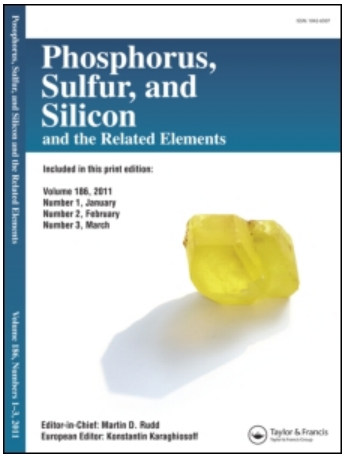


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# Synthesis of New Aminophosphonothiophene Derivatives

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# SYNTHESIS OF NEW AMINOPHOSPHONOTHIOPHENE DERIVATIVES

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*The reaction of $\gamma,\gamma'$-diphosphonylketones **1** with active methylenenitriles and sulfur in basic conditions led to the new 5-amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes **2**. These compounds were then used in the Horner-Wadsworth-Emmons reaction to give 5-amino-2-alkenyl-3-(phosphonoethyl)thiophenes **3**. The structure of all obtained products was confirmed by NMR ($^1H$, $^{31}P$, $^{13}C$) and IR spectroscopy.*

*Keywords:* 5-Amino-2-alkenyl-3-(phosphonoethyl)thiophenes; 5-amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes; $\gamma,\gamma'$-diphosphonylketones



## INTRODUCTION

In our preceding article,[1] we reported the synthesis of $\gamma,\gamma'$-diphosphonylketones and showed that their reaction with phenylhydrazine hydrochloride carried out under the Fischer reaction conditions leads to 2-(phosphonoethyl)3-(phosphonomethyl)indoles.

In order to broaden further the application field of $\gamma,\gamma'$-diphosphonylketones and persuing our research program regarding the synthesis of heterocyclic compounds bearing phosphonyl groups,[2–3] we now report on the synthesis of the new 5-amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes **2** by a Gewald type condensation[4–9] of $\gamma,\gamma'$-diphosphonylketones with active methylenenitriles in the presence of sulfur.

On the other hand, we show that the Horner-Wadsworth-Emmons (HWE) reaction[10–12] of compounds **2** with aldehydes provides a convenient access to 5-amino-2-alkenyl-3-(phosphonoethyl)thiophenes **3**.

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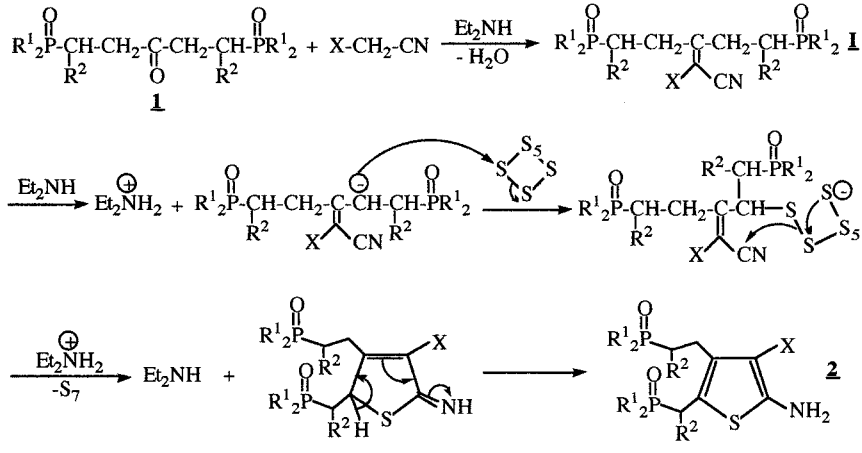
It is important to note that thiophene derivatives prepared via the Gewald reaction recently have seen an increasing interest due to the utility of these heterocycles as a starting point for the synthesis of many biologically active compounds.[8,13–17]

## RESULTS AND DISCUSSION

### Synthesis of 5-Amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes 2

Recently, we have shown that $\gamma$-ketophosphonates undergo Gewald condensation to give 2-amino-5-(phosphonomethyl)thiophenes.[18] We report here the extension of this reaction to $\gamma,\gamma'$-diphosphonylketones **1** which leads to a new class of aminophosphonothiophenes. Thus, treatment of compounds **1** with equimolar amounts of active methylenenitrile and sulfur using a catalytic amount of diethylamine in ethanol as solvent and heating the mixture at 50°C for 12–24 h gives the 5-amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes **2** in 56–78% yield (Scheme 1).

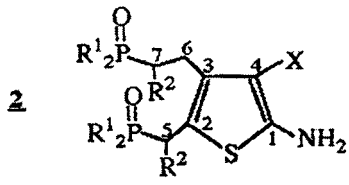


| | 2a | 2b | 2c | 2d | 2e | 2f |
|---|---|---|---|---|---|---|
| $R^1$ | EtO | EtO | Ph | Ph | EtO | EtO |
| $R^2$ | H | H | H | H | Ph | Ph |
| X | CN | $CO_2Et$ | CN | $CO_2Et$ | CN | $CO_2Et$ |

**SCHEME 1**

Based on some literature data,[4,19] we can propose the reaction mechanism of Scheme 1 which involves a condensation, catalyzed by

**TABLE I** $^{13}C$ NMR for Compounds **2**: $\delta$ in ppm ($J_{CP}$ in Hz)




| | **2a** | **2b** | **2c** | **2d** | **2e** | **2f** |
|---|---|---|---|---|---|---|
| $C_1$ | 164.2 | 164.4 | 163.8 | 164.1 | 162.0 | 163.2 |
| $C_2$ | 138.3 (6.9) | 139.5 (7.1) | 140.2 (7.0) | 141.3 (6.5) | 143.3 (7.0) | 142.5 (6.7) |
| $C_3$ | 117.5 (16.0) | 117.1 (16.4) | 117.8 (15.2) | 116.2 (15.5) | 116.8 (15.7) | 115.4 (16.9) |
| $C_4$ | 102.8 | 111.5 | 101.6 | 112.0 | 103.9 | 113.4 |
| $C_5$ | 27.3 (142.6) | 26.8 (141.4) | 33.0 (79.4) | 32.6 (78.5) | 42.0 (138.8:**2e**$_1$) | 42.8 (138.4:**2f**$_1$) |
| | | | | | 43.8 (138.5:**2e**$_2$) | 44.7 (138.0:**2f**$_2$) |
| $C_6$ | 28.7 | 27.4 | 29.9 | 29.4 | 25.0 (3.6) | 24.7 (3.2) |
| $C_7$ | 22.2 (145.5) | 22.0 (144.3) | 31.8 (80.5) | 31.5 (79.9) | 38.6 (144.5:**2e**$_1$) | 38.8 (144.2:**2f**$_1$) |
| | | | | | 38.9 (145.1:**2e**$_2$) | 39.2 (145.9:**2f**$_2$) |
| $C_8$ | 16.0–16.4 | 13.9–16.3 | 128.6–133.5 | 128.4–133.2 | 15.9–16.2 | 14.0–16.3 |
| $C_9$ | 63.2–64.3 | 61.9–63.2 | — | — | 62.1–63.9 | 61.8–63.0 |
| $C_{10}$ | — | — | — | — | 125.7–136.2 | 125.8–135.8 |
| $C_{11}$ | 112.1 | 166.2 | 114.0 | 167.3 | 114.8 (**2e**$_1$) | 164.7 (**2f**$_1$) |
| | | | | | 115.2 (**2e**$_2$) | 164.9 (**2f**$_2$) |
| $C_{12}$ | — | 61.9–63.2 | — | 61.5 | — | 61.8–63.0 |
| $C_{13}$ | — | 13.9–16.3 | — | 14.1 | — | 14.0–16.3 |



diethylamine, of the active methylenenitrile with the ketone **1**. The obtained intermediates **I** undergo a second base-catalyzed condensation with sulfur leading to compounds **2**.

The $^1H$, $^{13}C$, and $^{31}P$ NMR data confirm the structures of compounds **2** and are in accordance with some literature data.[18] The $NH_2$ protons show a broad singlet at $\delta = 8.2$–$8.8$ ppm. The $^{13}C$ NMR spectra display the characteristic signals of all carbons and particularly those corresponding to the thiophene ring (Table I).

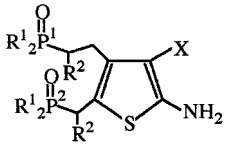
In addition, $^{31}P$, $^1H$, and $^{13}C$ NMR analysis of compounds **2e–f** shows a mixture of two diastereoisomers in an approximate 1:1 ratio which was estimated from the $^{31}P$ NMR spectra (Table II). Indexes 1 and 2 are attributed to the major and minor diastereoisomers respectively.

## Synthesis of 5-Amino-2-alkenyl-3-(phosphonoethyl)thiophenes 3

The presence of the activated phosphonomethyl group on the thiophene ring of compounds **2** allows them to perform HWE reaction. Thus, treatment of compounds **2** with various aldehydes at room temperature, using aqueous potassium carbonate as base and THF as solvent, led to

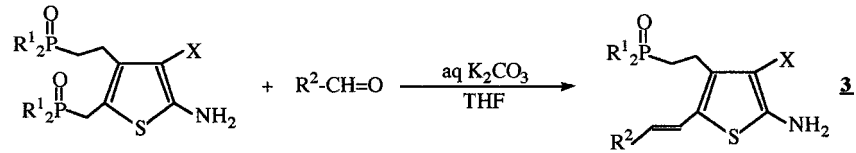
**TABLE II** $\delta$ $^{31}$P in ppm and % of Diastereoisomers for Compounds **2**

**2**



| | **2a** | **2b** | **2c** | **2d** | **2e$_1$** | **2e$_2$** | **2f$_1$** | **2f$_2$** |
|---|---|---|---|---|---|---|---|---|
| $\delta$ $P_1$ | 28.1 | 28.5 | 31.4 | 31.6 | 27.1 | 27.4 | 27.0 | 27.2 |
| $\delta$ $P_2$ | 28.2 | 28.7 | 31.5 | 31.8 | 28.1 | 27.5 | 27.4 | 27.3 |
| % dias | — | — | — | — | 58 | 42 | 53 | 47 |

the 5-amino-2-alkenyl-3-(phosphonoethyl)thiophenes **3** in moderate to good yields (Scheme 2).




| | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
|---|---|---|---|---|---|---|
| $R^1$ | EtO | EtO | Ph | Ph | Ph | EtO |
| $R^2$ | H | H | H | Me | Ph | Ph |
| X | CN | $CO_2Et$ | CN | CN | $CO_2Et$ | CN |

**SCHEME 2**

The reaction was found to be highly stereoselective. Indeed, compounds **3d–f** where a mixture of Z and E isomers is possible, have exclusively the E configuration. This was evidenced by the absence of signal doubling in the $^{31}$P (Table III), $^{13}$C (Table IV) and $^1$H NMR spectra. The E configuration was assigned on the basis of $^3J_{H-C=C-H}$ coupling constant values (16.1–16.8 Hz).

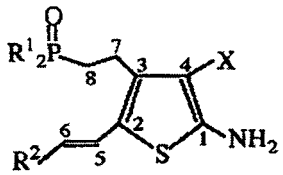
## EXPERIMENTAL SECTION

$^1$H, $^{31}$P, and $^{13}$C NMR spectra were recorded with $CDCl_3$ as 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

**TABLE III** $\delta$ $^{31}$P in ppm for Compounds **3**

| | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
|---|---|---|---|---|---|---|
| $\delta$ $^{31}$P | 27.8 | 28.0 | 31.1 | 31.5 | 30.8 | 27.3 |

**TABLE IV** $^{13}C$ NMR for Compounds **3**: $\delta$ in ppm ($J_{CP}$ in Hz)




**3**

$R^1$ $^{9}CH_3$-$^{10}CH_2$-O, $^{9}C_6H_5$

$R^2$ H, $^{11}CH_3$, $^{11}C_6H_5$

X $^{12}CN$, $^{12}CO_2$-$^{13}CH_2$-$^{14}CH_3$

| | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
|---|---|---|---|---|---|---|
| $C_1$ | 163.6 | 164.0 | 163.2 | 162.7 | 163.8 | 164.1 |
| $C_2$ | 144.0 | 144.3 | 144.9 | 145.5 | 145.8 | 144.7 |
| $C_3$ | 118.9 (15.5) | 118.3 (15.7) | 119.2 (15.0) | 118.8 (15.2) | 119.1 (15.0) | 119.4 (15.3) |
| $C_4$ | 102.0 | 113.2 | 101.2 | 101.5 | 113.8 | 101.8 |
| $C_5$ | 137.5 | 137.1 | 137.3 | 138.4 | 141.9 | 142.5 |
| $C_6$ | 116.0 | 115.7 | 115.8 | 125.6 | 126.4 | 126.8 |
| $C_7$ | 29.1 | 28.0 | 30.1 | 30.4 | 29.5 | 28.4 |
| $C_8$ | 22.8 (144.2) | 22.4 (143.6) | 32.2 (78.5) | 32.5 (79.7) | 31.9 (79.0) | 22.1 (144.6) |
| $C_9$ | 16.1 (6.5) | 16.0 (6.5) | 128.4–133.5 | 128.2–133.2 | 128.1–136.3 | 16.0 (6.7) |
| $C_{10}$ | 61.4 (6.3) | 61.2 (6.2) | — | — | — | 61.2 (6.3) |
| $C_{11}$ | — | — | — | 27.0 | 128.1–136.3 | 128.0–134.6 |
| $C_{12}$ | 112.5 | 166.3 | 112.8 | 112.6 | 167.1 | 112.8 |
| $C_{13}$ | — | 61.8 | — | — | 61.2 | — |
| $C_{14}$ | — | 15.2 | — | — | 14.9 | — |



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, qp: quintet, m: multiplet.

IR spectra were recorded in $CHCl_3$, on a Perkin Elmer Paragon 1000 PC spectrometer.

The progress of the reactions was controlled by TLC.

Purification of products was performed by column chromatography using silica gel 60 (Fluka).

## Synthesis of $\gamma,\gamma'$-Diphosphonylketones 1

The starting $\gamma,\gamma'$-diphosphonylketones **1** were synthesized as described in our preceding article.[1]

## Synthesis of 5-Amino-2-(phosphonomethyl)-3-(phosphonoethyl)thiophenes 2

To a mixture of $\gamma,\gamma'$-diphosphonylketone (0.01 mmol), active methylenenitrile (0.01 mmol) and sulfur (0.011 mmol, 0.35 g) in ethanol (40 mL), was added dropwise with stirring a solution of 1 mL of diethylamine in 10 mL of ethanol. The reaction mixture was then stirred at 50°C for the

time tr. The ethanol was removed under reduced pressure then $CHCl_3$ (100 mL) was added. The organic phase was washed with 5% aqueous HCl solution (2 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was chromatographed on silica gel column using a mixture of ethanol and petroleum ether 9/1 as eluent.

**2a**: Oil; Yield = 74%; tr = 12 h; $^1$H NMR: $\delta = 1.30$ (t; 6H; $^3J_{HH} = 7.0$; $C\underline{H}_3{-}CH_2{-}O$); 1.42 (t; 6H; $^3J_{HH} = 6.9$; $C\underline{H}_3{-}CH_2{-}O$); 1.92–3.60 (m; 6H; $CH_2{-}P{=}O$ and $CH_2{-}CH_2{-}P{=}O$); 3.96 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 6.9$; $CH_3{-}C\underline{H}_2{-}O$); 4.16 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3{-}C\underline{H}_2{-}O$); 8.27 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1260$ cm$^{-1}$; $\nu_{CN} = 2214$ cm$^{-1}$; $\nu_{NH_2} = 3281$–$3390$ cm$^{-1}$.

**2b**: Oil; Yield = 69%; tr = 24 h; $^1$H NMR: $\delta = 1.12$–$1.45$ (m; 15H; $C\underline{H}_3{-}CH_2{-}O$); 1.88–3.52 (m; 6H; $CH_2{-}P{=}O$ and $CH_2{-}CH_2{-}P{=}O$); 3.98–4.20 (m; 10H; $CH_3{-}C\underline{H}_2{-}O$); 8.45 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1268$ cm$^{-1}$; $\nu_{CO_2Et} = 1670$ cm$^{-1}$; $\nu_{NH_2} = 3377$–$3484$ cm$^{-1}$.

**2c**: m.p. 110°C; Yield = 62%; tr = 12 h; $^1$H NMR: $\delta = 1.87$–$3.31$ (m; 6H; $CH_2{-}P{=}O$ and $CH_2{-}CH_2{-}P{=}O$); 6.90–7.87 (m; 20H; H arom.); 8.34 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1265$ cm$^{-1}$; $\nu_{CN} = 2201$ cm$^{-1}$; $\nu_{NH_2} = 3276$–$3388$ cm$^{-1}$.

**2d**: m.p. 118°C; Yield = 56%; tr = 24 h; $^1$H NMR: $\delta = 1.32$ (t; 3H; $^3J_{HH} = 7.3$; $C\underline{H}_3{-}CH_2{-}O$); 1.90–3.48 (m; 6H; $CH_2{-}P{=}O$ and $CH_2{-}CH_2{-}P{=}O$); 4.27 (q; 2H; $^3J_{HH} = 7.3$; $CH_3{-}C\underline{H}_2{-}O$); 7.02–7.93 (m; 20H; H arom.); 8.52 (broad s; 2H; $NH_2$); IR $\nu_{P=O} = 1273$ cm$^{-1}$; $\nu_{CO_2Et} = 1672$ cm$^{-1}$; $\nu_{NH_2} = 3372$–$3480$ cm$^{-1}$.

**2e**: Oil; Yield = 78%; tr = 12 h; $^1$H NMR: $\delta = 0.90$–$1.28$ (m; 12 H; $C\underline{H}_3{-}CH_2{-}O$); 2.78–3.40 (m; 2H; $CH_2{-}C{=}C$); 3.51–3.74 (m; 2H; $CH{-}P{=}O$); 3.85–4.19 (m; 8H; $CH_3{-}C\underline{H}_2{-}O$); 6.80–7.43 (m; 10H; H arom.); 8.60 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1262$ cm$^{-1}$; $\nu_{CN} = 2220$ cm$^{-1}$; $\nu_{NH_2} = 3289$–$3394$ cm$^{-1}$.

**2f**: Oil; Yield = 70%; tr = 24 h; $^1$H NMR: $\delta = 0.92$–$1.35$ (m; 15 H; $C\underline{H}_3{-}CH_2{-}O$); 2.86–3.44 (m; 2H; $CH_2{-}C{=}C$); 3.60–3.81 (m; 2H; $CH{-}P{=}O$); 3.92–4.26 (m; 10H; $CH_3{-}C\underline{H}_2{-}O$); 6.87–7.49 (m; 10H; H arom.); 8.82 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1274$ cm$^{-1}$; $\nu_{CO_2Et} = 1667$ cm$^{-1}$; $\nu_{NH_2} = 3380$–$3486$ cm$^{-1}$.

## Synthesis of 5-Amino-2-alkenyl-3-(phosphonoethyl)thiophenes 3

To a mixture of 5-amino-2-(phosphonomethyl)-3-(phosphonoethyl)-thiophenes **2** (0.005 mmol) and aldehyde (0.006 mmol) in THF (25 mL), was added dropwise with stirring, a 6 M aqueous $K_2CO_3$ solution (2 mL). The reaction mixture was then stirred at room temperature for an additional 24 h. It was then diluted with water (50 mL) and extracted

with $CHCl_3$ (2 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was chromatographed on silica gel column using a mixture of ethanol and petroleum ether 9/2 as eluent.

**3a**: Oil; Yield = 62%; $^1$H NMR: $\delta = 1.26$ (t; 6H; $^3J_{HH} = 7.0$; C<u>H</u>$_3$–$CH_2$–O); 1.86–3.05 (m; 4H; $CH_2$–$CH_2$–P=O); 4.01 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3$–C<u>H</u>$_2$–O); 5.68–6.44 (m; 3H; $CH_2$=CH); 8.11 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1262$ cm$^{-1}$; $\nu_{CN} = 2212$ cm$^{-1}$; $\nu_{NH_2} = 3270$–$3378$ cm$^{-1}$.

**3b**: Oil; Yield = 57%; $^1$H NMR: $\delta = 1.22$ (t; 6H; $^3J_{HH} = 7.0$; C<u>H</u>$_3$–$CH_2$–O); 1.30 (t; 3H; $^3J_{HH} = 7.2$; C<u>H</u>$_3$–$CH_2$–O); 1.82–2.98 (m; 4H; $CH_2$–$CH_2$–P=O); 3.97 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3$–C<u>H</u>$_2$–O); 4.25 (q; 2H; $^3J_{HH} = 7.2$; $CH_3$–C<u>H</u>$_2$–O); 5.53–6.39 (m; 3H; $CH_2$=CH); 8.20 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1265$ cm$^{-1}$; $\nu_{CO_2Et} = 1668$ cm$^{-1}$; $\nu_{NH_2} = 3384$–$3492$ cm$^{-1}$.

**3c**: m.p. = 74°C; Yield = 52%; $^1$H NMR: $\delta = 1.79$–$3.15$ (m; 4H; $CH_2$–$CH_2$–P=O); 5.60–6.41 (m; 3H; $CH_2$=CH); 7.10–7.94 (m; 10H; H arom.); 8.17 (broad s; 2H; $NH_2$); IR $\nu_{P=O} = 1268$ cm$^{-1}$; $\nu_{CN} = 2208$ cm$^{-1}$; $\nu_{NH_2} = 3283$–$3395$ cm$^{-1}$.

**3d**: m.p. 81°C; Yield = 66%; $^1$H NMR: $\delta = 1.74$–$3.20$ (m; 4H; $CH_2$–$CH_2$–P=O); 1.91 (d; 3H; $^3J_{HH} = 5.2$; C<u>H</u>$_3$–CH=CH); 6.33–6.48 (m; 1H; $CH_3$–C<u>H</u>=CH); 6.50 (d; 1H; $^3J_{HH} = 16.8$; $CH_3$–CH=C<u>H</u>); 7.04–7.87 (m; 10H; H arom.); 8.08 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1265$ cm$^{-1}$; $\nu_{CN} = 2215$ cm$^{-1}$; $\nu_{NH_2} = 3290$–$3396$ cm$^{-1}$.

**3e**: m.p. 105°C; Yield = 70%; $^1$H NMR: $\delta = 1.28$ (t; 3H; $^3J_{HH} = 7.3$; C<u>H</u>$_3$–$CH_2$–O); 1.77–3.12 (m; 4H; $CH_2$–$CH_2$–P=O); 4.21 (q; 2H; $^3J_{HH} = 7.3$; $CH_3$–C<u>H</u>$_2$–O); 7.06–7.90 (m; 15H; H arom.); 7.14 (d; 1H; $^3J_{HH} = 16.1$; Ph–C<u>H</u>=CH); 7.21 (d; 1H; $^3J_{HH} = 16.1$; Ph–CH=C<u>H</u>); 8.24 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1270$ cm$^{-1}$; $\nu_{CO_2Et} = 1671$ cm$^{-1}$; $\nu_{NH_2} = 3376$–$3483$ cm$^{-1}$.

**3f**: Oil; Yield = 79%; $^1$H NMR: $\delta = 1.23$ (t; 6H; $^3J_{HH} = 7.0$; C<u>H</u>$_3$–$CH_2$–O); 1.80–3.02 (m; 4H; $CH_2$–$CH_2$–P=O); 3.99 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3$–C<u>H</u>$_2$–O); 7.02 (d; 1H; $^3J_{HH} = 16.3$; Ph–C<u>H</u>=CH); 7.11 (d; 1H; $^3J_{HH} = 16.3$; Ph–CH=C<u>H</u>); 7.30–7.54 (m; 5H; H arom.); 8.15 (broad s; 2H; $NH_2$); IR: $\nu_{P=O} = 1266$ cm$^{-1}$; $\nu_{CN} = 2211$ cm$^{-1}$; $\nu_{NH_2} = 3281$–$3387$ cm$^{-1}$.

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