SHORT PAPER

J. Chem. Research (S),
2002, 291–292

The synthesis of α-hydroxyphosphonates mediated by microwave irradiation under solvent-free conditions†

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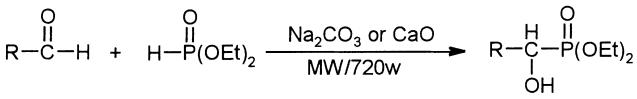
Microwave-assisted hydrophosphonylation of aldehydes under solvent-free conditions was found to be an efficient method for the preparation of α-hydroxyphosphonates; the method was reliable, efficient and high yielding.

Keywords: α-hydroxyphosphonates, aldehydes, solvent-free conditions

In recent years, considerable interest has been focused on the synthesis of phosphonic acids, particularly the α-substituted analogues that are an important class of compounds[1] with applications as antibiotics, antiviral agents and enzyme inhibitors.[2] Among the α-functionalised phosphonic acids, α-hydroxyphosphonic acid derivatives are gaining in interest in medicinal chemistry. It is well known that α-hydroxyphosphonates and phosphonic acids inhibit enzymes such as renin,[3] EPSP synthase,[4] HIV protease,[5] and more recently PTPases.[6] Moreover, other biologically significant α-substituted phosphonates and phosphonic acids are readily obtainable starting with α-hydroxyphosphonates.[7] Bioactive γ-aminophosphonic acids as well as γ-substituted vinyl phosphonates and phosphonic acids can also be obtained from allylic α-hydroxyphosphonates.[8] The base-catalysed hydrophosphonylation of aldehydes (the Pudovik reaction) is one of the most versatile methods for the preparation of α-hydroxyphosphonates.[9a,b] Synthesis of organic compounds in heterogeneous media is of growing interest because of the ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yield, lack of solvent and the low cost of the reaction in comparison with other homogeneous counterparts.[10] The application of microwave energy (MW) to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[11] Synthesis of molecules, which normally require a long time, can be achieved conveniently and very rapidly in a microwave oven. To our knowledge, there is no report in the literature on the synthesis of α-hydroxyphosphonates under solvent-free condition assisted by microwaves. As a part of our efforts to explore the utility of solvent-free conditions for the synthesis of organophosphorus compounds,[12–15] we describe here a new method for the preparation of α-hydroxyphosphonates. It is found that CaO or Na_2CO_3 under solvent-free conditions is capable producing high yields of α-hydroxyphosphonates from the reaction of diethyl phosphite with aldehydes (Scheme 1, Table 1).

As shown in Table 1, aliphatic aldehydes in the presence of CaO or Na_2CO_3 reacted with diethyl phosphite, to give the required products in excellent yields **(2a, 2b)**. The reaction also proceeded in good yields for substituted benzaldehyde **(2c–2i)**. The cinnemaldehyde, as an α,β-unsaturated aldehyde and α-naphthyl carbaldehyde as a polynuclear aromatic aldehyde also afforded the α-hydroxyphosphonates in excellent yields **(2j, 2k)**.

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction conditions, good yields and relative cleanliness with no tar formation in the reaction make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of aldehydes (enolisable and non-enolisable) was converted into corresponding α-hydroxyphosphonates using this method.



1 **2**

Scheme 1

Table 1 The preparation of α-hydroxyphosphonates **(2)** under solvent-free condition using microwave irradiation

Product (2)	R-	Time /min	Yield[a] /%	Yield[b] /%
a	$CH_3CH_2CH_2$-	2	92	90
b	$CH_3CH_2CH_2CH_2$-	2	98	95
c	C_6H_5-	2	75	70
d	*p*-$CH_3C_6H_4$-	2	65	65
e	*m*-$CH_3OC_6H_4$-	2	65	65
f	*p*-ClC_6H_4-	2	70	70
g	*m*-$NO_2C_6H_4$-	1	72	70
h	*p*-$NO_2C_6H_4$-	48[c]	75	75
i	*p*- $(CH_3)_2CHC_6H_4$-	4	79	75
j	C_6H_5-CH=CH-	2	85	82
k	α-$C_{10}H_7$-	2	90	88

[a]Isolated yields in Na_2CO_3.
[b]Isolated yields in CaO.
[c]Reaction time based on seconds.

Experimental

General: All chemicals were commercial products and distilled or recrystallised before use. All melting points were obtained by a Buchi 510 and are uncorrected. A commercially available pulse microwave at 2450 MHz (900 W) was used in all experiments. The infrared (IR) spectra were determined neat using an FTIR. ^{1}H NMR (at 500 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$).

In a typical case, benzaldehyde (0.53 g, 5 mmol), diethyl phosphite (0.83 g, 6 mmol) and Na_2CO_3 or CaO (1 g.) were mixed together in a flask and irradiated for 2 minutes (irradiation stopped and the reaction was monitored by TLC). The reaction mixture was allowed to cool (5 minutes), washed with dichloromethane and the solvent was then removed *in vacuo* to give the crude product. Purification of the residue by crystallisation from CH_2Cl_2/*n*-hexane gave the diethyl α-hydroxyphenylmethylphosphonate **(2c)**, in 75% (Na_2CO_3) and 70% (CaO) yields.

All products gave satisfactory spectral data in accord with the assigned structures.[12, 16] For **2j** as an example: White crystals (82%);

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

m.p = 105–106°C (*n*-hexane/CH_2Cl_2) [lit[17], m.p. 106.5–107°C]; ^{1}H-NMR ($CDCl_3$/TMS): 1.15 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 7.1), 3.94 (1H, ddq, J = 7.1, 11.2, 8.1 Hz), 4.09(1H, ddq, J = 7.1, 8.1, 11.2 Hz), 4.18 (2H, m), 4.3 (1H, br, OH), 4.4 (1H, dd, J_{HP} = 18, J_{HH} = 6 Hz), 6.08 (1H, dd, J = 6, 16 Hz), 6.4 (1H, d, J = 16), 6.9–7.4 (5H, m); ^{31}P-NMR ($CDCl_3$/H_3PO_4): 19.49; IR (KBr): 3250 (-OH), 1230 (P = O), 1045 (P-O-Et) cm^{-1}.

We thank the Institute for Advanced Studies in Basic Sciences (IASBS) for support of this work.

Received 5 June 2001; accepted 29 December 2001
Paper 01/909

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