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The influence of ultrasound on the addition of phosphites to thiophenecarbaldehydes

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Summary – Diethyl phosphites add to the carbonyl double bond of thiophenecarbaldehydes. This is solely an ionic process in the presence of a base, and ultrasound has no influence on it. However in the absence of base, a free radical mechanism occurs which is promoted by ultrasound. It is shown here that when the ionic process is catalyzed by triethylamine or potassium fluoride, it is faster than the free radical process in all conditions.

phosphite / ultrasound / thiophenecarbaldehyde

Introduction

Although ultrasound has been used in phosphorus chemistry during the last few years, there are few reports on the subject. Ultrasound can however be used to promote the deprotonation of various allylic phosphonium salts with butyllithium in the Wittig reaction [1]. The synthesis of polyarenes by the Wittig reaction of orthoquinones is dramatically accelerated by ultrasound with a significant increase in the yields in some cases [2]. The sonochemical Wittig-Horner reaction, which is catalyzed by an activated barium hydroxide catalyst, also occurs in interfacial solid-liquid conditions [3], and a significant improvement in the Wittig-Horner synthesis of allenyl sulfones and allene carboxanilides has been observed upon ultrasonic irradiation in the homogeneous phase [4]. The dechlorination reaction of the phosphonic dichloride $ArP(O)Cl_2$(Ar = 2,4,6-*t*-$Bu_3C_6H_2$) with magnesium under ultrasonic irradiation gave the sterically protected diphosphene oxide ArP(O) = PAr [5]. Diphosphines have been prepared with alkali metal followed by alkylation. Ultrasound irradiation is applied at the reductive cleavage stage, in order to assure the purity of the final products [6]. Some recent development in phosphirene chemistry under ultrasonic conditions have been reviewed [7]. Sonication substantially improves the rate of formation of diphosphene with respect to standard procedures [8]. Recently, we studied ultrasound effect on diethyl phosphite addition to thiophenic imines [9]. The rate enhancement for this homogeneous sonochemical reaction depends on the temperature, the nature of the solvent and the structure of the imine. The addition of phosphites to carbonyls has also been studied [10-16].

Here we report on the effect of ultrasound on the addition of phosphites to thiophenic aldehydes. As far as we know this is the first study on the subject.

Results and discussion

α-Hydroxyphosphites **2a-c** (scheme 1) were prepared using both classical and sonication methods. In all cases stoichiometric amounts of reactants were used : diethyl (**1**) or dimethyl (**1'**) phosphite and thiophene-2-(or -3-) carbaldehyde. In all the experiments toluene was the solvent and the concentration of each reactant was 1.49 mol L^{-1}. Some of the reactions were performed with thermostatic control.

A preliminary experiment [9] showed that without thermostatic control of the reaction medium under sonication, the temperature rose to a limit value which remained stable during the sonication. As the reaction time was at least 1 h, the temperature might be considered as constant. It is noteworthy that the limit value depends on the nature of the mixture. Diethyl phosphite **1** was reacted for 1 h with thiophene-2-carbaldehyde in the presence of a base such as triethylamine, with and without sonication, at a regulated temperature (20, 40, 60 and 80°C). No ultrasonic effects were recorded (table I). At any temperature, the amount of the addition product was the same for both methods. This indicates that the mechanism is purely ionic. Moreover ultrasound is known to have a very limited effect on ionic processes but a large effect on radical or single-electron-transfer processes.

In fact Lewis et *al* [17] showed that the ionization of the P-H bond in diethyl phosphite occurs in the

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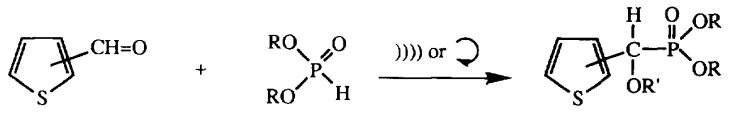


2-thienyl
3-thienyl

1 : R: Et
1': R: Me

		R	R'
2a	2-thienyl	Et	H
2b	3-thienyl	Et	H
2c	2-thienyl	Me	H
2d	2-thienyl	Me	Me

Scheme 1

Table I. Yields under sonication and classical conditions at several temperatures in the presence of Et_3N.

Reaction temperature (°C)	% of **2a**	
	Ultrasonic irradiation	Classical heating and stirring
20	5	5
40	12	12
60	20	20
80	37*	37*

* Byproducts are formed.
Solvent : toluene. Reaction time : 1 h. Reactant concentration : 1.49 mol L^{-1}.

presence of bases such as CH_3COO^-, CO_3^{2-} and NH_3 which are weaker than Et_3N.

Therefore, we can state that in the presence of a base the addition of diethyl phosphite to thiophene-2-carbaldehyde is an ionic process and ultrasound does not induce a radical process to any great extent.

There are reports [18-21] on the decomposition of hydroxyphosphonates in the presence of bases. This prompted us to use another base, such as KF [11], to assess its influence on the reaction under ultrasonic irradiation. At 60°C, with a concentration of 1.49 mol L^{-1} for each reactant (in toluene), **2a** is obtained within 1 h in 80% yield. This yield should be compared with that obtained in the presence of Et_3N (see table I), which shows that under ultrasonic irradiation the reaction is faster in the presence of KF.

In fact the reaction is too fast in the presence of KF. Reactions that are suitable for assessment of reaction rates should not be too sluggish or too fast. Apart from this preliminary investigation, therefore we did not use KF for further comparison and worked without base for the rest of our study.

In the following experiments, the solvent and the concentration of the reactants were the same as above, but there was no thermostatic control when the reaction was performed under ultrasound. In the ultrasound experiments, the temperature increased and stabilized at a limit value depending on the solvent and the nature of the reaction mixture. Thereafter, the classical procedure was performed at that limit value.

A mixture of diethyl phosphite and thiophene-2-carbaldehyde was sonicated in toluene. The temperature of the medium increased and stabilized at 104°C. The same reaction was performed at 104°C under classical stirring and heating. In both reactions the amount of the final product was measured after 1, 2, 2.5 and 3 h. The results showed an increase in the reaction rate when ultrasound was used (table II).

Table II. Yields of **2a** as a function of time in the presence of Et_3N at 104°C in toluene.

Reaction time (h)	% of **2a**	
	Ultrasonic irradiation	Classical heating and stirring
1	4	2
2	10	3
2.5	14	4
3	19	9

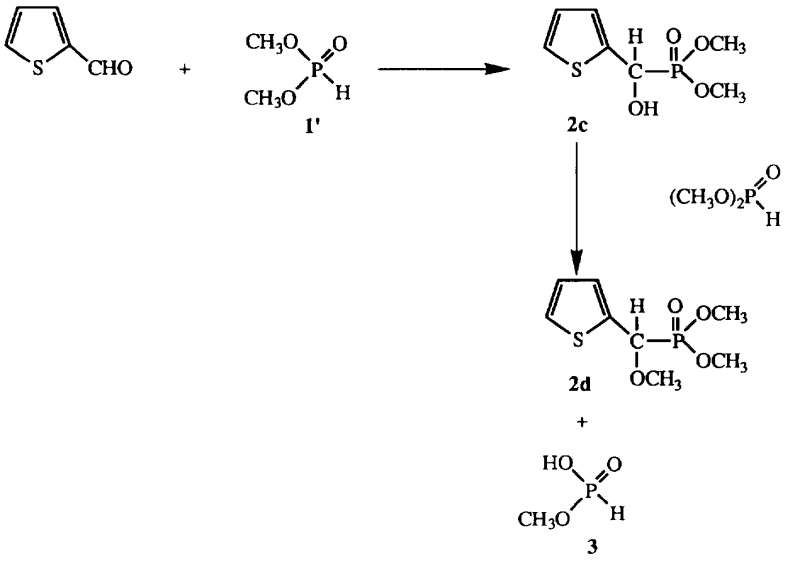
Reactant concentration : 1.49 mol L^{-1}.

The same experiment was performed with diethyl phosphite and thiophene-3-carbaldehyde. The reaction mixture temperature stabilized at 93°C under ultrasound, and so the same reaction was performed at 93°C under classical stirring. Table III shows the percentage of **2b** in both cases after 1, 2, 3 and 4 h. The addition was again faster under sonication.

Table III. Yields of **2b** as a function of time at 93°C in the absence of Et_3N under ultrasonic irradiation and classical heating and stirring

Reaction time (h)	% of **2b**	
	Ultrasonic irradiation	Classical heating and stirring
1	6	2
2	14	4
3	24	8
4	44	12

In a third experiment, dimethyl phosphite was reacted with thiophene-2-carbaldehyde. The temperature reached under sonication was 94°C. In addition to the expected product **2c**, two other compounds were obtained : **2d** and **3**, with both procedures. Table IV shows the percentages of **2c** and **2d** relative to the reaction time, from which can be inferred that the addition is faster when reaction medium is sonicated.



Scheme 2

Table IV. The effect of ultrasound versus classical heating and stirring on the formation of **2c** and **2d** in the absence of a base.

Reaction time (h)	Ultrasonic irradiation		Classical heating and stirring	
	% **2c**	% **2d**	% **2c**	% **2d**
1	6	0	0	0
2	15	4	1	0
3	22	11	2	0

These results obtained in the absence of a base such as Et_3N are easily understandable if the reactivity of $(RO)_2P(O)H$ is considered. It is well established that dialkyl phosphite reacts in two ways. An ionic process [17] may occur as follows.

$$RO_2P(O)\text{-}H + \text{Base} \longrightarrow RO_2P(O)^- + \text{Base } H^+$$

This is catalyzed by bases as weak as CH_3COO^- (pK_a = 4.8). Alternatively, a free radical process [22-25] may occur upon heating or photolysis. In fact both of these mechanisms may occur simultaneously; their ratio depends on the experiment conditions.

Our last three experiments were performed in the absence of Et_3N and so a free radical mechanism could be expected in addition to an ionic one. We have shown elsewhere that $(EtO)_2\dot{P}{=}O$ is generated when diethyl phosphite is sonicated. The formation of this radical intermediate has been evidenced by EPR and by the addition of radical initiators or scavengers [26]. Moreover, it has been shown that homogeneous phase reactions are sensitive to ultrasound when they proceed via a radical mechanism [27-29].

The reaction rate increase when ultrasounds were used in the experiments in tables II-IV is in good agreement with a free radical mechanism. It was thus interesting to compare the reaction rates under sonication with and without Et_3N in the reaction media.

Diethyl phosphite and thiophene-2-carbaldehyde were allowed to react in the absence of Et_3N at 80°C while being sonicated. No reaction product could be detected after 1 h of sonication. On the other hand, table I shows that when Et_3N is used the percentage of **2a** is 37% with and without sonication. This means that Et_3N is more efficient than ultrasound in enhancing the addition rate of dialkyl phosphites to thiophene-2-carbaldehyde.

The last point to discuss is the formation of **2d** and **3**. We did not isolate all of the phosphorus compounds, and so **2d** could be supposed to result from a reaction between two molecules of **2c** or between **2c** and remaining **1'**. Therefore, **2c** was sonicated under the conditions which led to **2d**. No reaction occurred. In contrast, sonication of a mixture of **2c** and thiophene-2-carbaldehyde yielded **2d** and another phosphorus compound ($\delta^{31}P$ = 7.69). This result allows us to suggest the reactions in scheme 2. The chemical shift of **3** is consistent with that observed for the second product with a ^{31}P NMR signal at δ = 7.69.

Experimental section

Melting points were determined with a Büchi Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC 80 or Bruker AC 250 spectrometers operating at 80.13 and 250.13 MHz for ^1H, 62.89 MHz for ^{13}C and 32.44 MHz for ^{31}P. Chemical shifts are expressed in parts per million positive values downfield from internal TMS (^1H and ^{13}C) and external 85% H_3PO_4(^{31}P). Coupling constants are expressed in hertz. TLC was performed on silica-gel plates (Riedel de Haën ref 37333) and preparative chromatography on columns of silica-gel (70-230 mesh). Sonication was carried out on Bioblock Vibracell 600 W (20 kHz) ultrasound generator with tip (ϕ = 13 mm). Control experiments have shown that diethyl phosphite **1** is stable under sonochemical conditions. Elemental analyses were performed by the Service de Microanalyse de l'Ecole Nationale Supérieure de Chimie

de Toulouse. Apart from **2c** all the products obtained were oils.

Assessment of the influence of ultrasound on reaction rates

The following experiments were not intended to isolate the products formed.

• *In the presence of Et_3N*

Reaction mixtures consisted of diethyl phosphite **1** (0.01 mol) or dimethyl phosphite **1'** (0.01 mol) and thiophene-2-(or -3-)carbaldehyde (0.01 mol) and triethylamine (0.01 mol) in toluene (6.7 mL). Two samples containing the same reactants at the same concentrations were prepared simultaneously at room temperature. One was sonicated without thermostatic control, the other was left under magnetic stirring in an oil bath kept at the same temperature as that reached within 2 min of ultrasonic irradiation. The reaction was monitored in both cases by ^{31}P NMR spectroscopy and by chromatography.

• *In the absence of Et_3N*

The reaction mixture consisted of diethyl phosphite **1** (0.01 mol) or dimethyl phosphite **1'** (0.01 mol) and thiophene-2-(or -3-)carbaldehyde (0.01 mol) in toluene (6.7 mL). Two samples containing the same reactants at the same concentrations were prepared simultaneously at room temperature. They were then heated in the same manner as the samples with Et_3N.

• *In the presence of KF*

A mixture of diethyl phosphite **1** (0.01 mol) and thiophene-2-carbaldehyde (0.01 mol) and KF (0.01 mol) were sonicated at 60°C for 1 h in toluene (6.7 mL). The reaction was monitored by ^{31}P NMR spectroscopy and chromatography.

General method for the synthesis of compounds **2a-d**

Our ultrasound generator could not be switched on for more than 3 h and so we decided to synthesize the products obtained in the comparative part of our study in a classical thermal way. Triethylamine was used to accelerate the reaction. The yields given here are therefore different from those given when comparing reaction rates. Diethyl phosphite **1** (0.01 mol) or dimethyl phosphite **1'** (0.01 mol) thiophene-2-(or -3-)carbaldehyde (0.01 mol) and Et_3N (0.01 mol) were mixed at room temperature in toluene (6.7 mL). The reaction was performed at 60°C under classical stirring and heating and monitored by ^{31}P NMR spectroscopy. The solvent was then evaporated and the crude products are purified by column chromatography on silica-gel using ethyl acetate as eluent.

• *Diethyl [hydroxy(2-thienyl)methyl]phosphonate* **2a**

IR (neat) : 1 250 cm^{-1}(P=O); 3 238 cm^{-1}(OH).

^1H NMR ($CDCl_3$) δ : 7.26 (m, 1H, CH thio); 7.16 (m, 1H, CH thio); 6.98 (m, 1H, CH thio); 5.20 (d, 1H, $^2J_{HP}$ = 11, CHP); 4.9 (s, 1H, OH); 4.16-4.01 (m, 4H, CH_2); 1.37-1.21 (m, 6H, CH_3).

^{13}C NMR ($CDCl_3$) δ : 139.6 (s, C_2 thio); 126.6 (s, thio); 126.1 (d, J_{CP} = 7.4, thio); 125.7 (d, J_{CP} = 3.1, thio); 66.5 (d, $^1J_{CP}$ = 167.1, CHP); 63.6 (d, $^2J_{CP}$ = 5.7, CH_2); 63.3 (d, $^2J_{CP}$ = 6.9, CH_2; 16.4 (d, $^3J_{CP}$ = 5.3, CH_3).

^{31}P NMR ($CDCl_3$) δ : 19.66. Yield : 80%.

Anal calc for $C_9H_{15}O_4PS$, C, 43.19; H, 6.04. Found : C, 43.01; H, 6.07.

• *Diethyl [hydroxy(3-thienyl)methyl]phosphonate* **2b**

IR (neat) : 1 233 cm^{-1}(P=O); 3 240 cm^{-1}(OH).

^1H NMR ($CDCl_3$) δ : 7.36-7.13 (m, 3H, CH thio); 5.06 (d, 1H, $^2J_{HP}$ = 3.3, CHP); 4.14-3.97 (m, 4H, CH_2); 1.27 (m, 6H, CH_3).

^{13}C NMR ($CDCl_3$) δ : 137.4 (s, C_3 thio); 128.2-126.4 (m, thio); 67.1 (d, $^1J_{CP}$ = 115.3, CP); 63.8-63.4 (m, CH_2); 16.1 (s, CH_3).

^{31}P NMR ($CDCl_3$) δ : 21.08. Yield : 61%.

Anal calc for $C_9H_{15}O_4PS$, C, 43.19; H, 6.04. Found : C, 43.44; H, 6.31.

• *Dimethyl [hydroxy(2-thienyl)methyl] phosphonate* **2c**

IR (KBr) : 1 250 cm^{-1}(P=O); 3 238 cm^{-1}(OH). Mp = 65°C.

^1H NMR (C_6D_6) δ : 7.24 (m, 1H, CH thio); 6.91 (m, 1H, CH thio); 6.75 (m, 1H, CH thio); (5.50 (d, 1H, $^2J_{HP}$ = 11.4, CHP); 3.46 (d, 3H, $^3J_{HP}$ = 8.6, CH_3); 3.41 (d, 3H, $^3J_{HP}$ = 8.7, CH_3).

^{13}C NMR (C_6D_6) δ : 141.3 (s, C_2 thio); 126.9 (s, thio); 126.3 (s, thio); 125.6 (s, thio); 66.5 (d, $^1J_{CP}$ = 168.3, CP); 54.0 (d, $^2J_{CP}$ = 7.1, CH_3); 53.3 (d, $^2J_{CP}$ = 7.2, CH_3).

^{31}P NMR (C_6D_6) δ : 21.61. Yield : 65%.

Anal calc for $C_7H_{11}O_4PS$, C, 37.83; H, 4.99. Found : C, 37.98; H, 4.86.

• *Dimethyl [methoxy(2-thienyl)methyl] phosphonate* **2d**

IR (neat) : 1 245 cm^{-1}(P=O).

^1H NMR (C_6D_6) δ : 7.10 (m, 1H, CH thio); 6.94 (m, 1H, CH thio); 6.73 (m, 1H, CH thio); 4.65 (d, 1H, $^2J_{HP}$ = 15.3, CHP); 3.50 (d, 3H, $^3J_{HP}$ = 10.4, CH_3); 3.40 (d, 3H, $^3J_{HP}$ = 10.4, CH_3); 3.10 (s, 3H, OCH_3).

^{13}C NMR (C_6D_6) δ : 136.6 (s, C_2 thio); 128.0 (s, thio); 127.3 (s, thio); 126.8 (s, thio); 75.7 (d, $^1J_{CP}$ = 177.0, CP); 58.5 (d, $^3J_{CP}$ = 13.2, OCH_3); 53.9 (d, $^2J_{CP}$ = 7.6, $POCH_3$); 53.7 (d, $^2J_{CP}$ = 7.8, $POCH_3$).

^{31}P NMR (C_6D_6) δ : 18.91.

Anal calc for $C_8H_{13}O_4PS$, C, 40.67; H, 5.54. Found : C, 40.47; H, 5.81. Yield : 75%.

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