 (C–NH_2); 167.8 (C = O); IR (neat): ν_{NH_2} = 3196–3310 cm^{-1}; ν_{CN} = 2221 cm^{-1}; $\nu_{C=O}$ = 1740 cm^{-1}; $\nu_{P=O}$ = 1240 cm^{-1}; ESI-MS: m/z = 347.335([M + H]$^+$).

3′c: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 28.5 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t; 3H; $^3J_{HH}$ = 9.0 Hz; C<u>H</u>$_3$–CH_2–O); 3.71 (s; 2H; C<u>H</u>$_2$–CO_2Et); 3.82 (d, 6H; $^3J_{PH}$ = 3 Hz; 2 C<u>H</u>$_3$–O); 4.17 (q; 2H; $^3J_{HH}$ = 9.0 Hz; CH_3–C<u>H</u>$_2$–O); 5.90 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}):12.6 (<u>C</u>H_3–CH_2–O); 34.9 (30.0 Hz; <u>C</u>H_2–CO_2Et); 58.9 (9.8 Hz;

CH_3–O); 67.0 (CH_3–$\underline{C}H_2$–O); 87.6 ($\underline{C}$–CN); 110.8 (CN); 112.1 (164.5 Hz; P–C–S); 145.3 ($\underline{C}$–CH_2–CO_2Et); 148.9 (C–NH_2); 163.2 (C = O); IR (neat): ν_{NH_2} = 3290–3380 cm^{-1}; ν_{CN} = 2210 cm^{-1}; $\nu_{C=O}$ = 1733 cm^{-1}; $\nu_{P=O}$ = 1250 cm^{-1}; ESI-MS: m/z = 319.262($[M + H]^+$).

3′d: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 21.5 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.29 (m; 6H; 2 $C\underline{H}_3$–CH_2–O); 3.14–4.31 (m; 4H; 2 CH_3–$C\underline{H}_2$–O); 3.39 (s; 2H; $C\underline{H}_2$–CO_2Et); 6.45 (broad s; 2H; NH_2); 7.21–7.83 (m; 10H; arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 12.7 ($\underline{C}H_3CH_2O_2C$–CH_2); 12,9 ($\underline{C}H_3CH_2O_2C$); 29.1 (30.9 Hz; $\underline{C}H_2$–CO_2Et); 59.9 ($CH_3\underline{C}H_2O_2C$–CH_2); 60.3 ($CH_3\underline{C}H_2O_2C$); 127.5 ($\underline{C}$–CO_2Et); 112.9 (98.1 Hz; P–C–S); 129.9 ($\underline{C}$–CH_2–CO_2Et); 161.6 (C–NH_2;) 162.0 (CH_2–$\underline{C}O_2$Et); 165.9 ($\underline{C}O_2$Et); Phenyl carbons: 127.58, 127.61, 128.1, 129.8, 129.9, 130.0, 131.5; IR (neat): ν_{NH_2} = 3300–3390 cm^{-1}; ν_{CN} = 2210 cm^{-1}; $\nu_{C=O}$ = 1740 cm^{-1}; $\nu_{P=O}$ = 1260 cm^{-1}; ESI-MS: m/z = 458.449($[M + H]^+$).

3′e: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 17.7 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–1.28 (m; 12H; 4 $C\underline{H}_3$–CH_2–O); 4.15–4.56 (m; 10H; 4 CH_3–$C\underline{H}_2$–O and $C\underline{H}_2$–CO_2Et); 5.03 (broad s; 2H; NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 12.9 ($\underline{C}H_3$–CH_2O_2C–CH_2–); 13.1 (4.5 Hz; $\underline{C}H_3$–CH_2–O–P); 17.2 ($\underline{C}H_3$–CH_2–O_2C); 28.5 (24.6 Hz; $\underline{C}H_2$–CO_2Et); 60.7 (CH_3–$\underline{C}H_2O_2C$–CH_2); 64.0 (6.0 Hz; CH_3–$\underline{C}H_2$–O–P); 67.0 (CH_3–$\underline{C}H_2$–O_2C); 109.5 (113.0 Hz; P–C–S); 114.4 ($\underline{C}$–CO_2Et); 129.5 ($\underline{C}$–CH_2–CO_2Et); 156.0 (C–NH_2); 157.0 (CH_2–$\underline{C}O_2$Et), 167.8 ($\underline{C}O_2$Et); IR (neat): ν_{NH_2} = 3338–3444 cm^{-1}; ν_{CN} = 2222 cm^{-1}; $\nu_{C=O}$ = 1740 cm^{-1}; $\nu_{P=O}$ = 1270 cm^{-1}; ESI-MS: m/z = 394.363($[M + H]^+$).

3′f: Oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = −8.7 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t; 3H; $^3J_{HH}$ = 6.0 Hz; $C\underline{H}_3$–CH_2–O); 3.46–4.71 (m; 8H; CH_3–$C\underline{H}_2$–O, $C\underline{H}_2$–CO_2Et and –O–$C\underline{H}_2$–$C\underline{H}_2$–O–); 5.79 (broad s; 2H; $N\underline{H}_2$) ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 13.2 (CH_3); 28.2 (23.4 Hz; $\underline{C}H_2$–CO_2Et); 59.2 (CH_3–$\underline{C}H_2$–O); 66.4 (6.0 Hz; –O–$\underline{C}H_2$–$\underline{C}H_2$–O); 97.6 ($\underline{C}$–CN); 96.0 (150.0 Hz; P–C–S); 105.6 (CN); 151.1 (9.1 Hz; $\underline{C}$–CH_2–CO_2Et); 161.9 (C–NH_2); 165.1 (C = O); IR (neat): ν_{NH_2} = 3320–3430 cm^{-1}; ν_{CN} = 2210 cm^{-1}; $\nu_{C=O}$ = 1740 cm^{-1}; $\nu_{P=O}$ = 1240 cm^{-1}; ESI-MS: m/z = 317.252($[M + H]^+$).

3′g: m.p. = 88°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = −14.6 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t; 3H; $^3J_{HH}$ = 6.0 Hz; $C\underline{H}_3$–CH_2–O); 2.37 (s; 6H; $2C\underline{H}_3$); 3.87 (d; 4H; $^3J_{PH}$ = 9.0 Hz; 2 $C\underline{H}_2$–O–P); 4.07 (s; 2H; $C\underline{H}_2$–CO_2E); 4.05–4.12 (m; 2H; CH_3–$C\underline{H}_2$–O); 5.78 (broad s; 2H; $N\underline{H}_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (J_{CP}): 13.2 ($\underline{C}H_3$–CH_2O_2C); 20.6 (2 CH_3): 28.3 ($Me_2\underline{C}$); 31.2 (6.0 Hz; $\underline{C}H_2$–CO_2Et); 57.4 (CH_3–$\underline{C}H_2$–O); 66.9 (6.0 Hz; 2 $\underline{C}H_2$–O–P); 89.0 ($\underline{C}$–CN); 104.9 (135.0 Hz; P–C–S); 111.2 (CN); 131.9 ($\underline{C}$–CH_2–CO_2Et); 146.7 (C–NH_2); 165.1 (C = O); IR (neat): ν_{NH_2} = 3215–3336 cm^{-1}; ν_{CN} = 2222 cm^{-1}; $\nu_{C=O}$ = 1732 cm^{-1}; $\nu_{P=O}$ = 1230 cm^{-1}; ESI-MS: m/z = 359.342($[M + H]^+$).

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