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Unexpected synthesis of novel O-ethyl-P-aryl-N-(thiophen-2-yl) phosphonamidothioates from ethyl 2-aminothiophene- 3-carboxylates and Lawesson's reagent

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Unexpected synthesis of novel *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioates from ethyl 2-aminothiophene-3-carboxylates and Lawesson's reagent

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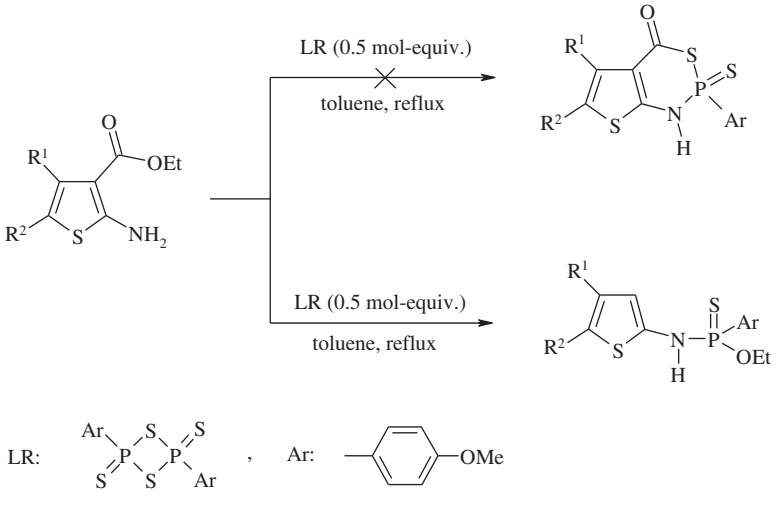
The reaction of ethyl 2-aminothiophene-3-carboxylates with a stoichiometric amount of Lawesson's reagent (LR) gave novel *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioate derivatives rather than the expected thienothiazaphosphorines. A possible reaction mechanism, involving a carbonyl sulfide extrusion, is proposed.



Keywords: thiophenes; Lawesson's reagent; thiophosphonamides; phosphonamidothioates; carbonyl sulfide extrusion

1. Introduction

2,4-Bis(p-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide [Lawesson's reagent (LR)] is widely used in heterocyclic synthesis, particularly for the construction of six-membered heterocyclic rings by reaction with 1,4-dipolar reagents.[1–4] In this area, we have previously

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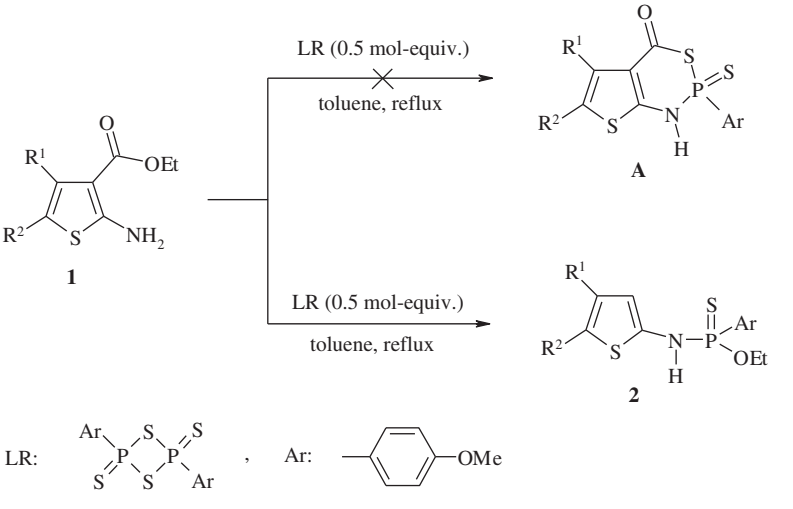
shown that 2-amino-3-cyanothiophenes react with LR, in stoichiometric ratio to give novel fused thienodiazaphosphorine derivatives.[5] We report, in the present investigation, the extension of this reaction to ethyl 2-aminothiophene-3-carboxylates. Our initial objective was to access new thienothiazaphosphorine derivatives. Contrary to our expectation, the reaction did not stop at this stage but gave the novel *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioates **2**, via a carbonyl sulfide extrusion.

It is interesting to note here that thiophene derivatives are an important class of compounds in medicinal chemistry with a wide range of biological properties, including anticancer,[6, 7] antimicrobial,[8–10] antiviral,[11] anti-inflammatory,[12, 13] and antifungal [14] activities. On the other hand, compounds bearing the thiophosphonamide functionality are known to exhibit antimalarial [15] and antitumor [16] activities. Some of these compounds are also known for their applications in agrochemistry as pesticide agents.[17]

2. Results and discussion

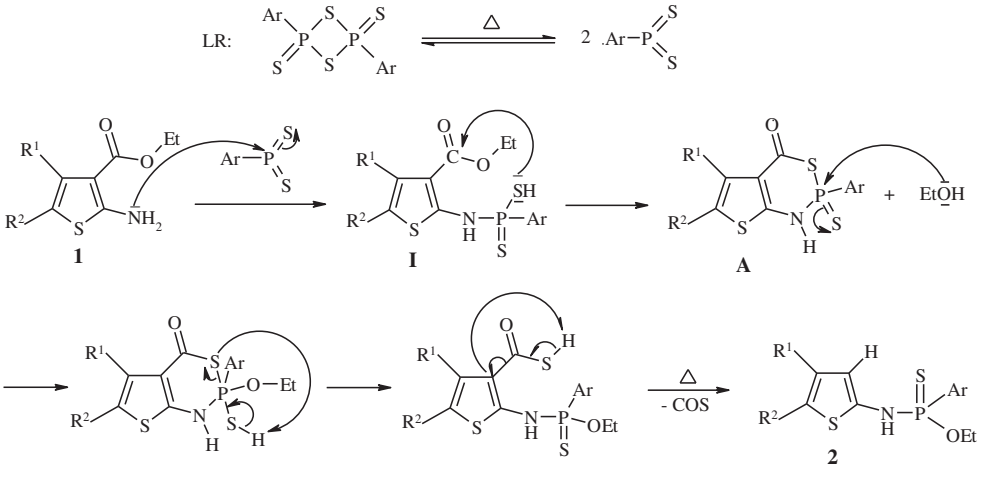
The starting ethyl 2-aminothiophene-3-carboxylates **1** were easily prepared according to the reported Gewald synthetic procedure.[18] Esters **1e** and **1g** are new compounds and their structures were established by examination of their IR, ^{1}H, and ^{13}C NMR data, whereas compounds **1a–d**, **1f**, and **1h** have been identified by comparison of their spectroscopic data with those of the literature.[18]

It was found that reaction of compounds **1** with a stoichiometric amount of LR (0.5 mol-equiv.), performed in refluxing toluene, for 72 h, led to *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioates **2** rather than the expected thienothiazaphosphorine derivatives **A** (Scheme 1).



Scheme 1. Synthesis of 2-thiophosphoramidothiophenes **2**.

A plausible mechanism for the formation of compounds **2** is depicted in Scheme 2. It is believed that the reaction begins with a nucleophilic attack of the NH_2 group on LR giving rise to the intermediate **I**. A subsequent intramolecular cyclization, through the nucleophilic attack of the sulfur atom on the ester function, generates the thiazaphosphorine intermediate **A**. The later recombines with ethanol to yield, after extrusion of carbonyl sulfide, the 2-thiophosphonamidothiophene **2** as final product.



Scheme 2. Proposed mechanism for the formation of compounds **2**.

Table 1. Substrate scope studies.

Entry	R^1	R^2	Product	Yield (%)[a]
1	$(CH_2)_4$		**2a**	74
2	$(CH_2)_3$		**2b**	66
3	Ph	H	**2c**	48
4	CH_3	CH_3	**2d**	54
5	Ph-CH_2	Ph	**2e**	62
6	CH_3	H	**2f**	70
7	CH_3	Ph-CH_2	**2g**	68
8	CH_3	Ph	**2h**	63

[a]Isolated yield.

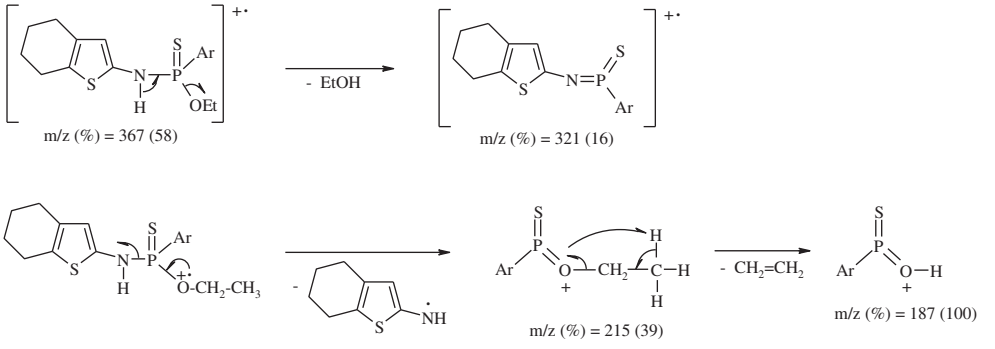
To the best of our knowledge, very little has appeared in the literature concerning the carbonyl sulfide extrusion.[19, 20] Thus, by developing new synthetic pathways involving such transformations, we would be able to obtain a better perspective on the mechanistic insights of these rare extrusions.

It is important to note that our attempts to stop the reaction at the stage of the thienothiazaphosphorine derivative **A**, by reducing the reaction time and lowering the temperature, failed. In all cases, the reaction furnished compounds **2** but in lower yields.

The scope of the reaction was assessed with a range of ethyl 2-aminothiophene-3-carboxylates with various substituents and different ring sizes. All substrates reacted to give *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioates **2**, in moderate to good yields (Table 1).

The formation of compounds **2** was confirmed by IR, NMR (^{1}H, ^{31}P, ^{13}C) and mass spectral data. The IR spectra revealed the presence of absorption bands toward 700 and 3300 cm^{-1} corresponding, respectively, to the P=S and N−H vibrators. The ^{1}H NMR spectrum of each compound **2** showed, in particular, a doublet around 10 ppm, ascribable to the N−H proton. Such a doublet is characteristic for the coupling with phosphorus with a $^2J_{PH}$ coupling constant of about 9–12 Hz. We also observed a singlet at 3.7 ppm assignable to the methoxy protons introduced by LR. The ethoxy group on the phosphorus atom gives a triplet and quartet at 1 and 4 ppm, respectively. The ^{31}P NMR shift recorded for compounds **2** was δ = 69–76 ppm which is consistent with the thiophosphoryl chemical shift values. The ^{13}C NMR spectra display the characteristic signals of all carbon atoms and particularly those corresponding to the thiophene ring. Of particular note

are the carbon atoms of the ethoxy group which resonate as two doublets at 16 and 60 ppm. The structures of the compounds **2** were supported additionally by the mass spectra which showed the correct molecular ion peaks. The different fragments in the EI-MS spectrum of compound **2a** are described in Scheme 3. In addition to the molecular ion which is present at m/z 367, we also observed a fragment at m/z 321 corresponding to the loss of EtOH. The α-cleavage with respect to the oxygen atom gave the fragment at m/z 215 which lost ethylene to give the base ion at m/z 187.



Scheme 3. Main fragments in the EI-MS spectrum of compound **2a**.

In conclusion, we have shown in the present investigation that the reaction of ethyl 2-aminothiophene-3-carboxylates with a stoichiometric amount of LR did not stop at the stage of the thienothiazaphosphorine derivatives but gave the novel *O*-ethyl-*P*-aryl-*N*-(thiophen-2-yl) phosphonamidothioates, via a carbonyl sulfide extrusion.

3. 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, and m: multiplet. Mass spectra were determined on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

3.1. *Synthesis of ethyl 2-aminothiophene-3-carboxylates (1)*

The starting esters **1** were prepared according to the reported Gewald synthetic procedure.[18]

Ethyl 2-amino-4-benzyl-5-phenylthiophene-3-carboxylate (1e). Yellow oil; Yield (%) = 78; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, 3H, $^3J_{HH} = 6.0$ Hz, C$\underline{H}_3-CH_2-O$); 4.11 (q, 2H, $^3J_{HH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 4.31 (s, 2H, CH_2-Ph); 6.55 (broad s, 2H, NH_2); 7.22–7.44 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.2$ (s, $\underline{C}H_3-CH_2-O$); 34.8 (s, Ph$-\underline{C}H_2$); 59.6 (s, $CH_3-\underline{C}H_2-O$); 106.6 (s, Ph$-CH_2-\underline{C}$=C$-$S); 133.8 (s, Ph$-CH_2-$C=$\underline{C}-$S); 144.2 (s, O=C$-\underline{C}$=C$-$S); 161.1 (s, S$-\underline{C}-NH_2$); 166.0 (s, O=$\underline{C}-O-CH_2-CH_3$); phenyl carbons:

δ = 125.5, 127.3, 128.4, 128.7, 129.1, 129.4, 132.2, 134.2; IR (neat): $\nu_{C=O}$ = 1674 cm^{-1}; ν_{NH2} = 3257−3414 cm^{-1}.

Ethyl 2-amino-5-benzyl-4-methylthiophene-3-carboxylate (1g). Yellow oil; Yield (%) = 57; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, 3H, $^3J_{HH}$ = 6, 0 Hz, C$\underline{H}_3$−CH_2−O); 2.09 (s, 3H, CH_3); 3.68 (s, 2H, CH_2); 4.10 (q, 2H, $^3J_{HH}$ = 6.0 Hz, CH_3−C$\underline{H}_2$−O); 6.05 (broad s, 2H, NH_2); 6.68–7.08 (m; 5H; arom-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5 (s, $\underline{C}H_3$−CH_2−O); 15.3 (s, $\underline{C}H_3$−C=C−S); 33.0 (s, Ph−$\underline{C}H_2$−C−S); 59.8 (s, CH_3−$\underline{C}H_2$−O); 106.1 (s, CH_3−$\underline{C}$=C−S); 128.6 (s, CH_3−C−$\underline{C}$=C−S); 131.1 (s, Ph−CH_2−$\underline{C}$−S); 162.7 (s, S−$\underline{C}$−NH_2); 166.1 (s, O=$\underline{C}$−O−CH_2−CH_3); phenyl carbons: δ = 125.8, 126.2, 140.4, 141.0; IR (neat): $\nu_{C=O}$ = 1673 cm^{-1}; ν_{NH2} = 3271−3452 cm^{-1}.

3.2. *General procedure for the synthesis of O-ethyl-P-aryl-N-(thiophen-2-yl) phosphonamidothioates (2)*

A mixture of ethyl 2-aminothiophene-3-carboxylate **1** (0.01 mol), LR (0.005 mol) and dry toluene (30 ml), was heated under reflux with magnetic stirring for 72 h. The reaction mixture was then concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using a mixture of ether and hexane (1:1) as eluent.

O-ethyl-P-(4-methoxyphenyl)-N-(4,5,6,7-tetrahydro-1-benzothiophen-2-yl)phosphonamidothioate (2a). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 69.9 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, 3H, $^3J_{H\text{-}H}$ = 6.0 Hz, C$\underline{H}_3$−CH_2−O); 1.69–2.79 (m, 8H, cyclic H); 3.72 (s, 3H, CH_3−O); 4.23 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3−C$\underline{H}_2$−O); 6.81–7.82 (m, 5H, arom-H); 9.96 (d, 1H, $^2J_{PH}$ = 9.0 Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.1 (d, $^3J_{CP}$ = 7.5 Hz, $\underline{C}H_3$−CH_2−O−P); 21.4 (s, $\underline{C}H_2$−CH_2−CH_2−C=C−S); 22.7 (s, $\underline{C}H_2$−CH_2−C=C−S); 24.3 (s, $\underline{C}H_2$−C=C−S); 26.3 (s, $\underline{C}H_2$−$(CH_2)_3$−C=C−S); 55.3 (s, CH_3−O); 61.7 (d, $^2J_{CP}$ = 9.1 Hz, CH_3−$\underline{C}H_2$−O−P); 112.2 (s, CH_2−$\underline{C}$=C−S); 114.0 (s, $\underline{C}$H=C−S); 147.0 (s, CH_2−C=$\underline{C}$−S); 152.6 (s, C=$\underline{C}$−NH); 162.7 (d, $^4J_{CP}$ = 3.0 Hz, C=$\underline{C}$−O−CH_3); phenyl carbons: δ = 123.6, 124.8, 128.7, 128.9, 137.5, 137.6; IR (neat): $\nu_{P=S}$ = 738 cm^{-1}; ν_{NH} = 3289 cm^{-1}; EI-HRMS: calculated for $C_{17}H_{22}NO_2PS_2$: 367.0830 (M^+), found: 367.0826.

O-ethyl-P-(4-methoxyphenyl)-N-(5,6-dihydro-4H-cyclopenta[b]thiophen-2-yl)phosphonamidothioate (2b). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 69.4 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3H, $^3J_{H\text{-}H}$ = 6.0 Hz, C$\underline{H}_3$−CH_2−O); 2.29–3.33 (m, 6H, cyclic H); 3.71 (s, 3H, CH_3−O); 4.16 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3−C$\underline{H}_2$−O); 6.73–7.93 (m, 5H, arom-H); 10.24 (d, 1H; $^2J_{PH}$ = 9.0 Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.6 (d, $^3J_{CP}$ = 8.3 Hz, $\underline{C}H_3$−CH_2−O−P); 27.8 (s, $\underline{C}H_2$−CH_2−C=C−S); 28.6 (s, $\underline{C}H_2$−C=C−S); 29.9 (s, $\underline{C}H_2$−$(CH_2)_2$−C=C−S); 55.2 (s, CH_3−O); 61.9 (d, $^2J_{CP}$ = 9.0 Hz, CH_3−$\underline{C}H_2$−O−P); 113.3 (s, CH_2−$\underline{C}$=C−S); 114.1 (s, $\underline{C}$H=C−S); 141.4 (s, CH_2−C=$\underline{C}$−S); 150.8 (s, C=$\underline{C}$−NH); 162.9 (d, $^4J_{CP}$ = 3.1 Hz, C=$\underline{C}$−O−CH_3); phenyl carbons: δ = 123.5, 125.2, 128.5, 128.8, 137.8, 138.0; IR (neat): $\nu_{P=S}$ = 738 cm^{-1}; ν_{NH} = 3281 cm^{-1}; EI-HRMS: calculated for $C_{16}H_{20}NO_2PS_2$: 353.0673 (M^+); found: 353.0671.

O-ethyl-P-(4-methoxyphenyl)-N-(4-phenylthiophen-2-yl) phosphonamidothioate (2c). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 75.9 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, 3H, $^3J_{H\text{-}H}$ = 6.0 Hz, C$\underline{H}_3$−CH_2−O); 3.71 (s, 3H, CH_3−O); 4.23 (quint, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3−C$\underline{H}_2$−O); 6.79–7.83 (m, 11H, arom-H); 10.12 (d, 1H, $^2J_{PH}$ = 9.0 Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6 (d, $^3J_{CP}$ = 3.0 Hz, $\underline{C}H_3$−CH_2−O−P); 55.3 (s, CH_3−O); 62.9 (d, $^2J_{CP}$ = 6.8 Hz, CH_3−$\underline{C}H_2$−O−P); 113.4 (s, Ph−$\underline{C}$=C−S); 113.9 (s, $\underline{C}$H=C−S); 143.1 (s, Ph−C=$\underline{C}$−S); 145.1 (s, C=$\underline{C}$−NH); 163.1 (d, $^4J_{CP}$ = 3.0 Hz, C=$\underline{C}$−O−CH_3); phenyl carbons: δ = 122.3, 123.8, 125.8, 127.3, 128.9, 129.0, 133.4, 134.5, 137.7, 137.8; IR (neat):

$\nu_{P=S} = 736\,cm^{-1}$; $\nu_{NH} = 3328\,cm^{-1}$; EI-HRMS: calculated for $C_{19}H_{20}NO_2PS_2$: 389.0673 (M^+), found: 389.0678.

O-ethyl-P-(4-methoxyphenyl)-N-(4,5-dimethylthiophen-2-yl)phosphonamidothioate (2d). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 69.9$ ppm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (t, 3H, $^3J_{H\text{-}H} = 6.0$ Hz, $C\underline{H}_3-CH_2-O$); 2.06 (s, 3H, $CH_3-C{=}C$); 2.15 (s, 3H, CH_3-C-S); 3.60 (s, 3H, CH_3-O); 4.10 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 6.62–7.77 (m, 5H, arom-H); 9.83 (d, 1H, $^2J_{PH} = 9.0$ Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.6$ (s, $\underline{C}H_3-C{=}C-S$); 14.4 (s, $\underline{C}H_3-C-S$); 16.1 (d, $^3J_{CP} = 7.5$ Hz, $\underline{C}H_3-CH_2-O-P$); 55.4 (s, CH_3-O); 61.8 (d, $^2J_{CP} = 5.3$ Hz, $CH_3-\underline{C}H_2-O-P$); 113.2 (s, $CH_3-\underline{C}{=}C-S$); 114.3 (s, $\underline{C}H{=}C-S$); 146.3 (s, $CH_3-C{=}\underline{C}-S$); 151.0 (s, $C{=}\underline{C}-NH$); 162.8 (d, $^4J_{CP} = 3.0$ Hz, $C{=}\underline{C}-O-CH_3$); phenyl carbons: $\delta = 121.6, 123.2, 129.0, 129.1, 133.7, 137.8$; IR (neat): $\nu_{P=S} = 733\,cm^{-1}$; $\nu_{NH} = 3271\,cm^{-1}$; EI-HRMS: calculated for $C_{15}H_{20}NO_2PS_2$: 341.0673 (M^+), found: 341.0672.

O-ethyl-P-(4-methoxyphenyl)-N-(4-benzyl-5-phenylthiophen-2-yl)phosphonamidothioate (2e). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 70.5$ ppm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.15$ (t, 3H, $^3J_{H\text{-}H} = 6.0$ Hz, $C\underline{H}_3-CH_2-O$); 3.62 (s, 3H, CH_3-O); 4.12 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 4.44 (s, 2H, CH_2-Ph); 6.75−8.10 (m, 15H, arom-H); 9.65 (d, 1H, $^2J_{PH} = 12.0$ Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 16.6$ (d, $^3J_{CP} = 3.2$ Hz, $\underline{C}H_3-CH_2-O-P$); 45.2 (s, $Ph-\underline{C}H_2$); 55.1 (s, CH_3-O); 62.5 (d, $^2J_{CP} = 9.0$ Hz, $CH_3-\underline{C}H_2-O-P$); 112.1 (s, $CH_2-\underline{C}{=}C-S$); 114.3 (s, $\underline{C}H{=}C-S$); 141.7 (s, $PH-CH_2-C{=}\underline{C}-S$); 157.7 (s, $C{=}\underline{C}-NH$); 163.0 (d, $^4J_{CP} = 3.1$ Hz, $C{=}\underline{C}-O-CH_3$); phenyl carbons: $\delta = 123.6, 125.2, 127.4, 128.1, 128.7, 128.9, 129.2, 129.9, 131.7, 132.1, 133.6, 134.8, 137.4, 137.6$; IR (neat): $\nu_{P=S} = 738\,cm^{-1}$; $\nu_{NH} = 3338\,cm^{-1}$; EI-HRMS: calculated for $C_{26}H_{26}NO_2PS_2$: 479.1143 (M^+); found: 479.1145.

O-ethyl-P-(4-methoxyphenyl)-N-(4-methylthiophen-2-yl) phosphonamidothioate (2f). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 69.6$ ppm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, 3H, $^3J_{H\text{-}H} = 6.0$ Hz, $C\underline{H}_3-CH_2-O$); 2.29 (s, 3H, $CH_3-C{=}C$); 3.73 (s, 3H, CH_3-O); 4.28 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 6.80−8.08 (m, 6H, arom-H); 10.18 (d, 1H, $^2J_{PH} = 12.0$ Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.0$ (s, $\underline{C}H_3-C{=}C-S$); 16.0 (d, $^3J_{CP} = 7.5$ Hz, $\underline{C}H_3-CH_2-O-P$); 55.3 (s, CH_3-O); 62.8 (d, $^2J_{CP} = 10.3$ Hz, $CH_3-\underline{C}H_2-O-P$); 113.3 (s, $CH_3-\underline{C}{=}C-S$); 114.6 (s, $\underline{C}H{=}C-S$); 149.7 (s, $CH_3-C{=}\underline{C}-S$); 155.5 (s, $C{=}\underline{C}-NH$); 163.1 (d, $^4J_{CP} = 3.0$ Hz, $C{=}\underline{C}-O-CH_3$); phenyl carbons: $\delta = 123.4, 125.2, 128.4, 128.7, 137.6, 137.7$; IR (neat): $\nu_{P=S} = 736\,cm^{-1}$; $\nu_{NH} = 3273\,cm^{-1}$; EI-HRMS: calculated for $C_{14}H_{18}NO_2PS_2$: 327.0517 (M^+), found: 327.0509.

O-ethyl-P-(4-methoxyphenyl)-N-(5-benzyl-4-methylthiophen-2-yl)phosphonamidothioate (2g). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 70.1$ ppm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (t, 3H, $^3J_{H\text{-}H} = 6.0$ Hz, $C\underline{H}_3-CH_2-O$); 2.28 (s, 3H, $CH_3-C{=}C$); 3.62 (s, 3H, CH_3-O); 3.83 (s, 2H, CH_2-Ph); 4.20 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 6.71–7.86 (m, 10H, arom-H); 10.00 (d, 1H, $^2J_{PH} = 9.0$ Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.3$ (s, $\underline{C}H_3-C{=}C-S$); 16.1 (d, $^3J_{CP} = 2.3$ Hz, $\underline{C}H_3-CH_2-O-P$); 32.9 (s, $Ph-\underline{C}H_2$); 55.1 (s, CH_3-O); 60.6 (d, $^2J_{CP} = 9.3$ Hz, $CH_3-\underline{C}H_2-O-P$); 113.1 (s, $CH_3-\underline{C}{=}C-S$); 114.0 (s, $\underline{C}H{=}C-S$); 140.8 (s, $CH_3-C{=}\underline{C}-S$); 147.3 (s, $C{=}\underline{C}-NH$); 162.6 (d, $^4J_{CP} = 3.0$ Hz, $C{=}\underline{C}-O-CH_3$); phenyl carbons: $\delta = 123.3, 124.7, 126.0, 127.0, 128.1, 128.3, 129.8, 133.5, 137.6, 137.7$; IR (neat): $\nu_{P=S} = 735\,cm^{-1}$; $\nu_{NH} = 3277\,cm^{-1}$; EI-HRMS: calculated for $C_{21}H_{24}NO_2PS_2$: 417.0986 (M^+), found: 417.0984.

O-ethyl-P-(4-methoxyphenyl)-N-(4-methyl-5-phenylthiophen-2-yl) phosphonamidothio-ate (2h). Brown oil; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 70.1$ ppm; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (t, 3H, $^3J_{H\text{-}H} = 6.0$ Hz, $C\underline{H}_3-CH_2-O$); 2.41 (s, 3H, $CH_3-C{=}C$); 3.79 (s, 3H, CH_3-O); 4.36 (quint, 2H, $^3J_{HH} = {}^3J_{PH} = 6.0$ Hz, $CH_3-C\underline{H}_2-O$); 6.91−8.20 (m, 10H, arom-H); 10.34 (d, 1H, $^2J_{PH} = 9.0$ Hz, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.4$ (s, $\underline{C}H_3-C{=}C-S$);

16.2 (d, $^{3}J_{CP} = 7.5$ Hz, $\underline{C}H_3-CH_2-O-P$); 55.3 (s, CH_3-O); 61.9 (d, $^{2}J_{CP} = 13.6$ Hz, $CH_3-\underline{C}H_2-O-P$); 113.9 (s, $CH_3-\underline{C}=C-S$); 114.2 (s, $\underline{C}H=C-S$); 148.6 (s, $CH_3-C=\underline{C}-S$); 153.9 (s, $C=\underline{C}-NH$); 163.0 (d, $^{4}J_{CP} = 3.1$ Hz, $C=\underline{C}-O-CH_3$); phenyl carbons: $\delta = 125.4$, 126.7, 127.7, 128.6, 128.8, 129.8, 130.5, 133.5, 137.7, 137.8; IR (neat): $\nu_{P=S} = 737\,cm^{-1}$; $\nu_{NH} = 3286\,cm^{-1}$; EI-HRMS: calculated for $C_{20}H_{22}NO_2PS_2$: 403.0830 (M^+), found: 403.0826.

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References

[1] El-Barbary AA, Lawesson SO. Studies on organophosphorus compounds—XXXVI: simple new routes to phosphorins from 2-hydroxy-, 2-mercapto-, and 2-aminobenzoic acids and their derivatives. Tetrahedron. 1981;37:2641–2646.
[2] Testa MG, Perrini G, Chiacchio U, Corsaro A. 1,2-dihydro-2-(4-methoxyphenyl)-2-sulphide-1,3,2-diazaphosphorin-4(3h)-thiones from 3-aminopropenenitrile derivatives and Lawesson's reagent. Phosphorus, Sulfur Silicon Relat Elem. 1994;86:75–80.
[3] Golovko TV, Soloveva NP, Granik VG. A new heterocyclic system: 2*H*-1,3,2-oxaazaphosphorino[6,5-*b*]pyrido[2',3'-*b*]indole. Mendeleev Commun. 1995;5:191–192.
[4] Shabana R, Atrees SS. Studies on organophosphorus compounds, part XVI. The reaction of 1,3,2,4-dithiadiphosphetane-2,4-disulfide with benzil dianils. A novel synthesis of 2H-1,3,6,2-thiadiazaphosphorine-2-sulfide derivatives. Phosphorus, Sulfur Silicon Relat Elem. 1995;102:9–13.
[5] Khalladi K, Touil S. Synthesis of novel fused thienodiazaphosphorine derivatives from 2-amino-3-cyanothiophenes and Lawesson's reagent. J Sulfur Chem. 2012;33:27–32.
[6] Brault L, Migianu E, Neguesque A, Battaglia E, Bagrel D, Kirsch G. New thiophene analogues of kenpaullone: synthesis and biological evaluation in breast cancer cells. Eur J Med Chem. 2005;40:757–763.
[7] Romagnoli R, Baraldi PG, Cruz-Lopez O, Tolomeo M, Di Cristina A, Pipitone RM, Grimaudo S, Balzarini J, Brancale A, Hamel E. Synthesis of novel antimitotic agents based on 2-amino-3-aroyl-5-(hetero)arylethynyl thiophene derivatives. Bioorg Med Chem Lett. 2011;21:2746–2751.
[8] Isloor AM, Kalluraya B, Pai KS. Synthesis, characterization and biological activities of some new benzo[b]thiophene derivatives. Eur J Med Chem. 2010;45:825–830.
[9] Bondock S, Fadaly W, Metwally MA. Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety. Eur J Med Chem. 2010;45:3692–3701.
[10] Subba RD, Rasheed S, Thaslim Basha SK, Naga Raju C, Naresh K. SiO2/ZnCl2 catalyzed α-aminophosphonates and phosphonated N-(substituted phenyl) sulfonamides of 2-aminothiophene: synthesis and biological evaluation. Der Pharma Chem. 2013;5:61–74.
[11] Rashad AE, Shamroukh AH, Abdel-Megeid RE, Mostafa A, El-Shesheny R, Kandeil A, Ali MA, Banert K. Synthesis and screening of some novel fused thiophene and thienopyrimidine derivatives for anti-avian influenza virus (H5N1) activity. Eur J Med Chem. 2010;45:5251–5257.
[12] Kumar PR, Raju S, Goud PS, Sailaja M, Sarma MR, Reddy GO, Kumar MP, Reddy VV, Suresh T, Hegde P. Synthesis and biological evaluation of thiophene [3,2-*b*] pyrrole derivatives as potential anti-inflammatory agents. Bioorg Med Chem. 2004;12:1221–1230.
[13] Fakhr IMI, Radwan MAA, El-Batran S, Omar ME, El-Salam A, El-Shenawy SM. Synthesis and pharmacological evaluation of 2-substituted benzo [b] thiophenes as anti-inflammatory and analgesic agents. Eur J Med Chem. 2009;44:1718–1725.
[14] Souza BCC, De Oliveira TB, Aquino TM, De Lima MCA, Pitta IR, Galdino SL, Lima EO, Gonçalves-Silva T, Militao GCG, Scotti L, Scotti MT, Mendonça FJB. Preliminary antifungal and cytotoxic evaluation of synthetic cycloalkyl[*b*]thiophene derivatives with PLS-DA analysis. Acta Pharm. 2012;62:221–236.
[15] Mara C, Dempsey E, Bell A, Barlow JW. Synthesis and evaluation of phosphoramidate and phosphorothioamidate analogues of amiprophos methyl as potential antimalarial agents. Bioorg Med Chem Lett. 2011;21:6180–6183.
[16] Maanen MJ, Smeets CJ, Beijnen JH. Chemistry, pharmacology and pharmacokinetics of N,N', N"-triethylenethiophosphoramide (ThioTEPA). Cancer Treat Rev. 2000;26:257–268.
[17] Stein RG, Wis K, Couch TL, III W. Phosphoramidates and thiophosphoramidates as pesticides. United States patent US 4,071,533. 1978 Jan 31.
[18] Gewald K, Schinke E, Boettcher H. 2-Amino-thiophene aus methylenaktiven Nitrilen, Carbonylverbindungen und Schwefel. Chem Ber. 1966;99:94–100.
[19] Valera NY, Boris AI. A new synthesis of 1,3-thiazines and their transformation into 1-substituted-6-alkyluracils by extrusion of carbonyl sulfide. Tetrahedron Lett. 2003;44:5279–5280.
[20] Xuefeng J, Lei S, Hui L, Akbar HK, Jason SC. Gas extrusion in natural products total synthesis. Org Biomol Chem. 2012;10:8383–8392.