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Ultrasound-promoted greener approach to synthesize α-hydroxy phosphonates catalyzed by potassium dihydrogen phosphate under solvent-free condition

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ABSTRACT

We report a new environmentally-benign, convenient, and facile methodology for the synthesis of α-hydroxyphosphonates from an aromatic/heteroaromatic aldehyde with triethyl phosphite in the presence of potassium dihydrogen phosphate (KH_2PO_4) under ultrasound-assisted solvent-free conditions. Furthermore, a series of compounds were synthesized and characterized by melting point, EI-MS, NMR, and IR tools. Utilization of easy reaction conditions, isolation, and purification makes this manipulation very interesting from an economic perspective.

1. Introduction

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[2–4] Among α-functional phosphonic acids, α-hydroxyphosphonic acids exhibit a EPSP synthase.[5] Moreover, they show anti-viral, anti-cancer,[6] and anti-bacterial activity with the quinoline nucleus.[7] In addition, α-hydroxy phosphonates serve as an attractive precursor in the synthesis of various α-substituted phosphonates and phosphonic acids, such as α-aminophosphonates and α-aminophosphonic acids. These compounds have both medicinal and synthetic importance.[8] α-Hydroxy phosphonates have been used for the synthesis of 1,2-diketones,[9] α-ketophosphonates.[10]

The traditional synthesis of α-hydroxyphosphonates involves the reaction between dialkyl phosphite and substituted aldehyde in the presence of various bases, such as ethyl magnesium bromide,[11] potassium fluoride on alumina,[12] quinine,[13] LDA,[14] MgO,[15] and DBU.[16] There are some disadvantages of using base catalyst, like harsh reaction condition, high temperature, long reaction time, strong bases, mixture of products, and poor yields.[17] Acid catalysts such as alumina[18] and $Ti(OPri)_2$[19] have been reported for the activation of aldehydes and dialkyl phosphonates in the Abramov reaction. There are a few reports describing the reaction of trialkyl phosphite with aldehydes or ketones in the presence of acid catalysts such as $LiClO_4{\cdot}Et_2O$ and TMSCl[20] and guanidine hydrochloride.[21] However, all the existed methods displayed their drawbacks, such as the environmental pollution caused by utilization of organic solvents, long reaction time, extreme reaction conditions, unsatisfactory yields, complicated operations. Therefore, there is an urgent need for the further development of an efficient and convenient method to construct such significant scaffold.

In recent years, solvent-free organic synthesis has offered more advantages as compared to their homogeneous counterparts due to the growing concern for the influence of organic solvents on the environment, on human body, besides economic demands and simplicity in the processes.[22]

Ultrasound-accelerated chemical reactions are well known and proceed via the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities,[23] therefore ultrasound irradiation has been established as an important technique in organic synthesis. Therefore, we herein describe the ultrasound-promoted procedure for the convenient and efficient synthesis of α-hydroxyphosphonates catalyzed by potassium dihydrogen phosphonates with many different species of aryl and heteroaryl aldehydes and triethyl phosphate under solvent-free conditions. Compared with the methods mentioned above, our reactions displayed their advantages: (i) greener synthesis without organic

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solvents is involved; (ii) shortened time and improved yields; (iii) mild conditions and ready operations.

2. Results and discussion

In continuation of our ongoing research work on the development of useful synthetic methodologies,[24] herein we report an efficient and practical method for the synthesis of α-hydroxyphosphonates using potassium dihydrogen phosphate (KH_2PO_4) as a catalyst under ultrasound irradiation in solvent-free condition (Fig. 1). Consequently several aryl and heteroaryl aldehydes with different substituents on the aromatic ring were subjected to the addition reaction. In all, the yields were excellent. The physical characteristic of potassium dihydrogen phosphate is acidic (pH 4.2–4.7) which has been used for the sonochemical synthesis of α-hydroxyphosphonates. The products were isolated in high yields (80–94%) (Scheme 1). The structures of the products were determined from their spectral (^{1}H NMR, IR, and MS) data.

In the current study, the commercially available catalyst potassium dihydrogen phosphate is used as a catalyst but its scope has not been fully explored. Potassium dihydrogen phosphate can be used as a buffer, neutralizing agent, sequestrant, yeast food, and also as an efficient heterogeneous acid catalyst.[25,26] KH_2PO_4 facilitates the formation of the α-hydroxyphosphonates under ultrasonic irradiation. The use of KH_2PO_4 catalyst under ultrasonic irradiation plays an important role in the synthesis and hence the reaction rate was improved and the reaction time was reduced. We have focused our attention on the effect of solvent on model reaction, where we have studied the effect of different solvents such as water, ethanol, methanol, dichloromethane, *N,N*-diethyl formamide, and acetonitrile. But the use of solvent-free approach was found to be better (Table 3, entry **3a**), because when the reaction is carried out in solvents like ethanol under ultrasonic irradiation, the reaction time is longer and the yields are comparatively low. Further increase in the reaction time gave no significant improvement in the yield of the product (Table 1, entries 1–7). We have also studied the sonochemical effect on model reaction by using diverse solvents. In all cases, the experimental results show that the reaction times are reduced and the yields of the products are increased under sonication. Based on the results of this study, it seems that the ultrasound irradiation improves the reaction times and yields. The obtained results are summarized in (Table 1, entries 1–7). Further we have optimized catalyst concentration on model reaction (Table 3, entry **3a**). The best result

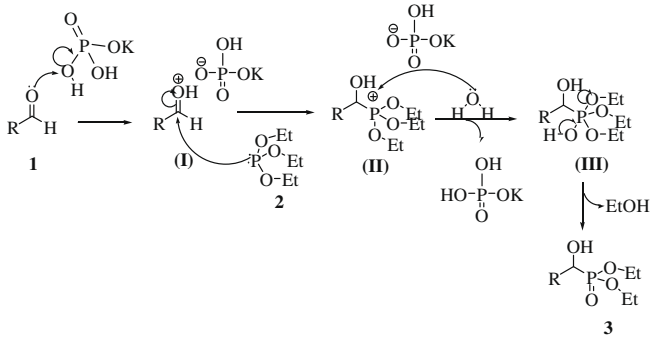
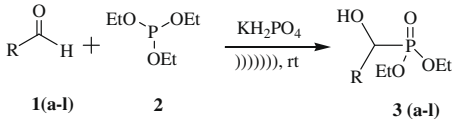


Figure 1. Proposed mechanism for α-hydroxyphosphonates using KH_2PO_4.



Scheme 1. Synthesis of various α-hydroxyphosphonates using KH_2PO_4 as a catalyst.

Table 1
Optimization of solvent effect on the model reaction[a]

Entry	Solvent	With US[a]		Without US[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Water	5		45	20
2	Ethanol	5	26	45	28
3	Methanol	5	32	45	53
4	DCM	5	44	45	60
5	DMF	5	27	45	45
6	Acetonitrile	5	38	45	56
7	Solvent free	5	86	45	80

[a] Reaction of benzaldehyde with triethyl phosphite in presence of potassium dihydrogen phosphate (KH_2PO_4) (5 mol %) under ultrasonic waves for 5 min.
[b] Reaction of benzaldehyde with triethyl phosphite in presence of potassium dihydrogen phosphate (KH_2PO_4) (5 mol %) under constant stirring for 45 min.
[c] Isolated yield.

Table 2
Screening of catalyst concentration on the synthesis of **3a**[a]

Entry	Catalyst (mol %)	Yield[b] (%)
1	0	No reaction
2	2.5	32
3	5.0	86
4	7.5	86
5	10.0	86

[a] Reaction of benzaldehyde with triethyl phosphite in presence of potassium dihydrogen phosphate (KH_2PO_4) (5 mol %) under ultrasonic waves for 5 min.
[b] Isolated yield.

Table 3
Ultrasound-promoted synthesis of α-hydroxyphosphonates catalyzed by KH_2PO_4 (**3a**–**o**)

Entry	Aldehyde	Time (min)	Yield (%)	Melting point (°C)	
				Found	Lit.
3a	Benzaldehyde	5	86	76–78	75–77[15]
3b	4-Methyl benzaldehyde	7	84	94–95	94–95[15]
3c	4-Methoxy benzaldehyde	6	80	119–120	120–121[15]
3d	4-Chloro benzaldehyde	12	92	67–68	67–68[15]
3e	2-Chlorobenzaldehyde	14	83	75–77	74–75[15]
3f	3-Hydroxy benzaldehyde	6	89	96–97	97–98.5[15]
3g	Cinnamaldehyde	15	80	105–107	105–106[15]
3h	4-Oxo-4*H*-chromen-3-carbaldehyde	14	80	170–172	172[27]
3i	6-Chloro,7-methyl-4-oxo-4*H*-chromen-3-carbaldehyde	18	88	178–180	178[27]
3j	2-Chloro 3-formyl quinoline	20	90	123–124	124–126[7]
3k	Propionaldehyde	30	56	146–148	147–154[17]
3l	Isobutyraldehyde	45	48	149–150	147–153[17]
3m	Cyclohexanone	120	No reaction	No reaction	No reaction
3n	Propenone	120	No reaction	No reaction	No reaction
3o	Acetophenone	120	No reaction	No reaction	No reaction

All the compounds characterized by their spectroscopy method ^{1}H NMR, mass, IR, and melting point from authentic sample.[28]
[a] Reaction of aldehyde and triethyl phosphite in presence of potassium dihydrogen phosphate (KH_2PO_4) (5 mol %) under ultrasonic waves.
[b] Isolated yield.

was obtained with 5 mol % of KH_2PO_4 under ultrasonic irradiation and solvent-free condition. The elevated amount of the catalyst did not give any improvement in the yield. However in the absence of catalyst KH_2PO_4, the reaction did not proceed even after extending reaction time; the results are summarized in (Table 2, entries 1–5). When the model reaction was attempted under ultrasonic irradiation and solvent-free condition, the reaction proceeds smoothly with 5 mol % of catalyst and completes within 5 min without a solvent under ultrasonic irradiation (Table 1, entry 7).

We also studied the reaction on aliphatic aldehydes which gave the corresponding low yields of products after prolonged reaction time. (Table 3, entries **3k**–**l**). The reaction on ketones does not show any conversion even after prolonged reaction time, increasing catalyst concentration, frequency and temperature of the ultrasonic bath. These results revealed that the reaction undergoes only on the aldehydes and not on ketones (Table 3, entries **3k**–**o**).

In conclusion, we describe a novel approach to explore the use of ultrasound irradiation for the synthesis of α-hydroxyphosphonates using potassium dihydrogen phosphate as a catalyst under solvent-free condition at ambient temperature within 5–45 min. In the given approach, when 10 mmol of substituted aldehydes reacts with 20 mmol of triethyl phosphite and 5 mol % of KH_2PO_4, the formation of α-hydroxyphosphonates was observed in very high yield. We believe that, sonochemical synthesis of α-hydroxyphosphonates using potassium dihydrogen phosphate as a catalyst-promoted methodology will be a valuable addition to the existing processes in the synthesis of α-hydroxyphosphonates (Table 3).

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References and notes

1. (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349; (b) Hiratake, J.; Oda, J. *Biosci. Biotechnol., Biochem.* **1997**, *61*, 211; (c) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 64; (d) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177; (e) Palacios, F.; Alonso, C.; Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1481.
2. Dingwall, J. G.; Campell, C. D.; Baylis, E. K. U.K. Patent Appl. 1(542), 1979, 938; *Chem. Abstr.* **1979**, *88*, 105559j.
3. Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. J. *Plant Growth Regul.* **1995**, *14*, 199.
4. Ishiguri, Y.; Yamada, Y.; Y. Kato, Y.; Sasaki, M.; Mukai, K. Eur. Patent Appl. EP 82-301905, 1982; *Chem. Abstr.* **1983**, *98*, 102686u.
5. Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han, C. Y.; Lin, K. C.; Pansegrau, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 115.
6. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587.
7. Pokalwar, R. U.; Hangarge, R. V.; Maske, P. V.; Shingare, M. S. *Arkivoc* **2006**, *xi*, 196.
8. (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193; (b) Li, Y. F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933; (c) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121; (d) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 295.
9. Olah, G. A.; Wu, A. *J. Org. Chem.* **1991**, *56*, 902.
10. Iorga, B.; Eymery, F.; Savignac, P. *Tetrahedron* **1999**, *55*, 2671.
11. Gawron, O.; Grelecki, C.; Reilly, W.; Sands, J. *J. Am. Chem. Soc.* **1953**, *75*, 3591.
12. Texier-Boullet, F.; Lequitte, M. *Tetrahedron Lett.* **1986**, *27*, 3515.
13. Smaardijk, A. A.; Noorda, S.; Bolhuis, F.; Wynberg, H. *Tetrahedron Lett.* **1985**, *26*, 493.
14. Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931.
15. Sardarian, A. R.; Kaboudin, B. *Synth. Commun.* **1997**, *27*, 543.
16. Pamies, O.; Backvall, J. E. *J. Org. Chem.* **2003**, *6*, 4815.
17. Goldman, W.; Soroka, M. *Synthesis* **2006**, 3019.
18. Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 916.
19. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 1527.
20. Azizi, N.; Saidi, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1255.
21. Heydari, A.; Arefi, A.; Khaksar, S.; Tajbakhsh, M. *Catal. Commun.* **2006**, *7*, 982.
22. Chen, R.; Breuer, E. *J. Org. Chem.* **1998**, *63*, 5107.
23. (a) Gaplovsky, A.; Gaplovsky, M.; Toma, S.; Luche, J. L. *J. Org. Chem.* **2000**, *65*, 8444; (b)Suslick, K. S., Ed.Ultrasound, Its Chemical, Physical and Biological Effects; VCH: Weinheim, 1988; (c) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616; (d) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544.
24. (a) Joshi, R. S.; Mandhane, P. G.; Diwakar, S. D.; Gill, C. H.; *Ultrason. Sonochem.* **2009**, doi:10.1016/j.ultsonch.2009.08.015; (b) Jadhav, G. R.; Shaikh, M. U.; Gill, C. H. *J. Heterocycl. Chem.* **2008**, 1287; (c) Jadhav, G. R.; Shaikh, M. U.; Kale, R. P.; Ghawalkar, A. R.; Nagargoje, D. R.; Gill, C. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6244; (d) Jadhav, G. R.; Shaikh, M. U.; Kale, R. P.; Gill, C. H. Chin. Chem. Lett.. *20* **2009**, 292.
25. Saikia, A.; Barthakur, M. G.; Borthakur, M.; Saikia, C. J.; Bora, U.; Borah, R. *Tetrahedron Lett.* **2006**, *47*, 43.
26. Feng, X.; Hong-Xia, L.; Jin-Ping, W.; You-Ping, T.; Jian-Jun, W. *J. Chem. Res.* **2008**, *12*, 707.
27. Reddy, B. M.; Ratnam, K. J.; Saikia, P. *J. Mol. Catal., A* **2006**, *25*, 238.
28. *General procedure:* A mixture of a substituted aldehyde (10 mmol), triethyl phosphite (20 mmol), and potassium dihydrogen phosphate (KH_2PO_4) (5 mol %) were placed in a round bottom flask. The mixture was irradiated under ultrasonic irradiation, the progress of the reaction was monitored by TLC, After completion, the reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (25 × 2 mL), which was then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the pure α-hydroxyphosphonates (Table 3). The products (**3a**–**l**) were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, mass spectra and melting point. Spectral data of principal compounds (**3c**): IR (KBr): 3258, 1230, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.41 (dd, 2H, *J* = 8.7, 2.8 Hz, Ar-H), 6.89 (d, 2H, *J* = 8.5 Hz, Ar-H), 4.95 (d, 1H, *J* = 10 Hz, P-CH), 3.93–4.09 (m, 4H, O–CH_2), 3.80 (s, 3H, Ar-O–CH_3), 1.27 (t, 3H, *J* = 7.8 Hz, CH_3), 1.21 (t, 3H, *J* = 7.8 Hz, CH_3); MS: *m*/*z*: 275; (**3j**): IR (KBr): 3240, 1210, 1045 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, ppm): 7.41 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.32 (t, 2H, *J* = 7.6 Hz, Ar-H), 7.23 (t, 1H, *J* = 7.2 Hz, Ar-H), 6.69 (dd, 1H, *J* = 16.4, 3.6 Hz, Ar-CH=C), 6.29 (dt, 1H, *J* = 16.4, 6.0 Hz, C=CH–C), 5.92 (dd, 1H, *J* = 12.8, 6.0 Hz, P-CH), 4.53 (br s, 1H, OH), 3.99–4.07(m, 4H, O–CH_2), 1.20 (t, 6H, *J* = 7.2 Hz, CH_3); MS: *m*/*z*: 271. (**3k**): IR (KBr): 3250, 1690, 1210, 1020 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, ppm): 8.31 (d, 1H, *J* = 3.6 Hz, Ar-H), 7.97 (s, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 6.27 (br s, 1H, OH), 6.27 (br s, 1H, OH), 5.16 (dd, 1H, *J* = 12.4, 6.8 Hz, P-CH), 4.01–4.08 (m, 2H, O–CH_2), 3.93–3.99 (m, 2H, O–CH_2), 2.4 (s, 3H, Ar-CH_3), 1.19 (t, 3H, *J* = 7.2, CH_3),1.11 (t, 3H, *J* = 7.2 Hz, CH_3); MS: *m*/*z*: 361. (**3n**): IR (KBr): 3240, 1230, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.55 (d, 1H, *J* = 3.4 Hz, Ar-H), 8.01 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.35 (t, 1H, *J* = 8.0, 7.6 Hz, Ar-H), 7.56 (t, 1H, *J* = 7.6, 6.8 Hz, Ar-H), 5.66 (d, 1H, *J* = 11.6 Hz, P-CH), 4.15-4.26 (m, 2H, O–CH_2), 4.03–4.14 (m, 2H, O–CH_2), 2.6 (br s, 1H, OH), 1.33 (t, 3H, *J* = 7.2 Hz, CH_3), 1.22 (t, 3H, *J* = 7.2 Hz, CH_3); MS: *m*/*z*: 330.