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Water mediated eco-friendly green protocol for one-pot synthesis of α-aminophosphonates at ambient conditions

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Abstract. Increasing environmental awareness and economic concerns have led to the consideration of highly efficient one-pot, three-component, green approaches for important organic synthons. We describe here a simple, elegant and high yielding protocol for the synthesis of α-aminophosphonates in totally solvent-free, catalyst-free conditions by reacting aldehydes, amines and trimethyl phosphite at ambient temperature.

Keywords. α-Aminophosphonates; aldehydes; amines; trimethyl phosphite; solvent-free.

1. Introduction

Design and development of products and processes that minimize the usage as well as generation of toxic substances have been the aim of green chemistry. Avoiding addition of supplementary chemicals, such as solvents, catalysts, promoters, etc. either in the reaction sequence or work-up process constitutes a significant step in accomplishing environmentally friendly reaction protocol. Further, designing synthetic methods at ambient temperature and pressure goes a long way in making the reaction totally clean, hazard-free and energy efficient. In continuation of our interest in developing environmentally benign efficient solvent-free protocols for the synthesis of important products, we describe here a simple, elegant and high yielding protocol for the synthesis of α-aminophosphonates in totally solvent-free, catalyst-free conditions at ambient temperature.

Organophosphorus compounds due to their high degree of biological and pharmacological spectrum have become the subject of immense interest in recent years.[1] Phosphorus analogues of the amino acids in which the carboxylic acid group is replaced by a phosphonate group have attracted particular interest in the preparation of isosteric analogues of numerous natural products.[2] Their utility as antagonists in the metabolism of amino acids as enzyme inhibitors and as pharmacological agents such as antibiotics, antiviral, etc. and many other applications are well-documented.[3] Thus, an efficient synthesis of these organophosphorus compounds is of great interest in recent times. A number of synthetic methods have been developed during the past two decades for the preparation of α-aminophosphonates through one-pot multicomponent reactions (MCRs).

Of all the reported methods, nucleophilic addition of dimethyl phosphite or trimethyl phosphite to imines (generated *in situ* from aldehydes and amines) catalysed by an acid, has emerged as an important method for the synthesis of α-aminophosphonates. One-pot synthesis of α-aminophosphonates directly from aldehyde, amine, and phosphite was first achieved with lanthanide triflate[4] as catalyst. Subsequently, many methods using different catalytic systems such as $SnCl_4$,[5] $BF_3.OEt_2$,[6] $MgBr_2$,[7] $InCl_3$,[8] $TaCl_5$-SiO_2,[9] $ZrCl_4$,[10] $Sc(DS)_3$,[11] $H_3PW_{12}O_{40}$,[12] $BiNO_3.5H_2O$,[13] Mg $(ClO_4)_2$,[14] β-cyclodextrin,[15] $AlCl_3$,[16] amberlyst-15,[17] TFA,[18] sulphamic acid,[19] $SbCl_3/Al_2O_3$,[20] TiO_2,[21] Al_2O_3-MW,[22] $ZrOCl_2.8H_2O$,[23] $ZrO(ClO_4)_2.6H_2O$,[24] SmI_2,[25] $LiClO_4$,[26] Oxalic acid,[27] ionic liquid,[28] $FeCl_3$,[29] silica sulphuric acid,[30] CSA,[31] (Bromodimethyl)sulphonium bromide,[32] H_3BO_3,[33] $Bi(OTf)_3$,[34] $NaHSO_4$-SiO_2,[35] Yttria-zirconia,[36] $HClO_4$-SiO_2,[37] and microwave[38] have been reported. Earlier Ranu *et al.*[39] reported the similar reaction under solvent-free conditions at higher temperature wherein the diethylphosphite is used as a nucleophile. Many of the reported methods have limitations that include use of organic solvents, expensive catalysts, harsh reaction conditions and low yields. Though few of the reported Lewis acids are less expensive and readily available, their efficiency is low owing to the fact that they are

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*For correspondence

either deactivated or decomposed by the presence of amines and/or water generated *in situ* during imine formation.[40] In order to overcome such limitations, there is a need for an efficient and convenient method for construction of such significant scaffolds. Most of the reported procedures claim only trace amount of products in a solvent less neat conditions at ambient temperature. To the best of our knowledge, this is the report where in the water generated *in situ* catalyses the synthesis of α-aminophosphonates in a solvent-free, and catalyst-free environment at ambient conditions.

2. Experimental

2.1 *Materials, methods and instruments*

All the chemicals used were of synthetic grade obtained. Analytical thin-layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates monitored completion of the reactions time to time. Visualization was accomplished with UV light (256 nm) and iodine. Melting points were determined on Fisher John's and are uncorrected. All the ^{1}H-NMR spectra are recorded on AVANCE 300 MHz in $CDCl_3$. Chemical shifts reported are on the δ-scale relative to TMS internal standard. The IR spectra recorded on SHIMADZU FT-IR SPECTROPHOTOMETER using 1% potassium bromide discs. Mass spectra recorded on Waters quadruple mass spectrometry.

2.2 *General procedure for preparation of α-aminophosphonates*

A mixture of aldehyde (1 mmol) and amine (1 mmol) was stirred at room temperature for 2 min and then trimethyl phosphite (1 mmol) was added. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (in case of solid products) and the products were separated by filtration and dried. The products obtained were pure enough for all practical purposes.

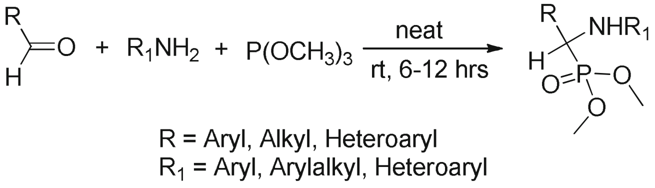
2.3 *Spectral data of unreported compounds*

2.3a *Dimethyl(phenethylamino)(phenyl) methylphosphonate (table 1, entry 12)*: Pale yellow solid, m.p. 217–219°C; IR (neat): 3384, 3036, 1524, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (brs, NH), 2.65–2.81 (m, 4H), 3.46 (d, 3H J = 10.57 Hz), 3.66 (d, 3H, J = 10.57 Hz), 3.99 (d, 1H, J = 20.39 Hz), 7.06–7.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.04, 48.94 (d, J_{CP} = 17.01 Hz), 53.24 (d, J_{CP} = 6.58 Hz), 59.55, 61.57, 126.03, 127.88, 128.25, 128.49, 129.33, 135.45, 137.43, 139.54; MS (ESI): *m/z* = 320 [M+H]$^+$; Anal. Calcd for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39. Found: C, 64.00; H, 6.90; N, 4.45.

2.3b *Dimethyl(phenylamino)(4-{3,5,6-trichloro-pyridin-2-yloxy}phenyl)methylphosphonate (table 1, entry 13)*: White solid, m.p. 165–167°C; IR (KBr): 3327, 1602, 1412, 1236, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.46 (d, J = 10.57 Hz, 3H), 3.76 (d, 3H, J = 10.57 Hz), 4.72-4.83 (m, 2H), 6.57 (d, 2H, J = 7.55 Hz), 6.68 (t, 1H, J_{12} = 7.55 Hz), 7.04–7.16 (m, 4H), 7.49–7.55 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.79 (d, J_{CP} = 6.58 Hz), 54.05 (d, J_{CP} = 8.78 Hz), 54.17, 56.18, 113.81, 117.85, 118.61, 121.46, 128.96, 129.20, 132.75, 140.72, 143.48, 144.56, 145.78, 152.65, 155.96; MS (ESI): *m/z* = 509 [M+Na]$^+$; Anal. Calcd for $C_{20}H_{18}Cl_3N_2O_4P$: C, 49.25; H, 3.72; N, 5.74. Found: C, 49.45; H, 3.68; N, 5.79.

2.3c *Dimethyl(phenylamino)(heptyl)methylphosphonate (table 1, entry 14)*: Yellow viscous liquid; IR (neat): 3310, 1607, 1478, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, J = 6.98 Hz), 1.21–1.73 (m, 10H), 1.79–1.93 (m, 1H), 3.64 (d, 3H, J = 10.57 Hz), 3.72 (d, 3H, J = 10.57 Hz), 3.91 (brs, NH), 6.57–6.69 (m, 3H), 7.07–7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.62, 22.11, 25.46, 28.58, 30.33, 31.16, 50.36, 52.08 (d, J_{CP} = 7.15 Hz), 53.17 (d, J_{CP} = 6.60 Hz), 112.83, 117.41, 128.86, 146.98; MS (ESI): *m/z* = 322 [M+Na]$^+$; Anal. Calcd for $C_{15}H_{26}NO_3P$: C, 60.18; H, 8.75; N, 4.68. Found: C, 60.27; H, 8.69; N, 4.85.

2.3d *Dimethyl(pyridin-2-ylamino)(thiophen-2-yl) methylphosphonate (table 1, entry 15)*: White solid, m.p. 145–147°C; IR (KBr): 3300, 1602, 1481, 1228, 1054, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (d, 3H, J = 10.57 Hz), 3.71 (s, 1H), 3.76 (d, 3H, J = 10.57 Hz), 5.13 (brs, NH), 6.01 (q, 1H), 6.45 (d, 1H, J = 8.31 Hz), 6.60 (q, 1H, J_{12} = 3.77 Hz,



Scheme 1. Eco friendly synthesis of α-aminophosphonates.

Table 1. Synthesis of α-aminophosphonates in noncatalytic and solvent free conditions.

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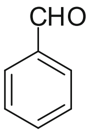
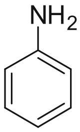
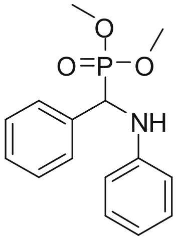
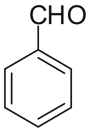
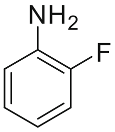
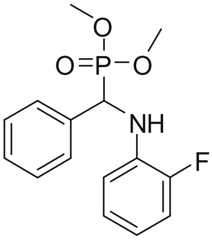
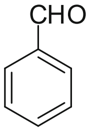
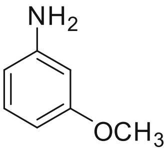
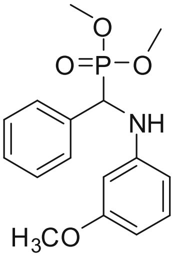
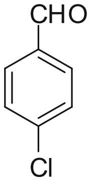
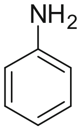
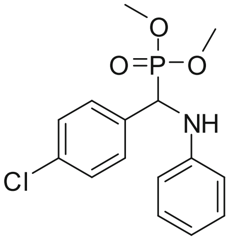
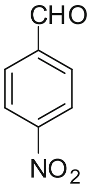
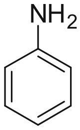
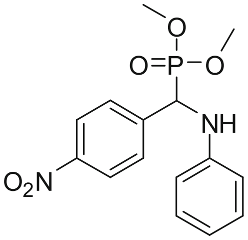
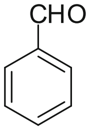
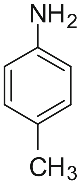
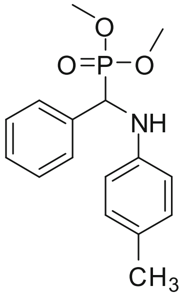
1				8	81	87–88[27]
2				8	83	94–95
3				7	84	118–119
4				7	78	90–91[27]
5				6	84	124–125[38]
6				9	86	70–71[38]

Table 1. (continued).

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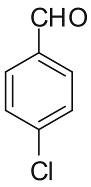
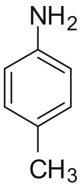
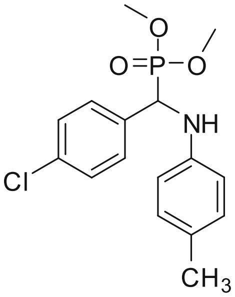
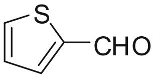
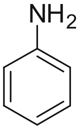
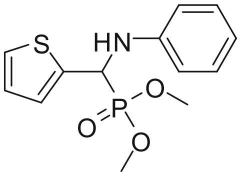
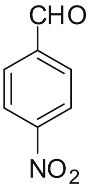
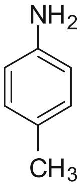
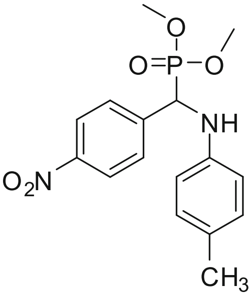
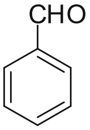
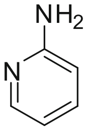
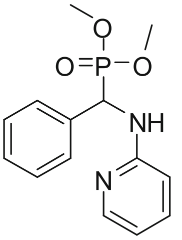
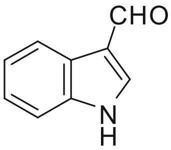
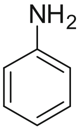
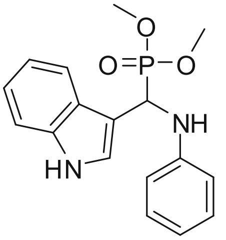
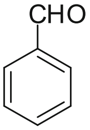
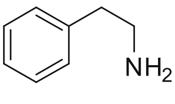
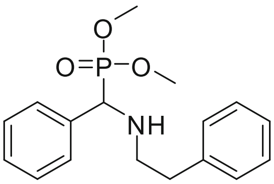
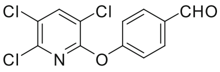
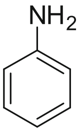
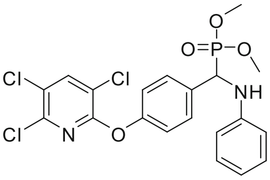
7				9	80	134–135
8				12	70	92–94[16]
9				5	88	211–213[28c]
10				12	80	142–143
11				12	68	135–136
12				6	88	217–219
13				8	70	165–167

Table 1. (continued).

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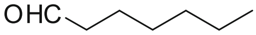
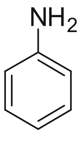
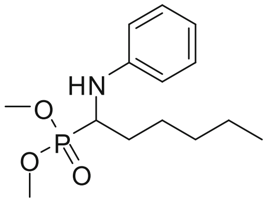
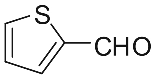
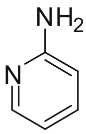
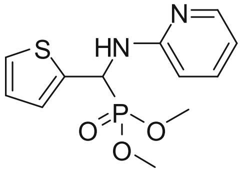
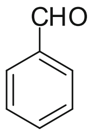
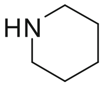
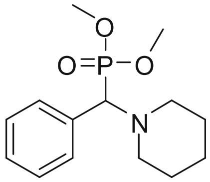
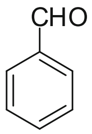
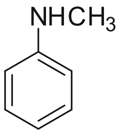
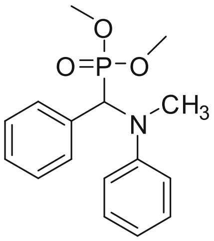
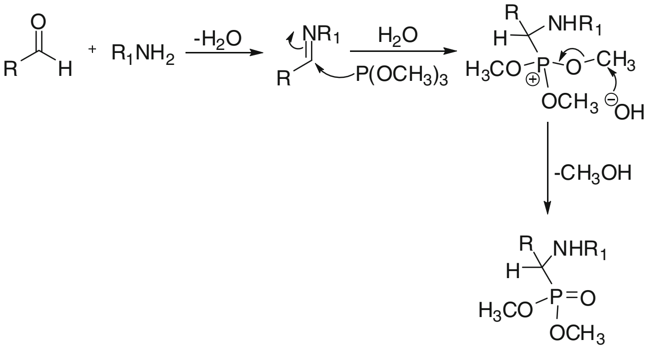
14				12	71	liqud
15				12	82	145–147
16				8	72	70–71[26c]
17				12	58	Gummy solid

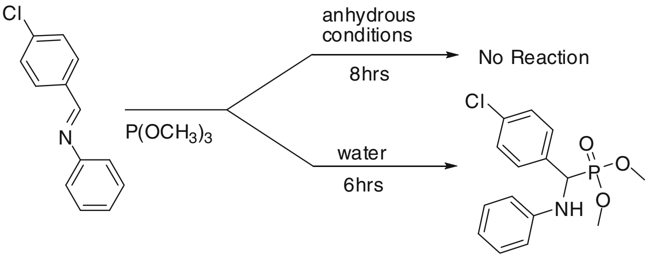
J_{13} = 6.04 Hz), 6.96 (q, 1H, J_{12} = 3.77 Hz, J_{13} = 5.28 Hz), 7.15–7.24 (m, 1H), 7.37 (m, 1H), 8.08 (d, 1H, J = 6.04 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.87, 48.01, 53.52 (d, $J_{CP} = 6.58$ Hz), 53.85 (d, $J_{CP} =$ 6.58 Hz), 109.20, 114.01, 125.05, 126.51, 126.99, 137.23, 139.38, 147.70, 156.38; MS (ESI): $m/z = 321$ $[M+Na]^+$; Anal. Calcd for $C_{12}H_{15}N_2O_3PS$: C, 48.32; H, 5.07; N, 9.39. Found: C, 48.39; H, 5.08; N, 9.47.



Scheme 2. Plausible mechanism.

3. Results and discussion

At the outset, taking the one-pot reaction of benzaldehyde, aniline and trimethyl phosphite (or triethyl phosphite) as a typical example, solvent-free noncatalytic protocol was attempted at ambient temperature. The reaction proceeds smoothly in 8 h to yield the corresponding α-aminophosphonates in 81% (with trimethyl phosphite) and 84% (with triethyl phosphite), with an optimum ratio of reactants being 1:1:1.1 (scheme 1).



Scheme 3. Synthesis of aminophosphonates from Schiff's base and trimethyl phosphite.

Table 2. Comparison of product yields in various methods.

	Substrates		Yield (%) of α-aminophosphonates			
Sl. No.	Aldehyde	Amine	BDMS [32]	$AlCl_3$ [16]	$ZrCl_4$ [10]	No catalyst
1	Aromatic	Aromatic	80	80	82	81
2	Aromatic	Aliphatic	83	80	85	88
3	Aliphatic	Aromatic	Trace	Trace	Trace	71
4	Aromatic	Aromatic secondary	Trace	Trace	Trace	58

To explore the scope of this protocol, we examined various aldehydes, amines as shown in table 1 with trimethyl phosphite. In general, all the reactions with variety of aryl, alkyl and heteroaryl aldehydes and aryl, arylalkyl and heteroaryl amines are clean and the α-aminophosphonates were obtained in high yields, under optimized conditions. Another salient feature of this approach is that the reaction proceeds well with the secondary amines also (table 1, entry 17). The electronic effects i.e., electron withdrawing groups on aldehydes (table 1, entry 5 and 9) and electron releasing groups on amines (table 1, entries 6, 7 and 9) increased the rate of reaction and yield of the products. Further, the reaction is also facile for the solid substrates i.e., when the aldehydes and amines involved are solids.

The mechanism of reaction (as shown in scheme 2) involves the nucleophilic addition of trimethyl phosphite on imine (generated *in situ* from aldehyde and amine) to produce a phosphonium intermediate, which in the presence of water looses methanol to give the desired aminophosphonates.

In order to prove the involvement of water in the reaction mechanism unambiguously, the reaction was performed with pre-synthesized imine, thereby avoiding water generated *in situ*. As expected, the reaction of the preformed imine with trimethyl phosphite did not proceed under moisture-free conditions where as the addition of water to the reaction medium in stoichiometric amount facilitated the progress in reaction (as shown in scheme 3). Intriguing aspect being that water is detrimental to the stability of trimethyl phosphite but it is the same water does help in completion of the reaction.[39]

A comparative evaluation of the method was done by with respect to other methods reported, such as Lewis acid catalysed and solvent-free protocol as shown in table 2. It was found that the present method takes longer time than others, the yields are comparable. Further, it is found that the method is superior when the aldehyde involved is aliphatic as well as with aromatic secondary amines and when aldehydes and amines involved are both solids.

4. Conclusion

A simple, efficient and elegant protocol for the one-pot synthesis of α-aminophosphonates from variety of aldehydes, amines and trimethyl phosphite in catalyst-free and solvent-free conditions at ambient temperature is presnted. The major highlight of the protocol is that it is in total agreement with the green chemistry principles: free of any chemical auxiliaries (solvent, catalyst, etc.) and energy efficient (ambient temperature). This approach for biologically significant compounds is an attractive and useful method fits very well in to the green synthetic procedures, compared to the existing innumerable methodologies. Further, this approach highlights the importance and relevance of water in promoting the reaction for the first time.

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