Korean J. Chem. Eng., 33(8), 2366-2373 (2016)
DOI: 10.1007/s11814-016-0098-2

pISSN: 0256-1115
eISSN: 1975-7220

An eco-friendly procedure for the efficient synthesis of diethyl α-aminophosphonates in aqueous media using natural acids as a catalyst

Abdelkader Hellal[*,**,***,†], **Salah Chafaa**[**], **and Lasnouni Touafri**[***]

*Laboratoire d'Electrochimie des Matériaux Moléculaires et des Complexes (LEMMC), Département Génie des Procédés, Facult de Technologie, Universit Ferhat Abbsas Sétif-1, Algeria
**Laboratoire de Valorisation des Substances Naturelles(LVSN), Universit Djilali Bounaâma de Khemis Miliana, 44225, Algeria
***Laboratoire de Physique et Chimie des Matériaux(LPCM), Universit Mouloud MAMMERI de Tizi-Ouzou, 15000, Algeria
(*Received 26 January 2015 • accepted 14 April 2016*)

Abstract−WE describe a new, convenient and high yielding procedure for the preparation of diethyl α-aminophosphonates in water by one-pot reaction of aromatic aldehydes, aminophenols and dialkyl phosphites in the presence of a low catalytic amount (10 mol%) of citric, malic, tartaric, and oxalic acids as a naturel, recyclable and highly stable catalyst.

Keywords: α-Aminophosphonates, Aminophenols, Natural Acids, Aqueous Media, Kabachnik-Fields Reaction

INTRODUCTION

Organophosphorus compounds are ubiquitous in nature and find applications in the fields of agriculture, medicine, and chemical industry [1-3]. Aminophosphonic acid derivatives constitute an important class of organophosphorus compounds due to their versatile biological activity [4]. α-Aminophosphonic acids are an important class of biologically active compounds that have received an increasing amount of attention because they are considered to be structural analogues of the corresponding α-aminoacids. For a long time the so-called 'phosphorus analogues' of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, $P(O)(OH)_2$, or phosphinic acid group, P(O)(OH)R (in which R may be H, alkyl, or aryl), as well as a phosphonate group, $P(O)(OR)_2$ (in which R may be alkyl, or aryl), have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products [5,6].

In this area, α-aminophosphonates as bioisosteric analogue of α-amino acids occupy an important place and reveal diverse and interesting biological and biochemical properties: pesticides [7], bactericides [8-10], antibiotics [8], HIV protease inhibitors [11], herbicides [12], enzyme inhibitors [13], antibacterial [14,15], antiviral [16], and antitumor agents [17], and may even be peptide mimics [18]. They also have several applications in the agricultural industry [19]. In view of the immense importance of α-aminophosphonates, researchers have focused on developing new methodologies for their synthesis [20]. However, many of these reported methods suffer from drawbacks such as the prolonged reaction time, use of expensive and hazardous phosphorus sources, high temperatures, multistep synthesis, stoichiometric amounts of catalyst, costly and moisture sensitive catalysts and use of highly toxic or toxic catalysts, low product selectivities and yields, use of harmful organic solvents, and also involve the use of expensive catalysts which are usually non-recoverable. Development of non-hazardous synthetic methodologies for organic reactions is one of the latest challenges to organic chemists.

Now, there is a need to develop new methodology in all areas of chemistry, like use of catalysts in organic synthesis process, and the growing concern for environmental demands the development of eco-friendly and economic processes wherein even less hazardous byproducts are not desirable, for example the use of high efficient and reusable solid acid catalyst such as $H_3PW_{12}O_{40}/SiO_2$ for sorbitol dehydration to isosorbide [21], $H_3PW_{12}O_{40}/CeXZr_{1-X}O_2$ catalysts [22], and ultrasound in chemical processes [23].

A large number of methods for the preparation of diverse α-aminophosphonates have been published since the first synthesis by Fields [20]. However, one-pot synthesis of α-aminophosphonates remains a favorite due to its versatile route and high-yielding reactions. In the last few decades, intensive synthetic studies were performed in the preparation of α-aminophosphonic acids and their esters [24-29]. The Kabachnik-Fields (phospha-Mannich) reaction involving the condensation of primary or secondary amines, oxo compounds (aldehydes and ketones) and >P(O)H species, especially dialkyl phosphites, represents a good choice for the synthesis of α-aminophosphonates that are of significant importance due to their biological activity. One-pot Kabachnik-Fields reaction can be promoted by acidic or basic catalysts, microwave irradiation, or by heating [30]. Several Lewis acid catalysts, such as InC_{l3} [31], $LiClO_4$ [32,33], $Mg(ClO_4)_2$ [34], $ZrOCl_25H_2O$ [35], $Al(H_2PO_4)$ [36], $BiCl_3$ [37], $FeCl_3$ [38], $YbCl_3$ [39], $In(OTf)_3$ [40], $Ce(OTf)_4$ [41], $Al(OTf)_3$ [42], CAN [43], $TaCl_5$-SiO_2 [44], and SmI_2 [45] solid acids (montmorillonite KSF, silica sulfuric acid, Amberlyst-15, and Amberlite-IR 120 [46], base catalysts such as $CaCl_2$ and PPh_3 and other catalysts such as ZnO, TiO_2, tosyl chloride, and mesoporous aluminosilicate nanocage [47] have also been used to promote this reaction.

†To whom correspondence should be addressed.
E-mail: haekpharm@yahoo.fr

However, these reactions could not be carried out efficiently in a single step with carbonyl, amine and phosphite functionalities because amines and the water formed during imine formation can decompose or deactivate these Lewis acids [48-50]. This problem was solved either by co-use of catalyst with dehydrating agent or by application of catalysts being stable in water, as, for example, Brønsted acids such as heteropoly acid, guanidine hydrochloride and supported oxalic acid [51-53]. These methods involve either long reaction times, low yields of the products, required stoichiometric amount of reagents, use of additives or expensive catalysts. One of the fundamental challenges and ultimate goals in organic synthesis is to perform the reactions in water [54,55]. Water is cheap, safe and reduces the use of harmful organic solvents. Therefore, it leads to the development of environmentally friendly chemical processes [56].

Although, today's environmental consciousness imposes the use of aqueous media as a solvent on both industrial and academic chemists [57,58]. Organic solvents are still used instead of water for mainly two reasons. First, most organic substances are insoluble in water and, as a result, water does not act as a reasonable reaction medium. Second, many reaction substrates, reagents and catalysts are decomposed or deactivated in water. Therefore, efforts to carry out organic reactions in water pose an important challenge in the area of reaction design.

However, there is a need to develop one-pot syntheses of α-aminophosphonates using water-tolerant catalysts. For several years, in our laboratory (LEMMC), Chafaa et al. have been involved in the discovery of novel α-aminophosphonates and studied the synthesis and biological effects of these interesting and perspective class biologically active compounds [59-65]. Due to the above-mentioned factors, in this paper we report the synthesis of α-aminophosphonates with high yield using a recyclable catalyst for applications in medicine and industry.

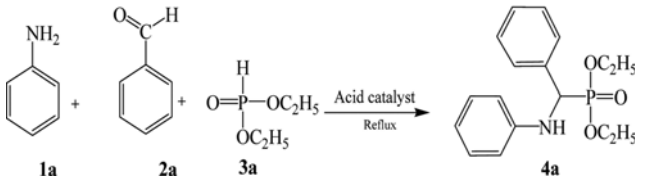
EXPERIMENTAL

1. General

Chemicals were purchased from Merck and Fluka Chemical Companies. All of the products were identified by their physical and spectral data. Infrared spectra were recorded on FT/IR JASCO 2400 (4,000-400 cm^{-1}). NMR spectra were recorded on a Bruker Avance 300 apparatus operating at 300 MHz with TMS as the internal standard. Chemical shifts are given in parts per million (ppm). Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet). ^{31}P NMR chemical shifts were referenced to external H_3PO_4 (85% w/w). The percentages of carbon, hydrogen and nitrogen were determined by elemental analyses using Perkin Elmer 2400 CHN Elemental Analyzer. Melting points were determined on a melting point apparatus and were uncorrected. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

2. Typical Procedure for the Synthesis of (Phenyl-phenylamino-methyl)-phosphonic Acid Diethyl Ester (4a)

A mixture of aniline **1a** (0.01 mol) and benzaldehyde **2a** (0.01 mol) was stirred at room temperature for 1 h, then diethylphosphite **3a** (0.01 mol) was added dropwise. Stirring was continued at room temperature for another 30 min, after which the mixture was added to the stirred solution of natural acids (10 mol%) in water (20 mL) and heated under reflux in an oil bath at 90 °C for an appropriate time. Water (20 mL) was added to the cooled reaction mixture and extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was washed with water (2×10 mL), separated, dried over $MgSO_4$ and filtered. Product (4a) was isolated by preparative plate chromatography eluted with n-hexane : EtOAc (1 : 1) (Scheme 1). Note that the catalysts were recycled by simple extraction of the product with water from the reaction mixture. The same procedure was carried used in the absence of catalysts.



Scheme 1. Synthesis of α-aminophosphonate (4a) via Kabachnik-Fields reaction.

The other compounds 4b to 4u were prepared employing a procedure similar to that described for compound 4a (Scheme 2).

3. Analytical Data

(Phenyl-phenylamino-methyl)-phosphonic acid diethyl ester (4a). Mol.Wt: 319.1. mp 90-92 °C. IR: 747 (P-C), 1,285 (P=O), 3,390 (NH) cm^{-1}; ^1H-NMR (DMSO-d_6) δ (ppm): 7.85-6.91 (m, 10H, Ar-H), 3.70-3.68 (d, J=14.2 Hz, J=10.6 Hz, 1H, P-CH), 4.77-4.69 (t, 1H, N-$H_{aliphatic}$), 3.41-3.37 (q, 4H, P-O-CH_2), 1.34-1.20 (m, 6H, P-O-CH_2-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 112-145 (CH_{Ar}), 63.7 (d, (CH_2)), 55.7 (s, (CH-P)), 15.5 (d, (CH_3)), ^{31}P-NMR (DMSO-d_6) δ: 20.43; Anal. cald. for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39; O, 15.03; P, 9.70. Found: C, 63.90; H, 6.89; N, 4.42.

[(4-Nitro-phenyl)-phenylamino-methyl]-phosphonic acid diethyl ester (4b). Mol.Wt: 364.1. mp 97-99 °C. IR: 756 (P-C), 1,212 (P=O), 3,380 (NH) cm^{-1}; ^1H-NMR (DMSO-d_6) δ (ppm): 7.83-6.95 (m, 9H, Ar-H), 3.67-3.48 (d, 1H, P-CH), 4.45-3.81 (t, 1H, N-$H_{aliphatic}$), 3.21-3.16 (m, 4H, P-O-CH_2), 1.23-1.08 (m, 6H, P-O-CH_2-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 110-149 (CH_{Ar}), 62.1 (d, (CH_2)), 55.7 (s, (CH-P)), 14.3 (d, (CH_3)), ^{31}P-NMR (DMSO-d_6) δ: 19.65; Anal. cald. for $C_{17}H_{21}N2O_5P$: C, 56.04; H, 5.81; N, 7.69; O, 21.96; P, 8.50. Found: C, 56.00; H, 5.79; N, 7.70.

[(4-Methoxy-phenyl)-phenylamino-methyl]-phosphonic acid diethyl ester (4c). Mol.Wt: 349.1. mp 100-10 °C. IR: 751 (P-C), 1,210 (P=O), 3,135 (NH) cm^{-1}; ^1H-NMR (DMSO-d_6) δ (ppm): 8.52-6.87 (m, 9H, Ar-H), 3.49-3.35 (d, 1H, P-CH), 4.69-4.20 (t, 1H, N-$H_{aliphatic}$), 3.23 (m, 4H, P-O-CH_2), 3.54 (s, 3H, Ar-OCH_3), 1.33 (m, 6H, P-O-CH_2-CH_3); ^{13}C-NMR (DMSO-d_6) δ: 112-160 (CH_{Ar}), 63.1 (d, (P-CH_2-C)), 55.7 (s, (CH-P)), 15.3(d, (P-C-CH_3)), 57.3 (s, (O-CH_3)), ^{31}P-NMR (DMSO-d_6) δ: 24.53; Anal. cald. for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01; O, 18.32; P, 8.87. Found: C, 61.86; H, 6.93; N, 4.02.

[(4-Hydroxy-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4d). Mol.Wt: 335.1. mp 135-139 °C. IR: 745 (P-C), 1,268 (P=O), 3,381 (NH) cm^{-1}; ^1H-NMR (DMSO-d_6) δ (ppm): 7.86-6.90 (m, 9H, Ar-H), 3.41-3.08 (d, 1H, P-CH), 3.77-3.71 (t, 1H, N-$H_{aliphatic}$),

3.01-2.88 (m, 4H, P-O-CH_2), 1.23-1.11 (m, 6H, P-O-CH_2-CH_3); 10.60 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 113.6-145 (CH_{Ar}), 64.1 (d, (P-$\underline{C}H_2$-C)), 57.7 (s, ($\underline{C}$H-P)), 14.1 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 20.79; Anal. cald. for $C_{17}H_{22}NO_4P$: C, 60.89; H, 6.61; N, 4.18; O, 19.08; P, 9.24. Found: C, 60.90; H, 6.60; N, 4.15.

[(4-Hydroxy-phenylamino)-(4-nitro-phenyl)-methyl]-phosphonic acid diethyl ester (4e). Mol.Wt: 380.1. mp 118-120 °C. IR: 765 (P-C), 1,263 (P=O), 3,340 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.84-6.95 (m, 8H, Ar-H), 5.66-5.18 (d, 1H, P-CH), 4.33-3.78 (t, 1H, N-$H_{aliphatic}$), 3.46-3.40 (m, 4H, P-O-$C\underline{H}_2$), 1.24-1.16 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.47 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 112.6-148 (CH_{Ar}), 62.7 (d, (P-$\underline{C}H_2$-C)), 57.8 (s, ($\underline{C}$H-P)), 13.1 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 21.87; Anal. cald. for C17$H_{21}N_2O_6P$: C, 53.69; H, 5.57; N, 7.37; O, 25.24; P, 8.14. Found: C, 53.66; H, 5.54; N, 7.40.

[(4-Hydroxy-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4f). Mol.Wt: 365.1. mp 145-147 °C. IR: 756 (P-C), 1,266 (P=O), 3,421 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.85-7.22 (m, 8H, Ar-H), 5.66-5.18 (d, 1H, P-CH), 4.65-3.91 (t, 1H, N-$H_{aliphatic}$), 3.56-3.51 (m, 4H, P-O-$C\underline{H}_2$), 2.39 (s, 3H, Ar-OCH_3), 1.13-1.10 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.58 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 113.9-148 (CH_{Ar}), 62.8 (d, (P-$\underline{C}H_2$-C)), 57.7 (s, ($\underline{C}$H-P)), 13.9 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.35; Anal. cald. for $C_{18}H_{24}NO_5P$: C, 59.17; H, 6.62; N, 3.83; O, 21.90; P, 8.48. Found: C, 59.14; H, 6.60; N, 3.85.

[(2-Hydroxy-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4g). Mol.Wt: 335.1. mp 109-111 °C. IR: 740 (P-C), 1,270 (P=O), 3,377 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.81-6.92 (m, 9H, Ar-H), 3.41-3.23 (d, 1H, P-CH), 3.71-3.66 (t, 1H, N-$H_{aliphatic}$), 3.11-2.89 (m, 4H, P-O-CH_2), 1.25-1.21 (m, 6H, P-O-CH_2-CH_3); 10.64 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 112.0-140.09 (CH_{Ar}), 64.6 (d, (P-$\underline{C}H_2$-C)), 57.5 (s, ($\underline{C}$H-P)), 14.2 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 21.80; Anal. cald. for $C_{17}H_{22}NO_4P$: C, 60.89; H, 6.61; N, 4.18; O, 19.08; P, 9.24. Found: C, 60.91; H, 6.58; N, 4.17.

[(2-Hydroxy-phenylamino)-(4-nitro-phenyl)-methyl]-phosphonic acid diethyl ester (4h). Mol.Wt: 380.1. mp 209-211 °C. IR: 745 (P-C), 1,263 (P=O), 3,330 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.81-6.91 (m, 8H, Ar-H), 5.62-5.11 (d, 1H, P-CH), 4.23-3.98 (t, 1H, N-$H_{aliphatic}$), 3.49-3.39 (m, 4H, P-O-$C\underline{H}_2$), 1.29-1.15 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.41 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 116.7-148.90 (CH_{Ar}), 62.0 (d, (P-$\underline{C}H_2$-C)), 57.3 (s, ($\underline{C}$H-P)), 13.1 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.99; Anal. cald. for $C_{17}H_{21}N_2O_6P$: C, 53.69; H, 5.57; N, 7.37; O, 25.24; P, 8.14. Found: C, 53.66; H, 5.54; N, 7.40.

[(2-Hydroxy-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4i). Mol.Wt: 365.1. mp 104-107 °C. IR: 750 (P-C), 1,270 (P=O), 3,441 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.71-7.20 (m, 8H, Ar-H), 5.60-5.11 (d, 1H, P-CH), 4.70-4.01 (t, 1H, N-$H_{aliphatic}$), 3.71-3.57 (m, 4H, P-O-$C\underline{H}_2$), 2.30 (s, 3H, Ar-OCH_3), 1.23-1.17 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.46 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 113.9-147.23 (CH_{Ar}), 62.6 (d, (P-$\underline{C}H_2$-C)), 57.7 (s, ($\underline{C}$H-P)), 13.7 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.35; Anal. cald. for $C_{18}H_{24}NO_5P$: C, 59.17; H, 6.62; N, 3.83; O, 21.90; P, 8.48. Found: C, 59.14; H, 6.60; N, 3.85.

[(2-Hydroxy-4-methoxy-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4j). Mol.Wt: 365.1. mp 114-116 °C. IR: 743 (P-C), 1,276 (P=O), 3,405 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.44-6.68 (m, 8H, Ar-H), 3.56-3.09 (d, 1H, P-CH), 4.35-3.68 (t, 1H, N-$H_{aliphatic}$), 2.91-3.56 (m, 4H, P-O-$C\underline{H}_2$), 2.51 (s, 3H, Ar-OCH_3), 1.23-1.10 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.39 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 103.9-146 (CH_{Ar}), 62.8 (d, (P-$\underline{C}H_2$-C)), 56.7 (s, ($\underline{C}$H-P)), 14.2 (d, (P-C-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 23.95; Anal. cald. for $C_{18}H_{24}NO_5P$: C, 59.17; H, 6.62; N, 3.83; O, 21.90; P, 8.48. Found: C, 59.13; H, 6.61; N, 3.86.

[(2-Hydroxy-4-methoxy-phenylamino)-(4-nitro-phenyl)-methyl]-phosphonic acid diethyl ester (4k). Mol.Wt: 410.1. mp 110-112 °C. IR: 741 (P-C), 1,271 (P=O), 3,401 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.43-6.67 (m, 7H, Ar-H), 5.66-5.18 (d, 1H, P-CH), 5.78-4.81 (t, 1H, N-$H_{aliphatic}$), 3.32-3.23 (m, 4H, P-O-$C\underline{H}_2$), 1.28-1.22 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 2.37 (s, 3H, Ar-OCH_3), 10.40 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 101.9-151 (CH_{Ar}), 62.5 (d, (P-$\underline{C}H_2$-C)), 55.7 (s, ($\underline{C}$H-P)), 14.0 (d, (P-C-$\underline{C}H_3$)), 56.0 (s, (O-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.43; Anal. cald. for $C_{18}H_{23}N_2O_7P$: C, 52.68; H, 5.65; N, 6.83; O, 27.29; P, 7.55. Found: C, 52.66, H, 5.67; N, 6.80.

[(2-Hydroxy-4-methoxy-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4l). Mol.Wt: 395.1. mp 183-186 °C. IR: 741 (P-C), 1,271 (P=O), 3,401 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.13-6.76 (m,7H, Ar-H), 3.50-3.12 (dd, J= 14.2 Hz, J=10.6 Hz, 1H, P-CH), 4.65-3.91 (t, 1H, N-$H_{aliphatic}$), 3.22-3.19 (m, 4H, P-O-$C\underline{H}_2$), 2.35 (s, 6H, Ar-OCH_3), 1.16-1.11 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 10.37 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 102.1-159 (CH_{Ar}), 62.9 (d, (P-$\underline{C}H_2$-C)), 55.3 (s, ($\underline{C}$H-P)), 14.3 (d, (P-C-$\underline{C}H_3$)), 56.8 (s, (O-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 19.98; Anal. cald. for $C_{19}H_{26}NO_6P$: C, 57.72; H, 6.63; N, 3.54; O, 24.28; P, 7.83. Found: C, 57.70; H, 6.64; N, 3.55.

[(2-Hydroxy-4-methyl-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4m). Mol.Wt: 349.1. mp 156-157 °C. IR: 762 (P-C), 1,256 (P=O), 3,375 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.87-6.95 (m, 7H, Ar-H), 3.43-3.00 (d, 1H, P-CH), 3.95-3.66 (t, 1H, N-$H_{aliphatic}$), 3.21-3.19 (m, 4H, P-O-$C\underline{H}_2$), 1.28-1.25 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 2.56 (s, 3H, Ar-CH_3), 10.38 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 112.1-145 (CH_{Ar}), 62.6 (d, (P-$\underline{C}H_2$-C)), 55.9 (s, ($\underline{C}$H-P)), 14.8 (d, (P-C-$\underline{C}H_3$)), 21.8 (s, (Ar-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 21.66; Anal. cald. for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01; O, 18.32; P, 8.87. Found: C, 61.87; H, 6.90; N, 4.05.

[(2-Hydroxy-4-methyl-phenylamino)-(4-nitro-phenyl)-methyl]-phosphonic acid diethyl ester (4n). Mol.Wt: 394.1. mp 134-136 °C. IR: 753 (P-C), 1,247 (P=O), 3,410 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.85-6.93 (m, 7H, Ar-H), 3.55-3.15 (d, 1H, P-CH), 5.15-4.68 (t, 1H, N-$H_{aliphatic}$), 3.34-3.27 (m, 4H, P-O-$C\underline{H}_2$), 1.13-1.08 (m, 6H, P-O-CH_2-$C\underline{H}_3$); 2.57 (s, 3H, Ar-CH_3), 10.43 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 113.1-140 (CH_{Ar}), 62.6 (d, (P-$\underline{C}H_2$-C)), 55.5 (s, ($\underline{C}$H-P)), 14.9(d, (P-C-$\underline{C}H_3$)), 21.2 (s, (Ar-$\underline{C}H_3$)), ^{31}P-NMR (DMSO-d_6) δ: 23.81; Anal. cald. for $C_{18}H_{23}N_2O_6P$: C, 54.82; H, 5.88; N, 7.10; O, 24.34; P, 7.85. Found: C, 54.80; H, 5.87; N, 7.12.

[(2-Hydroxy-4-methyl-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4o). Mol.Wt: 379.2. mp 100-102 °C. IR: 769 (P-C), 1,278 (P=O), 3,438 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.09-6.73 (m, 7H, Ar-H), 3.77-3.11 (d, 1H, P-CH), 4.82-4.60 (t, 1H, N-$H_{aliphatic}$), 3.00-2.93 (m, 4H, P-O-$C\underline{H}_2$), 2.54 (s, 3H, Ar-

CH_3), 1.06-1. 03 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 3.52 (s, 3H, Ar-OCH_3) 10.44 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6) δ: 113.9-141 (CH_{Ar}), 62.1 (d, (P-C$\underline{H}_2$-C)), 55.4 (s, (C$\underline{H}$-P)), 14.2 (d, (P-C-C$\underline{H}_3$)), 21.2 (s, (Ar-C$\underline{H}_3$)), 57.2 (s, (O-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 23.43; Anal. cald. for $C_{19}H_{26}NO_5P$: C, 60.15; H, 6.91; N, 3.69; O, 21.09; P, 8.16. Found: C, 60.17; H, 6.93; N, 3.68.

[(2-Hydroxy-4-nitro-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4p). Mol.Wt: 380.1. mp 96-97 °C. IR: 758 (P-C), 1,290 (P=O), 3,385 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.77-6.70 (m, 8H, Ar-H), 3.41-3.31 (d, 1H, P-CH), 4.65-3.91 (t, 1H, N-$H_{aliphatic}$), 2.91-2.88 (m, 4H, P-O-C$\underline{H}_2$), 1.29-1.27 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.43 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6) δ: 110-142 (CH_{Ar}), 62.1 (d, (P-C$\underline{H}_2$-C)), 55.1 (s, (C$\underline{H}$-P)), 14.7 (d, (P-C-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.57; Anal. cald. For $C_{17}H_{21}N_2O_6P$: C, 53.69; H, 5.57; N, 7.37; O, 25.24; P, 8.14. Found: C, 53.70; H, 5.55; N, 7.39.

[(2-Hydroxy-4-nitro-phenylamino)-(4-nitro-phenyl)-methyl]-phos-phonic acid diethyl ester (4q). Mol.Wt: 425.1. mp 143-145 °C. IR: 749 (P-C), 1,274 (P=O), 3,356 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.95-6.65 (m, 7H, Ar-H), 3.55-3.05 (d, 1H, P-CH), 3.99-3.69 (t, 1H, N-$H_{aliphatic}$), 2.89-2.83 (m, 4H, P-O-C$\underline{H}_2$), 1.31-1.28 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.44 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 111-148 (CH_{Ar}), 62.1 (d, (P-C$\underline{H}_2$-C)), 55.7 (s, (C$\underline{H}$-P)), 14.8 (d, (P-C-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 20.57; Anal. cald. for $C_{17}H_{20}N_3O_8P$: C, 48.01; H, 4.74; N, 9.88; O, 30.09; P, 7.28. Found: C, 48.00; H, 4.76; N, 9.86.

[(2-Hydroxy-4-nitro-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4r). Mol.Wt: 410.1. mp 122-124 °C. IR: 758 (P-C), 1,256 (P=O), 3,391 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.05-7.46 (m, 7H, Ar-H), 3.77-3.50 (d, 1H, P-CH), 4.47-3.77 (t, 1H, N-$H_{aliphatic}$), 3.21-3.16 (m, 4H, P-O-C$\underline{H}_2$), 2.34 (s, 3H, Ar-OCH_3), 1.28-1.23 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.40 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 110.9-143 (CH_{Ar}), 62.1 (d, (P-C$\underline{H}_2$-C)), 55.7 (s, (C$\underline{H}$-P)), 14.9 (d, (P-C-C$\underline{H}_3$)), 57.6 (s, (O-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 24.11; Anal. cald. for $C_{18}H_{23}N_2O_7P$: C, 52.68; H, 5.65; N, 6.83; O, 27.29; P, 7.55. Found: C, 52.70; H, 5.63; N, 6.80.

[(4-Chloro-2-hydroxy-phenylamino)-phenyl-methyl]-phosphonic acid diethyl ester (4s). Mol.Wt: 369.1. mp 86-88 °C. IR: 756 (P-C), 1,235 (P=O), 3,399 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.86-6.77 (m, 8H, Ar-H), 4.00-3.68 (d, 1H, P-CH), 4.99-4.60 (t, 1H, N-$H_{aliphatic}$), 2.97-2.93 (m, 4H, P-O-C$\underline{H}_2$), 1.07-1.03 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.48 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6) δ: 116.1-143.6 (CH_{Ar}), 62.8 (d, (P-C$\underline{H}_2$-C)), 55.8 (s, (C$\underline{H}$-P)), 14.5 (d, (P-C-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 22.90; Anal. cald. for $C_{17}H_{21}ClNO_4P$: C, 55.22; H, 5.72; Cl, 9.59; N, 3.79; O, 17.31; P, 8.38. Found: C, 55.20; H, 5.74; N, 3.78.

[(4-Chloro-2-hydroxy-phenylamino)-(4-nitro-phenyl)-methyl]-phos-phonic acid diethyl ester (4t). Mol.Wt: 414.1. mp 118-120 °C. IR: 743 (P-C), 1,278 (P=O), 3,410 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.75-6.58 (m, 7H, Ar-H), 4.15-3.33 (d, 1H, P-CH), 4.98-4.23 (t, 1H, N-$H_{aliphatic}$), 2.84-2.73 (m, 4H, P-O-C$\underline{H}_2$), 1.17-1.12 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.50 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6) δ: 115.4-142.8 (CH_{Ar}), 62.8 (d, (P-C$\underline{H}_2$-C)), 55.9 (s, (C$\underline{H}$-P)), 14.1 (d, (P-C-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 23.03; Anal. cald. for $C_{17}H_{20}ClN_2O_6P$: C, 49.23; H, 4.86; Cl, 8.55; N, 6.75; O, 23.14; P, 7.47. Found: C, 49.20; H, 4.87; N, 6.73.

[(4-Chloro-2-hydroxy-phenylamino)-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (4u): Mol.Wt: 399.1. mp 106-108 °C. IR: 741 (P-C), 1,266 (P=O), 3,433 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.55-6.88 (m, 7H, Ar-H), 3.70-3.18 (d, 1H, P-CH), 5.00-4.71 (t, 1H, N-$H_{aliphatic}$), 3.01-2.94 (m, 4H, P-O-C$\underline{H}_2$), 2.34 (s, 3H, Ar-OCH_3), 1.28-1.23 (m, 6H, P-O-CH_2-C$\underline{H}_3$); 10.31 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6) δ: 113.9-142.0 (CH_{Ar}), 62.3 (d, (P-C$\underline{H}_2$-C)), 55.4 (s, (C$\underline{H}$-P)), 14.2 (d, (P-C-C$\underline{H}_3$)), 56.6 (s, (O-C$\underline{H}_3$)), ^{31}P-NMR (DMSO-d_6) δ: 2.93; Anal. cald. for $C_{18}H_{23}ClNO_5P$:. C, 54.07; H, 5.80; Cl, 8.87; N, 3.50; O, 20.01; P, 7.75 Found: C, 54.09; H, 5.80; N, 3.53.

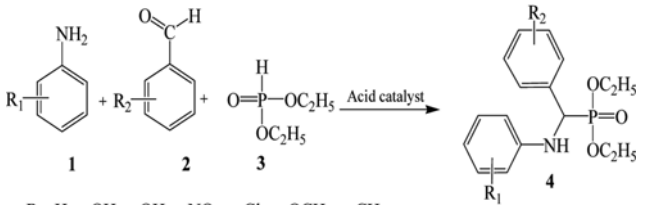
RESULTS AND DISCUSSION

We report here the successful application of natural acids for the preparation of various types of dialkyl α-aminophosphonates from the coupling reaction of aromatic aldehydes, aminophenols and dialkylphosphites in water. In the initial experiments, the one-pot, three-component reaction of aniline, benzaldehyde, and diethylphosphite was chosen as the model reaction to optimize the reaction conditions and the role of various natural catalysts was studied (Scheme 1).

The scope and limitations of the protocol were investigated by treating benzaldehyde, p-methoxybenzaldehyde, p-nitro-benzaldehyde, with aniline/aminophenols and diethylphosphite, in the absence of the catalyst (Table 1). After optimizing the reaction conditions, in order to examine the scope of this process, reactions of various electron-deficient aromatic aldehyde, various nucleophilic aromatic amines containing electron donating or electron withdrawing functional groups, and diethylphosphite were examined in the presence of natural acids as a catalyst to give the corresponding α-aminophosphonates (4a-4u) in high yields (Scheme 2).

To show the effect of the catalyst, one-pot reaction of aromatic aldehyde, aniline/aminophenols and diethylphosphite was examined in the absence of the catalyst. This reaction remained incomplete and the products formed were in a low yields, and the time taken was 9 to 16 h, which is considerably longer. It is pertinent to mention that the reaction hardly proceeded in the absence of catalyst. Regardless of the nature of the functional groups attached to the aldehydes and amines, all the reactions proceeded smoothly, generating the corresponding α-aminophosphonates in lowest yields.

However, aromatic aldehydes containing methoxy groups took longer times for completion. Therefore, the reaction time was re-



Scheme 2. Synthesis of α-aminophosphonates (4a-4u) via Kabachnik-Fields reaction.

Table 1. Reaction time and percentage yield of (4a-4u) in different reaction conditions

Cmpds	Substituents		% Yield/Reaction time (h)				
	R_1	R_2	No catalyst	Citric Ac.	Malic Ac.	Tartaric Ac.	Oxalic Ac.
4a	H	H	23/14	55/3.5	63/3	77/3	81/2
4b	H	p-NO_2	30/12	81/4	75/3,75	80/4	86/3,5
4c	H	P-OCH_3	29/12	66/5	55/5	65/6	75/3,75
4d	p-OH	H	35/11	88/3,5	85/3	90/2,5	95/1
4e	p-OH	p-NO_2	45/10	91/2,5	89/2,5	95/1	98/1
4f	p-OH	p-OCH_3	41/12	82/3,75	79/3,5	90/3	93/1,5
4g	o-OH	H	27/14	67/4	60/4	73/4	79/3
4h	o-OH	p-NO_2	30/15	77/4	75/4,5	82/4	85/3
4i	o-OH	p-OCH_3	29/12	64/4,25	54/4	63/4,5	71/4
4j	o-OH, p-OCH_3	H	33/13	77/3	73/3,5	85/3	90/2,5
4k	o-OH, p-OCH_3	p-NO_2	49/10	91/3	87/3,75	91/2,5	95/2
4l	o-OH, p-OCH_3	P-OCH_3	44/10	71/3	67/4	77/3,25	84/3
4m	o-OH, p-CH_3	H	47/11	75/3,75	72/3,5	82/3,5	88/3
4n	o-OH, p-CH_3	p-NO_2	46/9	86/3	83/3	88/3	91/2,5
4o	o-OH, p-CH_3	p-OCH_3	40/14	70/4	66/4	73/3,5	83/3
4p	o-OH, p-NO_2	H	22/16	58/5	55/5	63/5	67/4,55
4q	o-OH, p-NO_2	p-NO_2	19/23	69/5	60/5	69/5	70/4
4r	o-OH, p-NO_2	p-OCH_3	33/12	55/4,75	51/5,5	60/	62/5
4s	o-OH, p-Cl	H	37/13	61/4,5	58/4	68/4	71/3
4t	o-OH, p-Cl	p-NO_2	44/12	76/4	71/4,5	77/3,5	82/2.5
4u	o-OH, p-Cl	P-OCH_3	46/10	59/4	55/5	62/4	66/2,75

duced to 1-5 h by using natural acids as recyclable catalyst. These catalysts are mildly acidic with two acidic functional groups. Natural acids act as an efficient and recyclable acidic promoter, which yields good results. The reaction mechanism proceeds as in case of acid catalysts. In the optimization of reaction time, the yield of the product did not increase, when more than 10 mol% of catalysts was used. This suggested the use of 10 mol% of natural acids for 0.01 mol of reactants. The results are given in Table 1, which shows that, in the presence of catalysts, all reactions proceeded cleanly to give the corresponding α-aminophosphonates.

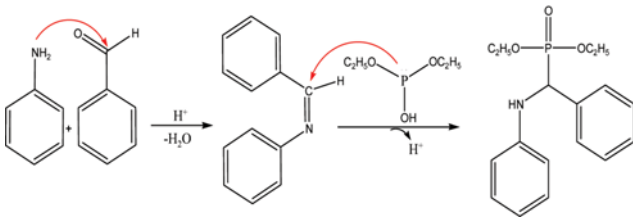
In these cases also, good conversions were observed within short times. Interestingly, amine substituted with electron donating group showed faster rates compared to the amine substituted with electron withdrawing group, possibly due to their higher basicity. Similar observation is noticed in case of aromatic aldehydes when they are attached with electron withdrawing required less time than the amine substituted with electron donating group.

Most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. Aniline, 2-hydroxy-4-chloro-aniline and 2-hydroxy-4-nitro-aniline are weaker bases due to delocalization of the nitrogen non-bonding electron pair into the aromatic ring. The basicity of these aromatic amines is less basic than 2-hydroxy-4-methyl-aniline and 2-hydroxy-4-methoxy-aniline because of a combination of two factors:

(1) The resonance stabilization of the free base form of aromatic amines. For Aniline, 2-hydroxy-4-chloro-aniline and 2-hydroxy-4-nitro-aniline, this resonance stabilization is a result of interaction of the unshared pair on nitrogen with the *pi* system of the aromatic ring. Because of this interaction, the electron pair on nitrogen is less available for reaction with electrophilic group. For the other arylamines the resonance stabilization is less and, therefore, the electron pair on the nitrogen is more available for reaction with electrophilic group; 2-hydroxy-4-methyl-aniline and 2-hydroxy-4-methoxy-aniline are stronger bases than Aniline, 2-hydroxy-4-chloro-aniline and 2-hydroxy-4-nitro-aniline.

(2) The second factor contributing to the decreased basicity of Aniline, 2-hydroxy-4-chloro-aniline and 2-hydroxy-4-nitro-aniline is the electron withdrawing effect of the *nitro* and *chloro* groups compared with the electron donating effect of *methyl* and *methoxy* groups. The unshared pair of electrons on nitrogen in an aromatic amine with an electron withdrawing effect is pulled toward the ring and, therefore, less available for protonation to form the conjugate acid of the amine. Electron releasing groups (methyl and methoxy) increase the basicity of aromatic amines, whereas electron-withdrawing groups (chloro, nitro) decrease their basicity. The decrease in basicity on halogen substitution is due to the electron withdrawing inductive effect of the electronegative halogen. The decrease in basicity on nitro substitution is due to a combination of inductive and resonance effects.

From the mechanistic point of view, we believe that the natural acids are the main active site in the reaction. It promotes the formation of imines by condensation of a carbonyl function and amine. The activated imine then reacts with diethylphosphite to generate the corresponding α-aminophosphonates. On the basis of the experimental results and the literature [66], possible mechanisms for the formation of aminophosphonates are presented in



Scheme 3. Plausible mechanism for the formation of aminophosphonate (4a).

Scheme 3. Macias et al. [67] have reported that the reaction between dialkyl phosphite and imine is the rate determining step of the Kabachnik-Fields reaction.

The superior catalytic activity of oxalic acid can be distinctly proved by a comparison of its acidity with the other acids. This difference is obviously due to high acidity of our catalyst compared with tartaric, malic and citric acids, thereby generating larger number of protons.

The reusability of the catalysts is a significant advantage and makes them useful for commercial applications [68]. For this purpose, the reaction of *para aminophenol* with para nitrobenzaldehyde and diethylphosphite was chosen as the model reaction in the presence of oxalic acid catalyst. After completion of the reaction (monitored by TLC), CH_2Cl_2 was added to the mixture. The aqueous layer was separated and used without further purification.

After the solid products were washed with water completely, the water containing oxalic acid (oxalic acid is more soluble in water than CH_2Cl_2) was evaporated under reduced pressure and the oxalic acid was recovered and reused. The recovered catalyst was reused in three runs without any loss of its activity (Table 2). The deactivation of the catalyst was low, although coke formation (reactant) was expected. The reaction was scaled up to 10 mmol of *para aminophenol, nitrobenzaldehyde* and diethylphosphite in the presence of 10 mol% of catalyst. The yield of the reaction was 96% after 55 min and 91% after the third run.

Thin layer chromatography (TLC) was employed to monitor the reaction progress and to determine the purity of the products. All the title compounds are readily soluble in polar organic solvents and melted in the temperature range of 90-147 °C. The IR spectra of compounds (4a-4u) showed the NH band in the range of 3,135-3,488 cm^{-1}. The sharp band observed in the range 1,210-1,290 cm^{-1} is due to the ν P=O, and a band for P-C stretching occurred in the range 739-763 cm^{-1}. All the stretching frequencies are compiled in Table 2. The ^{1}H NMR spectra of the compounds (4a-u) were recorded in the DMSO-d_6 solvent. The aromatic protons of α-aminophosphonic acid esters appeared as a multiplet in the region δ 6.67-8.85. The P-C-H group proton resonated as a multiplet in the range δ 3.08-4.30 due to coupling with phosphorus and N-H. The N-H proton signal appeared at δ 3.61-5.78 as a multiplet. The protons of P-O-CH_2-C that appeared as a quartet at δ 3.56-3.62 and P-O-C-CH_3 gave a triplet at δ 1.12-1.19. The carbon chemical shifts for P-C-H, P-O-$\underline{C}H_2$-CH_3 and P-OCH_2-$\underline{C}H_3$ in the title compounds were observed in the expected region. ^{31}P NMR signals appeared in the region 19.65-24.53 ppm for all the compounds (4a-4u).

Table 2. Reusability studies of catalyst for the synthesis of (4e)

Cycle	Fresh	1	2	3
Product isolated yield (%)	98	96	94	90
Recycling catalyst yield (%)	97	95	94	91

CONCLUSION

The synthesis of α-aminophosphonic acid esters (4a-4u) was achieved through a one-pot three-component reaction process, a Kabachnik-Fields reaction. It involves reactions among substituted aniline/aminophenols, substituted aromatic aldehydes, and dialkylphosphites in aqueous media at reflux temperature. In the absence of the catalyst, this reaction remained incomplete and the products formed were in a low yield (≤50%), and the time taken was 9 to 16 h, which is considerably long. It is pertinent to mention that the reaction hardly proceeded in the absence of catalyst. In the presence of natural acids as catalyst, the α-aminophosphonates were obtained in mild reaction conditions, considerably short reaction time (≤5 h), high yields and cost effectiveness. The structure of the synthesized α-aminophosphonates was established by elemental analysis, IR, ^{1}H, ^{13}C and ^{31}P-NMR spectral data. We found that natural acids can be used as a new and efficient catalyst for the preparation of a variety of α-aminophosphonates in good yields. This reaction system not only provides a novel method for the synthesis of biologically important α-aminophosphonates, but also extends the applicability of natural acids in organic synthesis in water, which leads to environmentally friendly chemical processes. This property combined with ease of recovery and catalyst reusability makes this method an economic, benign and waste-free chemical process for the synthesis of dialkyl α-aminophosphonates.

ACKNOWLEDGEMENTS

The authors are thankful to the Department of Engineering Process, Sétif-1 University for providing FT-IR, LSOA Laboratory-Oran University for providing NMR and other analysis.

REFERENCES

1. E. Breuer, The Chemistry of Organophosphorus Compounds, Vol. **4**, John Wiley & Sons, New York, USA (1996).
2. K. Srinivasulu, M. Anilkumar, C. Nagaraju and C. S. Reddy, *Arkivoc*, **14**, 100 (2007).
3. T. K. Prakasha, R. O. Day and R. R. Holmes, *J. American Chem. Soc.*, **116**(18), 8095 (1994).
4. R. A. Cherkasov and V. I. Galkin, *Usp. Khim.*, **67** 940 (1998).
5. (a) P. Kafarski and B. Lejczak, *Curr. Med. Chem. Anti-Cancer Agents*, **1**, 301 (2001); (b) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, **63**, 193 (1991); (c) R. L. Hil-derbrand, *The Role of Phosphonates in Living Systems*; CRC: Boca Raton, FL (1983).
6. R. Engel, *Synthesis of Carbon-Phosphorus Bond*; CRC: Boca Raton, FL (1988).
7. C. Fest and K. J. Schmidt, *The Chemistry of Organophosphorus Pesticides*, Vol. **12**, Springer (1982).

8. M. S. Bhatia and P. Pawanjit, *Experientia*, **32**(9), 1111 (1976).
9. P. N. Manne, S. D. Deshmukh, N. G. V. Rao, H. G. Dodale and S. N. Tikar, *Pestology*, **34**, 65 (2000).
10. D. Hendlin, E. O. Stapley, M. Jackson, H. Wallick, H. B. Woodruff, J. Birnbaum and A. K. Miller, *Science*, **166**(3901), 122 (1969).
11. A. M. Polozov and S. E. Cremer, *J. Organomet. Chem.*, **646**(1-2), 153 (2002).
12. L. X. Xiao, K. Li and D. Q. Shi, *Phosphorus, Sulfur Silicon Relat. Elem.*, **183**(12), 3156 (2008).
13. M. C. Allen, W. Fuhrer, B. Tuck, R. Wade and J. M. Wood, *J. Med. Chem.*, **32**(7), 1652 (1989).
14. F. R. Atherton, C. H. Hassall and R. W. Lambert, *J. Med. Chem.*, **29**(1), 29 (1986).
15. R. F. Pratt, *Science*, **246**(4932), 917 (1989).
16. J. Huang and R. Chen, *Heteroat. Chem.*, **11**, 480 (2000).
17. G. Lavielle, P. Hautefaye, C. Schaeffer, J. A. Boutin, C. A. Cudennec and A. Pierr, *J. Med. Chem.*, **34**(7), 1998 (1991).
18. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, **63**(1-2), 193 (1991).
19. (a) L. Maier, *Phosphorus, Sulfur Silicon Relat. Elem.*, **53**, 43 (1990). (b) L. Maier and P. J. Diel, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **57**, 57 (1991).
20. (a) R. Ghosh, S. Maiti, A. Chakraborty and D. K. Maiti, *J. Mol. Catal. A.: Chem.*, **210**, 53 (2004). (b) A. Heydari, H. Hamadi and M. Pourayoubi, *Catal. Commun.*, **8**, 1224 (2007). (c) S. Ambica, S. Kumar, C. Taneja, M. S. Hundal and K. K. Kapoor, *Tetrahedron Lett.*, **49**, 2208 (2008). (d) S. Chandrasekhar, S. Jaya Prakash, V. Jagadeswar and C. Narsihmulu, *Tetrahedron Lett.*, **42**, 5561 (2001). (e) N. Azizi and M. R. Saidi, *Tetrahedron*, **59**, 5329 (2003). (f) M. H. Sarvari, *Tetrahedron*, **64**, 5459 (2008). (g) S. Sobhani, E. Safaei, M. Asadi and F. J. Jalili, *Organomet. Chem.*, **693**, 3313 (2008). (h) S. M. Vahdat, R. Baharfar, A. Heydari, S. S. Baghbanian and S. Khaskar, *Tetrahedron Lett.*, **49**, 6501 (2008). (i) J. Akbari and A. Heydari, *Tetrahedron Lett.*, **50**, 4236 (2009). (j) A. Heydari, S. Khaskar and M. Tajbakhsh, *Tetrahedron Lett.*, **50**, 77 (2009). (k) A. Vinu, P. Kalita, V. V. Balasubramanian, H. Oveisi, T. Selvan, A. Mano, M. A. Chari and B. V. S. Reddy, *Tetrahedron Lett.*, **50**, 7132 (2009). (l) J. Uziel and J. P. Genet, *Russ. J. Org. Chem.*, **33**, 1521 (1997). (m) J. A. Ma, *Chem. Soc. Rev.*, **35**, 630 (2006). (n) V. P. Kukhar, V. A. Soloshonok and V. A. Solodenko, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **92**, 239 (1994). (o) M. Ordóñez, H. Rojas-Cabrera and C. Cativiela, *Tetrahedron*, **65**, 17 (2009). (p) V. P. Kukhar and H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity by Wiley*, New York (2000). (q) V. P. Kukhar, V. D. Romanenko and A. B. Hughes, *Chemistry of Aminophosphonic Acids and Phosphonopeptides, In Amino Acids, Peptides and Proteins in Organic Chemistry Wiley*, **4** (2009). (r) S. Kudrimoti and V. R. Bommena, *Tetrahedron Lett.*, **46**, 1209 (2005). (s) X.-J. Mu, M.-Y. Lei, J.-P. Zou and W. Zhang, *Tetrahedron Lett.*, **47**, 1125 (2006). (t) S. Bhagat and S. Chakraborti, *J. Org. Chem.*, **72**, 1263 (2007).
21. P. Sun, D. H. Yu, Y. Hu, Z. C. Tang, J. J. Xia, H. Li and H. Huang, *Korean J. Chem. Eng.*, **28**(1), 99 (2010).
22. H. J. Lee, S. Park, J. C. Jung and I. K. Song, *Korean J. Chem. Eng.*, **28**(7), 1518 (2010).
23. Y. J. Ahn, H. S. Kim and J. W. Lee, *Korean J. Chem. Eng.*, **27**(2), 723 (2010).
24. V. P. Kukhar and V. P. Solodenko, *Phosphorus, Sulfur Silicon Relat. Elem.*, **92,** 239 (1994).
25. D. Y. Hu, D. D. Wan, S. Yang, B. A. Song, P. S. Bhadury, L. H. Jin, K. Yan, F. Liu, Z. Chen and W. J. Xue, *Agric. Food Chem.*, **56**, 998 (2008).
26. S. Micheal, C. Jay, Z. Ding, S. Aaron, D. C. Atasi, D. Siddhartha and E. P. Stenen, *Org. Lett.*, **12**, 4596 (2010).
27. Z. Miao, J. Zhang, Z. Cui, B. Wang and R. Chen, *Helv. Chim. Acta*, **90**, 1932 (2007).
28. M. M. Kabachnik, T. N. Ternovskaya, E. V. Zobnina and I. P. Beletskaya, *Russ. J. Org. Chem.*, **38**, 484 (2002).
29. R. Hirschmann, A. B. Smith, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager and P. A. Sprengler, *S. J. Benkovic Science*, **265**, 234 (1994).
30. B. C. Ranu, A. Hajra and U. Jana, *Organic Lett.*, **1**(8), 1141 (1999).
31. M. R. Saidi and N. Azizi, *Syn. Lett.*, **8**, 1347 (2002).
32. N. Azizi and M. R. Saidi, *European J. Organic Chem.*, **2003**(23), 4630 (2003).
33. S. Bhagat and A. K. Chakraborti, *J. Organic Chem.*, **72**(4), 1263 (2007).
34. S. Bhagat and A. K. Chakraborti, *J. Organic Chem.*, **73**(15), 6029 (2008).
35. M. T. Maghsoodlou, S. M. Habibi Khorassani, R. Heydari, N. Hazeri, S. S. Sajadikhah and M. Rostamizadeh, *Chinese J. Chem.*, **28**(2), 285 (2010).
36. Z. P. Zhan and J. P Li., *Synth. Commun.*, **35**(19), 2501 (2005).
37. Z. Rezaei, H. Firouzabadi, N. Iranpoor, A. Ghaderi, M. R. Jafari, A. A. Jafari and H. R. Zare, *European J. Med. Chem.*, **44**(11), 4266 (2009).
38. F. Xu, Y. Q. Luo, J. T. Wu, Q. Shen and H. Chen, *Heteroat. Chem.*, **17**(5), 389 (2006).
39. R. Ghosh, S. Maiti, A. Chakraborty and D. K. Maiti, *J. Mol. Catal. A*, **210**(1-2), 53 (2004).
40. S. Sobhani and Z. Tashrifi, *Heteroat. Chem.*, **20**(2), 109 (2009).
41. S. Sobhani and Z. Tashrifi, *Synth. Commun.*, **39**(1), 120 (2009).
42. M. Kasthuraiah, K. A. Kumar, C. S. Reddy and C. D. Reddy, *Heteroat. Chem.,* **18**(1), 2 (2007).
43. S. Chandrasekhar, S. J. Prakash, V. Jagadeshwar and C. Narsihmulu, *Tetrahedron Lett.*, **42**(32), 5561 (2001).
44. Y. P. Tian, F. Xu, Y. Wang, J. J. Tang and H. L. Li, *J. Chem. Res.*, **2009**(2), 78 (2009).
45. A. K. Bhattacharya and K. C. Rana, *Tetrahedron Lett.*, **49**(16), 2598 (2008).
46. J. Hou, J. Gao and H. Zhang, *Appl. Organomet. Chem.*, **25**(1), 47 (2011).
47. S. P. Bhimagouda, G. Krishnamurthy, H. S. Bhojyanaik, R. L. Prashant and G. Manjunath, *European J. Med. Chem.*, **45**(8), 3329 (2010).
48. J. Zon, *Pol. J. Chem.*, **55**, 643 (1981).
49. S. Laschat and H. Kunz, *Synthesis*, 90 (1992).
50. J. P. Genet, J. Yziel, M. Port, A. M. Touzin, S. Roland and S. S. Thorimbert, *Tetrahedron Lett.*, **33**, 77 (1992). A. Heydari, H. Hamadi and M. Ayoubi, *Catal. Commun.*, **8**, 1224 (2007).
51. A. Heydari, H. Hamadi and M. Pourayoubi, *Catal. Commun.*, **8**, 1224 (2007).
52. A. Heydari and A. Arefi, *Catal. Commun.*, **8**, 1023 (2007).
53. S. M. Vahdat, R. Baharfar, M. Tajbakhsh, A. Heydari, S. M. Bagh-

banian and S. Khaksar, *Tetrahedron Lett*., **49**, 6501 (2008).
54. C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York (1997). See also: C. J. Li, *Chem. Rev*., **93**, 2023 (1993); C. J. Li and T. H. Chan, *Tetrahedron*, **55**, 11149 (1999); C. J. Li, *Tetrahedron*, **52**, 5643 (1996).
55. P. A. Grieco, Organic Synthesis in Water, Blackie Academic and Professional, London, 47 (1998).
56. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, By Permission of Oxford University Press, 30 (1998).
57. H. M. A. Asghar, S. N. Hussain, H. Sattar, E. Pelham, L. Roberts and N. W. Brown, *Korean J. Chem. Eng*., **31**(5), 834 (2014).
58. A. A. Amooey, S. Ghasemi, S. M. Mirsoleimani-azizi, Z. Gholaminezhad and M. J. Chaichi, *Korean J. Chem. Eng*., **31**(6), 1016 (2014).
59. V. Bohmer, W. Vogt, S. Chafaa, J. Meullemeestre, M. J. Schwing and F. Vierling, *Helv. Chim. Acta*, **76**, 139 (1993).
60. S. Chafaa, J. Meullemeestre, M. J. Schwing, F. Vierling and V. Bohmer, *Helv Chim. Acta*, **76**, 1425 (1993).
61. S. Chafaa, Ph. D. Thesis, University Louis Pasteur, Strasbourg (France) (1993).
62. F. Benghanem, S. Chafaa, G. Bouet and M. A. Khan, *Phosphorous, Sulfur, Silcon, Relat. Elem*., **170**, 159 (2001).
63. E. Bentouhami, G. Bouet and M. A. Khan, *Phosphorus, Sulfur Silicon, Relat. Elem*., **178**, 903 (2003).
64. E. Bentouhami, G. Bouet, M. J. Schwing and M. A. Khan, *J. Sol. Chem*., **35**, 889 (2006).
65. N. Aliouane, S. Chafaa, T. Douadi, J. J. Helesbeux, M. A. Khan, G. Bouet and O. Duval, *Phosphorus, Sulfur Silicon Relat. Elem*., **186**, 354 (2011).
66. R. A. Cherkasov and I. V. Galkina, *Russ. Chem. Rev*., **67**, 85 (1998).
67. Z. Duan, Y. Gu and Y. Deng, *Catal. Commun*., **7**, 651 (2006).
68. F. Matloubi-Moghaddam, H. Saeidian, Z. Mirjafary and A. Sadeghi, *J. Iran Chem. Soc*., **6**, 317 (2009).