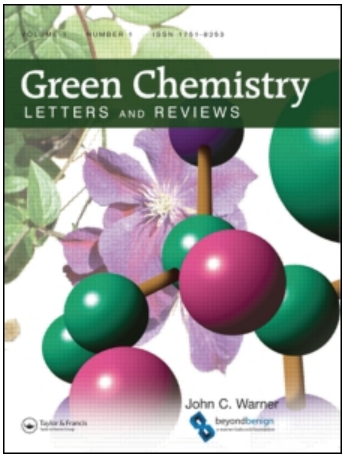

Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Potassium dihydrogen phosphate: an inexpensive reagent for the solvent-free, one-pot synthesis of α-aminophosphonates

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Online publication date: 13 October 2010

To cite this Article Joshi, Ratnadeep S. , Mandhane, Priyanka G. , Dabhade, Sanjay K. and Gill, Charansingh H.(2010) 'Potassium dihydrogen phosphate: an inexpensive reagent for the solvent-free, one-pot synthesis of α-aminophosphonates', Green Chemistry Letters and Reviews, 3: 3, 191 — 194
To link to this Article: DOI: 10.1080/17518251003660147
URL: http://dx.doi.org/10.1080/17518251003660147

Green Chemistry Letters and Reviews
Vol. 3, No. 3, September 2010, 191–194

Taylor & Francis
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RESEARCH LETTER

Potassium dihydrogen phosphate: an inexpensive reagent for the solvent-free, one-pot synthesis of α-aminophosphonates

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(Received 24 November 2009; final version received 25 January 2010)

An efficient procedure is described for the synthesis of α-aminophosphonates in the presence of catalytic amount of potassium dihydrogen phosphate (5 mol%) under solvent-free condition at room temperature. Triethyl phosphite reacts with imines (generated *in situ* from an aldehyde and an amine) to give corresponding coupled products in excellent yields. The present methodology presents several advantages, such as elevated yield, short reaction time, and easy work-up.

Keywords: potassium dihydrogen phosphate; α-aminophosphonates; solvent free; room temperature

Introduction

In the recent past, α-aminophosphonates have received enormous attention because they are considered to be the structural analogs of the corresponding α-aminoacids (*1*). The use of α-aminoalkyl phosphonates as enzyme inhibitors, antibiotics and pharmacological agents (*2*), herbicides (*3–5*), and haptens of catalytic antibodies (*6–8*), is well documented. Due to their structural analog to α-aminoacids, they may function as inhibitors of enzymes involved in the metabolism of proteins and amino acids. For example, the phosphonic analog of phenylalanine is an inhibitor of phenylalanine l-5-RNA-synthetase (*9*), phosphonodipeptide alafosfalin which is an antimicrobial agent (*10*).

A number of synthetic methods for the synthesis of 1-aminoalkyl phosphonates have been developed during the past 20 years (*11*), of these methods, the Kabachnik–Fields synthesis of 1-aminoalkyl phosphonates, catalyzed by a base or an acid is the most convenient. The key step in the Kabachnik–Fields synthesis of 1-aminoalkyl phosphonates is the nucleophilic addition of an amine to a carbonyl compound followed by the addition of a trialkyl or diaryl phosphite to the resulting imines. However, the formation of 1-hydroxy phosphonates or a product of its rearrangement frequently accompanies the formation of 1-aminoalkyl phosphonates, for this method various catalysts are used such as $LiClO_4$ (*12,13*), $TaCl_5$–SiO_2 (*14*), $InCl_3$ (*15*), $Sc(SO_4C1_2H_{25})_3$ (*16*), SiO_2/NH_4HCO_3 (*17*), lanthanide–triflate (*18*), CF_3CO_2H (*19*), $Mg(ClO_4)_2$ (*20*), $TiCl_4$ (*21*), $PhMe_3NCl$ (*22*), $In(OTf)_3$ (*23*), bromodimethyl sulfonium bromide (*24*), amberlite-IR 120 (*25*), $SbCl_3/Al_2O_3$ (*26*), alum (*27*), and iron(III) chloride (*28*).

In the organic synthesis and reactions, increasing attention is being focused on green chemistry using environmentally benign reagents and conditions, particularly solvent-free procedures (*29–31*), which often lead to clean, eco-friendly, and highly efficient procedures involving simplified work-ups.

The use of solid acid catalysts has gained a vast importance in organic synthesis due to their several advantages such as operationally simplicity, no toxicity, reusability, low cost, and easy isolation after completion of reaction. Potassium dihydrogen phosphate (KH_2PO_4) a buffer, neutralizing agent and yeast food, also emerged as an efficient heterogeneous acid catalyst (*32,33*).

Results and discussion

In the continuation of our research to develop methods for various organic transformations (*34–39*), we herein, report an eco-friendly, facile, and efficient methodology for the one-pot synthesis of primary α-aminophosphonates catalyzed by KH_2PO_4 at room temperature under solvent-free condition (Scheme 1).

We initially investigate the concentration of catalysts and the effect of different solvents on typical experiments on benzaldehyde **(1),** aniline **(2),** and triethyl phosphite **(3)** in the presence of catalyst KH_2PO_4 at room temperature.

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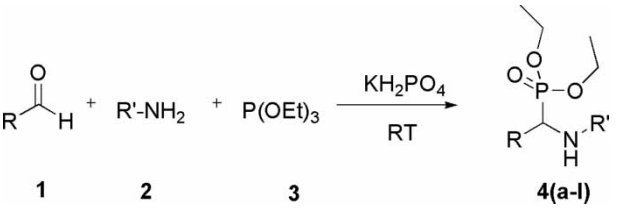
ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518251003660147
http://www.informaworld.com



Scheme 1. Synthesis of α-aminophosphonates.

We have optimized the catalyst concentration on model reactions. Five mol% of the catalyst was enough to endorse the reaction. An elevated amount of the catalyst did not progress the yield. The best result was obtained with 5 mol% of KH_2PO_4 under solvent-free condition at room temperature. However, in the absence of catalyst KH_2PO_4, the reaction did not proceed even after extending reaction time (1–2 h). The results are summarized in Table 1 (entries 1–7).

Furthermore, we have focused our attention on the effect of the solvent on model reaction; we have studied the effect of different solvents such as water, toluene, dichloromethane, ethanol, methanol, and acetonitrile. But the use of solvent-free approach was found to be better, because when the reaction is carried out in solvents like acetonitrile at room temperature, it takes a long reaction time (2–3 h) and the yields are comparatively low. Further increase in the reaction time gave no significant improvement (Table 2, entries 1–7). When the three component model reaction was attempted under solvent-free condition, the reaction proceeded smoothly at room temperature with 5 mol% of catalyst and completed within 30 min without solvent (Table 2, entry 7).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl/hetroaryl aldehydes with amines and triethyl phosphite in the 5 mol% of catalyst KH_2PO_4 under solvent-free condition at room temperature,

Table 1. Screening of catalyst concentration on model reaction.[a]

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	0	30	No reaction
2	1	30	20
3	2	30	35
4	3	30	48
5	4	30	67
6	5	30	93
7	6	30	93

[a]Reaction of benzaldehyde (10 mmol), aniline (10 mmol), and triethyl phosphite (20 mmol) in presence of KH_2PO_4 at room temperature.
[b]Isolated yield.

Table 2. Optimization of solvent effect on the model reaction.[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	Water	30	No reaction
2	Toluene	30	20
3	Dichloromethane	30	33
4	Ethanol	30	67
5	Methanol	30	72
6	Acetonitrile	30	78
7	Solvent-free	30	93

[a]Reaction of benzaldehyde (10 mmol) with aniline (10 mmol) and triethyl phosphite (20 mmol) in presence of KH_2PO_4 (5 mol%) room temperature.
[b]Isolated yield.

the results are shown in Table 3. The synthesized compounds were compared (MS, NMR, and IR) with compounds that were prepared by using the literature method (*2*) (Scheme 1). The comparison revealed that the compounds synthesized by the newly developed method were similar in all aspects to the reference compounds. The methodology developed here is simple with good to excellent yields.

The presence of electron-donating groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however, the presence of electron-withdrawing groups produced the corresponding α-aminophosphonate in shorter reaction time and in higher yields. Also, amines possessing electron-donating groups gave the corresponding products in good yields.

In conclusion, the KH_2PO_4 has been employed as a novel, mild, and very efficient catalyst for the convenient synthesis of α-aminophosphonates in excellent yields from a wide variety of aldehydes, amines, and triethyl phosphites. In addition, low cost of catalyst, solvent-free conditions, environmental friendliness and easy availability make this methodology a valid contribution to the existing processes in the field of α-aminophosphonates derivatives synthesis.

Experimental

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were obtaine in an open capillary in a paraffin bath. The progresses of the reactions were monitored by thin layer chromatography (TLC). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^1H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units $\triangle$ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

Table 3. One-pot synthesis of α-aminophosphonates[a] from benzaldehyde, amines, and triethyl phosphate in presence of KH_2PO_4.

Entry	R	R′	Time (min)	Yield[b] (%)
4a	Benzaldehyde	Aniline	40	93
4b	Benzaldehyde	4-Toludine	50	83
4c	Benzaldehyde	4-Chloroaniline	30	90
4d	Benzaldehyde	4-Anisidine	50	84
4e	4-Anisisaldehyde	Aniline	60	82
4f	4-Chlorobenzaldehyde	Aniline	30	92
4g	4-Nitrobenzaldehyde	Aniline	30	93
4h	3-Chlorobenzaldehyde	Aniline	30	92
4i	Benzo[1,3]dioxale-5-benzaldehyde	Aniline	40	94
4j	4-Hydroxy benzaldehyde	Aniline	50	85
4k	4-(Morpholino) benzaldehyde	Aniline	60	82
4l	2-Chloro-3-formyl quinoline	Aniline	60	75

[a]Reaction of reaction of aldehyde (10 mmol) with amines (10 mmol) and triethyl phosphite (20 mmol) in presence of KH_2PO_4 (5 mol%) at room temperature under solvent-free conditions.
[b]Isolated yield.

General procedure

A mixture of an aldehyde (10 mmol), amines (10 mmol), triethyl phosphite (20 mmol), and KH_2PO_4 (5 mol%) was stirred at room temperature for an appropriate time (Table 3). The reaction was monitored by TLC; after completion, the reaction mixture was extracted with ethyl acetate (3×25 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid compound was crystallized in ethanol and characterized by EI-MS, IR, and NMR.

(**4a**) M.P. (°C) 98–100, ^{1}H NMR ($CDCl_3$-400 MHz): 1.12 (3H, t), 1.29 (3H, t), 3.68 (1H, ddq, $J = 7.1$, 11.2, 8.1 Hz), 3.95 (1H, ddq, $J = 7.1$, 8.1, 11.2 Hz), 4.14 (2H, m), 4.75 (1H, br, −NH), 4.78 (1H, d, $J = 17.9$ Hz), 6.61 (2H, d, $J = 8.5$ Hz), 6.70 (1H, t, $J = 7.4$), 7.11 (2H, t, $J = 7.4$), 7.27 (1H, m), 7.34 (2H, t, $J = 7.4$ Hz), 7.49 (2H, m); IR (KBr) cm^{-1}: 3295 (−NH), 1233 (P-O), 1103–997 (P-O-Et) Es-MI.320 (M^+). (**4k**) M.P. (°C) 97–99, ^{1}H NMR ($CDCl_3$-400 MHz): 1.1(3H, t), 1.22 (3H, t), 2.8 (4H, m), 3.2 (4H, t), 3.70 (1H, ddq, $J = 7.5$, 10.8, 7.5 Hz), 3.90 (1H, ddq, $J = 7.5$, 10.8, 7.5 Hz), 4.05 (2H, m), 4.60 (1H, br, −NH), 4.75 (1H, d, $J = 16.1$ Hz), 6.54 (2H, d, $J = 8.1$ Hz), 6.95 (2H, t, $J = 7.0$ Hz), 6.90 (2H, t, $J = 7.0$ Hz), 7.12 (2H, m), 7.4 (2H, m). IR (KBr) cm^{-1}: 3298 (−NH), 2938 (Ar-CH), 1232 (P-O), 1255–938 (P-OEt) Es-MI.437 (M^+). (**4l**) M.P. (°C) 128–129 ^{1}H NMR ($CDCl_3$, △ ppm): 1.0 (3H, t, $J = 8$ Hz), 1.3 (3H, t, $J = 8$ Hz), 3.7 (1H, m), 3.9 (1H, m), 4.2 (2H, m), 4.9 (1H, s), 5.4 (1H, d, $J = 24$ Hz), 6.4 (1H, d), 6.6 (1H, t), 6.9 (1H, t, $J = 8$ Hz), 7.0 (2H, d, $J = 8$ Hz), 7.5 (1H, t, $J = 8$ Hz), 7.7 (1H, t, $J = 8$ Hz), 7.8 (1H, d), 8.0 (1H, d, $J = 8$ Hz), 8.3 (1H, d, $J = 8$ Hz). IR (KBr) cm^{-1}; 3395 (NH); 1236–1024 (P-O-Et) ES-MS: m/z 419.1 (M + 1) and 421(M + 3).

Acknowledgements

The authors are thankful to University Grants Commission, New Delhi, for awarding a fellowship and to the Head, Department of Chemistry, Dr Babasaheb Ambedkar Marathwada University, Aurangabad, for his valuable support and laboratory facilities.

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