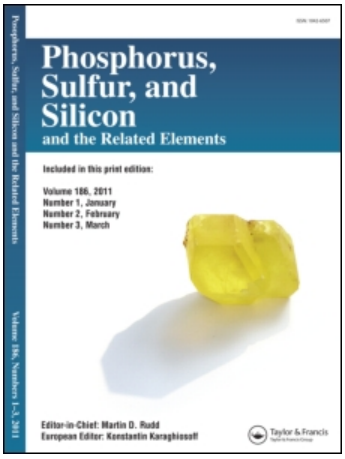


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Dialkyl-Hydroxymethylphosphonates in Heterogeneous Conditions

Thomas Jeanmaire[a]; Yves Hervaud[a]; Bernard Boutevin[a]
[a] Ecole Nationale Supérieure de Chimie de Montpellier, Montpellier, France

Online publication date: 27 October 2010

To cite this Article Jeanmaire, Thomas , Hervaud, Yves and Boutevin, Bernard(2002) 'Synthesis of Dialkyl-Hydroxymethylphosphonates in Heterogeneous Conditions', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 5, 1137 — 1145
To link to this Article: DOI: 10.1080/10426500211718
URL: http://dx.doi.org/10.1080/10426500211718

Phosphorus, Sulfur and Silicon, 2002, 177:1137–1145

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290092415

SYNTHESIS OF DIALKYL-HYDROXYMETHYLPHOSPHONATES IN HETEROGENEOUS CONDITIONS

Thomas Jeanmaire, Yves Hervaud, and Bernard Boutevin
Ecole Nationale Supérieure de Chimie de Montpellier, Montpellier, France

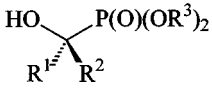
(Received December 4, 2001)

This article describes the synthesis of a series of dialkyl-hydroxymethylphosphonates bearing various alkyl ester groups by the Pudovik reaction. The employed method uses anhydrous potassium carbonate as a catalyst in heterogeneous (solid/liquid) or mixed (solid/liquid and homogenous) conditions. All these syntheses are performed without any phase transfer agent and involve an anionic intermediate in a low polar or apolar solvent. These different products, obtained with high yields, have been characterised by ^{1}H and ^{31}P NMR and also by mass spectrometry. A study of fragmentation in the FAB ionisation process is given.

Keywords: ^{1}H and ^{31}P NMR; hydroxymethylphosphonates; mass spectrometry

INTRODUCTION

Dialkyl α-hydroxyalkylphosphonates exhibit the following general structure (Scheme 1):

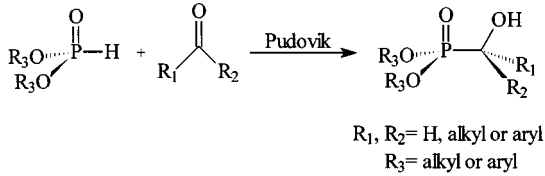


SCHEME 1 General structure of dialkyl α-hydroxyalkylphosphonates.

They are obtained mainly through hydrophosphonylation of carbonyl compounds such as aldehydes or ketones by dialkyl hydrogenphosphonates. This reaction, usually base-catalysed, is well known

Address correspondence to Y. Hervaud, Ecole Nationale Supérieure de Chimie, 8, rue de Ecole Normale, F-34296 Montpellier Cedex 5, France.

in phosphorus organic chemistry as the Pudovik reaction.[1–3] (see Scheme 2.)

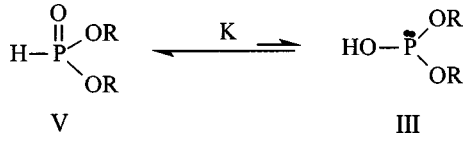


SCHEME 2 Pudovik reaction.

The literature indicates that aldehydic substrates are more reactive than ketones.[4]

$$R_1, R_2 = H, H > H, CH_3 > CH_3, CH_3.$$

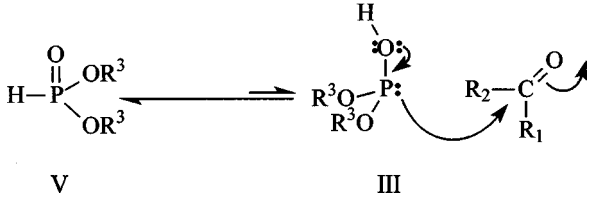
However, the nucleophilic behaviour of the phosphonate is ambiguous. Actually, there is a tautomeric equilibrium[5] (Scheme 3) between the dialkylhydrogenphosphonate with pentavalent phosphorus (V) and the corresponding dialkylphosphite trivalent form(III).



SCHEME 3 Tautomeric equilibrium of dialkylhydrogenphosphonates.

In the case of phosphorus ethylic esters, the equilibrium constant K equals 10^{-7} in water at 25°C. Moreover, although the tricoordinate form is the more acidic,[5–7] we observe only P-alkylation and no O-alkylation at all.

The active form is supposed to be tricoordinated(III) and the equilibrium can be described in Scheme 4.



SCHEME 4 Reactivity of dialkylhydrogenphosphonates toward carbonyl groups.

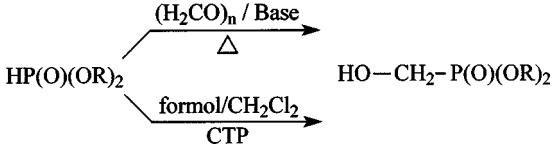
In the present work, we will only describe the synthesis of dialkyl hydroxymethylphosphonates $HOCH_2P(O)(OR)_2$ with R = Me, Et, and iPr according to the Pudovik method.

During the last few years, many organic syntheses involving anions (carbanions, oxanions. . .) have been perfomed in phase transfer catalysis conditions.[8] This technique allows to perform base catalyzed reactions with alkaline hydrolysis sensible reagents.[9]

The formaldehyde reagent is available either in solid polymeric paraformaldehyde $-(H_2CO)_n-$, or in aqueous formol form. With paraformaldehyde, the reaction can be carried out in solution or in bulk in the presence of basic catalysts such as alkaline metal alcoxide,[10] solid mineral bases like fluoride,[11] alumina,[12] and especially tertiary amines.[13–14] Nitrogenous catalysts are restricted to tertiary amines in order to avoid the Kabachnik-Fields reaction[15–16] which gives the α amino compound.

Uzlova et al.[17] used aqueous formol in liquid–liquid phase transfer catalysis (LL PTC) using the couple water/dichloromethane at room temperature, with sodium hydroxide as a catalyst and $(nBu)_4NHSO_4$ as phase transfer agent. Yields increase from 24% with R = Me to 53% with R = Et.

The two types of reaction are summarized in Scheme 5. In all cases, we note that the reactions are less and less exothermic in the order $R = CH_3 < C_2H_5 < iC_3H_7$. Thus the reaction in bulk of dimethylhydrogenphosphonate with formol is very exothermic and undergoes the formation of by-products.



SCHEME 5 General methods of synthesis of dialkyl hydroxymethylphosphonates.

Zimmerer[18] and Pelchowicz[19] showed, without giving rates, that sodio-derivatives of dialkylhydrogenphosphonate $(RO)_2P(O)Na$ isomerize, on heating, in dialkylalkylphosphonates $R{-}P(O)(OR)_2$ and monoalkylhydrogenphosphonates HP(O)(OR)(ONa). Particularly with methyl esters, isomerizations are complex and give various rearrangement products.

Rosenberg et al.[20] described the same synthesis in mild conditions, at room temperature, in methanol, with sodium methoxide as a catalyst, with a yield of 85%. Diisopropylhydrogenphosphonate is a

sterically hindered reagent and needs thermal activation[21] or the use of strong and not nucleophilic nitrogenous bases such as 1,8 diazabicyclo [5,4,0]undec-7-ene (DBU).[22]

Makosza and Wojciechowski[23] showed that anhydrous potassium carbonate is a strong enough base to deprotonate dialkylhydrogenphosphonate ($pKa \approx 15$) in heterogeneous solid-liquid conditions with small amounts of phase transfer agent (crown ether or quaternary ammonium). The advantage of this method is the direct applicability of dialkyl hydrogenphosphonate instead of their metal salts.

The authors have performed several Michael addition reactions with dialkylhydrogenphosphonate and electrophilic alkenes and also nucleophilic substitutions with good yields.

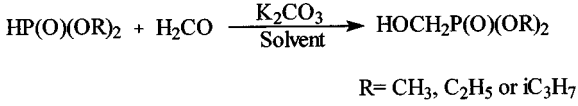
Furthermore, Bodarenko et al.[24] carried out alkylation of dialkylphosphonate with methyliodide and anhydrous potassium carbonate as a catalyst without any phase transfer agent. Also the separation difficulties of the crude product are avoided.

In this work, we have studied the reaction of various dialkylhydrogenphosphonates with paraformaldehyde, in heterogeneous or mixed conditions, with anhydrous potassium carbonate and without any phase transfer agent.

RESULTS AND DISCUSSION

We synthesized various dialkyl hydroxymethylphosphonates in solution with paraformaldehyde and anhydrous potassium carbonate as a catalyst. Carbonates are commonly used in heterogeneous phase as a non-nucleophilic solid "soft" base because they are easy to handle and to eliminate by filtration at the end of the reaction.[20]

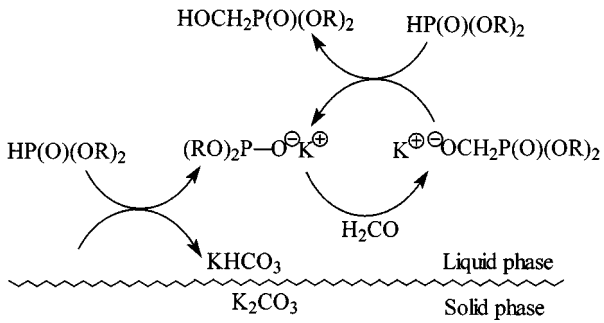
Syntheses, made without any phase transfer agent, at room temperature, can be schematised as follows in Scheme 6.



SCHEME 6 Pudovik reaction in heterogeneous conditions.

Scheme 7 represents the suggested mechanism of pudovic reaction in heterogeneous conditions.

The rate of conversion of dialkylhydrogenposphonate is followed by capillary GC. All the experimental data are gathered in Table I.



SCHEME 7 Proposed mechanism of Pudovik reaction in heterogeneous conditions.

Characteristics of these solvents are high calorific capacity (C_p) and medium to low dielectric constant (ε) as it is reported in Table II.

The solvents used have a various nature in term of acidity and polarity. Light alcohols such as methanol and ethanol, which are fairly polar and protic, are used. In these light alcohols, the catalyst is more soluble but the mixture remains heterogeneous. Isopropanol and cyclohexane have quite the same low polarity and only differ by their acidity.

In such conditions, the catalyst remains little or not soluble in the chosen solvents and by thus, the heterogeneity of the reaction is kept. High calorific capacities (Cp) allow to limit exothermicity during the reaction especially with dimethylhydrogenphosphonate.

It is necessary to use the alcohol corresponding to the phosphorus ester in order to avoid transesterification reactions.[25,26] These reations prove the existence of potassium alcoxide in the medium, generated by reaction of the catalyst with the solvent (it can be avoided in

TABLE I Experimental Conditions and Yields for the Addition of Dialkylhydrogenphosphonates to Paraformaldehyde in Various Solvents

R	Solvent	Time (h)	Yield GC
CH_3	C_6H_{12}	1	100
	CH_3OH	1	100
C_2H_5	C_6H_{12}	1	13
	C_6H_{12}	15	100
	C_2H_5OH	5	100
$CH(CH_3)_2$	C_6H_{12}	1	1
	C_6H_{12}	15	100
	$(CH_3)_2CHOH$	3	0
	$(CH_3)_2CHOH$[a]	1	100

[a]Reaction performed at 60°C.

TABLE II Calorific Capacities and Solvents Dielectric Constants

Solvent	Cp at 25°C (J/mol K)	ε
CH_3OH	81.1	33.0
C_2H_5OH	112.3	25.3
$(CH_3)_2CHOH$	156.5	2.64
C_6H_{12}	154.9	2.02

using cyclohexane for example). Besides this alcoxide may also act as catalyst.

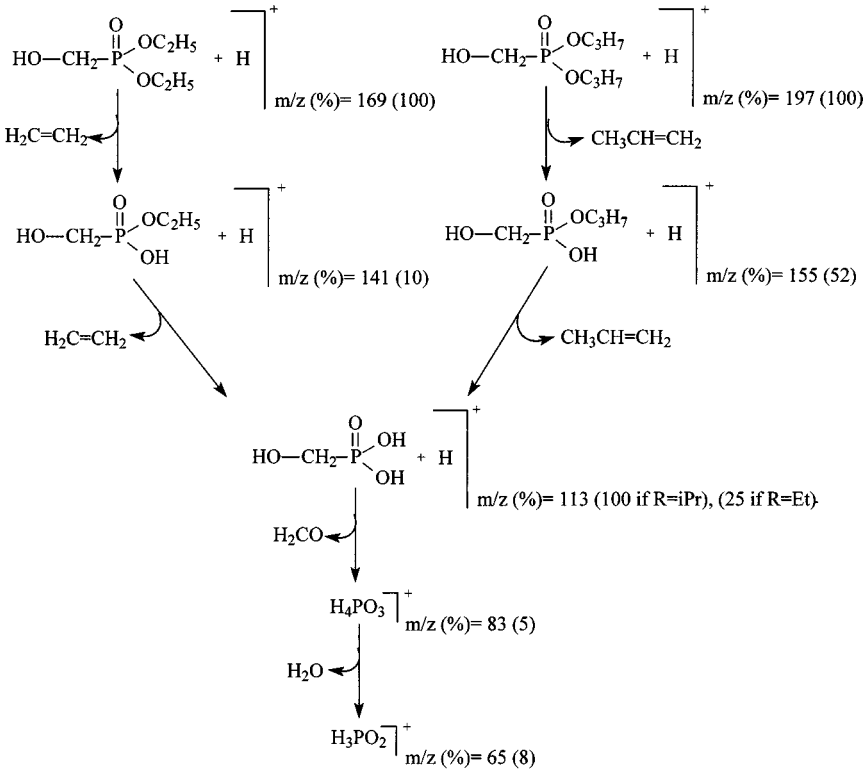
Whatever the nature of the solvent, we notice that the speed of the reaction increases in the following order $HP(O)(OiPr)_2 < HP(O)(OEt)_2 < HP(O)(OMe)_2$. Actually the reaction with dimethylhydrogenphosphonate is fast and exothermic while we observe a slow-down with the other phosphonates. This phenomenon can be explained on one hand by the increase of the steric hindrance which decreases the phosphonate nucleophilicity and on the other hand by the tautomeric equilibrium. Actually, the more the phosphonate bears a donor ester group, the more the equilibrium (Scheme 3) between the phosphonate pentavalent form $P^{v}(V)$ and the phosphite trivalent form $P^{III}(III)$ is shifted to the P(V) form to the detriment of the active P(III) form. In the case of diisopropyl esters, a soft thermical activation permits to reduce significantly the reaction time without undergoing the formation of by-products.

The various dialkyl α-hydroxymethylphosphonates have been studied in mass spectrometry (FAB+ ionisation) and all the molecular ions $(M + H)^+$ are observed with good intensities. All fragments are given as follows m/z and (abundance in percent). The fragmentation mechanisms of dimethyl hydroxymethylphosphonate are complex and we will only study the ethyl and isopropyl species.

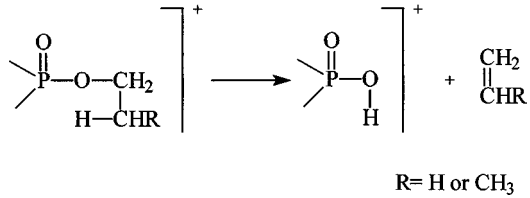
The different fragments are described in Scheme 8. We note the successive loss of ester by olefin elimination (ethylene and propylene respectively) leading to a common ion in the two products.

We notice that the loss of ester is preferential to the loss of the neutral formol molecule, actually no ions at $m/z = 139$ and 167 are detected. The olefin elimination needs the presence of hydrogen linked to the carbon β to the oxygen (Scheme 9). It implies that the abundance in the isopropyl series is higher than in ethyl one.

After the total loss of ester groups, we obtain a common ion fragment at m/z 113. It looses a neutral formol fragment to give a positive ion at m/z 83 which corresponds to the protonated phosphonic acid ($H_4PO_3^+$). By dehydration of the previous fragment, we obtain a new ion at m/z 65.



SCHEME 8 Detailed mass spectrometry of dialkylhydroxymethylphosphonates.



SCHEME 9 Mechanism of loss of phosphonate ester in mass spectrometry.

CONCLUSION

We have synthesised, in very high yields, a range of dialkyl hydroxymethylphosphonates bearing various ester groups, by the reaction involving dialkylhydrogenphosphonate and paraformaldehyde according to the Pudovik reaction. The method we used employed anhydrous

potassium carbonate as a catalyst in heterogeneous or mixed catalysis conditions. This reaction, taking place in solvents of various nature, shows that it is possible to generate anionic phosphonyl intermediates in heterogeneous conditions and without any phase transfer agent. This method, cheap and easy to perform, permits to obtain simply functionalised phosphonated products and may be useful for various base-catalyzed reactions involving dialkylhydrogenphosphonates.

EXPERIMENTAL PART

Into a two-necked round-bottomed flask, equipped with a condenser and a magnetic stirrer, was introduced dialkylhydrogenphosphonate $HP(O)(OR)_2$, paraformaldehyde, solvent and 5% (molar) of powdered anhydrous potassium carbonate K_2CO_3. The heterogeneous solution is vigorously stirred during various times. At the end of the reaction, the solution is filtered through 0.45 μm porosity filter and the solvent is removed under vacuum. The products are obtained with yields near 98%.

For example, we introduce 16.61 g (0.1 mmol) of diisopropyl hydrogenphosphonate, 3.6 g (0.12 mmol) of paraformaldehyde, 35 ml of isopropanol and 0.69 g (0.005 mmol) of anhydrous K_2CO_3. The solution is stirred vigorously during 1 h at 60°C, then treated as described before.

Dimethyl Hydroxymethylphosphonate

^{1}H NMR ($CDCl_3$) δ: 5.4 (s, 1H, OH); 3.7 (d, 2H, C$\underline{H}_2$—P, $^2J_{HP} = 6$ Hz); 3.6 (d, 6H, POC$\underline{H}_3$, $^3J_{HP} = 10.5$ Hz).
^{31}P NMR ($CDCl_3$) δ: 28.3 (s).
Bp = 92°C under 4 10^{-2} mbar.
FABMS (3-NOBA); m/z (%): 141 (100); 123 (8); 111 (7); 93 (16); 79 (25).

Diethyl Hydroxymethylphosphonate

^{1}H NMR ($CDCl_3$) δ: 5.2 (s, 1H, OH); 4.0 (m, 4H, —O—C$\underline{H}_2$CH$_3$); 3.7 (d, 2H, PC$\underline{H}_2$, $^2J_{HP} = 6$ Hz); 1.2 (t, 6H, —O—CH$_2$C$\underline{H}_3$, $^3J_{HH} = 7.3$ Hz).
^{31}P NMR ($CDCl_3$) δ: 25.92 (s).
Bp = 95°C under 5 10^{-2}mbar.
FABMS (3-NOBA); m/z (%): 169 (100); 141 (10); 113 (25); 83 (5); 65 (8).

Diisopropyl Hydroxymethylphosphonate

^{1}H NMR ($CDCl_3$) δ: 5.1 (s, 1H, OH); 4.6 (m, 2H, —O—C$\underline{H}$); 3.7 (d, 2H, C$\underline{H}_2$P, $^2J_{HP} = 6$ Hz); 1.2 (d, 12H, C($\underline{CH}_3$)$_2$).
^{31}P NMR ($CDCl_3$) δ: 24.08 (s).

Bp = 92°C under 2.5 10^{-2}mbar.
FABMS (3-NOBA); m/z (%): 197 (100); 155 (52); 113 (100); 83 (4); 65 (4).

REFERENCES

[1] R. Engel, *Synthesis of Carbon Phosphorus Bonds* (CRC Press, Florida, 1987), p. 101.
[2] R. Engel, *Organic Reactions* (Wiley & Sons, New York, 36, 1987), p. 175.
[3] K. Sasse, Gallenkamp, and Kruger, *α-Hyroxy-Alkan-Phosphonsäureestern aus Phosphorigsäureestern und Carbonylverbdgn.* 4.Aufl., Band XII/1, p475 HOUBEN-WEIL, New York 36(1987).
[4] A. N. Pudovik, M. G. Zimin, et A. M. Kurguzova, *J. Gen. Chem. SSSR*, **41,** 1981 (1971).
[5] J. P. Guthrie, *Can. J. Chem.*, C. A. 90:186166, **57,** 236 (1979).
[6] R. Gancarz and I. Gancarz, *Phosphorus Sulfur and Silicon*, **158,** 241 (2000).
[7] V. J. Blazis, K. J. Koeller, and C. D. Spilling, *J. Org. Chem.*, **60,** 931 (1995).
[8] A. Loupy and A. Haudrechy, *Effets de Milieu en Synthèse Organique* (Masson, Paris, Chapter IV, p. 201, 1996).
[9] M. C. Mitchell, R. J. Taylor, and T. P. Kee, *Polyhedron*, **4,** 433 (1998).
[10] V. S. Abramov and L. P. Semenova, *Zh. Obshch. Khim.*, **1,** 393 (1952).
[11] F. Texier-Boullet and A. Foucaud, *Synthesis*, 165 (1982).
[12] F. Texier-Boullet and A. Foucaud, *Synthesis*, 916 (1982).
[13] R. K. Zaripov and V. S. Abramov, *Izv. Akad. Nauk. SSSR*, **5,** 50 (1969).
[14] R. Fritz, R. Pretsch, B. Guettes, and M. Reichelt, Eur. Pat. 0 908 464 BASF, 1999, *C.A.*, **130,** 298305.
[15] B. P. Kotovich, *J. Gen. Chem. SSSR*, **57,** 1297 (1987).
[16] V. I. Galkin, E. R. Zvereva, and I. V. Galkina, *Phosphorus, Sulfur and Silicon*, **147,** 69 (1999).
[17] L. A. Uzlova and O. V. Eryuzheva, *Zh. Obshch. Khim.*, **5,** 1032 (1988).
[18] R. E. Zimmerer and R. G. Laughlin, *J. Org. Chem.*, **27,** 3576 (1962).
[19] Z. Pelchowicz, S. Brukson, and E. Bergmann, *J. Chem. Soc.*, 4348 (1961).
[20] A. Holy and I. Rosenberg, *Collect. Czech. Chem. Commun.*, **12,** 3447 (1982).
[21] A. Holy, *Collect. Czech. Chem. Commun.*, **3,** 649 (1993).
[22] F. Hammerschmidt, H. Kahlig, and N. Muller, *J. Chem. Soc. Perkin Trans. 1*, 365 (1991).
[23] M. Makosza and K. Wojciechowski, *Bull. Pol. Acad. Sci. Chem.*, **3–6,** 175 (1984).
[24] N. Bondarenko, M. Rudomino, and E. N. Tsvetkov, *Zh. Obshch. Khim.*, **60,** 1196 (1990).
[25] K. Troev and M. Simeonov, *Phosphorus, Sulfur and Silicon*, **19,** 363 (1984).
[26] M. J. Gallagher and R. Garbutt, *Phosphorus, Sulfur and Silicon*, **75,** 201 (1993).