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A convenient synthesis of phosphonothioic acids

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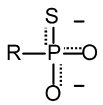
Abstract—A method for the convenient synthesis of phosphonothioates, or phosphonothioic acids, is reported. A significant advantage of the method is the alleviation of the need for purification of intermediates, other than washing with water. No chromatography is needed and the only purification step is the crystallization of the final product. The method uses standard reagents and should be applicable to the synthesis of phosphonothioic acids bearing a range of functional groups. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Thiophosphonates, or phosphonothioates acids and their salts (**1**), have been the subject of a number of patents and publications involving various uses including antiviral compounds,[1–4] plant growth regulators,[5] inhibitors of a number of different enzymes,[6,7] and as lubricants,[8] among others. The reported methods of preparation vary considerably. While these methods are suitable for specific compounds they often utilize conditions that would preclude application to the synthesis of derivatives bearing different or more labile functional groups. Methyl and, to a lesser extent, ethyl esters have often been used as protecting groups during syntheses of phosphates and phosphonates. However, while typically dimethyl or diethyl groups of phosphonate esters can be removed by treatment with trimethylsilyl iodide or trimethylsilyl bromide, this method fails or gives low yields of thio derivatives like **1**.[9] Deprotection of the dibenzyl esters of α,α-difluoromethylenephosphonothioic acids has been reported using sodium in liquid ammonia.[10] Recently the deprotection of diethyl α,α-difluoromethylenephosphonothioic acids via a thiono–thiolo rearrangement followed by Pd-catalyzed deallylation has been reported.[11]



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2. Results and discussion

We sought a synthetic approach that would be convenient, used standard reagents and that would allow the use of the commonly used methyl ester protecting group, which would aid the generality of the method. We report a synthetic approach that combines a number of steps consisting of reactions which have been individually reported before but which, when combined, gives an approach that is convenient and that also offers a significant practical advantage in that purification of intermediates is unnecessary. The multistage synthesis for the compounds reported here requires only a single purification step, namely, a simple crystallization of the final product. The phosphonothioic acids shown in Scheme 1 were prepared using this method. The general method involves the Michaelis–Becker alkylation by an alkyl halide of the anion of dimethyl phosphonothioate **3**,[12] which can be easily made by treating dimethyl phosphite with Lawesson's reagent. While synthetic approaches have been reported that perform this oxo–thio conversion at later stages,[10] the susceptibility of other functional groups to Lawesson's reagent led us to do this at the earliest stage possible in order to favor the generality of the approach.

We found the dimethyl esters **4** to be difficult to deprotect, as has been reported for other dialkyl esters of phosphonothioic acids.[9] In our hands, for example, propylphosphonothioic acid *O*,*O*-dimethyl ester **4a** did not react with iodotrimethylsilane at room temperature or in boiling dichloromethane, and in refluxing tetrachloromethane decomposition resulted. However we found that a two-step rearrangement involving mono-deprotection using trimethylamine under mild conditions to give **5** followed by reaction with methyl iodide gives the *O*,*S*-dimethyl ester **7** which, in contrast to the *O*,*O*-dimethyl ester, readily undergoes deprotection by

Keywords: phosphonothioic acid; phosphonothioate ester; thiono-thiolo rearrangement.

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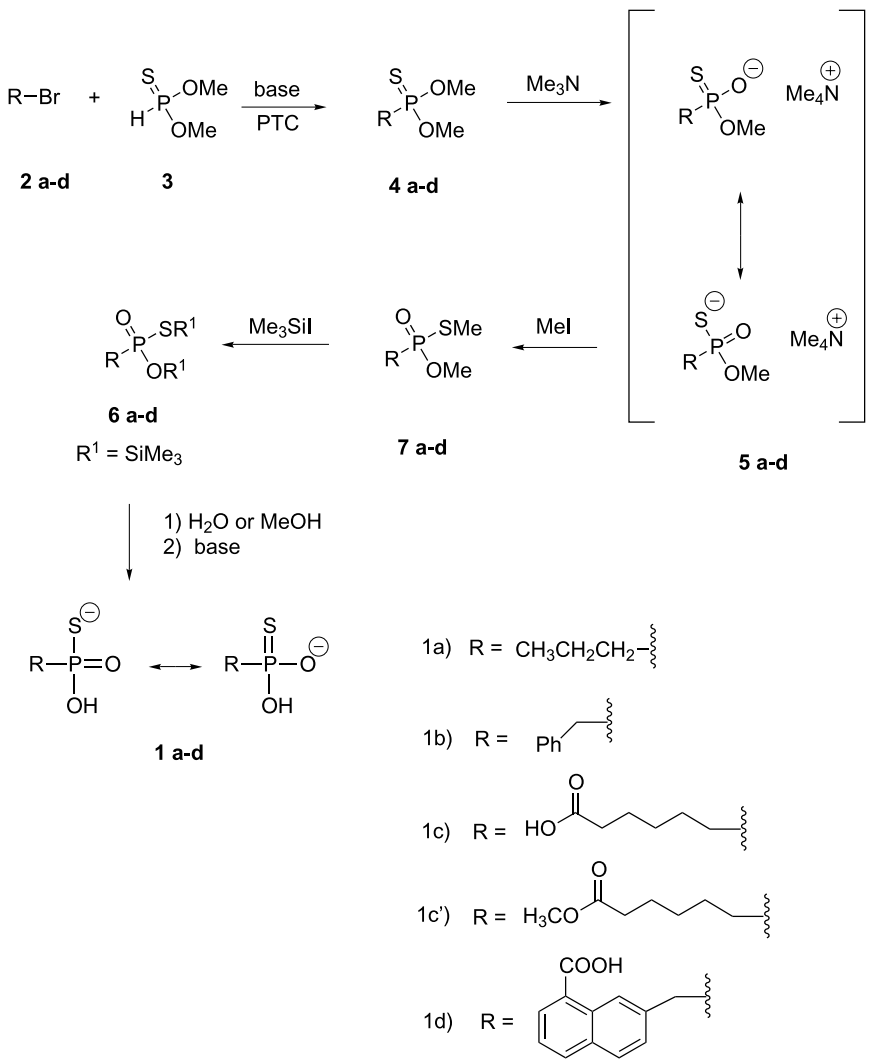

Scheme 1. Intermediates **4**–**7** were used in crude form and were not characterized. PTC, phase transfer catalysis.

trimethylsilyl iodide to give the disilyl ester **6**. This in turn is easily and rapidly hydrolyzed to give the final product.

In practice only the most rudimentary purification of intermediates is necessary. The crude *O*,*O*-dimethyl esters **4** are mono-deprotected with trimethylamine[13] to give the intermediates **5**; two of them precipitate from solution. The crude salts of **5** (or their water solutions) are treated with iodomethane to form the corresponding *O*,*S*-dimethyl ester **7**.[14,15] Again, this intermediate need not be purified beyond simple washing with water, drying, and removal of volatiles. The *O*,*S*-dimethyl ester **7** is easily di-dealkylated by iodotrimethylsilane under mild conditions. After removal of volatile materials under reduced pressure the silyl esters **6** are hydrolyzed with either methanol or water. This crude material, after removal of volatiles, is dissolved in acetone and treated with either trimethyl amine or with aniline to give the salts of the final products, which crystallize from the reaction mixture.

Although the demethylation with trimethylamine[13] is slow it was found to be superior to other methods utilizing *n*-butylamine,[16] thiourea[17] or sodium iodide.[11] Specifically, refluxing **4a** with *n*-butylamine in benzene for 24 h gave 11% of recovered substrate, and, after alkylation with iodomethane, only 24% of propylphosphonothioic acid *O*,*S*-dimethyl ester **7a** was obtained. A similar reaction with thiourea in boiling ethanol gave 14% recovered substrate and, after alkylation, 22% of **7a**. An attempt carried out with sodium iodide in refluxing 2-butanone gave only decomposition products.

3. Conclusion

Each of the individual steps in this synthetic approach has literature precedent, but the combination affords a method that is convenient, uses only standard and mild reagents, and that should be general. Even the product with the lowest final yield (24.8%) implies an average yield for the five steps of about 76%. A significant advantage of this approach is the alleviation of the need for purification of intermediates, and the absence of the need for chromatographic separations.

4. Experimental

4.1. General

All chemicals and solvents were purchased from commercial sources and used without purification. All melting points are uncorrected. All reactions with thiophosphorus compounds were carried out under a nitrogen atmosphere. Elemental analyses were performed by Atlantic Microlabs. ^{1}H NMR spectra were recorded at 400 MHz in DMSO-d_6 solutions using TMS as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz in D_2O using 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt as an internal standard or in DMSO-d_6 solutions using TMS as internal standard. ^{31}P NMR spectra were recorded at 162 MHz in DMSO-d_6 solutions using 85% phosphoric acid as an external standard.

4.2. Starting materials

Lawesson's reagent was prepared from anisole and P_4S_{10}.[18] Freshly prepared reagent gave better results than the commercial product. **2a** and **2b** were commercial products. 6-Bromohexanoic acid *tert*-butyl ester **2c** was synthesized by passing isobutylene through solution of 6-bromohexanoic acid in CH_2Cl_2 in presence of concentrated H_2SO_4[19] and used directly without purification in the next stage. Dimethyl thiophosphite **3** was obtained by refluxing dimethyl phosphite with Lawesson's reagent in benzene.[20] 7-Methylnaphthalene-1-carboxylic acid was prepared by acetylation of 2-methylnaphthalene to 1-(7-methyl-naphthalen-1-yl)-ethanone followed by oxidation with bromine.[21]

4.2.1. 7-Bromomethylnaphthalene-1-carboxylic acid. A suspension of *N*-bromosuccinimide (6.23 g, 0.035 mol) in a solution of 7-methylnaphthalene-1-carboxylic acid (6.2 g, 0.033 mol) in CCl_4 (200 mL) was refluxed in the presence of a trace of benzoyl peroxide for 2 h. The resulting white suspension was evaporated to dryness under reduced pressure, washed with hot water and dried to give the crude product (8.46 g, 96%). An analytical sample was recrystallized from benzene–ethanol mixture. Mp 209.5–211°C. ^{1}H NMR δ 13.20 (bs, 1H), 8.91 (bs, 1H), 8.30–7.95 (m, 3H), 7.72–7.54 (m, 2H), 4.92 (s, 2H). MS *m/e*: 266 (7, M^+), 185 (100, M−Br), 139 (30), 129 (13). Anal. Calcd for $C_{12}H_9BrO_2$: C, 54.37; H, 3.42. Found: C, 54.45; H, 3.44.

4.2.2. 7-Bromomethylnaphthalene-1-carboxylic acid *tert*-butyl ester (2d). Isobutylene was passed through suspension of 7-bromomethylnaphthalene-1-carboxylic acid (10.4 g, 39.2 mmol) in CH_2Cl_2 (150 mL) in presence of concentrated H_2SO_4 (1 mL) for 3 h, then mixture was stirred overnight. The resulting deep green solution was washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give crude **2d** (11.2 g, 88.8%) as a deep green oil. This compound was directly used for the subsequent Michaelis–Becker alkylation without further purification.

4.2.3. Propylphosphonothioic acid (1a), trimethylammonium salt. A solution of **3** (10.00 g, 79.4 mmol), **2a** (11.71 g, 95.2 mmol) and triethylbenzylammonium chloride (1.81 g, 7.94 mmol) in CH_2Cl_2 (200 mL) was cooled on an ice bath and a solution of NaOH (32 g, 0.8 mol) in water (32 mL) was added slowly with vigorous stirring. The ice bath was removed and the reaction mixture was stirred overnight. The reaction mixture was then washed with water, dried ($MgSO_4$) and solvent was removed under reduced pressure to afford crude **4a** (9.4 g). This material was dissolved in acetone (50 mL), liquid Me_3N (20 mL) was added, and the mixture left at room temperature for 7 days. Precipitated white crystals were filtered off, washed with acetone, and dried over P_4O_{10} to give extremely hygroscopic crude **5a** (7.40 g). This material was dissolved in CH_2Cl_2 (250 mL), MeI (9 mL) was added (a precipitate formed immediately) and the suspension was refluxed for 3 h. The mixture was cooled and washed with water, dried ($MgSO_4$), and solvent was removed under reduced pressure to give crude **7a** (4.48 g). This material was dissolved in CH_2Cl_2 (20 mL), cooled on an ice bath, and Me_3SiI (12.36 g) was added. After 1 h the ice bath was removed and the solution was left overnight. Volatiles were then removed under reduced pressure, and the residual red oil was dissolved in MeOH (50 mL). Solvent was then removed under reduced pressure, the residual red oil was dissolved in acetone (20 mL) and saturated with gaseous Me_3N (the solution became colorless). After removal of solvent under reduced pressure the colorless oil slowly crystallized to give the trimethylammonium salt of **1a** (5.54 g, 35% total yield from dimethyl thiophosphite). An analytical sample was recrystallized from acetone–Et_2O mixture. Mp 96–100°C. ^{1}H NMR δ 2.64 (s, 9H), 1.62–1.48 (m, 4H), 0.92 (t, J=7.1 Hz, 3H). ^{13}C NMR (D_2O) δ 47.6 (s, N–CH_3), 42.5 (d, J=100.7 Hz, P–CH_2), 20.1 (d, J=3.8 Hz, CH_3), 17.5 (d, J=18.3 Hz, CH_2). ^{31}P NMR δ 75.0. Anal. Calcd for $C_6H_{18}NO_2PS$: C, 36.17; H, 9.11; N, 7.03. Found: C, 36.10; H, 9.01; N, 6.94.

4.2.4. Benzylphosphonothioic acid (1b), trimethylammonium salt. A mixture of **3** (10.02 g, 79.5 mmol), **2b** (11.07 g, 87.5 mmol), dibenzo-18-crown-6 (1.43 g, 4 mmol) and anhydrous K_2CO_3 (16.49 g, 0.119 mol) in acetonitrile (240 mL) was vigorously stirred for 3 days. Insoluble material was filtered off, acetonitrile was removed by rotary evaporation, and the residue dissolved in CH_2Cl_2 (100 mL). This solution was washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual material was dissolved in warm acetone (100 mL), cooled, and a precipitate of crown ether (1.08 g) was filtered off. Removal of acetone from the filtrate yielded crude **4b** (14.24 g) contaminated mainly with remaining crown ether and dibenzyl sulfide (according to GCMS). The crude **4b** was dissolved in acetone (50 mL), liquid Me_3N (30 mL) was added, and the mixture was left in room temperature for 7 days. Precipitated white crystals were filtered off, washed with acetone, and dried over P_4O_{10} to give crude **5b** (12.30 g). This material was dissolved in CH_2Cl_2 (300 mL), MeI (14 mL) was added (a precipitate formed immediately) and the resulting suspension was refluxed for 3 h. After cooling the mixture was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give crude **7b** (8.37 g) as white crystals. A portion of this material (3.67 g) was dissolved in CH_2Cl_2 (20 mL), cooled with an ice bath, and Me_3SiI (7.87 g) was added. After 1 h the ice bath was removed and the solution

was left overnight. Volatiles were removed under reduced pressure, and the residual red oil was dissolved in MeOH (50 mL). Solvent was then removed under reduced pressure, the residual red oil dissolved in acetone (20 mL) and saturated with gaseous Me_3N (the solution became colorless). After removal of solvent under reduced pressure the colorless oil slowly crystallized to give the trimethylammonium salt of **1b** (3.49 g, 41% total yield from **3**). An analytical sample was recrystallized from acetone. Mp 152–154°C (with decomposition). ^{1}H NMR δ 7.32–7.09 (m, 5H), 3.03 (d, J=18.3 Hz), 2.48 (s, 9H). ^{13}C NMR (D_2O) δ 137.9 (d, J=8.4 Hz, $C_{aromatic}$), 132.8 (d, J=5.3 Hz, $CH_{aromatic}$), 131.2 (d, J=3.8 Hz, $CH_{aromatic}$), 129.2 (d, J=3.8 Hz, $CH_{aromatic}$), 47.9 (d, J=95.4 Hz, P–CH_2), 47.6 (s, N–CH_3). ^{31}P NMR δ 68.1. IR (KBr, cm^{-1}) 1599, 1478, 1452, 1066, 1028, 900, 784, 697, 594. Anal. Calcd for $C_{10}H_{18}NO_2PS$: C, 48.57; H, 7.34; N, 5.66. Found: C, 48.66; H, 7.36; N, 5.69.

4.2.5. 6-Thiophosphonohexanoic acid methyl ester (1c′), anilinium salt. A solution of **3** (4.56 g, 36.2 mmol), **2c** (10.00 g, 39.8 mmol) and triethylbenzylammonium chloride (0.82 g, 3.62 mmol) in CH_2Cl_2 (100 mL) was cooled on an ice bath and a solution of NaOH (14.5 g, 0.362 mol) in water (14.5 mL) was added slowly with vigorous stirring. The ice bath was removed and the mixture was stirred for 3 days, then washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give crude **4c** (8.00 g). This material was dissolved in acetone (30 mL), liquid Me_3N (20 mL) was added, and the mixture was left at room temperature for 2 weeks. The solvent was removed by rotary evaporation and the residue was dissolved in water (30 mL), then extracted with CH_2Cl_2. The aqueous solution of **5c** was concentrated to small volume and mixed with CH_2Cl_2 (100 mL). MeI (10 mL) was added (a precipitate formed immediately) and the suspension was refluxed for 3 h. After cooling the mixture was washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude **7c** (4.06 g). This material was dissolved in CH_2Cl_2 (20 mL), cooled on ice bath, and Me_3SiI (8.96 g) was added. After 1 h the bath was removed and the solution was left overnight. Volatiles were removed under vacuum, and the residual red oil was boiled with MeOH (50 mL). Solvent was then removed under reduced pressure, the red residual oil dissolved in MeOH (10 mL) and aniline (4 g) was added (the solution became colorless). After removing the solvent under vacuum, Et_2O (20 mL) was added and the resulting white precipitate was collected by filtration, washed with ether, and dried to give the anilinium salt of **1c′**, (2.87 g, 25% total yield from **3**). An analytical sample was recrystallized from acetone–Et_2O mixture. Mp 107–108°C. ^{1}H NMR δ 7.03–6.97 (m, 2H), 6.58–6.45 (m, 3H), 3.58 (s, 3H), 2.28 (t, J=7.4 Hz), 1.80–1.68 (m, 2H), 1.60–1.46 (m, 4H), 1.40–1.26 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 173.4 (s, C=O), 148.3 (s, $C_{aromatic}$), 128.9 (s, $CH_{aromatic}$), 116.0 (s, $CH_{aromatic}$), 114.1 (s, $CH_{aromatic}$), 51.2 (s, O–CH_3), 35.9 (d, J=106.0 Hz, P–CH_2), 33.2 (s, CH_2), 29.1 (d, J=17.5 Hz, CH_2), 24.1 (s, CH_2), 22.9 (d, J=3.1 Hz, CH_2). ^{31}P NMR δ 87.0. IR (KBr, cm^{-1}) 1735 (C=O), 1497, 1210, 1022, 915, 742, 689, 594, 502. Anal. Calcd for $C_{13}H_{22}NO_4PS$: C, 48.89; H, 6.94; N, 4.39. Found: C, 49.02; H, 6.91; N, 4.31.

4.2.6. 6-Thiophosphonohexanoic acid (1c), *p*-methylanilinium salt. Using the same procedure as described above from **3** (9.12 g, 72.4 mmol), an aqueous solution (100 mL) of crude **5c** was obtained. To this solution EtOH (200 mL) and MeI (20 mL) were added, and the mixture was refluxed for 3 h. Solvents were then removed by rotary evaporation, and the residue was dissolved in AcOEt (200 mL). This mixture was extracted with water dried ($MgSO_4$) and solvents were removed under reduced pressure to give crude **7d** (10.33 g). A portion of this material (3.22 g) was reacted with Me_3SiI as described for **1c**, then treated with cold water (10 mL) instead of MeOH, volatiles were removed under vacuum, and the residue was dissolved in Et_2O (10 mL) and *p*-toluidine (3.5 g) in ether (10 mL) was added. The resulting white precipitate was collected by filtration, washed repeatedly with ether, and dried to give the *p*-methylanilinium salt of **1d** (2.42 g, 34% total yield from dimethyl thiophosphite). An analytical sample was recrystallized from EtOH–acetone–Et_2O mixture. Mp 167–168°C (with decomposition). ^{1}H NMR δ 6.82 (d, J=7.6 Hz, 2H), 6.49 (d, J=8.1, 2H), 2.19 (t, J=7.4 Hz, 2H), 2.12 (s, 3H), 1.80–1.68 (m, 2H), 1.60–1.45 (m, 4H), 1.39–1.29 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 174.5 (s, C=O), 145.5 (s, $C_{aromatic}$), 129.3 (s, $CH_{aromatic}$), 124.5 (s, $C_{aromatic}$), 114.4 (s, $CH_{aromatic}$), 36.0 (d, J=106.0 Hz, P–CH_2), 33.5 (s, CH_2), 29.2 (d, J=17.5 Hz, CH_2), 24.2 (s, CH_2), 22.9 (d, J=3.8 Hz, CH_2), 20.1 (s, CH_3). ^{31}P NMR δ 87.0. IR (KBr, cm^{-1}) 1710 (C=O), 1510, 1224, 1014, 928, 808, 637, 591, 493. Anal. Calcd for $C_{13}H_{22}NO_4PS$: C, 48.89; H, 6.94; N, 4.39. Found: C, 48.80; H, 6.98; N, 4.35.

4.2.7. 7-Thiophosphonomethylnaphthalene-1-carboxylic acid (1d), *p*-methylanilinium salt. A solution of **3** (3.84 g, 30.5 mmol), crude **2d** (11.2 g, 34.9 mmol) and triethylbenzylammonium chloride (0.72 g, 3.17 mmol) in CH_2Cl_2 (100 mL) was cooled on ice bath and a solution of NaOH (12.7 g, 0.317 mol) in water (12.7 mL) was added slowly with vigorous stirring. The ice bath was removed and the mixture was stirred overnight, then washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude **4d** (10.38 g) as an orange oil. This material was dissolved in acetone (30 mL) and liquid Me_3N (25 mL) was added, and this mixture left at room temperature for 2 weeks. Solvent was then removed by rotary evaporation and the residue was dissolved in water (50 mL). This solution was extracted with AcOEt, then to the aqueous layer EtOH (150 mL) and MeI (10 mL) were added and the mixture refluxed for 3 h. Solvents were removed by rotary evaporation, the residue dissolved in AcOEt (125 mL) and extracted with water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give crude **7d** (4.44 g) as a thick orange oil. This material was reacted with Me_3SiI (8.00 g) in CH_2Cl_2 (25 mL) as above. Then a water–dioxane mixture (1:1, 20 mL) was added, after which volatiles were removed under vacuum. The residue was dissolved in a Et_2O–acetone mixture (4:1, 50 mL) and *p*-toluidine (3.9 g) in ether (20 mL) was added. The resulting white precipitate was collected by filtration, washed with ether and dried to give the *p*-methylanilinium salt of **1d** (4.39 g, 37% total yield from **3**). An analytical sample was recrystallized from an EtOH–acetone–Et_2O mixture. Mp 200–201°C (with decomposition). ^{1}H NMR δ 8.75–8.71 (m, 1H),

8.13–8.07 (m, 2H), 7.91 (d, J=8.6 Hz, 1H), 7.58–7.49 (m, 2H), 6.85 (d, J=7.6 Hz, 2H), 6.54 (d, J=8.1 Hz, 2H), 3.42 (d, J=18.8 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 168.7 (s, C═O), 144.9 (s, C_{phenyl}), 133.5 (d, J=8.4 Hz, $C_{naphthyl}$), 132.6 (d, J=1.5 Hz, $CH_{naphthyl}$), 132.2 (d, J=3.1 Hz, $C_{naphthyl}$), 130.6 (d, J=3.1 Hz, $C_{naphthyl}$), 129.8 (s, $CH_{naphthyl}$), 129.3 (s, CH_{phenyl}), 129.0 (d, J=4.6 Hz, $CH_{naphthyl}$), 127.9 (d, J=3.1 Hz, $CH_{naphthyl}$), 127.5 (d, J=1.5 Hz, $C_{naphthyl}$), 126.3 (d, J=8.4 Hz, $CH_{naphthyl}$), 125.0 (s, C_{phenyl}), 124.3 (s, $CH_{naphthyl}$), 114.7 (s, CH_{phenyl}), 44.7 (d, J=99.9 Hz, P–CH_2), 20.2 (s, Hz, CH_3). ^{31}P NMR δ 79.7. IR (KBr, cm^{-1}) 1663 (C═O), 1507, 1285, 1250, 1003, 941, 840, 653, 578, 488.Anal. Calcd for $C_{19}H_{20}NO_4PS$: C, 58.60; H, 5.18; N, 3.60. Found: C, 58.48; H, 5.21; N, 3.41.

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