# Catalyst free efficient synthesis and characterization of α-aminophosphonates

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**Abstract: The great demand in life science for new molecules of biological and medicinal importance has led to an extreme significance of the development of synthetic methodologies. For the synthesis of α-aminophosphonates using aldehydes or ketones, amines and alkyl phosphates in dry solvent in the room temperature or sometime by heating i.e., via Kabachnik-Fields reaction is the most promising and convenient route. With this concise method the products were formed in good yields. Compounds are characterized using FT-IR, multinuclear NMR, and analyses. The development of new class of α-aminophosphonates and their applications are reported.**

**Keywords: Kabachnik-Fields reaction, α-aminophosphonates, aldehydes, ketones and alkyl phosphates.**

## I. INTRODUCTION

Phosphorus compounds are biologically active molecules and exhibit a wide range of applications in the area of industrial, agricultural and medicinal chemistry. α-Aminophosphonate esters/aminophosphonic acids as mimics of the α-amino acids are showing a great deal of interest in medicinal chemistry due to their broad spectrum of biological properties as potent antibiotics[1]. α-aminophosphonates constitute an important class of compounds with diverse biological activities. Their diverse applications include inhibition of synthase, HIV protease, renin, enzyme inhibitors, anti-inflammatory and PTPases, some of these derivatives are potential antibiotics or herbicides. The activity of aminophosphonates as peptidomimetics[2], enzyme inhibitors[3], pharmacogenic agents[4], inhibitors of serine hydrolases[5] and antitumor agents[6-8]. They also find applications in the agricultural industry [9].

## II. EXPERIMENTAL

All the reactions were carried out at room temperature, only few are heated to about 5-6 hours at 50-60$^0$C. The Solvent used is dry ethanol and it is of analytical grade. Reactions were monitored with aid of TLC on 0.25mm pre-coated silica-gel plates. Visualization was carried out with UV light, iodine tank or potassium permanganate stain. The purity of the compounds was obtained by means of crystallization. The melting points were determined in an open capillary tube on a Melt-Temp apparatus and recorded without any correction. $^1$H, and $^{31}$P were recorded on Broker 500MHz spectrometer. Chemical shifts are given in ppm (δ). Coupling constants (J) are given in Herzt (Hz). The letters s, d, t, q, and m stand for singlet, doublet, triplet, quartet and multiplet respectively. The IR spectroscopic results were obtained by means of Agilent Resolutions Pro, Cary 600 series FT-IR spectrophotometer.

General procedure for the synthesis of the synthesis of α-hydroxyphosphonates(4a-g)

Aromatic aldehydes and ketones (1g, 1.0 equiv), aromatic amines (1g, 1.5 equiv) and dimethylphosphite (1g, 1.0 equiv) were mixed in 20mL dry ethanol contained in a round bottom flask. The resulting solution was placed in a one neck round bottomed flask fitted with magnetic stirrer, placed on 2MLH magnetic stirrer and then stirred for about 5 to 6 hours at room temperature; the progress of the reaction was monitored using TLC (eluent 20% ethylacetate). The solvent was evaporated at low pressure in a rotary evaporator and the compounds were isolated followed by washing with n-hexane and then taken for the analysis. In the present work, the synthesis of different acyclic alpha aminophosphonates(4a-g) has been presented.

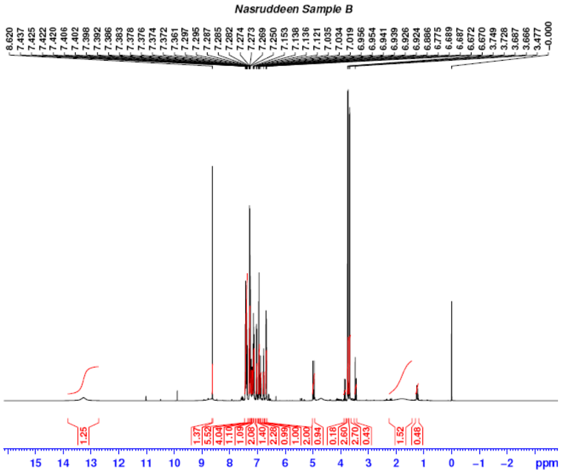

Fig. 1. H1 NMR spectra of Compound 4a

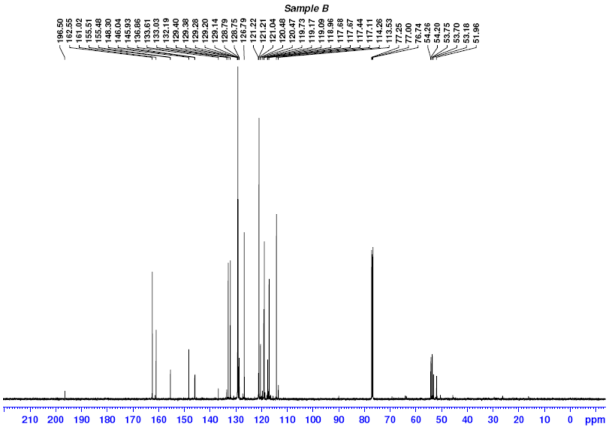

Fig.2. 13C NMR spectra of Compound 4a

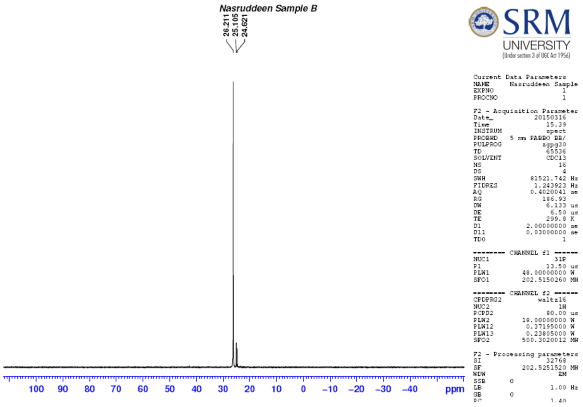

Fig.4. 31C NMR spectra of Compound 4a

Dimethyl (((2-chlorophenyl)amino)(1H-indol-3-yl)methyl)phosphonate (4a).

Yield (59%); mp 142-145$^0$C; IR (KBr) cm$^{-1}$ 3420(N-H), 1229(P=O), 1048(C-N) $^1$H NMR(CDCl$_3$) 6.5-7.5 Ar-H(δ), 3.6 P-C-H(δ), 3.70 N-H(δ),3.65 P-O-CH$_3$(δ) $^{31}$P NMR 27ppm

Dimethyl ((2-hydroxyphenyl) (phenylamino) methyl) phosphonate (4b)

yield(62%); mp 139-141$^0$C; IR (KBr) cm$^{-1}$ 3410(N-H), 1227 (P=O), 1034(C-N); $^1$H NMR(CDCl$_3$) 6.6-7.4 Ar-H(δ)3.7, P-C-H(δ) 3.74, N-H(δ) 3.66, P-O-CH$_3$(δ), $^{31}$P NMR 25ppm

Dimethyl (((2-chlorophenyl)amino)(p-tolyl)methyl)phosphonate (4c)

Yield(56%); mp 143-146$^0$C IR (KBr) cm$^{-1}$ 3403 (N-H), 1225 (P=O), 1044(C-N); $^1$H NMR(CDCl$_3$) 6.3-7.8 Ar-H(δ) 3.5 P-C-H(δ), 3.72 N-H(δ), 3.65 P-O-CH$_3$(δ), $^{31}$P NMR 26ppm

Dimethyl (1-(3-methoxyphenyl)-1-(phenylamino)ethyl)phosphonate (4d)

yield (65%); mp 141-144$^0$C IR (KBr) cm$^{-1}$ 3418 (N-H), 1229 (P=O), 1042(C-N); $^1$H NMR(CDCl$_3$) 6.5-7.3 Ar-H(δ)3.8, P-C-H(δ) 3.69, N-H(δ) 3.64, P-O-CH$_3$(δ), $^{31}$P NMR 28ppm

Dimethyl (3-phenyl-1-(phenylamino)allyl)phosphonate (4e)

Yield (60%); mp 138-140$^0$C; IR (KBr) cm$^{-1}$ 3408 (N-H), 1228 (P=O), 1037 (C-N); $^1$H NMR(CDCl$_3$) 6.7-7.1 Ar-H(δ), 3.5 P-C-H(δ), 3.67 N-H(δ), 3.66 P-O-CH$_3$(δ), $^{31}$P NMR 27ppm

Dimethyl (1-((2-chlorophenyl)amino)-3-phenylallyl)phosphonate (4f)

Yield (57%); mp 130-1320C; IR (KBr) cm$^{-1}$3416(N-H) 1226 (P=O), 1045(C-N); $^1$H NMR(CDCl$_3$) 6.4-7.5 Ar-H(δ)3.9, P-C-H(δ)3.71, N-H(δ)3.66, P-O-CH$_3$(δ), $^{31}$P NMR 26ppm

Dimethyl ((4-chlorophenyl) (phenylamino) methyl) phosphonate (4g)

yield(63%); mp 135-138$^0$C;IR (KBr) cm$^{-1}$ 3411 (N-H), 1224 (P=O), 1035 (C-N); $^1$H NMR($CDCl_3$) 6.5-7.9 Ar-H(δ), 3.8P-C-H(δ), 3.66N-H(δ), 3.65, P-O-$CH_3$(δ), $^{31}$P NMR 25ppm

## III. RESULTS AND DISCUSSION

Synthesis of α-aminophosphonates (4a-g) were conveniently accomplished by using three component one pot reaction of anilines (1) (1.5 eqv), and various aromatic aldehydes and ketones (2) (1 eqv) in the presence of ethanol as a solvent. The reaction mixture is stirred for one hour in room temperature in magnetic stirrer then it is stirred at elevated temperature (60-70 $^0$C) with condenser for 6-7 hrs and the progress of the reaction was monitored by TLC analysis at after every one hour. Then the reaction mixture was isolated followed by evaporating the solvent by Rotary evaporator. Then the product was washed repeatedly with hexane to get pure compound.

The reaction conditions were very mild and the alpha amino phosphonates in one-pot, three-component reaction of amines, dimethylphosphite, and various aldehydes/ ketones via *Kabachinik-Fields* reaction were formed exclusively without formation of any of undesired side products. Interestingly, the experiment was carried out without any catalyst or additives to effect the reaction. Another important feature of this reaction is the retention functionality such as chloro, methoxy, and hydroxyl.

## IV. CONCLUSION

In conclusion the approach to the above synthesis of alpha amino phosphonates presented, 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.

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