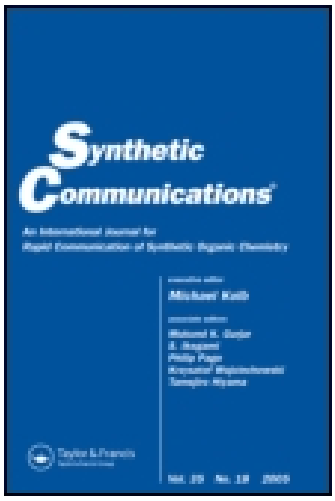

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Unexpected Thioketene Derivative Formation During Thioacyl Dithiophosphate Synthesis

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ABSTRACT

The scope and limitations of the thioacylation method using thioacyl dithiophosphates were investigated. Thioacyl dithiophosphates are formed in the reaction of acyl dithiophosphates with dithiophosphoric acid. However when the acyl moiety contains two α-substituents then a thioketene derivative is formed thus lowering the yield of expected thioacyl dithiophosphate.

Key Words: Thioketene derivatives; Thioacylation; Acyl dithiophosphates; Thioacyl dithiophosphates.

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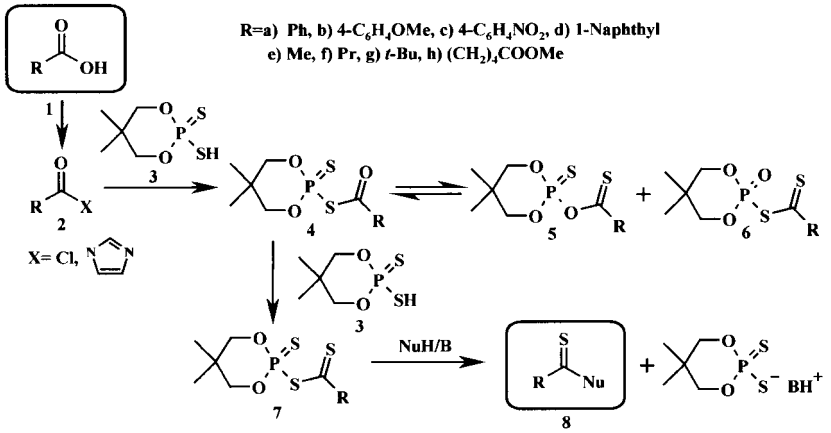
INTRODUCTION

Over the years, thioesters, thioamides (including thiopeptides) and thiohydroxamic acids have been the subject of interest of many laboratories because of their chemical and biological properties as well as technical applications. Thioacyl derivatives are mainly obtained by treating acyl derivatives with thionating agent such as P_2S_5 or Lawesson's reagent.[1–3] Another strategy consists in thioacylation of nucleophiles with active derivatives of thiocarboxylic acids. Unfortunately, the known thioacylating agents (e.g., thioacyl halides,[1] benzimidazolones,[4] trifluorosulfonyl sulfides[5]; *bis*(thioacyl) sulfides[6] or thioacyloxybenzotriazoles[7] etc.) show many disadvantages and most of them can only be prepared from dithiocarboxylic acids, which rarely are commercially available. They often are synthesized in low yield and are difficult to handle in pure form.

Recently we have discovered[8] a new strategy for the conversion of carboxylic acids **1** into thioacyl dithiophosphates **7** (Sch. 1). This class of compounds appeared to be very useful in the thioacylation of nitrogen or sulfur nucleophiles.

Acylation of dithiophosphoric acid yields acyl dithiophosphates **4** (Sch. 1) which tend to isomerise to *O*-thioacyl monothiophosphates **5** and very slowly to *S*-thioacyl monothiophosphates **6** (potential thioacylating reagents). However, at equilibrium substrate **4** generally dominates. In our method mixture of isomers **4**, **5** and **6** is treated with



Scheme 1. Thioacylation method starting from carboxylic acids via acyl dithiophosphates **4**.

dithiophosphoric acid to yield *S*-thioacyl dithiophosphates **7**, excellent thioacylating agents. These compounds are easy to obtain, they do not have to be isolated prior to thioacylation although in many cases isolation is simple and provides stable crystalline compounds. We have prepared[8] a set of anhydrides **7** in high yield for aromatic (**7a–d**) and aliphatic (**7e–h**) substituents. For both electron-donating (**7b**,**g**) and electron-withdrawing (**7c**) groups yields were high. The method was efficient for bulky residues (**7g**) as well as moieties with additional ester functionality (**7h**).

RESULTS AND DISCUSSION

However, when we attempted to obtain thioacyl dithiophosphates **7** with two α-substituents in acyl moiety (R=$CH(CH_3)_2$, $CH(CH_2CH_2)_2CH_2$) products with ca 86 ppm ^{31}P chemical shift appeared in the reaction mixtures. After prolonged heating of *S*-isobutyryl dithiophosphate **4i** (R^1=R^2=Me) with dithiophosphoric acid **3** an equilibrium mixture was formed with about 1:10 ratio of anhydride **7i** to the new compound. We managed to isolate this product and basing on analytical data, such as ^{31}P, ^{1}H and ^{13}C NMR (see Fig. 1) we assigned a structure of thioketene derivative **9i** ($R^1 = R^2 =$ Me) to this product (Sch. 2).

Compound **9i** is comparatively stable and can be crystallized from hot cyclohexane solution providing prismatic yellow crystals suitable for X-ray studies. Crystallographic analysis confirmed formerly proposed structure. Figure 2 shows the general view of the molecule **9i**. The 5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan (six membered) ring is in a chair conformation with bond distances and angles not significantly different from those found in other 1,3,2-dioxaphosphorinanes.[9–12] The P=S sulfur atom is in equatorial position while the position of sulfur S(2) of the side chain is axial. The bond lengths P(1)=S(1) 1.901(2) Å and P(1)–S(2) 2.082(2) Å are consistent with the literature data cited above. The torsion angles S(1)–P(1)–S(2)–C(6) 58.2(2)°, P(1)–S(2)–C(6)–S(3) 85.0(3)° and S(2)–C(6)–S(3)–C(10) 84.7(3)° around the bonds including sulfur atoms are *gauche*, while torsion angle C(6)–S(3)–C(10)–C(11) 174.5(5)° is *anti*. The S–C single type bonds show an excellent relationship between the bond length and the corresponding torsion angle. The S(2)–C(6) and S(3)–C(6) distances coincide with the standard deviations and are equal to 1.778(6) and 1.761(6) Å, respectively, but the S(3)–C(10) bond is shorter and is equal 1.718(6) Å. The conformation of the

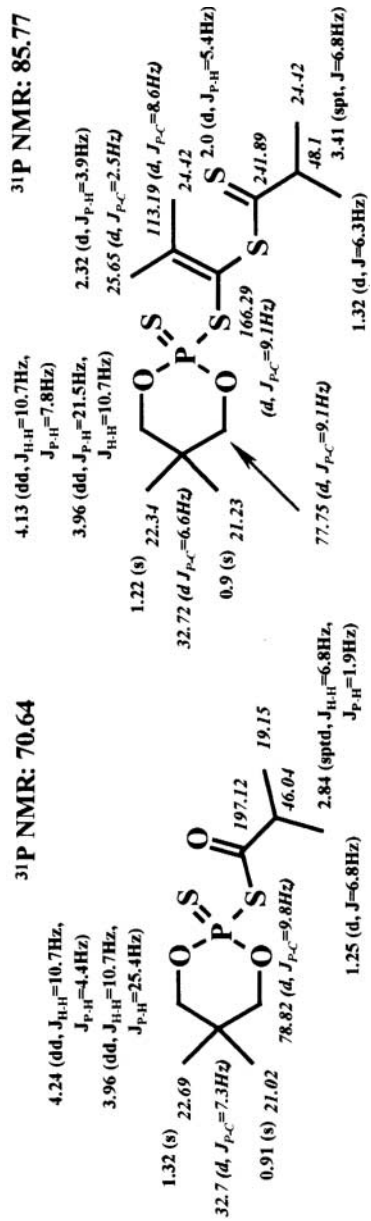
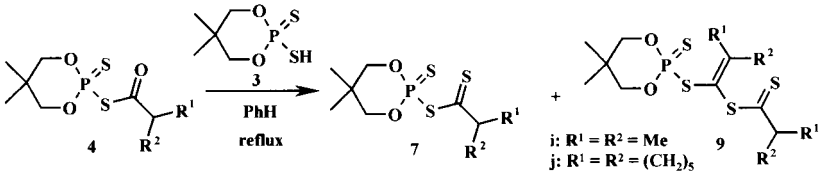


Figure 1. Analytical data for compounds **4i** and **9i**. ^{1}H NMR: normal text and ^{13}C *NMR*: *italics*.



Scheme 2. Formation of thioketene derivatives during synthesis of α,α-disubstituted thioacyl dithiophosphates.

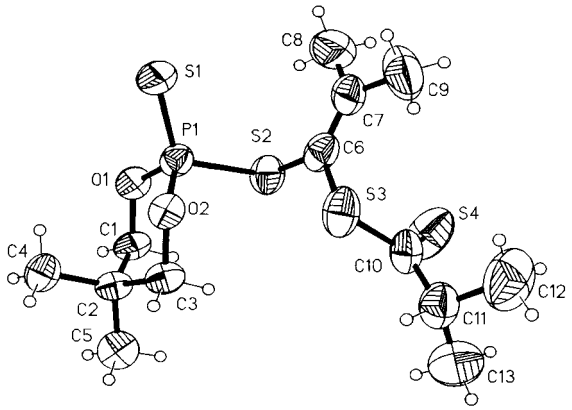
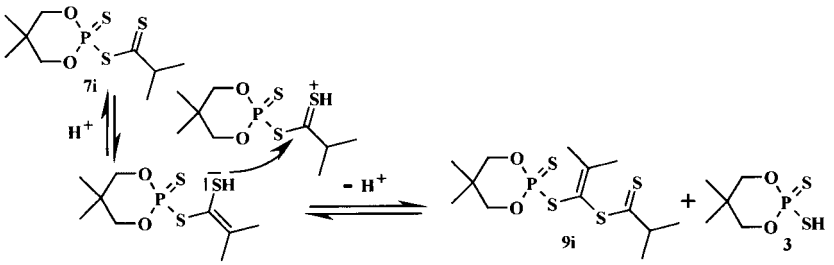


Figure 2. X-ray structure of compound **9i**, ORTP grap.

molecule may be described by the dihedral angles between the plane of S(1), P(1) and S(2) atoms, the planar 2-methyl-1-propeno-1,1-dithiolo fragment and the plane of valence bonds of C(10) atom in dithioisobutyrate moiety which are 83.7(1) and 86.4(1)°, respectively.

Formation of compound **9i**, as we believe, is based on the enolization of thioacyl dithiophosphate and the subsequent thioacylation of thiol group with the second equivalent of thioacyl dithiophosphate (Sch. 3).

In order to verify whether other α,α-disubstituted thioacyl dithiophosphates demonstrate similar reactivity we ran a reaction starting from cyclohexanecarboxylic acid derivative **4j** (R^1,R^2=$(CH_2)_5$). In that case following prolonged heating of compound **4j** with dithiophosphoric acid **3** an equilibrium mixture consisted of anhydride **7j** and thioketene derivative **9j** in 1:1 ratio. Isolation of the products was troublesome, thus we decided to convert compound **7j** into thioamide treating the reaction mixture with aniline. We obtained thioamide **8a** (R=$CH(CH_2)_5$,



Scheme 3. Probable mechanism of formation of compound **9i**.

Nu=NHPh). Compound **9j** does not react with amine and was isolated with 34% yield. For NMR data see Fig. 3.

In summary, acyl dithiophosphates possessing two substituents next to carbonyl group react with dithiophosphoric acid yielding enolizable thioacyl dithiophosphates. Subsequent reaction leads to the formation of a thioketene derivative. The product is stable in the presence of moisture and oxygen and does not thioacylate amines (at least at the same conditions as thioacyl dithiophosphates do). However other aliphatic acyl dithiophosphates with one (or non) 'α-substituent', prepared by us, treated with dithiophosphoric acid do not give substantial amount of the title derivatives consequently thioacyl dithiophosphates are formed with high yield and can be used for the efficient thioacylation.

EXPERIMENTAL

Acyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfides 4, General Procedure

Acyl chloride (3 mmol) was added to the solution of 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (**3**) (3 mmol) in benzene (10 mL). Subsequently, to the ice cooled solution triethylamine (0.303 g, 3 mmol) was added dropwise. Immediately triethylammonium chloride precipitated. After 15 min reaction mixture was filtered through a short pad of silica gel. After the solvent evaporation a pure product was obtained.

Isobutyryl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (4i): Yield 97.5%. HRMS: $M^+ = 268.03526$ (M calcd. for $C_9H_{17}O_3PS_2 = 268.03568$). IR: 1730 (C=O); 1046, 991 (P-O-C); 672 (P=S).

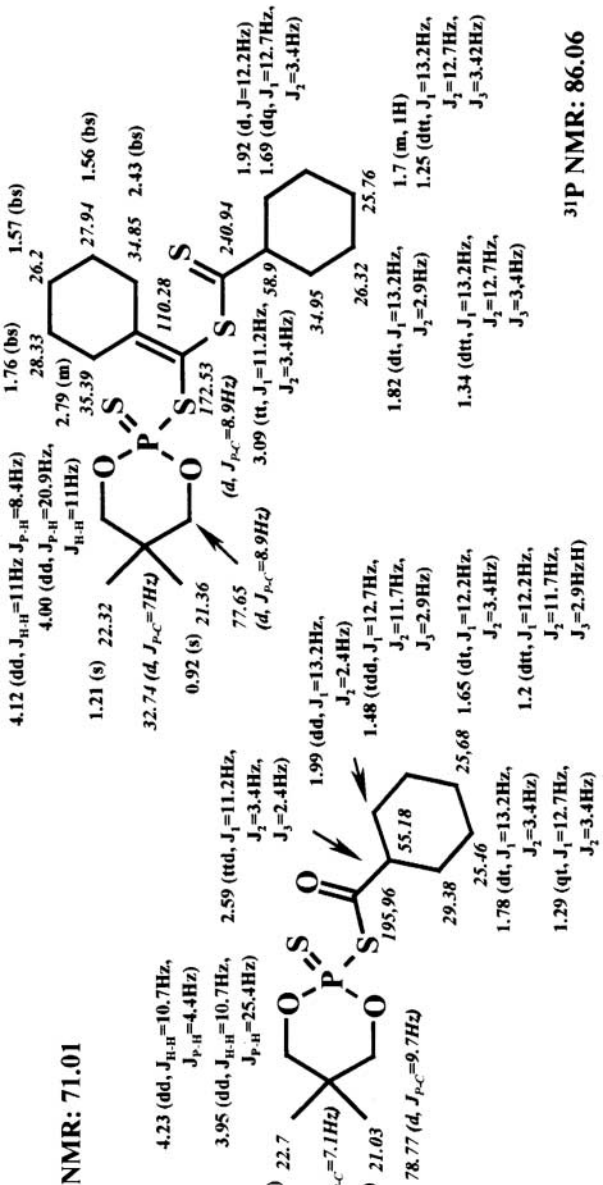


Figure 3. Analytical data for compounds **4j** and **9j**; ^{1}H NMR: normal text and ^{13}C *NMR: italics.*

Table 1. ^{1}H NMR data for compounds **4i**, **j** and **9i**, **j**.

No.	Me[a]	Me[e]	CH_2O[a]	CH_2O[e]	Residue
4i	0.91 (s)	1.32 (s)	3.96 (dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 25.4 Hz)	4.24 (dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 4.4 Hz)	2.84 (sptd, $J_{H\text{-}H}$ = 6.8 Hz, $J_{P\text{-}H}$ = 1.9 Hz) (C*H*); 1.25 (d, J = 6.8 Hz) ($CH(CH_3)_2$)
9i	0.9 (s)	1.22 (s)	3.96 (dd, $J_{P\text{-}H}$ = 21.5 Hz, $J_{H\text{-}H}$ = 10.7 Hz)	4.13 (dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 7.8 Hz)	2.32 (d, $J_{P\text{-}H}$ = 3.9 Hz); 2.0 (d, $J_{P\text{-}H}$ = 5.4 Hz) ($C=C(CH_3)_2$); 3.41 (spt, J = 6.8 Hz) (C*H*); 1.32 (d, J = 6.3 Hz) ($CH(CH_3)_2$)
4j	0.91 (s)	1.32 (s)	3.95 (dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 25.4 Hz)	4.23 (dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 4.4 Hz)	2.59 (ttd, J_1 = 11.2 Hz, J_2 = 3.4 Hz, J_3 = 2.4 Hz) (COC*H*); 1.99 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz); 1.48 (tdd, J_1 = 12.7 Hz, J_2 = 11.7 Hz, J_3 = 2.9 Hz) ($CH(CH_2CH_2)_2CH_2$); 1.78 (dt, J_1 = 13.2 Hz, J_2 = 3.4 Hz); 1.29 (qt, J_1 = 12.7 Hz, J_2 = 3.4 Hz) ($CH(CH_2CH_2)_2CH_2$); 1.65 (dt, J_1 = 12.2 Hz, J_2 = 3.4 Hz); 1.2 (dtt, J_1 = 12.2 Hz, J_2 = 11.7 Hz, J_3 = 2.9 HzH) ($CH(CH_2CH_2)_2CH_2$)
9j	0.92 (s)	1.21 (s)	4.00 (dd, $J_{P\text{-}H}$ = 20.9 Hz, $J_{H\text{-}H}$ = 11 Hz)	4.12 (dd, $J_{H\text{-}H}$ = 11 Hz $J_{P\text{-}H}$ = 8.4 Hz)	2.79 (m); 1.76 (bs); 1.57 (bs); 1.56 (bs); 2.43 (bs) ($C=C(CH_2)_5$); 3.09 (tt, J_1 = 11.2 Hz, J_2 = 3.4 Hz); 1.92 (d, J = 12.2 Hz) (CSC*H*); 1.69 (dq, J_1 = 12.7 Hz, J_2 = 3.4 Hz); 1.82 (dt, J_1 = 13.2 Hz, J_2 = 2.9 Hz) ($CH(CH_2CH_2)_2CH_2$); 1.34 (dtt, J_1 = 13.2 Hz, J_2 = 12.7 Hz, J_3 = 3,4 Hz) ($CH(CH_2CH_2)_2CH_2$); 1.7 (m, 1H); 1.25 (dtt, J_1 = 13.2 Hz, J_2 = 12.7 Hz, J_3 = 3.42 Hz) ($CH(CH_2CH_2)_2CH_2$)

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Table 2. ^{13}C NMR data for compounds **4i,j** and **9i,j**.

No.	Me[a]	Me[e]	Me_2C	CH_2O	Residue
4i	21.02	22.69	32.7 (d, $J_{P\text{-}C} = 7.3$ Hz)	78.82 (d, $J_{P\text{-}C} = 9.8$ Hz)	197.12 (CO); 46.04 (*C*H); 19.15 (CH(*C*H$_3$)$_2$)
9i	21.23	22.34	32.72 (d $J_{P\text{-}C} = 6.6$ Hz)	77.75 (d, $J_{P\text{-}C} = 9.1$ Hz)	166.29 (d, $J_{PC} = 9.1$ Hz) (*C*=C(CH$_3$)$_2$); 113.19 (d, $J_{P\text{-}C} = 8.6$ Hz) (C=*C*(CH$_3$)$_2$); 25.65 (d, $J_{PC} = 2.5$ Hz); 24.42 (C=C(*C*H$_3$)$_2$); 241.89 (CS); 48.1 (*C*H); 24.42 (CH(*C*H$_3$)$_2$)
4j	21.03	22.7	32.14 (d, $J_{P\text{-}C} = 7.1$ Hz)	78.77 (d, $J_{P\text{-}C} = 9.7$ Hz)	195.96 (CO); 55.18 (*C*H); 29.38 (CH(*C*H$_2$CH$_2$)$_2$CH$_2$); 25.46 (CH(CH$_2$*C*H$_2$)$_2$CH$_2$); 25.68 (CH(CH$_2$CH$_2$)$_2$*C*H$_2$)
9j	21.36	22.32	32.74 (d, $J_{P\text{-}C} = 7$ Hz)	77.65 (d, $J_{P\text{-}C} = 8.9$ Hz)	172.53 (d, $J_{P\text{-}C} = 8.9$ Hz) (*C*=C (CH$_2$)$_5$); 110.28 (C=*C*(CH$_2$)$_5$); 35.39; 28.33; 26.2; 27.94; 34.85 (C=C(*C*H$_2$)$_5$); 240.94 (CS); 58.9 (CSC*H*); 34.95 (CH(*C*H$_2$CH$_2$)$_2$CH$_2$); 26.32 (CH(CH$_2$*C*H$_2$)$_2$CH$_2$); 25.76 (CH(CH$_2$CH$_2$)$_2$*C*H$_2$)

Cyclohexanecarbonyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (4j). Yield 93.4%. HRMS (LSIMS): $M + H^+ = 309.07423$ (M calcd. for $C_{12}H_{22}O_3PS_2$=309.07480). IR: 1732 (C=O); 1045, 990 (P-O-C); 678 (P=S).

Reaction of Acyl 2-(5,5-Dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) Sulfides 4, with 5,5-Dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (3), General Procedure

The solution of acyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide (**4**) (3 mmol) and 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (**3**) (6 mmol) in 30 mL of benzene was heated under reflux for 17–21 h (until no essential changes were noticed in ^{31}P NMR spectrum). Subsequently the reaction mixture was washed with the aqueous solution of Na_2CO_3 and then water. Next organic layer was dried with $MgSO_4$ and benzene was evaporated.

Isobutyryl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxa-phosphorinanyl) sulfide (4i): as starting material: after 17 h of heating and workup as above 0.651 g of orange oil was obtained. Chromatography on silica gel (CH_2Cl_2:$(CH_2)_6$, 3:10) yielded 0.394 g (71%) of *S*-2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) *S*-thioisobutyryl 2-methyl-1-propeno-1,1-dithiol (**9i**). Crystallization from hot cyclohexane solution yielded yellow crystals. HRMS: $M^+ = 370.03178$ (M calcd. for $C_{13}H_{23}O_2S_4P$= 370.03186). IR: 1585 (C=C); 1211 (C=S); 1047, 994 (P-O-C); 687 (P=S); m.p.108–109°C. Crystallography: The prismatic yellow crystals of compound **9i** are monoclinic, space group $P2_1/c$, $a = 15.796(4)$, $b = 10.578(3)$, $c = 11.556(4)$ Å, $\beta = 101.46(2)^\circ$; $V = 1892.4(10)$ Å^3. The experimental data were collected from a monocrystal ($0.3 \times 0.15 \times 0.1$ mm) on a KUMA Diffraction KM4 diffractometer using graphite monochromatized Mo-Kα radiation (reflections collected 3612, unique 3422 [R(int)= 0.0658]); $T = 293(2)$K. Lattice parameters were determined from least-squares refinements of the 32 reflection with $9.1^\circ \leq 2\theta \leq 18.4^\circ$. The structure was solved by direct method and refined by full-matrix least-squares in anisotropic approximation using SHELX-97 programs.[13] Final R indices $R1 = 0.0446$, w$R2 = 0.0906$ for 1009 reflection with [$I > 2\sigma(I)$]. Positions of hydrogen atoms were calculated from geometrical consideration and refined as constrained to bonding atoms in a 'ride' mode. (Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 174564. Copies of the data can be obtained, free of charge, on application to

CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (0) 1223-336033 or E-mail: deposit@ccdc.cam.ac.uk]).

Cyclohexanecarbonyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (4j): as starting material: after 21 h of heating and workup as above 0.784g of orange oil was obtained, dissolved in 1 mL of benzene and treated with 0.25 g of aniline. After a few minutes anilinium dithiophosphate precipitated. Subsequently, after solvent evaporation, the residue was chromtographed on silica gel (THF:$(CH_2)_6$, 1:40) yielding 0.188 g (28.6%) of *N*-cyclohexanethiocarbonyl aniline (^{1}H NMR: 7.65 (d, $J = 7.3$ Hz, 2H); 7.81 (t, $J = 7.8$, 2H); 7.25 (t, 7.3 Hz, 1H); 2.64 (tt, $J = 11.7$, 3.4 Hz, 1H); 1.98 (dd, $J = 13.2$, 1.5 Hz, 2H); 1.86 (td, $J = 13.2$, 2.9 Hz, 2H); 1.73 (m, 1H); 1.69 (tdd, $J = 12.7$, 12.2, 3.4 Hz, 2H); 1.36 (tdt, $J = 13.2$, 12.7, 3.4 Hz, 2H); 1.26 (qt, $J = 12.7$, 3.4, 1H), ^{13}C NMR: 210.26; 138.83; 129.11; 127.08; 124.34; 56.65; 33.31; 26.21; 25.83) and 0.229 g (33.9%) of *S*-2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) *S*-cyclohexanethiocarbonyl cyclohexylidenemethanodithiol (**9j**). HRMS: $M^+ = 450.09664$ (M calcd. for $C_{19}H_{31}O_2S_4P$=450.09446). IR: 1568 (C=C); 1192 (C=S); 1045, 991 (P-O-C); 685 (P=S).

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