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Construction of the 1,2,3,4-Tetrahydro-1,4,6,2-oxathiazaphosphorine Ring System

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The novel 1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine ring system has been prepared by reaction of the sodium salt of diethyl mercaptomethylphosphonate with nitrile oxides, followed by cyclization of the resulting hydroximinoyl sulfide. The stability of the new ring system is investigated.

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Heterocyclic ring systems continue to play a pivotal role in the development of new pharmaceuticals and agrochemicals. New ring systems can provide scaffolds and building blocks for the exploration of chemical space free of patent competition.

As part of our interest in constructing novel ring systems for this purpose, we have investigated the synthesis of oxadiaza- and oxathiaza-phosphorines.

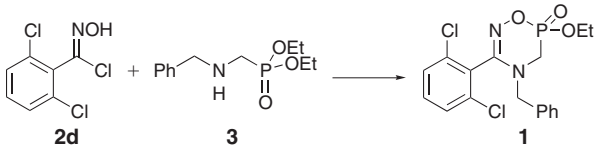
We reported[1] the first preparation of the 1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine ring system **1** by a one-step process from 2,6-dichlorobenzonitrile oxide generated in situ from the corresponding hydroximinoyl chloride **2d** and diethyl benzylaminomethylphosphonate **3** (Scheme 1).

It was envisaged that a similar process could be used to prepare the related 1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine ring system shown in compound **6**.

The sodium salt of diethyl mercaptomethylphosphonate **4** can be readily prepared from *S*-bromomethyl thioacetate.[2] Treatment of **4** with nitrile oxides in the presence of several bases did not, however, produce the corresponding tetrahydrooxathiazaphosphorine **6** but the intermediate hydroximinoyl sulfide **5**, Scheme 2.*

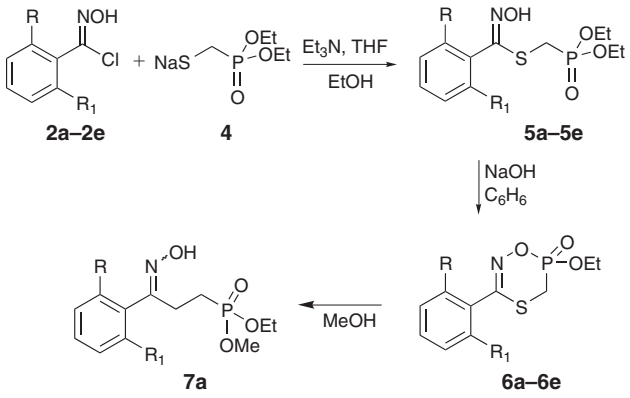
Cyclization of hydroximinoyl sufide **5** in the presence of several bases was investigated with little success: Nitrogenous bases, such as collidine and diisopropylethylamine, returned starting material, and piperidine resulted in the salt of the corresponding phosphonic acid. Sodium ethoxide, sodium hydride, and lithium diisopropyl amide did not react under mild conditions, and under more forcing conditions gave a mixture of unidentified products.

Cyclization of **5** was ultimately effected by treatment with anhydrous powdered sodium hydroxide in benzene to give the desired 1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorines **6**.



2d **3** **1**

Scheme 1. Synthesis of 1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine ring system **1**.



2a–2e **4** **5a–5e**

7a **6a–6e**

	R	R_1	Yield [%] of **5**	Yield [%] of **6**
a	H	H	48	67
b	H	F	77	57
c	H	Br	76	56
d	Cl	Cl	71	26
e	F	Cl	53	45

Scheme 2. Synthesis of 2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-oxides **6**.

Residual moisture on the sodium hydroxide was removed as the benzene azeotrope before addition of the sulfide **5**. Failure to remove this moisture resulted in only the hydrolysis product being obtained.

* This reaction was not investigated under the specific conditions ultimately used to provide the oxathiazaphosphorines **6**.

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This ring system demonstrates similar stability to the oxadiazaphosphorine system.[1] The oxathiazaphosphorine ring compounds can be stored for extended periods in a sealed container in the freezer. Some examples of compounds **6** were not stable to recrystallization and consequently accurate melting points could not be obtained in these cases. It was found that compound **6a** remained unchanged after stirring at room temperature or at 50°C for seven days with a two-fold excess of water in acetonitrile. After stirring for seven days in dry methanol ~10% of the heterocyclic ring system had been opened, whereas the ring system was completely opened after 18 h in dry methanol at 60°C to give compound **7a** as a mixture of *E* and *Z* isomers.

In conclusion, we have developed a short, efficient synthesis of 1,4,6,2-oxathiazaphosphorines. Their instability to ring-opening limits their use as building blocks for pharmaceuticals and agrochemicals containing the six-membered ring system. However, their susceptibility to nucleophilic attack at phosphorus could make them useful intermediates for preparation of a wide variety of substituted phosphorus species.

Experimental

Melting points were determined on a Bausch & Lomb hot-stage melting point apparatus and are uncorrected. Microanalyses were performed by the Campbell Microanalytical Laboratory (Dunedin, New Zealand). Infrared spectra were measured on a Perkin–Elmer 842 infrared spectrophotometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC200 at 200, 50.3, and 81.0 MHz respectively, or on a Bruker AV400 at 400 and 100.6 MHz, respectively, or a Bruker DRX500 at 500 and 125.8 MHz, respectively. Chemical shifts were measured in ppm relative to $CDCl_3$ and then related to tetramethylsilane (^{1}H, ^{13}C). H_3PO_4 was used as an external standard for ^{31}P NMR spectra. Positive- and negative-ion atmospheric pressure chemical ionization (APCI) mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V and the source was maintained at 100°C. High-resolution electron impact mass spectra (HR-EIMS) were recorded on a ThermoQuest MAT 95XL, using an ionization energy of 70 eV. Accurate mass measurements were obtained with a resolution of 5000–10 000 using perfluorokerosene (PFK) as the reference compound.

Synthesis of Diethyl S-*Benzohydroximinoylthiomethylphosphonates* ***5***

A solution of diethyl *S*-acetylthiomethylphosphonate[2] (20 mmol) in anhydrous ethanol (8 mL) was added to a stirred solution of sodium ethoxide (20 mmol) in ethanol (8 mL) maintained under nitrogen. The resulting mixture was stirred at room temperature for 2 h. A solution of the hydroximinoyl chloride (20 mmol) in anhydrous tetrahydrofuran (100 mL) was prepared. Half of this solution was added to that of the phosphonate, followed by triethylamine (20 mmol). The remainder of the hydroximinoyl chloride solution (50 mL) was then added and the resulting mixture was stirred at room temperature (1–6 days) before being concentrated under reduced pressure. The residue was taken up in ethyl acetate (500 mL) and water (250 mL). The organic layer was removed and washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in boiling ether, the solution was allowed to cool and the crystals were filtered off to give the diethyl *S*-benzohydroximinoylthiomethylphosphonate **5**. Additional material was obtained by radial thin-layer chromatography of the filtrate on 4 mm layers of Merck Kieselgel 60 PF_{254} using successive elution with dichloromethane, 1% methanol in dichloromethane, and 2% methanol in dichloromethane.

Diethyl S-*Benzohydroximinoylthiomethylphosphonate* ***5a***

White crystals, 48% yield, mp 75–77°C. (Found: C 47.8, H 5.9, N 4.9%. $C_{12}H_{18}NO_4PS$ requires C 47.5, H 6.0, N 4.6%.) ν_{max} (KBr)/cm^{-1} 3207 (OH), 1232 (P=O). δ_H 7.48–7.60 (2H, m, ArH), 7.35–7.45 (3H, m, ArH), 4.12 (4H, dq, *J* 7, 8, 2 × CH_2O), 3.00 (2H, d, *J* 14, CH_2P), 1.30 (6H, t, *J* 7, CH_3). δ_C 152.4 (J_{PC} 6.5), 132.9, 129.8, 128.8, 128.6, 63.0 (J_{PC} 5.1), 25.1 (J_{PC} 149.0), 16.3 (J_{PC} 5.8). δ_P 23.8. *m/z* (APCI) 326 (38%, $[M + Na]^+$), 207 (100), 130 (69).

Diethyl S-*2′-Fluorobenzohydroximinoylthiomethylphosphonate* ***5b***

White crystals, 77% yield, mp 104–105°C. (Found: C 45.1, H 5.4, N 4.6%. $C_{12}H_{17}FNO_4PS$ requires C 44.9, H 5.3, N 4.4%.) ν_{max} (KBr)/cm^{-1} 3201 (OH), 1233 (P=O). δ_H 7.31–7.47 (2H, m, ArH), 7.04–7.23 (2H, m, ArH), 4.09 (4H, dq, *J* 7, 8, 2 × CH_2O), 2.79 (2H, d, *J* 15, CH_2P), 1.27 (6H, t, *J* 7, CH_3). δ_C 159.8 (J_{FC} 250.7), 149.2 (J_{PC} 8.0), 131.9 (J_{FC} 8.7), 131.6 (J_{FC} 2.2), 124.6 (J_{FC} 3.6), 120.2 (J_{FC} 15.6), 116.0 (J_{FC} 21.0), 63.2 (J_{PC} 6.5), 24.3 (J_{PC} 147.5, J_{FC} 1.5), 16.2 (J_{PC} 5.9). δ_P 23.2. *m/z* (APCI) 344 (77%, $[M + Na]^+$), 207 (100), 130 (21).

Diethyl S-*2′-Bromobenzohydroximinoylthiomethylphosphonate* ***5c***

White crystals, 76% yield, mp 150–152°C. (Found: C 37.6, H 4.6, N 3.9%. $C_{12}H_{17}BrNO_4PS$ requires C 37.7, H 4.5, N 3.7%.) ν_{max} (KBr)/cm^{-1} 3220 (OH), 1244 (P=O). δ_H 7.60 (1H, m, *J* 8, ArH), 7.22–7.41 (3H, m, ArH), 4.09 (4H, dq, *J* 7, 8, 2 × CH_2O), 2.66 (2H, d, *J* 16, CH_2P), 1.28 (6H, t, *J* 7, CH_3). δ_C 153.4 (J_{PC} 9.5), 133.1, 133.0, 131.8, 131.3, 127.8, 123.3, 63.1 (J_{PC} 6.5), 24.2 (J_{PC} 146.1), 16.3 (J_{PC} 6.5). δ_P 23.2. *m/z* (APCI) 785 (17%, $[2M + Na]^+$), 404 (38%, $[M + Na]^+$), 207 (100), 130 (39).

Diethyl S-*2′,6′-Dichlorobenzohydroximinoylthiomethylphosphonate* ***5d***

White crystals, 71% yield, mp 144–145°C. (Found: C 38.9, H 4.4, N 3.9%. $C_{12}H_{16}Cl_2NO_4PS$ requires C 38.7, H 4.3, N 3.8%.) ν_{max} (KBr)/cm^{-1} 3212 (OH), 1243 (P=O). δ_H 7.27–7.42 (3H, m, ArH), 4.13 (4H, dq, *J* 7, 8, 2 × CH_2O), 2.66 (2H, d, *J* 18, CH_2P), 1.32 (6H, dt, *J* 0.7, 7, CH_3). δ_C 150.5 (J_{PC} 12.4), 135.7, 131.6, 130.0, 128.3, 63.2 (J_{PC} 5.8), 23.7 (J_{PC} 143.8), 16.3 (J_{PC} 6.0). δ_P 23.8. *m/z* (APCI) 393 (100%, $[M + Na]^+$), 207 (67).

Diethyl S-*2′-Chloro-6′-fluorobenzohydroximinoylthiomethylphosphonate* ***5e***

White crystals, 53% yield, mp 139–141°C. (Found: C 40.7, H 4.7, N 4.1%. $C_{12}H_{16}ClFNO_4PS$ requires C 40.5, H 4.5, N 3.9%.) ν_{max} (KBr)/cm^{-1} 3143 (OH), 1218 (P=O). δ_H 7.22–7.43 (2H, m, ArH), 7.07 (1H, dt, *J* 1, 8, ArH), 4.11 (4H, dq, *J* 7, 8, 2 × CH_2O), 2.70 (2H, d, *J* 16, CH_2P), 1.30 (6H, t, *J* 7, CH_3). δ_C 160.8 (J_{FC} 253.6), 146.9 (J_{PC} 10.2), 135.3 (J_{FC} 3.8), 132.0 (J_{FC} 9.4), 125.6 (J_{FC} 3.6), 119.8 (J_{FC} 20.4), 114.6 (J_{FC} 21.8), 63.2 (J_{PC} 6.5), 23.9 (J_{PC} 145.3), 16.2 (J_{PC} 6.5). δ_P 22.7. *m/z* (APCI) 378 (47%, $[M + Na]^+$), 207 (100), 129 (35).

Synthesis of 1,2,3,4-Tetrahydro-1,4,2,6-oxathiazaphosphorines ***6***

Sodium hydroxide pellets (ground and weighed under nitrogen; 0.6 mmol) were added under a stream of nitrogen to anhydrous benzene (50 mL) contained in a flask connected to a Dean–Stark trap maintained under nitrogen. The suspension was heated at reflux until 5 mL of benzene had collected, and was then allowed to cool a little before the hydroximinoylphosphonate (0.6 mmol) was added under a stream of nitrogen. The resulting mixture was heated at reflux for 2 h and the first 5 mL of benzene in the Dean–Stark trap was discarded. The suspension was cooled and filtered through glass-fibre paper. The filter cake was washed with dry benzene and the combined filtrates were concentrated under reduced pressure.

2-Ethoxy-5-phenyl-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-Oxide ***6a***

White crystals, 67% yield, mp 65–68°C. (HR-EIMS found: 257.026. $C_{10}H_{12}NO_3PS$ requires 257.027.) δ_H 7.71–7.80 (2H, m, ArH), 7.37–7.59 (3H, m, ArH), 4.18–4.43 (2H, m, CH_2O), 3.49 (1H, dd, *J* 14, 17,

CH_2P), 3.20 (1H, dd, *J* 14, 14, CH_2P), 1.39 (3H, t, *J* 7, CH_3). δ_C 163.5 (J_{PC} 20.4), 132.2, 131.7, 128.8, 128.0, 63.6 (J_{PC} 6.5), 21.0 (J_{PC} 137.3), 16.1 (J_{PC} 5.8). δ_P 12.3. *m*/*z* (EI) 257 (36%, $M^{+\bullet}$), 119 (100).

2-Ethoxy-5-(2-fluorophenyl)-1,2,3,4-tetrahydro-1,4,6,2- oxathiazaphosphorine 2-Oxide ***6b***

White semi-solid, 57% yield. (HR-EIMS found: 275.017. $C_{10}H_{11}FNO_3PS$ requires 275.017.) δ_H 7.42–7.68 (2H, m, ArH), 7.10–7.31 (2H, m, ArH), 4.26–4.46 (2H, m, CH_2O), 3.55 (1H, dd, *J* 14, 17, CH_2P), 3.21 (1H, dd, *J* 14, 15, CH_2P), 1.44 (3H, t, *J* 7, CH_3). δ_C 159.7 (J_{FC} 252), 158.4 (J_{FC} 2, J_{PC} 24), 133.3 (J_{FC} 8.3), 130.8 (J_{FC} 2), 124.6 (J_{FC} 4), 119.7 (J_{FC} 2), 116.6 (J_{FC} 22.2), 63.7 (J_{PC} 6.5), 21.5 (J_{PC} 135.9), 16.1 (J_{PC} 6.5). δ_P 7.6. *m*/*z* (EI) 275 (27%, $M^{+\bullet}$), 137 (100), 121 (40).

5-(2-Bromophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-Oxide ***6c***

White crystals, 56% yield.[†] δ_H 7.60–7.70 (1H, m, ArH), 7.29–7.44 (3H, m, ArH), 4.28–4.48 (2H, m, CH_2O), 3.56 (1H, dd, *J* 14, 17, CH_2P), 3.24 (1H, dd, *J* 14, 15, CH_2P), 1.46 (3H, t, *J* 7, CH_3). δ_C 162.1 (J_{PC} 24.4), 133.7, 132.6, 132.2, 131.0, 127.6, 122.8, 63.7 (J_{PC} 6.8), 21.6 (J_{PC} 136.6), 16.3 (J_{PC} 5.9). δ_P 7.7. *m*/*z* (EI) 319 (71%, [M − 18]), 317 (68), 199 (100), 197 (90), 185 (81), 183 (86).

5-(2,6-Dichlorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-Oxide ***6d***

White crystals, 26% yield. (HR-EIMS found: 324.949. $C_{10}H_{10}Cl_2NO_3PS$ requires 324.949.) δ_H 7.24–7.37 (3H, m, ArH), 4.20–4.41 (2H, m, CH_2O), 3.57 (1H, dd, *J* 14, 17, CH_2P), 3.21 (1H, dd, *J* 14, 15, CH_2P), 1.38 (3H, t, *J* 7, CH_3). δ_C 158.8 (J_{PC} 25.4), 135.3, 132.2, 129.3, 128.4, 63.7 (J_{PC} 7.3), 21.0 (J_{PC} 136.6), 16.2 (J_{PC} 5.8). δ_P 6.5. *m*/*z* (EI) 325 (12%, $M^{+\bullet}$), 189 (81), 187 (100).

5-(2-Chloro-6-fluorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-Oxide ***6e***

Colourless oil, 45% yield. (HR-EIMS found: 308.979. $C_{10}H_{10}ClFNO_3PS$ requires 308.979.) δ_H 6.97–7.65 (3H, m, ArH), 4.20–4.42 (2H, m, CH_2O), 3.53 (1H, dd, *J* 14, 17, CH_2P), 3.19 (1H, dd, *J* 14, 15, CH_2P), 1.40 (3H, t, *J* 7, CH_3). δ_C 160.4 (J_{FC} 254.3), 155.5 (J_{PC} 26.1), 134.7 (J_{PC} 2.9), 132.9 (J_{FC} 10.2), 125.8 (J_{FC} 3.6), 119.3 (J_{FC} 21.1), 114.6 (J_{FC} 21.1), 63.7 (J_{PC} 6.5), 21.0 (J_{PC} 135.9), 16.1 (J_{PC} 6.5). δ_P 5.4. *m*/*z* (EI) 309 (11%, $M^{+\bullet}$), 173 (49), 171 (100), 155 (51), 93 (49).

Ethyl Methyl S-*Benzohydroximinoylthiomethylphosphonate* ***7a***

2-Ethoxy-5-phenyl-1,2,3,4-tetrahydro-1,4,6,2-oxathiazaphosphorine 2-oxide **6a** (10 mg, 0.04 mmol) was heated in dry methanol (1 mL) at 60°C for 18 h. The solvent was removed and the product was isolated by preparative HPLC on an Alltima C18 5u column, using 50% methanol in water as the mobile phase, to give two products, *E* and *Z* oxime isomers [2 mg (*E* isomer), 5 mg (*Z* isomer), 64%]. *Z* isomer: White crystals. δ_H 7.54 (1H, br s, NOH), 7.43 (2H, d, *J* 8, ArH), 7.33 (2H, t, *J* 8, ArH), 7.14 (1H, t, *J* 8, ArH), 4.15–4.23 (2H, m, CH_2O), 3.81 (3H, d, *J* 11, CH_3O), 3.33 (2H, d, *J* 13, CH_2P), 1.35 (3H, t, *J* 7, CH_3). δ_C 132.9, 129.9, 129.0, 128.6, 63.3 (J_{PC} 6), 53.4 (J_{PC} 7), 22.7 (J_{PC} 152), 16.4 (J_{PC} 6). δ_P 25.2. *m*/*z* (APCI) 312 (100, $[M + Na]^+$), 193 (36).[‡] *E* isomer: (HR-EIMS found: 289.053. $C_{11}H_{16}NO_4PS$ requires 289.053.) δ_H 7.52–7.58 (2H, m, ArH), 7.40–7.46 (3H, m, ArH), 4.08–4.17 (2H, m, CH_2O), 3.74 (3H, d, *J* 11, CH_3O), 2.96 (2H, d, *J* 14, CH_2P), 1.32 (3H, t, *J* 7, CH_3). δ_C 132.2, 129.9, 129.0, 128.7, 63.1 (J_{PC} 6), 53.2 (J_{PC} 6), 24.8 (J_{PC} 149), 16.3 (J_{PC} 6). δ_P 23.6. *m*/*z* (APCI) 312 (100, $[M + Na]^+$), 272 (100), 244 (46), 193 (91), 169 (66).

References

[1] W. M. Johnson, A. Faux, G. Fallon, *Heterocycles* **1999**, *51*, 2479.

[2] G. K. Farrington, A. Kumar, F. C. Wedler, *Org. Prep. Proc. Intl* **1989**, *21*, 390.

[†] A molecular ion was not observed for this compound.

[‡] This compound was unstable to EI conditions so we were unable to obtain HRMS data.