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Microwave-Assisted Synthesis of α-Hydroxy-benzylphosphonates and -benzylphosphine Oxides

György Keglevich,[1] Viola Róza Tóth,[1] and Lászó Drahos[2]

[1]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

[2]*Hungarian Academy of Sciences, Chemical Research Center, H-1525 Budapest, Hungary*

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ABSTRACT: *A series of α-hydroxy-benzylphosphonates and -benzylphosphine oxides was synthesized by the Na_2CO_3-catalyzed microwave-assisted addition of dialkyl phosphites and dipenylphosphine oxide to P-substituted benzaldehydes. The solventless reaction provided the products in short reaction times and in 71–88% yield.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 22:15–17, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20649

INTRODUCTION

α-Hydroxyphosphonates are of significant biological and pharmaceutical interest [1]. They can be prepared by thermal noncatalyzed addition [2,3] and base or acid-catalyzed addition [2,4,5]. The main drawbacks of these procedures are the relatively long reaction times or the need to apply solvents. The solventless reaction using alumina [6,7], magnesia [8], or other solids, such as cesium fluoride [9], potassium fluoride [9], phosphates [10], sodium-modified hydroxyapatite [11], and sodium carbonate [12], brought a kind of breakthrough, but the reaction times were variable (10 min to 3 days).

To the best of our knowledge, only in one article was the effect of microwave (MW) irradiation studied on the addition of diethyl phosphite to aldehydes [12]. However, no temperatures were reported and the experiments cannot be reproduced, as the reactions were performed in a kitchen MW equipment [12]. We wished to elaborate a generally usable MW-assisted and solventless method for the synthesis of α-hydroxyphosphonates and α-hydroxyphosphine oxides under controlled MW conditions.

RESULTS AND DISCUSSION

First of all benzaldehyde was reacted with diethyl phosphite under solventless and MW conditions. After 3.5 h irradiation, α-hydroxy-benzylphosphonate **1a** was obtained in 80% yield (Table 1, entry 1). It was found that in the presence of Na_2CO_3 as the catalyst, the addition reaction was faster. Increasing the quantity of the catalyst from 5% to 75%, the reaction time decreased from 45 min to 20 min (Table 1, entries 2–5) (Scheme 1).

The following experiments applying *P*-substituted benzaldehydes and diethyl or dimethyl phosphite, as well as diphenylphosphine oxide were carried out in the presence of 75% of Na_2CO_3, in most cases for 20 min (Scheme 2).

Correspondence to: György Keglevich; e-mail: gkeglevich@mail.bme.hu.

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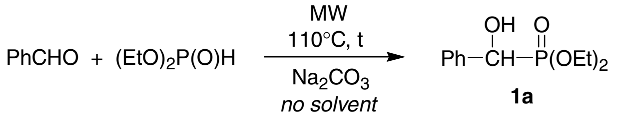
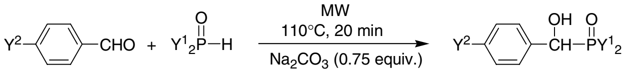


SCHEME 1



	Y^1
1	OEt
2	OMe
3	Ph

	Y^2
a	H
b	OMe
c	Me
d	NO_2
e	Cl

SCHEME 2

TABLE 1 Effect of Na_2CO_3 Catalyst on the Outcome of the Addition of Diethyl Phosphite to Benzaldehyde at 110°C under Solventless MW Conditions

Na_2CO_3 (equiv)	*t (min)*	*Yield (%)*	*Entry*
–	240	46	1
0.05	45	84	2
0.25	45	89	3
0.5	30	86	4
0.75	20	85	5

The additions took place smoothly and crystallization of the crude products from acetone–pentane afforded the α-hydroxy-benzylphosphonates (**1a–e**/**2a–e**) and α-hydroxy-benzylphosphine oxides (**3a–e**) in 71–88% yields. The products that are well known from earlier literature were identified by ^{31}P NMR chemical shifts, mass spectroscopy, and melting points (Table 2).

Our method is an environment friendly procedure for the addition of dialkyl phosphites and diphenylphosphine oxide to substituted benzaldehydes and may be of general value for the reaction of >P(O)H species with carbonyl derivatives.

In conclusion, ten α-hydroxy-benzylphosphonates and five α-hydroxy-benzylphosphine oxides were prepared by the MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to benzaldehydes in the presence of Na_2CO_3, under solventless conditions. The yields are between 71% and 88%.

EXPERIMENTAL

General

The ^{31}P NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4 MHz. Chemical shifts are downfield relative to 85% H_3PO_4. Mass spectrometry was performed on a ZAB-2SEQ instrument. The reactions were carried out in a 300W CEM Discover focused microwave reactor under isotermic conditions applying 50 W.

TABLE 2 Yields and Characterization of α-Hydroxy-benzylphosphonates **1**, **2**, and **3**

	Yield (%)	*$\delta^{31}P$*	*$\delta P^{lit.}$*	*MS*	*mp (°C)*	*$mp^{lit.}$ (°C)*	*Entry*
1a	85	21.5	22.0 [13]	245.1 (M + H)	74–75	74–76 [13]	1
2a	87	23.9	24.3 [14]	216.9 (M + H)	101–102	102 [14]	2
3a	88	32.7	33.2 [15]	309.3 (M + H)	173–175	173–175 [16]	3
1b	82	21.5	20.9 [17]	275 (M + H)	121–122	116 [17] 120–121.5 [8]	4
2b	84	23.4	23.8 [18]	245 (M – H)	73–74	72 [7] 72 [19]	5
3b	78	31.1	–	339 (M + H)	160–162	155 [20] 160–162 [21]	6
1c	87	21.7	22.0 [22]	276.3 (M + NH_4)	96–97	94–95 [8]	7
2c	62	24.0	23.8 [18]	231 (M + H)	92–93	92–93 [23] 98 [7]	8
3c	80	31.8	–	323 (M + H)	155–156	152.5–155 [21] 89 [17]	9[a]
1d	86	19.9	18.9 [17]	290.1 (M + H)	90–92	90–91 [24] 93–94 [25]	10[b]
2d	71	21.9	21.8 [18]	262.2 (M + H)	130–132	133 [25]	11
3d	80	31.1	–	354.3 (M + H)	189–91	186.5–188.5 [27] 191.5–193 [21]	12
1e	84	21.9	18.7 [8]	354.4 (M + H)	68–70	67–68 [8] 72–73 [28]	13
2e	72	22.1	–	273.0 (M + Na)	68–70	68 [7]	14
3e	79	33.1	–	343.2 (M + H)	183	181.5–183 [21] 188 [29]	15[a]

[a] 110°C, 0.5 h, 0.75 equiv of Na_2CO_3.

[b] 150°C, 1 h, 0.75 equiv of Na_2CO_3.

*General Procedure for Preparation of α-Hydroxy-benzylphosphonates (**1a–e**/**2a–e**)*

A mixture of 2.50 mmol of aromatic aldehyde (benzaldehyde 0.25 mL, *p*-methoxybenzaldehyde 0.30 mL, *p*-methylbenzaldehyde 0.29 mL, *p*-nitrobenzaldehyde 0.38 g, *p*-chlorbenzaldehyde 0.35 g), 2.50 mmol of dialkyl phosphite (diethyl phosphite 0.32 mL and dimethyl phosphite 0.23 mL) and 0.20 g (1.89 mmol) of Na_2CO_3 was homogenized to an extent it was possible and then heated at 110°C in a vial (open vessel) in a CEM Discover Microwave reactor for 20 min. The reaction mixture was extracted with 20 mL ethyl acetate. The organic phase was concentrated in vacuo. Crystallization from acetone–pentane afforded products **1a–e/2a–e** as white crystals (except for **1d** and **2d**, which were orange crystals; see Table 1).

*General Procedure for the Preparation of α-Hydroxy-benzylphosphine Oxides (**3a–e**)*

A mixture of 0.50 mmol of aromatic aldehyde (benzaldehyde 0.05 mL, *p*-methoxybenzaldehyde 0.06 mL, *p*-methylbenzaldehyde 0.24 mL, *p*-nitrobenzaldehyde 0.08 g, *p*-chlorbenzaldehyde 0.28 g) and 0.10 g (0.50 mmol) of diphenylphosphine oxide and 0.04 g (0.38 mmol) of Na_2CO_3 was heated at 110°C in a vial (open vessel) in a CEM Discover Microwave reactor for 20 min (except for **3c** and **3e**, when the reactions time was 30 min). The work-up procedure was similar as described above for products **1a–e/2a–e** to give products **3a–e** as white crystals (except for **3d**, which was orange crystals; see Table 1).

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