(s'), 159.7 (s'), 170.9 (s'); exact mass m/z calcd for $C_{29}H_{32}NO_6Si$ (M - C_4H_9) 518.19989, found 518.19722.

No identifiable products were isolated from a similar experiment using the slower eluting fraction from the cyclization of **59a**.

Acknowledgments

We thank the Natural Sciences and Engineering research Council of Canada for financial support, and the National Cancer Institute, Bethesda for the biological tests.

References & footnotes

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2 *Cf.* (a) German Pat. Appl. DE 3430365 A1, 17 Aug. 1984 (*Chem. Abstr.* **1985**, *103*, 104798c). (b) See also biological test data reported in this paper.

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9 In principle, the (silyloxy)ethyl substituent could be removed, after radical spirocyclization, by the sequence: $RCH_2CH_2OSiMe_2Bu\text{-}t \rightarrow RCH_2CH_2OH \rightarrow RCH{=}CH_2 \rightarrow RCHO \rightarrow RH$. The last step ($RCHO \rightarrow RH$) might, perhaps, be done by decarbonylation or by oxidation and radical

decarboxylation.

10 The tests were run at the NCI (Bethesda).

11 Supplied by Chemical Dynamics Corp., South Plainfield, NJ.

12 Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).

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Synthesis and pKa Evaluation of Model Phosphonamidic, Phosphonamidothioic, and Phosphonamidodithioic Acids

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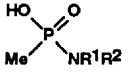
Abstract: Select phosphonamidic acids were synthesized that vary in the stepwise replacement of the phosphoryl oxygens for sulfur. The pKa values and spectroscopic properties were briefly examined. Copyright © 1996 Elsevier Science Ltd

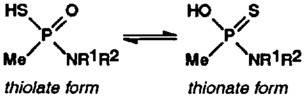
Recently, a number of physico-chemical and synthetic studies have been conducted using certain phosphonamidates [(R)(R^{1}R^{2}N)P(O)OH] that can act as stable transition state (TS) analogs by representing tetrahedral carbon intermediates formed during carboxamide bond hydrolysis. These TS analogs have been used to probe biological mechanisms,[1] as haptens for catalytic antibodies,[2] and act as enzyme inhibitors.[3] With interest in these tetrahedral phosphorus derivatives, we wished to examine how the chemical properties of these molecules are affected when the hydroxyl (P-OH) and/or phosphoryl (P=O) is progressively substituted by a sulfur atom. For example, the replacement of one or more of the phosphoryl oxygens by a sulfur would be expected to alter the acidity and certain spectroscopic properties. This paper describes the synthesis of model phosphonamidic acids that vary in the content of sulfur-phosphorus bonds, and compares certain specific chemical properties of these materials.

Methyl N-(substituted)phosphonamidates **1-3** (Fig. 1) were chosen as representative models using the following criterion: (a) to analyze the specific contribution from increased sulfur content, variations in the amide and alkyl group were minimized, (b) the amide group contains aliphatic bonds to avoid resonance or conjugation effects, (c) secondary amides analogs were included (i.e. R-NH-P=O) to more accurately simulate the carboxamide linkage of peptides, (d) an N-benzyl group was chosen to provide a chromophore, and (e) a P-Me group was chosen to reduce resonance and/or steric interactions that would alter the phosphonamidate properties.

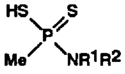
Figure 1



1abc: phosphonamidic acid



2abc: phosphonamidothioic acid (tautomers)



3b: phosphonamidodithioic acid

a: R^1 = H, R^2 = Bn
b: R^1 = H, R^2 = p-MeOBn
c: R^1 = Me, R^2 = Bn

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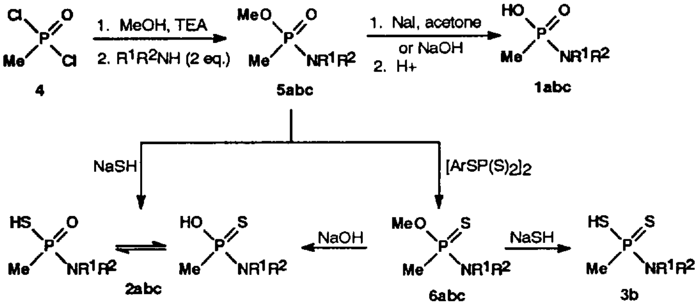
Overall, compounds **1-3** are intended to serve as truncated forms of phosphonopeptides[4] varying only in the degree of sulfur substitution. Some prior work has been published on the tautomeric composition of phosphorothioic [$(RO)_2P(O)SH$], phosphonothioic [$(RO)(R)P(O)SH$] and phosphinothioic [$(R^1)(R^2)P(O)SH$] acids,[5] but these molecules do not contain the relevant phosphonamide (P-N) linkage. To our knowledge, a comparative study of compounds of the type **1-3** has not yet been reported although phosphonamidate **1a** has been previously prepared.[6]

The synthesis of compounds **1-3** proceeded through the phosphonamidate esters **5a-c**, which were envisioned as divergent intermediates (Scheme 1). Methyl methylphosphonochloridate was prepared *in situ* (TEA, MeOH) from methyl phosphonic dichloride,[7] which reacted smoothly with the requisite benzylamine to give intermediates **5a-c** in 79-85% yield. Reaction of amine anions (via BuLi deprotonation) followed by stepwise reaction with **4** and methanol/TEA failed to produce **5a-c**. Attempts to directly prepare **1-3** from **4** failed including reaction with p-methoxybenzylamine followed by OH^- in an attempt to produce **1b**. The procedure outlined in Scheme 1 was found amenable to multi-gram scale preparation but decomposition of **5b** was noted upon storage.



Scheme 1

Dealkylation of **5a-c** using an equimolar amount of sodium iodide in acetone at reflux formed the phosphonamidic acids **1a-c** (75-83%) following neutralization. The ^{31}P NMR spectra shifted from a range of 32.8-35.4 ppm (for **5a-c**; lit. **5a** = 34.8)[6] to a range of 27.5-29.3 ppm (for **1a-c**; lit. **1a** = 26.6 in d_6-acetone)[6] consistent with the formation of a phosphonamidic acid. Compounds **1a-c** also were prepared by the hydrolysis of the corresponding phosphonamidate esters **5a-c** with 1.0 M NaOH in EtOH, however, this process gave lower yields. Likewise, sodium hydrosulfide (NaSH) was reacted with **5a-c** to form the phosphonamidothioic acids **2a-c** in 35-82% yield although this reaction was prone to poor yields due to competing dealkylation. A far more reliable path was undertaken in which compounds **2a-c** were formed in 55-85% yield by hydrolysis of the corresponding phosphonamidothionates **6a-c** (*vide infra*) using 1N NaOH. Compounds **6a-c** (*vide infra*) were prepared in 43-65% yield by reaction of **5a-c** with Lawesson's reagent [$(ArSPS_2)_2$].[8] Compounds **6a-c** showed characteristic thionate ^{31}P NMR resonances ranging from 83.6-85.8 ppm, which correlate well with related phosphonamidothionates, for example, $(Me)(MeO)P(S)NEt_2$ (δ ^{31}P = 87 ppm).[9]

Dithioic acid **3b** was prepared from phosphonamidothionate **6b** by reaction with sodium hydrosulfide in a THF-H_2O mixture at reflux to displace the methoxy group and produce the phosphonamidodithioic acid **3b** having a ^{31}P NMR absorbance at 67 ppm.[10] The upfield chemical shift of **3b** (67 ppm) and proximity to the phosphonamidothioic acid **2b** (64.9 ppm) raised the concern that dealkylation of the methoxy group by NaSH may have occurred. However, differences in the chromatographic properties, spectral characteristics and combustion analysis data of **2b** and **3b** supported the structural identity of **3b**. Infrared analysis did not yield any further confirmation of structure.

Because many phosphonamidates are used as stable TS analogs of carboxamide hydrolysis intermediates and are studied in reactions with proteins, the degree of ionization at physiologic pH should be of interest. The substitution of an oxygen by a sulfur is expected to alter the pKa, and therefore, a measure of the relative acidity of compounds **1**, **2** and **3** was undertaken to establish the influence of sulfur on the ionization. The pKa values were evaluated by standard acid-base titration[11] and using the weak acid equation, $pH = pKa + \log[(A^-)/(HA)]$.

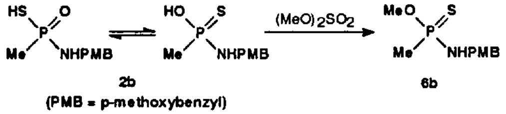
The pKa values of phosphonamidic acids **1a-c** (Table 1) ranged from 2.3-2.9 and agree with the previously reported pKa 2.90 for a related phosphonamidate [(n-hexyl)P(O)(OH)(NH-Leu-Trp-NHMe)].[12] The order of acidity **1b>1a>1c** may be explained, in part, by consideration of the corresponding zwitterionic species (e.g., $BnNH_2^+PO_2^-Me$) as the titrating species.[13] By virtue of the p-methoxy group, analog **1b** would better stabilize the protonated nitrogen than **1a** and lower the pKa. The N-methyl analog **1c** would be expected to be the least acidic if steric interactions at nitrogen reduce zwitterionic formation. Phosphonothioic acids **2a-c** were only marginally less acidic (pKa = 2.8-3.1) than the phosphonamidic acids and correspond well with the pKa reported for the phosphoramidothiolate, $c\text{-}C_6H_{11}P(O)(OMe)(SH)$ (pKa = 3.1).[14] The pKa value of phosphonamidodithioic acid **3b** was determined to be 2.3, a value possibly reflecting offsetting factors relative to **1b**. Phosphorus thioacids bearing the -SH group should ionize more readily than the corresponding -OH acid (lessened intermolecular hydrogen bonding) although the P=O is a stronger electron withdrawing group than the P=S. Thus, compound **3b** bears the weaker electron withdrawing group (P=S) but has a dissociating group (P-SH) that becomes highly stabilized as the conjugate base by two polarizable sulfur atoms.

Table 1. pKa and P-31 Chemical Shift Data (in ppm)

	1a	1b	1c	2a	2b	2c	3b
pKa (titrimetric)	2.70 (0.02)	2.30 (0.04)	2.90 (0.01)	2.86 (0.09)	3.13 (0.01)	2.83 (0.09)	2.31 (0.02)
δ P-31 (D_2O)	27.5	27.7	29.3	67.0	64.9	66.5	67.2

standard error reported in parentheses

Compounds **2a-c** should exist as the thiolate⇌thionate tautomers (Fig. 1) in solution (D_2O), which can undergo reactions at either oxygen or sulfur to afford different products. The chemical shift of compounds **2a-c** (65-67 ppm) suggests a preference for the thiono form (P=S linkage) although attempts to confirm the **2a-c** tautomeric composition by oxygen-17 or phosphorus-31 NMR failed. Interestingly, reaction of **2b** with an equimolar amount of dimethyl sulfate gave O-alkylation to afford compound **6b** in 60% yield (85.6 ppm; >90% by P-31 NMR) (Eqn. 1). This alkylation result was largely unexpected because in prior work, we showed that phosphorothioic acids of the type $(MeO)(R^1O)P(S)OH$ undergo reaction with dimethyl sulfate to form S-methyl phosphorothiolates via exclusive S-alkylation.[15]



(1)

Using Hammett analysis, Kabachnik determined the pKa's of phosphonodithioic acids [Me(R^1)P(S)(SH)] and phosphonothioic acids [Me(R^1)P(S)(OH)] in 7% aqueous ethanol.[5a] The pKa (1.7) for various phosphonodithioic acids (where R^1 = alkoxy) did not change with the nature of the alkoxy groups. Because the amino ligand is an electron donor, the pKa of phosphonamidodithioic acid (**3b**) should be slightly higher, which fits with our experimental data (pKa 2.31; **3b**). Kabachnik also found pKa = 1.8-1.95 for phosphonothioic acids of the type R^{1}R^{2}P(S)(OH) (R^1 = alkoxy),[5a] where the tautomer composition shifted to the thionate form (95%) as electron-releasing substituents increased. Since compounds **2a-c** represent the replacement of an alkoxy [in the Kabachnik study] by the stronger electron-releasing amine group, the pKa value is expected to be higher. Our experimental pKa = 2.8-3.1 for compounds **2a-c** therefore appears suitable based upon prior studies that suggest an increase in pKa value when an alkoxy group is substituted at phosphorus by an amino.[4b] The results in the study show that sulfur analogs of phosphonamidate TS analogs can be readily prepared and that the substitution of sulfur for phosphonamidate oxygens do not greatly alter the pKa value.

EXPERIMENTAL

^{1}H, ^{13}C and ^{31}P are taken at 400, 100.6, and 161.9 MHz, respectively. ^{1}H and ^{13}C NMR spectra were taken in D_2O or $CDCl_3$ using 0.05% dioxane or TMS as internal standards, respectively. ^{31}P NMR spectra were taken in the indicated deuterated solvents using phosphoric acid as an external standard. Analytical thin layer chromatography (TLC) was conducted with aluminum-backed silica plates. Visualization was accomplished with an ultraviolet (UV) lamp and/or ninhydrin, phosphomolybdic acid (PMA), dibromoquinone-4-chloroimide (DBQ), or ammonium molybdate staining reagents. All solvents and reagents were purified by standard literature methods. Air- or moisture-sensitive reactions were conducted under an argon atmosphere by utilizing standard techniques. The use of a well-ventilated hood is recommended for the preparation and handling of compounds **2a-c**, **3b**, and **6a-c** (stench; may be neutralized with dilute bleach solution).

General synthesis of N-(benzyl) methylphosphonamidic acids 1a-c. To a solution of phosphonamidate **5a-c** (4.3 mmol) in dry acetone (25 mL) was added sodium iodide (0.75 g, 4.3 mmol) and the reaction mixture heated to reflux. After 3 h, the solvent was evaporated to afford a white solid that was recrystallized from $CHCl_3$-ether. Alternatively, the free acid may be isolated by taking up the solid in 0.1 M citric acid solution, thrice extraction using ethyl acetate, drying the combined organic extracts over sodium sulfate, filtration, and evaporation of the solvent. The sodium salts were submitted for elemental analysis.

Methyl-N-(benzyl)phosphonamidic acid (**1a**):[6] Yield (83%); mp = 252-253 °C; ^{1}H-NMR (D_2O): δ 1.04 (3H, d, J = 12.8 Hz), 3.8 (2H, d, J = 9.2 Hz), 7.2 (5H, s); ^{13}C-NMR (D_2O): δ 40.9 (d, J = 120.5), 71.9, 153.9, 154.5, 155.7, 168.0; ^{31}P-NMR (D_2O): δ 27.5. Anal. Calc. for $C_8H_{11}NPO_2Na \cdot H_2O$: C, 44.45; H, 5.13; N, 6.48. Found: C, 44.55; H, 5.13; N, 6.36.

Methyl-N-(p-methoxybenzyl)phosphonamidic acid (**1b**): Yield (77%); mp = 195-197°C; ^{1}H NMR (D_2O): δ 1.2 (3H, d, *J* = 14 Hz), 3.8 (3H, s), 3.90 (2H, d, *J* = 3.4 Hz), 6.83 (2H, d, *J* = 8.2 Hz), 7.20 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (D_2O): δ 17.2 (d, *J* = 121.2), 47.4, 58.6, 117.2, 132.2, 137.1, 160.9; ^{31}P NMR (D_2O): δ 27.7. Anal. Calc. for $C_9H_{14}NPO_3Na{\bullet}3H_2O$: C, 37.12; H, 4.71; N, 4.79. Found: C, 37.16; H, 4.50; N, 4.79.

Methyl-N-(methyl)-N-(benzyl)phosphonamidic acid (**1c**): Yield (75%); mp = 235-236°C. ^{1}H-NMR (D_2O): δ 1.06 (3H, d, J = 15.2 Hz), 2.2 (3H, d, J = 10.0 Hz), 3.8 (2H, d, J = 6.8 Hz), 7.2 (5H, s). ^{13}C-NMR (D_2O): δ 37.8 (d, J = 121.1), 59.8, 79.5, 154.0, 154.3, 155.7, 166.6. ^{31}P-NMR (D_2O): δ 29.3. Anal. Calc. for $C_9H_{13}NPO_2Na{\cdot}H_2O$: C, 45.20; H, 5.47; N, 5.85. Found: C, 45.72; H, 5.64; N, 5.87.

General synthesis of N-(benzyl)methylphosphonamidothioic acid 2a-c.

Method A (reaction of phosphonamidate with NaSH): Phosphonamidates **5a-c** (2.2 mmol) and $NaSH{\bullet}H_2O$ (4.6 mmol) in THF-H_2O 2:1 (15 mL) were heated to reflux under argon for 3 h. After cooling to room temperature, the solvent was removed to afford a residue that was redissolved in water (10 mL), acidified to pH 4 with 1 M NaH_2PO_4 and extracted twice with isopropanol-$CHCl_3$ (1:9). The extracts were combined, dried over sodium sulfate and the solvent evaporated *in vacuo* to afford an oily semisolid. The product was recrystallized from EtOH.

Method B (hydrolysis of phosphonamidothionate): To phosphonamidothionates **6a-c** (5 mmol) dissolved in 20 mL of EtOH was added 1M NaOH (5 mL), and the reaction brought to reflux. After 2 h, the mixture was cooled and evaporated to a powder. The solid was washed with diethyl ether (3x20 mL) to afford the corresponding sodium salt, which was sufficiently pure for analysis. The acid was prepared by dissolving the sodium salt in 25 mL water, acidification to pH 3.5 with solid citric acid, and extraction with 4:1 chloroform-isopropanol (3 x 25 mL). The organic extracts were combined, washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated to afford a pungent, off yellow oil. Thioic acids **2a-c** were isolated by extraction showed reasonable purity by NMR but flash chromatography using chloroform-methanol (85:15) was routinely employed to purify them.

Methyl-N-(benzyl)phosphonamidothioic acid (**2a**): (82% yield); mp = 270-276 °C. ^{1}H-NMR (D_2O): δ 1.48 (3H, d, J = 14.0 Hz), 3.7 (1H, br s), 3.9 (2H, d, J = 6.8 Hz), 7.2 (5H, m): ^{13}C-NMR (D_2O): δ 14.0 (d, J = 122 Hz), 44.8, 126.9, 127.5, 128.5, 141.0, 141.1. ^{31}P-NMR (D_2O): δ 67.0. Anal. Calc. for: $C_8H_{11}NPOSNa$: C, 46.37; H, 5.35; N, 6.76. Found: C, 46.66; H, 5.69: N, 6.39.

Methyl-N-(p-methoxybenzyl)phosphonamidothioic acid (**2b**): (75% yield); mp = 160 °C (decomp.). ^{1}H NMR (D_2O): δ 1.2 (3H, d, *J* = 15.5 Hz), 3.8 (3H, s), 3.91 (2H, d, *J* = 7.9 Hz), 6.95 (2H, d, *J* = 8.2 Hz), 7.32 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (D_2O): δ 16.5 (d, *J* = 121.1), 46.7, 57.8, 116.4, 131.3, 136.1, 160.9; ^{31}P NMR (D_2O): 64.9. The sodium salt was submitted for elemental analysis. Anal. Calc. for $C_9H_{13}NPO_2SNa$: C, 42.68; H, 5.17; N, 5.53. Found: C, 42.65; H, 5.19; N, 5.55.

Methyl-N-(methyl)-N-(benzyl)phosphonamidothioic acid (**2c**): (77 % yield); mp = 230-234 °C. ^{1}H NMR (D_2O): δ 1.1 (3H, d, *J* = 15.2 Hz), 2.25 (3H, d, *J* = 10 Hz), 3.9 (2H, d, *J* = 6.4 Hz), 7.2-7.35 (5H, m); ^{13}C NMR (D_2O): δ 11.0 (d, *J* = 121.1), 32.8, 52.4, 127.0, 128.3, 128.4, 139.7, 160.9; ^{31}P NMR (D_2O): 66.5. Anal. Calc. for: $C_9H_{14}NOPSNa{\cdot}H_2O$: C, 42.35; H, 5.52; N, 5.49. Found: C, 42.77; H, 5.49: N, 5.69.

Methyl N-(p-Methoxybenzyl)phosphonamidodithioic acid (3b). Methyl N-p-methoxybenzyl phosphonamidothionate **6b** (0.100 g, 0.4 mmol) and NaSH (0.023 g, 0.4 mmol) in 10 mL THF-water (9:1) were heated at reflux for 5 h. The mixture was cooled to room temperature and stirring was continued for 12 h whereupon the solvent was evaporated, H_2O (10 mL) was added and the solution acidified with 1 M NaH_2PO_4 to pH 4. The aqueous solution was extracted with EtOAc (3 x 10 mL), dried over magnesium sulfate and evaporated to a yellow oil. The product was purified by flash chromatography using a 1-10% MeOH-EtOAc gradient. ^{1}H NMR: δ 1.75 (3H, d, J = 14 Hz), 3.8 (3H, s), 4.15 (2H, m), 6.9 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 8.7 Hz); ^{13}C NMR: δ 16.3 (d, J = 137.0), 46.5, 57.6, 116.9, 131.2, 136.5, 161.0; ^{31}P NMR ($CDCl_3$): 67.2. The sodium salt was submitted for analysis. Anal. Calc. for $C_9H_{13}NPOS_2Na$: C, 40.13; H, 4.86; N, 5.20; Found: C, 40.20; H, 4.83; N, 5.22.

General synthesis of methyl O-methyl-N-(benzyl)phosphonamidates 5a-c. To a solution of methylphosphonic dichloride (4 g, 30.08 mmol) in ether (50 mL) at room temperature was added a mixture of MeOH (1.2 mL, 30.1 mmol) and TEA (4.0 mL, 30.1 mmol) in ether (10 mL). The TEA•HCl was removed by filtration and the requisite benzylamine (60.2 mmol) in ether (10 mL) was added dropwise. After 15 minutes at room temperature, the mixture was diluted with ether (30 mL), the precipitate was filtered, and the solvent concentrated *in vacuo.* The crude product was chromatographed on silica gel to give yellow oils.

Methyl O-methyl-N-(benzyl)phosphonamidate (**5a**):[6] Chromatography using EtOAc-MeOH (95:5) affords 85% yield; ^{1}H-NMR ($CDCl_3$): δ 1.4 (3H, d, J =16.0 Hz), 3.2 (1H, br), 3.57 (3H, d, J = 11.2 Hz), 4.1 (2H, d, J = 8.0 Hz), 7.3 (5H, m); ^{13}C-NMR ($CDCl_3$): δ 12.0 (d, J = 141.0 Hz), 44.2, 49.7, 126.8, 128.2, 139.6; ^{31}P-NMR ($CDCl_3$) δ 32.8. Anal. Calc. for $C_9H_{14}NPO_2$; C, 54.26; H, 7.08; N, 7.03. Found: C, 54.22; H, 7.06; N, 7.01.

Methyl O-methyl-N-(p-methoxybenzyl)phosphonamidate (**5b**): Chromatography using CH_2Cl_2-MeOH (95:5) affords 83% yield; ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, dd, J = 16.0 Hz), 3.52 (3H, dd, J = 16.0 Hz), 3.72 (3H, s), 3.94 (2H, d, J = 8.0 Hz), 6.8 (2H, d, J = 6.8 Hz), 7.17 (2H, d, J = 6.8 Hz); ^{13}C NMR: δ 12.4 (d, J = 122.1) 43.9, 49.9, 56.0, 113.7, 128.2, 131.7, 156.6; ^{31}P NMR ($CDCl_3$): δ 35.4. Anal. Calc. for $C_{10}H_{16}NPO_3$: C, 52.40; H, 7.03; N, 6.11. Found: C, 52.00; H, 7.07; N, 6.04.

Methyl O-methyl-N-(methyl)-N-(benzyl)phosphonamidate (**5c**): Chromatography using EtOAc-MeOH (95:5) affords 79% yield; ^{1}H-NMR ($CDCl_3$): δ 1.4 (3H, d, J = 16 Hz), 2.5 (3H, d, J = 9.6 Hz), 3.5 (3H, d, J = 11.0 Hz), 4.1 (2H, d, J = 8.0 Hz), 7.3 (5H, s); ^{13}C-NMR ($CDCl_3$): 10.7 (d, J = 133.0 Hz), 32.0, 49.6, 51.6, 126.9, 127.7, 128.1, 137.6; ^{31}P-NMR ($CDCl_3$) δ 33.4. Anal. Calc. for $C_{10}H_{16}NPO_2$: C, 56.33; H, 7.56; N, 6.57. Found: C, 56.11; H, 7.45; N, 6.54.

General synthesis of methyl N-(benzyl) methylphosphonamidothionates 6a-c. To a solution of methyl phosphonamidate **5a-c** (4.3 mmol) in 25 mL of benzene was added Lawesson's reagent (2.1 mmol) followed by heating to reflux under argon for 2 h. After cooling, the solution was washed with 20 mL portions of 10% NaOH and brine. The organic layer was dried over sodium sulfate and concentrated to an oil. Purification on silica gel using petroleum ether-ether (7:3) gave low-melting solids or colorless oils in 55-65% yield.