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Catalyst and solvent-free, ultrasound promoted rapid protocol for the one-pot synthesis of α-aminophosphonates at room temperature

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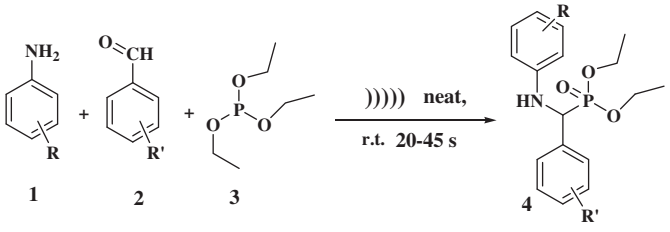
ABSTRACT

An ultrasound promoted easy, efficient, and environment friendly process has been devised for the synthesis of α-aminophosphonates within seconds through a one-pot three-component condensation of the aldehydes, amines, and triethylphosphite. The desired products were obtained in excellent yields and in high purity under solvent-free and catalyst-free conditions. Study with various aldehydes and amines reveals that ultrasound radiation plays a key role in the direct synthesis of α-aminophosphonates.

The structural resemblance of α-aminophosphonates with α-amino acids has brought them to the center of immense attention in recent years.[1] α-Aminophosphonates are among the most studied bioactive compounds which are reported to possess antitumor,[2] anti-inflammatory,[3] and antibiotic[4] activities. Their potential as good enzyme inhibitors,[5] herbicides,[6] peptide mimetics,[7] fungicides,[8] insecticides[9] plant growth regulators[10] etc is also well documented. The assortment of possibilities of practical use of α-aminophosphonates has stimulated considerable interest toward α-aminophosphonate chemistry and a plethora of synthetic methods have been reported for their preparation. Three-component condensation of an amine, aldehyde, and diethylphosphite or triethylphosphite is the most common and convenient method to construct such significant scaffold. Generally, these transformations are mediated by catalysts such as $ZrCl_4$,[11] $InCl_3$,[12] $MgBr_2$,[13] $TaCl_5$–SiO_2.[14]

The major drawback of the above mentioned processes, particularly those utilizing a single-pot procedure and involving moisture sensitive Lewis acids, is catalyst deactivation by water released during the reaction process.[15] This undesirable characteristic has been circumvented to some extent with the development of some catalytic systems like $NbCl_5$,[16] mesoporous aluminosilicate nanocage,[17] Silica sulfuric acid,[18] $Al(H_2PO_4)_3$,[19] $Ce(OTf)_4$,[20] $CeCl_3{\cdot}7H_2O$,[21] BF_3–SiO_2,[22] MoO_2Cl_2,[23] Choline chloride·$2ZnCl_2$ ionic liquid,[24] $Cd(ClO_4)_2 \times H_2O$,[25] Nano Fe_3O_4,[26] Although, these approaches are satisfactory for three component, one-pot synthesis of α-aminophosphonates, nevertheless the utilization of toxic solvents,



Scheme 1.

Table 1
Condensation of 4-chloroaniline, 4-chlorobenzaldehyde and triethylphosphite under different reaction conditions

Entry	Condition	Solvent	Time	Yield[a] (%)
1	30 °C without sonication	Acetonitrile	18 h	Traces
2	30 °C without sonication	No solvent	18 h	Traces
3	30 °C with sonication	No solvent	20 s	99
4	30 °C with sonication	Acetonitrile	20 s	79
5	Reflux without sonication	No solvent	2 h	10
6	Reflux without sonication	Acetonitrile	2 h	30

[a] HPLC yield.

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Table 2
Effect of Solvents on the condensation of 4-chloroaniline, 4-chlorobenzaldehyde and triethylphosphite under ultrasonication

Entry	Solvent	Time (S)	Yield[a] (%)
1	Solvent-free	20	99
2	Hexane	20	90
3	Ethyl acetate	20	89
4	Tetrahydrofuran (THF)	20	86
5	Dimethylformamide	20	85
6	Acetone	20	82
7	Acetonitrile	20	79
8	Methanol	20	79
9	Toluene	20	76
10	Dichloromethane	20	73
11	Ethanol	20	72
12	Water	20	65

[a] HPLC yield.

undesirable reaction conditions, expensive reagents, lengthened reaction times, costly catalysts, and formation of side products limit the exercise of these approaches. The development of a simple and inexpensive procedure for one-pot synthesis of α-aminophosphonate is needed.

Ultrasound assisted synthesis of organic compounds is a well established protocol and has been authenticated as a substitute energy source for organic reactions ordinarily accomplished through heating.[27] Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to afford improved yields and increased selectivities.[28] Therefore, ultrasound irradiation has been established as an important technique in organic synthesis. Taking advantage of this energy source some researchers have recently reported the ultrasound mediated solvent-free synthesis of α-aminophosphonates from aryl amines, aryl aldehydes, and triethylphosphite using different catalysts.[29]

To make this process more efficient, we herein describe the ultrasound promoted procedure with rapid kinetics under mild conditions, good atom-efficiency, simple work-up, and easy purification procedure for the synthesis of α-aminophosphonates with different

Table 3
Ultrasound promoted condensation of anilines, benzaldehydes and triethylphosphite under solvent free and catalyst free conditions

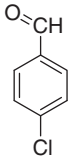
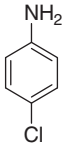
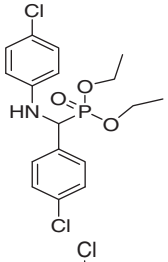
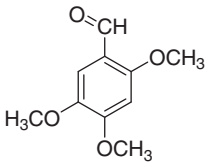
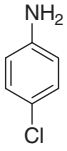
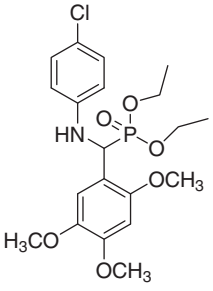
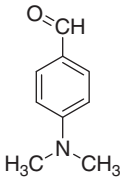
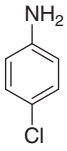
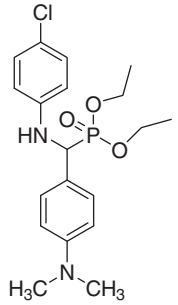
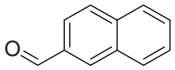
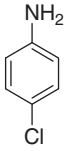
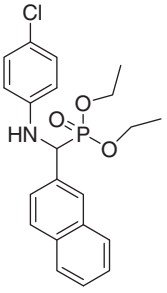
Entry	Aldehyde	Amine	Product	Time (S)	Yield (%)
1			 **4a**	20	99
2			 **4b**	45	86
3			 **4c**	20	81
4			 **4d**	20	84

Table 3 (*continued*)

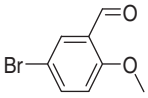
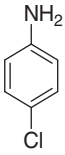
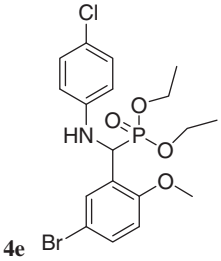
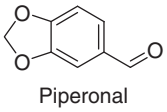
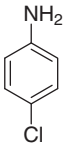
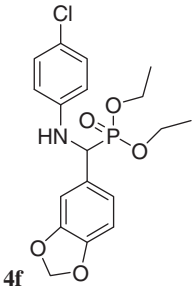
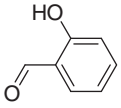
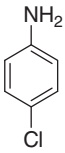
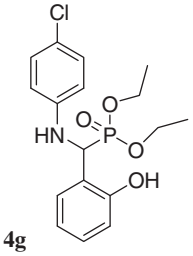
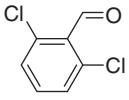
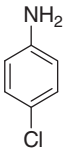
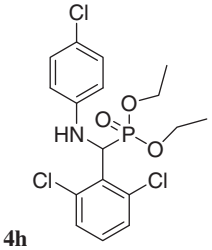
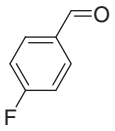
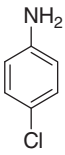
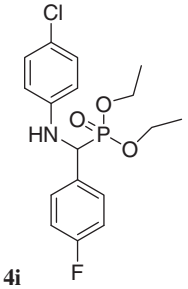
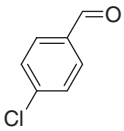
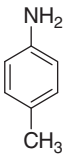
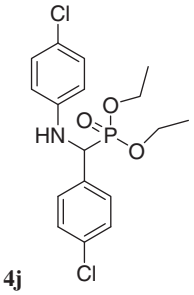
Entry	Aldehyde	Amine	Product	Time (S)	Yield (%)
5			 **4e**	20	80
6	 Piperonal		 **4f**	20	87
7			 **4g**	20	84
8			 **4h**	20	92
9			 **4i**	25	95
10			 **4j**	20	96

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Table 3 (*continued*)

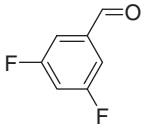
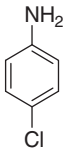
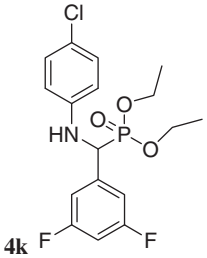
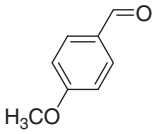
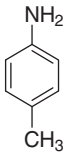
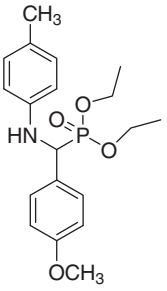
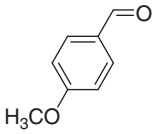
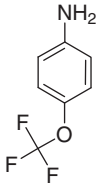
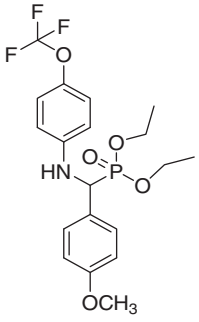
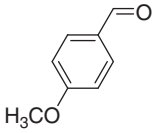
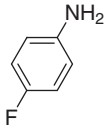
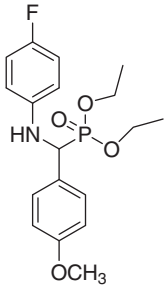
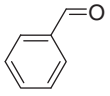
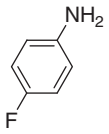
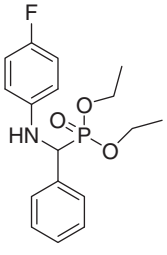
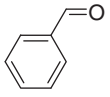
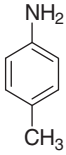
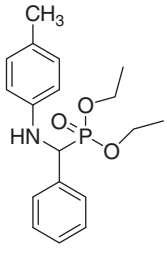
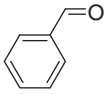
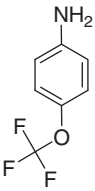
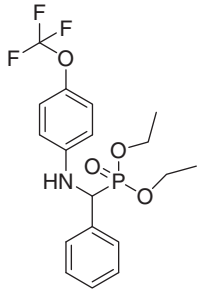
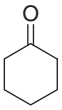
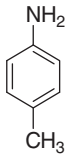
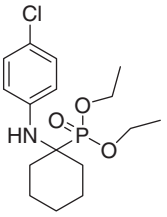
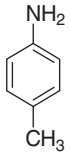
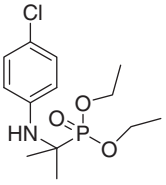
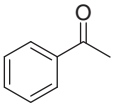
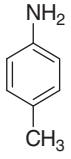
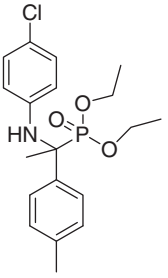
Entry	Aldehyde	Amine	Product	Time (S)	Yield (%)
11			 **4k**	20	91
12			 **4l**	20	95
13			 **4m**	20	87
14			 **4n**	30	88
15			 **4o**	20	91
16			 **4p**	25	88

Table 3 (*continued*)

Entry	Aldehyde	Amine	Product	Time (S)	Yield (%)
17			 **4q**	20	87
18			 4r	4 h	Traces
19			 4s	5 h	No reaction
20			 4t	4 h	Traces

species of aryl amines, aryl aldehydes, and triethylphosphite in catalyst free and solvent-free conditions (Scheme 1).

We investigated the solvent-free and catalyst-free ultrasound promoted multicomponent synthesis of α-aminophosphonates at room temperature. Initially, we attempted one pot coupling of 4-chloroaniline (1 mmol), 4-chlorobenzaldehyde (1 mmol) and triethylphosphite (1.3 mmol) as the model reaction to optimize the reaction conditions. To our surprise the reaction proceeded efficiently with 100% conversion to afford the corresponding α-aminophosphonate (99% yields) within dramatically shorter time (20 s) at room temperature (Table 1, entry 3).[30] The products were purified through recrystallization without applying any chromatographic technique. This avoids use of large quantities of volatile organic solvents usually required for work-up and purification in many existing procedures. When the reaction was carried out with and without solvents at room temperature exclusive of exposing to ultrasonic radiations, merely traces of the product were observed even after 18 h. (Table 1, entry 1–2). In the absence of ultrasound radiations increased temperature also could not enhance the reaction rate or product yield (Table 1, entry 5–6). Evidently, the sonochemical effect might be the key factor to the high efficiency of the one-pot and solvent-free reactions. Screening of different solvents such as water, ethanol, methanol, dichloromethane, *N,N*-diethylformamide, toluene, hexane and acetonitrile for this reaction and their comparison with the solvent-free approach proved that better results are obtained in solvent-free conditions (Table 2, entry 1–12).

Once, the reaction conditions were optimized we further attempted to understand the general reactivity of other carbonyl compounds and amines. To study the scope and the limitations of this novel method, we investigated the reaction using several electron-donating and electron-withdrawing substituted benzaldehydes as well as amine with triethylphosphite under solvent-free conditions. The reaction was found to be compatible with various functional groups such as Cl, Br, F, OMe, OEt, NO_2, and OH with excellent chemoselectivity. Various aromatic aldehydes containing electron donating or electron withdrawing functional groups were treated with various amines and did not show any remarkable difference in the yield of the desired products. The results are given in Table 3 which shows that all the reactions preceded clean, to give the corresponding α-aminophosphonate. It was observed that aniline substituted with electron withdrawing group requires less time than the amine substituted with electron donating group. Similar observation is noticed in case of aromatic aldehydes when they are attached with electron withdrawing and electron donating groups. Furthermore increase in the reaction time of lower yielding reactions (e.g., Table 3, entry 2) could not bring any significant improvement in the yield of the product (Fig. 1).

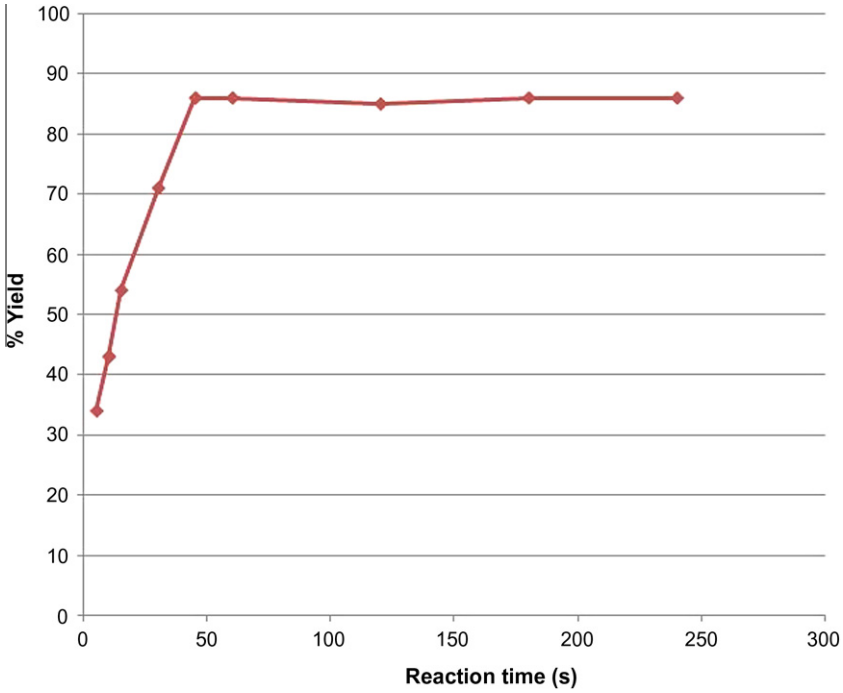


Figure 1. Effect of reaction time on the yield of **4b**.

In all cases, the experimental results show that the reaction times are reduced and the yields of the products are increased under sonication without using any catalyst. Based on the results of this study, it seems that the ultrasound irradiations are sufficient to draw this reaction in the absence of any catalyst with decreased reaction times and improved yields of α-aminophosphonates. Though the protocol is general but is not universal, because the α-aminophosphonates obtained from corresponding ketones were very less in yield under these conditions. When aldehydes were replaced with ketones the yields were found to be very less even after 4–5 h (Table 3, entry 18–20). Here the products from acetophenone and cyclohexanone were obtained in traces, acetone shows no reaction.

In conclusion we report an ultrasound promoted, catalyst free and solvent-free efficient, convenient, methodology for the synthesis of α-aminophosphonates with short reaction time, good to excellent yields, and high selectivity.

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30. *Typical procedure for one-pot synthesis of α-aminophosphonates:* A mixture of an aniline (1 mmol) and an aldehyde (1 mmol) was taken with triethylphosphite (1.3 mmol) in a 5 ml glass test tube (Scheme 1) with total reaction volume 0.4–0.5 ml approximately. The reaction mixture was placed at room temperature for specified time under ultrasonic irradiation, performed in a Bandelin Sonorex Super RK 510 H ultrasonic bath with Inner tank dimensions l × w × d: 300 × 240 × 150 mm, Exterior dimensions l × w × h: 325 × 265 × 305 mm, *Frequency:* 35 kHz and Ultrasonic peak output: 640 W∗. Progress of the reaction was monitored by TLC (silica gel) using ethyl acetate–hexane as eluent. After completion of the reaction (as indicated by TLC), the mixture was quenched with water and extracted with ethyl acetate, dried ($MgSO_4$) then concentrated under reduced pressure to afford the crude product. The crude product thus obtained was purified by the process of crystallization and the spectral data (^1H, ^{13}C NMR, HRMS, IR) were obtained and analyzed after comparison with the authentic samples. ^1H, ^{13}C NMR of some representative compounds are provided in supplementary information.