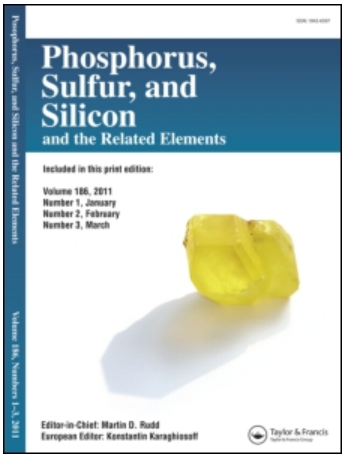

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SYNTHESIS OF NEW α-KETOPHOSPHONATES

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SYNTHESIS OF NEW α-KETOPHOSPHONATES

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Using the Arbuzov reaction, asymmetrical or symmetrical benzyl α-ketophosphanates can be synthesized. In the case of symmetrical benzyl α-ketophosphonates, it was observed that the modification of benzyl groups influences the yield of the Arbuzov reaction.

Keywords: α-ketophosphonate; benzyl groups; Arbuzov reaction

INTRODUCTION

The α-ketophosphonates are commonly used as reactive intermediates, mainly in the preparation of bisphosphonates[1,2,3,4]. They are usually obtained by the Arbuzov reaction, that consists of addition of acyl chlorides to trialkylphosphite compounds.

Our work focuses on the synthesis of various new α-ketophosphonate structures: The asymmetrical structure $(PhCH_2O)(CH_3O)P(O)COR$ and the symmetrical structures $(PhCH_2O)_2P(O)COR$, $(NO_2PhCH_2O)_2P(O)COR$, $(CH_2(O_2)Ph\ CH_2O)_2P(O)COR$

ASYMMETRICAL α-KETOPHOSPHONATES

The first step starts with a trialkylphosphite, namely the dimethylbenzylphosphite $(P(OCH_3)_2OCH_2Ph)$. The addition of several acyl chlorides to this compound leads to the formation of a mixture of two compounds (Fig 1, **1** and **2**)

Product **2** is the most abundant (65%). This implies a greater lability of the benzyl groups than the methyl groups. Distillation allows the separation of compound **2** leaving the α-ketophosphonates **1** pure, in a yield of approximately 35%.

The ^1H NMR of **1** (Table I) are characterized by two doublets. For example with R= $(CH_2)_3CH_3$ at δ 3.7 ppm, a doublet corresponds to the two protons of the benzyl group ($^3J_{POCH}$ = 8 Hz) and at δ 5.1 ppm, a doublet corresponds to the three protons of the methyl group ($^3J_{POCH}$ = 11 Hz).

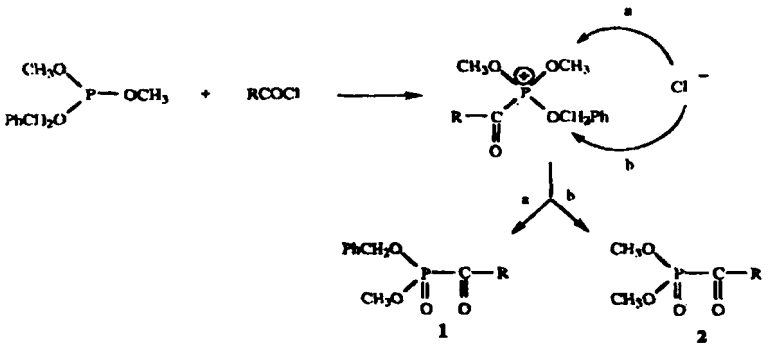
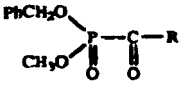


FIGURE 1

TABLE I Spectral data of asymmetrical α-ketophosphonates



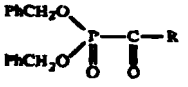
R	*N°*	*NMR ^{31}P* δP *(ppm)*	*NMR ^{1}H*	
			δH *(ppm)*	*J (Hz)*
$(CH_2)_3COOEt$	1	−3.9	δ = 1.24 (t) (3H)	$^3J_{HCCH}$=7
			δ = 2.45 (m) (6H)	
			δ = 3.7 (d) (3H)	
			δ = 4.11 (q) (2H)	$^3J_{HCOP}$=11
			δ = 5.1 (d) (2H)	$^3J_{HCCH}$=7
			δ = 7.37 (s) (5H)	$^3J_{HCOP}$=8.8
$(CH_2)_3CH_3$	2	− 3.73	δ = 0.8 (t) (3H)	$^3J_{HCCH}$=7
			δ = 1.5 (m) (4H)	
			δ = 2.8 (t) (2H)	
			δ = 3.7 (d) (3 H)	$^3J_{HCCP}$=7
			δ = 5.1(d) (2H)	$^3J_{HCOP}$=11
			δ = 7.4 (s)(5H)	$^3J_{HCOP}$=8
CH_3	3	−3.97	δ = 1.7 (d) (3H)	$^3J_{HCCP}$=5.4
			δ = 3.7 (d) (3H)	$^3J_{HOCP}$=11
			δ = 5.1 (d) (2H)	$^3J_{HOCP}$=8.5
			δ = 7.4 (s) (5H)	
OCH_3	4	−4.49	δ = 3.3 (s) (3H)	
			δ = 3.6 (d) (3H)	$^3J_{HCOP}$=11.2
			δ = 4.9 (d) (2H)	$^3J_{HCOP}$=8.3
			δ = 7.2 (s) (5H)	
$CH(CH_3)_2$	5	−4.1	δ = 1.2 (d) (6H)	
			δ = 3.9(m) (3H)	$^3J_{HCOP}$=8
			δ = 5.2 (d) (2H)	$^3J_{HCOP}$=11
			δ = 7.4 (s) (5H)	$^3J_{HCCH}$=7

SYMMETRICAL BENZYL α-KETOPHOSPHONATES

-α-ketophosphonates esterified by CH_2Ph groups.

These compounds are obtained by the addition of acyl chloride RCOCl to the tribenzylphosphite $P(OCH_2Ph)_3$. However because of the intrinsic reactivity of these benzyl molecules, reported in a preceeding work [5], it was not possible to obtain the α-ketophosphonates selectively using the classical Arbuzov method. The mixture of tribenzylphosphite and acyl chloride leads to 50% of the symmetrical α-ketophosphonate $(PhCH_2O)_2P(O)COR$ and 50% of the bisphosphonic ester $(PhCH_2O)_2(O)PC(R)(OH)P(O)(OCH_2Ph)_2$. Any attempt at separation degrades the α-ketophosphonate. The α-ketophosphonate with $R = OCH_3$ is however an exception, and because of the stability due to the conjugation of the oxygen of the methoxy group with the double bond of the carbonyl group, it is possible to obtain only the α-ketophosphonate by reaction of the tribenzylphosphite $P(OCH_2Ph)_3$ with CH_3OCOCl (table II).

TABLE II NMR data of the symmetrical benzyl α-ketophosphonate



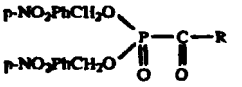
R	N°	NMR ^{31}P δ (ppm)	NMR ^{1}H	
			δ (ppm)	J (Hz)
OCH_3	6	6.06	δ = 3.7 (d) (3H) δ = 5.16 (d) (4H) δ = 7.13(s) (10H)	$^3J_{HCOP}$=8

The effect produced by the modification of benzyl groups in the α-ketophosphonate has been studied.

-α-ketophosphonates esterified with pNO_2PhCH_2 groups.

The modification of the aromatic radical with electron withdrawing p-NO_2 groups affects the result of the Arbuzov reaction, promoting the formation of 75% symmetric bisphosphonic esters and 23% α-ketophosphonate. It is however possible to extract in ether the formed α-ketophosphonate and to isolate it after evaporation of the solvent as a white powder. Spectral characteristics of these compounds are given in table III.

TABLE III NMR Data of the symmetrical α-ketophosphonates

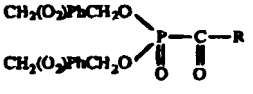


R	*N°*	*NMR ^{31}P*		*NMR ^{1}H*	
		δP (ppm)	*$^{3}J_{POCH}$(Hz)*	*δH (ppm)*	*J (Hz)*
$(CH_2)_3COOEt$	7	-6.05 (q)	9	δ = 1.24 (t) (3H) δ = 2.45 (m) (6H) δ = 4.11 (q) (2H) δ = 5.3 (m) (4H) δ = 7.53; 8.16 (8H) (s)	$^{3}J_{HCOP}$=7 $^{3}J_{HCCH}$=7 $^{2}J_{HCH}$=8.5
$(CH_2)_3CH_3$	8	- 4.9 (q)	8.5	δ = 0.9 (t) (3H) δ = 1.45 (m) (4H) δ = 2.35 (t) (2H) δ = 5.27 (m) (4H) δ = 7.8:8.15 (8H)(s)	$^{3}J_{HCOP}$=6.5 $^{3}J_{HCOP}$=8 $^{2}J_{HCH}$=9.5

- α-ketophosphonates esterified with piperonyl groups.

It is possible to selectively obtain these compounds by the Arbuzov reaction by adding tripiperonylphosphite to the acyl chlorides. In contrast to the preceeding compounds, the bisphosphonic symmetrical ester is almost absent (< 5%). NMR data are given in table IV. The α-ketophosphonates are however quite unstable at ambient temperature and quickly hydrolyze to give the α-ketophosphonic acid, $(HO)_2P(O)COR$.

TABLE IV NMR data of α–ketophosphonates esterified by piperonyl groups



R	*N°*	*NMR ^{31}P*		*NMR ^{1}H*	
		δP (ppm)	*$^{3}JP_{OCH}$(Hz)*	*δ H (ppm)*	*J (Hz)*
CH_3	9	-3.8 (q)	8.6	δ = 1.4 (t) (3H) δ = 5 (m) (4H) δ = 5.8 (s) (2H) δ = 6.63;6.70 (s) (6H)	$^{3}J_{HCCP}$=5.4
$(CH_2)_3CH_3$	10	-4.5 (q)	8.3	δ = 0.8 (t) (3H) δ = 1.62 (m)(4H) δ = 2.43 (t) (2H) δ = 5.27(m) (4H) δ = 6.61;6.68 (s)(6H)	$^{3}J_{HCCH}$=7 $^{3}J_{HCCH}$=7

Identification is allowed with compound N° 9 (table IV) where hydrolysis of the two piperonyl groups produces a compound showing a coupling constant $^3J_{PCCH}$= 5.4Hz, due to the coupling between the phosphorus and the methyl protons.

Indeed, for all symmetrical or asymmetric α-ketophosphonates, coupling between the protons that are on the side chain in an α position and the phosphorus atom was never observed, except for the case where R = Me. We think that this peculiarity is linked to geometrical aspects of the molecule.

DISCUSSION

The differences in reactivity observed between symmetrical α-ketophosphonates are interesting because they allow identification of new factors that are able to influence the Arbuzov reaction. This reaction, obtained from trimethylphosphite ($P(OMe)_3$) and acyl chloride leads almost exclusively to the α-ketophosphonates[2]. The esterification with benzyl groups reduced this yield to 50%. When benzyl groups are changed to p-nitrobenzyl, the yield was reduced to 25% on average. On the other hand, the replacement of benzyl groups by piperonyl groups drives the reaction to a significant production of α-ketophosphonate.

According to our observations, the main factor is the stability of the α-ketophosphonate. The α-ketophosphonates esterified by two methyl groups are stable. The replacement of a methyl group by a benzyl group decreases the stability of the α-ketophosphonate, inducing easy cleavage of the P-C bond. The liberated compound reacts then with another molecule of α-ketophosphonate to give the bisphosphonic ester $(PhCH_2O)_2(O)PC(R)(OH)P(O)(OCH_2Ph)_2$. The addition of an electron withdrawing group NO_2 in the para position to the phenyl group, again decreases the stability of the α-ketophosphonate. In the case of piperonyl groups, the two para and meta oxygens of the aromatic ring, stabilize the α-ketophosphonate.

EXPERIMENTAL

- Preparation of $(MeO)_2POCH_2Ph$

A mixture of 11.88 g (0.11 mol) of benzyl alcohol and 11.11 g (0.11 weak) of triethylamine in 60 ml of ether is added to a 100 ml tricol containing 15 g (0,11 mol) of $(MeO)_2PCl$, with stirring under dry nitrogen atmosphere at 100°C. At the end of the addition, the stirring is continued 4 h to ambient temperature. The

tricthylamine chlorhydrate is then filtered and washed with ether. The ether is then evaporated and the residue is distilled.

Rdt= 60% (E_{16mm}= 70°C)

NMR^{31}P : δ= 138.73 ppm, $^{3}J_{POCH3}$ = 10.94Hz, $^{3}J_{POCH2}$= 8.08Hz

- Synthesis of asymmetrical α-ketophosphonates

One equivalent of acid chloride is added in one equivalent of dimethylbenzylphosphite under a current of nitrogen gas (the reaction is very exothermic), at a temperature maintained between 0°C and –10°C, . At the end of the addition, the reactive mixture is stirred during 2 h at room temperature until the alkyl chloride is completely released. The symmetrical α-ketophosphonate $(CH_3O)_2P(O)COR$ is separated from the asymmetrical one by distillation (E_{2mmHg}= 29°C). The asymmetrical α-ketophosphonate is then extracted with ether and recovered in the form of a colorless liquid, after evaporation of the solvent.

- Preparation of tribenzylphosphite (or tris(p-nitrobenzyl)phosphite or tripiperonylphosphite)

One equivalent of $P(NMe_2)_3$ and three equivalents of benzyl alcohol, (or p-nitrobenzylalcohol or piperonylalcohol) are heated to 100°C for 2 hours. The compound obtained is then extracted three times with 50 ml of ether. This allows to isolate the phosphite that is a yellow powder for tris(p-nitrobenzyl)phosphite, and a colorless liquid for tribenzylphosphite and tripiperonylphosphite. The yield of this reaction is quantitative.

- Synthesis of symmetrical α-ketophosphonates

One equivalent of acid chloride is added to one equivalent of tribenzylphosphite under a current of nitrogen, at a temperature maintained between – 10°C and – 20°C. At the end of the addition, the reaction mixture is allowed to warm to ambient temperature and stirred one hour. The mixture obtained is then extracted three times with 50 ml of ether. The solvent is then evaporated and the α-ketophosphonate is isolated as a liquid (benzyl and piperonyl esterified α-ketophosphonates) or as a white powder (p-nitrobenzyl esterified α–ketophosphonates).

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