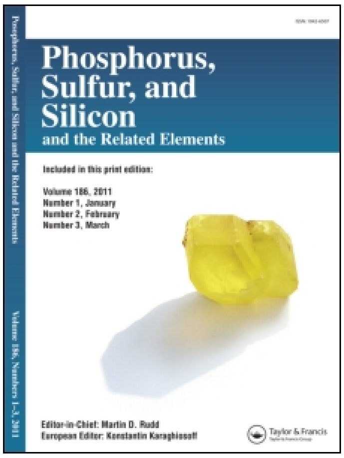

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Reaction of Phosphonodithioformates with Nucleophilic Reagents; Potential Synthetic Uses

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REACTION OF PHOSPHONODITHIOFORMATES WITH NUCLEOPHILIC REAGENTS ; POTENTIAL SYNTHETIC USES.

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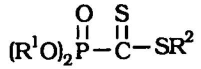
Abstract: The reactivity of phosphonodithioformates with trialkylphosphites,organometallics and thiols is studied. The thiophilic addition of these nucleophilic reagents makes the aforementioned dithioesters, suitable precursors of substituted methylene bis-phosphonates and Wittig-Horner reagents.

Phosphodithioformates **1** are readily available compounds from dialkylphosphites and carbon disulfide [1]. For these non-enethiolisable dithioesters, the thiophilic addition of nucleophiles to the thiocarbonyl group was expected to be enhanced by its conjugation with the α–phosphonyl substituent [2]. This communication concerns the reactions of these functionalised dithioesters with some nucleophilic reagents. Stabilised ylids, precursors of substituted methylene bis-phosphonates (compounds of biological interest), are prepared with trialkylphosphites and Wittig-Horner reagents are obtained via the thiophilic addition of organometallics and thiols.



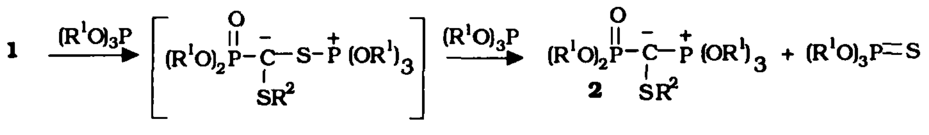
$$(R^1O)_2\overset{O}{\overset{\|}{P}}-\overset{S}{\overset{\|}{C}}-SR^2$$

1

R^1 = Et , iPr ; R^2 = Me, Et, $MeOCH_2OCH_2$, $C_{12}H_{25}$, Allyl, Crotyl

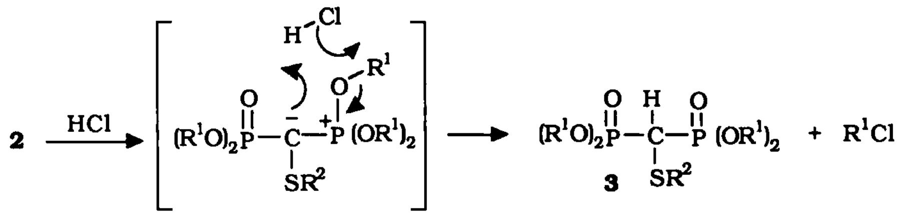
REACTION WITH TRIALKYLPHOSPHITES

The reactions of trialkylphosphites with thiocarbonyl compounds are quite varied. Products of coupling reactions [3], alkenes [4] or phosphonium ylids [5] are obtained via thiophilic addition and desulfurisation. Carbophilic addition [6] and enethiolisation [7] are also observed. From phosphonodithioformates **1**, which react (via an assumed thiophilic addition and desulfurisation) with two equivalents of trialkylphosphite, stabilized phosphonium ylids **2** were isolated.

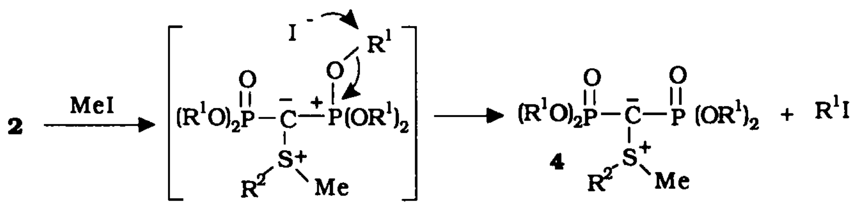


$$1 \xrightarrow{(R^1O)_3P} \left[(R^1O)_2\overset{O}{\overset{\|}{P}}-\underset{SR^2}{\overset{-}{C}}-S-\overset{+}{P}(OR^1)_3\right] \xrightarrow{(R^1O)_3P} \underset{\mathbf{2}}{(R^1O)_2\overset{O}{\overset{\|}{P}}}-\underset{SR^2}{\overset{-}{C}}-\overset{+}{P}(OR^1)_3 + (R^1O)_3P{=}S$$

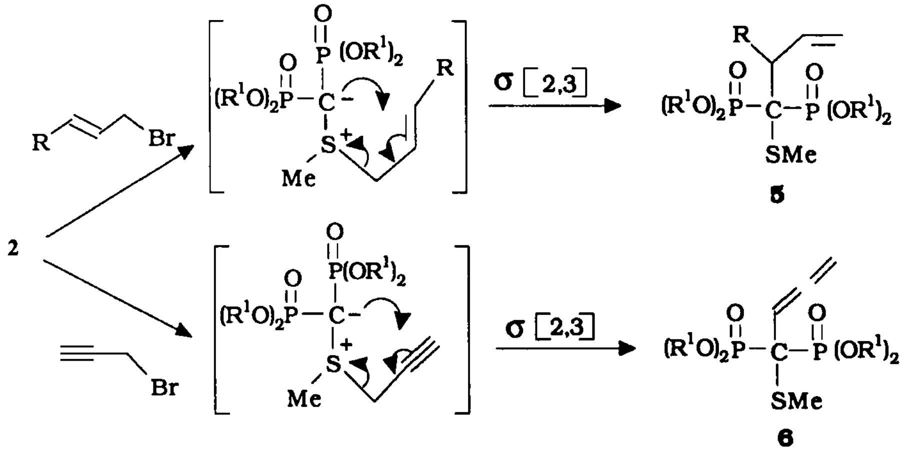
Protonation of the central carbon with Arbuzov-type dealkylation of the phosphonium moiety was observed by reaction of **2** with hydrochloric acid. Alkylthiomethylene bis-phosphonates **3** were obtained quantitatively.



With methyl iodide, S-methylation with alkoxyphosphonium-dealkylation led quantitatively to very stable sulfonium ylids **4**.

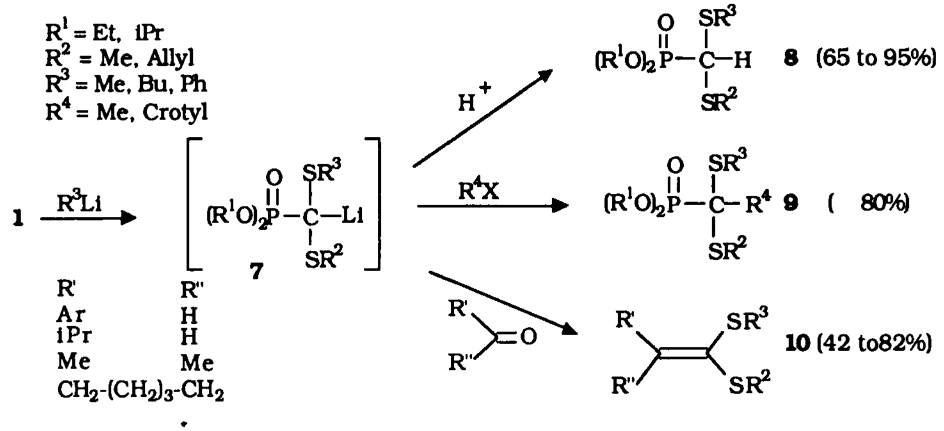


Addition of allylic or propargylic bromide to ylides **2** led to the respective allylic or allenic bis-phosphonates (**5** and **6**). This C-alkylation with inversion of the unsaturated chain is rationalized by a [2,3] sigmatropic rearrangement of an initially formed allylic or propargylic sulfonium ylid.

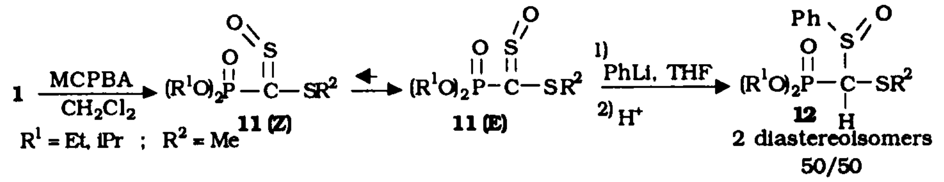


REACTION WITH ORGANOMETALLICS

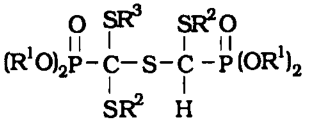
Dithioacetals of formylphosphonates [8,9] are known to be useful Wittig-Horner reagents for the synthetis of ketene dithioacetals. The thiophilic addition of organolithium compounds to phosphonodithioformates **1** led readily to metallated dithioacetals of formylphosphonates **7** which can be protonated (**8**), alkylated (**9**) or used "in situ" as Wittig-Horner reagents (**10**).



Oxidation of **1** with metachloroperbenzoic acid gave the sulfine **11**, equally suitable for thiophilic addition of organometallics [10].



An excess of Grignard reagent is necessary in order to obtain the magnesium analogue of **7** to avoid its thiophilic addition to the starting phosphonodithioformate which leads to **13**.

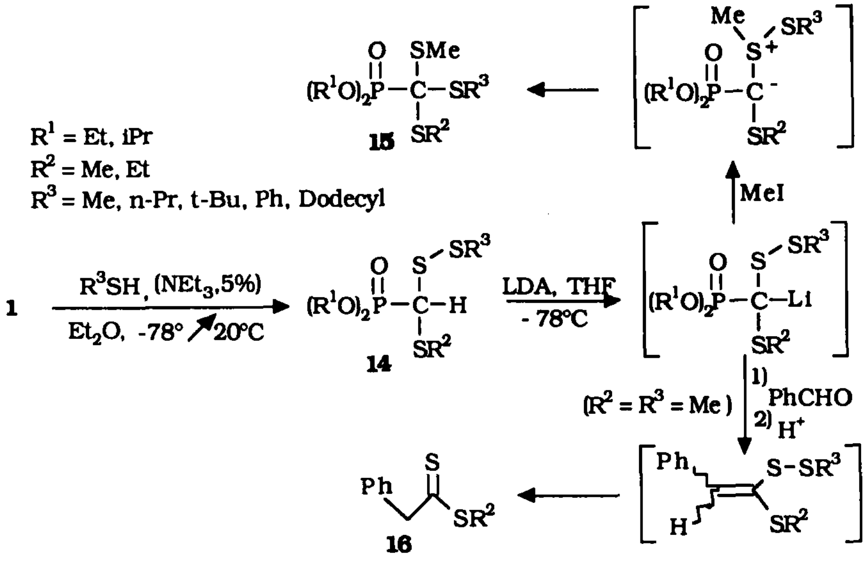

13

$$(R^1O)_2P(O)-C(SR^3)(SR^2)-S-C(SR^2)(H)-P(O)(OR^1)_2$$

REACTION WITH THIOLS

Although the addition of amines to phosphonodithioformates **1** was exclusively carbophilic (and was used to prepare the corresponding thioamides), the base catalyzed addition of thiols to phophonodithioformates **1** led nearly quantitatively to the dithioacetal-disulfides **14**. This regioselectivity demonstrates again the tendency of these α-phosphonodithioesters to undergo thiophilic addition.

The reactivity of metallated dithioacetal-disulfides was examined:



Metallation of the dithioacetals **14** followed by methylation led to (tris-alkylthio)-methylphosphonates **15** .The formation and rearrangement of an intermediate ylid is assumed to explain this reaction. When benzaldehyde was added to the metallated dithioacetal **14** (R^2 = Me; R^3 = Me) dithioester **16** (40%, non-optimised yield) was isolated after work up.

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