Synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters via nucleophilic aromatic substitution

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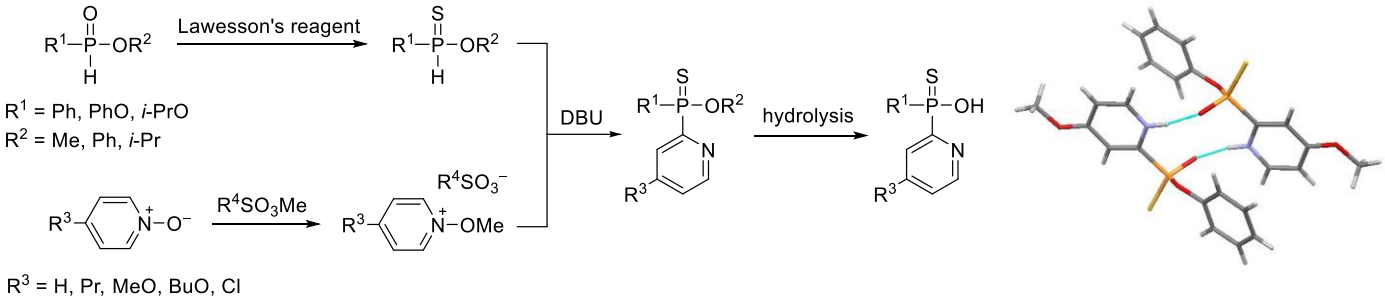
Abstract

In this study, we developed a method for the synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters using easily accessible starting materials, *H*-phosphinate and *H*-phosphonate esters and pyridine *N*-oxides. The *H*-phosphinate and *H*-phosphonate esters were sulfurized to give *H*-thiophosphinate and *H*-thiophosphonate esters. The pyridine *N*-oxides were converted into *N*-methoxypyridinium sulfonates, which were then used for nucleophilic aromatic substitution with the *H*-thiophosphinate/thiophosphonate esters to afford 2-pyridylthiophosphinate monoesters and 2-pyridylthiophosphonate diesters. Finally, alkaline hydrolysis and subsequent neutralization afforded various 2-pyridylthiophosphinic acids and 2-

pyridylthiophosphonate monoesters in good yields. The structure of a 2-pyridylthiophosphonate monoester was determined using X-ray crystallographic analysis.



Key words:

2-pyridyl, thiophosphinic acid, thiophosphinate, thiophosphonate, nucleophilic aromatic substitution

Introduction

2-Pyridylphosphine oxide, 2-pyridylphosphinate, and 2-pyridylphosphonate derivatives have been used in coordination chemistry as bidentate ligands. Various applications such as selective extraction of precious metal ions[1] and syntheses of luminescent complexes[2] and transition metal catalysts[3] have been reported. In particular, 2-pyridylphosphinic acids and 2-pyridylphosphonate monoesters with free P–OH groups form very stable complexes with various kinds of metal ions[4] and have very recently been successfully applied to the development of lanthanide complexes for cellular optical imaging.[2f_h] Herein, we describe our study on the synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters wherein one of the oxygen atoms on the phosphorus center is replaced by sulfur. Oxygen to sulfur exchange has long been used in organophosphorus chemistry to alter coordination behavior.[5] We expect that 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters will be novel bidentate ligands with different coordination behavior from those of the parent 2-pyridylphosphinic acids and 2-pyridylphosphonate monoesters. Despite such potential usefulness, the syntheses of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters have not yet been reported in the literature, to the best of our knowledge. Under these circumstances, we began our study on the synthesis of these compounds and have reported the synthesis of some 2-

pyridylthiophosphinate monoesters via the nucleophilic aromatic substitution (S_NAr) reaction of *H*-thiophosphinate esters in a previous communication.[6] In this study, we report the complete details and further extension of the study to the synthesis of various 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters.

Results and Discussion

2-Pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters were synthesized according to Scheme 1. First, *H*-phosphinate and *H*-phosphonate esters **1** were converted into *H*-thiophosphinate and *H*-thiophosphonate esters **2** (**Step 1**). Various 4-substituted pyridine *N*-oxides **3** were methylated at the 1-position by methyl sulfonates to afford *N*-methoxypyridinium sulfonates **4** (**Step 2**), which were then used to introduce 2-pyridyl groups with R^3 substituents onto the phosphorus atoms of **2** by a DBU-promoted S_NAr reaction,[7] giving 2-pyridylthiophosphinate and phosphonate esters **5** (**Step 3**). Finally, compounds **5** were hydrolyzed to afford the 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters **6** (**Step 4**).

Methyl phenylphosphinate **1a**, diphenyl phosphonate **1b**, and diisopropyl phosphonate **1c** were used as starting materials. The P=O to P=S conversion of **1a**–**c** using Lawesson's reagent[8] is summarized in Table 1. We previously reported that **1a** was efficiently converted into **2a** at room

temperature (RT) using 0.5 equiv of Lawesson's reagent, though some unidentified byproducts with higher polarity than the desired **2a** were generated as the reaction time was prolonged.[6] As in that report, the yield of **2a** was maximized when the reaction was finished within 1.5 h (entries 1, 2). In contrast, the conversion of **1b** did not progress at RT (entry 3). The reaction proceeded under reflux conditions and the desired product **2b** was obtained (entry 4), though the yield was low due to the generation of some polar byproducts. The reaction was therefore conducted at 60 °C (entry 5) to suppress the generation of byproducts and **2b** was obtained in good yield when the amount of Lawesson's reagent was increased to 0.7 equiv (entry 6). The same tendency was observed for another *H*-phosphonate diester **1c**; a large proportion of byproducts were observed under reflux conditions, while the desired **2c** was obtained in good yield when the reaction was conducted at 60 °C (entries 7, 8).

Next, *N*-methoxypyridinium sulfonates **4a**–**e** were synthesized (Table 2). Heating a mixture of pyridine *N*-oxide **3a** and methyl tosylate at 100 °C over 8 h without solvent completely converted **3a** into *N*-methoxypyridinium tosylate **4a**, as reported in the literature;[9] however, an attempt to synthesize compound **4b** under the same conditions resulted in decomposition of the product (entry 2). We found that compound **3b** was much more reactive than **3a** due to the electron-donating 4-propyl group and the reaction was complete within 10 min (entry 3).

Prolonged heating caused decomposition of the resulting **4b**, as shown in entry 2. Compound **4c** with a 4-methoxy group was even more sensitive to heat, resulting in the generation of a complex mixture within 20 min (entry 4). Therefore, the reaction was conducted at RT using CH_2Cl_2 as a solvent (entry 5). Compound **3d**, with similar reactivity to **3c**, was also methylated under similar conditions (entry 6). In contrast, compound **3e** with an electron-withdrawing 4-chloro group was not methylated with methyl tosylate, even at 100 °C over 12 h (entries 7, 8). The methylation of **3e** was therefore carried out with more reactive methyl triflate to give **4e** (entry 10). Compounds **4a**–**e** were thus obtained and used for the introduction of 2-pyridyl groups without purification.

The *N*-methoxypyridinium sulfonates **4a**–**e** were then allowed to react with compounds **2a–c** in the presence of DBU in MeCN at −40 °C, the conditions optimized through the synthesis of 2-pyridylphosphinates,[6] giving 13 kinds of 2-pyridylthiophosphinate and 2-pyridylthiophosphonate esters **5a**–**m** in 54–93% yields (Table 3). The reactions were quenched after **2a**–**c** were completely consumed (TLC). The reactions of **2a** were completed with 1.5 molar equiv of **4a**–**e** (entries 1–5), whereas 2 molar equiv of **4a**–**e** were necessary to drive the reactions of **2b** and **2c** to completion (entries 6–13). The reaction rate was dependent on the R^3 substituent as follows:

Cl > H > Pr > MeO, BuO, indicating that the reactivity of **4** increased with a decrease of the electron density on the pyridine ring.

Finally, compounds **5a**–**f**, **h**, **j** were subjected to alkaline hydrolysis and subsequent neutralization with acid to synthesize 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters **6a**–**f**, **h**, **j** (Table 4). Compound **5a** was hydrolyzed with a solution of triethylamine in MeOH aq. to give **6a** in 89% yield after neutralization with 1 M HCl (entry 1). In contrast, the alkaline hydrolysis of **5b** was not promoted by triethylamine (entry 2), but required 1 M NaOH in MeOH aq., which afforded compound **6b** in 84% yield (entry 3). Compounds **5c**–**e** were also hydrolyzed by 1 M NaOH in MeOH aq. to give **6c**–**e** in 63–74% yields (entries 4–6). The hydrolysis of diphenyl ester **5f** with 1 M NaOH in MeOH aq. resulted in the formation of the fully hydrolyzed 2-pyridylthiophosphonic acid (entry 7). Therefore, **5f** was hydrolyzed using triethylamine at 50 °C. In this case, the hydrolysis was conducted in THF aq. in place of MeOH aq. to prevent an ester exchange reaction, giving the desired **6f** in 62% yield after cation-exchange using ion-exchange resin (entry 8). Ester **5h** was also converted into **6h** under the same conditions used for **6f** except for the prolonged reaction time (entry 9). Because the hydrolysis of diisopropyl ester **5j** was not promoted by triethylamine under reflux conditions or with MW irradiation (entries 10, 11), **5j** was hydrolyzed by 1 M NaOH. The desired **6j** was

obtained in 58% yield when the hydrolysis was conducted at 75 °C (entry 12); **6j** was not obtained due to overhydrolysis under reflux conditions (entry 13).

The structure of 2-pyridylthiophosphonate monoester **6h** was unambiguously determined by X-ray crystallographic analysis (Figure 1). The X-ray structure of **6h** showed that the compound was crystallized as a racemic compound, in which two pairs of the (*R*)- and (*S*)-isomers were contained in a unit cell (Figure 2). Each pair was formed by two hydrogen bonds between the OH groups on the phosphorus and the nitrogen atom of the pyridine ring (O–N distance = 2.660 Å, O–H–N angle = 169.28°). The hydrogen bonds might contribute to a small O1–P–C angle (94.33°) and a large O2–P–S angle (119.59°) by pulling the oxygen and the pyridyl group closer to each other. Tables S 1 and S 2 (Supplemental Materials) present the X-ray data collection parameters and selected bond lengths and angles.

Conclusion

In conclusion, the study described herein has provided the first method for the synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters. An unambiguous structural analysis of a 2-pyridylthiophosphonate monoester by X-ray crystallography was also conducted for the first time. We consider that the 2-pyridylthiophosphinic acids and 2-

pyridylthiophosphonate monoesters will be useful for the preparation of novel bidentate ligands with unique coordination behaviors.

Experimental

General information

Commercially available reagents were used without purification. Dry organic solvents were prepared by appropriate procedures prior to use. The other organic solvents were reagent grade and used as received. All reactions in dry solvents were carried out under argon. Analytical thin-layer chromatography (TLC) was performed on Merck TLC plates (No. 5715) precoated with silica gel 60 F_{254}. Silica gel column chromatography was carried out using Kanto silica gel 60N (spherical, neutral, 40–50 or 63–210 μm). The ^{1}H, ^{13}C and ^{31}P NMR spectra (400, 100, 161.7 MHz) were recorded on a JNM-AL-400 or a JNM-ECS-400 spectrometer (JEOL). Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR. $CDCl_3$ (77.0 ppm) and C_5D_5N (123.87 ppm, central peak on the right side) were used as internal standards for ^{13}C NMR in $CDCl_3$ and C_5D_5N, respectively. 85% H_3PO_4 was used as an external standard (δ 0.0) for ^{31}P NMR. ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicity is indicated as follows: s (singlet); d (doublet); dd (doublet of doublets); t (triplet); q (quartet); sext (sextet); dsept (doublet of septets); m (multiplet); br (broad). High-

resolution mass spectra were recorded on a Waters Xevo Q-Tof mass spectrometer (ESI-TOF). The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR for 5h and 6h as representative examples (Figures S 1 – S 6).

Methyl phenylthiophosphinate **2a**[6,10]

Lawesson's reagent (4.05 g, 10.0 mmol) was added to a stirred solution of methyl phosphinate **1a** (3.12 g, 20.0 mmol) in dry toluene (40 mL) at RT. The resultant mixture was further stirred for 1.5 h at RT. Insoluble materials were removed by suction filtration. The filtrate was diluted with toluene (30 mL) and washed with H_2O (30 mL). The aqueous layer was extracted with toluene (3 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **2a** (2.63 g, 15.3 mmol, 76%) as a slightly yellowish liquid. ^{1}H and ^{31}P NMR spectra were identical to those reported in the literature.[6,10]

Diphenyl thiophosphonate **2b**

Lawesson's reagent (8.49 g, 21.0 mmol) was added to a stirred solution of diphenyl phosphonate **1b** (7.03 g, 30.0 mmol) in dry toluene (60 mL) at RT. The resultant mixture was then heated at 60 °C with stirring for 4 h. The mixture was allowed to cool to RT and insoluble

materials were removed by suction filtration. The filtrate was diluted with toluene (30 mL) and washed with H_2O (30 mL). The aqueous layer was extracted with toluene (2 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–CH_2Cl_2 (1:1, v/v)) to afford **2b** (5.31 g, 21.2 mmol, 71%) as a slightly yellowish liquid, which solidified to white crystals upon standing at –20 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 668.4 Hz, 1H), 7.37 (t, J = 8.0 Hz, 4H), 7.25–7.16 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (d, J_{PC} = 10.7 Hz), 129.7, 125.7, 121.1 (d, J_{PC} = 5.7 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 64.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}O_2PS^+$ 251.0290; Found 251.0301.

Diisopropyl thiophosphonate **2c**

Lawesson's reagent (8.50 g, 21.0 mmol) was added to a stirred solution of diisopropyl phosphonate **3c** (4.98 g, 30.0 mmol) in dry toluene (60 mL) at RT. The resultant mixture was then heated at 60 °C with stirring for 3 h. The mixture was allowed to cool to RT and insoluble materials were removed by suction filtration. The filtrate was diluted with toluene (30 mL) and washed with H_2O (30 mL). The aqueous layer was extracted with toluene (2 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–CH_2Cl_2 (7:3,

v/v)) to afford **2c** (4.29 g, 23.5 mmol, 78%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 644.8 Hz, 1H), 4.85 (dsept, *J* = 11.2, 6.4 Hz, 2H), 1.34 (dd, *J* = 6.4, 4.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.4 (d, J_{PC} = 6.6 Hz), 23.7 (d, J_{PC} = 4.2 Hz), 23.4 (d, J_{PC} = 5.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 65.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_6H_{15}NaO_2PS^+$ 205.0423; Found 205.0441.

Methyl phenyl(2-pyridyl)thiophosphinate **5a**

A mixture of pyridine *N*-oxide (1.43 g, 15.0 mmol) and methyl *p*-toluenesulfonate (2.79 g, 15.0 mmol) was heated at 100 °C for 8 h to afford *N*-methoxypyridinium tosylate **4a**[9] as a white solid, which was used without purification. DBU (2.24 mL, 15.0 mmol) and a solution of the thus obtained **4a** in dry MeCN (20.0 mL) were subsequently added to a stirred solution of **2a** (1.72 g, 10.0 mmol) in dry MeCN (12.5 mL) at –40 °C, and the resultant mixture was further stirred for 10 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (15 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($(CH_2Cl_2$–MeOH (100:1 to 99:1, v/v)) to afford **5a** (1.92 g, 7.70 mmol, 77%) as a slightly yellowish oil. NMR spectra were identical to those in the literature.[6.]

Methyl phenyl(4-propyl-2-pyridyl)thiophosphinate **5b**

A mixture of 4-propylpyridine *N*-oxide (0.823 g, 6.00 mmol) and methyl *p*-toluenesulfonate (1.12 g, 6.01 mmol) was heated at 100 °C for 10 min to afford *N*-methoxy-4-propylpyridinium tosylate **4b** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.0 Hz, 2H), 7.86 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 4.41 (s, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 1.65 (sext, *J* = 7.6 Hz, 2H), 0.94 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 143.4, 140.3, 139.3, 129.1, 128.5, 125.7, 69.4, 37.3, 22.6, 21.0, 13.4. Compound **4b** thus obtained was used without purification. DBU (0.898 mL, 6.00 mmol) and a solution of **4b** in dry MeCN (15 mL) were subsequently added to a stirred solution of **2a** (0.686 g, 4.00 mmol) in dry MeCN (5.0 mL) at –40 °C, and the resultant mixture was further stirred for 1 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (30 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–AcOEt (8:1, v/v)) to afford **5b** (0.724 g, 2.48 mmol, 62%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.2 Hz, 1H), 8.10–8.03 (m, 3H), 7.53–7.43 (m, 3H), 7.17 (t, *J* = 2.4 Hz, 1H), 3.76 (d, *J* = 14.4 Hz, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.67 (sextet, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (d, J_{PC} = 140.2 Hz), 152.2 (d, J_{PC} = 11.4 Hz), 150.0 (d, J_{PC} = 20.0 Hz), 132.4 (d, J_{PC} = 109.6 Hz), 132.1 (d, J_{PC} = 2.9 Hz), 132.0 (d, J_{PC} = 10.5 Hz), 128.3 (d, J_{PC} = 13.3 Hz), 128.1 (d, J_{PC} = 26.7 Hz), 125.4 (d, J_{PC} = 3.8 Hz), 51.7 (d, J_{PC} = 5.7 Hz), 37.3, 23.4, 13.7. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 78.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}NOPS^+$ 292.0919; Found 292.0907.

Methyl 4-methoxy-2-pyridyl(phenyl)thiosphosphinate **5c**

A mixture of 4-methoxypyridine *N*-oxide (0.188 g, 1.50 mmol), methyl *p*-toluenesulfonate (0.279 g, 1.50 mmol), and dry CH_2Cl_2 (2.0 mL) was stirred at RT for 6 h, and then concentrated to dryness to give *N*-methoxy-4-methoxypyridinium tosylate **4c** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.36 (s, 3H), 4.08 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 143.4, 142.4, 139.2, 128.4, 125.5, 114.3, 69.2, 58.2, 20.9. Compound **4c** thus obtained was used without purification. DBU (0.224 mL, 1.50 mmol) and a solution of **4c** in dry MeCN (3.5 mL) were subsequently added to a stirred solution of **2a** (0.174 g, 1.00 mmol) in dry MeCN (1.5 mL) at –40 °C, and the resultant mixture was further stirred for 2 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (8 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 20 mL). The organic layers were

combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–AcOEt–CH_2Cl_2 (6:2:2, v/v/v)) to afford **5c** (0.213 g, 0.762 mmol, 76%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.6 Hz, 1H), 8.08–8.02 (m, 2H), 7.81 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.52–7.41 (m, 3H), 6.83 (ddd, *J* = 5.6, 2.4, 1.6 Hz, 1H), 3.86 (s, 3H), 3.75 (d, *J* = 14.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (d, J_{PC} = 15.3 Hz), 157.9 (d, J_{PC} = 140.1 Hz), 151.5 (d, J_{PC} = 22.9 Hz), 132.2 (d, J_{PC} = 110.6 Hz), 132.2 (d, J_{PC} = 2.8 Hz), 131.9 (d, J_{PC} = 11.5 Hz), 128.3 (d, J_{PC} = 13.3 Hz), 114.2 (d, J_{PC} = 29.5 Hz), 111.4 (d, J_{PC} = 2.9 Hz), 55.5, 51.8 (d, J_{PC} = 5.7 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 79.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}NO_2PS^+$ 280.0556; Found 280.0543.

Methyl 4-butoxy-2-pyridyl(phenyl)thiophosphinate **5d**

A mixture of 4-buthoxypyridine *N*-oxide (0.502 g, 3.00 mmol), methyl *p*-toluenesulfonate (0.559 g, 3.00 mmol), and dry CH_2Cl_2 (4.5 mL) was stirred at RT for 27 h, and then concentrated to dryness to give *N*-methoxy-4-butoxypyridinium tosylate **4d** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 6.6 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 6.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.31 (s, 3H), 4.20 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 1.76 (m, 2H), 1.43 (sext, *J* = 7.6 Hz, 2H), 0.94 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 143.5, 142.5,

139.3, 128.5, 125.7, 114.7, 71.4, 69.3, 30.1, 21.1, 18.7, 13.4. Compound **4d** thus obtained was used without purification. DBU (0.450 mL, 3.01 mmol) and a solution of **4d** in dry MeCN (6.00 mL) were subsequently added to a stirred solution of **2a** (0.344 g, 2.00 mmol) in dry MeCN (2.50 mL) at –40 °C, and the resultant mixture was further stirred for 2.5 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (15 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–CH_2Cl_2 (3:7, v/v)) to afford **5d** (0.471 g, 1.47 mmol, 74%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.6 Hz, 1H), 8.08–8.03 (m, 2H), 7.81 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.53–7.42 (m, 3H), 6.81 (ddd, *J* = 5.8, 2.6, 1.8, 1H), 4.05 (dt, *J* = 6.4, 2.8 Hz, 2H), 3.76 (d, *J* = 13.6 Hz, 3H), 1.82–1.75 (m, 2H), 1.49 (sextet, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J_{PC} = 15.2 Hz), 157.4 (d, J_{PC} = 139.2 Hz), 151.3 (d, J_{PC} = 22.9 Hz), 132.0 (d, J_{PC} = 109.7 Hz), 132.0 (d, J_{PC} = 2.9 Hz), 131.7 (d, J_{PC} = 11.5 Hz), 128.0 (d, J_{PC} = 13.4 Hz), 114.7 (d, J_{PC} = 29.6 Hz), 111.3 (d, J_{PC} = 1.9 Hz), 67.8, 51.5 (d, J_{PC} = 5.7 Hz), 30.5, 18.8, 13.5. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 79.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}NO_2PS^+$ 322.1025; Found 322.1030.

Methyl 4-chloro-2-pyridyl(phenyl)thiophosphinate **5e**

Methyl trifluoromethanesulfonate (0.328 mL, 3.00 mmol) was added dropwise to a stirred solution of 4-chloropyridine *N*-oxide (0.389 g, 3.00 mmol) in dry CH_2Cl_2 (4.5 mL) at 0 °C. The mixture was allowed to warm to RT, further stirred for 1 h, and concentrated under reduced pressure to afford *N*-methoxy-4-chloropyridinium triflate **4e** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, *J* = 7.0 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 2H), 4.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 141.7, 130.0, 120.3 (q, J_{CF} = 318.0 Hz), 70.0. Compound **4e** thus obtained was used without purification. DBU (0.450 mL, 3.01 mmol) and a solution of **4e** in dry MeCN (7.5 mL) were subsequently added to a stirred solution of **2a** (0.344 g, 2.00 mmol) in dry MeCN (2.5 mL) at –40 °C, and the resultant mixture was further stirred for 30 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (15 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane–AcOEt (4:1, v/v)) to afford **5e** (0.489 g, 1.72 mmol, 86%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.25 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.55–7.44 (m, 3H), 7.36–7.34 (m, 1H), 3.77 (d, *J* = 14.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

158.3 (d, J_{PC} = 139.2 Hz), 150.9 (d, J_{PC} = 21.0 Hz), 145.0 (d, J_{PC} = 16.2 Hz), 132.5 (d, J_{PC} = 2.8 Hz), 132.0 (d, J_{PC} = 11.4 Hz), 131.5 (d, J_{PC} = 110.6 Hz), 128.4 (d, J_{PC} = 14.3 Hz), 127.9 (d, J_{PC} = 27.7 Hz), 125.5 (d, J_{PC} = 2.9 Hz), 51.8 (d, J_{PC} = 5.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 77.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}ClNOPS^+$ 284.0060; Found 284.0063.

Diphenyl 2-pyridylthiophosphonate **5f**

N-Methoxypyridinium tosylate **4a** was prepared from pyridine *N*-oxide (0.0951 g, 1.00 mmol) and methyl *p*-toluenesulfonate (0.186 g, 1.00 mmol) as described in the synthesis of **5a**, and used without purification. DBU (0.150 mL, 1.00 mmol) and a solution of the thus prepared **4a** in dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2b** (0.126 g, 0.503 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 30 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5f** (0.135 g, 0.412 mmol, 82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 4.8 Hz, 1H), 8.23 (t, *J* = 7.6 Hz, 1H), 7.82 (m, 1H), 7.44 (m, 1H), 7.32–7.28 (m, 4H), 7.20–7.14 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (d, J_{PC} = 192.6 Hz), 150.2 (d, J_{PC} = 15.3 Hz), 150.1 (d, J_{PC} = 17.2

Hz), 136.5 (d, J_{PC} = 12.4 Hz), 129.3, 127.8 (d, J_{PC} = 30.5 Hz), 126.2 (d, J_{PC} = 3.8 Hz), 125.3 (d, J_{PC} = 1.9 Hz), 121.7 (d, J_{PC} = 4.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 73.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}NO_2PS^+$ 328.0556; Found 328.0576.

Diphenyl 4-propyl-2-pyridylthiophosphonate **5g**

N-Methoxy-4-propylpyridinium tosylate **4b** was prepared from 4-propylpyridine *N*-oxide (0.274 g, 2.00 mmol) and methyl *p*-toluenesulfonate (0.372 g, 2.00 mmol) as described in the synthesis of **5b**, and used without purification. DBU (0.300 mL, 2.01 mmol) and a solution of the thus prepared **4b** in dry MeCN (3.0 mL) were subsequently added to a stirred solution of **2b** (0.250 g, 1.00 mmol) in dry MeCN (2.0 mL) at –40 °C, and the resultant mixture was further stirred for 1 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (7 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5g** (0.200 g, 0.541 mmol, 54%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 0.8 Hz, 1H), 8.06 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.33–7.28 (m, 5H), 7.20–7.15 (m, 6H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.68 (sextet, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (d, J_{PC} = 190.7 Hz), 152.5 (d, J_{PC} = 13.4 Hz), 150.3 (d, J_{PC} = 8.6 Hz),

150.2 (d, J_{PC} = 23.9 Hz), 129.4, 128.4 (d, J_{PC} = 31.5 Hz), 126.4 (d, J_{PC} = 3.8 Hz), 125.4 (d, J_{PC} = 1.9 Hz), 121.9 (d, J_{PC} = 4.8 Hz), 37.2, 23.3, 13.6. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 74.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}NO_2PS^+$ 370.1025; Found 370.1024.

Diphenyl 4-methoxy-2-pyridylthiophosphonate **5h**

N-Methoxy-4-methoxypyridinium tosylate **4c** was prepared from 4-methoxypyridine *N*-oxide (0.125 g, 1.00 mmol) and methyl *p*-toluenesulfonate (0.186 g, 1.00 mmol) as described in the synthesis of **5c**, and used without purification. DBU (0.150 mL, 1.00 mmol) and a solution of the thus prepared **4c** in dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2b** (0.125 g, 0.500 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 2 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5h** (0.155 g, 0.434 mmol, 87%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.6 Hz, 1H), 7.80 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.34–7.30 (m, 4H), 7.20–7.16 (m, 6H), 6.98–6.96 (m, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (d, J_{PC} = 18.1 Hz), 155.9 (d, J_{PC} = 192.7 Hz), 151.8 (d, J_{PC} = 26.7 Hz), 150.3 (d, J_{PC} = 8.5 Hz), 129.4, 125.4, 121.9 (d, J_{PC} = 3.8

Hz), 114.8 (d, J_{PC} = 33.3 Hz), 112.0 (d, J_{PC} = 3.8 Hz), 55.5. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 74.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}NO_3PS^+$ 358.0661; Found 358.0677.

Diphenyl 4-chloro-2-pyridythiophosphonate **5i**

N-Methoxy-4-chloropyridinium triflate **4e** was prepared from 4-chloropyridine *N*-oxide (0.130 g, 1.00 mmol) and methyl trifluoromethanesulfonate (0.109 mL, 1.00 mmol) as described in the synthesis of **5e**, and used without purification. DBU (0.150 mL, 1.00 mmol) and a solution of the thus prepared **4e** n dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2b** (0.125 g, 0.500 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 10 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added, and the mixture was allowed to warm to RT and extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5i** (0.168 g, 0.464 mmol, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.2 Hz, 1H), 8.23 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.42 (dt, *J* = 5.2, 2.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 4H), 7.20–7.14 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (d, J_{PC} = 193.6 Hz), 151.2 (d, J_{PC} = 25.8 Hz), 150.1 (d, J_{PC} = 8.6 Hz), 145.1 (d, J_{PC} = 18.1 Hz), 129.5, 128.2 (d, J_{PC} = 31.5 Hz), 126.4

(d, J_{PC} = 2.8 Hz), 125.6, 121.8 (d, J_{PC} = 3.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 71.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}ClNO_2PS^+$ 362.0166; Found 362.0176.

Diisopropyl 2-pyridylthiophosphonate **5j**

N-Methoxypyridinium tosylate **4a** was prepared from pyridine *N*-oxide (0.951 g, 10.0 mmol) and methyl *p*-toluenesulfonate (1.86 g, 10.0 mmol) as described in the synthesis of **5a**, and used without purification. DBU (1.50 mL, 10.0 mmol) and a solution of the thus prepared **4a** in dry MeCN (20.0 mL) were subsequently added to a stirred solution of **2c** (0.912 g, 5.00 mmol) in dry MeCN (5.0 mL) at –40 °C, and the resultant mixture was further stirred for 30 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (30 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5j** (1.13 g, 4.36 mmol, 87%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.4 Hz, 1H), 8.04 (m, 1H), 7.77 (m, 1H), 7.37 (m, 1H), 4.98 (dsept, J = 10.4, 6.2 Hz, 2H), 1.39 (d, *J* = 6.2 Hz, 6H), 1.27 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 (d, J_{PC} = 193.5 Hz), 150.0 (d, J_{PC} = 23.1 Hz), 135.9 (d, J_{PC} = 12.3 Hz), 126.3 (d, J_{PC} = 28.0 Hz), 125.2 (d, J_{PC} = 4.1 Hz), 72.2 (d,

J_{PC} = 6.6 Hz), 23.7 (d, J_{PC} = 4.1 Hz), 23.3 (d, J_{PC} = 5.7 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 74.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_2PS^+$ 260.0869; Found 260.0870.

Diisopropyl 4-propyl-2-pyridylthiophosphonate **5k**

N-Methoxy-4-propylpyridinium tosylate **4b** was prepared from 4-propylpyridine *N*-oxide (0.137 g, 1.00 mmol) and methyl *p*-toluenesulfonate (0.186 g, 1.00 mmol) as described in the synthesis of **5b**, and used without purification. DBU (0.150 mL, 1.00 mmol) and a solution of the thus prepared **4b** in dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2c** (0.0909 g, 0.499 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 1 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt–CH_2Cl_2 (8:1:1, v/v/v)) to afford **5k** (0.117 g, 0.388 mmol, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.8 Hz, 1H), 7.88 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.18 (m, 1H), 4.96 (dsept, *J* = 10.4, 6.2 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 1.68 (sextet, *J* = 7.4 Hz, 2H), 1.39 (d, *J* = 6.2 Hz, 6H), 1.27 (d, *J* = 6.2 Hz, 6H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (d, J_{PC} = 189.7 Hz), 151.7 (d, J_{PC} = 12.4 Hz), 149.9 (d, J_{PC} = 23.9 Hz), 126.8 (d, J_{PC} =

28.7 Hz), 125.4 (d, J_{PC} = 2.8 Hz), 72.3 (d, J_{PC} = 5.7 Hz), 37.3, 23.8 (d, J_{PC} = 3.9 Hz), 23.5 (d, J_{PC} = 5.7 Hz), 23.3, 13.6. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 75.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{25}NO_2PS^+$ 302.1338; Found 302.1326.

Diisopropyl 4-methoxy-2-pyridylthiophosphonate **5l**

N-Methoxy-4-methoxypyridinium tosylate **4c** was prepared from 4-methoxypyridine *N*-oxide (0.100 g, 0.799 mmol) and methyl *p*-toluenesulfonate (0.149 g, 0.800 mmol) as described in the synthesis of **5c**, and used without purification. DBU (0.119 mL, 0.797 mmol) and a solution of the thus prepared **4c** in dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2c** (0.0732 g, 0.402 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 3 h at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added, and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5l** (0.0930 g, 0.321 mmol, 80%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.2 Hz, 1H), 7.62 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.86 (ddd, *J* = 5.2, 2.6, 2.2 Hz, 1H), 4.96 (dsept, *J* = 10.4, 6.4 Hz, 2H), 3.90 (s, 3H), 1.39 (d, *J* = 6.4 Hz, 6H), 1.27 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (d, J_{PC} = 17.2 Hz), 158.1 (d, J_{PC} = 190.7 Hz), 151.4 (d, J_{PC} =

25.8 Hz), 113.2 (d, J_{PC} = 30.5 Hz), 111.1 (d, J_{PC} = 2.9 Hz), 72.4 (d, J_{PC} = 6.6 Hz), 55.3, 23.8 (d, J_{PC} = 3.8 Hz), 23.5 (d, J_{PC} = 4.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 75.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3PS^+$ 290.0974; Found 290.0983.

Diisopropyl 4-chloro-2-pyridylthiophosphonate **5m**

N-Methoxy-4-chloropyridinium triflate **4e** was prepared from 4-chloropyridine *N*-oxide (0.104 g, 0.803 mmol) and methyl trifluoromethanesulfonate (0.0875 mL, 0.800 mmol) as described in the synthesis of **5e**, and used without purification. DBU (0.119 mL, 0.797 mmol) and a solution of the thus prepared **4e** in dry MeCN (2.0 mL) were subsequently added to a stirred solution of **2c** (0.0727 g, 0.399 mmol) in dry MeCN (0.50 mL) at –40 °C, and the resultant mixture was further stirred for 10 min at the same temperature. A 0.2 M NaH_2PO_4 aqueous solution (4 mL) was added and the mixture was allowed to warm to RT. The mixture was then extracted with AcOEt (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to afford **5l** (0.108 g, 0.368 mmol, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.2 Hz, 1H), 8.02 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.38 (dt, *J* = 5.2, 2.0 Hz, 1H), 4.98 (dsept, *J* = 10.8, 6.4 Hz, 2H), 1.40 (d, *J* = 6.4 Hz, 6H), 1.29 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (d, J_{PC} = 191.6 Hz), 150.9 (d, J_{PC} = 24.8 Hz), 144.6

(d, J_{PC} = 17.2 Hz), 126.7 (d, J_{PC} = 29.6 Hz), 125.5 (d, J_{PC} = 3.8 Hz), 72.8 (d, J_{PC} = 6.7 Hz), 23.8 (d, J_{PC} = 3.8 Hz), 23.5 (d, J_{PC} = 5.7 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 72.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{18}ClNO_2PS^+$ 294.0479; Found 294.0474.

Phenyl(2-pyridyl)thiophosphinic acid **6a**

A mixture of **5a** (1.81 g, 7.27 mmol), triethylamine (10.7 mL, 76.8 mmol), methanol (24 mL), and water (51 mL) was heated to reflux for 8 h. The mixture was then allowed to cool to RT, concentrated to some extend under reduced pressure, and lyophilized. The residue was dissolved in water (20 mL), and subsequent addition of 1 M HCl aq. (7.27 mL) precipitated a white solid, which was collected by suction filtration and dried *in vacuo* to give **6a** (1.52 g, 6.49 mmol, 89%) as a white solid. ^{1}H NMR (400 MHz, pyridine-d_5) δ 14.2 (br, 1H), 8.70 (d, J = 4.8 Hz, 1H), 8.66–8.58 (m, 3H), 7.68–7.63 (m, 1H), 7.48–7.38 (m, 3H), 7.15–7.11 (m, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 164.1 (d, J_{PC} = 134.5 Hz), 150.1 (d, J_{PC} = 19.0 Hz), 140.8 (d, J_{PC} = 106.8 Hz), 136.2 (d, J_{PC} = 9.5 Hz), 132.7 (d, J_{PC} = 10.5 Hz), 131.1 (d, J_{PC} = 2.9 Hz), 128.4 (d, J_{PC} = 12.4 Hz), 126.6 (d, J_{PC} = 24.8 Hz), 124.5 (d, J_{PC} = 2.9 Hz). ^{31}P NMR (161.7 MHz, pyridine-d_5) δ 58.6. ESI-HRMS: *m*/*z* calcd for $C_{11}H_9NOPS^-$ $[(M – H)^-]$ 234.0148, found 234.0124.

Phenyl(4-propyl-2-pyridyl)thiophosphinic acid **6b**

A mixture of **5b** (0.724 g, 2.48 mmol), methanol (12 mL), and 1 M NaOH aq. (24 mL) was heated to reflux for 3 h. The mixture was then allowed to cool to RT and concentrated under reduced pressure. The residue was dissolved in water (10 mL), cooled to 0 °C, and 1 M HCl aq. (24 mL) was added. The resultant precipitate was collected by suction filtration at RT, and dried *in vacuo* to afford **6b** (0.579 g, 2.09 mmol, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 6.0 Hz, 1H), 8.27–8.21 (m, 2H), 7.98 (d, J = 7.6 Hz, 1H), 7.45–7.44 (m, 4H), 2.72 (t, J = 7.8 Hz, 2H), 1.71–1.62 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J_{PC} = 6.7 Hz), 160.0 (d, J_{PC} = 84.8 Hz), 140.4 (d, J_{PC} = 5.7 Hz), 138.5 (d, J_{PC} = 112.5 Hz), 131.8 (d, J_{PC} = 11.5 Hz), 131.1 (d, J_{PC} = 2.8 Hz), 129.8 (d, J_{PC} = 13.3 Hz), 128.2 (d, J_{PC} = 13.3 Hz), 125.4, 37.9, 22.9, 13.5. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 47.3. ESI-HRMS: m/z calcd for $C_{14}H_{15}NOPS^-$ $[(M - H)^-]$ 276.0617, found 276.0621.

4-Methoxy-2-pyridyl(phenyl)thiophosphinic acid **6c**

A mixture of **5c** (0.213 g, 0.763 mmol), methanol (3.0 mL), and 1 M NaOH aq. (6.0 mL) was stirred for 1.5 h at RT and concentrated under reduced pressure. The residue was dissolved in water (3.0 mL), cooled to 0 °C, and 1 M HCl aq. (6.0 mL) was added. The mixture was then allowed to warm to RT, concentrated under reduced pressure, and lyophilized. The residue was washed with H_2O (8 mL) and dried *in vacuo* to afford **6c** (0.140 g, 0.528 mmol, 69%) as a white

solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 6.8 Hz, 1H), 8.25–8.20 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.44 (s, 3H), 7.01 (d, *J* = 6.8 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 167.0 (d, J_{PC} = 13.2 Hz), 165.3 (d, J_{PC} = 126.9 Hz), 150.5 (d, J_{PC} = 20.0 Hz), 141.1 (d, J_{PC} = 108.8 Hz), 132.8 (d, J_{PC} = 9.8 Hz), 131.1, 128.5 (d, J_{PC} = 12.4 Hz), 113.8 (d, J_{PC} = 24.7 Hz), 110.6, 55.7. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 48.2. ESI-HRMS: *m*/*z* calcd for $C_{12}H_{11}NO_2PS^-$ [(M – H)$^-$] 264.0254, found 264.0250.

4-Butoxy-2-pyridyl(phenyl)thiophosphinic acid **6d**

A mixture of **5d** (0.322 g, 1.00 mmol), methanol (3.0 mL), and 1 M NaOH aq. (6.0 mL) was heated to 50 °C for 1.5 h. The mixture was then allowed to cool to RT and concentrated under reduced pressure. The residue was dissolved in water (3.0 mL), cooled to 0 °C, and 1 M HCl aq. (6.0 mL) was added. The resultant precipitate was collected by suction filtration at RT and dried *in vacuo* to afford **6d** (0.227 g, 0.739 mmol, 74%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 6.8 Hz, 1H), 8.25–8.19 (m, 2H), 7.58 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.43–7.40 (m, 3H), 6.98 (dd, *J* = 6.8, 2.4 Hz, 1H), 4.13 (m, 2H), 1.81–1.74 (m, 2H), 1.45 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (d, J_{PC} = 9.5 Hz), 162.5 (d, J_{PC} = 83.9 Hz), 142.3 (d, J_{PC} = 5.8 Hz), 138.6 (d, J_{PC} = 111.6 Hz), 131.8 (d, J_{PC} = 11.4 Hz),

131.1 (d, J_{PC} = 2.9 Hz), 128.2 (d, J_{PC} = 12.3 Hz), 114.7 (d, J_{PC} = 14.3 Hz), 112.1, 70.1, 30.4, 18.8, 13.6. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 48.1. ESI-HRMS: *m*/*z* calcd for $C_{15}H_{17}NO_2PS^-$ [(M – H)$^-$] 306.0723, found 306.0712.

4-Chloro-2-pyridyl(phenyl)thiophosphinic acid **6e**

A mixture of **5e** (0.489 g, 1.72 mmol), methanol (7.5 mL), and 1 M NaOH aq. (15 mL) was heated to reflux for 2 h. The mixture was then allowed to cool to RT and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and 1 M HCl aq. (24 mL) was added. The resultant precipitate was collected by suction filtration and dried *in vacuo* to afford **6e** (0.291 g, 1.08 mmol, 63%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 5.6 Hz, 1H), 8.25–8.19 (m, 2H), 8.09 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.62 (dt, *J* = 6.4, 1.0 Hz, 1H), 7.53–7.45 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J_{PC} = 83.9 Hz), 152.7 (d, J_{PC} = 10.5 Hz), 142.3 (d, J_{PC} = 6.6 Hz), 137.0 (d, J_{PC} = 115.4 Hz), 132.0 (d, J_{PC} = 11.5 Hz), 131.7 (d, J_{PC} = 1.9 Hz), 130.1 (d, J_{PC} = 14.3 Hz), 128.5 (d, J_{PC} = 13.3 Hz), 126.2. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 49.2. ESI-HRMS: *m*/*z* calcd for $C_{11}H_8ClNOPS^-$ [(M – H)$^-$] 267.9758, found 267.9753.

Phenyl 2-pyridylthiophosphonate **6f**

A mixture of **5f** (0.164 g, 0.501 mmol), triethylamine (0.350 mL, 2.51 mmol), and THF–H_2O (1:2, v/v) (4.0 mL) was heated at 50 °C for 3 h, allowed to cool to RT, and concentrated under

reduced pressure. The residue was dissolved in water (2 mL) and passed through a column of Amberlite IR-120 (H^+ form) (7 g). The eluent was lyophilized to give **6f** (0.0777 g, 0.309 mmol, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.6 Hz, 1H), 8.47 (t, J = 7.4 Hz, 1H), 8.33 (m, 1H), 7.77 (m, 1H), 7.22–7.17 (m, 4H), 7.06–7.01 (m, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 162.9 (d, J_{PC} = 173.6 Hz), 154.1 (d, J_{PC} = 8.6 Hz), 149.7 (d, J_{PC} = 21.0 Hz), 136.5 (d, J_{PC} = 10.5 Hz), 129.7, 127.5 (d, J_{PC} = 26.7 Hz), 124.8 (d, J_{PC} = 2.8 Hz), 124.0, 122.9 (d, J_{PC} = 3.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 48.3. ESI-HRMS: m/z calcd for $C_{11}H_9NO_2PS^-$ [$(M - H)^-$] 250.0097, found 250.0087.

Phenyl 4-methoxy-2-pyridylthiophosphonate **6h**

A mixture of **5h** (0.155 g, 0.434 mmol), triethylamine (0.600 mL, 4.30 mmol), and THF–H_2O (1:2, v/v) (4.0 mL) was heated at 50 °C for 23 h, allowed to cool to RT, and concentrated under reduced pressure. The residue was dissolved in water (2 mL) and passed through a column of Amberlite IR-120 (H^+ form) (7 g). The eluent was lyophilized to give **6h** (0.0746 g, 0.265 mmol, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, J = 6.6, 1.4 Hz, 1H), 7.85 (dd, J = 9.6, 2.8 Hz, 1H), 7.20 (m, 4H), 7.09–7.01 (m, 2H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (d, J_{PC} = 11.5 Hz), 158.3 (d, J_{PC} = 130.7 Hz), 151.7 (d, J_{PC} = 9.5 Hz), 142.1 (d, J_{PC} = 8.6 Hz), 129.3, 124.2, 121.5 (d, J_{PC} = 4.7 Hz), 114.3 (d, J_{PC} = 15.3 Hz), 112.8, 57.3. ^{31}P NMR (161.7

MHz, $CDCl_3$) δ 48.9. ESI-HRMS: *m*/*z* calcd for $C_{12}H_{11}NO_3PS^-$ [(M – H)$^-$] 280.0203, found 280.0193.

Isopropyl 2-pyridylthiophosphonate **6j**

A mixture of **5j** (0.734 g, 2.83 mmol), methanol (5.0 mL), and 1 M NaOH aq. (10 mL) was heated at 75 °C for 9 h. The mixture was then allowed to cool to RT and concentrated under reduced pressure. The residue was dissolved in water (5 mL) and passed through a column of Amberlite IR-120 (H^+ form) (40 g). The eluent was lyophilized. The residue was washed with CH_2Cl_2–Et_2O (1:1, v/v) (20 mL) and dried *in vacuo* to give **6j** (0.356 g, 1.64 mmol, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 6.0 Hz, 1H), 8.40 (t, *J* = 7.6 Hz, 1H), 8.34–8.29 (m, 1H), 7.80–7.76 (m, 1H), 4.92 (dsept, *J* = 11.2, 6.2 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (d, J_{PC} = 130.6 Hz), 144.0 (d, J_{PC} = 8.6 Hz), 140.8 (d, J_{PC} = 7.6 Hz), 129.6 (d, J_{PC} = 12.4 Hz), 125.6, 70.7 (d, J_{PC} = 6.7 Hz), 24.3 (d, J_{PC} = 3.9 Hz), 24.1 (d, J_{PC} = 4.8 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 48.7. ESI-HRMS: *m*/*z* calcd for $C_8H_{11}NO_2PS^-$ [(M – H)$^-$] 216.0254, found 216.0250.

X-ray structure analysis

The measurement of **6h** was carried out on a Rigaku/MSC Mercury CCD diffractometer with graphite-monochromated Mo–*K*α radiation (λ = 0.71069 Å). Reflection data were collected at

193 K using a Rigaku XR-TCS-2-050 temperature controller. The structure was solved by direct methods (Sir2014)[11] and refined by full-matrix least-squares procedures (SHELXL-2014)[12] using the Yadokari-XG 2009.[13] The X-ray quality crystals were obtained by slow evaporation of a CH_2Cl_2 solution of **6h**. The crystal was cut from a grown crystal and attached to the tip of a MiTeGen MicroMount™. The crystal data and structure refinement results are summarized as the supplementary material.

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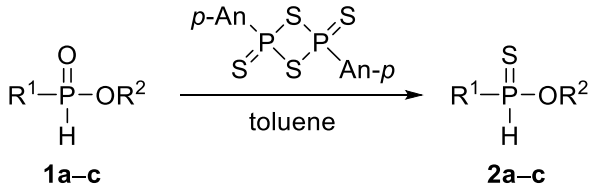
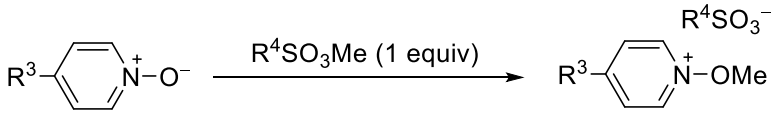
Table 1. Synthesis of *H*-thiophosphinate and *H*-thiophosphonate esters **2a–c**.



1a–c **2a–c**

entry	R^1	R^2	Lawesson's reagent	temperature	time (h)	product	isolated yield (%)
1	Ph	Me	0.5 equiv	RT	6	**2a**	68
2	Ph	Me	0.5 equiv	RT	1.5	**2a**	76
3	PhO	Ph	0.5 equiv	RT	3	**2b**	0
4	PhO	Ph	0.5 equiv	reflux	2	**2b**	41
5	PhO	Ph	0.5 equiv	60 °C	2	**2b**	51
6	PhO	Ph	0.7 equiv	60 °C	4	**2b**	71
7	*i*-PrO	*i*-Pr	0.5 equiv	reflux	1	**2c**	56
8	*i*-PrO	*i*-Pr	0.7 equiv	60 °C	3	**2c**	78

Table 2. Synthesis of *N*-methoxypyridium sulfonates **4a–e**.

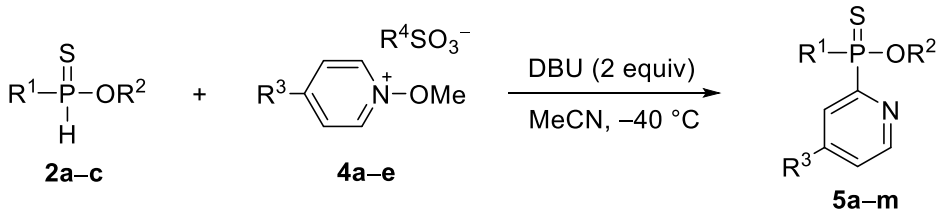


3a–e **4a–e**

entry	R^3	R^4	solvent	conditions	product	results[a]
1	H	*p*-MeC_6H_4	neat	100 °C, 8 h	**4a**	complete conversion
2	Pr	*p*-MeC_6H_4	neat	100 °C, 8 h	**4b**	complex mixture
3	Pr	*p*-MeC_6H_4	neat	100 °C, 10 min	**4b**	complete conversion
4	MeO	*p*-MeC_6H_4	neat	100 °C, 20 min	**4c**	complex mixture
5	MeO	*p*-MeC_6H_4	CH_2Cl_2	RT, 6 h	**4c**	complete conversion
6	BuO	*p*-MeC_6H_4	CH_2Cl_2	RT, 27 h	**4d**	complete conversion
7	Cl	*p*-MeC_6H_4	CH_2Cl_2	RT, 12 h	–	no reaction
8	Cl	*p*-MeC_6H_4	neat	100 °C, 12 h	–	no reaction
9	Cl	CF_3	neat	RT, 2 min	**4e**	side reaction
10	Cl	CF_3	CH_2Cl_2	0 °C then RT, 1 h	**4e**	complete conversion

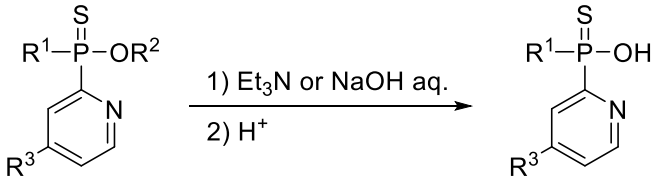
[a] ^{1}H NMR analysis.

Table 3. Synthesis of 2-pyridylthiophosphinate and 2-pyridylthiophosphonate esters **5a**–**m**.



entry	**2**	R^1	R^2	**4** (equiv)	R^3	R^4	time	product	isolated yield (%)
1	**a**	Ph	Me	**a** (1.5)	H	*p*-MeC_6H_4	10 min	**5a**	77
2	**a**	Ph	Me	**b** (1.5)	Pr	*p*-MeC_6H_4	1 h	**5b**	62
3	**a**	Ph	Me	**c** (1.5)	MeO	*p*-MeC_6H_4	2 h	**5c**	76
4	**a**	Ph	Me	**d** (1.5)	BuO	*p*-MeC_6H_4	2.5 h	**5d**	74
5	**a**	Ph	Me	**e** (1.5)	Cl	CF_3	30 min	**5e**	86
6	**b**	PhO	Ph	**a** (2.0)	H	*p*-MeC_6H_4	30 min	**5f**	82
7	**b**	PhO	Ph	**b** (2.0)	Pr	*p*-MeC_6H_4	1 h	**5g**	54
8	**b**	PhO	Ph	**c** (2.0)	MeO	*p*-MeC_6H_4	2 h	**5h**	87
9	**b**	PhO	Ph	**e** (2.0)	Cl	CF_3	10 min	**5i**	93
10	**c**	*i*-PrO	*i*-Pr	**a** (2.0)	H	*p*-MeC_6H_4	30 min	**5j**	87
11	**c**	*i*-PrO	*i*-Pr	**b** (2.0)	Pr	*p*-MeC_6H_4	1 h	**5k**	78
12	**c**	*i*-PrO	*i*-Pr	**c** (2.0)	MeO	*p*-MeC_6H_4	3 h	**5l**	80
13	**c**	*i*-PrO	*i*-Pr	**e** (2.0)	Cl	CF_3	10 min	**5m**	92

Table 4. Synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters **6a**–**f**, **h**, **j**.



5a–f, **h**, **j** **6a–f**, **h**, **j**

entry	R^1	R^2	R^3	base	conditions	**6**	isolated yield (%)
1	Ph	Me	H	Et_3N (10.5 equiv)	MeOH–H_2O (1:2, v/v), reflux, 8 h	**6a**	89
2	Ph	Me	Pr	Et_3N (10.5 equiv)	MeOH–H_2O (1:2, v/v), reflux, 33 h	**6b**	0
3	Ph	Me	Pr	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), reflux, 3 h	**6b**	84
4	Ph	Me	MeO	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), RT, 1.5 h	**6c**	69
5	Ph	Me	BuO	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), 50 °C, 1.5 h	**6d**	74
6	Ph	Me	Cl	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), reflux, 2 h	**6e**	63
7	PhO	Ph	H	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), reflux, 3 h	**6f**	–[a]
8	PhO	Ph	H	Et_3N (5 equiv)	THF–H_2O (1:2, v/v), 50 °C, 3 h	**6f**	62
9	PhO	Ph	MeO	Et_3N (10 equiv)	THF–H_2O (1:2, v/v), 50 °C, 23 h	**6h**	61
10	*i*-PrO	*i*-Pr	H	Et_3N (10.5 equiv)	MeOH–H_2O (1:2, v/v), reflux, 4 h	**6j**	0
11	*i*-PrO	*i*-Pr	H	Et_3N (10.5 equiv)	MeOH–H_2O (1:2, v/v), MW, 100 °C, 3 h	**6j**	0
12	*i*-PrO	*i*-Pr	H	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), 75 °C, 9 h	**6j**	58
13	*i*-PrO	*i*-Pr	H	1 M NaOH aq.	MeOH–H_2O (1:2, v/v), reflux, 4 h	**6j**	0

[a] 2-Pyridylthiophosphonic acid was generated as a major byproduct.

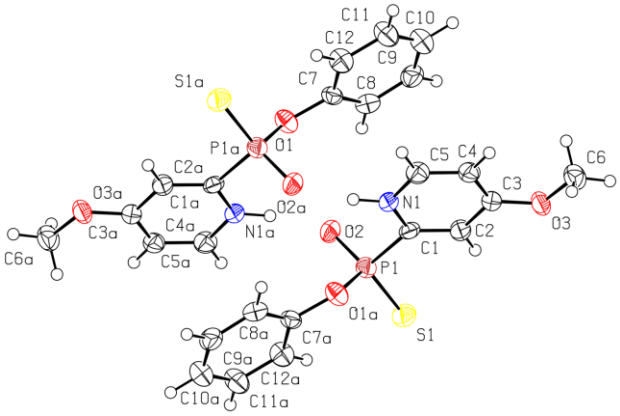


Figure 1. ORTEP drawing of a pair of (*R*)- and (*S*)-**6h** (thermal ellipsoids drawn at 50% probability level).

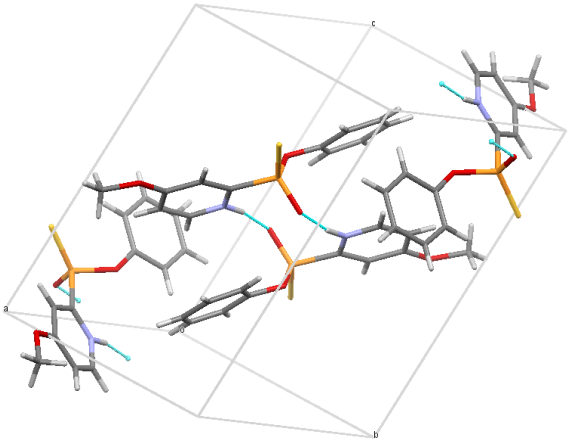
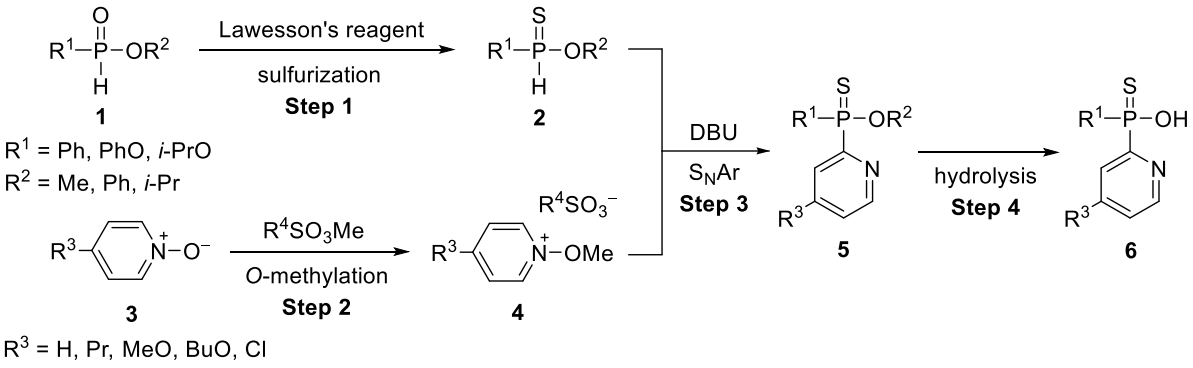


Figure 2. Molecular arrangement of **6h** in a unit cell with intermolecular hydrogen bonds.



Scheme 1. Synthesis of 2-pyridylthiophosphinic acids and 2-pyridylthiophosphonate monoesters **6** via S_NAr reaction.