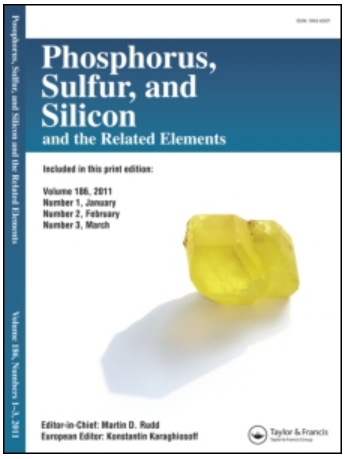

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NEW CONVENIENT SYNTHESIS OF PHOSPHONIC KETENE DITHIOACETALS USING POTASSIUM FLUORIDE ON ALUMINA

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NEW CONVENIENT SYNTHESIS OF PHOSPHONIC KETENE DITHIOACETALS USING POTASSIUM FLUORIDE ON ALUMINA

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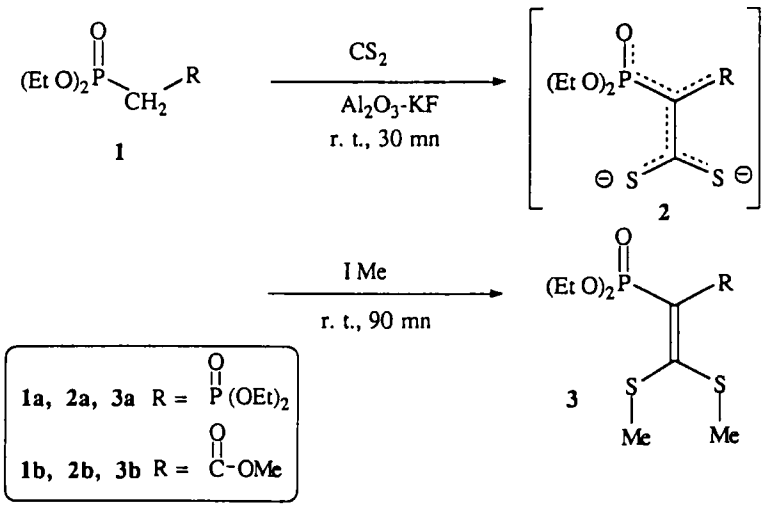
A new, simple and effective method using Alumina-KF as a solid basic catalyst for the preparation of phosphonic ketene dithioacetals is described. The reaction of these ketene dithioacetals with amines was studied.

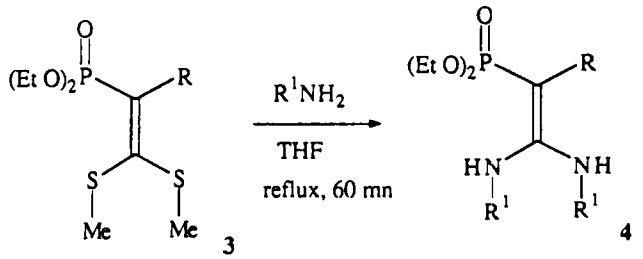
Key words: Phosphonate; ketenedithioacetal; solid basic catalyst; potentially active drugs

The condensation of active methylene compounds with carbon disulfide leads to ketene dithioacetals, useful and versatile compounds available for both nucleophilic and electrophilic attacks.[1,2] We have previously described the preparation of several alpha-keto, alpha-cyano and alpha-carboxyl ketene dithioacetals using potassium fluoride on alumina as a basic catalyst.[3] We report here the preparation of phosphonic ketene dithioacetals by this easy and efficient method, slightly modified for this application.

The phosphonic active methylene compounds is placed with carbon disulfide in an open vial and the addition of potassium fluoride on alumina generates the anion which is quenched with halogenide. The ketene dithioacetal is then obtained by rinsing the solid with methylene chloride. The product is obtained pure by evap-



Scheme I Preparation of the phosphonic ketene dithioacetals on KF/Al_2O_3.



4	R	R^1NH_2
a	$P(O)(OEt)_2$	$EtNH_2$
b	$P(O)(OEt)_2$	$HONH_2$
c	$P(O)(OEt)_2$	$HOCH_2CH_2NH_2$

Scheme II Reaction with amines.

oration of the by-products under reduced pressure and filtration on silica-gel. No distillation was necessary. This avoided thermal decomposition of the product (Scheme I). The potassium fluoride on alumina is easily prepared from potassium fluoride and chromatographic neutral alumina.[6]

The first preparation of tetraethyl 2,2-dimethylthioethenediylidene diphosphonate **3a** was described very recently by another method,[4] but the obtained yield was only 43%. Our method has the advantage of needing no inert atmosphere, no aggressive reactants nor liquid-liquid extraction, and the yield is quantitative.

Reaction of these ketene dithioacetals with amines[5] leads to the compounds **4** (Scheme II). Steric factors play an important role in the ease of the reaction: while RCH_2NH_2 type amines reacted easily, more hindered amines did not react. We obtained no reaction with aniline, adamantanamine, isopropylamine or diethylamine.

Trying to carry out the reactions in alcohol, we had evidences for the substitution of the methylthio group by an ethoxyl, in the presence of a strong enough base. This aspect of the reactivity of phosphonic ketene dithioacetals will be discussed in a next paper.

The ketene dithioacetals were deprotected to free phosphonic and carboxylic acids upon treatment with trimethylsilyl bromide. These phosphonic acids may have antiviral properties due to their analogy with natural pyrophosphates. Biological tests on HIV are in progress at Rhône-Poulenc-Rorer's.

EXPERIMENTAL

Infrared spectra were recorded in KBr or between NaCl plates on a Perkin Elmer 684 IR spectrophotometer, absorptions in cm^{-1}. Proton NMR spectra (PMR) were recorded in ppm downfield from internal Me_4Si on a Varian EM 360 instrument (60 MHz). ^{13}C NMR spectra were recorded in ppm downfield from internal Me_4Si on a Brucker WP 60, as were the ^{31}P NMR spectra, in ppm downfield from external H_3PO_4. Mass spectra (MS) were recorded on a Nermag R10-10H spectrometer. Alumina-KF is prepared as previously described.[6]

Tetraethyl 2,2-Di(methylthio)ethenediylidenediphosphonate (**3a**). *Typical procedure*: Carbon disulfide (22 mmol; 1.3 ml) is added to tetraethyl methylenediphosphonate (20 mmol; 5 ml) in THF (50 ml). Alumina-KF (32 g) is added. The mixture is stirred on a shaker for 30 min. Iodomethane (44

TABLE I

Amines prepared

4	Reaction time	Purification	Yield (%)	mp (°C)	IR ν (cm^{-1})	MS (70 eV) m/z (%)
a	60 mn	chromatography	75	<50	1640, 1450, 1340, 1240, 1040, 965, 800	386 (M^+, 7.5) 341 (2.5), 249 (79), 206 (44), 44 (100)
b	48 h	acido-basic	20	50 (dec)	1590,1040, 960, 730	
c	48 h	chromatography	50	<50	1440, 1240 1040, 960, 800	416 (M^+-2, 10) 255 (6), 45 (100)

TABLE II

Amines prepared: physical data

4	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ	^{31}P NMR ($CDCl_3$) δ
a	1.3 (t, 12 H, -O-C-CH_3)	15 (N-C-$\underline{C}H_3$)	29.3
	1.3 (t, 6 H, N-C-CH_3)	16 (O-C-$\underline{C}H_3$)	
	3.1 (dq, 4 H, N-CH_2)	40.9 (N-C-$\underline{C}H_3$)	
	4.0 (m, 8 H, O-CH_2)	61 (O-C-$\underline{C}H_3$)	
	8.5 (s, 2 H, N-H)	119 (t, $^1J_{C\text{-}P}$=150 Hz, P-C)	
		170 (t, $^2J_{C\text{-}P}$=10 Hz, P-C-$\underline{C}$)	
b	1.3 (t, 12 H, O-C-CH_3)	16.3 (O-C-$\underline{C}H_3$)	12.5
	4.1 (m, 8 H, O-CH_2)	61 (O-$\underline{C}H_2$)	
	9 (m; NH)	171 (t,$^2J_{C\text{-}P}$=21 Hz,P-C-$\underline{C}$)	
c	1.3 (t, 12 H, O-C-CH_3)	16 (O-CH_2-$\underline{C}H_3$)	18.8
	2.6 (m, 4H, N-C-CH_2)	53 & 57 (N-$\underline{C}H_2$-$\underline{C}H_2$-OH)	
	3.6 (q, 4 H, N-CH_2)	62 (O-$\underline{C}H_2$-CH_3)	
	4.1 (m, 8 H, O-CH_2)	96 (t, $^1J_{C\text{-}P}$=215 Hz, P-C-P)	
		168 (P-C-$\underline{C}$)	

mmol; 2.8 ml) is then added, and the mixture stirred for 60 min. It is then filtered, and the solid is washed with methylene chloride. The solvent is evaporated under reduced pressure, and the by-products (mainly dimethyl trithiocarbonate) are distilled at T < 120°C and 0.1 mm Hg. The product is a yellow liquid obtained pure by dissolution in methylene chloride, filtration on silica-gel and evaporation of the solvent. The yield is 95%.

^1H NMR (CCl_4) δ: 1.35 (*t*, *J* = 7 Hz, 12H, P—O—C—CH_3), 2.6 (*s*, 6H, S—CH_3), 4.1 (*dq*, $J_1 = J_2$ = 7 Hz, P—O—CH).

IR (NaCl): 1420, 1230, 1025, 960, 790.

^{13}C NMR ($CDCl_3$) δ: 16.3 (P—O—C—$\underline{C}H_3$), 20.5 (S—CH_3), 62.5 (P—O—C), 116.5 (*t*, *J* = 172 Hz, P—C—P), 179.7 (S—C—S).

^{31}P NMR ($CDCl_3$) δ: 12.5.

MS (70 eV) m/z (%): 392 (M^+, 1.3), 345 (2.72), 331 (7.82), 49 (100).

Anal. Calcd. for $C_{12}H_{26}O_6P_2S_2$: S, 16.3. Found: 16.2.

Methyl 2-(dimethylthio)methylene-2-diethylphosphonoacetate (**3b**). Prepared by a similar procedure, from triethyl phosphonoacetate (20 mmol; 4 ml). Yellow liquid, obtained with 85% yield.

^{1}H NMR (CCl_4) δ: 1.3 (*t*, 6H, P—O—C—CH_3), 2.4 (*m*, 6H, S—CH_3), 3.7 (*s*, 3H, C—O—CH_3), 4.1 (*m*, 4H, O—CH_2).
IR (NaCl): 1725, 1425, 1420, 1160, 1050, 960.
^{13}C NMR ($CDCl_3$) δ: 17 (P—O—C—$\underline{C}H_3$), 20.5 (S—CH_3), 52 (C—O—$\underline{C}H_3$), 62 (P—O—C), 129.0 (*d*, J = 184 Hz, P—C), 158.4 (*d*, J = 6 Hz, P—C—$\underline{C}$), 162 (S—C—S).
^{31}P NMR ($CDCl_3$) δ: 8.2.
MS (70 eV) m/z (%): 315 (MH^+, 78), 283 (85), 253 (34), 44(100).
Anal. Calcd. for $C_{10}H_{21}O_5PS_2$: S, 20.3. Found: 20.5.

Reaction of **3** *with amines. Typical procedure*: The ketene dithioacetal (5 mmol) is added to a solution of the free amine (15 mmol) in 25 ml THF. The mixture is heated at 65°C for the time indicated in Table I. After cooling, the product is obtained by filtration. It is then purified by filtration on silica-gel or by using its acido-basic properties: dissolution in acidic water—extraction with methylene chloride—made basic with NaOH—washing with water—evaporation of the organic solvent at 20°C under reduced pressure, dissolution in acetone and precipitation of the hydrochloride upon treatment with HCl (indicated in Table I and Table II).

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