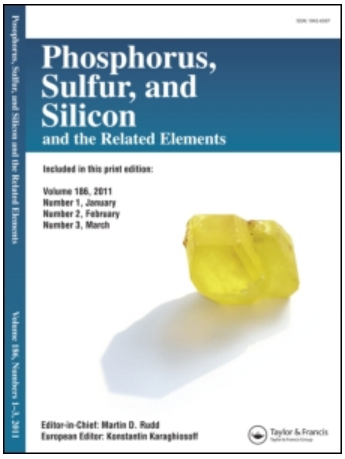

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THE REACTION BETWEEN THIOPHOSGENE AND TRIALKYL PHOSPHITES

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THE REACTION BETWEEN THIOPHOSGENE AND TRIALKYL PHOSPHITES

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The reaction between trialkyl phosphites and thiophosgene, even at low temperature, does not lead to esters of thiocarbonyl bisphosphonic acid as had previously been reported. The initial products appear to be stabilised phosphorus ylids formed by two carbophilic and one thiophilic reactions between thiophosgene and the trialkyl phosphite with no desulfuration. Following thermal or acidic treatment, the ylids undergo protonation-dealkylation reactions to give phosphorothio-substituted methane bisphosphonates.

Key words: Carbophilic addition; methane bisphosphonates; thiophilic addition; thiophosgene; trialkyl phosphites; ylids.

INTRODUCTION

In the course of our search for new pyrophosphate analogs with antiviral activity, we wished to synthesise the thione (**1**, X = S, R = H) corresponding to carbonyl bisphosphonic acid (**1**, X = O, R = H) which can inhibit the reverse transcriptase induced by HIV (Human Immunodeficiency Virus), the causative agent of AIDS [1]. *O,O*-Dialkyl thiocarbonyl bisphosphonate esters (**1**, X = S) have only been mentioned once in the literature and are claimed to be formed as the product of the reaction between thiophosgene and triethyl phosphite [2]. In our hands, however, this reaction does not produce the claimed thiocarbonyl bisphosphonate and we present here the results of our study of the reaction between thiophosgene and trialkyl phosphites.

$$(RO)_2P(O)\underset{\underset{X}{\|}}{C}P(O)(OR)_2 \qquad (RO)_3P$$

(1) **(2)**

RESULTS

We expected to obtain the required thiocarbonyl bisphosphonate (X = S) from an Arbusov reaction between thiophosgene and a trialkyl phosphite, and hence in our initial experiments thiophosgene was treated with a twofold molar excess of

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trialkyl phosphite. However, the molar ratio of the two reactants appears to have little effect on the products of the reaction and essentially similar products were obtained with 3:1, 4:1 or 5:1 molar ratios of trialkyl phosphite to thiophosgene and in no case could the thione (**1**, X = S) be detected by NMR spectroscopy. In a typical experiment, the trialkyl phosphite (**2**, R = (a) Me, (b) Et or (c) i-Pr) was added at −78°C to a solution of thiophosgene in tetrahydrofuran or hexane and the mixture allowed to warm slowly to room temperature. The main products of these reactions were deduced to be the ylids (**3a–c**) from spectroscopic data as we were unable to isolate them pure. These ylids presumably arise from two carbophilic and one thiophilic additions of trialkyl phosphite to thiophosgene with the concomitant elimination of two equivalents of alkyl chloride. The ylids were usually obtained together with the fully esterified phosphorothio-substituted methane bisphosphonates (**4a–c**) (ca 7–27%). When the reaction mixture was then treated with gaseous hydrogen chloride in dichloromethane at 0°C or warmed to 100–110°C for 16 h, compounds (**4a–c**) were the only detectable products.

Even with freshly distilled thiophosgene, we were unable to obtain the ylids without the formation of some (**4a–c**). This was presumably due to the difficulty in removing all traces of hydrogen chloride resulting from slight hydrolysis of the thiophosgene. The presence of hydrogen chloride in the thiophosgene could also explain the formation of small amounts (2–5%) of dialkyl phosphites which could be detected with the related trialkyl phosphate (4–12%) in the reaction mixtures. Indeed, we observe the total transformation of (**3a**) into (**4a**) with an increase in the yields of the dialkyl phosphite and trialkyl phosphate by-products when the reaction was carried out deliberately using a partially hydrolysed sample of thiophosgene.

The structures of compounds (**3**) and (**4**) were deduced from their NMR spectra (Table II). The ^{31}P NMR spectra of (**3a–c**) consists of ABX systems with large $J(AB)$ ($^2J(P_AP_B) \sim 120$ Hz) and small $J(AX)$ and $J(BX)$ ($^3J(P_AP_C) \sim {}^3J(P_BP_C) = 3.5$–$6$ Hz). For these three compounds, the signals centered at $\delta(P_A) \sim 28$, 27.5 and 26 ppm, can be attributed to the phosphorus atoms in the phosphonate residues. As might be expected [3], the phosphorus atoms P_B of the

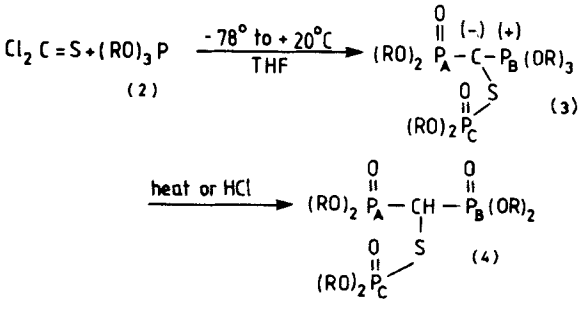

FIGURE 1 Formation of ylids (**3**) and bisphosphonates (**4**) in reaction between thiophosgene and trialkyl phosphites (**2**).

trialkoxy phosphonium residues in the ylids, gave rise to signals centered at $\delta(P_B) \sim 55$, 49.5 and 46.5 ppm. The signals due to P_C were distorted triplets centered at $\delta(P_C) \sim 30.5$, 28.5 and 27 ppm., consistent with the proposed phosphorothioate structure for these phosphorus atoms [4, 5].

For the bisphosphonates (**4a–c**), the expected doublets centered at $\delta \sim 19$, 16.5 and 15.5 ppm. were observed for P_A and P_B together with triplets for P_C centered at ~28, 24 and 22.5 ppm. with $^3J(P_AP_C) \sim {}^3J(P_BP_C) \sim 12$ Hz.

In the ^{13}C NMR spectra of the ylids (**3a–c**), a distorted triplet of doublets of very low intensity was observed between 9 and 14 ppm. which could be attributed to the negatively charged carbon atom of the ylids as these signals had $J(CP_A) \sim J(CP_B) \sim 220$ Hz. The presence of these signals at high fields and the large coupling constant are consistent with the presence of a planar trigonal carbon atom of an ylid with high localisation of the negative charge on this carbon atom [6, 7]. The signal due to the corresponding carbon atom in the bisphosphonates (**4a–c**) appears in the region δ 35–39 ppm. and the coupling constant $^1J(CP)$ is only 139 Hz.

Surprisingly, in the ^1H NMR spectra of (**4a–c**) a quartet was observed for the proton attached to the bridge carbon atom instead of the expected triplet of doublets which would be expected from a large $^2J(HP) = {}^2J(HP)$ and a smaller $^3J(HP)$ coupling. The presence of this quartet implies the quasi-equivalence of these three coupling constants (ca 22 Hz) which was confirmed by ^{31}P NMR experiments. Irradiation of the methine proton of (**4a**) caused a simplification of the P_C signal of the fully coupled spectrum and allowed us to determine the $^3J(HP)$ coupling to be 21 Hz. When the isopropyl methine protons in compound (**4c**) were irradiated, the P_C signal appeared as a doublet of triplets with $^3J(P_AP_C) = {}^3J(P_BP_C) = 12$ Hz and $^3J(HP_C) = 20$ Hz (this last coupling was slightly attenuated by an off-resonance effect). In nitrogen analogues of compounds (**4a–c**), $^3J(HP)$ coupling constants from 11 to 14.5 Hz have been observed [8].

MECHANISM OF THE REACTION

In order to ascertain whether the thiocarbonyl bisphosphonates could be isolated at low temperature and in an attempt to gain some insight into the mechanism, the reactions between thiophosgene and trialkyl phosphites were followed by ^{31}P NMR in the temperature range −80 to −20°C. The reactions begin slowly at −80° with triethyl or tri-isopropyl phosphites and at −60° with trimethyl phosphite. As the reactions proceeded, the peaks in the NMR spectra due to the phosphites diminished and in every case a doublet appeared between 37.5 and 46 ppm. together with a triplet centered between 24.5 and 28 ppm. The relative intensities of the doublet and triplet were 2:1. The chemical shifts and multiplicites of these signals suggest the intermediacy in these reactions of (**5a–c**) (formally written with localised charges). At −40°C, when an excess of thiophosgene was used, all the trialkyl phosphite was consumed and (**5a–c**) were the principle reaction products.

Above −40°C, in the reactions with triethyl and trimethyl phosphite the signals due to (**5a**) and (**5b**) decreased in intensity with the appearance of the signals due

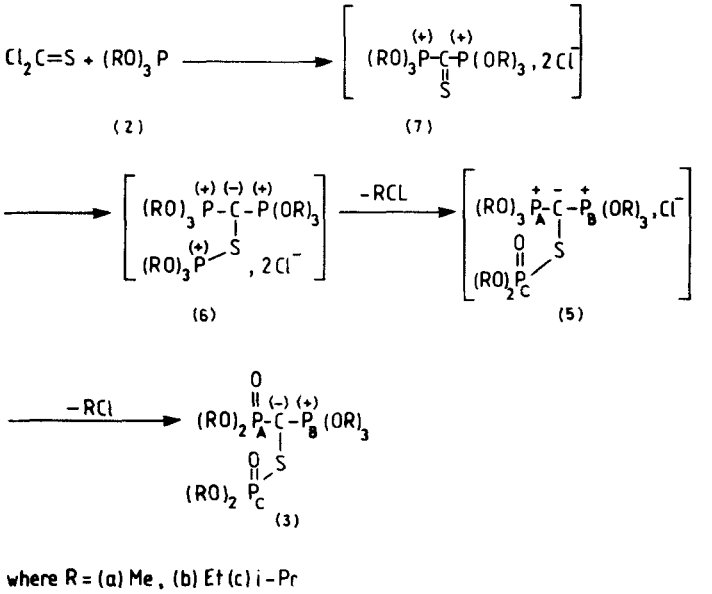

FIGURE 2 Intermediates in the formation of ylids (**3**) formed in the reaction between thiophosgene and trialkyl phosphites (**2**).

to the ylids (**3a**) and (**3b**) (the formation of small amounts of (**4a**) and (**4b**) could be detected at the same time). Species (**5c**) was more stable than (**5a**) or (**5b**) and its signal in the ^{31}P NMR spectrum of the reaction disappeared only at room temperature.

The formation of (**5a–c**) could be due to a monodealkylation of the intermediates (**6**) as soon as they were formed. In support of this hypothesis, we observed in the ^{13}C NMR spectrum of the reaction between thiophosgene and triethyl phosphite at −60°C, signals due to the two carbon atoms of ethyl chloride. This dealkylation appears to occur only at the trialkylphosphonium residue α- to the sulfur atom. Electronegative substituents on the phosphorus atom facilitate these elimination reactions and in this case they can occur at low temperatures. This is the case with the salts $(RO)_3P^+SCl$, Cl^- which lose RCl at −30° to give $(RO)_2P(O)SCl$ [9]. With our compounds (**5a–c**) a second dealkylation can occur at higher temperature to produce the ylids (**3a–c**). Neither the intermediates (**6**) nor their probable precursors the thiocarbonyl bisphosphonium dichlorides (**7**) could be detected in our reactions by ^{31}P NMR spectroscopy.

The reaction of trialkyl phosphites with thiocarbonyl compounds has a variety of synthetic applications including the syntheses of tetrathiafulvalenes [10], the formation of carbenes leading to alkenes [11], and the formation of phosphorus ylids [12, 13]. These reactions all appear to result from an initial thiophilic addition of the phosphite to the thiocarbonyl residue and ylid formation implies a desulfuration reaction carried out by a second equivalent of phosphite leading to an *O,O',O''*-trialkyl thiophosphate. Carbophilic addition to the thiocarbonyl group [14] and enethiolisation [15] have also been reported. In our reactions formation of this thiophosphate was not observed, stable ylids (**3a–c**) being the

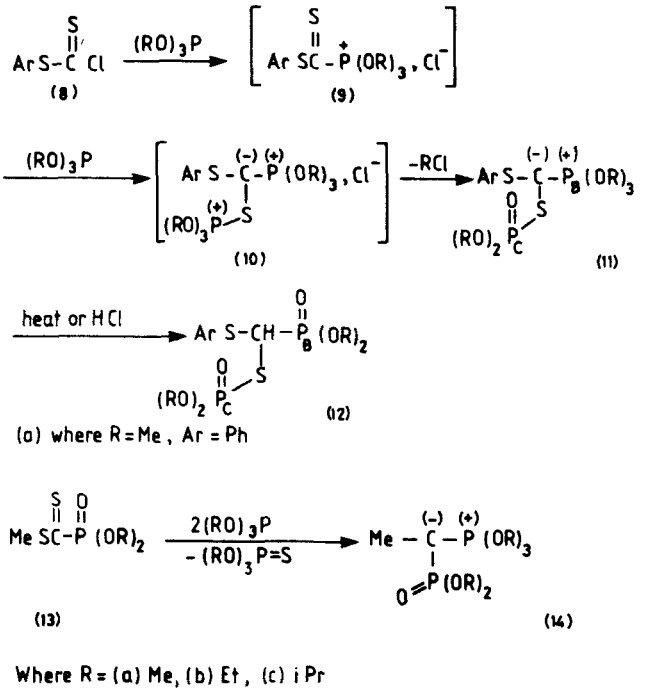

FIGURE 3 Reaction between aryl chlorodithioformates and trialkyl phosphites (**2**).

result of nucleophilic attack by chloride ions on the alkoxy substituents at phosphorus. Formation of ylids such as (**11**) without desulfuration has previously been observed in the addition of trialkyl phosphites to aryl chlorodithioformates (**8**) (Figure 3) [16].

The intermediate formation of $ArSC(S)P(O)(OR)_2$ can be excluded as we have recently observed the formation of an ylid (**14**) *with desulfuration* from an analogous dithioester (**13**) and we can propose a similar mechanism to that outlined in this paper for the reaction of the chlorodithioformate leading to the ylid (**11**) [17].

In the patent [16] which describes the preparation of compounds (**11**), only microanalyses are given to support their proposed ylid structures and no spectroscopic data are mentioned. In order to compare the NMR spectra of (**11**) with those of our ylids (**3a–c**), we prepared (**11a**) by the addition of trimethyl phosphite to phenyl chlorodithioformate. The reaction which was carried out in a d^6-benzene/hexane mixture was followed by ^{31}P NMR and was seen to begin slowly at −20°C with the appearance of narrow doublets at 48 [$^+P(OMe)_3$] and 31 ppm. [—S—P(O)$(OMe)_2$].

These chemical shifts are consistent with an ylid structure for (**11a**) but neither of the possible intermediates in this reaction (**9**) or (**10**) could be detected. The reaction was complete after 24 h at room temperature and in addition to (**11a**), compound (**12a**) could be detected by ^{31}P NMR (7%). Thus, (**11a**) undergoes protonation-dealkylation in a manner similar to that observed with the ylids

(**3a–c**) either on heating or following treatment with hydrochloric acid to yield (**12a**).

The NMR characteristics of (**11a**) and (**12a**) are very similar to those of (**3a–c**) and (**4a–c**) (Table II). In particular, a low field signal (dd ~ d) with a large ^1J(CP) coupling constant (268 Hz) due to the ylid carbon atom was observed in the ^{13}C NMR spectrum of (**11a**). In the ^{1}H NMR spectrum of (**12a**), the methine proton appears as a triplet indicating [as for (**4a–c**)] a quasi-equivalence of the ^2J(HP) and ^3J(HP) coupling constants (~16 Hz).

A characteristic of the ylids (**3a–c**) and (**11a**) is that thermal protonation–dealkylation occurs rather than the more usual migration of an alkyl group from the trialkoxyphosphonium residue to the ylid carbon [13, 14]. However, such thermal protonation has already been observed in the reaction of thiobenzophenone with trialkyl phosphites [17]. We did not detect any evolution of ethylene during the heating of (**3b**) and the protonation occurred as readily with MeO- as with EtO- or iPrO-phosphorus substituents. These observations appear to rule out protonation with the formation of alkenes but do not allow us to clarify the reaction mechanism which has already been discussed [18] but not elucidated.

EXPERIMENTAL

Thiophosgene and the trialkyl phosphites were commercially available and were distilled prior to use. All reactions were carried out under nitrogen.

^{1}H NMR spectra were recorded on a Varian EM 360 spectrometer at 60 MHz. ^{13}C and ^{31}P NMR spectra were recorded on a Bruker WP 80 SY spectrometer. Chemical shifts (ppm.) are given relative to tetramethylsilane (internal standard) or 85% H_3PO_4 (external standard). The following abbreviations are used to describe the spectra: s, singlet; d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet; M, several multiplets. Infrared spectra were recorded on a Perkin Elmer 684 spectrometer either as liquid films or solutions in CCl_4. Low resolution electron impact mass spectra were recorded on a Varian CH 5 spectrometer at 70 eV. High resolution EI mass spectra were recorded on a Kratos MS 80 spectrometer with a DS 55 data system.

Preparation of O,O-Dialkyl S-[(dialkoxyphosphinyl) (trialkoxyphosphoranylidene) methyl] phosphorothioates (**3**). The trialkyl phosphite (**2**, 30 mmol.) in tetrahydrofuran (THF) (15 ml.) was added to a cold (−78°C) solution of thiophosgene (15 mmol.) in THF (30 ml.). The mixture was left in the cooling bath and allowed to warm to room temperature over 16 h. Solvent and excess thiophosgene were removed in vacuo and the residual oils were analysed by ^{13}C and ^{31}P NMR and mass spectrometry.

The spectroscopic characteristics for the ylids (**3a–c**) and (**11a**) are given in Table II.

Preparation of O,O-Dialkyl S-[bis-(dialkoxyphosphinyl)-methyl] phosphorothioates (**4**). The crude ylids (**3a–c**) were dissolved in dichloromethane (20 ml) and the solutions cooled to 0°C before being

TABLE I

Molar ratios (%) of products from reactions between thiophosgene and trialkyl phosphites (**2**) (as determined by ^{31}P NMR)

$(RO)_3P$ (**2**)	(**3**)	(**4**)	$(RO)_2P(O)H$	$(RO)_3PO$
a: R = Me	63	23	2	12
b: R = Et	84	7	5	4
c: R = i-Pr	65	27	4	4

TABLE II

Characteristics of ylids (**3a–c**) and (**11a**)

	3a	**3b**	**3c**	**11a***	
^{31}P NMR DATA					
	Chemical Shifts ($CDCl_3$) (ppm)				
δ_{P_A} (dd)	28.15	27.63	25.90	—	
δ_{P_B} (dd)	55.05	49.69	46.69	48.3	(d)
δ_{P_C} (dd)	30.68	28.70	27.03	30.8	(d)
	Coupling Constants (Hz)				
$^2J(P_AP_B)$	123.8	120	130	—	
$^3J(P_AP_C)$	5.5	5.6	6	—	
$^3J(P_BP_C)$	3.5	5.3	6	3.3	
^{13}C NMR DATA#					
	Chemical Shifts ($CCl_4 + C_6D_6$) (ppm)				
	3a	**3b**	**3c**		
δ(ylid C) (td)	9.60	11.60	13.70	10.27	(dd ~ d)
	Coupling Constants (Hz)				
$^1J(CP_A) \sim {}^1J(CP_B)$	220	222	223	268	
$^2J(CP)$	4	4	4	2.5	
	Electron Impact Mass Spectra (parent ions, $M^{\pm}$ m/z)				
	386	484	582		—

* Prepared as in ref [16] from trimethyl phosphite and phenyl chlorodithioformate. NMR spectra recorded in $CCl_4 + C_6D_6$.

\# In addition, signal due to the alkoxy groups were as follows: (**3a**) $\underline{C}H_3OP_B$ 51.75 ppm (d, $^2J(CP_B) = 5.1$ Hz), $\underline{C}H_3OP_C$ 53.37 ppm (d, $^2J(CP_C) = 5.9$ Hz), $\underline{C}H_3OP_A$ 55.74 ppm (d, $^2J(CP) = 6.65$ Hz). (**3a**) $\underline{C}H_3CH_2$ 15.50 ppm (m), $CH_3\underline{C}H_2$ 60.18, 62.39, 64.61 ppm (**3d**) $^2J(CP) = 5.2$, 6.2, 6.7 Hz). (**3c**) $\underline{C}OP_A$ 67.70 ppm (d, $^2J(CP_A) = 6$ Hz), $\underline{C}OP_C$ 70.10 ppm ($^2J(CP) = 7$ Hz), $\underline{C}OP_B$ 73.6 ppm (d, $^2J(CP_B) = 7$ Hz).

saturated with HCl gas. After 20 min., the solvent was removed in vacuo and the phosphorothioates (**4a–c**) were isolated as pale brown oils. Alternatively, compounds (**4a–c**) could be obtained by heating crude (**3a–c**) under nitrogen in an oil bath at 100–110°C for 16 h. The crude phosphorothioates were purified when required by chromatography on silica gel (eluant: acetone) and their properties are given below. All NMR spectra were recorded in solution in $CDCl_3$ unless otherwise stated.

(**4a**) *R = Me*. Crude yield 95%, purified yield 52%. Analysis: found S, 8.62%, calc. for $C_7H_{19}O_9PS$, S 8.72%. ^{1}H NMR (C_6D_6): 3.2–3.9 (M, OCH_3), 4.25 (q, $^2J(HP) = {}^2J(HP) \sim {}^3J(HP) \sim 22$, P_A—C*H*—P_B). ^{31}P NMR: 19.07 (d, $^3J(P_AP_C) = {}^3J(P_BP_C) \sim 12$, P_A and P_B), 20.73 (t, $^3J(P_CP_A) = {}^3J(P_CP_B) = 12$, P_C). ^{13}C NMR 35.3 (td ~ t $^1J(CP_A) = {}^1J(CP_B) = 139$, $^2J(CP_C) = 4.3$ Hz, P_A-*C*-P_B), 54.4 (narrow *M*,

TABLE III

^{31}P NMR Characteristics of Compounds (5)*

	5a	**5b**	**5c**
$\delta_{P_A} = \delta_{P_B}$(d)(ppm)	46.26	42.50	37.69
δ_{P_C} (t)(ppm)	27.75	24.38	24.76
$J(P_AP_C) = J(P_BP_C)$ (Hz)	5.3	5.5	5.6

* In THF, $CDCl_3$.

OCH_3), off-resonance 35.3 (~dt), 54.4 (~q), off-decoupling 35.3 (dtq, $^1J(CH) \sim {}^1J(CP_A) = {}^1J(CP_B) = 139$), 54.4 ppm. (~q, $^1J(CH) = 149$ Hz). EI mass spectrum [*m/z*, (%)] 372 (22) M^+, 263(31), 246(76), 187(28), 104(29), 93(100). Accurate mass: found $(M)^+$ *m/z* 371.9927, calc. for $C_7H_{19}O_9P_3S$ 371.9962. IR (film) $cm.^{-1}$ 1255 (P═O), 1180 (P—OMe).

(**4b**) *R = Et.* Yield 83% (relative to $(EtO)_3P$ determined by ^{31}P NMR using $(MeO)_3PO$ as standard). ^1H NMR 1.38 (~t, $J(HH) = 7$ Hz, O—CH_2—CH_3), 3.94 (q, $^2J(HP_A) = {}^2J((HP_B) \sim {}^2J(HP_C) = 22$ Hz, P_A—CH—P_B), 4.13 (~qi, $J(HH) \sim {}^2J(HP) = 7$ Hz, S—P—O—CH_2—CH_3), 4.28 ppm. (~qi, $J(HH) \sim {}^2J(HP_A) = {}^2J(HP_B) = 7$ Hz, C—P—O—CH_2—CH_3). ^{31}P NMR 16.74 (d, $^3J(P_AP_C) = {}^3J(P_BP_C) \sim 12$ Hz, P_A and P_B), 24.26 ppm. (t, $^3J(P_AP_C) = {}^3J(P_BP_C) \sim 12$ Hz, P_C). ^{13}C NMR 16.39 (narrow M, P—O—CH_2CH_3), 36.63 (dt, $^1J(CP_A) = {}^1J(CP_B) = 139$, $^2J(CP_C) = 4.4$ Hz, P_A—C—P_B), 63.78 ppm. (M, P—O—CH_2—CH_3); off-decoupling, 16.39 (~q, $^1J(CH) = 148$ Hz), 36.63 (ddt ~ q, $^1J(CP_A) = {}^1J(CP_B) \sim J(CH) = 139$, $^2J(CP) = 4.4$ Hz), 63.78 (~*t*, $^1J(CH) = 148$ Hz). IR (film) $cm.^{-1}$ 1255 (P═O), 1165 (P—OEt). Mass spectrum: found $(M)^+$ *m/z* 456.0906, calc. for $C_{13}H_{31}O_9P_3S$: 456.0901.

(**4c**) *R = i-Pr.* Yield 88% relative to triisopropyl phosphite as determined by ^{31}P NMR as for (**4b**). ^1H NMR 1.4 (d, $^3J(HH) = 7$ Hz, CH—CH_3), 3.9 (q, $^2J(HP_A) = {}^2J(HP_B) \sim {}^3J(HP_C) = 22$ Hz, P_A—CH—P_B). 4.46–5.16 m, CH—O—P). ^{31}P NMR 15.57 (d, $^3J(P_AP_C) = {}^3J(P_BP_C) = 12$ Hz, P_A and P_B), 22.49 ppm. (t, $^3J(P_AP_C) = {}^3J(P_BP_C) = 12$ Hz, P_C). When the isopropyl proton signal was irradiated in an off-resonance, off-decoupled spectrum the splitting changed to (dt, $^3J(P_AP_C) = {}^3J(P_BP_C) = 12$, $^3J(HP_C) = 20$ Hz). ^{13}C NMR 24.0 (M, CH—CH_3), 39.04 (dt, $^1J(CP_A) = {}^1J(CP_B) = 140$, $^3J(CP_C) = 4$ Hz, P_A—C—P_B), 73.25–72.04 ppm. (M, >CH—). IR (film) $cm.^{-1}$ 1255 (P═O), 1185 (P—O—iPr). Mass spectrum: found $(M)^+$ *m/z* 540.1807, calc. for $C_{19}H_{43}O_9P_3S$ 540.1840.

NMR Characteristics of Compound (**12a**). Compound (**12a**) was detected in samples of (**11a**) prepared as described. ^1H NMR 4.8 ppm. (t, $J(HP_B) = J(HP_C) = 16$ Hz), ^{31}P NMR 20.80 (d, $J(P_BP_C) = 18$ Hz, P_B), 22.49 (d, P_C). ^{13}C NMR 48.2 ppm. (dd, $J(CP_B) = 155$, $J(CP_C) = 4.3$ Hz, S—CH—P_B).

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