SYNTHESES, NMR CHARACTERIZATION AND SEMI-EMPIRICAL STRUCTURAL STUDIES OF DITHIAPHOSPHOLANE DERIVATIVES

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SYNTHESES, NMR CHARACTERIZATION AND SEMI-EMPIRICAL STRUCTURAL STUDIES OF DITHIAPHOSPHOLANE DERIVATIVES

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A new synthetic route for the preparation of 2-chloro-1,3,2-dithiaphospholane 1 is reported with a better yield than the previous one[11]. A one-pot preparation of S,S'-bis(1,3,2-dithia-phospholane)-1,2-ethanedithiol 2 is also described. These compounds were characterized using multinuclear NMR, mass and IR spectroscopies. Their ^{1}H NMR spectra were fully resolved by NMR spectra simulation. Semi-empirical structural studies suggest that compound 1 is found, at room temperature, as only one conformer whereas compound 2 can be found, at room temperature, as a mixture of conformers.

INTRODUCTION

The chemistry of 5-membered ring systems containing phosphorus is well established[1] and most of the reports deal with compounds containing phosphorus-oxygen bonds and those about ring systems containing phosphorus sulfur bonds are scarce. Their foremost applications are: use in the development of specific immunoassays for the detection of pesticides[2], polymerisation reactions[3],[4], syntheses of naturally occurring lipids[5],

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as a reagent to analyze labile hydrogen functional groups on coal materials[6] and on coordination chemistry[7]. Dithiaphospholane and its analogues can also be employed in a variety of organic reactions. It is generally accepted that displacement of the chlorine from the 2-chloro-1,3,2-dithiaphospholane **1** by a nucleophile is analogous to the S_N2 process at a saturated carbon[8]. In this way a variety of reactions of 2-chloro-1,3,2-dithiaphospholane **1** has been described. Compound **1** is known to react with alchools[9], thiols, carboxylic acids, phenols, amines[6]and, more recently, it has been reported to react with nucleoside to afford oligo(deoxyribunucleoside phosphorodithioate)[10]. Our main motivation on this work is the complexation studies, since to the best of our knowledge, only one report has appeared in the literature dealing with the complexation reactions of dithiaphospholane derivatives[7].

RESULTS AND DISCUSSION

• 2-chloro-1,3,2-dithiaphospholane-1

The synthesis of 2-chloro-1,3,2-dithiaphospholane **1** was first described by Denney and co-workers[11] and it consists of treatment of 1,2-ethanedithiol with PCl_3 in presence of triethylamine and ether as a solvent, but the reported yield was very low, *ca.* 31%. By contrast, **1** has been obtained from a one-pot reaction of 1,2-ethanedithiol with an excess of PCl_3, in a much higher yield (69%). The product was fully characterised by ^1H; ^{13}C, ^{31}P NMR, IR and mass spectroscopy.
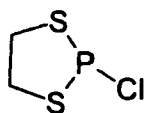
1

The $^{13}C\{^1H\}$ NMR spectrum of **1** consists of a doublet at δ 42.4 with a coupling constant $^2J_{CP} = 2.2$ Hz. A comparison with $^{13}C\{^1H\}$ NMR data obtained for 2-chloro-1,3,2-dioxaphospholane (δ 65.0; $^2J_{CP} = 8.7$ Hz)[12]
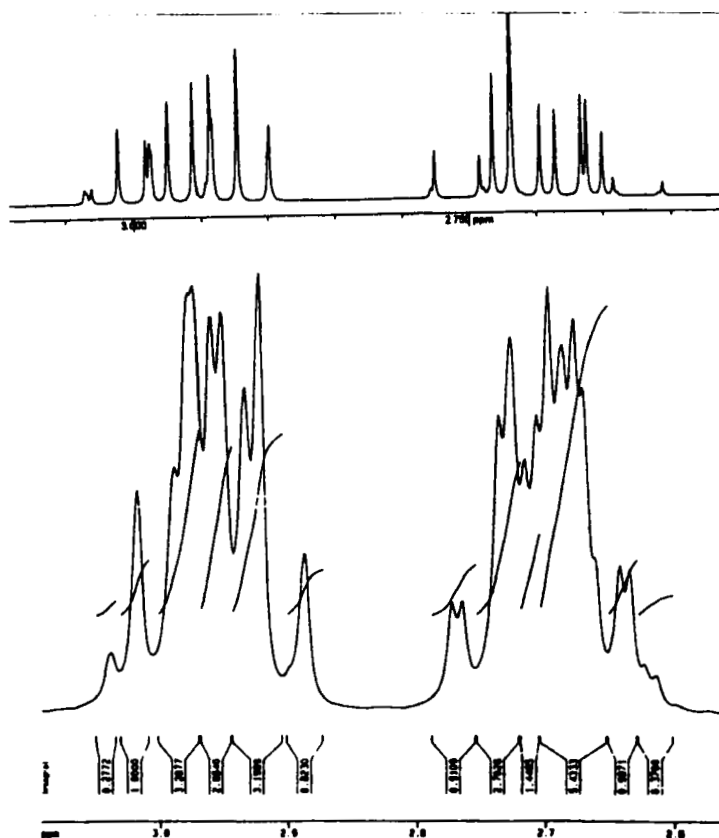
FIGURE 1 ^{1}H NMR spectrum of 1 calculated (top) observed (bottom) (200.3 MHz; toluene-d$_6$)

shows a shielding of the carbons when bonded to a less electronegative sulfur, as would be expected and due to the fact that the C-S bond has a length larger than the C-O bond causing the C-P coupling constant being smaller. The ^{31}P{^{1}H} NMR spectrum of 1, in a toluene solution, shows a singlet at δ 169.4 which agrees with the results found before (δ 170.7 in a benzene solution[11],[13] and δ 179.2 as a neat sample[9]) and is very similar to the one found for 2-chloro-1,3,2-dioxaphospholane (δ 167.5)[12]. Two multiplets, δ2.9 – δ3.0 and δ2.6 – δ2.8, are observed on the ^{1}H NMR

spectrum of 1 and it was simulated as an [AA'BB'X] spin system (Fig. 1). The calculated coupling constants are shown in Table I.

TABLE I Calculated ^{1}H NMR data for compound 1

	1
δ_A	2.962
$\delta_{A'}$	2.960
δ_B	2.698
$\delta_{B'}$	2.694
$^2J_{AB} = {}^2J_{A'B'}$	−5.35 Hz
$^3J_{A'B}$	17.47 Hz
$^3J_{AB'}$	8.86 Hz
$^3J_{AA'} = {}^3J_{BB'}$	9.20 Hz
$^3J_{AX} = {}^3J_{A'X} = {}^3J_{BX} = {}^3J_{B'X}$	0.0 Hz

A PM3 semi-empirical geometric optimization of 1 was carried out employing the SPARTAN™, followed by a conformational search (employing both Systematic and Osawa methods), with and without dihedral angles restrain and, in either study, only one conformation was found, fig. 2 (Heat of Formation: − 25.6 kcal/mol; Dipole moment: $\times = -0.4$ Y = 0.6 Z = 3.1; Total Dipole: 3.2 D; Translational Entropy: 41.0 cal/mol K; Rotational Entropy: 29.121 cal/mol K; Vibrational Entropy: 18.0 cal/mol K; Total Entropy: 88.2 cal/mol K). The charges are listed in Table II and the dihedral angles are shown in Table III.

In a previous work[14], Albrand and colls. propose two possible conformations for the Cl of 1,3,2-diathiaphospolanes: an envelope with either the phosphorus or one of the sulfurs on the flap position or a half-chair with a C_2 axes passing trough the phosphorus and the middle of the C-C bond. Later on, Gonbeau and co-workers[15] carried out MNDO calculations and found that the half-chair would be the preferential conformer. However, our PM3 calculations point to an envelope conformer with a Cl-cis carbon flap tending to a half-chair (the dihedral angle between the C(5) and the plane S(6)-P(2)-S(8) is almost zero, − 2.8 degrees, and the dihedral angle between the C(4) and the plane C(5)-S(6)-P(2) is around 23 degrees), see Fig. 2. The simulated and the actual ^{1}H NMR spectra show the presence of four different hydrogens, where the coupling constants between the H(A)-H(B') and the H(A')-H(B) differ considerably. Therefore, they do not agree with a half-chair structure where one expects only two different
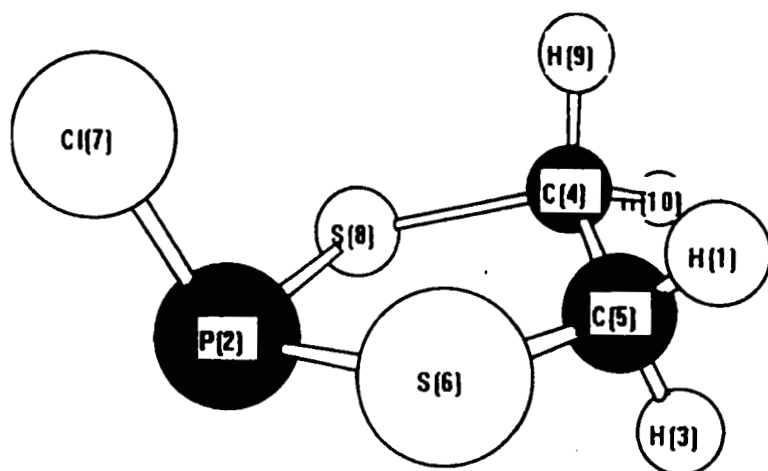
FIGURE 2 PM3 semi-empirical geometric optimization of 1

sets of hydrogens (a pair of double doublets) but is in accordance with the spectrum of a envelope conformer with a C flap.

TABLE II Calculated charges for compound 1

Atom	H 1	P2	H3	C4	C5	S6	Cl7	S8	H9	H 10
Charge/ (eV)	−0.04	0.04	−0.04	0.45	0.26	−0.34	−0.20	−0.38	−0 03	−0.03

TABLE III Calculated dihedral angle for 1

	Dihedral angle
H1-C5-C4-H9	−32.9°
H1-C5-C4-H10	84.2°
H3-C5-C4-H9	−150.3°
H3-C5-C4-H10	−33.1
H1-C5-S6-P2	145.5°
H3-C5-S6-P2	−100.9°
H9-C4-S8-P2	−93.9°
H10-C4-S8-P2	152.3°
S6-C5-C4-S8	−36.6°

• S,S'-bis(1,3,2-dithiaphospholane)-1,2-ethanedithiol – 2

Compound **2** had been obtained before by treatment of 2-(dimethyl-amine)-1,3,2-dithiaphospholane with 1,2-ethanedithiol in a very low yield (31%)[16]. Herein its synthesis was carried out in two different ways: (i) treatment of neat PCl_3 with neat 1,2-ethanedithiol on the proportion of 2:3, at ice temperature or (ii) by reaction of **1** with 1,2-ethanedithiolate in THF.
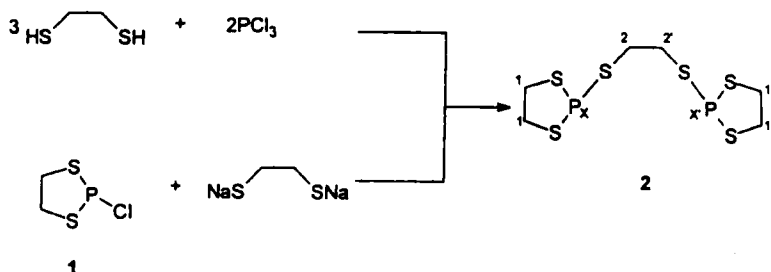
Both routes are considered better than the one described before, since it has the advantage to produce **2** with a better yield (97%) and the first is one-pot reaction without any side-products being formed. A third route has also been experimented: treatment of **1** with 1,2-ethanedithiol and sodium in THF, but that one can be considered as a variant of the second method, with a very low yield. The white solid product obtained is insoluble in the most common organic solvents and very soluble in carbon disulfide. Its $^{31}P\{^1H\}$ NMR spectrum in solid state shows a singlet at δ 99.5 whereas on a CS_2 solution a singlet at δ 112.3 is observed. Its chemical shift is in agreement with the one found before by Burgada and co-workers[16] and fits well with the studies carried out by Verkade[6]. They have shown that the products from the reaction of 2-chloro-1,3,2-dithiaphospholane **1** with a series of thiols have chemical shifts characteristically varying from δ 102 to δ 113. A triplet at δ 112.3, with a $^3J_{PH} = 9.5$ Hz is observed on its ^{31}P NMR spectrum, as a result from the coupling of phosphorus to the hydrogen nuclei of the bridging 1,2-ethanedithiol. The $^{13}C\{^1H\}$ NMR spectrum of **2** (Fig. 3) consists of an [A₄BB'XX'] spin system with a singlet at δ 40.5 corresponding to the four carbons at the phosphorus rings (C¹) and a doublet of doublets at δ 35.2 corresponding to the carbons nuclei on the

1,2-ethanedithiol bridge (C^2 and $C^{2'}$). The coupling constants obtained from the simulated spectrum (Fig. 3) are shown in Table IV.
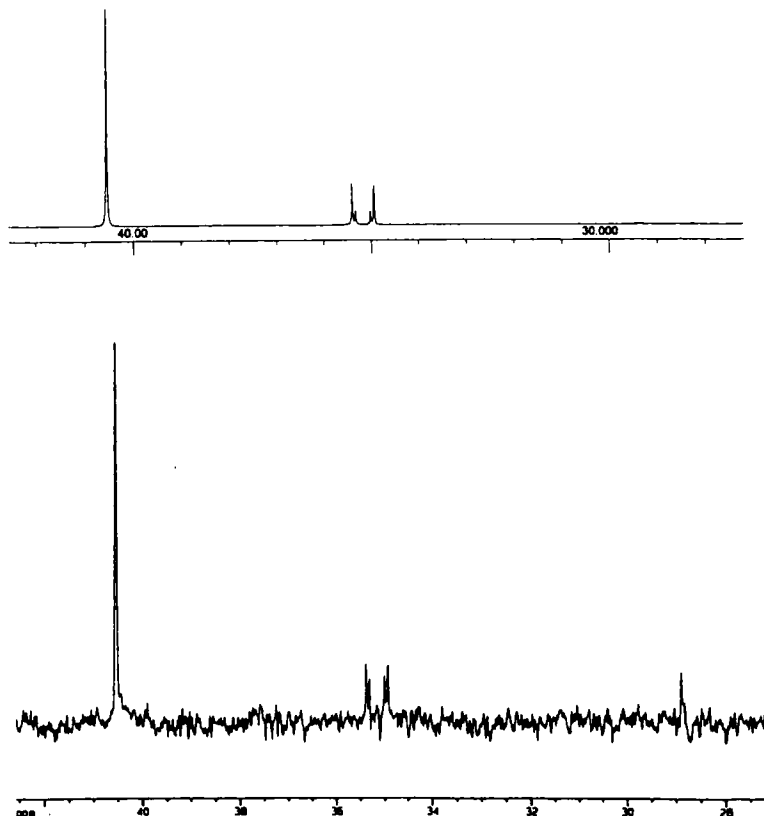
FIGURE 3 $^{13}C\{^1H\}$ NMR spectrum of **2** calculated (top) and observed (bottom) (50.33 MHZ; CS_2/CDCl$_3$ solution)

TABLE IV Calculated $^{13}C\{^1H\}$ NMR data for compound **2**

δ_1	$\delta_2=\delta_{2'}$	$^2J_{2X}$	$^2J_{2'X'}$	$^3J_{2X'}$	$^3J_{2'X}$
40.53	35.18	23.14	−19.24	0.0	3.90

Two multiplets ($\delta3.26 - \delta3.54$ and $\delta2.96 - \delta3.02$) are observed in the ^1H NMR spectrum of **2** (Fig. 4). On the basis of its HMQC NMR studies, the

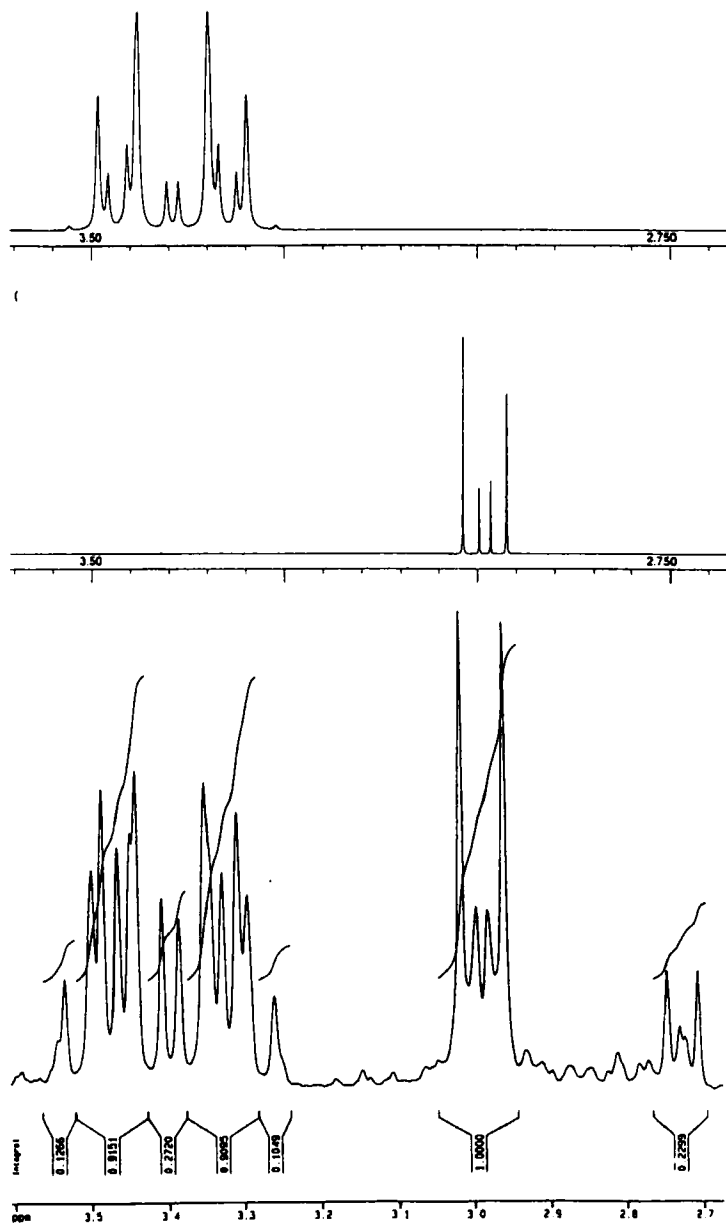FIGURE 4 ^{1}H NMR spectra of 2 calculated (top) and observed (bottom) (200.3 MHz; CS$_2$/CDCl$_3$) solution)

first multiplet can be assigned to the hydrogen nuclei from the phosphorus ring units whereas the latter can be attributed to the hydrogen nuclei from the 1,2-ethanedithiol bridge. The ^{1}H NMR spectrum of 2 also suggests the presence of two conformers since a multiplet, similar to the one found between $\delta 2.96$ and $\delta 3.02$, is observed between $\delta 2.71$ and $\delta 2.75$. A simulation of its ^{1}H NMR spectrum (Fig. 4) reveals that it can be understood as superimposition of two sub-spectra corresponding to a [AA′BB′XX′]$_2$+[AA′BB′XX′] spin system and the calculated coupling constants are shown in Table V.

TABLE V Calculated ^{1}H NMR data for compound 2

	Ring	Bridge
$\delta_A = \delta_{A'}$	3.461	2.991
$\delta_B = \delta_{B'}$	3.329	2.991
$^3J_{AA'}$	6.01	0.00
$^3J_{BB'}$	5.29	0.00
$^2J_{AB} = {}^2J_{A'B'}$	−10.33	0.00
$^3J_{AB} = {}^3J_{AB'}$	−0.11	0.00
$^3J_{AX} = {}^3J_{BX}$	0.00	11.06
$^4J_{AX'} = {}^4J_{BX'}$	0.00	0.00
$^4J_{AX} = {}^4J_{BX}$	0.00	4.14
$^3J_{A'X'} = {}^3J_{B'X'}$	0.00	−6.92

2
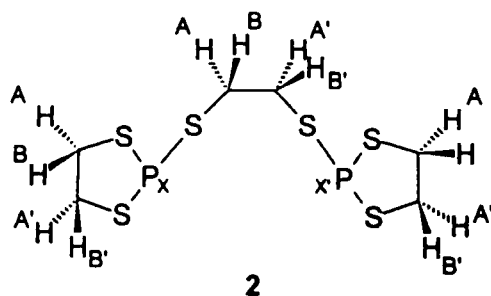
A PM3 semi-empirical study was also carried out for **2** followed by a conformational search employing the Systematic and the Osawa methodology and eighteen possible conformers were found. However, they were distributed in three groups according to the dihedral angle between the acyclic sulfurs. Six of the conformers had a −77° or a 118° angle between the acyclic sulfurs, meaning a gauche conformation, for eleven of them a 180° angle was determined, meaning an anti conformation, and only one showed a 0° dihedral angle between the hydrogen atoms, though it also showed a 118° angle between the sulfurs (Table VI). The lowest energetic conformers showed a gauche conformation (Fig. 5), with their calculated Heat of Formation spreading from −10.9 to −8.9 kcal/mol. The anti conformers had their Heat of Formation around −3.2 kcal/mol and for the most energetic one a + 4.4 kcal/mol Heat of Formation was calculated. Those observations imply that the dihedral angle between the hydrogens, of the central ethyl group, is the determining factor of the conformational equilibrium. Moreover, it means that the rotation of cyclic groups around the P-S bond is almost free. Calculated data for compound **2** are shown in Table VI and VII.

TABLE VI Angles and heat of formation for the conformers of 2

	Angle	*degrees*	*Heat of Formation/(Kcal/mol)*
gauche ~ 60°	H(13)-C(11)-C(12)-H(17)	−76	−10.9 to −8.9
	H(14)-C(11)-C(12)-H(17)	40	
	H(13)-C(11)-C(12)-H(15)	168	
	S(7)-C(11)-C(12)-S(16)	−77	
anti	H(13)-C(11)-C(12)-H(17)	177	~ −3.2
	H(14)-C(11)-C(12)-H(17)	−66	
	H(13)-C(11)-C(12)-H(15)	58.3	
	S(7)-C(11)-C(12)-S(16)	180	
gauche ~120°	H(13)-C(11)-C(12)-H(17)	117	+ 4.2
	H(14)-C(11)-C(12)-H(17)	−125	
	H(13)-C(11)-C(12)-H(15)	−0.4	
	S(7)-C(11)-C(12)-S(16)	119	

TABLE VII Calculated charges for compound 2

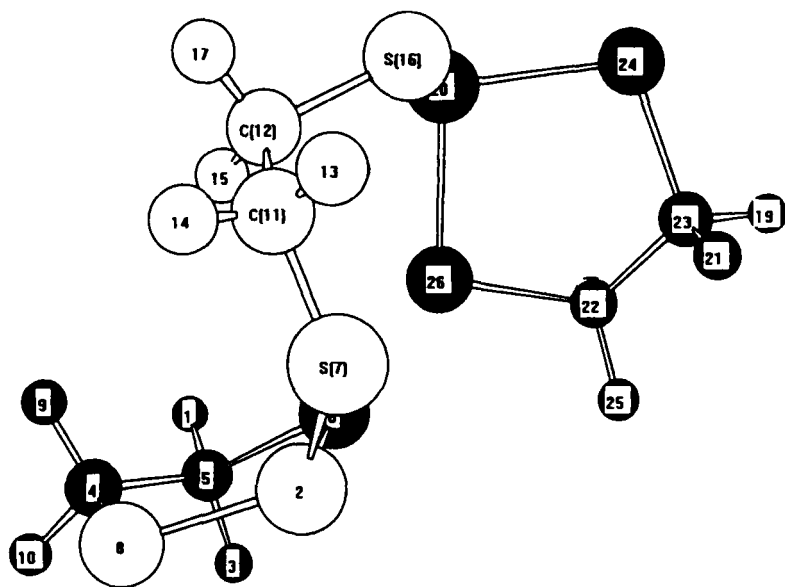| Atom	Charge/ (eV)	Atom	Charge/ (eV)	Atom	Charge/ (eV)
P 2	0.21	P20	0.10	C 11	0.84
C 4	0.38	C 22	0.07	H 13	−0.20
S 6	−0.07	S 24	−0.30	H 15	0.14
S 8	−0.36	S 26	−0.12	H 17	−0.06
H 10	−0.02	H 1	0.03	H 19	−0.05
C 12	0.02	H 3	0.05	H 21	−0.04
H 14	−0.14	C 5	−0.09	C 23	0.41
S 16	−0.25	S 7	−0.47	H 25	−0.01
H 18	−0 01	H 9	−0.05		

FIGURE 5 PM3 semi-empirical geometric optimization of 2

CONCLUSION

Dithiaphospholane is a very important class of compounds with application in several areas and a facile method to obtain these compounds is even more important. We do believe that these methods herein described are going to help those working with dithiaphospholane derivatives since they are much more simple than the previous one reported, and all of them have shown improvements in terms of yield.

EXPERIMENTAL

All reactions were carried out either under dry dinitrogen in Schlenk tubes or by use of high-vacuum techniques. Glassware was flame-dried in vacuum, and solvents were dried, freshly distilled under dinitrogen, and degassed prior to use. The ^{31}P NMR spectra were recorded on Bruker DRX400 spectrometer whereas the ^{13}C and ^{1}H NMR spectra were recorded on Bruker DRX200. Chemical shift data were recorded at ambient temperatures and are quoted in δ units, with positive values to low field of the indicated reference (85% H_3PO_4 solution; solvent and TMS, respectively) and corrected with respect to the appropriate deuterium frequency. Coupling constants are quoted in Hertz. NMR simulations were carried out using the program gNMR v.3.6 from Cherwell Scientific Publishing. Infra-red spectra were recorded on a Perkin Elmer Paragon 500 FT-IR spectrometer and the attributions were based on semi-empirical PM3 frequency calculation. Elemental analysis was obtained on a Perkin Elmer 2400 CHN. The GC/MS was recorded on a HP 5890 Series II/HP5989A spectrometer.

Preparation of 2-chloro-1,3,2-dithiaphospholane 1

1,2-Ethanedithiol (20g; 0.21mol) was added to PCl_3 (86.6g; 0.63mol) at room temperature. The mixture was stirred for 3h and then the excess of PCl_3 was distilled to yield the title product as an uncolored liquid. (23,3g; 69%)

^{31}P{^{1}H} NMR data (161.98 MHz; toluene-d$_8$): δ 169.4 (s); ^{1}H NMR data (200.3 MHz; toluene-d$_8$): δ 3.04 − 2.89 (m; 2H; CH$_2$); δ 2.77 − 2.61

(m; 2H; CH_2); $^{13}C\{^1H\}$ NMR data (50.33 MHz; toluene-d_8): δ 42.4 (d) $^2J_{CP}$=2.2 Hz; Mass spectrum (EI, 70eV; m/z): 158 [M]$^+$; 130 [PS$_2$Cl]$^+$; 123 [C$_2$H$_4$S$_2$P]$^+$; 95 [C$_2$H$_4$P]$^+$; 63 [S$_2$]$^+$; IR(NaCl support; cm^{-1}): 645 (ν_{sC-S}); 663 (ν_{asC-S}); 683 (δ_{C-S}twisting); 828 (δ_{CH} twisting); 937 (δ_{CH} wagging); (ν_{C-C}); 1187; 1230; 1275; 1412 (δ_{CH} scissoring); 2912 (ν_{C-H}).

Preparation of S,S'-bis-(1, 3, 2-dithiaphospholane)1,2-ethanedithiol 2

METHOD A

PCl$_3$ (6.3g; 0.04mol) was added to 1,2-Ethanedithiol (5.6g; 0.06mol) at ice temperature. The mixture was stirred for 1h and a white solid was obtained (6.53g; 97%).

METHOD B

To a THF solution of NaSCH$_2$CH$_2$SNa (0.4g; 0.003mol) was added a solution of 1 (1g; 0.006mol), also in THF. The mixture was stirred for 10h at room temperature. After this time the white solid obtained was filtered and washed with water (1.49g; 70%).

C$_6$H$_{12}$S$_6$P$_2$ requires C: 21.3%; H: 3.5% found C: 20.9%; H: 3.2%; $^{31}P\{^1H\}$ NMR data (161.98 MHz; CS$_2$/CDCl$_3$): δ 112 (s); ^{31}P NMR data (161.98 MHz; CS$_2$/CDCl$_3$): δ 112 (t) $^3J_{PH}$ = 9.55Hz; $^{31}P\{^1H\}$ NMR data (161.98 MHz; solid): δ 99 (s); ^1H NMR data (200.3 MHz; CS$_2$/CDCl$_3$): δ 3.39 (m; 8H; 4CH$_{2(cyclic)}$); δ 2.99 (m; 4H; 2CH$_{2(acyclic)}$); $^{13}C\{^1H\}$ NMR data (50.33 MHz; CS$_2$/CDCl$_3$): δ 40.53 (s; 4CH$_2$; C^1) δ 35.18 (m; 2CH$_2$; C^2); IR(CsI disc; cm^{-1}): 439; 460; 465; 469; 473; 481; 488 (ν_{sP-S}: ν_{asP-S} and δ_{P-S}) 642; 669; 685; 726 (ν_{sC-S}; ν_{asC-S} and δ_{C-S}); 818 (δ_{CH} twisting); 937; 984 (δ_{CH} scissoring); 1194 (ν_{C-C}); 233; 1274 (δ_{HCH} scissoring); 1400; 1422 (δ_{C-C} twisting); 2817; 2918; 2957; 2967 (ν_{C-H}).

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