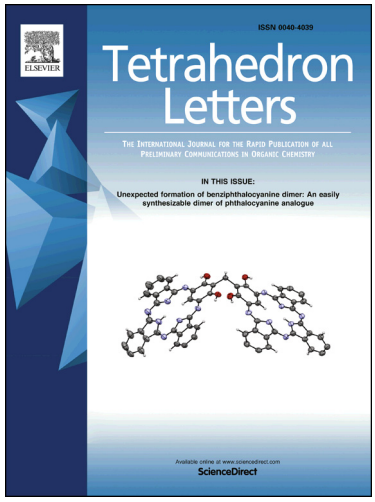
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Synthesis of symmetrically and unsymmetrically substituted *S,S*-dialkyl phosphonodithioates.

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ABSTRACT

Herein, we report the synthesis of a range of *S,S*-dialkyl alkylphosphonodithioates. Symmetrically substituted analogues were readily prepared from the corresponding phosphonic dichlorides in good to moderate yields, while unsymmetrically substituted variants were obtained by a sequential alkylation-deprotection-alkylation strategy.

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1. Introduction

In the course of our research regarding the synthesis of biologically active phosphonates through the bioisosteric replacement of oxygen with sulfur, we required a robust method for accessing symmetrically and unsymmetrically substituted *S,S*-dialkyl phosphonodithioates. The phosphonothioate motif is present in several commercially important agrochemicals, including pesticides such as Parathion, Ethion, Fenitrothion, Fenthion, Isoxathion and Malathion.[1] Interestingly, Parathion and Malathion both contain a phosphorus-sulfur double bond which is key to their activity. In contrast, compounds such as Echothiophate, Dementon, Omethoate, Phentoate, Malaoxon and Oxydemeton contain a phosphorus-sulfur single bond which is required for their activity.

Little systematic study on the formation of symmetrically substituted *S,S*-dialkyl phosphonodithioates has occurred to date. Older reports confirm that this underexplored functional group may be accessed by oxidation of the corresponding dithiophosphite with dinitrogen tetroxide in moderate to good yields.[2] The synthesis of phosphonodithioates using phosphonic dichloride precursors has also been demonstrated; however, reaction conditions are specific to individual substrates, highlighting the absence of a general method for accessing these compounds.[3-6]

We have found that the preparation of these compounds *via* nucleophilic displacement of chloride is challenging compared to the synthesis of their *O,O*-dialkyl equivalents. In this publication, a general method for the synthesis of symmetrically substituted phosphonodithioates is reported, with the majority of these constituting novel compounds. Additionally, we describe the synthesis of unsymmetrically substituted members of this class bearing low molecular weight side-chains using a sequential alkylation-deprotection-alkylation strategy.

2. Results and Discussion

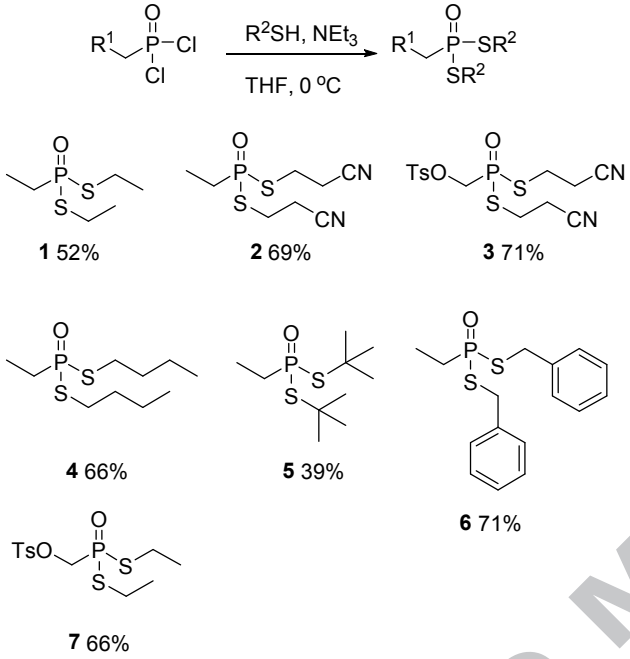
Symmetrically substituted *S,S*-dialkyl phosphonodithioates **1-7** were accessed by reacting the requisite phosphonic dichloride with the corresponding alkanethiol in anhydrous THF, facilitated by triethylamine (Scheme 1).[7] The reaction also proceeds in dry diethyl ether or dichloromethane, albeit in lower yields and is accompanied by disulfide formation. Unless care is taken to deoxygenate the

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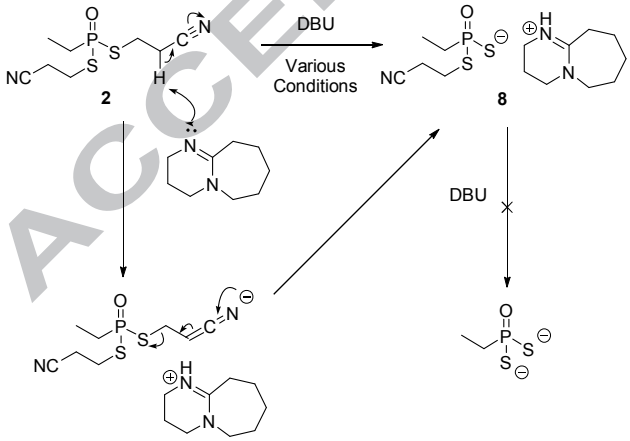
solvents prior to the reaction, oxidative dimerization of the thiol to the corresponding disulfide causes considerable yield loss. Since removing the disulfide by-products requires careful column chromatography, minimizing their formation is highly desirable.

We found that reaction of the thiol with sodium hydride to form the corresponding thiolate anion prior to addition of the phosphonic dichloride also affords the desired phosphonodithioates. However, formation of the disulfide by-product is increased under these conditions and yields tended to be lower. It has been noted previously that disulfide formation is accelerated under strongly basic conditions.[8] An attempt to adapt the base-free methodology employed by Acharya and co-workers[9] for the preparation of closely related *O,O*-dialkyl phosphonates by replacing alcohols with the analogous thiols was unsuccessful.



Scheme 1. Preparation of symmetrical *S,S*-dialkyl phosphonodithioates

We next investigated whether **2** might serve as a useful synthon for the preparation of *S*,*S*-dialkyl phosphonodithioates. Treating **2** with DBU furnished mono-deprotected **8** exclusively as its DBU salt, irrespective of the number of equivalents of DBU employed or the reaction time (Scheme 2). It is worth noting that when a single equivalent of DBU is used, the reaction proceeds to completion within 90 minutes and the mono-deprotected product can be isolated cleanly by removal of the solvent *in vacuo*. The identification of this compound as a 1:1 salt is supported by the matching integration of signals arising from the DBU cation and the thiophosphonate anion in the ^{1}H-NMR spectrum. Additionally, the carbon adjacent to the protonated nitrogen is deshielded in **8** compared to the same atom in non-protonated DBU (165 ppm vs. 158 ppm).[10]



Scheme 2. Proposed mechanism for the formation of **8**

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The probable reaction mechanism outlined in Scheme 2 is similar to that described previously for related cyanoethyl deprotection reactions.[11] The reaction is believed to proceed *via* initial deprotonation adjacent to the nitrile group promoting E1cB elimination to furnish the mono-deprotected product. Following mono-deprotection of **2**, acrylonitrile - a potent Michael-acceptor - is produced. It is possible that the bis-deprotected product is not isolated due to reaction of the dianion, which is more reactive than the monoanion, with acrylonitrile to afford **8**. Evans and co-workers observed a similar phenomenon when attempting to remove both cyanoethyl protecting groups from a phosphonate and instead isolated the mono-deprotected product in the absence of an electrophile.[12]

In contrast, the reaction of phosphonodithioate **2** with DBU in the presence of a large excess of methyl iodide cleanly furnished dimethylated phosphonodithioate **9** in good yield (Scheme 3). It seems likely that *in situ* methylation of the anionic intermediates allows for the successful removal of both cyanoethyl groups. Additionally, it was found that the formation of **9** could take place in a stepwise fashion with intermediates **8**, **10** and **11** being isolated and characterized. Methylation of the mono-deprotected product **8** with methyl iodide furnished the unsymmetrically substituted phosphonodithioate **10**.[13] Compound **10** was then subjected to further treatment with DBU, effecting a second E1cB elimination to give **11**. Finally, subsequent alkylation of **11** affords *S,S*-dimethyl phosphonodithioate **9**. Unsymmetrically substituted phosphonodithioates **12** and **13** were accessed upon the ethylation of **8** and **11**, respectively. The synthesis of **9**, **10**, **12** and **13** avoids the use of low molecular weight thiols which are difficult to handle owing to their volatility and strongly unpleasant odour.

3. Conclusion

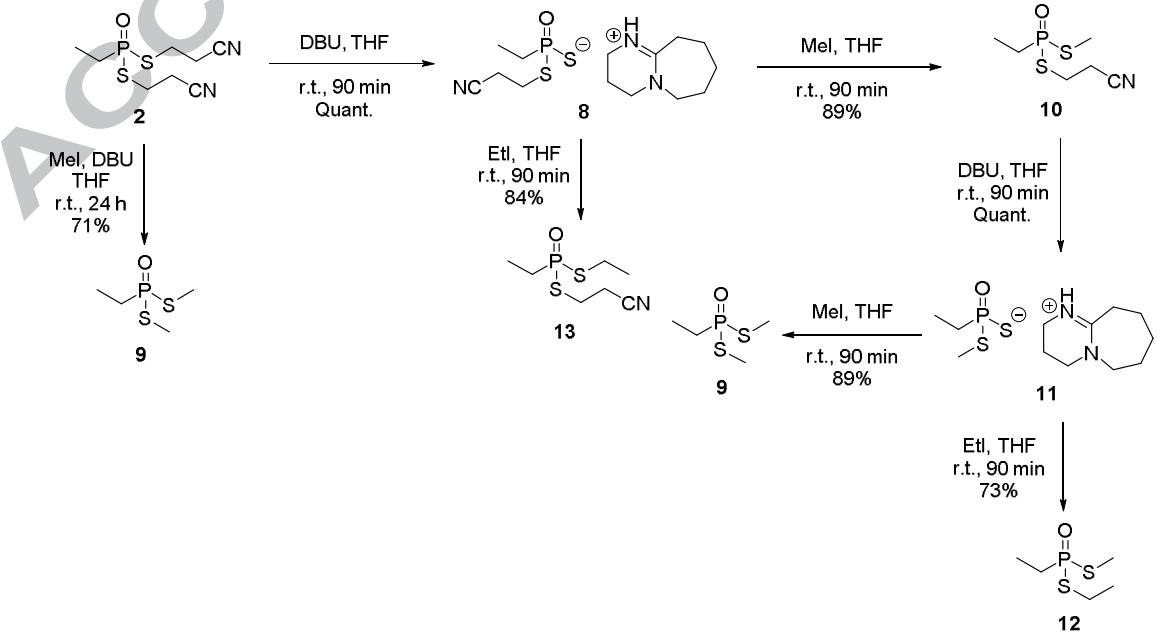
Symmetrically substituted *S,S*-dialkyl phosphonodithioates were conveniently prepared according to the method described. This work demonstrates the synthetic utility of **8** as a convenient precursor to unsymmetrically substituted members of this series. This approach has the further advantage of avoiding malodorous, low molecular weight thiols.

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Supporting Information

Full characterization of novel compounds is provided in the electronic supplementary information.



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Scheme 3. Synthesis of unsymmetrical *S,S*-dialkyl phosphonodithioates

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7. Representative Procedure: *S,S*-Di(2-Cyanoethyl) Ethylphosphonodithioate (2)

To a stirred solution of ethyl phosphonic dichloride (587 mg, 4 mmol, 1.00 eq.) in anhydrous THF (40 mL) under a nitrogen atmosphere at *ca*. 0 ^{o}C, was added a solution of 3-mercaptopropionitrile (700 mg, 8 mmol, 2.00 eq.) and triethylamine (800 mg, 8.00 mmol, 2.00 eq.) in THF (10 mL) over five minutes. This was accompanied by the instantaneous precipitation of triethylamine hydrochloride as a colourless solid. The reaction mixture was allowed to warm to room temperature then stirred overnight after which time the starting thiol was no longer evident by TLC. The reaction mixture was then filtered by gravity and the flask washed with THF (10 mL). The filtrate was concentrated *in vacuo* and the oily yellow remains were reconstituted in CH_2Cl_2 (40 mL) and sequentially washed with 1M NaOH (15 mL), brine (15 mL), 2M HCl (15 mL) and brine (15 mL), before being dried over magensium sulfate and concentrated *in vacuo* to furnish the title compound as a yellow oil which was used without further purification. IR ν_{max} (NaCl, cm^{-1}): 2985, 2935, 2251, 1640, 1457, 1418, 1289, 1193, 1032, 742, 708, 559. δ_H (400 MHz, $CDCl_3$, ppm): 1.24 (C**H**$_3$-CH_2-P(=O), 3H, dt, $J_{H\text{-}P}$ = 24.29 Hz, $J_{H\text{-}H}$ = 7.61 Hz), 2.23 (CH_3C**H**$_2$-P(=O), 2H, dq, $J_{H\text{-}P}$ = 12.61 Hz, $J_{H\text{-}H}$ = 7.61 Hz), 2.75-2.88 (CN-C**H**$_2$, 4H, m) 3.07 – 3.21 (S-C**H**$_2$, 4H, m). δ_C (100 MHz, $CDCl_3$, ppm): 6.95 (**C**H_3-CH_2-P(=O), d, $J_{P\text{-}C}$ = 6.10 Hz), 20.2 (CN-**C**H_2, d, $J_{P\text{-}C}$ = 2.12 Hz) , 26.1 (S-**C**H_2, d, $J_{P\text{-}C}$ =

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3.26 Hz), 32.4 (CH_3-**C**H_2-P(=O), d, J_{P-C} = 73.27 Hz), 117.7 (CN). δ_P (175 MHz, $CDCl_3$, ppm): 71.45. HRMS (ESI^+): Calc. mass $C_8H_{14}N_2OPS_2$ [M+H] = 249.0280; Found 249.0283.

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10. Representative procedure: Preparation of DBU Salt (8)

To a stirred solution of **2** (100 mg, 0.40 mmol, 1.00 eq.) in THF (5 mL) was added DBU (61 mg, 0.40 mmol, 1.00 eq.) in THF (5 mL) at room temperature. The resulting suspension was stirred for 90 minutes after which time complete consumption of the starting material was confirmed by TLC. The solvent was removed *in vacuo* affording the title compound as a pale oil (136 mg, 0.39 mmol, 99%). IR ν_{max} (NaCl, cm^{-1}): 3375, 2920, 2847, 2134, 1961, 1647, 1403, 1384, 1101. δ_H (400 MHz, $CDCl_3$, ppm): 1.23 (3H, dt, J_{H-P} = 22.10 Hz, J_{H-H} = 7.41 Hz), 1.75 (6H, m), 2.00-2.15 (4H, m), 2.80-2.93 (4H, m), 2.98-3.09 (2H, m), 3.47-3.53 (6H, m), 6.29 (DBU-H^+ bs). δ_C (100 MHz, $CDCl_3$, ppm): 8.78 (d, J_{C-P} = 5.01 Hz), 21.42 (d, J_{P-C} = 2.71 Hz), 24.11, 26.25, 26.82. 28.49 (d, J_{C-P} = 2.98 Hz), 29.00, 32.21 32.43, 36.63 (J_{C-P} = 79.83 Hz), 48.66, 54.33, 119.11 (**C**N), 165.92 (DBU; N-**C**(=N)). δ_p (175 MHz, $CDCl_3$, ppm): 85.38. HRMS (ESI$^-$): Calc. mass ($C_5H_9NOPS_2^-$): 194.2268; Found: 194.2277.

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13. Representative Procedure: *S*-Methyl-*S*-(2-Cyanoethyl) Ethylphosphonodithioate (10).

To a stirred solution of DBU salt (**8**) (193 mg, 1.00 mmol, 1.00 eq.) in anhydrous THF (5 mL) was added methyl iodide (283 mg, 2.00 mmol, 2.00 eq.) in anhydrous THF (5 mL). The reaction was stirred for 90 minutes at room temperature after which time no starting material was evident by TLC. The solvent was then removed *in vacuo*, and the yellow oily remains were reconstituted in CH_2Cl_2 (20 mL) and washed with water (3 x 20 mL). The organic solution was dried over magnesium sulfate and concentrated *in vacu*o to afford the title compound as a yellow oil (184 mg, 0.89 mmol, 89%). IR ν_{max} (NaCl, cm^{-1}): 2986, 2937, 2251, 1640, 1453, 1422, 1276, 1173, 1032, 742, 728, 555. δ_H (400 MHz, $CDCl_3$, ppm): 1.23 (3H, dt, J_{H-P} = 23.63 Hz, J_{H-H} = 7.48 Hz, $CH_2C\mathbf{H_3}$), 2.19 (2H, dq, J_{H-P} = 12.50 Hz, J_{H-H} = 7.48 Hz, $C\mathbf{H_2}CH_3$), 2.33 (3H, d, J_{H-P} = 13.37 Hz, $SC\mathbf{H_3}$), 2.82 (2H, td, J_{H-H} = 6.91 Hz, J_{H-P} = 3.26 Hz $SCH_2C\mathbf{H_2}CN$), 3.10 (2H, dt, J_{H-P} = 14.38 Hz, J_{H-H} = 6.91 Hz, $SC\mathbf{H_2}CH_2CN$). δ_C (100 MHz, $CDCl_3$, ppm): 6.94 (d, J_{C-P} = 6.13 Hz, $\mathbf{C}H_3CH_2$), 12.14 (d, J_{C-P} = 4.38 Hz, $S\mathbf{C}H_3$), 20.41 (d, J_{C-P} = 3.11 Hz, $\mathbf{C}H_2CN$), 25.90 (d, J_{C-P} = 3.55 Hz, $\mathbf{C}H_2S$), 31.36 (d, J_{C-P} = 72.18 Hz, $\mathbf{C}H_2P$), 117.14 (**C**N). δ_P (175 MHz, $CDCl_3$): 71.94. HRMS (ESI^+): Calc. Mass for $C_6H_{13}NOPS_2$ [M+H] = 210.0071; Found = 210.0087.

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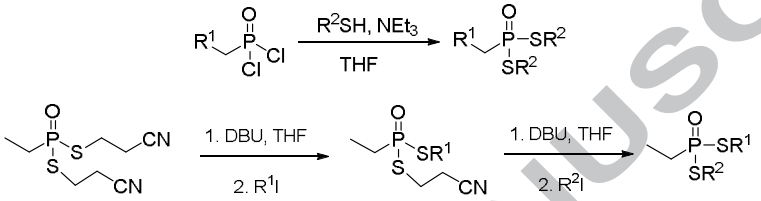
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