György Keglevich*, Zita Rádai and Nóra Zsuzsa Kiss

To date the greenest method for the preparation of α-hydroxyphosphonates from substituted benzaldehydes and dialkyl phosphites

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Abstract: Recent synthetic methods for α-hydroxyphosphonates comprise a green, solvent-free accomplishment of the Pudovik reaction that was typically followed by extractions and recrystallization, or even by chromatography, or other operations. We now developed a general procedure applying 10% of triethylamine as the catalyst and a minimum quantity of acetone as the solvent, giving the products in a pure form after a reflux of 5–120 min following the addition of some *n*-pentane and crystallization on cooling.

Keywords: α-hydroxyphosphonates; green synthesis; green work-up; Pudovik reaction.

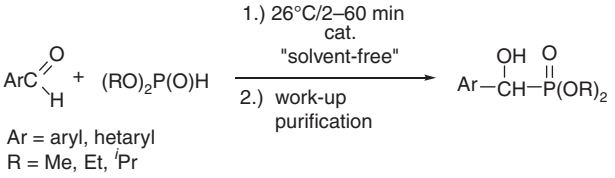
1 Introduction

The synthesis of α-hydroxyphosphonates is an ever-green topic due to the biological activity of these compounds. α-Hydroxyphosphonates may exhibit antibacterial [1], antiviral [2], anti-HIV [3], anticancer [4], enzyme inhibitor [5], and pesticide [6] properties. The biological activity was basically attributed to the P–C moiety and to the structural similarity of phosphonic acids to phosphate ester acids and carboxylic acids [7].

The best synthesis for α-hydroxyphosphonates is the Pudovik reaction involving the nucleophilic addition of dialkyl phosphites to carbonyl compounds. The addition may be performed by simple heating [8, 9] and in a base- or acid-catalyzed manner [8, 10, 11]. These procedures require solvents, and the reaction times are relatively long. Microwave-assisted variations were also described applying sodium carbonate as the base in the absence of any solvent [12, 13]. A number of solvent-free methods were reported, when the addition took place on the surface of solids, such as alumina [14, 15], magnesia [16], cesium fluoride [17, 18], potassium fluoride [17, 18], phosphates [19], and sodium-modified hydroxyapatite [20]. Even newer solvent-free variations have been reported, where a part of the reaction components (the aldehyde or the catalyst, or both) were in the solid phase. These newer solid-phase and solvent-free accomplishments are summarized in Scheme 1 and Table 1.

In the first case, equimolar mixtures of the benzaldehyde derivative, diethyl phosphite, and piperazine were grinded in a mill at room temperature for 2–10 min [21]. The work-up comprised washing with water, extraction with ethyl acetate, drying, evaporation, and purification by column chromatography to afford the α-hydroxyphosphonates in 82%–96% yields (Table 1, entry 1). The second method reacted the benzaldehydes with 1.1 equivalents of dimethyl phosphite in the presence of 1 equivalent of magnesium chloride and 3 equivalents of triethylamine at 50°C for 2 h with stirring [22]. The α-hydroxyphosphonates were obtained after extractions with ethyl acetate, evaporation, and crystallization in yields of 90%–97%. No details were provided on the crystallization (Table 1, entry 2). The third series of experiments used 1.1 equivalents of diethyl phosphite and 10% of barium hydroxide. The heterogeneous mixture was stirred for 4–10 min [23]. Then, the organic components were obtained by extraction with dichloromethane. The residue of the evaporation was washed with hexane or recrystallized from the mixture of ethyl acetate-hexane to furnish the adducts in yields of 70%–98% (Table 1, entry 3). The next accomplishment involved the reaction of equimolar mixtures of the aldehydes, diethyl phosphite, and sodium carbonate in a mill for 10 min [24]. After washing the mixture with water, the product was extracted with ethyl acetate. Following drying and evaporation, the residue was crystallized from acetone-pentane providing the α-hydroxyphosphonates in yields of 75%–85% (Table 1, entry 4). Aromatic aldehydes and dialkyl phosphites were also reacted in the presence of 5% of potassium phosphate with stirring [25]. Extraction with dichloromethane and concentration led to crude products of sufficient purity. The yields fell in the range of 92%–98% (Table 1, entry 5). In another method, equimolar

***Corresponding author: György Keglevich,** Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary, e-mail: gkeglevich@mail.bme.hu
Zita Rádai and Nóra Zsuzsa Kiss: Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary



Scheme 1: General protocol for the synthesis of α-hydroxyphosphonates.

mixtures (2.5 mmol) of the aldehyde and the dialkyl phosphite along with 1 g of the sodium-modified fluoroapatite were stirred by a spatula [26]. Yields at 80%–90% of the α-hydroxyphosphonates were obtained after extraction with dichloromethane, evaporation, and recrystallization (Table 1, entry 6). The addition of 1.5 equivalents of dimethyl phosphite to aldehydes in the presence of 20% of silica-supported tungstic acid gave the α-hydroxyphosphonates in yields of 85%–96% after a 30 min reaction time following a work-up comprising extraction with dichloromethane, washing with water, drying, evaporation, and purification by column chromatography (Table 1, entry 7) [27]. Last but not least, the benzaldehyde derivative was reacted with 1.2 equivalent of the phosphite in the presence of 0.1% of *n*-butyl lithium [28]. Extraction with ethyl acetate, evaporation, and washing with hexane was claimed to lead to yields of 90%–99% (Table 1, entry 8).

The authors, in most of the cases, emphasized the "green aspects" of their procedures. According to Table 1, the Pudovik reactions were indeed performed under green chemical conditions avoiding the use of solvents. In a few cases, the heterogeneity of the reaction mixtures required the use of mills. However, the work-up comprised extraction (Table 1, entries 1–7), recrystallization (Table 1, entries 3 and 6), or even column chromatography (Table 1, entries 1 and 7) applying solvents, such as mainly ethyl acetate and dichloromethane. In certain cases, other operations, like washing with water (Table 1, entries 1, 4, and 7), were also necessary. Although the products are solids, recrystallization was applied only in two cases mentioned above to prepare entirely pure α-hydroxyphosphonates. Not in all cases (Table 1, entries 5 and 8) was the purity of the products confirmed. It can be seen that though the additions were performed under environmentally friendly (solvent-free) conditions, the work-up procedures were, in a part of the cases, rather complex (Table 1, entries 1, 4, and 7) that cannot be said robust, or in other instances the purity may be questioned (Table 1, entries 5 and 8).

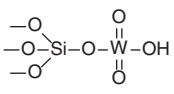
2 Materials and methods

The ^{31}P spectra were taken on a Bruker Avance-300 instrument operating at 121.5 MHz. The mass spectroscopic measurements were performed using an Agilent 6130 quadrupole MS (Kromat Kft., Budapest, Hungary) in positive electrospray mode. The melting points were determined by differential scanning calorimetry (DSC) measurements using a Setaram DSC 92 instrument (Setaram Instrumentation, Caluire, France). All reagents are from Sigma-Aldrich, Budapest, Hungary.

2.1 General procedure for the preparation of α-hydroxyphosphonates

A mixture of 11.0 mmol of aromatic aldehyde or ketone (benzaldehyde: 1.2 g, *p*-chlorobenzaldehyde: 1.5 g, *p*-nitrobenzaldehyde: 1.7 g,

Table 1: Green "solvent-free" preparation of α-hydroxyphosphonates as described in the literature.

Entry	Equivalent(s) of $(RO)_2P(O)H$	Catalyst	Quantity	Work-up	Purification	Yield (%)	Remark	Reference
1	1		1 equivalent	W (H_2O), Ex (EtOAc), D, Ev	Chrom	82–96	mill	[21]
2	1.1	$MgCl_2/Et_3N$	1/3 equivalent	Ex (EtOAc), Ev	Cryst	90–97	50°C/2 h	[22]
3	1.1	$Ba(OH)_2$	10 mol%	Ex (DCM), Ev	W(Hex) or Recryst	70–98		[23]
4	1	Na_2CO_3	1 equivalent	W (H_2O), Ex (EtOAc), D, Ev	Cryst	75–85	mill	[24]
5	1	K_3PO_4	5 mol%	Ex (DCM), Ev	–	92–98	crude prod.	[25]
6	1	Na-modified fluoroapatite	1 g/2.5 mmol substrate	Ex (DCM), Ev	Recryst	80–98	stirring with a spatula	[26]
7	1.5		20 m%	Ex (DCM), W (H_2O), D, Ev	Chrom	85–96		[27]
8	1.2	^{n}BuLi	0.1 mol%	Q (EtOAc), Ev	W(Hex)	90–99		[28]

W, Washing; Ex, extraction; Ev, evaporation; D, drying; Q, quenching; Chrom, chromatography; Cryst, crystallization; Recryst, recrystallization.

Table 2: Experimental details for the preparation of α-hydroxyphosphonates (**1**, **2**, and **3**).

	Time (min)	Yield (%)	δ^{31}P	δ ^{31}P [lit]	[M+H$^+$]	Mp (°C)	Mp [lit] (°C)	Entry
1a	10	95	23.8	24.3 [29]	217.1	100–101	101–102 [13, 30]	1
1b	10	90	23.2	22.1 [13]	251.0	101–102	104–105 [31]	2
1c	5	95	22.3	21.8 [32]	262.0	129–130	129–131 [33] 130–132 [13]	3
1d	5	95	22.3	22.2 [15]	262.0	112–113	109–109.5 [34]	4
1e	30	89	24.1	23.8 [32]	231.1	99–100	98 [15] 102–103 [31]	5[a]
1f	120	86	24.1	23.8 [15]	277.1	125–126	124 [15]	6[b]
2a	60	78	21.7	19.4 [16]	245.1	83–84	83–84 [35, 36]	7
2b	70	79	21.0	18.7 [16]	279.0	74–75	73–74 [37, 38]	8
2c	45	88	20.0	18.4 [16]	290.1	89–90	90–92 [13]	9
3a	180	40	26.2	26.0 [31]	231.1	130–131	130 [15] 134–135 [30]	10[c]
3c	45	81	24.8	–	276.1	170–171	–	11[c]

[a]In these cases, 0.2 equivalent triethylamine was used. [b]In these cases, 0.3 equivalent triethylamine was used. [c]In these cases, 1 equivalent triethylamine was used. [lit], reference literature.

o-nitrobenzaldehyde: 1.7 g, *p*-methylbenzaldehyde: 1.3 g, veratraldehyde: 1.8 g, acetophenone: 1.2 g, *p*-nitroacetophenone: 1.7 g), 11.0 mmol of dialkyl phosphite (dimethyl phosphite: 1.1 ml or diethyl phosphite: 1.4 ml) and 1.10 mmol (150 μl) of triethylamine was stirred in 1 ml of acetone at reflux. After 5–180 min (for details, see Table 2), 6 ml of pentane was added to the reaction mixture, and it was cooled to 5°C. The product crystallized from the reaction mixture. Filtration of the reaction mixture afforded products **1a**, **1b**, **1e**, **1f**, **2a**, **2b**, **3a**, and **3c** as white crystals, **1d** as yellow crystals, and **1c** and **2c** as orange crystals, all in a purity of >99%.

2.2 Dimethyl 1-hydroxy-1-(4-nitrophenyl)ethylphosphonate (3c)

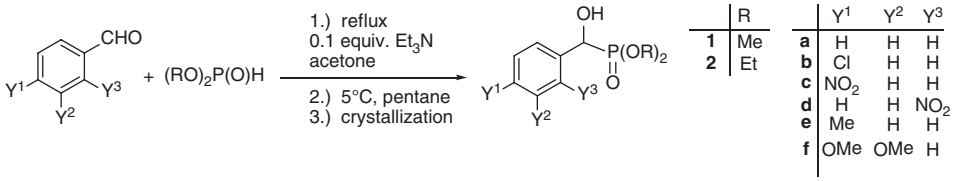
^{31}P NMR ($CDCl_3$) δ: 24.8; ^{1}H NMR ($CDCl_3$) δ: 1.85 (d, J=15.2, CH_3 overlapped by OH, total intensity 4H), 3.69 (d, J=9.9, 3H, OCH_3), 3.79 (d, J=9.8, 3H, OCH_3), 7.76–7.81 and 8.15–8.24 (m, 4H, Ar); ^{1}H NMR ($CDCl_3$) δ_{lit} [39]: 1.88 (d, J=15.6 Hz, 3H), 3.73 (d, J=10.4 Hz, 3H), 3.82 (d, J=10.0 Hz, 3H), 7.80–7.83 (m, 2H), 8.23–8.26 (m, 2H).

3 Results and discussion

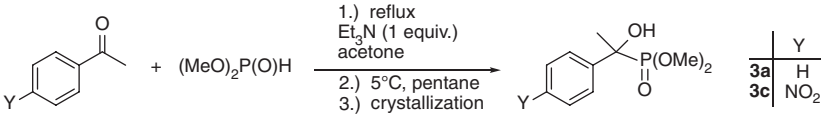
To bridge the drawbacks of the recent procedures reported [19–28], we wished to develop a procedure involving a robust work-up. However, as a compromise, the reaction of the benzaldehyde derivative and dialkyl phosphite had to be conducted in the presence of a minimum quantity of acetone as the solvent (1.2–1.8 g aldehyde in 1 ml of acetone), using 10% of triethylamine as the catalyst. Depending on the substituents in the aromatic ring, in case of dimethyl phosphite as the reagent, the completion required 5–120 min. The presence of the electron-withdrawing nitro group promoted the reaction, while electron-donating alkyl and alkoxy groups led to slower reactions and lower yields, even with the use of 20%–30% catalyst. Using diethyl phosphite, the additions required a longer reaction time. The work-up was simple, as comprised the addition of some *n*-pentane and crystallization on standing. Filtration of the precipitated α-hydroxyphosphonates (**1a–f** and **2a–c**) led to yields of typically 78%–95% (Scheme 2 and Table 2).

It is noteworthy that the method could be extended to the reaction of less reactive acetophenones and dimethyl phosphite. In these cases, one equivalent of the catalyst had to be applied, and the yields were variable (Scheme 3 and Table 2).

All α-hydroxyphosphonates (**1a–f**, **2a–c**, and **3a/3c**) were known from the literature and identified by ^{31}P NMR and melting point (see Table 2).



Scheme 2: Our method for the preparation of α-hydroxyphosphonates described in this article.



Scheme 3: Preparation of sterically congested α-hydroxyphosphonates.

4 Conclusions

A number of green variations of the Pudovik reaction have been published for the synthesis of α-hydroxyphosphonates. Although no solvent was used during the addition of dialkyl phosphites to the C=O group substituted benzaldehydes, less care was directed to the work-up comprising extraction, crystallization, and even chromatography. We have now developed a protocol applying a minimum quantity of acetone as a reaction medium, and after an appropriate reflux and the addition of some *n*-pentane, the pure product crystallizes out and can be removed by filtration.

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Conflict of interest statement: The authors declare that they have no conflicting interests regarding the publication of this article.

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Bionotes

György Keglevich

György Keglevich graduated from Technical University of Budapest in 1981 as a chemical engineer. He obtained his DSc in 1994 and became a professor in 1996. He has been the Head of the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, since 1999. He deals with organophosphorus, P-heterocyclic, and environmentally friendly chemistry. He is the author or co-author of approximately 450 papers. He is the member of the Editorial Board of *Heteroatom Chemistry*, *Phosphorus, Sulfur, Silicon*, and *Current Microwave Chemistry.* He holds different editorial responsibilities with *Current Organic Chemistry*, *Current Organic Synthesis*, *Current Green Chemistry*, *Letters in Organic Chemistry*, *Letters in Drug Design and Discovery*, and *Current Catalysis*.

Zita Rádai

Zita Rádai graduated from Budapest University of Technology and Economics in 2016 as a chemical engineer. She started her PhD studies at the Department of Organic Chemistry and Technology in the subject of microwave-assisted and organophosphorus chemistry in 2016.

Nóra Zsuzsa Kiss

Nóra Zsuzsa Kiss graduated from Budapest University of Technology and Economics in 2011 as a chemical engineer. She received her PhD in 2014 on the subject of microwave-assisted organophosphorus chemistry. In 2016, she became a permanent member of the teaching staff as an assistant professor at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics.