Heteroatom Chemistry
Volume 5, Number 5/6, 1994

Sulfenylation of α-Phosphoryl Sulfides. Chemical Evidence for Intermediate Formation of α-Phosphoryl Trithioorthoformate [1]

Piotr Bałczewski and Marian Mikołajczyk*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-363 Łódź, Sienkiewicza 112, Poland

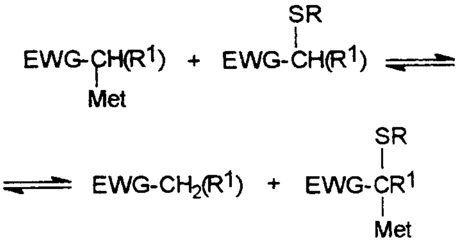
Received 4 July 1994

ABSTRACT

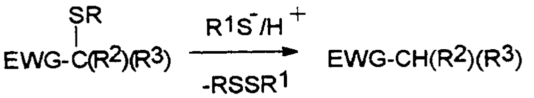
1-Lithio-1-(diethoxyphosphoryl)methyl methyl sulfide **1-Li** *was reacted with diphenyl disulfide in a tetrahydrofuran solution to give predominantly diethyl methylthio(phenylthio)methylphosphonate* **2** *accompanied by a small amount of diethyl bis(phenylthio)methyl phosphonate* **3**. *The latter was the main product when the reaction was performed in the absence of the solvent. The formation of* **3** *was explained through the desulfenylation of the transiently formed diethyl methylthiobis(phenylthio)methylphosphonate* **4** *with lithium benzenethiolate and confirmed by* ^{31}*P NMR measurements at low temperature.*

INTRODUCTION

Among the rich family of sulfenylating compounds, organic disulfides are convenient reagents frequently used to introduce an alkyl-, allyl-, or arylsulfenyl group into an α-activated position of an appropriate molecule [2,3]. The main characteristic of the sulfenylation reaction is a fast proton migration from the sulfenylation product to an anionic substrate due to a greater acidity of the former. Therefore, in a typical sulfenylation reaction, only a half amount of a substrate is usually consumed (Equation 1). In order to perform the sulfenylation reaction efficiently, one has to apply short reaction times, low reaction temperatures, or appropriate experimental procedures involving a sequential addition of substrates in a proper ratio. From the mechanistic point of view, it is interesting to point out that, according to some literature suggestions, exhaustively sulfenylated products may be formed in this reaction. However, they are destroyed by the nucleophilic thiolate attack at the sulfur atom [4,5] (Equation 2).



$$\text{EWG-}\underset{\text{Met}}{\text{C}}\text{H(R}^1\text{)} + \text{EWG-}\overset{\text{SR}}{\text{C}}\text{H(R}^1\text{)} \rightleftharpoons \text{EWG-CH}_2\text{(R}^1\text{)} + \text{EWG-}\overset{\text{SR}}{\underset{\text{Met}}{\text{C}}}\text{R}^1 \quad (1)$$



$$\text{EWG-}\overset{\text{SR}}{\text{C}}\text{(R}^2\text{)(R}^3\text{)} \xrightarrow[\text{-RSSR}^1]{\text{R}^1\text{S}^-/\text{H}^+} \text{EWG-CH(R}^2\text{)(R}^3\text{)} \quad (2)$$

EWG - electronwithdrawing group

(C=O, COOR, RSO_2, etc)

The latter reaction was assumed to take place

---

*To whom correspondence should be addressed.

1042-7163/94/$5.00 + .25

in the desulfenylation of carbonyl sulfides [6] and α,α'-disulfonyl dithioacetals [7].

Due to the great synthetic value of α-sulfenylated phosphonates [8], some time ago, we elaborated a convenient synthesis of α-sulfenylated phosphonates starting from α-unsubstituted phosphonates and organic disulfides [9]. Depending on the experimental procedure and the ratio of reagents, we were able to obtain either α-phosphoryl sulfides or α-phosphoryl dithioacetals. However, the formation of α-phosphoryl trithioorthoformates as exhaustively sulfenylated products has never been observed [10,11]. Now, we have reinvestigated this reaction and would like to present evidence for the intermediate formation of such species.

RESULTS AND DISCUSSION

A careful reinvestigation of the sulfenylation reaction of **1-Li** with diphenyl disulfide (**1**/*n*-BuLi/PhSSPh = 1/2/1.5) [9] revealed that the carrying out of the reaction in a tetrahydrofuran solution, followed by quenching (NH_4Cl or HCl, aqueous solutions), evaporation of the solvents, and further chromatographic purification afforded diethyl methylthio(phenylthio)-methylphosphonate **2** in 70–90% yield accompanied by a small amount (5–20%) of bis(phenylthio)methylphosphonate **3** (Scheme 1, Procedure A).

However, a change of the workup procedure, i.e., evaporation of the solvents prior to acidification (NH_4Cl, aqueous solution), resulted in the formation of **3** as the main reaction product (Scheme 1, Procedure B). The other compounds found in the crude reaction mixture were the following: **1**, **2**, unreacted PhSSPh, PhSH (resulting from PhSLi + H_3O^+), *n*-BuSPh (resulting from PhSSPh + *n*-BuLi), and PhSSMe. Detection of the latter unsymmetrical disulfide deserves special attention, since its presence in the reaction mixture, in combination with the formation of **3**, might confirm the anticipated attack of lithium benzenethiolate at the sulfur atom of the methylthio group in the intermediate bis(phenylthio)methylthiomethylphosphonate **4** (Scheme 2).

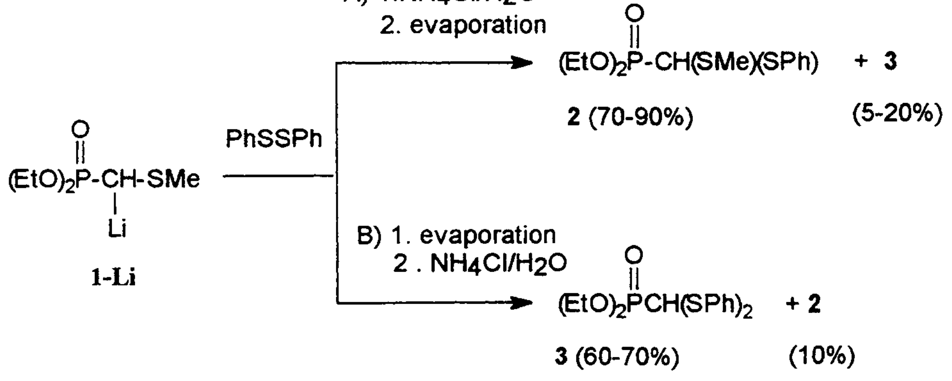
Theoretically, unsymmetrical methyl phenyl disulfide could also arise from the nucleophilic thiolate attack at the sulfur atom in **1** or **2**. Such a reaction would require formation of $(EtO)_2P(O)CH_2Li$ or $(EtO)_2P(O)CH(Li)SPh$, respectively, which however are much worse leaving groups than $(EtO)_2P(O)C(Li)(SPh)_2$(**3-Li**), expected from such an attack on **4**.

Moreover, the thiolate attack on **2** should be faster than α-proton exchange between **1-Li** and **2**, otherwise it would have to occur on the lithiated species **2-Li**, which is less probable from the point of view of energetics considerations. To check this possibility, **2** was reacted with the PhSSPh/PhSLi reagent system (prepared from PhSH and *n*-BuLi) in a very concentrated THF solution at room temperature, but, even after 1.5 h reflux, we did not find **3** in the reaction mixture. Therefore, we think that the reasonable explanation of the formation of **3** rests on the desulfenylation by lithium benzenethiolate of the transiently formed **4** as a product of the exhaustive sulfenylation of **2** with diphenyl disulfide (Scheme 3).

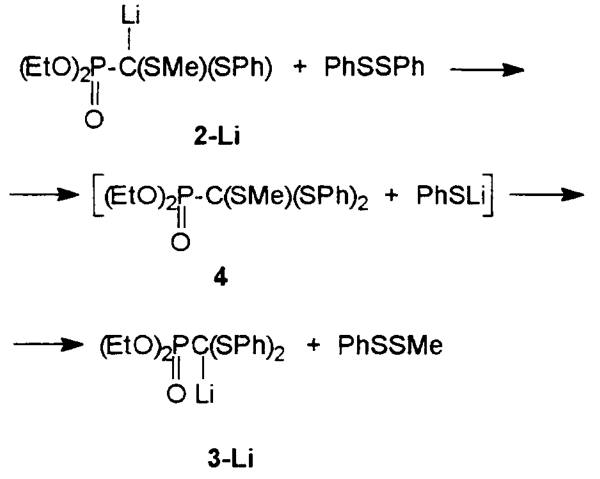
A second mechanistic possibility involves the retro-Stevens rearrangement of the hindered **4** to give the sterically released ylide **5** [11], followed by its reaction with lithium benzenethiolate to give **3-Li** and PhSSMe (Scheme 3).

In order to confirm the transient formation of **4** and its subsequent desulfenylation, ^{31}P NMR monitoring at low temperature was employed (see the Experimental section). The α-phosphoryl trithioorthoester **4** was synthesized at −50°C from **2-Li** and phenylsulfenyl chloride under the free lithium benzenethiolate conditions in order to avoid a spontaneous desulfenylation (Scheme 4).

The ^{31}P NMR chemical shift, δ = 15.6, attributed to **4** remained in good accord with the range of the chemical shifts, δ = 14.68–17.30, observed

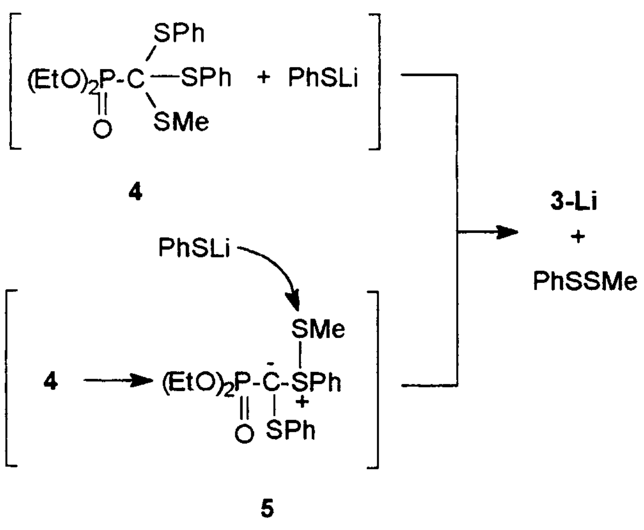


SCHEME 1



SCHEME 2

for other α-phosphoryl trithioorthoesters [12]. Upon treatment of **4** so formed with lithium benzenethiolate, its signal at $\delta = 15.6$ disappeared, and two signals of the α-lithio derivatives **3-Li** (major) and **2-Li** (minor) arose in the spectrum. This result allows us to conclude that the thiolate attack may occur both at the PhS and MeS sulfur atoms; however, the former remains predominant, especially in the absence (or in the presence of a limited amount) of tetrahydrofuran. The major pathway of desulfenylation of **4** may be explained in terms of a direct attack at the methylthio sulfur atom to give **3-Li** as a better stabilized leaving group. This result fits well with the previously reported desilylation reaction of $(EtO)_2P(O)C(SiMe_3)(SMe)_2$ by a thiolate anion occurring at the silicon atom and affording $(EtO)_2P(O)C(Li)(SMe)_2$ [13].



SCHEME 3

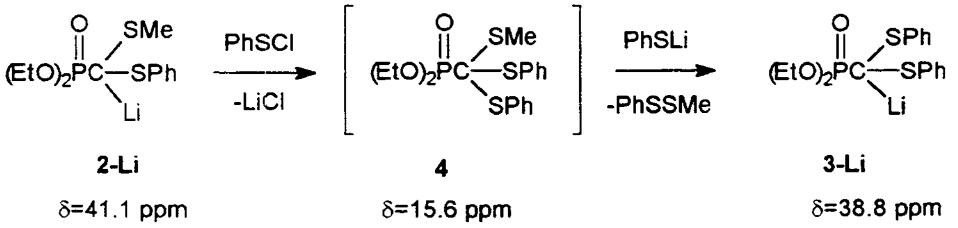
In summary, this article describes desulfenylation of the transiently formed trithioorthoformate moiety $C(SR)_3$ in **4** by lithium benzenethiolate in the absence of solvent, which can be considered as an extension of the earlier known or postulated desulfenylations of the sulfide C-SR [6] and the dithioacetal $C(SR)_2$ [4–7] moieties by thiolates in solution.

EXPERIMENTAL

The reagent grade tetrahydrofuran was kept over solid KOH and distilled from lithium aluminum hydride. ^1H NMR spectra were recorded with a R12B Perkin-Elmer (60 MHz), a Tesla 35487C (80 MHz), or a Bruker MSL (300 MHz) spectrometer. The ^{31}P NMR spectra were obtained with a Jeol JNM-C-60H (24.3 MHz) or a Bruker HFX-72 (36.4 MHz) spectrometer using 85% H_3PO_3 as the external standard. The ^{31}P NMR measurements at low temperatures were performed using a Bruker MSL 300 (121.49 MHz), 10 mm NMR tubes, and a mixture of THF/THF-d_8 in a ratio 10:1 as a solvent. MS spectra were recorded on a LKB 2091 mass spectrometer connected to a gas chromatograph. Column chromatography was done on 60 Merck silica gel (70–230 mesh) using a gradient of benzene/acetone as eluent.

Diethyl Methylthio(phenylthio)-methylphosphonate **2**

This compound was prepared according to Ref. [9]. A careful column chromatography of the crude reaction product gave **2** (70–90%, $n_D = 1.5510$; Ref. [9]: 1.5526) and **3** (5–20%, $n_D^{20} = 1.5798$; Ref. [9]: 1.5819).



SCHEME 4

Diethyl Bis(phenylthio)methylphosphonate **3**

To a stirred solution of **1** (1.90 g, 0.01 mol) in tetrahydrofuran (25 mL), a solution of *n*-butyllithium (0.011 mol) in *n*-hexane was added dropwise under nitrogen at −60°C. The solution was stirred at this temperature for 10 minutes, and then a solution of diphenyl disulfide (2.18 g, 0.01 mol) in tetrahydrofuran (10 mL) was added. After 15 minutes of stirring, the reaction mixture was treated with a solution of *n*-butyllithium (0.0055 mol) in *n*-hexane and, after an additional 10 minutes, with a solution of diphenyl disulfide (1.09 g, 0.005 mol) in tetrahydrofuran (8 mL). The mixture was stirred for 10 minutes and warmed to room temperature. Solvents were evaporated using a vacuum rotoevaporator (water bath, 30–40°C) and, to the residue, CH_2Cl_2 and a saturated aqueous solution of NH_4Cl were added. The organic layer was washed with water, dried over $MgSO_4$, filtered, and evaporated to give a crude product, which was purified either by distillation or column chromatography. According to GC/MS, spectroscopic techniques, and comparison with original samples, the crude product contained the following nonphosphorus compounds: PhSH [*m/z*: 110 (M^+; 100), 109(53), 84(25), 77(23)]; MeSSPh [*m/z*: 156 (M^+; 100), 141(61), 109(40)]; *n*-BuSPh [*m/z*: 166 (M^+; 72), 123(43), 110(100)]; PhSSPh [*m/z* 218 (M^+; 100), 109(71)]; and the compounds containing phosphorus: **1** (6%), **2** (10%), **3** (75%). Column chromatography afforded **3** in 60–72%; yield (1.8–2.2 g). Distillation (~200°C/0.1 Torr) of a crude sample (2.65 g) gave two fractions: 1.13 g (I) and 0.78 g (II) of which the latter contained pure **3** (n_D^{20} = 1.5825; Ref. [9]; 1.5819).

^{31}P NMR Measurements at Low Temperatures

To a solution of **2** (45 mg, 0.147 mmol) in THF a stoichiometric amount of *n*-BuLi was added at −50°C. A signal due to **2** at δ = 19.1 disappeared and a new signal of **2-Li** at δ = 41.1 appeared in the spectrum. The addition of stoichiometric amounts of phenyl sulfenyl chloride caused disappearance of the signal due to **2-Li** and appearance of a new signal at δ = 15.6, which was attributed to the α-phosphoryl trithioorthoester **4**. Upon addition of lithium benzenethiolate (prepared from PhSH and *n*-BuLi at −50°C), the latter signal disappeared and two signals at δ = 41.1 (minor) due to **2-Li** and δ = 38.8 (major) due to **3-Li** appeared in the spectrum. The final hydrolysis of the reaction mixture revealed two signals at δ = 19.1 and δ = 19.3 attributed to **2** and **3**, respectively.

ACKNOWLEDGMENT

Financial support by the State Committee for Scientific Research (Grant No. 2 2684 9203) is gratefully acknowledged.

REFERENCES

[1] Organosulfur Compounds Part LIII. For Part LII, see M. Mikołajczyk, W. H. Midura, S. Grzejszczak, F. Montanari, M. W. Wieczorek, J. Karolak-Wojciechowska, *Tetrahedron*, in press.

[2] B. M. Trost, *Chem. Rev.*, *78*, 1978, 763.

[3] B. M. Trost: in C. J. M. Stirling (ed): *Organic Sulfur Chemistry*, Butterworth and Co., London, 1975, pp. 237-63.

[4] B. Wladislaw, L. Marzorati, G. Ebeling, *Phosphorus, Sulfur, Silicon*, *48*, 1990, 163.

[5] An intramolecular thiolate attack at sulfur was proposed to explain desulfenylation of α-methylthio-α-phosphorylthioacetamides. P. Bałczewski, P. Graczyk, W. Perlikowska, M. Mikołajczyk, *Tetrahedron*, *49*, 1993, 10111.

[6] M. Oki, W. Funakoshi, A. Nakamura, *Bull. Chem. Soc. Jpn.*, *44*, 1971, 828.

[7] J. S. Grossert, P. K. Dubey, *J. Chem. Soc., Chem. Commun.*, 1982, 1138.

[8] M. Mikołajczyk, P. Bałczewski: α-Phosphoryl Substituted Organosulfur Compounds, in E. Block (ed): *Advances in Sulfur Chemistry*, Jai Press, Greenwich, CT, 1994, in press.

[9] M. Mikołajczyk, P. Bałczewski, S. Grzejszczak, *Synthesis*, 1980, 127.

[10] M. Mikołajczyk, S. Grzejszczak, A. Chefczyńska, A. Zatorski, *J. Org. Chem.*, *44*, 1979, 2967.

[11] For formation of the P-C-S ylides, see (a) B. G. Christensen, R. A. Firestone: Ger. Pat., 1 924 135 (1969), Merck and Co., Inc.: *Chem. Abstr. 72*, (1970) 43870; (b) K. Kondo, D. Tunemoto, *J. Chem. Soc., Chem. Commun.*, 1972, 952; (c) K. Kondo, Y. Lin, D. Tunemoto, *J. Chem. Soc., Perkin Trans., I*, 1974, 1279; (d) W. Illger, A. Liedhegener, M. Regitz, *Liebigs Ann. Chem.*, *760*, 1972, 1; (e) A. Baceiredo, G. Bertrand, S. Sicard, *J. Am. Chem. Soc.*, *107*, 1985, 4781.

[12] A. Bulpin, S. Masson, *J. Org. Chem.*, *57*, 1992, 4507.

[13] M. Mikołajczyk, P. Bałczewski, *Synthesis*, 1989, 101.