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Uncatalyzed and Solvent-Free One-Pot Three Component Synthesis of α–Amino Phosphonates

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This paper is dedicated to Prof. Habib Firouzabadion on the occasion of his 65th birthday and also his retirement.

An innovative route to preaper a number of variously substituted α-aminophosphonate is presented. The protocol avoids the use of any catalyst, organic solvents, and dry reaction conditions. The synthesis of α-aminophosphonates in the present study represents a three-component reaction in which no intermediate formation of either an imine or α-hydroxy phosphonate was observed.

Keywords: Catalyst free, Solvent free, α-Aminophosphonates, Aldehydes, Amine

INTRODUCTION

In recent years, considerable interest has been focused on the synthesis of α-aminophosphonates, because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis. In these connections, the utilities of α-aminophosphonates as peptide mimics, [1] enzymes inhibitors, [2, 3] haptens of catalytic antibodies, [4] and antibiotics and pharmacologic agents [5, 6] are well documented.

Recently, various methodologies have been developed for the synthesis of α–aminophosphonates. [7-11] Among these methods, the nucleophilic addition of phosphites to imines, catalyzed by a base or an acid, is the most convenient. Sodium ethoxide has been mainly used for this purpose since the pioneering work of Pudovik [12] and Lewis acids such as $SnCl_2$, $SnCl_4$, BF_3-Et_2O, $ZnCl_2$, and $MgBr_2$ have been also used. However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine, and dialkyl phosphite because the amines and water that exist during imine formation can decompose or deactivate Lewis acids. [13] This disadvantage has been overcome by recent procedure using a combination of Lanthanide triflate and magnesium sulfate. However, the utilization of a solvent and molecular sieves or magnesium sulfate is required. Apart from using different catalysts, different reaction media such as microwave, [14] ultrasound-assisted, [15] and solvent free conditions [16] have also been investigated. The methodologies reported have disadvantages such as the requirement for high reaction temperatures, prolonged reaction periods, an excess of costly dehydrating reagent/catalysts, moisture sensitive catalysts, and special apparatus. Moreover, the efficiency of the procedures reported is limited to the reaction of highly electrophilic carbonyl compounds and strongly nucleophilic amines.

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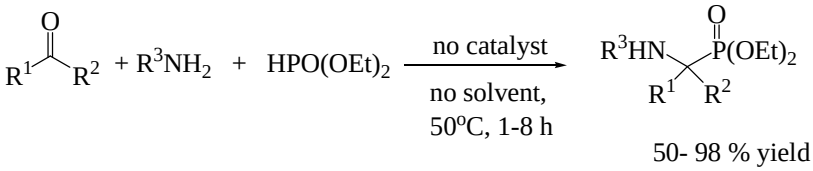


Scheme 1

Considering the importance of this class of compounds, the development of a green approach for their synthesis is desirable.

As continuation of my studies on the use of solvent free conditions [17] in organic synthesis, I am currently involved in a project on developing the easy synthesis of α–aminophosphonates under solvent-free conditions, via a catalyst free three component strategy (Scheme 1).

EXPERIMENTAL

All chemicals were obtained from Merck or Fluka chemical companies. The known compounds were identified by the comparison of their melting points and ^{1}H NMR with the authentic samples. The progress of the reactions was followed by TLC using silica-gel SILG/UV 254 plates. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General procedure for synthesis of α–aminophosphonates:

Carbonyl compound (1 mmol), amine (1 mmol) and diethyl phosphite (1 mmol) were mixed and stirred at 50°C. The progress of the reaction was monitored by TLC (eluent: EtOAc: *n*-hexane, 20:80). The α-aminophosphonates were isolated by silica gel short column chromatography of the final mixture. The structure of the product was confirmed by ^{1}H NMR, IR and comparison with authentic samples obtained commercially or prepared by reported methods. Typical spectral data:

(Table 2, entry 16): ^{1}H NMR ($CDCl_3$): δ (ppm): 6.93 (4H, d, *J*=2.8 Hz), 6.48 (4H, d, *J*=2.8 Hz), 4.89 (2H, s), 3.42-3.70 (8H, m), 3.39 (6H, s), 2.60 (4H, t), 2.10 (2H, br, NH), 0.85 (12H, t); ^{13} C NMR ($CDCl_3$): δ (ppm): 16.0, 54.9, 60.4, 62.5, 113.6, 129.4, 161.3; *m/z* (70 ev): M^+= 572 (100%).

(Table 2, entry 17): ^{1}H NMR ($CDCl_3$): δ (ppm): 7.22 (2H, d, J=3.4 Hz), 6.69 (2H, d, J=3.4 Hz), 4.77 (1H, s), 3.73-3.88 (4H, m), 3.60 (3H, s), 3.48 (2H, t), 2.87 (1H, brs, NH), 2.63 (2H, m), 1.07 (2H, m), 0.95 (6H, t); ^{13}C NMR ($CDCl_3$): δ (ppm): 16.2, 30.4, 46.2, 55.0, 59.3, 61.2, 62.5, 68.4, 114.1, 127.1, 131.3, 159.1; *m/z* (70 ev): M^+= 331 (100%).

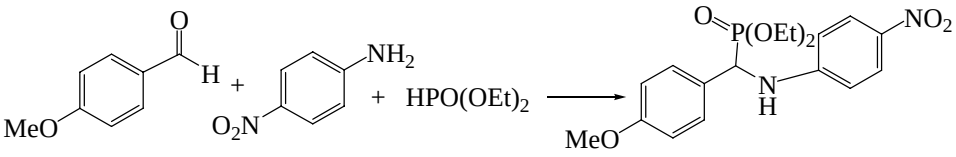
RESULTS AND DISCUSSION

An uncatalyzed synthesis of α-aminophosphonates was first attempted by the reaction between 4-methoxybenzaldehyde, 4-nitroaniline and diethyl phosphite using THF as the solvent. It is important to note that, the presence of the methoxy group in 4-methoxybenzaldehyde reduces the electrophilicity of the carbonyl carbon through resonance and the strong electron withdrawing property of nitro group in 4-nitroaniline decreases the nucleophilicity of the amine group. Thus, the combination of these substrates constitutes a model reaction for evaluating the efficiency of a procedure. Hence, after the reaction mixture was stirred for 48 h, no desired product was detected (Table 1, entry 1). Similar results were obtained when the reaction were carried out in different solvents such as toluene, EtOH, MeCN, and CH_2Cl_2 (entries 2-5).

Catalyst-free reactions under solvent free conditions were then explored. The reaction of 4-methoxybenzaldehyde, 4-nitroaniline and diethyl phosphite at 50°C for 6 h gave the desired product in 98% yield (Table 1, entry 7)

Based on the above observation, it was deduced to study the general reactivity's of other carbonyl compounds and amines. Firstly, the reactions of 4-methoxybenzaldehyde with different aryl and alkyl amines to carry out the three component coupling under catalyst-free and solvent-free conditions was investigated. The obtained results are listed in Table 2.

Table 1. Optimization for the synthesis of (4-methoxyphenyl)-(4-nitrophenyl) phosphonic acid diethyl ester under catalyst-free conditions



Entry	Reaction medium	Time (h)	Yields[a] %
1	THF, reflux	48	0
2	PhMe, reflux	48	0
3	EtOH, reflux	48	0
4	MeCN, reflux	48	0
5	CH_2Cl_2 , reflux	48	0
6	solvent free, r.t.	24	50
7	Solvent free, 50°C	6	98

[a] Yields are the isolated compounds.

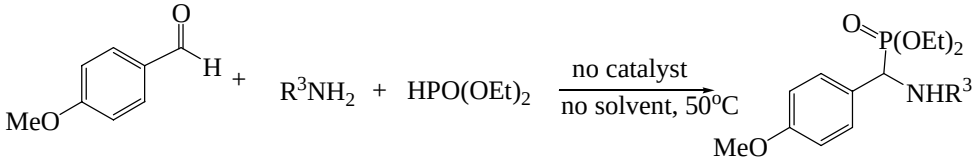
It was found that there were no remarkable electronic and steric effects on the progress of three-component couplings using different substituted aromatic amines. Anilines with *p*-, *o*- and *m*-substituents (Table 2, entries 1-14) resulted in the corresponding α-amino phosphonates in excellent yields, while *p*-methoxyaniline as a reactive amine (Table 2, entry 13) and *o*-trifluromethylaniline as a deactivated one (Table 2, entry 3) were both highly efficient substrates in this catalyst- and solvent-free procedure. Apart from the above amines, aliphatic amines were also selected to carry out the three-component couplings. As for propyl amine, ethylene diamine and 3-aminopropanol (Table 2, entries 15-17), they could provided the target products in reasonable yields. In addition, secondary amines like piperdine, and morpholine (Table 2, entries 18, 19) were acted as effective candidates for this transformation.

The reactivity's of aldehydes involved in the three component couplings under catalyst free and solvent-free conditions were also tested and the results were tabulated in Table 3.

We found that some electronic and steric effects in aromatic aldehydes affect this three component coupling reaction. Aromatic aldehydes with electron-donating group like *p*-methoxy (Table 3, entry 7) undergo the one-pot reaction as well as that with electron-withdrawing group like *p*-nitro (Table 3, entry 8). However, the steric effect from the substituent positions seemed to have considerable impact. For *p*-chloro, *m*-chloro, *o*-chloro and 2, 6-dichlorobenzaldehyde (Table 3, entries 2-4 and 9, respectively), the reaction time were prolonged and the yields of products were also decreased in the same sequence. Moreover, heteroaromatic, α, β-unsaturated and aliphatic aldehydes were all effective substrates to successfully perform this catalyst- and solvent-free Mannich-type reaction. Some ketones were also screened to carry out the three-component coupling by this method and the results were listed in Table 4.

Due to the lower reactivity of ketones than aldehydes, the coupling reactions involved with ketones were carried out at 80 °C under uncatalyzed and solvent free conditions. For both the aliphatic ketones like cyclohexanone and 3, 3-dimethyl-2-butanone (Table 4, entries 1 and 2), the expected products were smoothly achieved in 90% and 55% yields, respectively. However, no product was obtained when aromatic ketones like acetophenone (Table 4, entry 3) was involved in this one-pot reaction under catalyst- and solvent-free conditions.

Table 2. Uncatalyzed and solvent-free coupling of 4-methoxybenzaldehyde and anilines with diethyl phosphite



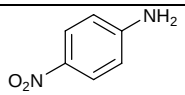
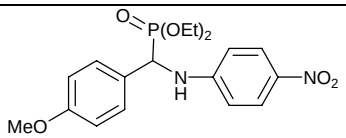
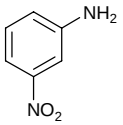
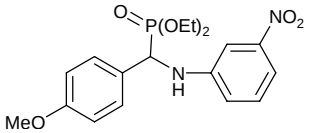
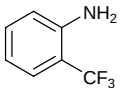
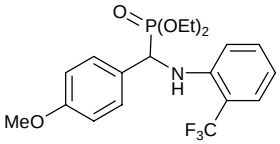
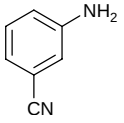
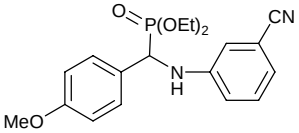
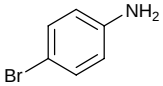
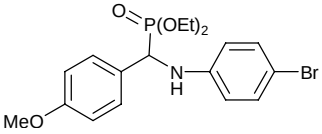
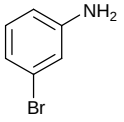
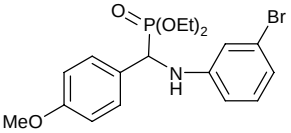
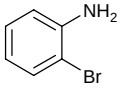
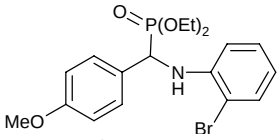
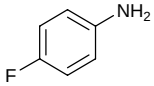
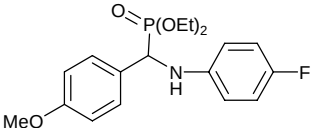
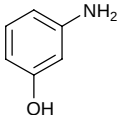
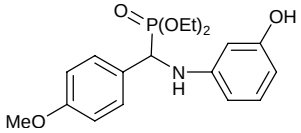
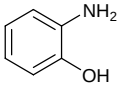
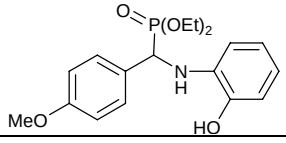
Entry	Amine	Product	Time(h)	Yields[a] %
1			6	98
2			5	98
3			5	83
4			4.5	88
5			1.5	92
6			2	90
7			4	98
8			1	98
9			1.5	95
10			1	80

Table 2. continued

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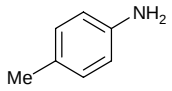
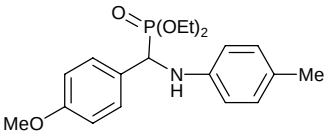
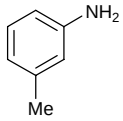
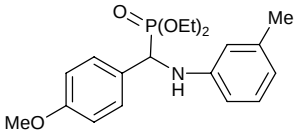
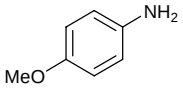
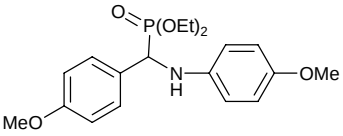
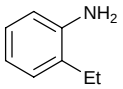
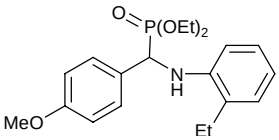
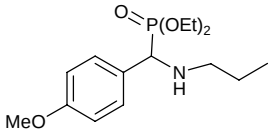
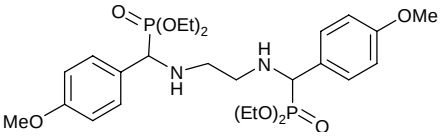
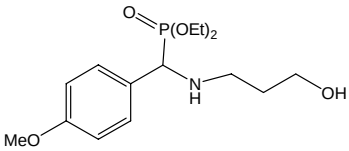
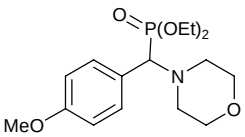
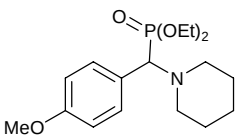
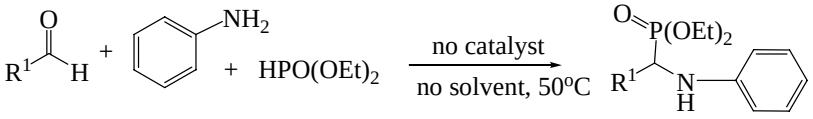
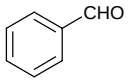
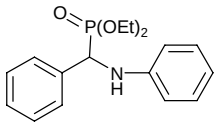
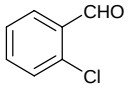
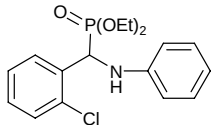
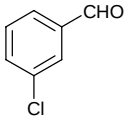
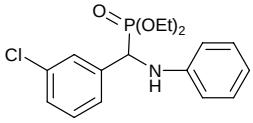
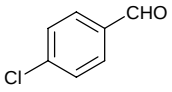
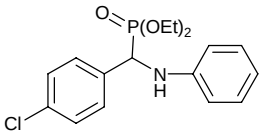
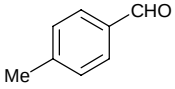
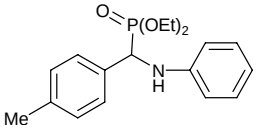
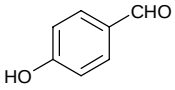
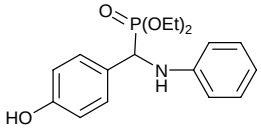
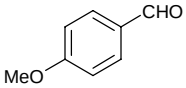
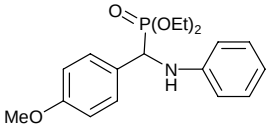
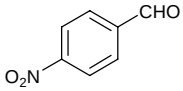
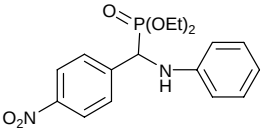
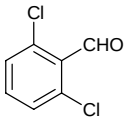
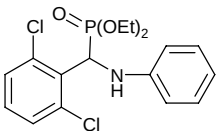
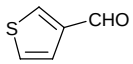
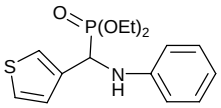
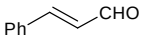
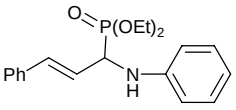
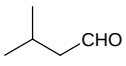
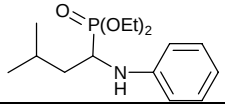
11			2	92
12			2	98
13			0.5	93
14			2	87
15	$CH_3CH_2CH_2NH_2$		3	50
16	$H_2NCH_2CH_2NH_2$		3	70
17	$HOCH_2CH_2CH_2NH_2$		2	86
18			4	92
19			3	85

[a] Isolated yields

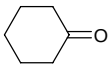
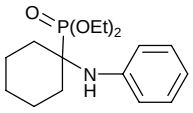
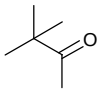
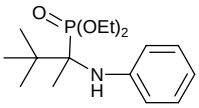
Table 3. Uncatalyzed and solvent-free coupling of aniline and aldehydes with diethyl phosphite



Entry	Aldehyde	Product	Time (h)
1			1.5
2			4.5
3			4
4			2
5			2.5
6			1
7			3.5
8			1
9			5
10			1
11			1
12			2

[a)] Isolated yields

Table 4. Uncatalyzed and solvent-free coupling of aniline and ketones with diethyl phosphite[a]

Entry	Adehyde	Product	Time(h)	Yields[b]%
1			2	90
2			8	55
3		No reaction	24	0

[a] The reactions were carried out at 80°C. [b] Isolated yields.

CONCLUSIONS

In conclusion, the approach to α-aminophosphonates presented herein avoids the use of any catalyst, organic solvent, and dry reaction conditions. This makes the purification of the final products very simple. This protocol represents a promising green route to synthesis of this class of compounds.

ACKNOWLEDGEMENTS

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