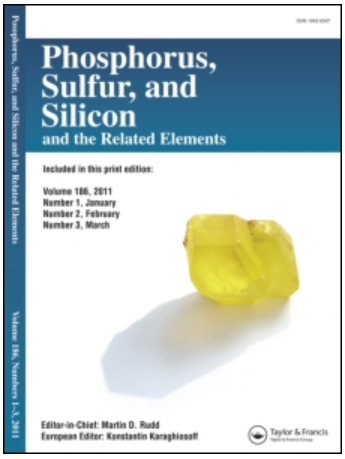

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SULFENOCYCLIZATION REACTION OF 3-METHYL-1,2-BUTADIENEPHOSPHONATE WITH METHYL (DIMETHYLTHIO) SULFONIUM ANTIMONATE

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Reaction of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1** with sulfenating reagents such as methylsulfenyl chloride and methyl bis(methylthio) sulfonium hexachloroantimonate (MDTSAN) has been investigated. In the case of MDTSAN, 2,5-dihydro-2,2-dimethoxy-4-methylthio-1,2-oxaphospholium hexachloroantimonate **5** was isolated. Heating or treatment of **5** with a 10 % aqueous solution of a mixture of sodium and potassium carbonates lead to formation of 2,5-dihydro-4-methylthio-1,2-oxaphosphole 2-oxide **2**. A possible mechanism involving formation of thiiranium and/or carbenium ions as reaction intermediates has been discussed.

Keywords: 3-methyl-1,2-butadienylphosphonic dimethyl ester; methyl bis (methylthio) sulfonium hexachloroantimonate (MDTSAN); sulfenocyclization reaction; 2,5-dihydro-2,2-dimethoxy-4-methylthio-1,2-oxaphospholium hexachloroantimonate; 2,5-dihydro-4-methylthio-1,2-oxaphosphole 2-oxide

INTRODUCTION

Reactions of electrophilic addition to phosphorylated allenes have been intensively investigated in the past 20 years. It has been shown[1] that depending on the structure of the starting allenic compound as well as the type of the electrophilic reagent, the reactions proceed with cyclization of the allenic system bearing a phosphoryl group (O=P-C=C=C) to give heterocyclic compounds in most cases. Thus, the reaction of alkyl (aryl) sulfenyl chlorides with allenephosphonic dialkyl esters leads to a mixture of

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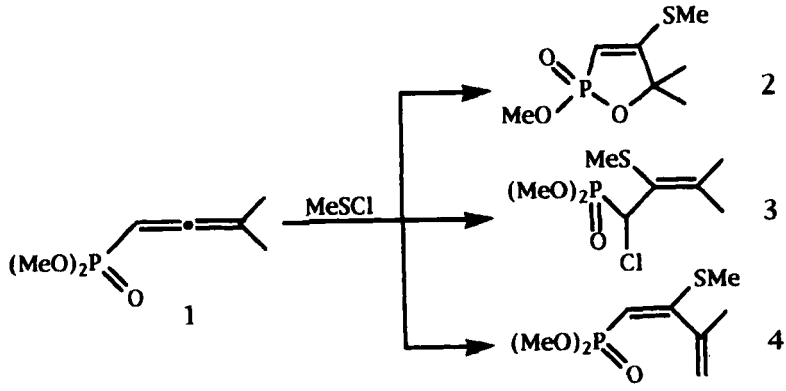
2,5-dihydro-1,2-oxaphosphole and 2,1- and/or 2,3-adducts depending on the degree of substitution at the C^1 and C^3 atoms of the allenic system, on the nature of these substituents, and on the type of the hydrocarbon part of the sulfenyl chloride.[1a] For example, the reaction of the 3-methyl-1,2-butadienephosphonic dimethyl esters **1** and methylsulfenyl chloride in CCl_4, $CHCl_3$ or $ClCH_2CH_2Cl$ proceeds with formation of a mixture of 2,5-dihydro-1,2-oxaphosphole **2** (46 %), 2,1-adduct **3** (15 %) and 3-methyl-2-methylthio-1,3-butadienephosphonic dimethyl esters **4** (4 %) according to **Scheme 1**:[2]



SCHEME 1

On the other hand, the sulfenocyclization reaction of alkenes and alkynes, containing an internal nucleophile suitable for cyclization, is a regioselective (in some cases, regiospecific) reaction.[3] The phosphorylated allene **1** contains a phosphonate group as an internal nucleophile and from this point of view, is a convenient substrate for investigation of the sulfenocyclization reaction. In contrast with the alkenic and alkynic substrates, the allene **1** possesses two heaping double bonds which poses the question for the hemoselectivity together with that for the regioselectivity of this reaction.

As a part of our continuing study on the chemistry of the phosphorylated highly unsaturated compounds, we now report the results on the hemo- and regioselectivity of the sulfenocyclization reaction of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1**.

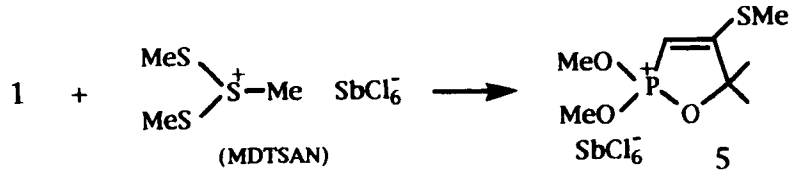
RESULTS

We established that the reaction of the allenephosphonate **1** with methylsulfenyl chloride in tetrahydrofuran or 1,4-dioxane at −20 °C leads to a mixture of 2,5-dihydro-5,5-dimethyl-2-methoxy-4-methylthio-1,2-oxaphosphole 2-oxide **2** (60 % in THF and 57 % in dioxane) and 1-chloro-3-dimethyl-2-methylthio-2-butenephosphonic dimethyl esters **3** (9 and 7 % respectively).

The products formed **2** and **3** were isolated by preparative TLC on silica gel using a mixture of hexane, ethylacetate, methanol and a water solution of ammonia in the ratio 12 : 10 : 1.5 : 1 as a mobile phase. The structure of the cyclic compound **2** (R_f 0.22) and the 2,1-adduct **3** (R_f 0.36) were confirmed by ^1H NMR and IR spectra, which were fully in accordance with those reported.[2]

One of the typical sulfenylating reagents used in the sulfenocyclization reactions of double and triple bond compounds is methyl bis(methylthio) sulfonium hexachloroantimonate (MDTSAN).[3,4] It transfers very efficiently the MeS^+ at the double or triple bond, leaving behind dimethyl disulfide, which is very poorly nucleophilic and usually does not interfere with the reaction. In order to improve the hemo- and regioselectivity of the sulfenocyclization reaction of the allenephosphonate **1**, we synthesized and used MDTSAN as reagent. It was prepared by the reaction of dimethyl disulfide with antimonium pentachloride in dichloromethane at 0 °C with 92 % yield,[5] probably *via in situ* formation of methylsulfenyl chloride from dimethyl disulfide and antimonium pentachloride and further reaction with dimethyl disulfide.[6]

The reaction of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1** with MDTSAN proceeds hemo- and regiospecifically, only the cyclic 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-4-methylthio-1,2-oxaphospholium hexachloroantimonate **5** being obtained according to **Scheme 2**:



SCHEME 2

The cyclic salt **5** was isolated with good yield (65 %) by precipitation with hexane as light green crystals and characterized by ^{1}H and ^{31}P NMR and IR spectra and elemental analysis. Formation of the five-membered ring was assumed on the basis of the olefinic proton in the ring which appears at low field (δ 5.15 ppm) as a doublet in the ^{1}H NMR spectrum. The coupling constant of this proton with phosphorus ($^{2}J_{HP}$ 26.2 Hz) is in agreement with the data reported for similar structures.[2,7] The chemical shift of ^{31}P as determined with respect to 85 % H_3PO_4 appears at δ 52.4 ppm which is in accordance with the literature data for phosphonium hexachloroantimonates.[7,12] The IR spectrum of **5** exibit absorption bands characteristic for the endocyclic double bond (1545 cm^{-1}), for the endocyclic P-O-C (987 cm^{-1}) and exocyclic Me-O-P (1052 cm^{-1}) moieties, as well as the absence of a band for the phosphoryl group. The data from elemental analysis confirm the structure of the compound obtained.

The TLC investigation of the crude product showed a chromatographical spot for the cyclic product **5** and another one for the starting allenephosphonate **1** and full absence of the spots for the 2,1-adduct **3**, the 1,3-butadienephosphonate **4** or for other products, i. e. the sulfenocyclization reaction of the phosphorylated allene **1** with MDTSAN proceeds strongly hemo- and regiospecifically.

The heating of the cyclic phosphonium haxachloroantimonate **5** at 50–60 °C or its treatment with 10 % solution of a mixture of sodium carbonate and potassium carbonate led to decomposition of the phosphonium salt with elimination of methyl chloride and formation of the 2,5-dihydro-1,2-oxaphosphole 2-oxide **2**.

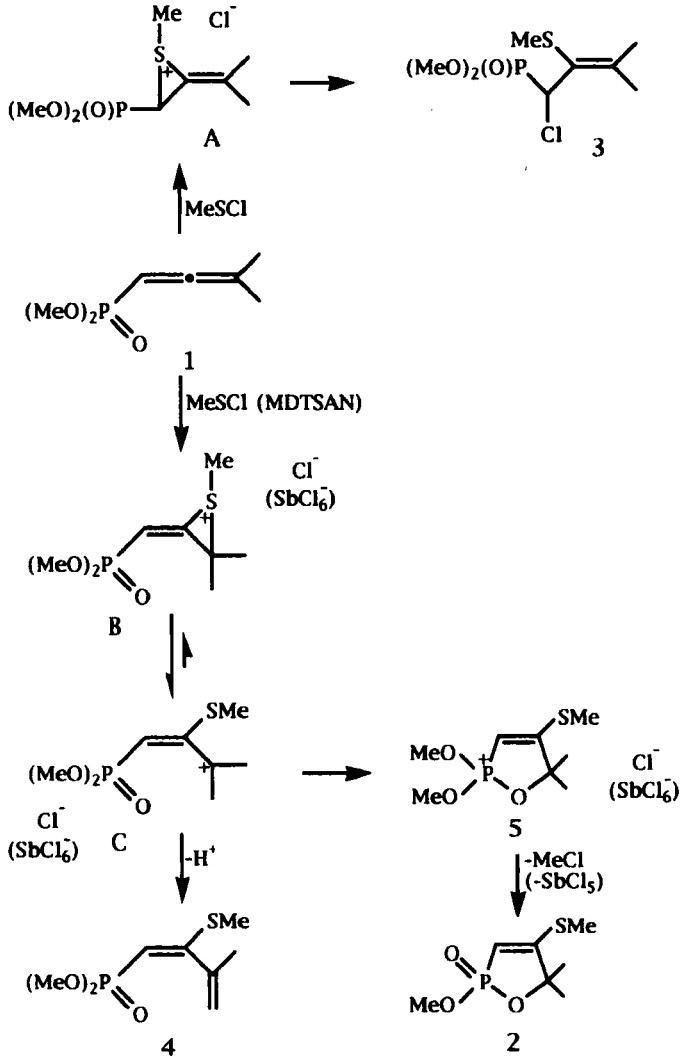
DISCUSSION

The experimental data published earlier on the sulfenocyclization reaction of the 3-methyl-1,2-butadienephosphonate **1** with methylsulfenyl chloride in polychloroalkanes,[2] and our results with the same reagent in THF or 1,4-dioxane as well as with MDTSAN, allowed us to put forward the following mechanism of the reaction.

Evidently, the first step of the reaction is an attack of the electrophilic reagent upon the allenic double bond system[9–11] with formation of the thiiranium (episulfonium) ions **A** (1,2-attack) and/or **B** (2,3-attack) (see

Scheme 3). Their stabilization depends on the ability of sulfur to localize positive charge as well as on the electronic and steric effects of the substituents at the thiiranium ring.[10,11] From general considerations, the thiiranium ion **B** probably is more stabilized than the ion **A** because of the stabilizing effects of both methyl groups in **B** and the destabilizing one of the phosphonate group in **A**. From this point of view, the attack on the 2,3-double bond is evidently favored. At the same time, however, the ion **B** exists in equilibrium with the acyclic carbenium ion **C**, which is evidently shifted largely towards the tertiary ion **C**, leading mainly, by intramolecular P=O attack, to the sulfenocyclization reaction (intermediate **5**) with subsequent elimination of methyl chloride (second stage of an Arbuzov type rearrangement) and formation of the cyclic product with tetracoordinated phosphorus **2**. Another possibility for stabilization of the carbenium ion **C** is a proton elimination[3] from one of the methyl groups at position **3**, with formation of the 2-methylthio-1,3-butadienephosphonate **4**. Thus, the reaction of the allenephosphonate **1** with methylsulfenyl chloride in polychloroalkanes affords a mixture[2] of the heterocyclic product **2** (46 %), the 2,1-adduct **3** (15 %) and the 1,3-butadienephosphonate **4** (4 %), i. e. in this case the reaction is hemo- (attack mainly on the 2,3-double bond) and regioselective (formation predominantly of one (**2**) of the products).

When the reaction was carried out in THF or 1,4-dioxane, it is possible that the solvent-separated ion pairs **A, B** and **C** are formed. The nucleophilic back side attack of Cl^- on **A** is hindered. On the other hand, however, the equilibrium between the thiiranium ion **B** and the open carbenium ion **C** in these solvents is shifted towards the ion **C** in greater degree than by the reaction in polychloroalkanes, which is evidently due to the solvation effect of THF and 1,4-dioxane. In the first one it is more probable that the cyclic intermediate **5** derives from the solvent-separated ion pair **C** (maybe double sided solvated cation), which collapses to product **2** after shifting the equilibrium from the tightly bound ion pair to solvent saparated one. As a result, the ratio of the cycle **2** to the 2,1-adduct **3** is 60 % to 9 % in THF and 57 % to 7 % in dioxane, while in polychloroalkanes, because of its low polarity, the diffuse thiiranium ion is more favored than in THF or dioxane, and the 2,1-adduct is obtained in 15 %.[2] The engagement of the chloride anion in the solvent-separated ion pair **C** is probably the reason the deprotonation of the **C** does not occur and the 1,3-diene **4** is no in this case.



SCHEME 3

Using the bulky MDTSAN as sulfenylating reagent evidently leads to the hemo- and regiospecifically of the reaction, i. e. the reagent attacks only the steric less hindered C^2-C^3double bond of the allenic system with formation only of the cyclic phosphonium hexachloroantimonate **5**. In this

case, the low nucleophilicy of the anion strongly hinders the attack on the methoxy group thus avoiding the interaction in the stage of formation of the phosphonium salt **5**. Such an attack takes place in the heating or in alkaline media, after the collapse of the complex anion $SbCl_6^-$ to the simple Cl^-, and leads to the 2,5-dihydro-1,2-oxaphosphole 2-oxide **2**.

In summary, the above results indicate that the methyl bis (methylthio) sulfonium hexachloroantimonate (MDTSAN) is an efficient reagent for the synthesis of the 2,5-dihydro-1,2-oxaphosphole system from phosphorylated allenes *via* intramolecular ring closure. Whereas this cyclization is also possible with other reagents, the isolation of the phosphonium hexachloroantimonate **5** confirms the assumption that the heterocyclization reactions of the 1,2-alkadienephosphonic dialkyl esters with electrophilic reagents very probably proceed through a phosphonium intermediate.[1,2]

EXPERIMENTAL

Method of analysis

NMR spectra were obtained on a BRUCKER WM-250 spectrometer for solutions in $CDCl_3$ or d_6-DMSO operating at 250.1 (^1H) and 161.9 MHz (^{31}P). Chemical shifts are in parts per million downfield from internal TMS (^1H) and external 85% H_3PO_4 (^{31}P).

IR spectra were recorded with an IR-72 spectrophotometer (Carl Zeiss, Jena). Elemental analyses were carried out by the University of Shoumen Microanalytical Service Laboratory.

The melting points were measured in open capillary tubes and are uncorrected. The solvents were purified by standard methods. Reactions were carried out in oven-dried glassware under an argon atmosphere and exclusion of moisture. All compounds were checked for their purify on TLC plates.

Starting materials

3-Methyl-1,2-butadienephosphonic dimethyl ester (**1**) was synthesized from phosphorus trichloride and 2-methyl-3-butyne-1-ol in the presence of pyridine according to the literature.[8] Methylsulfenyl chloride was freshly

prepared from dimethyl disulfide and sulfuryl chloride at −20 °C and used without purification. Methyl bis(methylthio) sulfonium hexachloroantimonate (MDTSAN) was prepared from dimethyl disulfide and antimonium pentachloride according to the literature.[5]

Chromatographic Investigations

The qualitative TLC investigations and the R_f value determinations were carried out on silicagel "Merck" 60 F_{254} pre-coated aluminium sheets, using ethylacetate-hexane 2:1 as a mobile phase with threefold development.

Preparative TLC separations of the mixtures of products were carried out on silicagel "Merck" 60 DGF_{254} pre-coated glass sheets with threefold development. A mixture of hexane, ethylacetate, methanol and water solution of ammonia in the ratio 12:10:1.5:1 was used as a mobile phase. This phase was prepared in the following mater: the mixture of solvents was stirred and left until the full separation of the two layers. The upper layer, before use, was filtered through a paper filter for drying.

Reaction of 3-methyl-1,2-butadienephosphonic dimethyl ester 1 with methylsulfenyl chloride in tetrahydrofuran (THF) or 1,4-dioxane

To a solution of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1**(10 mmol) in dry THF or 1,4-dioxane (10 ml) at −20 °C was added dropwise with stirring a solution of methylsulfenyl chloride, prepared from dimethyl disulfide (5 mmol) and sulfuryl chloride (5 mmol) in the same solvent (10 ml). The stirring was continued for 1h at the same temperature and 3h at room temperature. Then the solvent was removed using a rotatory evaporator and the residue was chromatographed on preparative TLC to give the pure products **2** and **3**.

2,5-Dihydro-5,5-dimethyl-2-methoxy-4-methylthio-1,2-oxaphosphole 2-oxide 2

Yield: 60 % in THF and 57 % in dioxane, R_f 0.25. The product **2** is a known compound whose spectroscopic properties were fully in accord with those reported.[2]

1-Chloro-3-methyl-2-methylthio-2-butenephosphonic dimethyl ester 3

Yield: 9 % in THF and 7 % in dioxane, R_f 0.36. The NMR and IR spectral data of product **3** were in good agreement with the literature data.[2]

Reaction of 3-methyl-1,2-butadienephosphonic dimethyl ester 1 with methyl bis (methylthio) sulfonium hexachloroantimonate (MDTSAN)

To a solution of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1** (7 mmol) in dry dichloromethane (10 ml) at −20 °C was added dropwise with stirring a solution of MDTSAN (7 mmol) in the same solvent (10 ml). The colour of the reaction mixture changed from yellow through orange to purple. The stirring was continued for 1h at the same temperature and 3h at room temperature. Then dry hexane (20 ml) was added to the reaction mixture and light green crystals were precipitated, filtered and washed lavishly with dry hexane to give the pure product **5**. The TLC investigation of the filtrate showed only a chromatographical spot for the starting material **1**.

2,5-Dihydro-2,2-dimethoxy-5,5-dimethyl-4-methylthio-1,2-oxaphospholium hexachloroantimonate 5

Yield: 65 %; m. p. 83–4 °C; $C_8H_{16}O_3PSCl_6Sb$, Calcd., %: P 5.55, Cl 38.14; Found, %: P 5.43, Cl 38.05. IR spectra (nujol), cm^{-1}: 987 (P-O-C), 1052 (Me-O-P), 1545 (C=C). ^1H NMR spectra, δ: 1.69 (s, 6H, 2Me), 2.48 (s, 3H, MeS), 3.85 (d, 6H, $^3J_{HP}$ 12.2 Hz), 5.15 (d, 1H, $^2J_{HP}$ 26.2 Hz). ^{31}P NMR spectra, δ: 52.4.

Synthesis of 2,5-dihydro-5,5-dimethyl-2-methoxy-4-methylthio-1,2-oxaphosphole 2-oxide 2 from the cyclic phosphonium hexachloroantimonate 5

Method a: The crystals of **5** were dissolved in dichloromethane (20 ml) and washed with 10 % solution of a mixture of sodium carbonate and potassium carbonate. The bilayer mixture was stirred vigorously at room temperature for 1 h. After phase separation, the aqueous phase was washed with 2N HCl and saturated NaCl and extracted with dichloromethane (2 × 20 ml). The combined organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on preparative TLC to give the pure product **2**. Yield: 64 %.

Method b: Heating of the crystals **5** at 50–60 °C for 1 h led to a residue, which after preparative TLC purification, gave the pure product **2**. Yield: 44 %.

NMR and IR spectra of the cyclic product **2** prepared in both methods were identical[2] with the spectra of the product prepared in the reaction of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1** with methylsulfenyl chloride in THF or 1,4-dioxane.

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