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THE USE OF PHOSPHONODITHIOFORMATES FOR THE SYNTHESIS OF KETENE DITHIOACETALS

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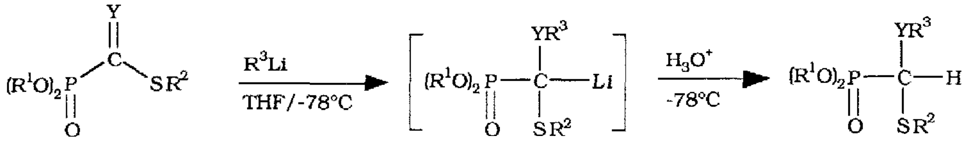
Summary : Phosphonodithioformates 1 undergo thiophilic addition with both organolithium and Grignard reagents to give metallated dithioacetals of formyl-phosphonates 2, available for protonation, alkylation or use in Wittig-Horner reactions. Oxidation of 1 by meta-chloroperbenzoic acid leads to the corresponding sulphine 4 equally suitable for thiophilic addition.

Dithioesters are known to undergo either thiophilic [1] or carbophilic [2] addition with organometallic reagents. Moreover, in the case of organolithium compounds, α-deprotonation [3], when possible, can compete with these additions. Phosphonodithioformates **1** are non-enethiolisable, functionalised dithioesters easily accessible from dialkylphosphites and carbon disulphide [4]. Previous work by our research group [5] and a recent review [6] have shown that thiophilic addition of organometallic reagents to a thiocarbonyl group is enhanced by an α–carbonyl substituent ; the analogous α–phosphonic ester group found in phosphonodithioformates **1** was expected to produce the same effect, allowing the generation of metallated dithioacetals of formyl-phosphonates **2**, suitable for Wittig-Horner reactions [7a,b,c]. Such a carbanion has previously been obtained by the basic deprotonation of the corresponding dithioacetal, prepared by an Arbusov Reaction between trialkylphosphites and chlorodithioacetals [7d], by the addition of dialkyl sulphides to the methanephosphonate carbanion [7e,f], and by the reactions of diethoxymethane phosphonates [7g] or chloro(arylthio)methanephosphonates [8] with thiols. We describe here, the reaction of phosphonodithioformates **1** with organolithium compounds and Grignard reagents which readily led to these carbanions and their subsequent protonation, alkylation and also their use in Wittig-Horner reactions to synthesise ketene dithioacetals, important intermediate reagents in organic synthesis [7a].

When the phosphonodithioformate **1** was treated with one equivalent of organolithium reagent followed by hydrolysis, the corresponding dithioacetal **3** was obtained in high yield. This result confirmed a thiophilic addition with the formation of a lithiated carbanion **2**. (scheme and table 1) :



Y = S **1** **2** **3**
Y = SO **4** **5** **6**

SCHEME 1

It can be seen that the yields for an isopropyl group at R^1 are 7-8 % higher than the corresponding values for an ethyl group and a slight increase in the yield was observed when phenyllithium was used as the organometallic reagent. When a crotyl chain is introduced at R^2, no [2,3] sigmatropic rearrangement was observed [9, 10].

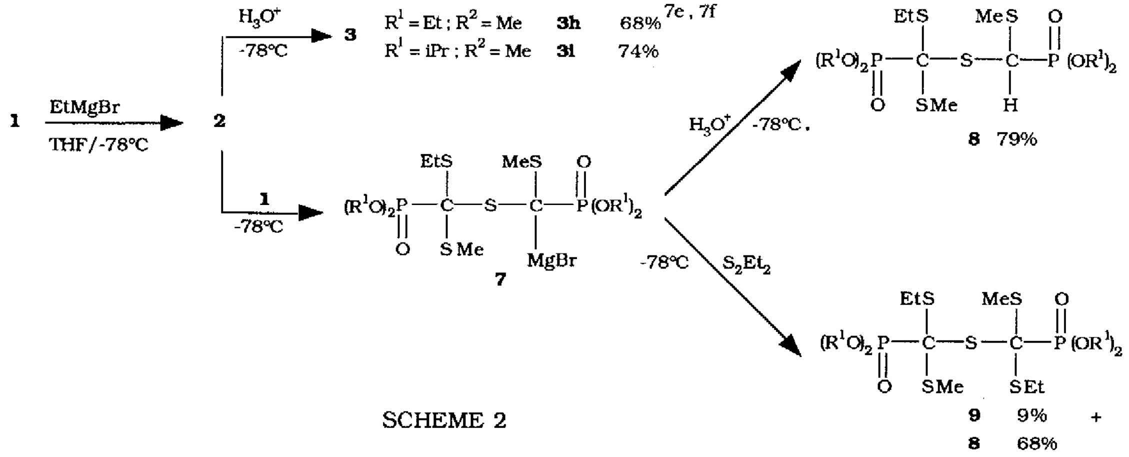
Compound	R1	R2	R3	Yield %	Reference
3a	Et	Me	Me	80 *	7d
3b	iPr	Me	Me	87 *	16
3c	Et	Me	nBu	68 *	7f
3d	iPr	Me	nBu	76 *	16
3e	Et	Me	Ph	86 *	16
3f	iPr	Me	Ph	94 *	16
3g	Et	Crotyl	Ph	63 *	16
6b	iPr	Me	Me	35	16
6d	iPr	Me	nBu	31	16
6f	iPr	Me	Ph	37	16

*see footnote [11]

TABLE 1

The corresponding stable sulphine **4** was prepared by treatment of the dithioester **1** (R^1 = Et) with one equivalent of meta-chloroperbenzoic acid in methylene chloride at 0°C. The E sulphine was the initial isomer kinetically formed which progressively changed to the thermodynamically stable Z isomer over a 24 h period at room temperature [12].The sulphine **4**, as obtained, underwent the expected thiophilic addition [13] when treated with a lithium reagent . After hydrolysis,the lithiated dithioacetal **5** led to the formation of two diastereomers **6** in an approximate 1 : 1 ratio.

By contrast, when the dithioformate **1** was treated with one equivalent of Grignard reagent, (scheme 2) the major product , obtained after hydrolysis, was compound **8**, identified by NMR, mass and infra-red spectroscopy. Chemical verification of the result was obtained by treating the dithioester **1** with one equivalent of Grignard reagent followed by diethyl disulphide to obtain the symmetrical product **9**. These products may have been obtained via a competing secondary reaction between the metallated carbanion **2**, itself adding thiophilically to the starting dithioester **1**, to give the coupled intermediate **7**



SCHEME 2

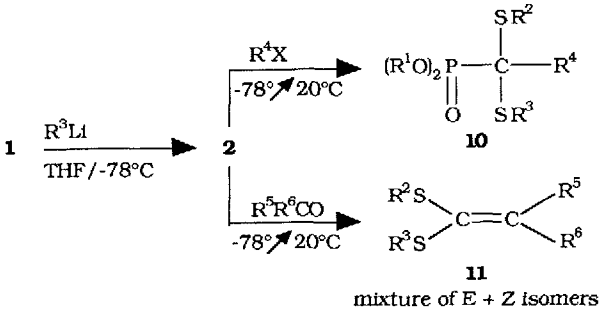
The high yields of the coupled products, obtained when using one equivalent of organomagnesium reagent, show once more that for a simple thiophilic addition two equivalents of Grignard reagent are required for one equivalent of dithioester [1,2]. To obtain the dithioacetal **3** in a comparable yield range to those obtained with organolithium compounds, a large excess (five equivalents) of Grignard reagent was required. This excess makes the carbanion, obtained from these reagents, unsuitable for use *in situ* in Wittig-Horner reactions.

The lithiated carbanion **2**, prepared from the phosphonodithioformate **1** and an organolithium reagent, was treated with 1.2 equivalents of alkyl or allyl halide , after work-up and purification by silica gel chromatography, phosphonodithioacetals **10a-c'** were obtained (scheme 3 and table 2).

Compound	R^1	R^2	R^3	R^4	Yield %	Reference
10a	Et	Me	Me	Me	80	16
10b	iPr	Me	Me	Me	82	16
10c	Et	Me	Me	Crotyl	60	16
10c'	Et	Me	Me	CH_2=CH-C(Me)H	12	16

TABLE 2

The isolated yields were very similar for **10a** and **10b** : compounds differing only in the R^1 substituent . Compounds **10c**, containing the crotyl chain and its isomer **10c'**, with an inverted crotyl chain, are the two major products obtained after alkylation with crotyl bromide. Partial or complete alkylation with inversion of the allylic chain is commonly observed with stabilized carbanions such as α-alkylthio or α-alkylseleno enolates [9, 10]. The formation of an intermediate ylid which undergoes a [2,3] sigmatropic rearrangement or an S_N2' reaction[14] could explain the formation of **10c'**.



SCHEME 3

When one equivalent of aldehyde or ketone was added directly to the lithiated carbanion **2**, the expected ketene dithioacetals **11** were obtained after hydrolysis and purification with the yields indicated below (scheme and table 3) :

Compound	R^1	R^2	R^3	R^5	R^6	Yield %	References
11a	iPr	Me	Me	Me	H	31	3,7a
11b	iPr	Me	Ph	iPr	H	42	16
11c	iPr	Me	Me	Ph	H	82	3,7a
11d	iPr	Me	Me	pMeO-C_6H_4	H	73	16
11e	iPr	Me	Me	Me	Me	53	3,7a
11f	iPr	Me	Ph	- $(CH_2)_5$ -		61	16

TABLE 3

The following is a *standard experimental procedure* for all of these reactions. Under an inert atmosphere, the dithioester **1** (1mmole) is added, dropwise at -78°C, to a solution of organolithium reagent (1.2mmole) in dry THF (5mL). The metallated carbanion **2** is treated at -78°C with a solution of methanol, RX, or RR'CO (1.3mmole) in THF (5mL).For the reactions with enolisable carbonyl compounds, higher yields were obtained by raising the temperature from -78°C to room temperature immediately after the addition [15].The solvent is evaporated and the crude product extracted between diethyl ether and a saturated solution of ammonium chloride , washed with brine and dried over anhydrous sodium sulphate. The solvent is evaporated and the product purified by gel chromatography or distillation.Identification of the new products was obtained by investigation of their ^1H, ^{31}P, ^{13}C and mass spectra and by sulphur analysis[16].

The regioselectivity of the addition of other nucleophilic reagents with phosphonodithioformates is currently under investigation

References

(1) Léger, L.; Saquet, M. *Bull. Soc. Chim. Fr.* **1975**, 657-666.

(2) Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron* . **1977**, 33, 2949-2954.

(3) Berrada, S.; Metzner, P.; Rakotonirina, R. *Bull. Soc. Chim. Fr.* **1985**, 881-890.

(4) Grisley, D.W. *J. Org. Chem.* ***1961***, 26, 2544-2546.

(5) Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron Lett.* **1976**, 4295-4296.

(6) Viola, H.; Hartenhauer, H.; Mayer, R. *Z. Chem.* **1988**, 28, 269-277.

(7) (a) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B. *Tetrahedron.* **1978**, 34, 3081-3088.

(b) Mikolajczyk, M.; Midura, W.; Grzejszczak, S. *Tetrahedron Lett.* **1984**, 25, 2489-2492.

(c) Mikolajczyk, M.; Balczewski, P.; Graczyk, P. *Phosphorus & Sulphur.* **1987**, 30, 225-228.

(d)Mlotkowska, B.; Gross, H.; Costisella, B.; Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A. *J. F. Prakt. Chem.* **1977**, 319, 17-22.

(e) Mikolajczyk, M.; Grzejszczak, S.; Chefczynska, A.; Zatorski, A. *J. Org. Chem.* **1979**, 44, 2967-2972.

(f) Mikolajczyk, M.; Balczewski, P.; Grzejszczak, S. *Synthesis.* **1980**, 127-129.

(g) Gross, H.; Keitel, I.; Costisella, B.; Mikolajczyk, M.; Midura, W. *Phosphorus & Sulphur.* **1983**, 16, 257-262.

(8) Kim, T.H.; Oh, D.Y. *Synth. Commun..* **1988**, 18, 1611-1614.

(9) Reich, H.J.; Cohen, M.L. *J. Am. Chem. Soc.* ***1979***, 101, 1307-1308.

(10) Ogura, K.; Furukawa, S.; Tsuchihashi, G.I. *J. Am. Chem. Soc.* **1980**, 102, 2125-2127.

(11) Purification of product **3** was attempted by chromatography on silica and fluorosil gel and by classical and bulb to bulb distillation (at reduced pressure). The same technique did not prove to be suitable for all cases and for a significant comparison, the yields were determined by ^{1}H NMR of the crude product, using benzene or methylene chloride as an internal standard.

(12) The E sulphine was previously prepared by the reaction between diethyl trimethylsilylmethane phosphonate with sulphur dioxide [13]. ^{1}H NMR (CCl_4) ; Z sulphine : δ-SC$\underline{H}_3$= 2.73 ppm, E sulphine : δ-SC$\underline{H}_3$= 2.53 ppm.

(13) Porskamp, P.A.T.W.; Lammerlink, B.H.M.; Zwanenburg, B. *J. Org. Chem.* **1984**, 49, 263-268.

(14) Solomon, M.; Hoekstra, W.; Zima, G.; Liotta, D. *J. Org. Chem.* **1988**, 53, 5058-5062.

(15) Although no thorough yield optimisation was carried out , it was noticed that at -78°C, no attack of the carbonyl group by the carbanion was observed. Furthermore, basic deprotonation by the carbanion at the α–position of the aldehyde/ketone was thought, when possible, to be taking place as the dithioacetal **3** and a small amount of the enolate ketone condensation product were both isolated under these conditions. Further investigations using deuterated acetone have confirmed these results.

(16) NMR characteristics of the new products:^{1}H NMR (CCl_4) , δ (ppm) : **3b** 3.43 ; **3d** 3.48 ; **3e** 3.98 ; **3f** 3.80 ; **3g** 3.87 ; **3i** 3.57 .(doublets ; $^2J_{HP}$ = 18 Hz ; P-C-$\underline{H}$) ; **6b** 3.92 & 4.37 ; **6d** 3.85 & 4.31 . (doublets ; $^2J_{HP}$ = 17 & 21 Hz ; P-C-$\underline{H}$; 2 diastereoisomers) ; **6f** 3.57 & 4.03 .(doublets ;$^2J_{HP}$ = 18 & 19 Hz ; P-C-$\underline{H}$; 2 diastereoisomers).

^{31}P NMR ($CDCl_3$) , δ (ppm) : **8** 15.87 & 18.82 ; 9 19.05 ; **10a** 22.08 ; **10b** 20.20 ; **10c** 21.36 ; **10c'** 21.86 .(singlets).

^{13}C NMR ($CDCl_3$) , δ (ppm) : **11b** 130.66 & 156.03 ; **11d** 129.38 & 133.06 ; **11f** 119.89 & 155.72 (singlets ; $=\underline{C}R_2$ & $=\underline{C}(SR)_2$ respectively) .

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