

Solvent and Catalyst Free Three-component Coupling of Carbonyl Compounds, Amines and Triethylphosphite; a new Synthesis of α -Amino-phosphonates

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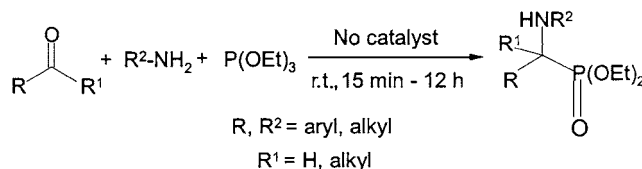
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Abstract: The first solvent and catalyst free three-component coupling of carbonyl compounds, amines and triethylphosphite is achieved producing α -aminophosphonates at ambient temperature in very high yields.

Key words: three-component coupling, carbonyl compounds, amines, triethyl phosphite, α -aminophosphonates



Scheme 1

The development of efficient methodologies involving novel reaction media including 'solventless' chemistry is gaining prominence.¹⁻⁵ Our group has been involved in this research area and we serendipitously observed that a three-component coupling between the carbonyl compound, an aliphatic/aryl amine and triethyl phosphite was facile in the absence of solvent as well as an external catalyst. This reaction in presence of solvent (diethyl ether/dichloromethane) always required external Lewis acid catalyst. The products obtained, namely α -aminophosphonates, have major roles to play in peptidomimetics,⁶ hapten design in antibody generation⁷ and also in enzyme inhibitory activity.⁸ A few of the one-pot literature procedures for α -aminophosphonate synthesis involve catalysis by lithium perchlorate,⁹ $\text{BF}_3\cdot\text{OEt}_2$, SnCl_2 and SnCl_4 ,¹⁰ ZnCl_2 or MgBr_2 ,¹¹ lanthanide triflates,¹² $\text{TaCl}_5\text{-SiO}_2$,¹³ indium chloride,¹⁴ montmorillonite clay and ZrCl_4 .¹⁵ Most of these procedures involve diethylphosphite as the phosphonate source.

We first investigated the reaction between benzaldehyde (entry 1, 5 mmol), aniline (5 mmol) and triethylphosphite (5 mmol) by stirring all the reactants together.¹⁶ After 15 minutes, the reaction mixture was adsorbed on silicagel and eluted with petroleum ether–ethyl acetate to obtain the product in 95% yield. The product obtained was comparable with a known sample in all respects including spectral data. Similarly, the three-component coupling of a variety of carbonyl compounds and amines with triethylphosphite was studied systematically, the results of which are summarized in Table 1 (Scheme 1).

The coupling of benzaldehyde with an electron rich amine (entry 2) and triethyl phosphite proceeded smoothly providing the α -aminophosphonate in 93% yield. The reac-

tion of benzaldehyde with benzylamine (entry 3) required longer reaction time (8 h) and the product yield was 93%. In the case of the coupling of (*S*)-(-)-phenylethylamine with benzaldehyde and triethyl phosphite (entry 4) the product yield was 85% with 86% diastereomeric excess (in favor of *S,R*-diastereomer), whereas the reported de with the Lewis acid catalyzed procedure was only 66%.

The efficiency of the reaction was examined with several aromatic aldehydes including normal (entry 5), electron rich (entry 6), electron deficient (7, 8 and 9) and heterocyclic aldehydes (entry 10). Further generality of this method was demonstrated by 3-component coupling reactions between aliphatic aldehydes and aromatic/aliphatic amines (entries 11–18) and triethyl phosphite. More importantly ketones (entries 19, 20) also underwent smooth 3-component coupling albeit requiring longer reaction times.

In conclusion the present protocol describes the first simple and efficient method for solvent free synthesis of α -aminophosphonates. The reaction proceeds using neither solvent nor any catalyst at room temperature, which leads to an ecologically and economically advantageous process.




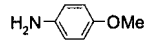

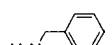

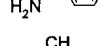
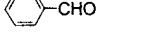

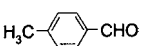
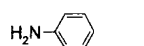
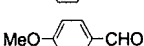

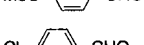

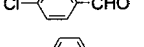
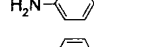


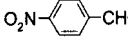

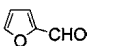
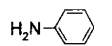
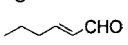
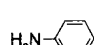
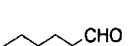
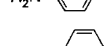

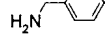
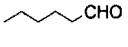
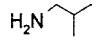
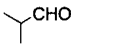
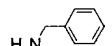
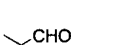



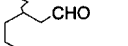

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Table 1 Solvent and Catalyst Free One-pot Synthesis of α -Amino-phosphonates

Entry	Carbonyl compound	Carbonyl compound	Time (min)	Yield ^a (%)
1			15	95
2			15	93
3			8 ^b	93
4			12 ^{b,c}	85
5			15	94
6			20	90
7			30	89
8			30	93
9			15	95
10			20	94
11			60	92
12			45	93
13			60	91
14			60	93
15			60	90
16			45	95
17			45	94
18			60	84
19			12 ^b	80
20			12 ^b	85

^a Isolated after column chromatography and characterised by ¹H NMR and Mass spectroscopy.^b Time in hours.^c 86% de (HPLC).

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- (16) **Representative Procedure:** Benzaldehyde (5 mmol), aniline (5 mmol) and triethyl phosphite (5 mmol) were added successively and the mixture was stirred for 15 min at r.t. After completion of the reaction (monitored by TLC), the reaction mixture was adsorbed on silica gel and eluted with petroleum ether–EtOAc (7:3) to give (phenyl-phenylamino-methyl)-phosphonic acid diethylester. ¹H NMR (200 MHz, CDCl₃): δ = 7.45 (d, J = 7.4 Hz, 2 H), 7.35–7.20 (m, 3 H), 7.04 (t, J = 8.2 Hz, 2 H), 6.68–6.50 (m, 3 H), 4.98 (d, J = 8.2 Hz, 2 H), 4.78 (d, J = 6.7 Hz, 2 H), 4.66 (d, J = 7.4 Hz, 2 H), 4.18–3.98 (m, 2 H), 3.92–3.82 (m, 1 H), 3.70–3.54 (m, 1 H), 1.26 (t, J = 7.4 Hz, 3 H), 1.08 (t, J = 6.7 Hz, 3 H). MS (FAB): m/z = 319 [M⁺], 210, 182, 119, 109, 91, 77, 55. FT-IR (KBr): 3310, 2924, 1452, 1239, 1029 cm⁻¹.