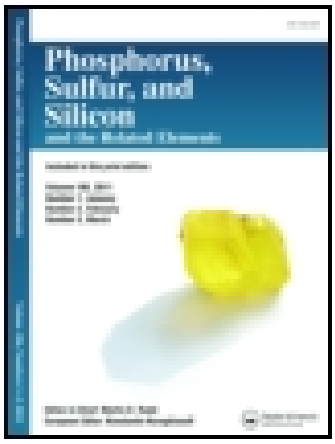



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# Synthesis and structural studies of phosphonothioamidates

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# Synthesis and structural studies of phosphonothioamidates

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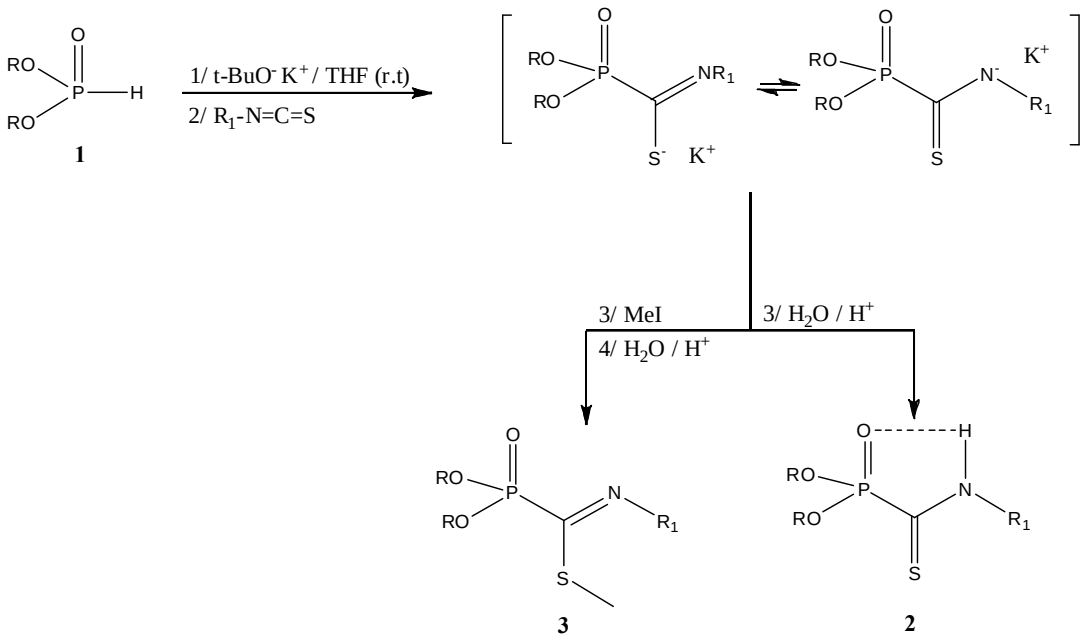
Abstract

The reaction of isothiocyanates with dialkylphosphites in the presence of strong base yielded the phosphonothioamides **2**. Treatment of **2** with methyl iodide afforded the corresponding thioimidates **3** with high yields. All compounds were characterized on the basis of their IR, NMR Spectroscopy ($^{1}H$, $^{13}C$, $^{19}F$ and $^{31}P$) and in some cases by elemental analysis, HRMS data and calculations using Density Functional Theory (DFT)-B3LYP//6-311G** and evolution study by $^{31}P$-NMR in an external lock with $D_2O$. The conformational molecular structure of compounds **2d** and **2f** were determined by single-crystal X-ray diffraction analysis.




Keywords

phosphonothioamidates, phosphonatesthioimidates, X-ray, DFT

## 1. Introduction

Thioamides are commonly known for their biological activity [1] as antifungal and anticancer [2] agents, are used in the development of peptide [3] and protein chemistry [3]. Many studies describe the preparation of thioamide derivatives[1],[2],[5-12], as the best known methods of adding isothiocyanates to secondary amines[1], or the thionation of amides[2],[4],[5]; by the reaction of dialkylphosphite with isothiocyanate which gave reasonable yields of phosphothioamidates[11]-[12]. Furthermore They were a preparation of triethylphosphite-pyridinium iodide and isothiocyanates[13]. The synthesis of thioimidates derivatives has been the prominent research discussed in different academic studies [14-16].In the present work, we report on the synthesis of a series of phosphonothioamidates**2**and the corresponding methyl alkylated thioimidates **3**.

## 2. Results and discussion

### 2.1. Synthesis

#### 2.1.1 *Preparation of phosphonothioamidates**2a-h***

A general strategy based on the reaction of isothiocyanates with dialkylphosphites**1** in the presence of potassium tert-butoxide in anhydrous THF, followed by acid hydrolysis at room temperature is a useful method to prepare the thioamide derivatives**2a-h**. The synthetic approach to obtain thioamides followed the reactions shown in **Table 1**. The thioamide derivatives **2a-h** were obtained in high yields in *s-Cis* conformation, which is the most favored major product in general [17]. It is worth noting that, as far as we are aware, these compounds are all new except product **2h** which was previously described by Tashma [11] using NaH as the base.

After following the steps for the preparation of compounds above, we have used $^{31}$P-NMR spectroscopy for the detection of intermediate reaction in THF in an external lock with $D_2O$and we give the case of **2f** as example. From the $^{31}$P-NMR spectrum, the signal of diethylphosphite in anhydrous THF appears at 7.1 ppm. By adding the t-BuOK, the $^{31}$P-NMR spectrum shows the appearance of new signals between 154.7 and 145.1ppm corresponding to potassium diethyl phosphate. The addition of Ph-N=C=S to potassium diethyl phosphate gives potassium(diethoxyphosphoryl)-N-phenylmethanimidothioate and carbonothioyl (phenyl)amide. This is confirmed by the presence in the NMR spectrum in THF in external lock with $D_2O$ of two signals in the range 5.8 and 3.2ppm assignment to the two anions. After acid hydrolysis, a signal appearing at -1.7ppm refers tothe compound **2f** (**Scheme 1**).

All the compounds were characterized by their $^{31}$P-NMR and $^{19}$F-NMR spectra which displayed one signal. For example, for **2** (entry d**)**, we note the appearance of one signal at 0.1ppm in the $^{31}$P-NMR and -112.3ppm in the $^{19}$F-NMR spectra. The structures of the latter products were confirmed by the presence of a characteristic signal due to the secondary amine $NHR_1$ proton at 8-11ppm in their $^{1}$H NMR spectra. The IR spectra of compounds **2a, c-f** and **h** displayed absorption bands in $CHCl_3$ at 1520.0ï 1650.0cm$^{-1}$, 1240.1ï 1250.5cm$^{-1}$ and intense absorption band at 3153.9-3249.1cm$^{-1}$. These bands can be assigned to the stretching vibrations of the $\upsilon_{C=C}$, $\upsilon_{PO}$ and $\upsilon_{NH}$, respectively. The $^{13}$C NMR spectra of the thioamides **2** shows a doublet signal at 189.0-192.5ppm with a coupling constant of 183.0 Hz, which is typical for a C=S group and at 115.0-134.0ppm, which is typical for a $C_{arom}$ fragment.

### 2.1.2. Preparation of phosphonothioamidates **3a-f**

The most convenient method was to generate the phosphonothioimidate **3a-f** derivatives *in-situ* by treating thioamides **2** with methyl iodide. In this way, dialkylphosphite (1.0 equiv), therefore t-BuOK (1.5 equiv), $R_1NCS$ (1.0equiv), and methyl iodide (1.0 equiv) were mixed in a suitable solvent at room temperature to give the desired phosphonothioimidates in good overall yield (**Table 2**).

Taking the example of case of **3a**, the signal of dimethylphosphite in anhydrous THF appears at 10.3ppm. After addition of t-BuOK, the signal at 152.7ppm characterizing the potassium dimethyl phosphate was observed. Adding phenyl isothiocyanate to the phosphonium potassium salt produces the anion potassium sulfide and azide at 3.8-3.7ppm. After S-methylation followed by acid hydrolysis, the appearance of signal at -3.5ppm, confirms the thioimidate structure with *Syn* conformation (**Scheme 2**).

In the IR spectra in $CHCl_3$ of the compounds **3a-f**, the appearance of the absorption bands at 1645-1650 $cm^{-1}$ and 1235 $cm^{-1}$ corresponding to the stretching vibrations of the $\upsilon_{C=C}$ and $\upsilon_{C=N}$ and $\upsilon_{PO}$ respectively. The $^{13}$C-NMR spectra in $CDCl_3$of the compounds thioimidates shows a doublet signal at 200 ppm with a coupling constant of 196 Hz, which is typical for a N=C-SMe fragment and 10.3-16.3 ppm, which is typical for a S-$CH_3$ fragment. The signal of S-Me in the $^1$H-NMR spectrum was observed at 2.1ppm with the absence of the secondary amine proton signal. Only one signal was detected in the $^{31}$P-NMR spectra for all compounds confirming the structure of **3a-f** with a *Syn* conformation. For example, the $^{31}$P-NMR spectrum of **3a**in $CDCl_3$ shows one signal at -3.5ppm.

2.2. X-Ray analysis

The X-Ray analysis shows that the phosphonothioamidates**2d** and **2f** adopt an *s-Cis* conformation structure in the solid state (**Figs.1**and **2**). The structure is built up from $C_9H_{11}FNO_3PS$ and $C_{11}H_{16}NO_3PS$ molecules stabilized by N-H..O intermolecular hydrogen bonds (**Tables 5-6**). The distances and the angles of the compounds **2d** and **2f** are summarized in the table **3** and **4**.

2.3. DFT calculations

To study the relative stability of the different considered molecular species we have performed DFT electronic structure calculations. All the minimum energy structures were determined by the B3LYP functional implemented in the Gaussian 03 series of programs [17-[18] using the 6-311G** basis set. The optimization of each structure was considered as converging with a maximum gradient less than 0.0001. No frozen coordinates and no symmetry restriction were used. (**Figure 3**)



## 3. Conclusion

A new series of phosphonothioamidates **2a-h** were synthesized with good yields. The methyl alkylated analogs **3a-f** were obtained in situ and isolated in good yields. The X-ray structures of phosphonothioamidates**2d** and **2f** were determined and showed that these compounds exist in the the *s-Cis* form.

## 4. Experimental section

4.1. General

$^{1}H$, $^{13}C$, $^{19}F$ and $^{31}P$ NMR spectra were recorded at 300, 75, 282 and 121 MHz respectively on a Bruker AC-300 with TMS as internal reference (for $^{1}H$ and $^{13}C$), $CHF_3$ (for $^{19}F$) and $H_3PO_4$ (for $^{31}P$) in $CDCl_3$.

The melting point was determined by Büchi. Infrared spectra were recorded by using Shimadzu FTIR 8400S.Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with $NH_3$ gas. High-Resolution Mass Spectrometry (HRMS) analyses were performed at the ñCentre Commun de Spectrométrie de Masseò in Lyon (France), on a Micro-TOFOII Thermofischer Scientific for electro-spray ionization (ESI) measurements. CHN elementary were performed at the INRAP (National Institute of Physico-Chemical Analysis (INRAP) Bio-technopole Sidi Thabet, Tunisia) Perkin Elmer Model: Analyzer 2400 series II CHN.

The study of the evolution of the reaction mixture was performed by $^{31}P$ NMR using in an external lock with $D_2O$. The Supplemental Materials file presents sample $^{1}H$, $^{31}P$ and $^{19}F$ NMR spectra of selected products (Figures S 1 ï S 14)

4.2. Crystallographic information

CCDC-965890 and CCDC-1001884 of the compounds (**2d)** and (**2f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/

**General procedure for the preparation of phosphonothioamidates (2a-h)**

A solution composed by dialkylphosphite**1** (0.02 mol, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise to a solution of potassium tert-butoxide (0.025 mol, 1.5 equiv) in anhydrous THF (30 mL). Continuous stirring at room temperature and under a nitrogen atmosphere for 1 h. Isothiocyanate (0.02 mol, 1.0 equiv) in dry THF (10 mL) was added to the reaction mixture.

After 3h of stirring at room temperature, the hydrolysis was performed with an aqueous saturated $H_2O$/HCl solution. The aqueous layer was then extracted by $CHCl_3$. After drying ($MgSO_4$ or $Na_2SO_4$), filtration and solvent evaporation, the residue obtained was recrystallized with ethanol.The oily and viscous mixture residue was purified by column chromatography on Ether to give pure product.

**(2a). dimethyl phenylcarbamothioylphosphonate** Yellow solid; yield= 92%; mp 102.3°C; $^1$H NMR $\delta_H$ (ppm): 3.94 ( d, J= 11.1 Hz, 6H, $CH_3$), 7.25-7.51 ( m, 5H, $H_{arom}$), 10.65 (d, J= 8.7 Hz, 1H, NH).$^{13}$C NMR $\delta_C$ (ppm): 189.0 (d, J= 183.7Hz, C=S), 137.9(d, J= 15.7Hz, $C_{ipso}$), 122.1-127.6 ($C_{arom}$), 55.4 (s, MeO). $^{31}$P NMR $\delta_H$ (ppm): (2a ) = 0.2. IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): NH= 3153.9, $(C=C)_{arom}$ = 1601.6, PO = 1249.3. for m/z for $C_9H_{12}NO_3PS$ 245g.mol$^{-1}$ found m/z: 244.95 ($M^+$), $PO(OMe)_2$:109.90, S=C=NPh: 134.87.

**(2b).dimethyl cyclohexylcarbamothioylphosphonate** Yellow solid; yield= 80%; mp 108.8°C; $^1$H NMR $\delta_H$ (ppm): 1.07ï 2.27 ( m, 11H, $H_{cyclohexyl}$), 3.88 (d, J= 1.4 Hz, 6H, $CH_3$), 4.26 ï 4.63 (m, 1H, $H_{ipso}$ ), 8.89 (s, 1H, NH ).$^{13}$C NMR $\delta_C$ (ppm): 189.6 (d, 180.4Hz, C=S), 55.2 (s, $C_{ipso}$), 53.8(d, 8Hz, MeO), 24.0-30.9 ($C_{hexyl}$). $^{31}$P NMR $\delta_P$ (ppm): (2b ) = 0.3. IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): NH= 3195.8, $(C\text{-}C)_{hexyl}$= 1640.8, PO = 1246.6. m/z for $C_9H_{18}NO_3PS$ : 251g.mol$^{-1}$ found m/z: 251.02 ($M^+$), $PO(OMe)_2$:109.90, NH($C_6H_{11}$): 97.94.

**(2c). dimethyl benzylcarbamothioylphosphonate** Yellow viscous; yield= 70%; $^1$H NMR $\delta_H$ (ppm): 3.80 ( d, J= 11Hz, 6H, $CH_3$),7.34-7.28 (m, 5H, $H_{arom}$), 4.87 ( d, J= 1.8Hz, 2H, $CH_2$), 8.89 (s, 1H, NH ).$^{13}$C NMR $\delta_C$ (ppm): 191.2(d, 182.9Hz, C=S), 55.1 (s, $C_{ipso}$), 48.9(d, 9Hz, MeO), 128.3-134.4 ($C_{arom}$). $^{31}$P NMR $\delta_P$ (ppm): (2c ) = 0.1. IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): NH= 3217.9, $(C=C)_{arom}$= 1649.2, PO = 1249.1. Anal. Calc. for $C_{10}H_{14}NO_3PS$ (259g.mol$^{-1}$): C, 46.33; H, 5.40; N, 5.40; found C, 46.33; H, 5.41; N, 5.40%.

**(2d).dimethyl (*p*-fluorophenyl)carbamothioylphosphonate** Orange crystal; yield= 96%;

mp118.6.°C; $^{1}$H NMR $\delta_H$ (ppm): 3.92 ( d, J=11.1 Hz, 6H, $CH_3$), 7.10-7.95 ( m, 4H, $H_{arom}$), 10.82 (s, 1H , NH).$^{13}$C NMR $\delta_C$ (ppm): 189.3(d, 184.8Hz, C=S), 160.9 (d, 248.2Hz, C-F), 134.1(q, 12.82Hz, $C_{ipso}$), 115.8-124.5 ($C_{arom}$), 55. 1 (d, J= 7.54Hz, MeO). $^{31}$P NMR $\delta_P$ (ppm): (2d)= 0.1. $^{19}$F NMR $\delta_H$ (ppm): (2a)= -112.3. IR ($CHCl_3$ , υ $cm^{-1}$): NH= 3249.1, $(C=C)_{arom}$ = 1649.4, PO = 1250.1.Mr for $C_9H_{11}FNO_3PS$: 263g.mol$^{-1}$ found Mr=263.22g.mol$^{-1}$. Anal. Calc. for $C_9H_{11}FNO_3PS$ (263.22g.mol$^{-1}$): C, 41.03; H, 4.17; N, 5.31; found C, 40.83; H, 5.28; N, 5.30%.

**(2e). dimethyl (*p*-chlorophenyl)carbamothioylphosphonate** Yellow solid; yield= 84%; mp 86.4°C; $^{1}$H NMR $\delta_H$ (ppm): 3.90 ( d, J= 11.1 Hz, 6H, $CH_3$), 7.10-7.98(m, 4H, $H_{arom}$), 10.60 (s, 1H , NH).$^{13}$C NMR $\delta_C$ (ppm): 189.3 (d, 184.89Hz, C=S), 130.0 (s, C-Cl), 136.5(s, $C_{ipso}$), 123.5-132.9($C_{arom}$), 55. 5 (d, J= 6.7Hz, MeO). $^{31}$P NMR $\delta_P$ (ppm): (2e)= 1.4. IR ($CHCl_3$ , υ $cm^{-1}$): NH= 3246.5, $(C=C)_{arom}$= 1647.8, PO = 1249.5. Anal. Calc. for $C_9H_{11}ClNO_3PS$ (279g.mol$^{-1}$): C, 38.70; H, 3.94; N, 5.01; found C, 38.25; H, 3.82; N, 4.97 %.

**(2f). diethyl phenylcarbamothioylphosphonate** Yellow crystal; yield= 87%; mp 46.3°C; $^{1}$H NMR $\delta_H$ (ppm): 1.26 ( d, J= Hz, 6H, $CH_3$), 4.25 (d, J= 14.3Hz, 4H, $CH_2$ ), 6.84-8.68(m, 5H,

$H_{arom}$ ), 11.38 (s, 1H, NH ). $^{13}C$ NMR $8_C$ (ppm): 190.5 (d, 183.3Hz, C=S), 65.3(d, 22.7Hz, $CH_2$), 138.2(d, 15.7Hz, $C_{ipso}$), 122.8-128.7($C_{arom}$), 15.4(d, 6.2Hz, Me). $^{31}P$ NMR $8_P$ (ppm): (2f) = -1.7, IR ($CHCl_3$ , υ $cm^{-1}$): NH= 3201.9, $(C=C)_{arom}$= 1601.2, PO= 1250.5. Mr for $C_{11}H_{16}NO_3PS$: 273g.$mol^{-1}$ found Mr=273.28g.$mol^{-1}$.Anal. Calc. for $C_{11}H_{16}NO_3PS$ (273.28g.$mol^{-1}$): C, 48.30; H, 5.85; N, 5.12; found C, 48.29; H, 5.85; N, 5.12%.

**(2g). diethyl cyclohexylcarbamothioylphosphonate** Yellow solid; yield= 80%; mp52°C;$^1H$ NMR $8_H$ (ppm): 0.21-0.98 ( m, 17H, $CH_3$ , $H_{hexyl}$), 4.13-4.35 (m, 4H, $CH_2O$), 9.03 (s, 1H, NH)$^{13}C$ NMR $8_C$ (ppm): 191.0 (d, 179.6Hz, C=S), 65.0 (d, 6.8Hz, $CH_2$), 53.8(d, J= 7.5 Hz, $C_{ipso}$), 24.6-30.8($C_{hexyl}$), 16.2 (d, 6.2Hz, Me). $^{31}P$ NMR $8_P$ (ppm): (2g) = -1.6. IR ($CHCl_3$ , υ $cm^{-1}$): NH= 3197.1, $(C\text{-}C)_{hexyl}$ = 1526.6, PO = 1240.1. Anal. Calc. for $C_{11}H_{22}NO_3PS$ (279g.$mol^{-1}$): C, 47.31; H, 7.88; N, 5.01; found C, 47.28; H, 7.65; N, 5.00%.

**(2h). diethyl benzylcarbamothioylphosphonate** Yellow solid; yield= 82%; mp 68°C; $^1H$ NMR $8_H$ (ppm): 1.33 ( d, J= 6.7Hz, 6H, $CH_3$), 3.99 ï 4.32 (m, 4H, $CH_2$), 4.87 (d, J= 1.7Hz, 2H, $CH_2$), 7.36-7.30 (m, 5H, $H_{arom}$), 9.77 (s, 1H, NH ).$^{13}C$ NMR $8_C$ (ppm): 192.6 (d, 181.5Hz, C=S), 135. 4(s, $C_{ipso}$), 128.0-128.4($C_{arom}$), 65.1 (d, $CH_2$), 49.0 (d, 8.9Hz, $CH_{2)benzyl}$), 16.1(d, 65.1Hz, Me).$^{31}P$ NMR $8_P$ (ppm): (2h) = -1.9. IR ($CHCl_3$ , υ $cm^{-1}$): NH= 3229.3, $(C=C)_{arom}$= 1521.1, PO = 1248.1. Anal. Calc. for $C_{12}H_{18}NO_3PS$ (287g.$mol^{-1}$): C, 50.17; H, 6.27; N, 4.87; found C, 49.87; H, 6.02; N, 4.30%.

**General procedure for the preparation of phosphonothioimidates (3a-f)**

The same procedure applied for the preparation of phosphonoamidates, has been used to prepare the phosphonothioimidates. Before the acid hydrolysis by $H_2O$/HCl, we have to add dropwise the methyl iodide MeI(0.02 mol, 1.0 equiv) in anhydrous THF (10 mL) during 1h. The

aqueous layer was then extracted with $CHCl_3$. After drying ($MgSO_4$ or $Na_2SO_4$), filtration and solvent evaporation, the residue obtained was recrystallized with ether and petroleum ether.

**(3a).(Z)-methyl (dimethoxyphosphoryl)-N-phenylmethanimidothioate** Pink solid; yield= 82%; mp 74°C; $^1$H NMR $\delta_H$ (ppm): 2.16 (s, 3H , SMe), 3.54 (d, 10.80Hz, 6H, $CH_3$), 7.07-7.57 (m, 5H, $H_{arom}$). $^{13}$C NMR $\delta_C$ (ppm): 204.2 (d, 196.1Hz, -C=N-), 131.2 (s, $C_{ipso}$), 123.7-129.3($C_{arom}$), 53.5 (d, 6.2Hz, MeO), 10.4 (s, SMe). $^{31}$P NMR $\delta_P$ (ppm) (**3a**) = - 3.5. IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): (**C=N**)= 1646.0, (**PO**)= 1232.1. Anal. Calc. for $C_{10}H_{14}NO_3PS$ (259g.mol$^{-1}$): C, 46.33; H, 5.40; N, 5.40; found C, 46.32; H, 5.40; N, 5.40%.

**(3b).(Z)-methyl (dimethoxyphosphoryl)-N-cyclohexylmethanimidothioate** Yellow solid; yield= 68%; mp 82°C; $^1$H NMR $\delta_H$ (ppm): 1.05-2.17 (m, 10H, $H_{cyclohexyl}$), 2.35 (s, 3H, SMe), 3.47 (q, 7Hz, 1H, $H_{ipso}$ ), 3.67 (d, 10.8Hz, 6H, $CH_3$).$^{13}$C NMR $\delta_C$ (ppm): 204.9 (d, 193.8Hz, -C=N-), 65.8 (s, $C_{ipso}$), 24.7-50.6($C_{hexyl}$), 53.6 (d, 4.2Hz, MeO), 10.5 (s, SMe).$^{31}$P NMR $\delta_P$ (ppm)(**3b**) = - 4.4.IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): (**C=N**)= 1645.1, (**PO**)= 1233.2. Anal. Calc. for $C_{10}H_{20}NO_3PS$ (265g.mol$^{-1}$): C, 45.28; H, 7.57; N, 5.28; found C, 45.25; H, 7.55; N, 5.27%.

**(3c).(Z)-methyl(dimethoxyphosphoryl)-N-benzylmethanimidothioate** Yellow viscous; yield= 70%; $^1$H NMR $\delta_H$ (ppm): 2.21 (s, 3H, SMe) , 3.40 ( d, 10.7Hz, 6H, $CH_3$), 3.96 (s, 2H, $CH_{2)benzyl}$ ),7.52 (m, 5H, $H_{arom}$). $^{13}$C NMR $\delta_C$ (ppm): 205. 0 (d, 194.2Hz, -C=N-), 133. 4 (s, $C_{ipso}$), 128.3-129.1 ($C_{arom}$), 53.3 (d, 6.10Hz, MeO), 43.3(s, $CH_{2)benzyl}$), 10.3 (s, SMe). $^{31}$P NMR $\delta_P$ (ppm) (**3c**) = - 3.9. IR ($CHCl_3$ , $\upsilon$ cm$^{-1}$): (**C=N**)= 1648.8, (**PO**)= 1232.8.Anal. Calc. for $C_{11}H_{16}NO_3PS$ (273g.mol$^{-1}$): C, 48.35; H, 5.86; N, 5.12; found C, 48.18; H, 5.63; N, 5.09%.

**(3d).(Z)-methyl (diethoxyphosphoryl)-N-phenylmethanimidothioate** Pink solid; yield= 85%; mp: 108°C. $^{1}$H NMR $\delta_H$ (ppm): 1.07 (d, 4Hz, 6H, $CH_3$), 2.14 (s, 3H , SMe), 3.88 (t, 6.2Hz, 4H, $CH_2$), 7.41 ( m, 5H, $H_{arom}$). $^{13}$C NMR $\delta_C$ (ppm): 204.7 (d, 194.8Hz, -C=N-), 131. 4 (s, $C_{ipso}$), 128.2-129.4($C_{arom}$), 62.8 (d, 6.10Hz, $CH_2O$), 16.3 (d, 6.5Hz, SMe), 10.5 (s, Me). $^{31}$P NMR $\delta_P$ (ppm): (**3d**) = - 2.0. IR ($CHCl_3$ , $\upsilon$ $cm^{-1}$):(**C=N**)= 1646.6, (**PO**)= 1227.0. Anal. Calc. for $C_{12}H_{18}NO_3PS$ (287g.mol$^{-1}$): C, 50.17; H, 6.27; N, 4.87; found C, 50.17; H, 6.28; N, 4.87%.

**(3e). (Z)-methyl (diethoxyphosphoryl)-N-cyclohexylmethanimidothioate** Yellow solid; yield= 59%; mp 72°C; $^{1}$H NMR $\delta_H$ (ppm): 1.34 (d, 4.1Hz, 6H, $CH_3$), 1.50 ( m, 10H, $H_{cyclohexyl}$), 2.31 (s, 3H, SMe) , 4.10 (t, 3.6Hz, 4H, $CH_2$ ), 4.34( m, 1H, $H_{ipso}$). $^{13}$C NMR $\delta_C$ (ppm):205.7 (d, 192.3Hz, -C=N-), 64.7( d, 6.7Hz, $C_{ipso}$), 24.7-50.6 ($C_{hexyl}$), 62.5 (d, 6Hz, -$CH_2O$), 16.6 (d, 6.5Hz, Me), 10.5(s, SMe). $^{31}$P NMR $\delta_P$ (ppm):(**3e**) = - 4.5. IR ($CHCl_3$ , $\upsilon$ $cm^{-1}$): (**C=N**)= 1648.6, PO= 1217.1. Anal. Calc. for $C_{12}H_{24}NO_3PS$ (293g.mol$^{-1}$): C, 49.14; H, 8.19; N, 4.77; found C, 49.08; H, 8.14; N, 4.75%.

**(3f). (Z)-methyl (diethoxyphosphoryl)-N-benzylmethanimidothioate** Yellow oil; yield= 72%; $^{1}$H NMR $\delta_H$ (ppm): 1.12 ( d, 7.1H, $CH_3$), 2.23 (s, 3H, SMe), 3.82 (s, 2H, $CH_{2)benzyl}$), 3.85 (t,6.2Hz, 4H, $CH_2$), 7.57(m, 5H, $H_{arom}$). $^{13}$C NMR $\delta_C$ (ppm): 205.2 (d, 194.10, -C=N-), 133.4 (s, $C_{ipso}$), 128.5-129.2($C_{arom}$), 62.6 (d, 6Hz, -$CH_2O$), 43.3 (s, $CH_{2)benzyl}$), 16.4 (d, 6.5Hz, Me), 10.53 (s, SMe). $^{31}$P NMR $\delta_P$ (ppm)(**3f**) = - 4.8. IR ($CHCl_3$ , $\upsilon$ $cm^{-1}$):(**C=N**)= 1649.2, (**PO**)= 1230.9. Anal. Calc. for $C_{13}H_{20}NO_3PS$ (301g.mol$^{-1}$): C, 51.82; H, 6.64; N, 4.65; found C, 51.60; H, 6.60; N, 4.58%.

**X-ray structure analysis:**

1. Structure of $C_9H_{11}FNO_3PS$

The title compound crystallizes in the monoclinic system, space group $P2_1/c$. The parameters of the unit cell are: a = 5.673(1) Å, b = 13.440(1) Å, c = 15.576(1) Å and ϐ = 91.38(3)° **(Table 7).** The structure is built up from $C_9H_{11}FNO_3PS$ molecules stabilized by N-H...O intermolecular hydrogen bonds **(Table 5)**. The cell contains Z = 4 formula groups. The dihedral angle S1 - C3 - N1 - H7 is 163(2)°. The atoms S1 and H7 deviate upon and under the plane formed by N1, C3 and P1 atoms (respectively 0.012(9) Å and -0.20(3) Å). Data collection is provided by Enraf-Nonius CAD-4 diffractometer using molybdenum Kŭradiation (A = 0.71073 Å).

The structure was solved by SHELXS-97 program[20] and refined by SHELXL-97 program[21]. The final reliability factors are $R_1$ = 0.0548 and $wR_2$ = 0.1626, these values correspond to 1757 reflections and 175 parameters (intensity I > 2 ů(I)). Molecular graphics are provided by the Diamond program[22].

The cif file is registered under CCDC 965890 number at Cambridge Crystallographic Data Center.

2. Structure of $C_{11}H_{16}NO_3PS$

The title compound crystallizes in the orthorhombic system, space group $P2_12_12_1$. The parameters of the unit cell are a = 7.611(1) Å, b = 9.135(1) Å, c = 20.186(1) Å **(Table 7).** The structure is built up from $C_{11}H_{16}NO_3PS$ molecules stabilized by N-H..O intermolecular hydrogen bonds **(Table 6).**The cell contains Z = 4 formula groups. The structure was solved by SHELXS-97 program [20]and refined by SHELXL-97 program[21]. The final reliability factors are $R_1$ = 0.0336 and $wR_2$ = 0.0909, these values correspond to 2657 reflections and 211 parameters (intensity I > 2 ů(I)). Molecular graphics are provided by Diamond program[22]. The cif file is registered under CCDC 1001884 number at Cambridge Crystallographic Data Center.

**Acknowledgment**

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**References and notes.**


1. Polshettiwar, V.; Kaushik, M. P.; *Tetrahedron Lett*. **2006**, 47, 2315ï 2317.
2. Siemeling, U.; Rother, D.; *J. Organomet. Chem*. **2009**, 694, 1055ï 1058.
3. Zabicky, J.; (dir.). The Chemistry of Amides, Interscience, John Wiley and Sons, New York, Londres. **1970**, 96.
4. Thanigaimalai, P.; Sharma, V. K.; Lee, K.; Yun, C. Y.; Kim, Y.; Jung, S. H.; *J. Bioorg Med. Chem. Lett*. **2010,** 20, 4771ï 4773.
5. Bose, D. S.; Idrees, M.; Todewale, I. K.; Jakka, N. M.; Venkateswara, R.; *Eur. J. Med. Chem*. **2012,** 50, 27-38.
6. Davies, C. D.; Elliotta, M. C.; Wood, J. L.; *Tetrahedron*. **2006,** 62, 11158ï 11164.
7. Bondock, S.; Shymaa, A.; Etman, H. A.; Badria, F. A.; *Eur. J. Med. Chem*. **2012**, 48, 192-199.
8. Trofimov, B. A.; Malõkina, A. G.; Borisova, A. P.; Nosyreva, V. V.; Shemyakina, O. A.; Kazheva, O. N.; Shilov.; G. V. Dyachenko, O. A.; *Tetrahedron Lett*. **2008**, 49, 3104ï 3107.
9. Dixon, S.; Whit, R. J.; *Tetrahedron Lett*. **2006**, 47, 8147ï 8150.
10. Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S.; *Tetrahedron Lett*. **2012**, 53, 7113-7116.
11. Zeev, T.; *J.Org.Chem*. **1982**, 47, 3012- 3015.
12. Babak, K.; Hazegh, Z.; *Heteroatom Chemistry*. **2009**, 20, 250-253.
13. Kolodyazhnaya, A. O.; Kolodyazhnaya, O. O.; Kolodyazhnyi, O. I.; *Russian Journal of General Chemistry* (English). **2010**, 80, 709ï 722.
14. Augustin, M.; Rudorf, W. D.; Schmidt. U, *Tetrahedron*. **1976**, 32, 3055-3061.

15. Karl Dieter, R.; *Tetrahedron*. **1986**, 42, 3029-3096.

16. Rudorf, W. D.; Schierhorn, A.; Augustin, M.; *Tetrahedron*. **1979**, 35, 551-556.

17. Rao, C. N. R.; Gurudath Rao, K.; Goel, A.; Balasubramanian, D.; *J. Chem. Soc. A. Inorg. Phys. Theor*. **1971**, 3077-3083.

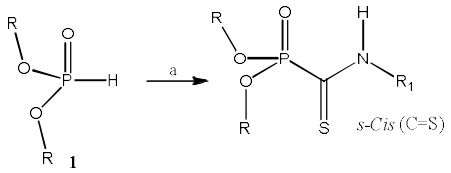
18. Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

19. SHELXS-97. G. M. Sheldrick. ActaCryst.1990, A46, 467.

20.SHELXL-97 - A program for crystal structure refinement. G. M. Sheldrick, University of Gî ttingen, Germany, 1997.

21. Diamond Version 2.1e, Klaus Brandenburg. Copyright © 1996-2001 Crystal Impact GbR.

**Table 1**: Approach to the synthesis of thioamides

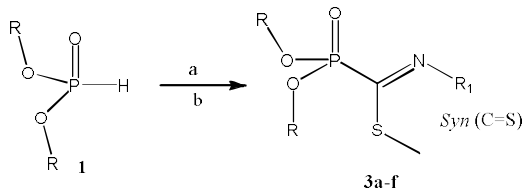



**2a-h**

| | R | $R_1$ |
|---|---|---|
| a | Me | Ph |
| b | Me | c-$C_6H_{11}$ |
| c | Me | Bn |
| D | Me | *p*-F-Ph |
| E | Me | *p*-Cl-Ph |
| F | Et | Ph |
| G | Et | c-$C_6H_{11}$ |
| H | Et | Bn |

**reaction conditions:** (a) t-BuOK / THF (dry) r.t, $R_1$-N=C=S, $H_2O/H^+$

**Table 2 :** Preparation of Phosphonothioamidates




| | R | $R_1$ |
|---|---|---|
| a | Me | Ph |
| b | Me | c-$C_6H_{11}$ |
| c | Me | Bn |
| d | Et | Ph |
| e | Et | c-$C_6H_{11}$ |
| f | Et | Bn |

**reaction conditions:** (a) t-BuOK / THF (dry) r.t, $R_1$-N=C=S; (b) MeI, $H_2O/H^+$

**Table 3: Distances (A°) and Angles (°) of the compound 2d**

| Compound | 2d |
|---|---|
| P1-C3 | 1.824(3) |
| P1=O3 | 1.453(2) |
| P1-O1 | 1.545(2) |
| P1-O2 | 1.565(2) |
| C3-N1 | 1.565(2) |
| C3=S1 | 1.652(3) |
| O3é H7 | 2.04 |
| N1 C3P1 | 113.1(2) |
| N1 C3 S1 | 127.4(2) |
| C3 N1 C4 | 126.4(2) |
| O3 P1 C3 | 110.75(12) |



**Table 4: Distances (A°) and Angles (°) of the compound 2f**

| Compound | 2f |
|---|---|
| P1-C5 | 1.821(2) |
| P1=O3 | 1.4616(16) |
| P1-O1<br>P1-O2 | 1.5606(17)<br>1.5648(16) |
| C5-N1 | 1.327(3) |
| C5=S1 | 1.648(2) |
| O3é H1 | 2.09 |
| N1 C5 P1 | 115.39(16) |
| N1 C5 S1 | 127.99(17) |
| C5 N1 C6 | 127.53(19) |
| O3 P1 C5 | 112.09(10) |

**Table 5:** Hydrogen bond of **2d**

| X-H..Y | H..O(Å) | N..O(Å) | N-H-O(°) |
|---|---|---|---|
| N1-H7..O3[i] | 2.04 | 2.789(3) | 159(2)° |

i: 2-x, 1-y,1-z

**Table 6:** Hydrogen bond of **2f**

| X-H..Y | H..O(Å) | N..O(Å) | N-H-O(°) |
|---|---|---|---|
| N1-H1..O3[i] | 2.09 | 2.819(3) | 152(2)° |

i: 2-x, 1/(2+y),1/(2-z)



**Tables 7: Crystal Structure and Data Refinement Parameters of $C_9H_{11}FNO_3PS$ and $C_{11}H_{16}NO_3PS$**

| **Compound** | **2d** | **2f** |
|---|---|---|
| Empirical Formula | $C_9H_{11}FNO_3PS$ | $C_{11}H_{16}NO_3PS$ |
| Formula Weight | 263.22 $g.mol^{-1}$ | 273.28 |
| Crystal System / Space Group | Monoclinic / $P2_1/c$ | Orthorhombic / $P2_12_12_1$ |
| a / Å | 5.673(1) | 7.611(1) |
| b / Å | 13.440(1) | 9.135(1) |
| c / Å | 15.576(1) | 20.186(1) |
| / ° | 90.00 | 90.00 |
| ϐ / ° | 91.38(1) | 90.00 |
| ɔ / ° | 90.00 | 90.00 |
| V / $Å^3$ | 1187.3(2) | 1403.7(2) |
| Z | 4 | 4 |
| $D_{calc}$ ($g/cm^3$) | 1.472 | 1.293 |
| ε ($mm^{-1}$) | 0.411 | 0.341 |
| Crystal size (mm) | 0.2 0.2 0.2 | 0.2 0.2 0.2 |
| Color / Shape | Yellow / Plate | Yellow / Plate |
| Temp (K) | 298(2) | 298(2) |

| | | |
|---|---|---|
| Theta range for collection | 2° - 26.98° | 2.02° ï 26.99° |
| Reflections collected | 3712 | 3062 |
| Independent reflections | 1757 | 2657 |
| Data/restraints/parameters | 3712/0/175 | 3062/0/211 |
| Goodness of fit on $F^2$ | 1.043 | 1.06 |
| Final R indices [I > 2ů(I)] | 0.0548 | 0.0336 |
| R indices (all data) | 0.0864 | 0.0425 |
| Largest difference peak/hole | 0.401 | 0.242 |



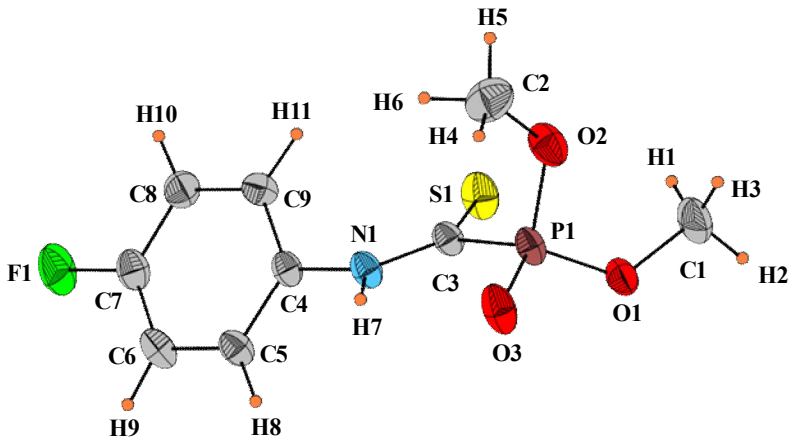



**Figure 1:** ORTEP representation of compound **2d.**

(Displacement ellipsoids with 30 % of probability)

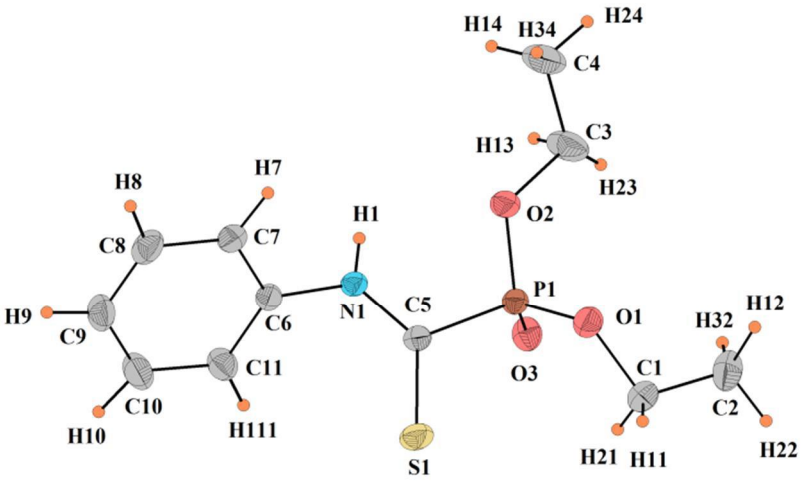
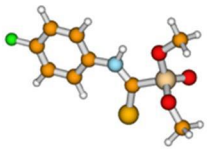



**Figure 2:** Molecular representation of **2f**.

(Displacement ellipsoïds are drawn at the 20% probability level)



*s-Cis***1**

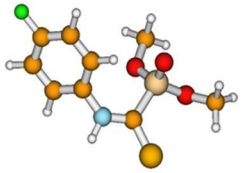
E= -1469.6814047 u.a

ϟG= 2 kcal/mol

*s-Cis* **2**

E= -1469.6845694 u.a

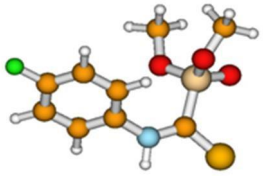
ϟG= 0kcal/mol



*s-Trans* **1**

E= -1469.6756842u.a

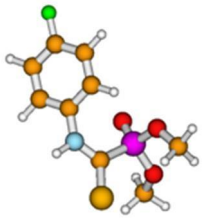
ϟG= 5.6 kcal/mol



*s-Trans***2**

E= -1469.6701853 u.a

ϟG= 9 kcal/mol

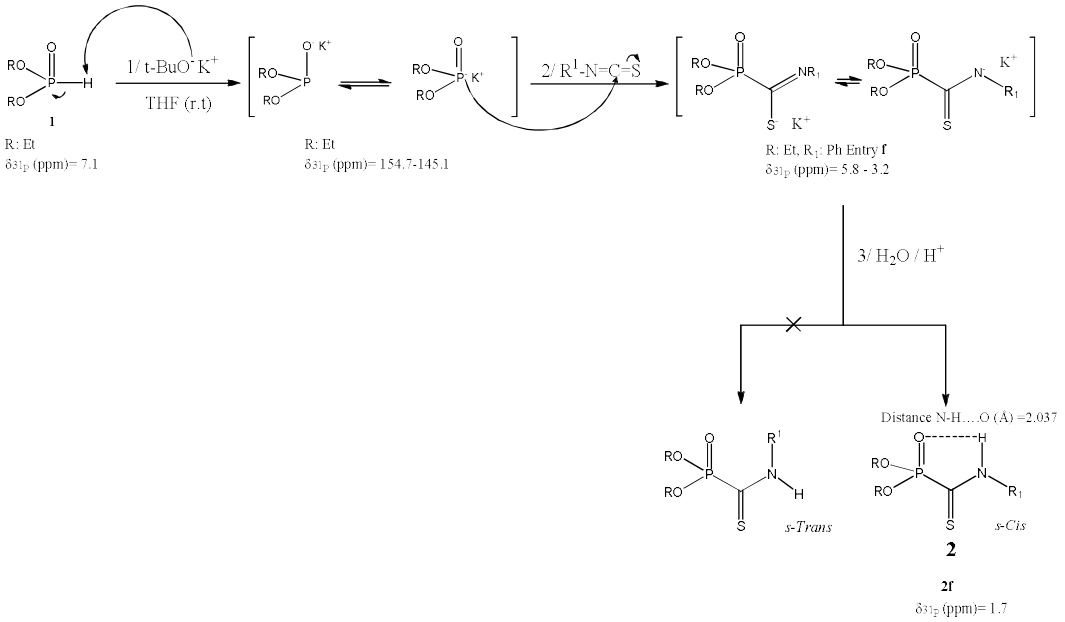


*s-Trans* **3**

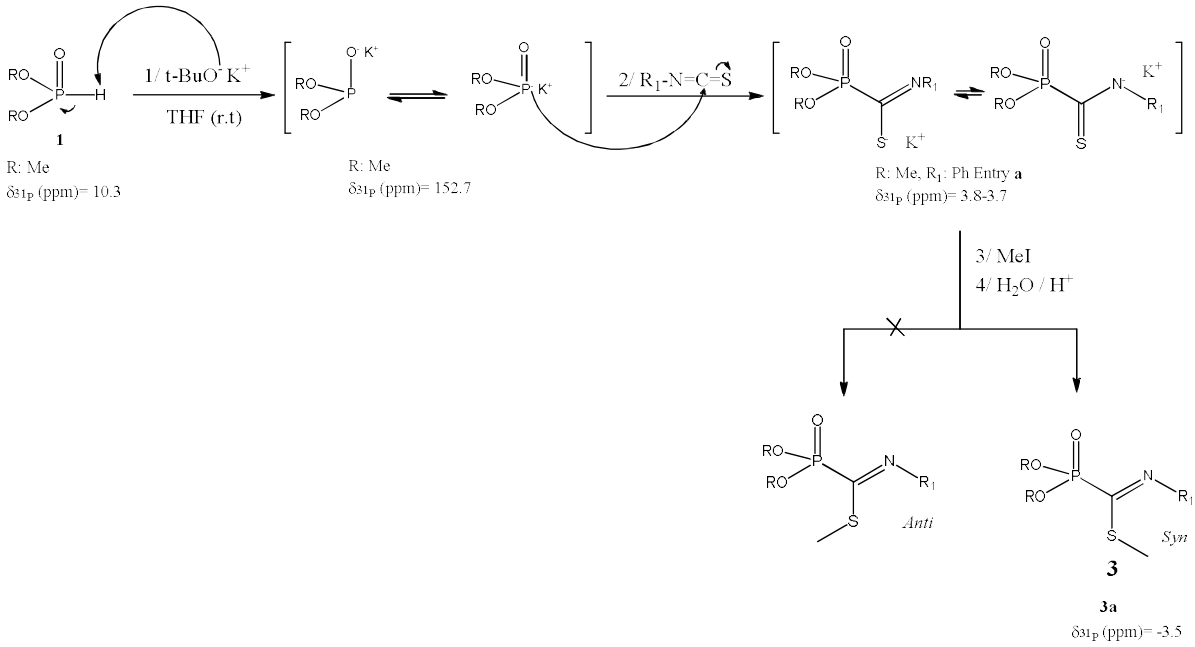
E= -1469.6725156 u.a

ϟG= 7.6 kcal/mol

**Figure 3:** DFT calculations of the compound **2d**




**Scheme 1:** Proposed mechanism of the reaction




**Scheme 2:** Proposed mechanism of the reactions