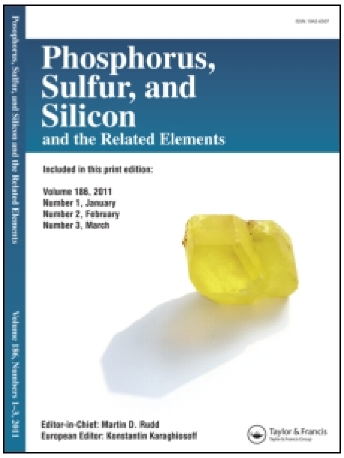

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Heuzé, B. , Lemarié, M. , Vazeux, M. , Gulea, M. , Masson, S. , Sene, A. , Jaffrès, P. A. , Alberti, A. and Macciantelli, D.(2009) 'Synthesis of Methylene Bisphosphonates from Carbon Disulfide and Phosphites via Desulfurization: A Mechanistic Study', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 4, 820 — 829
To link to this Article: DOI: 10.1080/10426500802715528
URL: http://dx.doi.org/10.1080/10426500802715528

Phosphorus, Sulfur, and Silicon, 184:820–829, 2009
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802715528

Synthesis of Methylene Bisphosphonates from Carbon Disulfide and Phosphites via Desulfurization: A Mechanistic Study

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The reaction of carbon disulfide with an excess of sodium dialkylphosphite in an aprotic solvent led to the formation of the carbanion of methylene bisphosphonate and sodium thiophosphate. The mechanistic study of this unexpected reaction, using both ^{31}P *NMR and ESR spectroscopy, suggests the formation of a radical intermediate able to abstract a hydrogen atom from the solvent.*

Keywords Dialkylphosphite; desulfurization; methylene bisphosphonate; phosphonodithioformate; thiocarbonyl radical

INTRODUCTION

Several studies dealing with the reaction of a dialkylphosphite anion with carbon disulfide have been reported in the literature. In each case, depending on the experimental protocol, different products are formed (Scheme 1). In one study, the addition of sodium dialkylphosphite to an excess of carbon disulfide (5 equiv) in tetrahydrofuran (THF) at

Received 18 December 2007; accepted 5 February 2008.

Dedicated to Professor Marian Mikołajczyk from the CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

Authors thank the "Ministère de la Recherche et des Nouvelles Technologies", CNRS (Centre National de la Recherche Scientifique), the "Région Basse-Normandie," and the European Union (FEDER funding) for financial support.

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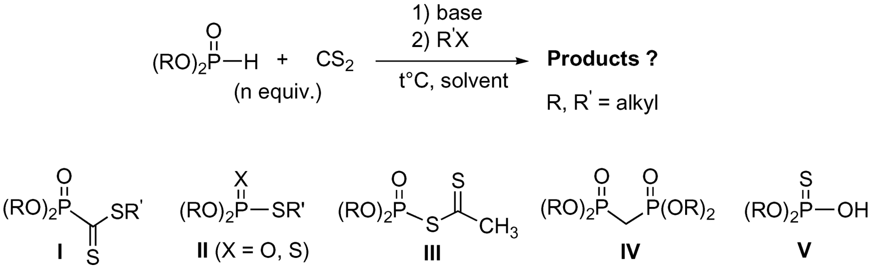
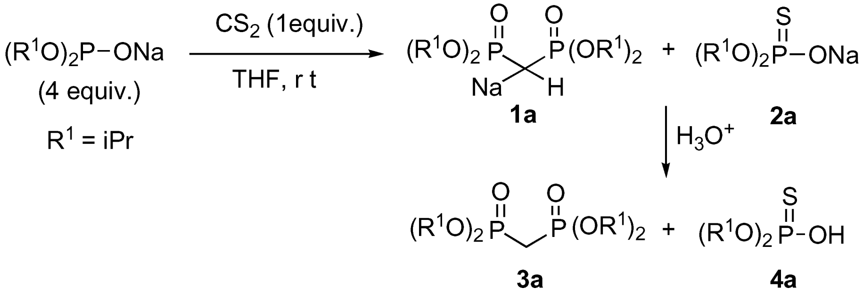


SCHEME 1

temperatures below 5°C, followed by *S*-alkylation of the sodium phosphonodithioformate intermediate, leads to the corresponding phosphonodithioesters **I** in good yield.[1] In a second study, equimolar amounts of the same reagents in diethyl ether at 20°C are used giving a rise to alkyl O,O'-dialkyl phosphorothioate **II** ($X = O$) after the *S*-alkylation step.[2] It has also been reported that the same reaction involving sodium dialkylthiophosphite (instead of sodium dialkylphosphite), carried out in ethanol at 2–8°C, leads to sodium thiophosphono-dithioformate in a poor yield together with a noncharacterized mixture of products. According to the authors, when the reaction is performed at 50°C, the only characterized product, after alkylation, is an alkyl O,O'-dialkyldithiophosphorothioate **II** ($X = S$).[3] Another study, devoted to the influence of temperature on the course of the reaction, reports a thermal rearrangement of the sodium phosphonodithioformate at 70–100°C, leading after methylation to phosphoryl ethanedithioate **III**.[4] More recently, it has been shown that an excess of carbon disulfide is not necessary to obtain phosphonodithioformates in good yield when the reaction is performed at 23°C by using cesium carbonate as a base in N,N-dimethylformamide (DMF) and in the presence of tetrabutylammonium iodide.[5] In our presently discussed experiments, carbon disulfide is added to an excess of sodium dialkylphosphite in an aprotic solvent at room temperature, leading to tetralkyl methylene bisphosphonate **IV** and dialkyl thionophosphoric acid **V**. This surprising result, which implies a desulfurization of carbon disulfide, prompted us to examine the mechanism of this transformation.

RESULTS AND DISCUSSION

Sodium diisopropylphosphite was prepared by the reaction of sodium hydride with diisopropylphosphite at 0°C in dry THF. Carbon disulfide (0.25 equiv) was then added at room temperature (Scheme 2). The



SCHEME 2

reaction, monitored by ^{31}P NMR, showed after 3 hours the disappearance of the signal at $\delta = 151$ ppm of the sodium diisopropylphosphite, while two new signals ($\delta = 40.5$ and 57 ppm) appeared. Weak signals in the range between –3 and 6 ppm were also detected, indicating the presence of minor non-identified byproducts containing phosphorus atom. After protonation, the two strong signals were detected at 17.4 and 60.6 ppm. The two corresponding products were separated (utilizing the difference in solubility in water and in an organic solvent), then purified and characterized as tetraisopropyl methylene bisphosphonate **3a** (52% yield) and diisopropyl thionophosphoric acid **4a** (53% yield). Therefore, the signals observed before protonation were easily attributed to the corresponding sodium salts **1a** (40.5 ppm) and **2a** (57 ppm), respectively. The formation of the carbanion **1a** was also confirmed by the addition of isobutanal to the mixture of **1a** and **2a**, which afforded the expected vinylphosphonate[7] in 45% yield via the Horner–Wadsworth–Emmons reaction.[6]

Then, a series of experiments were carried out using two different solvents, THF and cyclohexane (C_6H_{12}), and various phosphites ($R^1 = i$Pr, Et, Ph, Me). In all cases, the anions **1** and **2**, as well as the products **3** and **4**, obtained after protonation, were observed by ^{31}P NMR spectroscopy. ^{31}P NMR chemical shifts of all species involved in the reaction are given in Table I. Products **3a–d** and **4a–d** were isolated and characterized; yields are given in Table II.

To determine the exact stoichiometry of the reaction, we prepared mixtures of salts **1a** and **2a** of known concentration, and we established a correlation between their ratio and their integration by using the ^{31}P NMR spectroscopy. From this calibration, it was determined that two moles of the thiophosphate **2** per one mole of the metallated methylene bisphosphonate **1** were formed in this reaction. Therefore, 4 equiv of sodium dialkylphosphite for 1 equiv of carbon disulfide were needed to complete the reaction.

TABLE I ^{31}P NMR Chemical Shifts (δ, ppm) of the Species Involved in the Reaction of CS_2 with an Excess of Phosphite

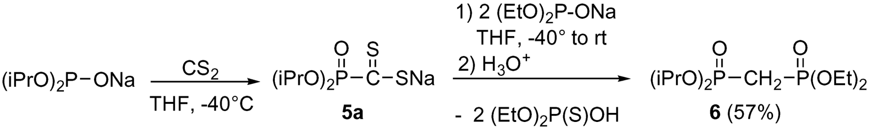
R^1	*i*Pr	Et	Ph	Me	Solvent
$(R^1O)_2P(O)H$	2.9	6	1.9	9.1	THF, $CDCl_3$
$(R^1O)_2P\text{-}ONa$	151	150.7	148.2	153.8	THF, C_6D_6
$(R^1O)_2P(O)\text{-}CHNaP(O)(OR^1)_2$	40.5	41.7	32.6	44.6	THF, C_6D_6
$(R^1O)_2P(O)\text{-}CH_2\text{-}P(O)(OR^1)_2$	17.4	19.1	10.6	21.3	THF, $CDCl_3$
$(R^1O)_2P(S)\text{-}ONa$	56.7	58.8	49.6	62.2	THF, C_6D_6
$(R^1O)_2P(S)\text{-}OH$	60.6	61	46.2	46.2	THF, $CDCl_3$

The formation of **1** showed that an excess of dialkylphosphite caused a complete desulfurization of the carbon disulfide. Because we used an aprotic and completely anhydrous solvent, the origin of the hydrogen atom, unexpectedly found on the central carbon atom in **1**, appeared to be a major problem in the explanation of a mechanism for this reaction. However, based on the results obtained so far, it was already possible to rule out some hypothesis. As the reaction proceeded also in cyclohexane, i.e., in a solvent without any acidic proton, the possibility of a basic deprotonation of the solvent could be ruled out. A deprotonation at the carbon atom α to the oxygen of the phosphoryl alkoxy group could also be excluded because the reaction also proceeded with diphenylphosphite. An excess of NaH, which could be captured by a carbenoid species, could also be excluded because the reaction carried out with NaD did not show any incorporation of deuterium in the methylene bisphosphonate. Finally, according to the literature,[9] we could not consider the already observed secondary reaction between dialkylphosphite and its sodium salt, leading to$(R^1O)P(H)O_2Na$ as a potential source of proton. Therefore, the possible mechanism was examined step by step. As expected, the first reaction was a carbophilic addition of the sodium dialkylphosphite (R = *i*Pr) to carbon disulfide

TABLE II Yields of Isolated Compounds 3 and 4

R^1	Solvent	Product 3 (yield,%)	Product 4 (yield,%)
*i*Pr	THF	**3a** (52)	**4a** (53)
*i*Pr	C_6H_{12}	**3a** (51)	**4a** (42)
Et	C_6H_{12}	**3b** (53)	**4b** (20)
Ph	THF	**3c** (40)	**4c**[a]
Me	THF	**3d**[a]	**4d**[a]

[a] Not isolated.



SCHEME 3

leading to the sodium phosphonodithioformate **5a** (Scheme 3). The formation of this intermediate was indeed observed when the reaction was monitored by ^{31}P NMR at –40°C (δ = –5 ppm). The reaction did not go further at this temperature, and this demonstrated the possibility to carry out the synthesis of alkyl phosphonodithioformates without an excess of carbon disulfide at low temperature. One application of these reaction conditions should be the possibility of preparing mixed methylene bisphosphonates by the reaction of carbon disulfide with two different dialkylphosphites. Indeed, this was achieved by the addition of one equivalent of sodium diisopropylphosphite to carbon disulfide at –40°C followed by the addition of 3 equiv of sodium diethylphosphite. The reaction was allowed to occur at room temperature and after protonation, the mixed diisopropyl-diethyl methylene bisphosphonate **6** was isolated in 57% yield (Scheme 3).

As the second step, a thiophilic or carbophilic addition of another equivalent of sodium diisopropylphosphite to **5a** could be proposed, leading to the postulated intermediates **i1** or **i2** (S to C migration of the phosphono group is known to occur easily,[10] Scheme 4). Elimination of Na_2S from **i2** would not be in accordance with the stoichiometry of the reaction, which generated **2** equiv of dialkyl thionophosphoric acid **4** per one equivalent of methylene bisphosphonate **3**. Besides, since we operated in aprotic and dry solvent, the main problem to rationalize the formation of the mono metallated methylene bisphosphonate could be resumed by the following question: "Where did the hydrogen atom come from?" In order to determine if a radical intermediate could be involved in this process, the reaction was carried out in the cavity of an ESR spectrometer. A very weak and short living signal was detected as a doublet, 28 G, $g = 2.01187$. Such a coupling has already been observed for phosphonodithioformate radical adducts,[11] but in the present case, the g factor was larger. Then, the same experiment was carried out in the presence of a small amount of ^{t}BuNO as a radical scavenger. A 1:1:1 triplet (Figure 1), typical for a nitroxide radical was detected ($a_N = 12.41$ G, $g = 2.00633$). The absence of coupling with phosphorus excluded the possibility of a phosphononitroxide radical formation.

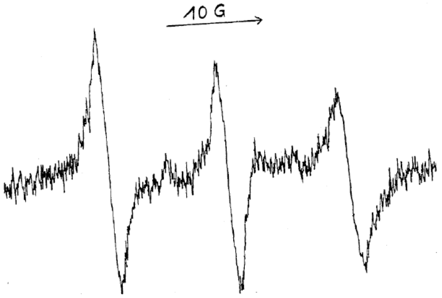
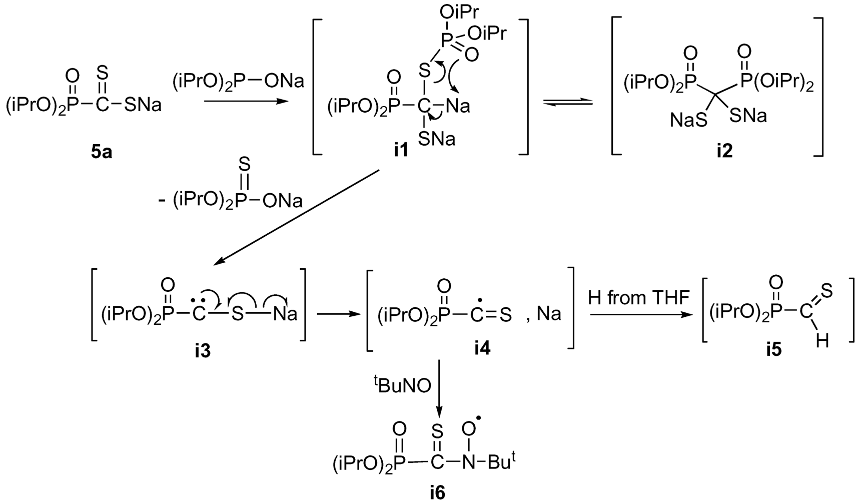


FIGURE 1 ESR signal observed when reacting an excess of $(EtO)_2P(O)Na$ with CS_2, in the presence of ^tBuNO.

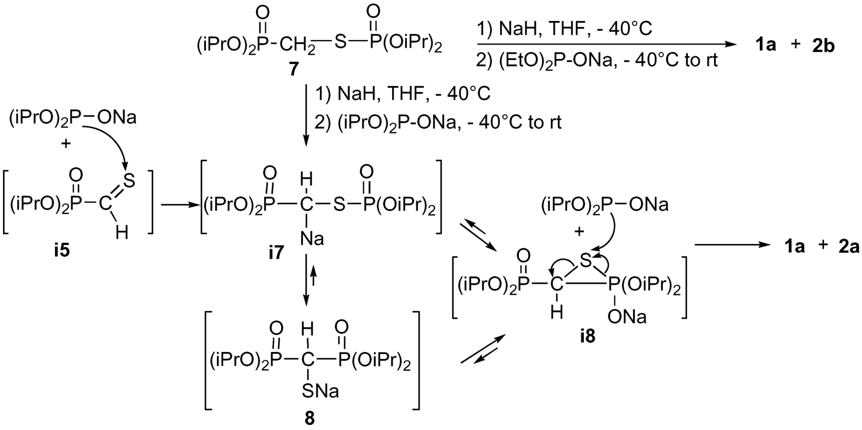
The relatively small nitrogen coupling constant would be more consistent with a nitroxide linked to an electron-withdrawing group as it would be the case in a phosphonothioacylated nitroxide such as **i6** (Scheme 4). The stabilized radical species **i6** would come from the trapping of the phosphonothiocarbonyl radical **i4**.[12] If this is true, rationalization of the formation of **i4** is again not evident. The first step could be the elimination of one equivalent of sodium thiophosphate with formation of the carbene-thiolate **i3**, which would then generate the phosphonothiocarbonyl radical **i4** and sodium metal. Then, **i4** could capture one hydrogen atom from the solvent (THF or C_6H_{12}) to afford the phosphonothioformaldehyde **i5**, which is an unknown and probably



SCHEME 4

very unstable species. Such a chemical reduction of a sodium cation is not common. However, if such a mechanism is really involved, electron transfer and hydrogen abstraction could be followed by a second electron transfer from sodium metal to the unstable generated tetrahydrofuranyl or cyclohexyl radical leading back to metallated tetrahydrofuran or cyclohexane. This sequence might proceed in a solvent cage.

Starting from this assumed phosphonothioformaldehyde **i5**, the access to the metallated methylenebisphosphonate **1a** via a second desulfurization can be more easily interpreted. Thiophilic addition of the sodium dialkylphosphite to the thiocarbonyl would lead to the carbanion **i7**, which can be in equilibrium with **i8** and with the thiolate **8** (Scheme 5). Our previous work concerning the reactivity of the carbanion **i7** has shown (using ^{31}P NMR) that at –40°C the intermediate **i7** was not stable enough to be characterized and the detected form was the thiolate **8** resulting from a [1,2]-sigmatropic rearrangement.[10] It has been also shown that **8** can easily loose sulfur at room temperature. Therefore, to confirm that thiolate **8** is an intermediate, which is then desulfurized by sodium diakylphosphite, we have treated independently prepared phosphonomethyl phosphorothioate **7**[10] with NaH at –40°C, then added one equivalent of sodium diisopropylphosphite, allowed the mixture to warm up to room temperature. Monitoring the reaction by ^{31}P NMR, we observed the formation of anions **1a** and **2a**. Moreover, the same reaction performed with addition of sodium diethylphosphite, led to **1a** and **2b**, as expected.



SCHEME 5

Therefore, for the last step, we propose a loss of sulfur, which can be either spontaneous with a subsequent reaction with dialkylphosphite or assisted by sodium dialkylphosphite (possibly via the intermediate **i8**), affording the sodium carbanion of the methylene bisphosphonate **1a** and the second equivalent of sodium thiophosphate **2a**.

CONCLUSION

In conclusion, these results show that the addition of an excess of sodium dialkylphosphite to carbon disulfide at room temperature can lead in an aprotic solvent to a complete desulfurization of the latter with formation of the sodium methylene bisphosphonate and thiophosphate. A study of this reaction, using in particular ^{31}P NMR and ESR spectroscopy, demonstrates that the addition can be stopped at the phosphonodithioformate stage by maintaining a low temperature ($<$ –40°C) and suggests that at higher temperatures further addition of dialkylphosphite leading to the methylene bisphosphonate carbanion proceeds through a radical mechanism involving a phosphonothiocarbonyl radical.

EXPERIMENTAL

The quality of the solvents used was RS. THF was purified with a PURESOLV apparatus developed by Innovative Technology Inc. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker DPX 250 MHz spectrometer. Low temperature experiments and reaction monitoring by ^{31}P NMR were done on a Bruker DRX 400 MHz spectrometer. ^{31}P NMR spectra were recorded with 85% phosphoric acid solution as an external reference. The coupling constants (J) are reported in Hertz (Hz).

ESR spectra were recorded with an upgraded Bruker ER200D/ESP300 spectrometer equipped with a dedicated data station for the acquisition and manipulation of the spectra, a standard variable temperature device, a NMR gaussmeter for the calibration of magnetic field, and a frequency counter for the determination of g-factors that were corrected with respect to that of perylene radical cation in concentrated sulfuric acid. In a typical experiment of radical trapping, a THF solution of sodium dialkylphosphite (4 equivs.) and carbon disulfide (1 equiv.) to which a few crystals of tBuNO had been added, was allowed to react inside the cavity of the ESR spectrometer.

Typical Procedure for the Reaction of an Excess of Sodium Dialkylphosphite with Carbon Disulfide: Synthesis of Diisopropyl Methylene Bisphosphonate 3a and Diisopropyl Thiophosphoric Acid 4a

Diisopropyl phosphite (4 mL, 24 mmol) was added dropwise under nitrogen to a suspension of NaH (28.8 mmol, 1.2 equiv.) in dry THF (25 mL) at –5 to 0°C. Then, the mixture was stirred for 3 h at 20°C, and carbon disulfide (9.6 mmol, 0.4 equiv.) was added dropwise. The color of the reaction mixture became brown. Stirring was continued for 3 h, then the mixture was poured onto a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the product was purified by vacuum distillation (110–115°C at 3.10^{-2} mbar) to give the compound **3a** as a pale yellow oil (52%). The aqueous phase was acidified with a solution of HCl (2N), then extracted twice with Et_2O. The organic phase was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the product purified by vacuum distillation (77–80°C at 7.10^{-3} mbar) to give the compound **4a** as a pale yellow oil (53%).

3a: ^{31}P NMR (101.25 MHz, $CDCl_3$): $\delta = 17.4$. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 6.2$ Hz, 12H, CH_3); 1.29 (d, $J = 6.2$ Hz, 12H, CH_3); 2.30 (t, $J = 21.1$ Hz, 2H, PCH_2); 4.61–4.79 (m, 4H, CH-O). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 23.9$ (d, $J = 5.2$ Hz, CH_3); 24.1 (d, $J = 2.6$ Hz, CH_3), 27.7 (t, $J = 138.2$ Hz, PCH_2); 71.2 (t, $J = 3.1$ Hz, CHOP). MS-EI (m/z ,%): 344 (M^+, 28), 302 (100), 286 (31), 260 (82), 242 (29), 218 (67), 202 (49), 176 (47). Anal. calcd. for $C_{13}H_{30}O_6P_2$: C, 45.30; H, 8.80%. Found: C, 45.44; H, 8.73%.

4a: ^{31}P NMR (101.25 MHz, $CDCl_3$): $\delta = 60.6$. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.34$, 1.35 (2d, $J = 6.2$ Hz, 12H, CH_3); 4.76 (dsept, $J = 6.2$ Hz, $J = 9.8$ Hz, 2H, CH-O); 7.23 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 23.5$ (d, $J = 5.0$ Hz, CH_3), 23.6 (d, $J = 5.0$ Hz, CH_3); 73.5 (d, $J = 6.1$ Hz, CHOP). MS-EI (m/z,%): 198 (M^+, 32), 187 (17), 141 (13), 114 (100), 97 (18), 86 (24), 60 (22), 45 (96), 43 (85). Anal. calcd. for $C_6H_{15}O_3PS$: C, 36.36; H, 7.63; S, 16.18%. Found: C, 36.60; H, 7.31; S, 16.20%.

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