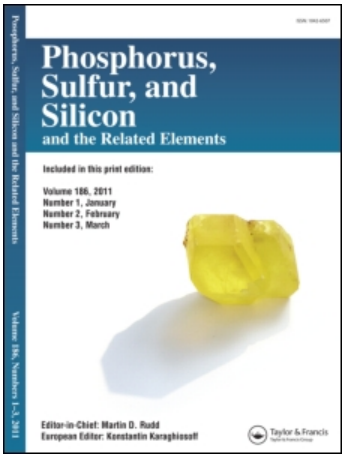

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SYNTHESIS OF STERICALLY HINDERED PHOSPHONAMIDOTHIOLATES AND PHOSPHONAMIDODITHIOATES

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SYNTHESIS OF STERICALLY HINDERED PHOSPHONAMIDOTHIOLATES AND PHOSPHONAMIDODITHIOATES

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The synthesis of sterically hindered t-butyl phosphonamidothiolate and t-butyl phosphonamidodithioate compounds has been conducted. These materials are intended to serve as precursors to study the oxidative bioactivation of certain phosphorothiolate pesticides

Keywords: Phosphonamidothiolates; phosphonamidodithioates; sterically hindered phosphonates; synthesis

INTRODUCTION

Organophosphorus (OP) insecticides primarily impart their toxic action by inhibiting an essential serine residue in the active site of [acetyl]cholinesterase.[1] Potent OP cholinesterase inhibitors usually contain a phosphoryl (P═O) group and a good leaving group X in their structure. The P═O bond is electron-deficient at phosphorus making it reactive toward highly nucleophilic species. Furthermore, a good leaving group aids formation of the phospho-serine linkage. In the absence of either or both of these important chemical features, OP compounds generally lack *in vitro* anticholinesterase activity. For example, phosphorothionate insecticides (**1**; P═S), are poor cholinesterase inhibitors *in vitro* despite the presence of a good leaving group. Oxidation of phosphorothionates results in oxons (**2**: P═O) that are potent phosphorylating agents and presumed responsible for the intoxication of target and non-target organisms (eq. 1).

OP compounds that possess the P═O linkage but do not contain a viable leaving group (e.g., O,O,S-trimethylphosphorothiolate **3**, methamidophos **4** and acephate **5**; eq. 2) also show relatively poor *in vitro* anticholinesterase reactiv-

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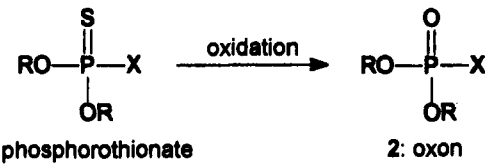
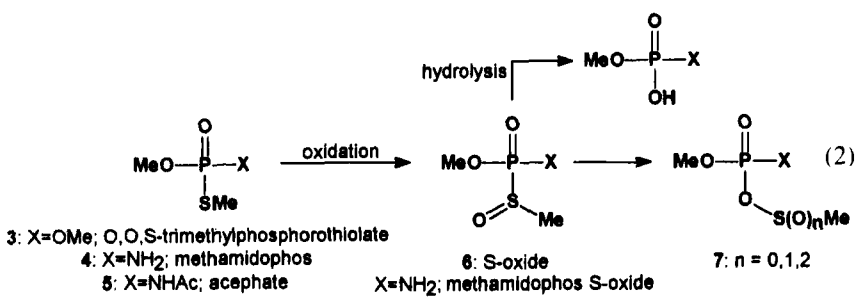


1: phosphorothionate 2: oxon (1)

ity.[2,3] On occasion, the *in vitro* anticholinesterase potency does not always correlate with *in vivo* toxicity, for example, methamidophos **4** is a poor *in vitro* inhibitor of cholinesterase but a potent inhibitor *in vivo*. This dichotomy suggests that **4** is either highly efficient at reaching essential targets (e.g., brain cholinesterase) and/or is metabolically transformed *in vivo* to a more potent phosphorylating agent.[3] A likely site of biotransformation is the sulfur atom which undergoes chemical oxidation to form the rearranged, sulfur esters **7**, presumably through initial formation of the S-oxide (**6**: eq. 2).[4]



3: X=OMe; O,O,S-trimethylphosphorothiolate
4: X=NH_2; methamidophos
5: X=NHAc; acephate
6: S-oxide
X=NH_2; methamidophos S-oxide
7: n = 0,1,2 (2)

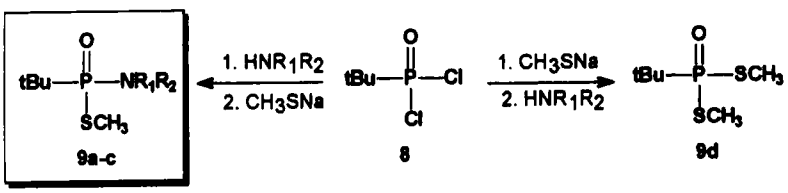
Phosphorus thiolester S-oxides **6** represent highly reactive species that may be potent phosphorylating agents[5] and possibly responsible, in part, for the enhance anticholinesterase potency of **4** *in vivo*. S-oxide reactivity also imparts hydrolytic instability (eq. 2) making S-oxides transitory species and, to date, difficult to isolate and characterize.

In an effort to circumvent the putative hydrolytic instability of phosphorothiolate S-oxides and possibly isolate and identify a stable S-oxide, we undertook a brief synthesis of select sterically hindered S-methyl phosphonamidothiolates molecules **9** (eq. 3) as possible precursors to stable S-oxides and as potential substrates for oxidizing enzymes that would test the active site structural limit. In our design, a *tert*-butyl phosphonate (P-C) ligand was chosen to both avoid the problem of ester hydrolysis (as with phosphates) and to more closely position a sterically congested moiety near the phosphorus atom to deter attack by nucleophiles. Amidate groups (P-NR_1R_2) were chosen to permit variation in the steric component and to impart a strong electron-donating group that would

further reduce hydrolysis reactions. Last, an S-methyl group was desired in the products so that relevance to studies of methamidophos oxidation could be maintained.

RESULTS AND DISCUSSION

Our initial approach to prepare hindered phosphonamidothiolates sought to sequentially react the commercially available t-butylphosphonic dichloride **8** with a disubstituted amine (R_1R_2NH) and MeSNa (eq. 3).

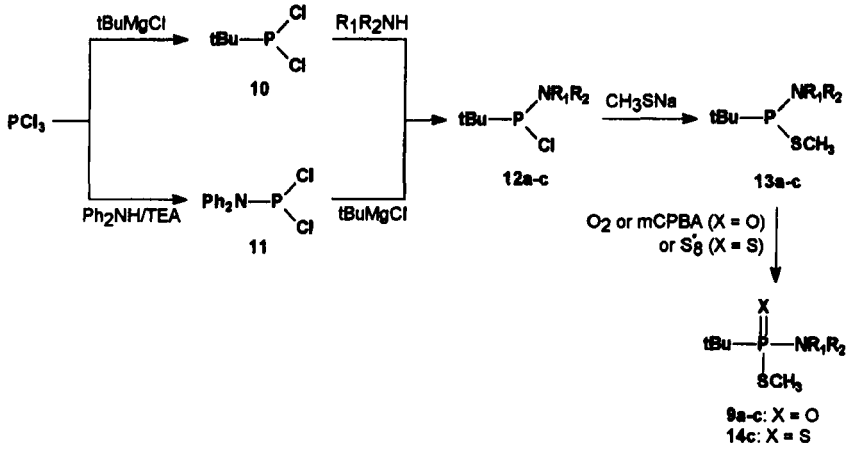


(3)

However, when **8** was reacted with diethylamine ($R_1 = R_2 = Et$) in ether containing triethylamine (1 equiv.; RT, 24 h) or at reflux (40°C, 15 h), only starting material was observed, as indicated by a ^{31}P NMR spectrum of the reaction mixture. Reversing the order of reagent addition did not afford **9a**, rather, reaction of **8** with MeSNa (1 equiv.) in THF proceeded very slowly and gave a 50:50 mixture of starting material and S,S-dimethyl-t-butylphosphonodithioate **9d** (eq. 3). The structure of **9d** was confirmed through spectral and combustion analysis.

This failed approach was consistent with previous reports[6] that **8** reacted with amines only at very high temperatures (ca. 140–150°C) and unfortunately gives the diamide (disubstituted product) as the major product. Therefore, the use of t-butylphosphonic dichloride was abandoned in favor of a more promising method in which t-butylphosphonic dichloride **10**[7] (the trivalent analogue of **8**) served as the key intermediate (Scheme 1).

The syntheses of the target hindered phosphonamidothiolates **9a–c** and dithioate **14c** were accomplished via a one-pot, 4-step reaction sequence starting from PCl_3 (Scheme 1) per the procedure outlined below. Owing to changes in the steric composition and reactivity of the intermediates, different orders of reagent addition were required to prepare compounds **9a/9b** and **9c** and therefore, separate pathways are described. Phosphorus-31 NMR chemical shifts were used throughout the sequence to monitor the reactions and these values are indicated in parentheses where appropriate.



SCHEME 1

Synthesis of N,N-Diethyl, S-Methyl-t-Butylphosphonamidothiolate (9a) and N-t-Butyl, S-Methyl-t-Butylphosphonamidothiolate (9b) (Scheme 1).

Phosphorus trichloride (δ = 218.6 ppm) was reacted with t-butyl magnesium chloride in THF (0°C, 2 h) to produce t-butylphosphinic dichloride **10** (δ = 201.1 ppm; lit.[7] 198.6 ppm in benzene). Without extraction or isolation, a THF solution of the desired amine Et_2NH (2 equiv.), or $tBuNH_2$ (2 equiv.) was added to **10** while maintaining the reaction temperature at 0°C. After allowing the reaction mixture to reach room temperature the corresponding N,N-diethylchlorophosphinamide **12a** and N-t-butylchlorophosphinamide **12b** were observed at δ = 160.0 ppm (lit.[8] 156.7 ppm in CCl_3F) and 141.5 ppm, respectively. The S-methyl-t-butylphosphonamidites **13a** (δ = 124.2 ppm) and **13b** (δ = 100.1 ppm) were obtained by direct treatment of chlorophosphinamides **12a** and **12b** with solid MeSNa (rt, 24 h). Air oxidation of **13a** and **13b** furnished **9a** (δ = 69.6 ppm) and **9b** (δ = 57.1 ppm), respectively, to conclude the four-step, one-pot sequence. Oxidation to the phosphonates was conveniently performed by vigorously stirring the crude products (**13a** and **13b**) in air or by bubbling air through a solution of CH_2Cl_2. The oxidation step can also be accomplished with meta-chloroperoxybenzoic acid (mCPBA) but careful reaction conditions must be maintained to avoid over-oxidation and loss of the thiolate group. The isolated yields (not optimized) for **9a** and **9b** were 42% and 23%, respectively, after purification by flash chromatography. Although, intermediates **11–13** were generally not isolated (except **13c**), ^{31}P NMR monitoring was crucial to the reaction success.

Synthesis of N,N-Diphenyl-S-Methyl-t-Butylphosphonamidothiolate (9c) and N,N-Diphenyl-S-Methyl-t-Butylphosphinamidothiolate (13c) (Scheme 1)

Our preliminary experiments determined that the addition of diphenylamine (containing triethylamine) to t-butylphosphinic dichloride **10** did not form **12c** as was successful in the case of the aliphatic amines. The low reactivity of **10** towards Ph_2NH was not surprising in light of the reduced nucleophilicity of diphenylanilines. Therefore, a reversed order of addition of the t-butylmagnesium chloride and Ph_2NH was performed. Accordingly, a solution of Ph_2NH (1 equiv.) and triethylamine (1 equiv., TEA) in ether was slowly added to a solution of PCl_3 previously cooled to 0°C to afford **11**. A slow addition was required (approx. 30 min) in order to avoid the formation of di- and trisubstituted byproducts. A ^{31}P NMR spectrum of the reaction mixture after 5 h showed the exclusive formation of **11** with a chemical shift of δ = 150.0 ppm (lit.[9] 151.3 ppm in toluene).

The intermediate chloroamidite **12c** was easily obtained by reacting the mixture containing **11** with two equivalents of 1M t-BuMgCl in THF. During the preparation of **12c** the ammonium salt, formed in the previous step, consumed the first equivalent of the Grignard reagent. After overnight stirring, a ^{31}P NMR of the reaction mixture showed a single signal at δ = 145.0 ppm corresponding to **12c**. The reaction mixture was filtered under vacuum to remove the precipitated salts. Solid MeSNa was added to the filtrate and the mixture stirred under a nitrogen atmosphere resulting in a peak at δ = 118.9 ppm corresponding to **13c**. Interestingly, attempts to oxidize **13c** by bubbling air through a solution in CH_2Cl_2 failed. Even after 48 h of air exposure no oxidation to form **9c** was observed. The unique stability of compound **13c** allowed its isolation as a colorless oil, which solidified at 0°C, following column chromatography. In contrast, the compounds **13a** and **13b** were only identified spectroscopically due to their ready oxidation in air.

Oxidation to form **9c** was eventually accomplished by slow addition of a dilute solution of mCPBA (1 equiv.) to a chilled (0°C) solution of **13c** in CH_2Cl_2. The oxidation reaction appeared to be almost instantaneous under these conditions as shown by ^{31}P NMR. Therefore, the reaction mixture was worked up quickly (approx. 30 min) after completing the addition of mCPBA to avoid further oxidation and/or side reactions with the m-chlorobenzoic acid formed during oxidation.

The synthetic sequence was next examined for application to thionate (P = S) preparation (Scheme 1). The N,N-Diphenylphosphonamidite **13c** was reacted with recrystallized elemental sulfur (rather than reacted with air or mCPBA in the case of **9c**) to afford the dithioate **14c** in quantitative yield. Formation of the

thionate linkage (P═S) was monitored and confirmed by ^{31}P NMR which showed the characteristic 40 ppm downfield shift relative to **9c** (62 ppm)[10] near 110 ppm.

In this paper, we showed that sterically congested phosphonamidothiolates or dithioates can be easily accessed in fair overall yield using either of two possible routes representing *one-pot, four step* syntheses. The route chosen depends upon the basicity of the amine ligand that is to be introduced. The sequence is amenable to formation of the corresponding thionates, and in certain instances, the trivalent intermediates may be isolated. With the representative S-methyl phosphonamidothiolates in hand, we can now examine the oxidation of the thiolate linkage.

EXPERIMENTAL

General Comments: All reactions were carried out in oven dried glassware under a nitrogen atmosphere unless otherwise specified. Melting points were determined on a Melt-Temp II apparatus and are uncorrected. All solvents and reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were purified when necessary by standard literature methods.[11] Analytical TLC was conducted on E. Merck aluminum-backed, 0.2 mm silica gel 60 F_{254}, TLC plates. Flash chromatography was performed with Kieselgel 60, 230–400 mesh (Merck Co.).

Proton (^1H), carbon (^{13}C), and phosphorus (^{31}P) NMR spectra were taken on a Varian Unity-Plus 400-MHz spectrometer at 400, 100.6, and 161.9 MHz, respectively. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) referenced to TMS or $CDCl_3$. ^{31}P NMR chemical shifts are relative to 85% phosphoric acid (H_3PO_4 external standard in $CDCl_3$ or D_2O). GC-MS data were obtained on Hewlett-Packard 5890A Gas Chromatograph-5970 Series Mass Selective Detector. Elemental analyses were performed by Midwest Microlab of Indianapolis, IN.

N,N-diethyl-S-methyl-t-butylphosphonamidothiolate (9a): To a solution of PCl_3 (2.23 mL, 3.50 g, 25.5 mmol) in 50 mL of dry THF maintained at 0°C (ice bath) was added 25.5 mL of a 1 M tBuMgCl solution (THF) dropwise over a period of 30 min using an addition funnel. After 2 h of stirring, Et_2NH (5.30 mL, 3.75 g, 51.0 mmol) in 15 mL THF was slowly added to the reaction mixture over 20 min. The reaction was allowed to warm up to room temperature and was stirred for another 4 h. The resulting mixture was quickly filtered under vacuum to remove most of the insoluble salts. The filtrate was treated with MeSNa (1.80

g, 25.6 mmol) added in one portion and stirred overnight at room temperature. The solvent was removed under vacuum and the residue was dissolved in 50 mL of ether and filtered. The solvent was removed and crude **13a** was stirred while open to the air for about 16 h, resulting in oxidation to **9a**. This product was purified by flash chromatography (silica gel, EtOAc) affording 2.42 g (42%) of pure **9a**. Data for **9a**: R_f = 0.32 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 3.14–3.34 (m, 4H), 2.19 (d, J_{PH} = 10.5 Hz, 3 H), 1.20 (d, J_{PH} = 17.5 Hz, 9 H), 1.14 (t, J_{HH} = 7.1 Hz, 6 H). ^{13}C NMR ($CDCl_3$) δ 39.44 (d, J_{PC} = 3.1 Hz), 38.95 (d, J_{PC} = 95.4 Hz), 25.33 (s), 14.25 (d, J_{PC} = 2.3 Hz), 9.15 (d, J_{PC} = 3.1 Hz). ^{31}P NMR ($CDCl_3$) δ 69.6. GC-MS m/e 223 (M^+), 208, 166, 151, 138, 120 (base), 104, 72, 57. Anal. Calcd. for $C_9H_{22}ONPS$: C, 48.41; H, 9.93; N, 6.27. Found: C, 48.16; H, 10.13; N, 6.24.

Partial spectroscopic data for the other intermediates in the reaction: **10**: ^{31}P NMR (THF) δ 201.1. **12a**: ^{31}P NMR (THF) δ 160.0. **13a**: ^{1}H NMR ($CDCl_3$) δ 3.05–3.13 (m, 4 H), 2.19 (d, J_{PH} = 11.4 Hz, 3 H), 1.11 (d, J_{PH} = 13.8 Hz, 9 H), 1.08 (t, J_{HH} = 7.1 Hz, 6 H). ^{31}P NMR ($CDCl_3$) δ 124.2. GC-MS m/e 207 (M^+), 150 (base), 136, 120, 102, 72, 57.

N-t-butyl-S-methyl-t-butylphosphonoamidothiolate (9b): The same procedure was used as for **9a** replacing Et_2NH with $tBuNH_2$. Yield: 23% Data for **9b**: R_f = 0.46 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 2.32 (d, J_{PH} = 11.0 Hz, 3 H), 1.38 (d, J_{PH} = 0.3 Hz, 9 H), 1.21 (d, J_{PH} = 17.3 Hz, 9 H), -NH- was not seen. ^{13}C NMR ($CDCl_3$) δ 52.72 (d, J_{PC} = 4.6 Hz), 37.81 (d, J_{PC} = 94.6 Hz), 32.06 (d, J_{PC} = 3.8 Hz), 24.74 (s), 13.19 (d, J_{PC} = 3.1 Hz). ^{31}P NMR ($CDCl_3$) δ 57.1. Anal. Calcd. for $C_9H_{22}ONPS$: C, 48.41; H, 9.93; N, 6.27. Found: C, 48.56; H, 10.01; N, 6.37.

Partial spectroscopic data for the other intermediates in the reaction: **12b**: ^{1}H NMR ($CDCl_3$) δ 2.85–3.05 (bs, 1 H), 1.28 (d, J_{PH} = 0.95 Hz, 9 H), 1.11 (d, J_{PH} = 13.6 Hz, 9 H). ^{31}P NMR ($CDCl_3$) δ 141.5. **13b**: ^{1}H NMR ($CDCl_3$) δ 2.23 (d, J_{PH} = 10.5 Hz, 3 H), 1.92–2.00 (bs, 1 H), 1.23 (d, J_{PH} = 0.8 Hz, 9 H), 1.09 (d, J_{PH} = 13.5 Hz, 9 H). ^{31}P NMR δ 99.7 ($CDCl_3$); 100.1 (THF).

N,N-diphenyl-S-methyl-t-butylphosphonoamidothiolate (9c): Metachloroperoxybenzoic acid (85%, 0.75 g, 3.70 mmol) was dissolved in 35 mL of $CHCl_3$ and added dropwise (ca. 20 min, via addition funnel) to a solution of **13c** (1.02 g, 3.36 mmol) in 20 mL of $CHCl_3$ previously cooled to 0°C with an ice bath. After 5 minutes, 40 mL of sat. $NaHCO_3$ solution was added to the reaction and the mixture was partitioned in a separatory funnel. The organic layer was removed, and the aqueous layer was extracted thrice more with 30 mL portions of CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4 and the solvent evaporated. The product was purified by column chromatography (silica gel, 90:10, 80:20, 70:30 hexane:EtOAc solvent gradient was used) to afford

0.96 g (90%) of **9c** as a viscous oil that crystallized upon standing. Data for **9c**: R_f = 0.17 (7:3 hexane:EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.37–7.43 (m, 4 H), 7.19–7.26 (m, 4 H), 7.07–7.14 (m, 2 H), 2.21 (d, J_{PH} = 10.8 Hz, 3 H), 1.13 (d, J_{PH} = 18.2 Hz, 9 H). ^{13}C NMR ($CDCl_3$) δ 145.14 (d, J_{PC} = 2.3 Hz), 128.81 (s), 128.68 (d, J_{PC} = 3.0 Hz), 125.83 (s), 39.85 (d, J_{PC} = 93.1 Hz), 25.74 (s), 11.37 (d, J_{PC} = 3.0 Hz). ^{31}P NMR ($CDCl_3$) δ 61.7. Anal. Calcd. for $C_{17}H_{22}ONPS$: C, 63.93; H, 6.94; N, 4.39. Found: C, 63.78; H, 6.90; N, 4.40.

S,S-Dimethyl-t-Butylphosphonodithiolate (9d)

To a solution of tert-butylphosphonic dichloride **8** (0.50 g, 2.86 mmol) in 30 mL in dry THF was added solid MeSNa (0.20 g, 2.86 mmol) in one portion. The resulting heterogeneous mixture was stirred for five days and monitored by ^{31}P NMR which indicated a 50:50 mixture of the dithiolate **9d** and unreacted starting material. The monosubstituted phosphonothiolate intermediate was not observed. An additional equivalent of MeSNa (0.20 g, 2.86 mmol) was added to complete the reaction. The reaction mixture was filtered and the solvent removed under vacuum affording a clear oily material. The product was purified by column chromatography (10 g silica gel, 7.3 hexane:EtOAc) affording 0.39 g (100%) of **9d** as a white solid. mp. 25–30°C. Data for **9d**: R_f = 0.14 (hexane:EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 2.35 (d, J_{PH} = 11.6 Hz, 6 H), 1.27 (d, J_{PH} = 19.7 Hz, 9 H). ^{13}C NMR ($CDCl_3$) δ 41.78 (d, J_{PC} = 70.2 Hz), 24.61 (s), 12.27 (d, J_{PC} = 3.8 Hz). ^{31}P NMR ($CDCl_3$) δ 85.5. Anal. Calcd. for $C_6H_{15}OPS_2$: C, 36.35; H, 7.63. Found: C, 36.27; H, 7.66.

N,N-Diphenyl-S-Methyl-t-Butylphosphinamidothiolate (13c)

A solution of diphenylamine (3.50 g, 20.7 mmol) and triethylamine (2.13 g, 2.95 mL, 21.0 mmol) in 15 mL of ether was added dropwise over 30 min to a 0°C solution of PCl_3 in 50 mL of ether. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 5 h. The mixture was recooled to 0°C and t-butylmagnesium chloride (41.0 mmol, 41.0 mL, 1.0 mol/L in THF) was added over 30 min. The reaction was allowed to warm up to room temperature and stirred overnight. The mixture was quickly filtered under vacuum (fritted glass) to remove the insoluble salts. Solid MeSNa (1.60 g, 23.0 mmol) was added to the filtrate in one portion. The resulting mixture was stirred for 16 h at room temperature. A ^{31}P NMR spectrum of the reaction mixture showed the presence of some unreacted $tBuPClNPh_2$ **12c** (δ = 145.0 ppm), and an addi-

tional 0.80 g of MeSNa was added to the reaction and the mixture stirred for two days after which, the ^{31}P NMR spectrum revealed that the reaction was complete. The mixture was filtered and the solvent evaporated affording 6.88 g of crude product as an oil. The product **13c** was purified by chromatography on silica gel using hexane: EtOAc gradients (100:0, 95:5, 90:10) to afford 3.90 g (64%) of product as a colorless oil which crystallized upon standing in the refrigerator. Small amounts (ca. 0.1 g of each) of **9d** and **9c** were also isolated. Data for **13c**: R_f = 0.55 (9:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 7.22–7.35 (m, 8 H), 7.03–7.09 (m, 2 H), 2.32 (d, J_{PH} = 12.7 Hz, 3 H), 1.05 (d, J_{PH} = 14.4 Hz, 9 H). ^{13}C NMR ($CDCl_3$) δ 149.67 (d, J_{PC} = 7.6 Hz), 128.74 (s), 125.99 (d, J_{PC} = 6.9 Hz), 123.70 (s), 36.14 (d, J_{PC} = 18.3 Hz), 27.45 (d, J_{PC} = 12.3 Hz), 15.65 (d, J_{PC} = 28.2 Hz). ^{31}P NMR ($CDCl_3$) δ 118.9. Anal. Calcd. for $C_{17}H_{22}NPS$: C, 67.30; H, 7.31; N, 4.62. Found: C, 67.34; H, 7.37; N, 4.74.

N,N-diphenyl-S-methyl-t-butylphosphonamidodithioate (14c)

To a solution of **13c** (0.50 g, 1.65 mmol) dissolved in 10 mL of toluene was added 2.10 g of elemental sulfur (S_8). The resulting mixture was refluxed in an oil bath (130–140°C) for 2 h. After cooling to room temperature, TLC and ^{31}P NMR of the reaction mixture showed the reaction to be complete. Excess sulfur was removed by filtration after cooling the reaction in an ice bath. The filtrate was evaporated affording a crude oil contaminated with some unreacted sulfur. The product was purified by column chromatography using 9:1 hexane: EtOAc as the solvent. This gave 0.55 g (100%) of pure product as a viscous yellow oil. Data for **14c**: R_f = 0.40 (9:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 7.10–7.60 (m, 10 H), 2.27 (d, J_{PH} = 14.0 Hz, 3 H), 1.22 (d, J_{PH} = 19.4 Hz, 9 H). ^{13}C NMR ($CDCl_3$) δ 146.30 (d, J_{PC} = 2.2 Hz), 130.07 (d, J_{PC} = 3.0 Hz), 128.96 (s), 126.71 (d, J_{PC} = 1.5 Hz), 43.13 (d, J_{PC} = 68.7 Hz), 26.36 (s), 14.64 (d, J_{PC} = 3.8 Hz). ^{31}P NMR ($CDCl_3$) δ 109.9. Anal. Calcd. for $C_{17}H_{22}NPS_2$: C, 60.87; H, 6.61; N, 4.18. Found: C, 60.93; H, 6.67; N, 4.15.

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