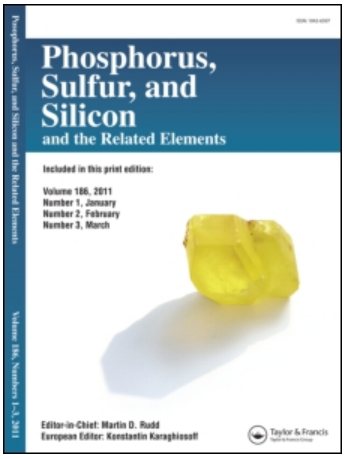

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The Reactions of Phosphonodithioformates with Nucleophilic Reagents

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THE REACTIONS OF PHOSPHONODITHIOFORMATES WITH NUCLEOPHILIC REAGENTS

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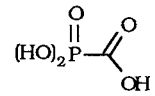
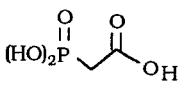
The reactions of phosphonodithioformates with trialkylphosphites, organometallics, hydrides, radicals, amines and thiols have been studied. The results obtained demonstrate that these phosphonodithioesters can be used for carbon-carbon bond formation *via* their reaction with organometallics (ketene dithioacetals, homologation of aldehydes) and for the preparation of substituted methylene bis-(phosphonates) via stabilised ylids. They are radical trapping agents and also precursors of a large variety of new functionalised phosphonates which may have biological activities [thiocarbamoylphosphonates, (aminomethyl)-, [tris-(alkylthiomethyl)]- and (mercaptomethyl)-phosphonate derivatives].

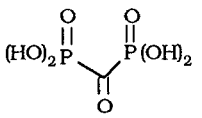
Key Words phosphonate, dithioester, phosphonodithioformate, addition of nucleophiles

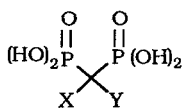
INTRODUCTION

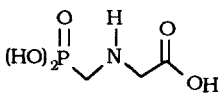
The interest of phosphonates, in addition to their use as synthetic intermediates, is their biological activity resulting from their structural similarity to phosphates. In particular some are enzyme inhibitors or good metal complexing agents and are widely used in medicine and agriculture.[1] Examples are phosphonoformic (Foscarnet)[2], phosphonoacetic and carbonyl bis-(phosphonic) [3] acids which have antiviral properties (in particular anti-HIV), methylene bis-phosphonic acid derivatives (pyrophosphate analogues) such as "clodronate" used in bone disease therapy[4], aminophosphonic acid such as "glyphosate"[5-10] (a well known herbicide) and also (phosphonomethoxyethoxy)adenine or PMEA, a non cyclic nucleoside analogue and relatively promising anti-HIV agent.[11]

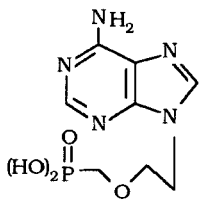

Foscarnet



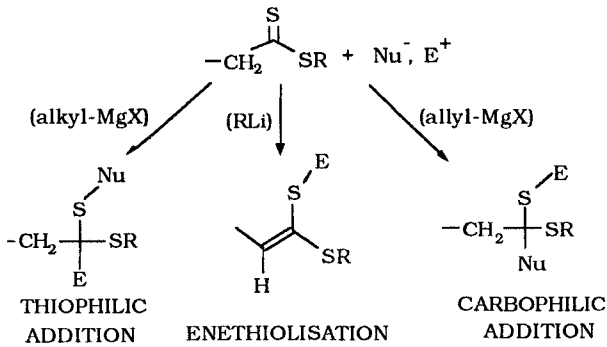



Clodronate
X = Y = Cl

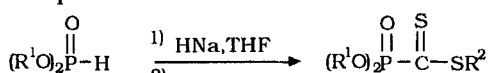

Glyphosate


PMEA

Therefore the initial reason for our interest in phosphonodithioformates was the idea that, in these phosphonates, the substitution of oxygen (on phosphorus or on carbon) by sulfur might increase the metal chelating properties which were thought to be linked to the antiviral activity.[12] Enhancement of this activity was actually observed in some cases[13] but unfortunately not with phosphonodithioformates, sulfur analogues of Foscarnet. However, as far as the chemical properties are concerned, we found that these compounds, which cumulate two functions, phosphonate and dithioester, each well known for their synthetic potential, present interesting reactivity. They are, in particular, intermediates for carbon-carbon bond formation, precursors of new sulfur substituted pyrophosphate analogues and of a variety of new functionalised phosphonates with potential biological activities.



The chemistry of dithioesters has been an important research theme in our laboratories[14,15] and it is now well known that the reaction of nucleophilic reagents with dithioesters can proceed *via* three different routes : the thiophilic addition (addition of the nucleophilic moiety to the sulfur atom, an example of which being the reaction of alkyl Grignard reagents), the carbophilic addition (observed in particular with allylic Grignard reagents), and the α-deprotonation or enethiolisation (when there is as least one proton α to the thiocarbonyl group) which was often observed with the more basic nucleophiles such as organolithium compounds.



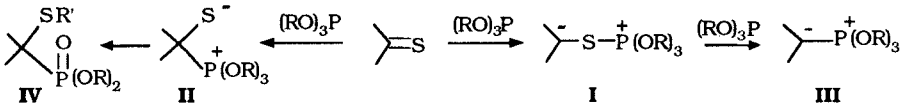
R^1 = Et, iPr R^2 = Me, allyl, crotyl, dodecyl, MEM

Phosphonodithioformates **1** are non enethiolisable functionalised dithioesters easily accessible *via* the reaction of carbon disulfide with the sodium salt of a dialkylphosphite followed by an S-alkylation. We used this reaction described by Grisley[16] to obtained phosphonodithioesters with various R^1 and R^2 groups. Previous work by our research

group [17] and a more recent review from Viola, Hartenauer and Mayer[18] have pointed out that the thiophilic addition to a thiocarbonyl group is enhanced by an α-carbonyl or sulfonyl substituent. The α-phosphonyl group found in phosphonodithioformates was expected to produce the same effect and herein are presented our results concerning the addition of some nucleophilic reagents to the thiocarbonyl group of these phosphonodithioesters. The reactions of phosphonodithioformates with trialkylphosphites, organolithium and magnesium reagents, hydrides, radicals, amines, thiols together with some synthetic applications will be dicussed.

TRIALKYLPHOSPHITES

Previous studies have shown the versatility of the addition of this reagent to thiocarbonyl compounds.[19] With 1,3-dithiolethiones, the well known coupling reaction with desulfuration is observed, leading to tetrathiafulvalenes, components of organic conductors[20, 21, 22]. COREY and co-workers[23] have observed alkene formation from bicyclic 1,3-dithiolane thiones. Desulfurization with formation of an ylid was observed from a 1,3 dithiacyclohexanethione[24, 25] and also from hexafluorothioacetone[26]. An initial thiophilic addition is generally assumed in all these reactions leading to a dipolar intermediate **I**, the evolution of which depends on the nature of the substituents of the thiocarbonyl group (desulfuration leading to intermediate carbenes is most often involved in these reaction pathways).

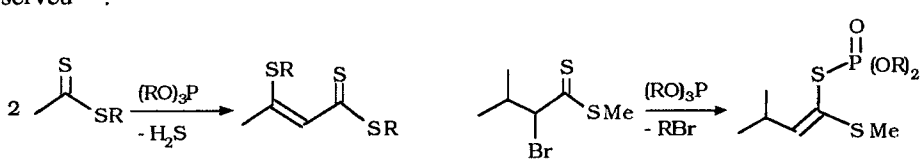


IV **II** **I** **III**

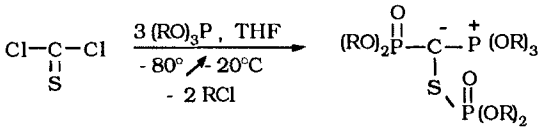
R' = H or R

On the contrary, with cyclohexanethione, a carbophilic addition followed by an internal alkylation or protonation of the assumed intermediate **II** gives α-mercapto or alkylthio-phosphonates.[27,28]

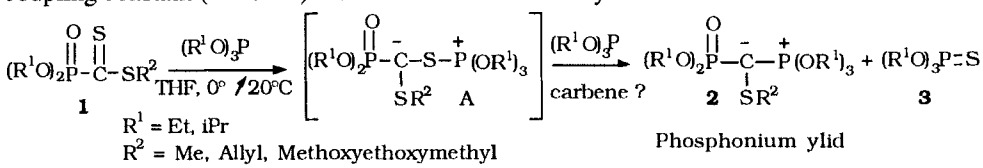
Only two studies concerning dithioesters have been published previously : from an alkyl dithioacetate a deprotonation and Claisen type reaction occurs[29] and from an α-bromodithioester, elimination of bromine with formation of a ketene dithioacetal is observed [30].



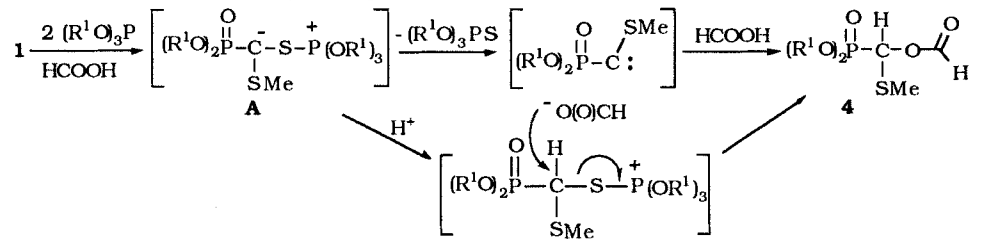
Both carbophilic and thiophilic additions followed by Arbuzov type dealkylations leading to a stable phosphonium ylid have been observed by ourselves in a previous study concerning the addition of trialkylphosphite to thiophosgene.[31]



With phosphonodithioformates **1**, the addition of two equivalents of triethyl or triisopropyl phosphite gave phosphonium ylids **2** and thiophosphates **3** (in nearly quantitative yield) [32] *via* a thiophilic addition leading to the dipolar intermediate **A**, then reaction with a second equivalent of trialkylphosphite with desulfurisation. An intermediate carbene is possible in this process. The stabilized ylids are easily characterised by ^{1}H, ^{31}P and ^{13}C NMR. In particular, a high field signal for the central carbon and a large C-P coupling constant (~200 Hz) are characteristic of these ylids.

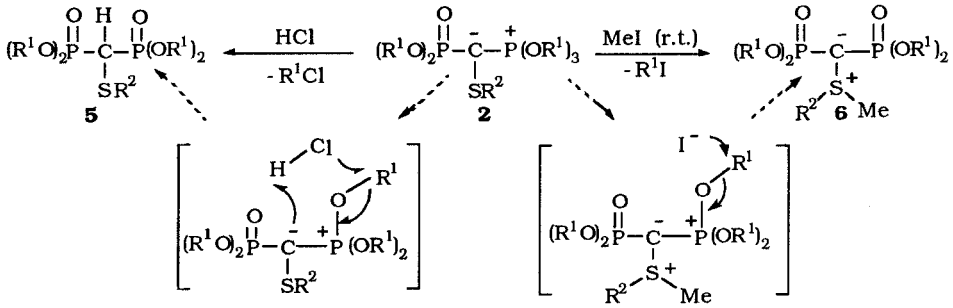


A relatively similar reaction was recently observed for the addition of trialkyl phophite with aryl substituted acyl phosphonates[33] and the formation of secondary products can be explained by intramolecular carbene insertion. We were not able in our case to prove the formation of an intermediate carbene but when the reaction was carried out in the presence of formic acid, a formate **4** is the main product formed. This could result from an insertion reaction of the carbene in the acid or by a protonation of the dipolar intermediate **A** followed by a thiophosphate-formate substitution.

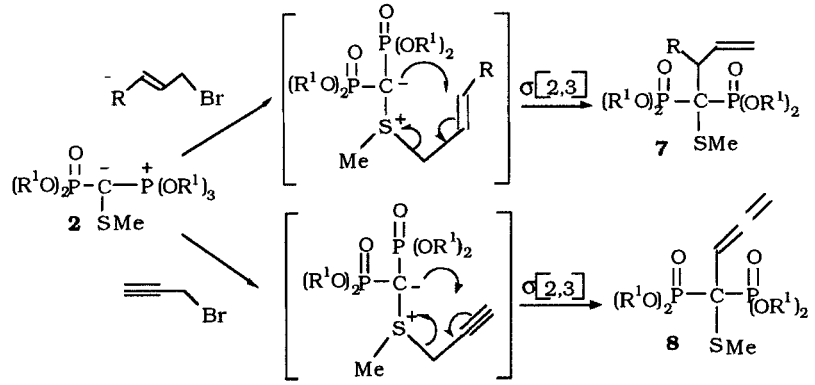


When treated with hydrochloric acid, the phosphonium ylids **2** led quantitatively to alkylthiomethylene bis-(phosphonate) **5**. This reaction proceeds, very likely, through a protonation at the negatively charged carbon with an Arbuzov type dealkylation of the phosphonium moiety.

By addition of methyl iodide to the phosphonium ylid **2**, no methylation on the central carbon was observed and we obtained quantitatively a very stable sulfonium ylid **6** which can even be flash distilled when R^2 = Me. Methylation of the sulfur atom with an Arbuzov type dealkylation can easily explain this result. With R^1 = ethyl or isopropyl, the alkyliodide formed by the Arbuzov dealkylation could *a priori* interfere in the reaction. In fact, these alkyliodides are much less reactive than methyl iodide and do not react at room temperature with the phosphonium ylid. With benzyl bromide, a S-methyl, S-benzyl sulfonium ylid **6** was equally obtained.

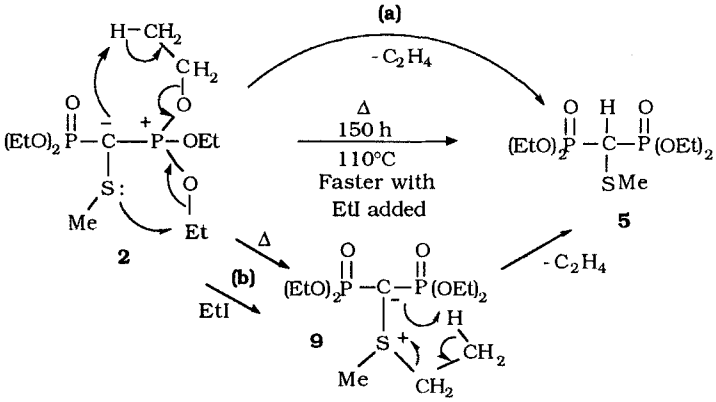


With an allylic halide, the final product is not a sulfonium ylid but a bis-(phosphonate) **7** resulting from an allylation on the central carbon atom, with inversion of the allylic chain. The mechanism we propose for this reaction (confirmed by a crossover experiment) is an initial allylation on the sulfur leading to an S-allylic ylid which readily undergoes a [2,3] sigmatropic rearrangement. The same reaction performed with propargylic bromide affords an allenic methylene bis-(phosphonate) **8**. Derivatives of methylene bis-(phosphonates) which are new pyrophosphate analogues, can thus be obtained via the reaction of trialkylphosphite with phosphonodithioformates.

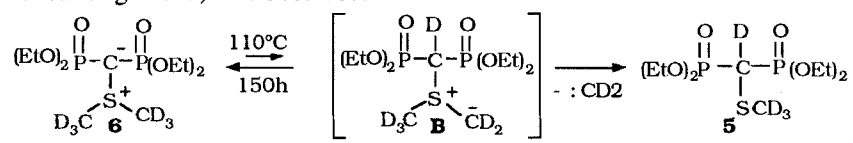


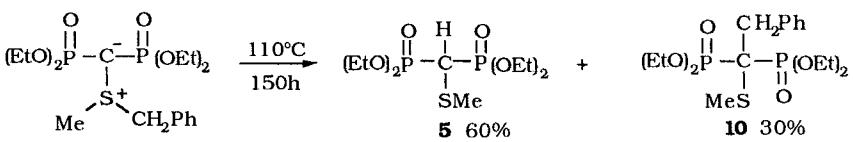
These phosphonium and sulfonium ylids **2** and **6** stabilised by the phosphonyl groups, subsequently have reduced reactivity. They don't react with carbonyl compounds even in refluxing tetrahydrofuran. However, at temperatures above 100°C they undergo an

auto-protonation - dealkylation leading to the methylene bisphosphonate **5** obtained previously by hydrochloric acid treatment. For example, when the phosphonium ylid **2** (R^1 = Et) was warmed in a sealed tube at 110°C for several hours we observed its complete transformation into the bis-(phosphonate) **5**. A direct protonation with elimination of ethylene (path **a**) can be envisaged. However, as an intermediate methyl-ethyl sulfonium ylid **9** was isolated in an uncomplete reaction, a mechanism (path **b**)involving a migration of an ethyl group from oxygen to sulfur followed by a thermal protonation of **9** (with elimination of ethylene) can be assumed. An increase of the reaction rate by the presence of ethyl iodide which can alkylate the sulfur atom of **2** (with Arbuzov type dealkylation) to give **9** is in favour of this mechanism.

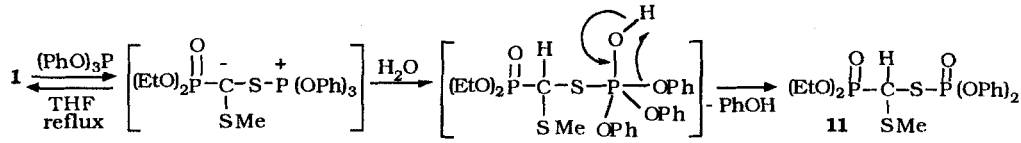


A more amazing observation is that the thermal transformation of a sulfonium ylid into a bisphosphonate was also observed from the S-dimethyl ylid **6**. No elimination of ethylene can be involved here and we proposed an internal protonation leading to a non stabilised sulfonium ylid which eliminates the carbene to give the bis-(phosphonate) **5**. To confirm this hypothesis, we prepared the corresponding deuterated sulfonium ylids **6** and we actually observed the formation of the bis-(phosphonate) **5** deuterated on the central carbon atom. With the S-methyl, benzyl sulfonium ylid, together with the S-methyl bis-(phosphonate) **5**, the bis-(phosphonate) **10** resulting from the transfer of the benzyl group (Stevens rearrangement) was observed.



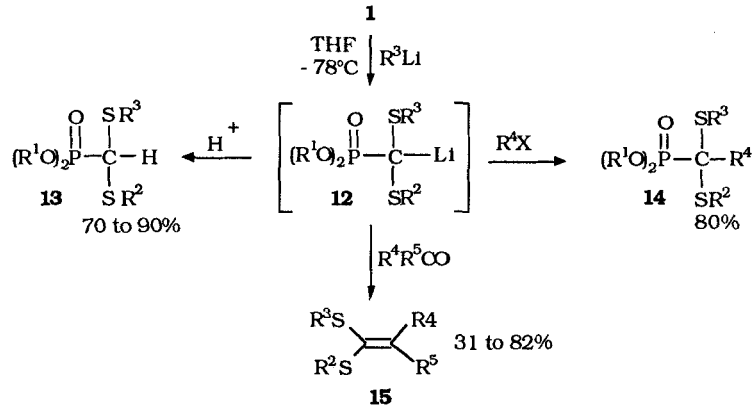


It is noteworthy that we did not observe the formation of any phosphonium ylid by reaction of the less reactive tri**phenyl**phosphite with phosphonodithioformates. With this reagent a reaction occurred only in the presence of water. A thiophosphate **11** resulting from a thiophilic addition without any desulfurization is obtained together with one equivalent of phenol. The formation of this thiophosphate can be explained by a reversible thiophilic addition of the phosphite, the addition of water to the resulting dipolar intermediate followed by the elimination of phenol.



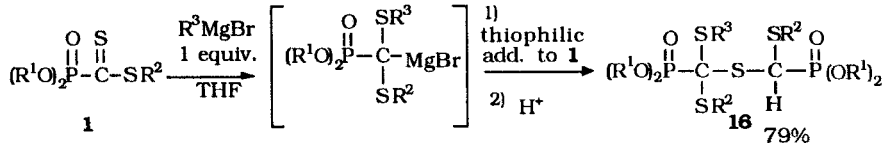
ORGANOMETALLICS

As we could expect for these non enethiolisable dithioesters activated by an electron withdrawing group, the addition of organolithium reagents was thiophilic and led to a lithiated phosphonodithioacetal **12** which was protonated or alkylated to give dithioacetals **13** or **14** in good to excellent yields.[34] Protected formyl and acyl phosphonates are thus obtained. The better yields were obtained with R¹= iPr and the addition of PhLi. It was shown previously that the lithiated phosphonodithioacetals can be used as Wittig-Horner-Wadworth-Emmons reagents for the synthesis of ketenedithioacetals (useful intermediates in organic synthesis)[35]. From these same lithiated dithioacetals **12**, prepared by thiophilic addition and then condensed *in situ* with aliphatic or aromatic aldehydes or ketones ketene dithioacetals **15** were easily prepared.[34]

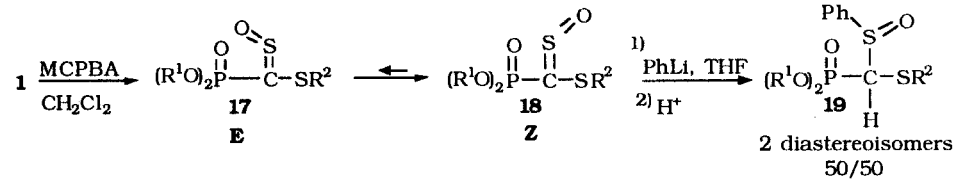


We have also examined the reactivity of Grignard reagents with the phosphonodithioformates but they appeared much less convenient than the lithium compounds for one pot Wittig-Horner reactions. With one equivalent of Grignard reagent,

the main product **16** isolated after hydrolysis results from the thiophilic addition of the metallated dithioacetal to the starting dithioester. It is necessary to use a large excess of Grignard reagent to minimize the formation of this coupled product.

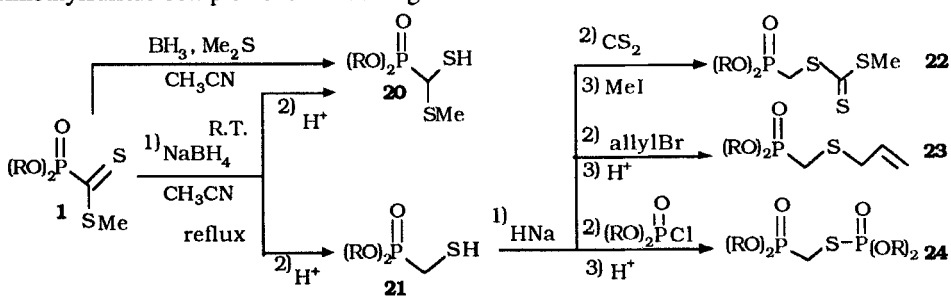


Sulfines of phosphonodithioformates were prepared by oxidation of phosphonodithioformates **1** with *meta*-chloroperbenzoic acid. The E sulfine **17**, initially formed, rearranged completely, over 24 hours, into its Z-isomer **18.** From this sulfine, a thiophilic addition of phenyllithium was observed, affording after hydrolysis a mixture of two diastereoisomers **19**.



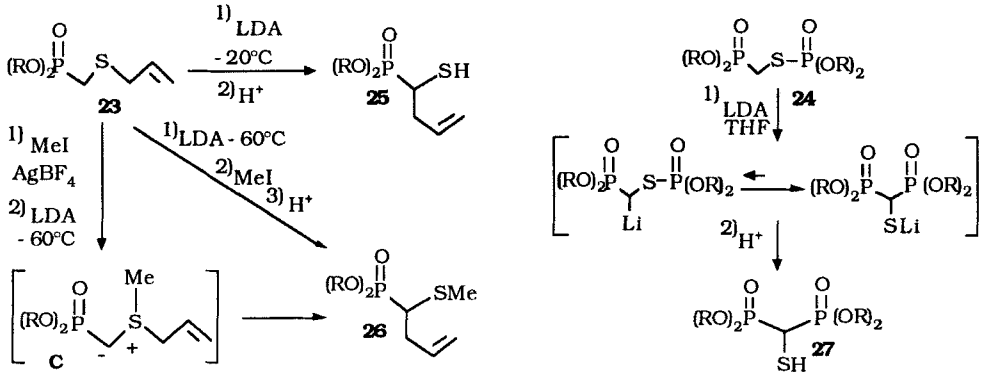
HYDRIDES

(α-Mercaptomethyl)phosphonates are less well known that their hydroxy or amino analogues. We found that the dithioester function of phosphonodithioformates can be selectively reduced by sodium borohydride in acetonitrile.[36] Hemidithioacetals **20** were obtained at 20°C. At reflux temperature, (mercaptomethyl)phosphonates **21** were isolated in very good yields and this is a convenient route to such compounds prepared previously by two other ways.[37, 38] Only hemidithioacetals were obtained with the borane-dimethylsulfide complex even in boiling acetonitrile.



The sodium salt of (mercaptomethyl)phosphonates can be used for the preparation of other functionalised phosphonates.[36] Some examples are trithiocarbonates **22**, by condensation with carbon disulfide (or dithiocarbamates with an isothiocyanate), S-allylic

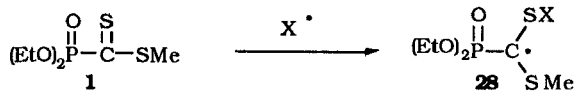
derivatives such as **23** by addition of allylic halides and thiophosphates **24**, by phosphorylation with chlorophosphate. Moreover, we found that compounds **23** and **24** are themselves precursors of new (mercaptomethyl)phosphonate derivatives.



Deprotonation at -20°C of the (S-allylthiomethyl)phosphonates **23** led quantitatively to an allylic α-mercaptophosphonate **25** resulting from a 2,3-sigmatropic rearrangement.[39] In the presence of methyl iodide, the same rearrangement leading to the methylated homologue **26** was observed at lower temperature (- 60°C). We also observed the sigmatropy at - 60°C via the addition of a base to the corresponding sulfonium salt (prepared by methylation of **23** in the presence of $AgBF_4$), that is to say *via* the non isolated S-allyl, S-methyl ylid **C**. Therefore, such an intermediate ylid resulting from an alkylation on sulfur could also be suggested for the rearrangement of the carbanion in the presence of methyl iodide which also occurs at -60°. Further experiments are in progress concerning these sigmatropic rearrangements (mechanism, stereochemistry, synthetic uses) which have also been observed by us with other allylic derivatives (S-crotyl, S-methallyl, S-prenyl). Another interesting result we have recently observed is the complete thiophosphate-mercaptophosphonate conversion by metallation of the S-(phosphonomethyl)thiophosphate **24**. The mercapto methylene bis-(phosphonate) **27**, surprisingly not previously described was isolated. It is noteworthy that the inverse rearrangement is usually observed with α-hydroxyphosphonates.

RADICALS

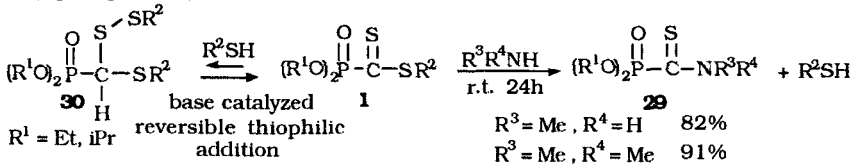
In collaboration with A. Hudson from the University of Sussex and A. Alberti from the Italian CNR of Bologna, we studied the addition of various alkyl, alkoxyl, thiyl, and organometallic radicals. In all cases, a thiophilic attack of the radicals led to rather persistant spin adducts **28** which could be studied by ESR spectroscopy.[40] Therefore phosphonodithioformates appears as new and potentially useful radical trapping agents.



X = Me, Bz, t-Bu, Phe, Ot-Bu, SMe, SPhe, $SiPh_3$, $GePh_3$, $SnPh_3$, $PbPh_3$

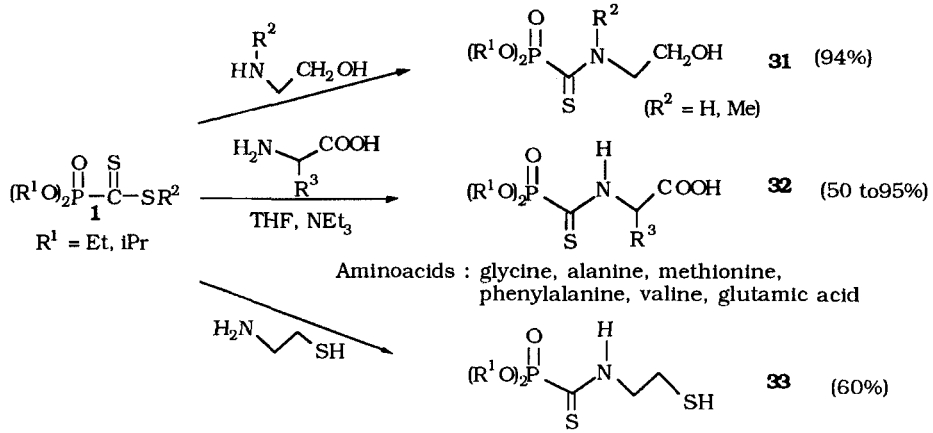
AMINES

The reaction of alkylamines with dithioesters is a well known reaction.[41] A carbophilic addition readily occurs at room temperature leading to thioamides. However, the regioselectivity of the reaction of amines with a dithioester bearing a strong electron withdrawing α-substituant favorising a thiophilic addition, could have been modified. This was not the case with phosphonodithioformates and alkyl- or dialkyl-amines. The usual carbophilic addition of these "hard" nucleophiles leading to thioamides was observed. The reaction is nearly instantaneous at room temperature. However, the synthetic interest of this "phosphonothiocarbonylation" reaction of amines which leads to (thiocarbamoyl)-phosphonates (or phosphonothioamides) **29** was apparently limited by the formation of a secondary product (about 30%) of a dithioacetal-disulfide **30**. This product results from the thiophilic addition (in basic medium) of the thiol liberated in the reaction to the thiocarbonyl group of the starting phophonodithioformates. Such an addition has already been mentioned in some cases with thiocarbonyl group activated by electron withdrawing groups.[18] However, further studies (vide infra) related to the preparation and stability of these dithioacetal-disulfides demonstrated the reversibility of this thiophilic addition of thiols. This observation led us to check if this reversibility could be observed by increasing the reaction time of the phosphonothiocarbonylation of amines. The formation of the thioamide being irreversible, we actually observed with methylamine or dimethylamine, after about 24 hours, the quasi disapearence of the dithioacetal disulfide **30** and the thioamides **29** were isolated in very good yields. Therefore, the reaction of amines with phosphonodithioformate appears a convenient method for the preparation of thiocarbamoylphosphonates.[42]



Only a few thiocarbamoylphosphonates had previously been described and they were prepared by addition of dialkylphosphites to isothiocyanates[43] or by an Arbuzov type reaction between trialkylphosphites and thiocarbamoyl chlorides.[44] However, in these reactions, nitrogen substituents are limited to alkyl or phenyl group. Some of these compounds present herbicidal and pesticidal properties.[45] Therefore we decided to check

the efficiency of the phosphonothiocarbonylation in the case of functionalised amines. New functionalised phosphonates **31**, **32** (glyphosate type compounds) and **33** were thus prepared in good yields with aminoethanols, with various L-aminoacids in the presence of one equiv. of triethylamine and with aminoethanethiol.

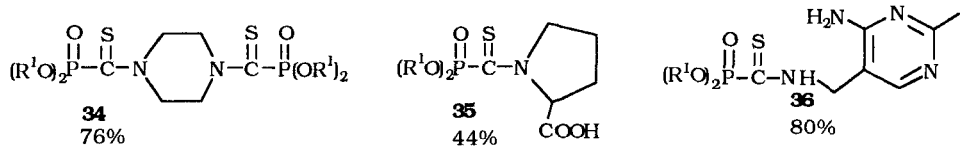


31 (94%) (R^2 = H, Me)

32 (50 to95%)

33 (60%)

Other new thiocarbamoylphosphonates **34**, **35** and **36** were obtained from piperazine, proline and with an aminoethylaminopiperidine.

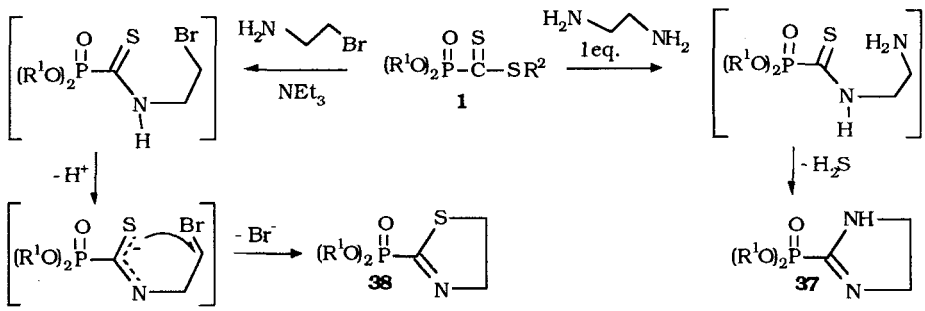


34 76%

35 44%

36 80%

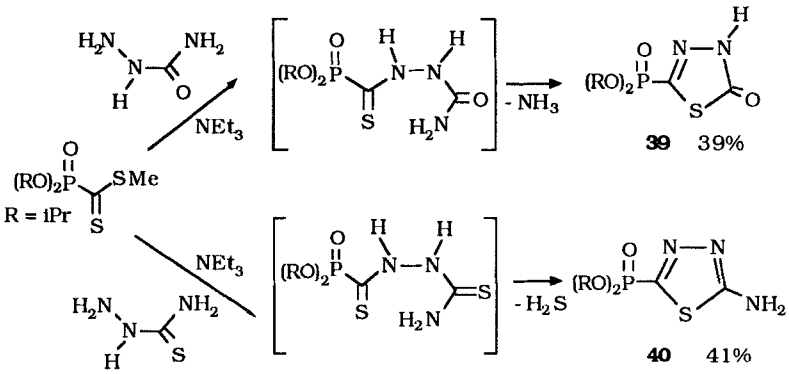
The phosphonothiocarbonylation of functionalised amines was sometimes followed by a cyclisation and elimination reaction leading to the formation of new phosphonyl substituted heterocycles. This was the case with one equiv. of ethylene diamine which gave, after elimination of hydrogen sulfide, the phosphonodiazoline **37** and also with bromoethylamine (in the presence of ethylamine) which led, after elimination of hydrobromic acid, to a phosphonothiadiazoline **38**.



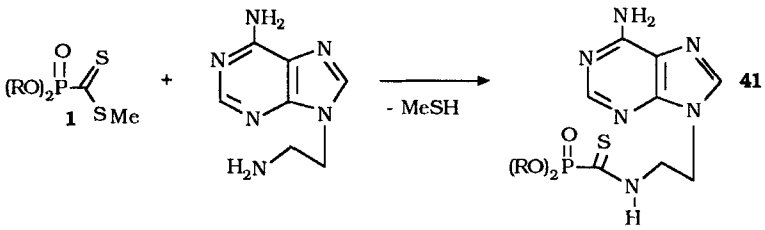
38

37

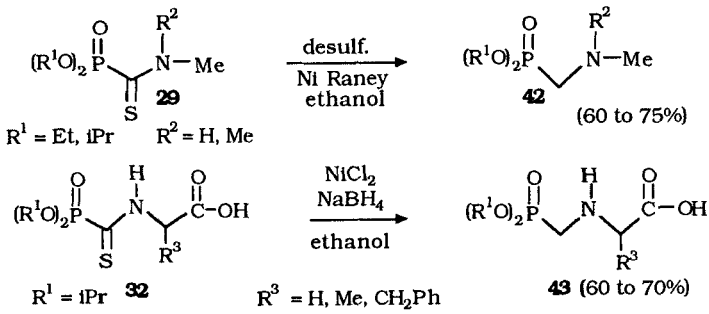
With the semicarbazide, cyclisation with elimination of ammonia gave a phospohono-thiadiazolone **39** and with the thiosemicarbazide, cyclisation with elimination of hydrogensulfide led to a phosphono-amino-thiadiazole **40**.



A thiocarbamoylphosphonate **41**, presenting some analogy with the anti-HIV nucleoside PMEA (introduction scheme), was also prepared from aminoethyladenine (an amine not previously describe, that we prepared via alkylation of the sodium salt of adenine by the protected mesylate of aminoethanol). Unfortunately, no inhibition of the reverse transcriptase of HIV was observed with this thioamide and we are going to desulfurize this compound to get the aza-analogue of the PMEA.



Aminomethylphosphonic acids, (a good example being glyphosate), are very often biologically active and are potential enzyme inhibitors.[1a] We studied the desulfurization of thiocarbamoylphosphonate as a new preparative method of such compounds. We found that Raney nickel can be used to desulfurize N-alkyl substituted thiocarbamoyl phosphonates **29** into aminophosphonates **42**. This reagent was not siutable for functionalised thiocarbamoylphosphonates substituted by a carboxylic function such as **32** (partial reduction into alcool). However, these compounds were smoothly desulfurized in 15 min. by nickel boride, prepared *in situ* from nickel chloride and sodium borohydride, without any reduction of the acid function. New functionalised aminophosphonates **43** could thus be isolated in 60 to 70% yield.



29 R^1 = Et, iPr R^2 = H, Me

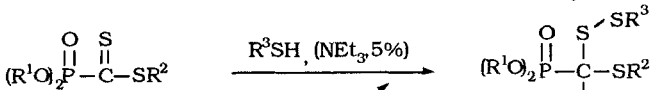
42

32 R^1 = iPr R^3 = H, Me, CH_2Ph

43 (60 to 70%)

THIOLS

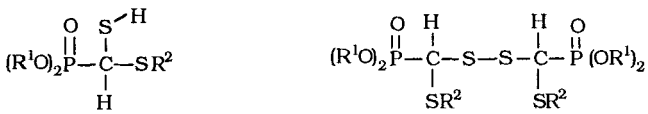
The obtention of dithioacetal-disulfides as a secondary product in the reaction of amines with phosphonodithioformates, incited us to study the addition of thiols to these dithioesters, catalysed by a tertiary amine. Various thiols were added to phosphonodithioformates at low temperature in the presence of a catalytic amount of triethylamine. Dithioacetal-disulfides **44** were obtained in excellent yields.[46]



1 44

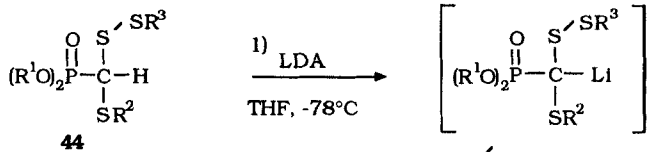
R^1 = Et, iPr ; R^2 = Me, allyl ; R^3 = tBu, n-Pr, Me, Ph, Bz, dodecyl

The optimum conditions to get these disulfides without secondary products are: low temperature, a catalytic quantity of base and an inert atmosphere to prevent any oxidation. When the reaction was performed at room temperature, an hemidithioacetal **45**, (reduction product), was isolated, together with **44**, as by-product. With one equivalent of triethylamine, the formation the disulfide **46**, was the main product formed.



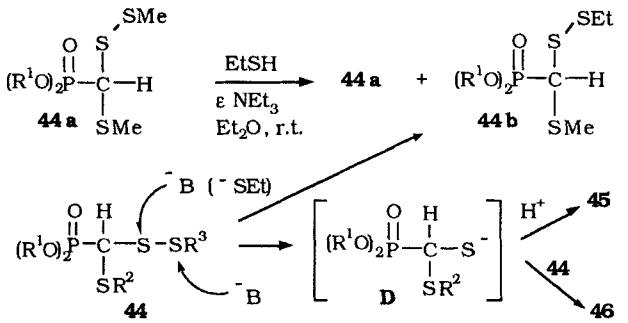
45 46

We studied the behavior of the dithioacetal-disulfides **44** after metallation with LDA at low temperature and protonation. When methanol, saturated by hydrochloric acid, was used for the protonation (at low temperature), the starting dithioacetal was integraly recovered. No apparent breaking of the S-S bond occurs in these conditions. However, the coupling product **46** was mainly observed when water or methanol alone was added for protonation and the mixture allowed to warm up to room temperature in the basic medium.

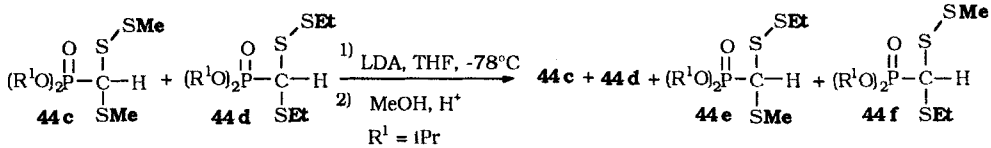


	46	+	44
	%		%
THF/H_2O	95		5
MeOH	75		25
MeOH/HCl	0		100

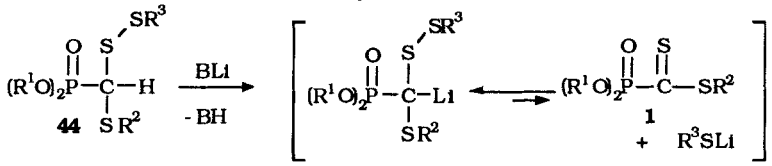
Moreover, we observed an easy exchange of the alkylthio group of the disulfide moiety when the dithioacetal **44a** (SMe, SMe) was treated with another thiol (EtSH) in the presence of triethylamine. A mixture of **44a** and **44b** (SEt, SMe) was obtained. To explain this scrambling and also the formation of the by-products (**45** and **46**) obtained during basic hydrolysis, we can assume, besides the possible retro-addition of the thiol, an attack, by the anionic species (such as EtS^-) on the sulfur atoms of the S-S bond. In particular, this can lead to the thiolate **D**, precursor of the phosphono hemidithioacetal **45** (reduction product). This thiolate can also react with the disulfide **44** to give the coupled product **46**.



Furthermore, we found that the treatment of a 50/50 mixture of two differently substituted disulfides **44c** (SMe ; S-S-Me) and **44d** (SEt ; S-S-Et) by LDA followed by a protonation led to a scrambling involving the cleavage of the disulfide bond with the formation of a mixture of four products (**44c-f**) in equal proportion.

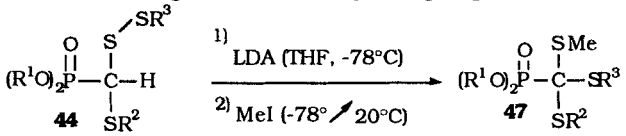


This scrambling can be explained by a deprotonation at the dithioacetal function followed by the formation of an equilibrium resulting from the cleavage of the disulfide function. This result indicates a reversibility of the addition of the thiols in a basic medium.



BLi = LDA

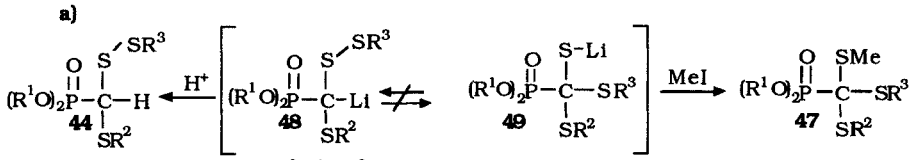
When the metallation of the dithioacetal disulfide **44** was followed by methylation, the expected C-alkylation product was not isolated. Instead, [(tris-alkylthio)methyl]phosphonates **47**, were isolated in 65 to 75 % yield after purification. These products result from a migration of the alkylthio group from sulfur to carbon.



R^1= i-Pr, Et ; R^2= Me, Et ; R^3= Me, Et, t-Bu

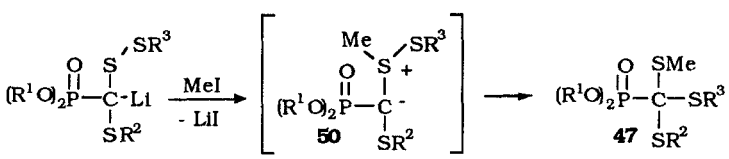
To explain the different pathways observed for protonation and alkylation of the metallated dithioacetal-disulfide, we could envisage a reversible alkylthiomigration at the carbanionic stage (mechanism **a**), with a fast protonation of the carbanionic form **48** leading to the starting dithioacetal **44**, and a slow methylation of the same **48**, this methylation taking place more readily on the sulfur atom of the thiolate form **49** to give **47**.

a)



if $R^2 \neq R^3$, scrambling was not observed

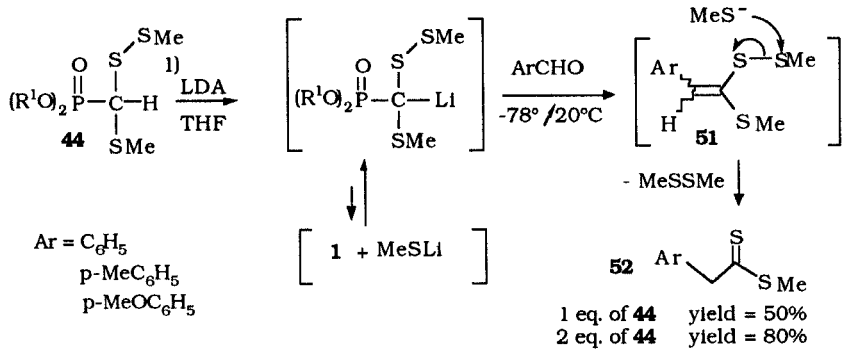
b)



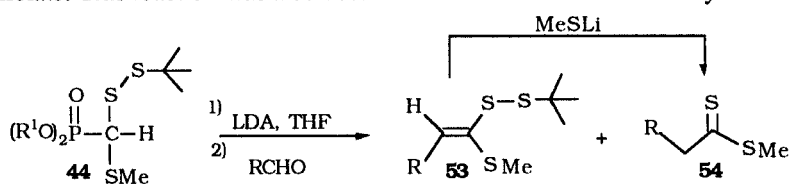
However, this mechanism can be excluded because when R^2 was different to R^3 no exchange of these group was observed after protonation.

Therefore, we would suggest mechanism (**b**) with again an initial alkylation of sulfur instead of carbon, then the formation of S-alkylthio, S-methyl sulfonium ylids **50** which then rearrange (Stevens type rearrangement) into the tris-alkylthio compounds **47**.

We then studied the possibility of using these dithioacetal disulfides as Wittig-Horner reagents after deprotonation by LDA. With the S,S-methyl dithioacetaldisulfide 44 (S-SMe) and aromatic aldehydes we obtained the corresponding dithiosters **52** with one carbon homologation. However the yields of these reactions never exceeded 50% with one equivalent of dithioacetaldisulfide. Two equivalents were necessary to get 80% yields. This result can be explained by the formation of an intermediate ketene dithioacetal disulfide **51** followed by the cleavage of the disulfide bond by anionic species, in particular the methyl thiolate which results from the equilibrium due to the reversibility mentioned previously.

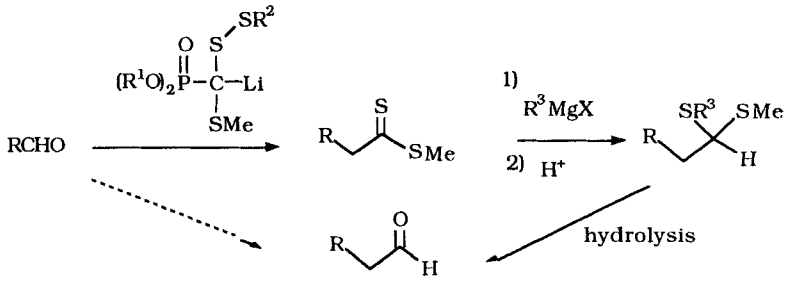


In order to prevent this simultaneous cleavage of the S-S bond by a steric effect, we used the S-S-*tert*-butyl disulfide. In this case ketene dithioacetal-disulfides **53** could be isolated as unique or main products together with the dithioesters and a complete transformation into dithioesters **54** could be obtained by treatment with the lithium methylthiolate. This reaction was also observed with a non aromatic aldehyde.



	R = Ph	82%	0%
	R = p MePh	44%	24%
(2 eq. of II)	R = iPr	43%	30%

This last reaction which is the first example of the synthetic use of a lithiated carbanion α to a disulfide function, is the tranformation of aldehydes into dithioesters with one carbon homologation. Since dithioesters, via the thiophilic addition of Grignard reagent, can be easily transformed into dithioacetals (masked aldehydes), this reaction can be used for the homologation of aldehydes.



CONCLUSION

We hope this review demonstrates the interest of phosphonodithioformates as synthetic intermediates. These difunctional compounds can be used for carbon-carbon bond formation *via* their reaction with organometallics (ketene dithioacetals, homologation of aldehydes) and for the access to substituted methylene bis-(phosphonates) *via* stabilised ylids. They are radical trapping agents and also precursors of a large variety of new functionalised phosphonates such as thiocarbamoylphosphonates, (aminomethyl)-, [tris-(alkylthio)methyl)]- and (mercaptomethyl)- phosphonate derivatives which may have metal complexing properties and/or biological activities.

ACKNOWLEDGEMENT

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