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An Expedient Synthesis of Symmetrical Tetra-alkyl Monothiopyrophosphates.

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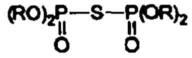
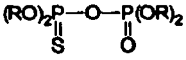
Abstract: The reaction of readily available dialkyltrimethylsilyl phosphites $(RO)_2POSiMe_3$ 5 with sulfur dichloride leads to tetra-alkyl *sym*-monothio-pyrophosphates $(RO)_2P(O)SP(O)(OR)_2$ 1 in high yield. The method is suitable for the synthesis of tetra t-butyl thiopyrophosphate 1d.

Oligoanhydrides of phosphorus acids are essential compounds in the storage of chemical energy and metabolism regulation in living organisms. Their sulfur analogues are of growing importance in biological studies including the *sym*-thiopyrophosphoric acid $(HO)_2P(O)\text{-}S\text{-}P(O)(OH)_2$.[1] Monothiopyrophosphates can exist in two isomeric forms 1 and 2 as well as the corresponding acids 1 and 2 (R=H).



$$(RO)_2\underset{O}{\overset{\|}{P}}-S-\underset{O}{\overset{\|}{P}}(OR)_2$$

1



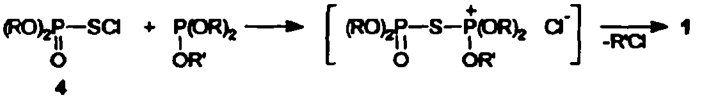
$$(RO)_2\underset{S}{\overset{\|}{P}}-O-\underset{O}{\overset{\|}{P}}(OR)_2$$

2

Synthesis of the compounds 2 is based on phosphorylation of the dialkylphosphorothioates salts 3 or other procedures in which this reaction is involved as a crucial step. Salts 3 are always phosphorylated on the hard oxygen centre.[2] It has been demonstrated that the structure 1 is not involved in these phosphorylations.[3]

$$\underset{3}{(RO)_2P(S)O^-} + X\text{—}P(O)(OR)_2 \longrightarrow 2 \qquad (1)$$

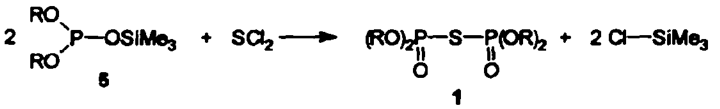
The unique route of formation of the structure 1 via dialkoxyoxophosphorane sulfenyl chlorides 4 has been discovered in this laboratory. Sulfenyl chlorides 4 react with the P^{III} centre to form the >P(O)-S-P(O)< system.[4]



$$\underset{\mathbf{4}}{(RO)_2\underset{O}{\overset{\|}{P}}{-}SCl} + \underset{OR'}{\overset{|}{P}}(OR)_2 \longrightarrow \left[(RO)_2\underset{O}{\overset{\|}{P}}{-}S{-}\underset{OR'}{\overset{+}{P}}(OR)_2\ Cl^-\right] \xrightarrow[-R'Cl]{} \mathbf{1} \qquad (2)$$

The reaction (2) is very strongly dependent on ligands at the tricoordinate phosphorus[5] and only when R'=$SiMe_3$ leads to the *sym*- thiopyrophosphates 1 in a very high yield[4].

Our more recent efforts were directed towards the synthesis of the thiopyrophosphates containing substituents that could serve as protective groups which are removable without breaking up of the >P(O)-S-P(O)< system. Having this in mind we decided to investigate the reaction of dialkyltrimethylsilyl phosphites 5 with sulfur dichloride. We have found that the reaction of two equivalents of dialkyltrimethylsilyl phosphite 5 with one equivalent of sulfur dichloride proceeds very smoothly at low temperatures and provides the thiopyrophosphates 1 in high yield.



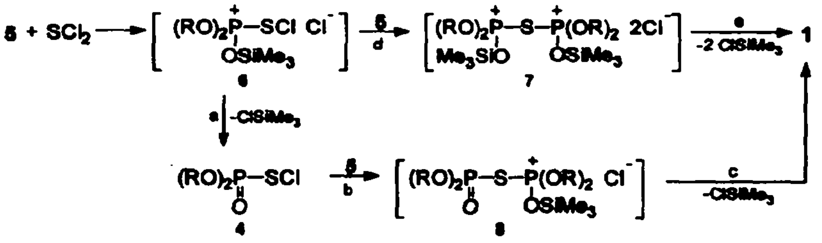
$$2\ \underset{\mathbf{5}}{(RO)_2P{-}OSiMe_3} + SCl_2 \longrightarrow \underset{\mathbf{1}}{(RO)_2\underset{O}{\overset{\|}{P}}{-}S{-}\underset{O}{\overset{\|}{P}}(OR)_2} + 2\ Cl{-}SiMe_3 \qquad (3)$$

Table 1. Synthesis of *sym*-monothiopyrophosphates 1.

	R	Y (%)	δ ^{31}P NMR	
1a	Me	95	17.8	CH_2Cl_2
1b	Et	85	16.0	$CDCl_3$
1c	i-Pr	90	13.7	$CDCl_3$
1d[6]	t-Bu	95	6.1	Et_2O
1e	t-$BuCH_2$	82	16.3	$CDCl_3$
1f	R_2=$Me_2C(CH_2)_2$	91	6.7	$CDCl_3$

Dialkyltrimethylsilyl phosphites 5 were prepared from the appropriate dialkyl phosphites and trimethylsilyl chloride in the presence of triethylamine.[7] The reaction was carried out in dichloromethane or diethyl ether under strictly anhydrous conditions in an argon atmosphere. Small amounts of impurities were removed by chromatography on silanised silica gel. By the method (3) we were able to prepare for the first time the tetra-t-butyl thiopyrophosphate **1d** (R=t-Bu). This compound which decomposes slowly at room temperature was prepared in 95% yield.

Over a large range of temperatures we failed to observe by ^{31}P NMR spectroscopy formation of sulfenyl chlorides 4 and phosphonium intermediates 6, 7 and 8 at any phase of the reaction (3). Intermediates of these types have been observed earlier in the case of alkoxy substituents.[5,8] One can consider two ways of formation of the thiopyrophosphates 1 which are indicated in scheme (4).



(4)

If the pathway a,b and c is involved one must accept that the reaction between sulfenyl chloride 4 and the trimethylsilylphosphite 5 (step b) is much faster then the conversion of the phosphonium salt 6 into the chloride 4 (step a). A similar assumption is necessary to explain formation of the diphosphonium salt 7 via the pathway d and e. According to our experience the former pathway (a, b and c) seems to be more likely.

General Procedure:

A solution of sulfur dichloride (1.03g, 10 mmol) in methylene chloride or diethyl ether (10 ml) was added dropwise to a stirred solution of two equivalents of dialkyltrimethylsilyl phosphite (5) (20 mmol) in 10 ml of CH_2Cl_2 or Et_2O at -50°C. The solution was stirred until ambient temperature was reached. Stirring was continued for another 15 min. The solvent was evaporated off at reduced pressure. If purification was required the liquid compounds (1 a-c) were purified by column chromatography using silica gel 60 silanised (dimethylsilan derivative, 63-200 μm, Merck, 1:40 by weight; eluent benzene-chloroform); compounds (1 e,f) were recrystallized from diethyl ether - hexane.

The spectroscopic properties of the thiopyrophosphates 1a-c,e,f are in agreement with authentic samples[4] and their purity was confirmed by elemental analysis and M.S.

Acknowledgments

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