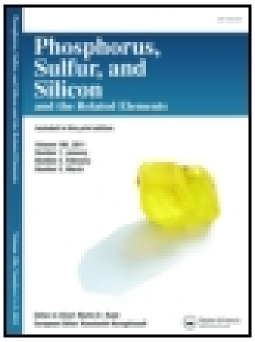

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Catalyst free one-pot synthesis of α-aminophosphonates in aqueous ethyl lactate

Ge Gao, Meng-Nan Chen, Li-Ping Mo, and Zhan-Hui Zhang

National Demonstration Center for Experimental Chemistry Education, College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang, China

ABSTRACT
An highly efficient and environmentally friendly process for the synthesis of α-aminophosphonates has been devised, through a one-pot three-component condensation of various aldehydes, amines and triethyl phosphate in water-ethyl lactate under ultrasonic irradiation conditions at room temperature. The expected products were obtained in high yield without the need for any additional catalyst.

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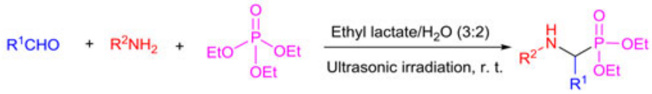
GRAPHICAL ABSTRACT



1. Introduction

In the organic synthesis process, the reaction medium plays a vital role in promoting the contact between the reactants and even changing the progress of the reaction. Therefore, the search for new green reaction solvents with unique properties and functions is still important in current green organic synthesis research. In recent years, biomass-derived ethyl lactate (EL) has attracted widespread attention as a new type of a green and economically viable alternative to traditional solvents. It has favorable characteristics such as stability, non-corrosiveness and good solubility in water and organic compounds.[1] Due to its low toxicity, EL has been approved by FDA (Food and Drug Administration) and EFSA (European Food Safety Authority) for use as a food and pharmaceutical additive.[2] EL can be produced by fermentation of renewable carbohydrate feedstocks derived from corn and soybeans.[3] Moreover, ethyl lactate is soluble in paraffin oil, which actually leads to the formation of some van der Waals interactions. Therefore, this ester provides different solvent properties that may cover a large number of solutes.[4] It has been demonstrated to be a good extractive solvent for various food and bioactive compounds such as caffeine,[5] amino acids,[6] polyphenols[7] and carotenoid.[8] In addition, EL has also applied as a green reaction medium in some useful organic reactions[9] to prepare some important compounds such as 1,4-benzothiazines,[10] spirooxindole-pyran derivatives,[11] polyfunctionalized alkenes,[12] bis(Indolyl)methanes,[13] 4(3*H*)-quinazolinones,[14] quinoxalines,[15] enaminones[16] and 2-pyrazoline derivatives.[17]

Over the past few decades, with the increasing demand for environmentally friendly, sustainable and efficient synthesis strategies in green chemistry, catalyst-free, solvent-mediated protocols for the preparation of organic compounds has emerged as an important strategy due to their simple workup, low cost, reduced pollution, and avoiding the impact of catalysts on sensitive substrates.[18] In these processes, some green solvents such as glycerol,[19] fluorinated alcohols,[20] water,[21] and deep eutectic solvent (DES)[22–24] have often been utilized as solvent and catalyst to promote organic chemical reactions. At the same time, multi-component reactions (MCRs) allow the assembly of simple precursors in a single synthesis operation without isolation of the intermediates, producing products containing most of the atoms in the starting materials. MCRs have been shown to be more powerful and superior than the traditional stepwise approach due to their atomic economy, energy efficiency, simplicity of operation, and generally excellent productivity.[25] Therefore, the catalyst-free MCRs have acquired new dimensions in various research works to produce elaborate libraries of biological active compounds.

α-Amino phosphonates have been the focus in recent years because of their structural analogy to the corresponding α-amino acids as well as heterocyclic phosphonates. As a result of continuous efforts, utilization of α-amino phosphonates is expanding into many new channels. They have been found to exhibit a vital role in industrial, biological, synthetic organic chemistry and medicinal chemistry.[26]

CONTACT Zhan-Hui Zhang zhanhui@126.com College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang 050024, China.

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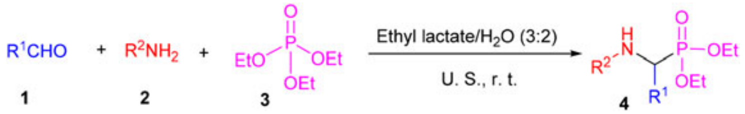

Scheme 1. Synthesis of α-aminophosphonates.

Therefore, the development of an efficient and convenient method to α-amino phosphonates is of great significance and highly desirable. The three-component reaction involving amine, aldehyde and dialkyl phosphonate or triethyl phosphate is a simple and straightforward method for the synthesis of α-aminophosphonates. This transformation proceeds via an in situ imine formation, followed by phospha-Mannich reaction between phosphite nucleophile and imine electrophile to form an N–C–P bond. Usually, this reaction was carried out in the presence of various catalysts, such as aqueous formic acid,[27] zinc di(L-prolinate),[28] $NbCl_5$,[29] $CeCl_3{\cdot}7H_2O$,[30] $HfCl_2$,[31] $BF_3{\cdot}OEt_2$,[32] $SbCl_3/Al_2O_3$,[33] gold complex,[34] ceric ammonium nitrate,[35] dehydroascorbic acid capped magnetite (DHAA-Fe_3O_4),[36] nano-magnetic sulfated zirconia ($Fe_3O_4@ZrO_2/SO_4^{2-}$),[37] phosphomolybdic acid,[38] dodecatungstophosphoric acid (DTP/SiO_2),[39] xanthan sulfuric acid,[40] sulfated polyborate,[41] propylphosphonic anhydride(T3P®),[42] or TiO_2.[43] Although these methods have demonstrated their efficiency in α-amino phosphonates, they are also suffer from some drawbacks such as long reaction times, poor yields, the need for stoichiometric catalysts, harsh reaction conditions with the use of acids, the use of toxic solvents and high reaction temperatures. Moreover, the water formed during imine formation decomposes or deactivates those humidity-sensitive Lewis acids or Brønsted acids. Therefore, the development of a milder, convenient and environmentally benign approach to overcome these shortcomings is still under investigation.

With our ongoing interest toward the development of new environmentally friendly synthetic methodologies,[44–48] herein, we wished to develop a convenient, ultrasound assisted catalyst free synthesis of α-aminophosphonates via the condensation of aldehydes, amines, and triethyl phosphate using water-ethyl lactate as the reaction medium (Scheme 1).

2. Results and discussion

In our preliminary examination, benzaldehyde, aniline, and triethyl phosphate were chosen as the model substrates to optimize the reaction conditions and the results were collected in Table 1. At room temperature, some solvents were examined under ultrasound irradiation, and it is observed that the reaction formed only low yield in ethyl acetate, DMF, H_2O, CH_2Cl_2, $CHCl_3$, PEG 400, THF, MeOH, EtOH, and CH_3CN. It is interesting to note that reaction resulted in 75% in the EL (Table 1, entry 13). Inspired by these results, we further optimized the conditions by varying the different ratios of EL/H_2O. The results show clearly that EL/H_2O (3:2) was the most efficient in producing the expected product **4a** with the highest yield (Table 1, entry 22). At the same time, we also investigated the effect of ultrasound irradiation (USI) on the reaction. It was found that although the reaction time was extended to 90 min at room temperature, the reaction could not achieve complete conversion without USI (Table 1, entry 23). Upon increasing the temperature (30 °C, 60 °C, 80 °C and 100 °C) in the absence of ultrasound irradiation, product **4a** was obtained in yields of 87%, 88%, 90% and 93%, respectively (Table 1, entries 24–27). Therefore, it clearly shows that USI accelerates the reaction as compared with the results obtained under heating conditions.

To demonstrate the practicability and reliability of the developed process, we conducted the model reaction on a large scale under similar conditions. The reaction of benzaldehyde, (100 mmol), aniline (100 mmol), and triethyl phosphate (100 mmol) successfully worked to afford the product **4a** in an excellent yield (Table 1, entry 28).

With the optimized conditions established, the scope and generality of this novel strategy were evaluated by reacting varieties of aldehydes, amines, and triethyl phosphate in aqueous ethyl lactate under ultrasonic irradiation. As illustrated in Table 2, benzaldehyde with different substituents was explored and it was found that the benzaldehyde bearing both electron rich and deficient group are well tolerated

Table 1. Optimization of reaction conditions^a.

Entry	Solvent	Time (min)	Yield (%)^b
1	no	90	trace
2	EtOAc	90	35
3	DMF	90	40
4	CH_2Cl_2	90	48
5	$CHCl_3$	90	50
6	PEG 400	90	51
7	THF	90	55
8	EtOH	90	57
9	H_2O	90	42
10	EtOH/H_2O (1:1)	90	49
11	MeOH	90	58
12	CH_3CN	90	59
13	EL	30	75
14	EL/H_2O (9:1)	30	77
15	EL/H_2O (8:1)	30	80
16	EL/H_2O (4:1)	30	84
17	EL/H_2O (2:1)	30	91
18	EL/H_2O (1:1)	30	86
19	EL/H_2O (1:2)	30	80
20	EL/H_2O (1:3)	30	75
21	EL/H_2O (1:5)	30	65
22	EL/H_2O (3:2)	30	95
23	EL/H_2O (3:2)	90	75
23^c	EL/H_2O (3:2)	90	80
24^{c,d}	EL/H_2O (3:2)	90	87
25^{c,e}	EL/H_2O (3:2)	90	88
26^{c,f}	EL/H_2O (3:2)	90	90
27^g	EL/H_2O (3:2)	30	93
28^h	EL/H_2O (3:2)	30	93

^{a}The reaction was performed with benzaldehyde (1.0 mmol), aniline (1.0 mmol) and triethyl phosphate (1.0 mmol) in 3 ml solvent at room temperature under ultrasonic irradiation. ^{b}Isolated yield. ^{c}Without sonication. ^{d}30 °C. ^{e}60 °C. ^{f}80 °C. ^{g}100 °C. ^{h}The reaction was carried out in 100 mmol scales.

Table 2. Ultrasound-assisted synthesis of α-aminophosphonates in EL/H_2O.

Entry	Aldehydes	R^2	Product	Time (min)	Yield (%)[a]	mp (°C)
1	C_6H_5CHO	C_6H_5	**4a**	40	95	90–91[40]
2	3-$OMeC_6H_4CHO$	C_6H_5	**4b**	41	92	102–104[35]
3	4-$OMeC_6H_4CHO$	C_6H_5	**4c**	40	94	102–104[40]
4	4-MeC_6H_4CHO	C_6H_5	**4d**	40	89	64–65[40]
5	4-FC_6H_4CHO	C_6H_5	**4e**	19	95	84–85[42]
6	2-ClC_6H_4CHO	C_6H_5	**4f**	25	94	88–89[40]
7	3-ClC_6H_4CHO	C_6H_5	**4g**	25	94	89–91[40]
8	4-ClC_6H_4CHO	C_6H_5	**4h**	20	95	59–60[40]
9	4-BrC_6H_4CHO	C_6H_5	**4i**	22	94	96–98[34]
10	4-$NO_2C_6H_4CHO$	C_6H_5	**4j**	29	94	96–97[40]
11	2-Furaldehyde	C_6H_5	**4k**	40	89	51–52[40]
12	Cyclohexanecarboxaldehyde	C_6H_5	**4l**	47	79	oil[40]
13	C_6H_5CHO	3-MeC_6H_4	**4m**	44	92	125–129[32]
14	C_6H_5CHO	4-MeC_6H_4	**4n**	40	94	116–118[40]
15	C_6H_5CHO	3-ClC_6H_4	**4o**	24	94	122–124[32]
16	C_6H_5CHO	4-ClC_6H_4	**4p**	25	94	112–114[40]
17	C_6H_5CHO	2-BrC_6H_4	**4q**	25	94	111–114[32]
18	C_6H_5CHO	4-$NO_2C_6H_4$	**4r**	45	89	144–145[40]
19	4-$OMeC_6H_4CHO$	4-$OMeC_6H_4$	**4s**	40	94	118[43]
20	4-$OMeC_6H_4CHO$	3-MeC_6H_4	**4t**	46	94	86[43]
21	4-$OMeC_6H_4CHO$	4-ClC_6H_4	**4u**	45	94	109–110[49,50]
22	4-MeC_6H_4CHO	4-MeC_6H_4	**4v**	40	90	90–91[33]
23	3-ClC_6H_4CHO	4-MeC_6H_4	**4w**	25	94	85–86[50]
24	4-BrC_6H_4CHO	4-MeC_6H_4	**4x**	25	95	111–112[33]

[a] Isolated yield.

to furnish corresponding products in high to excellent yields. Generally, the electronic properties of substrates had no pronounced effects on the yields. In addition, the steric influence of the substituents of benzaldehyde was not obvious. Notably, the treatment of heteroaromatic carbaldehydes such as 2-furaldehyde with aniline and triethyl phosphate also proceeded smoothly and gave the desired product **4k** in 89% yield. It is also important to note that the reactions were efficient for aliphatic aldehydes such as cyclohexanecarboxaldehyde (entry 12) under similar reaction conditions. Additionally, aniline bearing electron-donating and electron-withdrawing groups on the benzene ring proceeded smoothly and offered the respective products in high yield. Strongly electron-poor aromatic amines such as 4-nitroaniline also worked well in this reaction, leading to the desired product in high yield (Table 2, entry 18). These results demonstrate that this protocol provided an efficient, facile and practical method for the synthesis of α-aminophosphonates.

In conclusion, we have developed a convenient and practical approach for synthesis of α-aminophosphonates via one-pot three-component reaction in water-ethyl lactate under ultrasound irradiation conditions at room temperature. This reaction allows broad functional group compatibility, mild and neutral reaction conditions, easy product separation and purification, avoidance of toxic solvents, catalyst free, and operational simplicity. The further use of aqueous ethyl lactate in the preparation of other heterocyclic organic compounds is currently underway in our laboratory.

3. Experimental

The chemicals used were obtained from commercial sources and were used as received without purification. Ultrasound irradiation was performed in KH5200V ultrasonic cleaner with a 40 KHz processing frequency and a normal power of 250 W. Melting points were determined on X-5 apparatus and were uncorrected. The IR spectra were obtained with KBr power-pressed pellets in the range of 400–4000 cm^{-1} using a Thermo Fisher is 50 spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV III-500 or Zhongke Niujin AS 400 spectrometer using TMS as internal standard. The mass spectra were performed on a 3200 Qtrap instrument with an ESI source. The Supplemental Materials contains sample spectroscopic characterization data including ^1H and ^{13}C NMR spectra for products **4** (Figures S1–S80).

4. General procedure for synthesis of α-aminophosphonates

Aldehydes (1.0 mmol), amines (1.0 mmol), and triethyl phosphate (1.0 mmol) were put into a 25 ml round-bottomed flask in ethyl lactate/water (3:2, 3 ml). The reaction flask was located in the ultrasonic bath and irradiated at room temperature for the appropriate time. After completion of the reaction as indicated by TLC, the mixture was extracted with ethyl acetate (10 ml ×3). The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was then subjected to preparative TLC to give pure product by using mixed ethyl acetate and petroleum ether as an eluent.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ORCID

Zhan-Hui Zhang http://orcid.org/0000-0002-1082-5773

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