Fe_3O_4@SiO_2-imid-PMA^n catalyzed synthesis of α-aminophosphonates.

A green one-pot three-component synthesis of α-aminophosphonates under solvent-free conditions and ultrasonic irradiation using Fe_3O_4@SiO_2-imid-PMA^n as magnetic catalyst

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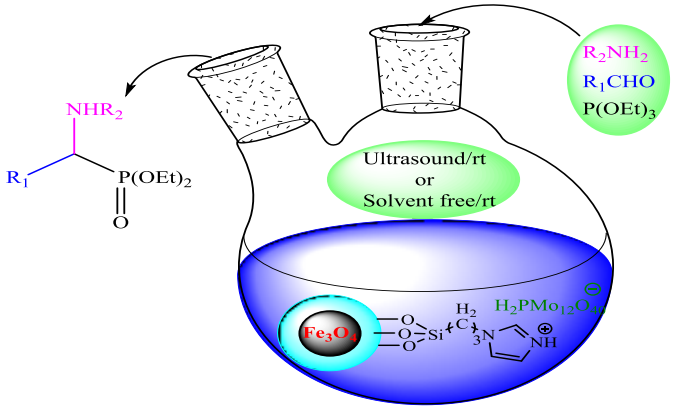
Abstract

An efficient and environment friendly process for the synthesis of α-aminophosphonates has been devised. Through a one-pot three-component condensation of various aldehydes, amines, and triethyl phosphite in the presence of Fe_3O_4@SiO_2-imid-PMA^n nanoparticles as magnetic catalysts under solvent-free conditions and ultrasonic irradiation, α-aminophosphonates were obtained with excellent yields. The reactions under solvent-free conditions at room temperature are compared with the ultrasonic-assisted reactions. This new procedure has notable advantages such as short reaction time, excellent yields, easy purification, and absence of any tedious workup or purification. The aforementioned catalyst could be easily recovered by an external

magnetic field and can be reused for six consecutive reaction cycles without significant loss of activity. In addition, SEM and DLS of the catalyst after the reaction cycle were investigated.

GRAPHICAL ABSTRACT



Keywords

α-Aminophosphonates; Multi-component reaction; One-pot synthesis; Solvent-free reaction; Green synthesis; Ultrasonic irradiation.

1. Introduction

α-Aminophosphonates are structurally analogous to amino acids. They have been found to exhibit a pivotal role in synthetic organic chemistry as well as in medicinal chemistry.[1,2] The medicinal importance and biological effects of α-aminophosphonate derivatives, such as antithrombotic agent,[3] anticancer agent,[4] antihypertensive agents,[5] anti-inflammatory agent,[6] catalytic antibodies,[7] potential antioxidants,[1] antibiotic,[4] biotryticides[8] enzyme inhibitors,[9] carriers of hydrophilic organic molecules across phospholipid membranes,[10] HIV protease,[11] and peptidases and proteases[12] have stimulated scientific research to develop many synthetic procedures for them. Also, they can be used as fungicides,[13] herbicides,[14] insecticides,[15] plant virucides[16] and hypothetical radio protecting agent.[17] These methods include the use of Brønsted acids such as Amberlite-IR 120,[18] sulfamic acid,[19] hypophosphorus acid,[20] CF_3CO_2H,[21] oxalic acid[22] and Lewis acids such as $Al(H_2PO_4)_3$,[23] $Na_2CaP_2O_7$,[24] $LiClO_4$,[25] $SbCl_3/Al_2O_3$,[26] $InCl_3$,[27] $BiCl_3$,[28] $ZrCl_4$,[29] $FeCl_3$,[30] $SiO_2@TaCl_5$,[31] TiO_2,[32] $Yb(PFO)_3$[33] (bromodimethyl)sulfonium bromide[34] and trimethylanilinium chloride.[35] However, many of the reported synthetic protocols for the synthesis of α-aminophosphonates suffer from one or more disadvantages such as using toxic, expensive and moisture sensitive catalysts, long reaction times, poor yields, harsh reaction conditions, tedious separation procedures and the use of heavy metal catalysts. Therefore, the development of a new catalytic system to overcome these shortcomings and fulfill the criteria of an effective, convenient, and green protocol for the synthesis of α-aminophosphonates is still a challenge.

In recent years, magnetite (Fe_3O_4) nanoparticles have attracted increasing interest due to the interesting properties including a low toxicity, superparamagnetism, biocompatibility, large

surface to volume ratio and wide application range including magnetic resonance imaging, targeted gene therapy, magnetic data storage, drug delivery systems, biosensors, environmental remediation, ion exchange separation, magnetic bioseparations, treatment of cancer and catalysis.[36-40] For many applications, magnetic nanoparticles are suitable because they are chemically stable and uniform in size. Nevertheless, magnetic nanoparticles easily aggregate because of anisotropic dipolar attraction and alter their magnetic properties. Therefore, a protection layer is important to avoid such limitations from occurring.[41] For this purpose, silica has been widely used because of its stability under different reaction conditions and due to the fact that it can be easily functionalized for diverse applications.[42] Recently, surface functionalized magnetic nanoparticles have been developed in a range of organic transformations, and the studies on immobilization of organo catalysts on core-shell nanoparticles have been reported.[43-46]

In our previous study,[47] $H_3PMo_{12}O_{40}$ nanoparticles were synthesized and these nano-heteropolyacids were immobilized onto the imidazole functionalized $Fe_3O_4@SiO_2$ nanoparticles. Compared to other substrates (silica, active carbon, nano-titania and acidic ion-exchange resins), $Fe_3O_4@SiO_2$-imid nanoparticles have various advantages such as low leaching, high loading capacity and simple and efficient recovery procedure. Fig. 1 presents the procedure for the stepwise preparation of $Fe_3O_4@$ SiO_2-imid-PMA^n.

In the present research, we describe an efficient, facile, and convenient procedure for the synthesis of α-aminophosphonates by condensation of various aldehydes with amines and triethyl phosphite in the presence of $Fe_3O_4@SiO_2$-imid-PMA^n in a one-pot three-component synthesis under solvent-free conditions and ultrasonic irradiation at room temperature.

2. Results and discussions

In our previous work,[47] the Fe_3O_4, $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2$-imid-PMA^n nanocatalysts were characterized by various methods such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), Fourier transform infrared (FT-IR), vibrating sample magnetometer (VSM) etc. The presence of vibration bands at 556, 794, 864, 956,1055,1095, 1454 and 2792-2985 cm^{-1} which is due to the Fe–O, Mo–O_e–MO, Mo–O_c–MO, Mo–O_t, P–O, Si–O–Si, C = N and CH bonds respectively, demonstrates the existence of $Fe_3O_4@SiO_2$-imid-PMA^n (Fig. 1).[47] Fig. 1 shows the XRD pattern for $Fe_3O_4@SiO_2$-imid-PMA^n nanoparticles. For $Fe_3O_4@SiO_2$-imid-PMA^n nanoparticles, the presence of the silica and imid-PMA^n layers on the Fe_3O_4 nanoparticles, leads to an amorphous structure and the disappearance of peaks corresponding to Fe_3O_4 and PMA^n.[47] The magnetic properties of nanoparticles were measured by VSM at room temperature. The saturation magnetization of Fe_3O_4, $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2$-imid-PMA^n is 63.4, 39.7, 33.2 emu/g, respectively.[47] As shown in Fig. 1, $Fe_3O_4@SiO_2$-imid-PMA^n nanoparticles have spherical shapes with approximately 50 nm diameters. The size distribution of these is centered at a value of 55 nm.[47]

In continuation of our research work of developing methods in various organic transformations, herein we describe $Fe_3O_4@SiO_2$-imid-PMA^n as a heterogeneous acid catalyst for the synthesis of α-aminophosphonates in a one-pot reaction under solvent-free reaction conditions or ultrasonic irradiation at room temperature (Scheme 1).

Initially, we attempted the one pot coupling of benzaldehyde (1 mmol), aniline (1 mmol), and triethyl phosphite (1.2 mmol) as the model reaction to optimize the reaction conditions. First, we

examined the reaction in the presence of varying amounts of the catalyst. The results are presented in Table 1. The best result was achieved by carrying out the reaction with a (0.015 g: 1 mmol: 1 mmol: 1.2 mmol) ratio of Fe_3O_4@SiO_2-imid-PMA^n catalyst, benzaldehyde, aniline and triethyl phosphite under solvent free conditions at room temperature (Table 1, entry 4). Use of a higher amount of the catalyst did not improve the yield (Table 1, entry 5) while a decrease of the amount of catalyst resulted in lower yields under the same conditions (Table 1, entries 2, 3). The results show clearly that the catalyst is effective for this transformation. In the absence of the catalyst the reaction did not take place even after longer reaction times (Table 1, entry 1).

Then, we conducted the reactions in CH_2Cl_2, $CHCl_3$, CH_3CN, THF, Et_2O, EtOH, C_2H_5OH/H_2O and H_2O as solvents and under solventless conditions (Table 1, entries 4 and 6-13). The presented data in Table 1 show that the reaction proceeded efficiently under solvent-free conditions and resulted in high yields of the desired product (Table 1, entry 4).

To investigate the ability of ultrasonic irradiation for the acceleration of the reaction, we examined the model reaction under ultrasonic irradiation at room temperature and with various amounts of catalyst. As shown in Table 1, the best results were obtained in the presence of 0.005 g of catalyst (Table 1, entry 15).

However, the synthesis of organic compounds under ultrasound irradiation is been limited by the need of a specialized apparatus that may not be available in many laboratories. Because of this limitation, herein we report both ultrasonic irradiation in the presence of 0.005 g of catalyst and also under solvent-free conditions in the presence of 0.015 g of catalyst at room temperature for the synthesis of α-aminophosphonates.

Due to the above observations, a range of various aldehydes and amines was investigated to determine the method's scope and limitations. The results are summarized in Table 2. Aromatic aldehydes substituted with either electron-withdrawing or electron-donating groups underwent the reaction smoothly and gave the products in excellent yields, whereas aliphatic aldehydes afforded phosphonates in good yields, which is expected that aromatic aldehydes have higher reactivity than aliphatic aldehydes. In conclusion, aldehydes bearing electron-withdrawing groups required shorter times and gave higher yields (Table 2). The reactivity of heterocyclic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde with aromatic amines produced the corresponding products in excellent yields (Table 2, entries 20, 21). Moreover, in all of the above cases, ultrasonic irradiation gave comparable yields of products but within shorter reaction times, compared to solvent-free conditions at room temperature.

To demonstrate the value of the present work in comparison with some of the reported catalysts in the literature, the data on the reaction between benzaldehyde, aniline and triethyl phosphite are summarized in Table 3. This study showed that Fe_3O_4@SiO_2-imid-PMA^n performs its catalytic role in a shorter reaction time and gives a higher yield of the desired product under solvent-free conditions and ultrasonic irradiation at room temperature (Table 3, entry 10). Moreover, some of the catalysts listed in Table 3 are not reusable and thus our reusable catalyst and methodologies represent a better alternative compared to the reported methods for the production of the corresponding products.

The magnetic separability of the prepared magnetic catalyst was tested in ethyl acetate solution by placing a magnet beside the glass cylinder. As displayed in Fig. 2a, without an outer magnet, Fe_3O_4@SiO_2-imid-PMA^n prepared could be well dispersed in ethyl acetate solution to form a

suspension. With the aid of an external magnetic field, the nanoparticles were attracted to the magnet and separated easily from the solution, which suggest that the catalyst possesses good separability and magnetism.

The recovery and reusability of the catalyst were examined in the synthesis of α-aminophosphonates (Fig 2b). After the separation of products, the catalyst was washed with ethanol, dried and stored for another consecutive reaction run. The activity of the catalyst did not get much affected in terms of yields after six successive runs for the model reaction. It revealed that the catalyst displayed very good reusability.

SEM and DLS images of the catalyst after the sixth synthesis cycle of α-aminophosphonate **(1a)** under solvent-free conditions at room temperature are shown in Fig. 2c,d. The SEM image shows that the nanoparticles exhibit approximately spherical shapes. Additionally, the hydrodynamic diameter of catalyst was investigated by use of the DLS technique. As shown in Fig. 2d, a narrow size distribution of Fe_3O_4@SiO_2-imid-PMA^n NPs was obtained with a mean diameter of around 65 nm. Generally, the size of catalysts will be increased after each cycle and leaching of $H_3PMo_{12}O_{40}$ and the increase of the catalyst size leads to decreases in the yield.

2. Experimental

2.1. Materials and physical measurements

All chemicals were purchased from Merck, Fluka or Acros Chemical Companies in high purity and used without any further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 MHz Spectrometer in $CDCl_3$ solvent using TMS as an internal standard reference. Fourier transform infrared spectroscopy (FT-IR) analysis of the samples was taken on a Shimadzu FT-IR 8300 spectrophotometer and the sample and KBr were pressed to

form a tablet. Scanning electron microscopy (SEM) image was obtained on Philips XL-30ESEM. Dynamic light scatterings (DLS) were recorded on a HORIBALB550. Sonication was performed using an ultrasound cleaning bath (KQ-250B, China) with a frequency of 30 Hz and voltage of 220 V. Melting points were determined with a Buchi 510 instrument in open capillary tubes and are uncorrected. Determination of the purity of the substrate and monitoring of the reaction were accomplished by thin layer chromatography (TLC) on a silica gel polygram SILG/UV 254 plates. All products were identified by comparison of their spectral data and physical properties with those of the authentic sample and all yields refer to isolated products. The Supplemental Materials contains characterization data and sample ^{1}H and ^{13}C NMR spectra (Figures S 1 -- S 8).

2.2. General procedure

2.2.1. Preparation of Fe_3O_4@SiO_2-imid-PMA^n

Fe_3O_4@SiO_2-imid-PMA^n nanoparticles were prepared in our previous work.[59-64]

2.2.2. General procedure for synthesis of α-aminophosphonates

To a mixture of aldehyde (1 mmol), amine (1 mmol) and triethyl phosphite (1.2 mmol) was added Fe_3O_4@SiO_2-Imid-PMA^n (0.015 g or 0.005 g), and the mixture was stirred under solvent-free conditions or sonicated at room temperature for a particular period of time as given in Table 2. The progress of the reaction was monitored by TLC (eluent: EtOAc/*n*-hexane, 30:70). After the reaction was complete, EtOAc (2×5 mL) was added to the reaction mixture and the catalyst was separated by magnetic field. The filtrate was dried and the organic medium was removed with a rotary evaporator under reduced pressure. The residue was purified by silica gel column

chromatography eluting with *n*-hexane-ethyl acetate (7:3) to afford the corresponding pure α-aminophosphonate.

4. Conclusion

In conclusion, the present communication reports an efficient green synthesis of α-aminophosphonates in excellent yield with short reaction times via one-pot three-component reaction in the presence of Fe_3O_4@SiO_2-imid-PMA^n nanoparticles under solvent free or ultrasound conditions at room temperature. Short reaction time achieved by ultrasonication is an additional advantage of this reaction. This method provides notable advantages such as easy preparation, easy separation, thermal stability, and heterogeneous nature of the catalyst, easy product separation and purification, solvent-free conditions, excellent yields of desired products, short reaction times, lower loading of catalyst compared with the other methods and hence environmentally benign methodology that makes this method a useful and attractive process for the synthesis of these important compounds. In addition, the catalyst was recycled and reused six times by using an external permanent magnet without considerable loss of catalytic activity.

Selected spectral data

Diethyl (phenyl)(phenylamino)methanephosphonate (**1a**)

White solid, M.P. = 85-86°C (lit. 86°C);[32,65] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 1.05 (t, 3H, $J_{H,H}$ = 7.1 Hz, $OCH_2\underline{CH_3}$), 1.28 (t, 3H, $J_{H,H}$ = 7.1 Hz, $OCH_2\underline{CH_3}$), 3.60-3.67 (m, 1H, $OC\underline{H_2}CH_3$), 3.90-3.92 (m, 1H, $OC\underline{H_2}CH_3$), 4.05-4.14 (m, 2H, $OC\underline{H_2}CH_3$), 4.74 (d, 1H, $^2J_{P,H}$ = 26.4 Hz, CHP), 4.82 (br s, 1H, NH), 6.57-6.69 (m, 3H, ArH), 7.04 (t, 2H, $J_{H,H}$ = 7.2 Hz, ArH), 7.22-7.33 (m, 3H, ArH), 7.45-7.47 (d, 2H, $J_{H,H}$ = 7.2 Hz, ArH) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ:* 16.1 (d, $^3J_{C,P}$ = 6.2 Hz, $OCH_2\underline{CH_3}$), 16.3 (d, $^3J_{C,P}$ = 6.2 Hz, $OCH_2\underline{CH_3}$), 54.8 (d, $^1J_{C,P}$ = 150.0 Hz, CP), 63.2 (d,

$^{2}J_{C,P}$ = 6.5 Hz, O<u>CH$_2$</u>CH$_3$), 63.3 (d, $^{2}J_{C,P}$ = 6.5 Hz, O<u>CH$_2$</u>CH$_3$), 113.8, 118.3, 127.8, 127.8, 128.5, 128.5, 129.1, 135.9, 146.2, 146.4 (ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ = 21.066 ppm; MS (70 eV), m/e: 319 (M^+), 182 [M-P(O)(OEt)$_2$]. Anal. Calcd for $C_{17}H_{22}NO_3P$: C, 63.95; H, 6.89; N, 4.39; Found: C, 63.88; H, 6.99; N, 4.30%.

Diethyl (phenyl)-*N*-(4-methylphenylamino)methanephosphonate (1b)

White solid; M.p. = 116 °C (lit.117-118 °C);[33] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.15 (t, 3H, $J_{H,H}$ = 7.0 Hz, OCH$_2$<u>CH$_3$</u>), 1.31 (t, 3H, $J_{H,H}$ = 7.0 Hz, OCH$_2$<u>CH$_3$</u>), 2.21 (s, 3H, CH$_3$), 3.70-3.76 (m, 1H, O<u>CH$_2$</u>CH$_3$), 3.92-4.02 (m, 1H, O<u>CH$_2$</u>CH$_3$), 4.11-4.20 (m, 2H, O<u>CH$_2$</u>CH$_3$), 4.72-4.82 (m, 2H, CH, NH), 6.55 (d, 2H, $J_{H,H}$ = 8.2 Hz, ArH), 6.94 (d, 2H, $J_{H,H}$ = 8.1 Hz, ArH), 7.29-7.38 (m, 3H, ArH), 7.48-7.51 (m, 2H, ArH) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 16.6 (d, $^{3}J_{C,P}$ = 5.8 Hz, OCH$_2$<u>CH$_3$</u>), 16.8 (d, $^{3}J_{C,P}$ = 5.8 Hz, OCH$_2$<u>CH$_3$</u>), 20.76 (CH$_3$), 56.7 (d, $^{1}J_{C,P}$ = 150.4 Hz, CH), 63.6-63.7 (O<u>CH$_2$</u>CH$_3$), 114.4, 128.0-130.1, 136.4, 144.2-144.5 (ArH) ppm; MS (70 eV), m/e: 333 (M^+), 196 [M – diethyl(phenyl)-*N*-(phenyl)aminomethanephosphonate P(O)(OEt)$_2$]; Anal. Calcd for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20; Found: C, 64.79; H, 7.21; N, 4.13%.

Diethyl (4-hydroxyphenyl)(phenylamino)methanephosphonate (1e)

Viscous colorless oil;[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.89 (t, 3H, $^{2}J_{H,H}$ = 7.1 Hz, OCH$_2$C<u>H$_3$</u>), 1.04-1.12 (t, 3H, $J_{H,H}$ = 7.1 Hz, OCH$_2$C<u>H$_3$</u>), 3.48-3.54 (m, 1H, OC<u>H$_2$</u>CH$_3$), 3.70-3.76 (m, 1H, OC<u>H$_2$</u>CH$_3$), 3.84-3.91 (m, 2H, OC<u>H$_2$</u>CH$_3$), 4.55 (d, 1H, $^{2}J_{P,H}$ = 23.6 Hz, CHP), 4.96 (s, 1H, PhOH), 5.45 (br s, 1H, NH), 6.40-6.50 (m, 3H, ArH), 6.64 (d, 2H, $J_{H,H}$ = 6.5 Hz, ArH), 6.86 (d, 2H, $J_{H,H}$ = 7.1 Hz, ArH), 7.08 (d, 2H, $J_{H,H}$ = 6.5 Hz, ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ = 21.29 ppm; Anal. calcd for $C_{17}H_{22}NO_4P$: C, 60.89; H, 6.61; N, 4.18; Found: C, 60.77; H, 6.54; N, 4.09%.

Diethyl (4-methoxyphenyl)(phenylamino)methanephosphonate (**1f**)

Viscous colorless oil;[52,65] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 1.10, (t, 3H, $J_{H,H}$ = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.24, (t, 3H, $J_{H,H}$ = 7.1 Hz, $OCH_2\underline{CH_3}$), 3.75 (s, 3H, $O\underline{CH_3}$), 3.67-3.71, (m, 1H, $O\underline{CH_2}CH_3$), 3.89-3.96, (m, 1H, $O\underline{CH_2}CH_3$), 4.06-4.14, (m, 2H, $O\underline{CH_2}CH_3$), 4.67-4.76 (m, 2H, CHP, NH), 6.57-6.70 (m, 3H, ArH), 6.83 (d, 2H, $J_{H,H}$ = 10.0 Hz, ArH), 7.06 (t, 2H, $J_{H,H}$ = 7.5, ArH), 7.35-7.40 (m, 2H, ArH) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ:* 16.2 (d, $^{3}J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 16.4 (d, $^{3}J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 54.1 (d, $^{1}J_{C,P}$ = 150.0 Hz, CP), 55.2 ($O\underline{CH_3}$), 63.2 (d, $^{2}J_{C,P}$ = 6.5 Hz, $O\underline{CH_2}CH_3$), 113.9, 114.1, 118.3, 127.6, 128.9, 129,0, 129.1, 146.2, 146.5, 159.3 (ArH) ppm; IR (KBr, Cm^{-1}): 3292 (NH), 1231 (P = O), 1049 (P-OEt); ^{31}P NMR (120 MHz, $CDCl_3$): *δ* = 21.284 ppm; MS (70 eV), m/e: 349 (M^+), 212 [M-P(O)$(OEt)_2$]; Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01; Found: C, 61.79; H, 6.98; N, 3.94%.

Diethyl(4-methoxyphenyl)(4-methoxyphenylamino)methanephosphonate (1h)

White solid, M.p. = 120-121°C (lit. 118°C);[32] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 1.09 (t, 3H, $J_{H,H}$ = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.27 (t, 3H, $J_{H,H}$ = 7.0 Hz, $OCH_2\underline{CH_3}$), 3.40 (s, 6H, $O\underline{CH_3}$), 3.62-3.70 (m, 1H, $O\underline{CH_2}CH_3$), 3.87-3.92 (m,1H, $O\underline{CH_2}CH_3$), 4.03-4.12 (m, 2H, $O\underline{CH_2}CH_3$), 4.62 (d,1H, $^{2}J_{P,H}$ = 24.2 Hz, CHP), 5.45 (br s, 1H, -NH), 6.51 (d, 2H, $J_{H,H}$ = 7.5 Hz, ArH), 6.67 (d, 2H, $J_{H,H}$ = 7.2 Hz, ArH), 6.96 (d, 2H, $J_{H,H}$ = 8.5 Hz, ArH), 7.20 (d, 2H, $J_{H,H}$ = 8.5 Hz, ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$) *δ* = 22.3 ppm; MS (70 eV), m/e: 379, 253, 241, 226, 171, 184, 128, 92, 77; Anal. Calcd for $C_{19}H_{26}NO_5P$: C, 60.16; H, 6.86; N, 3.69; Found: C, 60.05; H, 6.76; N, 3.61%.

Diethyl (4-methoxyphenyl) (4-nitrophenyl amino)methanephosphonate (1i)

Yellow solid, M.p. = 114-115°C (lit. 115°C);[66] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 0.89 (t, 3H, J_{HH} = 7.1 Hz, $OCH_2\underline{CH_3}$), 0.97 (t, 3H, J_{HH} = 7.1 Hz, $OCH_2\underline{CH_3}$), 3.42 (s, 3H, PhOMe), 3.81-3.90 (m,

4H, O$\underline{CH_2}CH_3$), 4.55 (d, 1H, $^{2}J_{HP}$ = 23.7 Hz, CHP), 6.38 (d, 2H, $J_{H,H}$ = 9.1 Hz, ArH), 6.55 (d, 2H, $J_{H,H}$ = 8.5 Hz, ArH), 6.65 (br s, 1H, NH), 7.13 (dd, 2H, $J_{H,H}$ = 8.5, 2.1 Hz, ArH), 7.96 (d, 2H, $J_{H,H}$ = 9.1 Hz, ArH); ^{31}P NMR (120 MHz, $CDCl_3$) δ = 22.2 ppm; Anal. Calcd for $C_{18}H_{23}N_2O_6P$: C, 54.82; H, 5.88; N, 7.10; Found: C, 54.78; H, 5.83; N, 7.06%.

Diethyl (phenylamino)(p-tolyl)methanephosphonate (1l)

White solid, M.p. = 61-62°C (lit. 60°C);[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.97 (t, 3H, $J_{H,H}$ = 7.0 Hz, OCH$_2\underline{CH_3}$),1.10 (t, 3H, $J_{H,H}$ = 7.0 Hz, OCH$_2\underline{CH_3}$), 2.12 (s, 3H, Ph$\underline{CH_3}$), 3.52-3.55 (m, 1H, O$\underline{CH_2}CH_3$), 3.73-3.80 (m, 1H, O$\underline{CH_2}CH_3$), 3.92-4.00 (m, 2H, O$\underline{CH_2}CH_3$), 4.61 (d, 1H, $^{2}J_{P,H}$ = 24.1 Hz, CHP), 4.97 (br s, 1H, NH), 6.44-6.53 (m, 3H, ArH), 6.79-7.02 (m, 4H, ArH), 7.22 (d, 2H, ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$) δ = 19.89 ppm; Anal. Calcd for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20; Found: C, 64.78; H, 7.21; N, 4.16%.

Diethyl (4-chlorophenyl)(phenylamino)methanephosphonate (1m)

White solid, M.p. = 55-57°C (lit. 57°C);[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.12 (t, 3H, $J_{H,H}$ = 7.1 Hz, OCH$_2\underline{CH_3}$), 1.25 (t, 3H, $J_{H,H}$ = 7.1 Hz, OCH$_2\underline{CH_3}$), 3.69-3.79 (m, 1H, O$\underline{CH_2}CH_3$), 3.96-4.0 (m, 1H, O$\underline{CH_2}CH_3$), 4.09-4.15 (m, 2H, O$\underline{CH_2}CH_3$), 4.60-4.77 (m, 2H, CHP, NH), 6.54 (d, 2H, $J_{H,H}$ = 7.8 Hz, ArH), 6.57 (t, 1H, $J_{H,H}$ = 7.3 Hz, ArH), 7.03 (t, 2H, $J_{H,H}$ = 7.8 Hz, ArH), 7.28-7.32 (m, 2H, ArH), 7.39-7.43 (m, 2H, ArH) ppm; ^{13}CNMR (62.9 MHz, $CDCl_3$) δ: 16.2 (d, $^{3}J_{C,P}$ = 5.6 Hz, OCH$_2\underline{CH_3}$), 16.4 (d, $^{3}J_{C,P}$ = 5.6 Hz, OCH$_2\underline{CH_3}$), 54.3 (d, $^{1}J_{C,P}$ = 150, CP), 63.3 (d, $^{2}J_{C,P}$ = 6.5 Hz, O$\underline{CH_2}CH_3$), 63.4 (d, $^{2}J_{C,P}$ = 6.5 Hz, O$\underline{CH_2}CH_3$), 113.8, 118.6, 128.8, 129.1, 129.2, 129.2, 133,7, 134.6, 145.8, 146.1 (ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$) δ = 20.00 ppm; MS (70 eV), m/e: 353 (M^+), 355 (M^{+2}), 216 [M-P(O)(OEt)$_2$]; Anal. Calcd for $C_{17}H_{21}ClNO_3P$: C, 57.72; H, 5.98; N, 3.96; Found: C, 57.64; H, 5.91; N, 3.88%.

Diethyl (2-chlorophenyl)(phenylamino)methanephosphonate (1n)

White solid, M.p. = 89 °C (lit. 88-90°C);[66] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 0.95 (t, 3H, $J_{H,H}$ = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.20 (t, 3H, $J_{H,H}$ = 6.9 Hz, $OCH_2\underline{CH_3}$), 3.53-3.56 (m,1H, $O\underline{CH_2}CH_3$), 3.75-3.82 (m, 1H, $O\underline{CH_2}CH_3$), 4.09- 4.15 (m, 2H, $O\underline{CH_2}CH_3$), 5.33 (d, 1H, $^{2}J_{H,P}$ = 24.8 Hz, CHP), 6.4 (br s, 1H, NH), 6.56 (d, 2H, $J_{H,H}$ = 7.8 Hz, ArH), 6.58 (t, 1H, $J_{H,H}$ = 7.2 Hz, ArH), 6.95-7.10 (m, 6H, ArH); ^{31}P (120 MHz, $CDCl_3$): δ = 20.01 ppm; Anal. Calcd for $C_{17}H_{21}ClNO_3P$: C, 57.72; H, 5.98; N, 3.96; Found: C, 57.65; H, 5.91; N, 3.89%.

Diethyl (4-bromophenyl)(phenylamino)methanephosphonate (1o)

White solid; M.p. = 66-67 °C (lit. 66-68°C);[59] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 1.17 (t, 3H, $J_{H,H}$ = 8.75 Hz, $OCH_2\underline{CH_3}$), 1.28 (t, 3H, $J_{H,H}$ = 8.75 Hz, $OCH_2\underline{CH_3}$), 3.69-3.79 (m, 1H, $O\underline{CH_2}CH_3$), 4.09-4.13 (m, 3H, $O\underline{CH_2}CH_3$), 4.66-4.76 (m, 2H, CHP, NH), 6.53-6.57 (m, 3H, ArH), 7.10 (t, 2H, $J_{H,H}$ = 7.5 Hz, ArH), 7.33-7.76 (m, 4H, ArH) ppm; ^{13}CNMR (62.9 MHz, $CDCl_3$) *δ:* 16.2 (d, $^{3}J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 16.4 (d, $^{3}J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 54.4 (d, $^{1}J_{C,P}$ = 150, CP), 63.2 (d, $^{2}J_{C,P}$ = 6.5 Hz, $O\underline{CH_2}CH_3$), 63.4 (d, $^{2}J_{C,P}$ = 6.5 Hz, $O\underline{CH_2}CH_3$), 113.8, 118.6, 121.8, 121.9, 129.2, 129.4, 129.5, 131,7, 131.8, 135.1, 145.8, 146.1 (ArH) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ = 20.197 ppm; MS (70 eV), m/e: 399, 397 (M^+); Anal. Calcd for $C_{17}H_{21}BrNO_3P$: C, 51.27; H, 5.28; N, 3.52; Found: C, 57.18; H, 5.21; N, 3.43%.

Diethyl (4-nitrophenyl)(phenylamino)methanephosphonate (1q)

Bright yellow solid, M.p. = 121-122°C (lit. 120°C);[32] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 1.16 (t, 3H, $J_{H,H}$ = 6.9 Hz, $OCH_2\underline{CH_3}$), 1.26 (t, 3H, $J_{H,H}$ = 6.9 Hz, $OCH_2\underline{CH_3}$), 3.86-4.17 (m, 4H, $O\underline{CH_2}CH_3$), 4.90 (d, 1H, $^{2}J_{P,H}$ = 25.2 Hz, CHP), 5.21 (br s, 1H, NH), 6.55 (d, 2H, $J_{H,H}$ = 7.7 Hz, ArH), 6.67 (t, 1H, $J_{H,H}$ = 7.1 Hz, ArH), 7.06 (t, 2H, $J_{H,H}$ = 7.1 Hz, ArH), 7.66 (dd, 2H, $J_{H,H}$ = 8.5,

2.2 Hz, ArH), 8.13 (d, 2H, $J_{H,H}$ = 8.5 Hz, ArH) ppm; IR (KBr, cm^{-1}): 3287 (NH), 1232 (P = O), 1054 (P-OEt); ^{31}P (120 MHz, $CDCl_3$): δ = 21.4 ppm; MS (70 eV), m/e: 364.12 (M^+), 226; Anal. Calcd for $C_{17}H_{21}N_2O_5P$: C, 56.04; H, 5.81; N, 7.69; Found: C, 55.91; H, 5.73; N, 7.52%.

Diethyl (3-nitrophenyl)(phenylamino)methanephosphonate (1s)

Yellow crystalline solid, M.p. = 97-98°C(lit. 95-97°C);[33] ^1H NMR (250 MHz, $CDCl_3$) δ: 1.09 (t, 3H, $J_{H,H}$ = 7.0Hz, $OCH_2\underline{CH_3}$); 1.20 (t, 3H, $J_{H,H}$ = 7.0 Hz, $OCH_2\underline{CH_3}$), 3.73-4.15 (m, 4H, $O\underline{CH_2}CH_3$), 4.82 (d, 1H, $^2J_{P,H}$ = 24.8 Hz, CHP), 5.46 (br s, 1H, NH), 6.48-6.65 (m, 3H, ArH), 7.01 (t, 2H, $J_{H,H}$ = 7.8 Hz, ArH), 7.40 (t, 1H, $J_{H,H}$ = 7.5 Hz, ArH), 7.76 (d, 1H, $J_{H,H}$ = 7.7 Hz, ArH), 8.05 (d, 1H, $J_{H,H}$ = 9.5 Hz, ArH), 8.29 (s, 1H, ArH) ppm; ^{13}C NMR (62.9 MHz,$CDCl_3$) δ: 16.2 (d, $^3J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 16.4 (d, $^3J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_3}$), 56.7 (d, $^1J_{C,P}$ = 150.1 Hz, CP), 63.4 (d, $^2J_{C,P}$ = 6.9 Hz, $O\underline{CH_2}CH_3$), 63.8 (d, $^2J_{C,P}$ = 6.9 Hz, $O\underline{CH_2}CH_3$), 113.7, 118.8, 122.8, 122.9, 129.2, 133.8, 133.9, 138.8, 138.9, 145.6, 145.8, 148.4 (ArH) ppm; Anal. Calcd for $C_{17}H_{21}N_2O_5P$: C, 56.04; H, 5.81; N, 7.69; Found: C, 55.95; H, 5.71; N, 7.55%.

Diethyl (phenylamino)(thiophen-2-yl)methanephosphonate (1u)

White solid, M.p. = 68-69°C (lit. 70°C);[32] ^1H NMR (250 MHz, $CDCl_3$) δ: 0.78 (t, 3H, $J_{H,H}$ = 7.1 Hz, $OCH_2\underline{CH_3}$), 1.10 (t, 3H, $J_{H,H}$ = 7.1 Hz, $OCH_2\underline{CH_3}$), 3.82-4.11 (m, 4H, $O\underline{CH_2}CH_3$), 4.5 (1H, NH), 4.97 (d, 1H, $^2J_{P,H}$ = 23.65 Hz, CHP), 6.68-6.70 (m, 3H, ArH), 6.89-6.91 (m, 1H, ArH), 7.04-7.15 (m, 4H, ArH) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 16.3 (d, $^3J_{C,P}$ = 5.8 Hz, $OCH_2\underline{CH_3}$), 16.4 (d, $^3J_{C,P}$ = 5.8 Hz, $OCH_2\underline{CH_3}$), 52.1 (d, $^1J_{C,P}$ = 158.2 Hz, CP), 63.4 (d, $^2J_{C,P}$ = 7.0 Hz, $O\underline{CH_2}CH_3$), 63.6 (d, $^2J_{C,P}$ = 7.0 Hz, $O\underline{CH_2}CH_3$), 114.0, 118.9, 124.0, 125.2, 126.1, 127.1, 129.2, 139.9, 146.1 (ArH) ppm; MS (70 eV): m/e = 325 [M^+], 188 [M-P(O)$(OEt)_2$]; Anal. Calcd for $C_{15}H_{20}NO_3PS$: C, 55.37; H, 6.20; N, 4.31; Found: C, 55.30; H, 6.13; N, 4.26%.

Diethyl (n-propyl)-*N*-(phenyl)aminomethanephosphonate (1w)

Viscous colourless oil;[52] ^{1}H NMR (250 MHz, $CDCl_3$) *δ:* 0.84 (t, 3H, $J_{H,H}$ = 7.2 Hz, CH_3), 1.09-1.24 (m, 6H, $OCH_2\underline{CH_3}$), 1.50-1.82 (m, 4H, $(\underline{CH_2})_2CH_3$), 3.60-3.65 (m, 2H, NH, CHP), 3.94-4.09 (m, 4H, $O\underline{CH_2}CH_3$), 6.58 (d, 2H, $J_{H,H}$ = 8.2 Hz, ArH), 6.65 (d, 1H, $J_{H,H}$ = 7.4 Hz, ArH), 7.09 (t, 2H, $J_{H,H}$ = 7.6 Hz, ArH) ppm; MS (70 eV), m/e: 285 (M^+), 148 [M-P(O)$(OEt)_2$]; Anal. Calcd for $C_{14}H_{24}NO_3P$: C, 58.93; H, 8.48; N, 4.91; Found: C, 58.85; H, 8.41; N, 4.84%.

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Table 1. Optimization of the amount of catalyst and solvent in a one-pot synthesis of the model reaction.[a]

Entry	Catalyst amount (g)	Solvent	Conditions	Time (min)	Yield (%)[b]
1	-	Solvent-Free	$P(OEt)_3$	120	-
2	0.005	Solvent-Free	$P(OEt)_3$	30	77
3	0.01	Solvent-Free	$P(OEt)_3$	30	92
4	0.015	Solvent-Free	$P(OEt)_3$	20	96
5	0.02	Solvent-Free	$P(OEt)_3$	20	93
6	0.015	CH_2Cl_2	$P(OEt)_3$	20	86
7	0.015	$CHCl_3$	$P(OEt)_3$	30	81
8	0.015	CH_3CN	$P(OEt)_3$	60	78
9	0.015	THF	$P(OEt)_3$	60	73
10	0.015	Et_2O	$P(OEt)_3$	60	67
11	0.015	C_2H_5OH	$P(OEt)_3$	60	78
12	0.015	C_2H_5OH/H_2O	$P(OEt)_3$	80	66
13	0.015	H_2O	$P(OEt)_3$	80	64
14	0.015	Solvent-Free	$HP(O)(OEt)_2$	70	82
15	0.005	Solvent-Free	Sonication (30 kHz)/$P(OEt)_3$	4	98
16	0.01	Solvent-Free	Sonication (30 kHz)/$P(OEt)_3$	4	96

[a]Reaction condition: benzaldehyde (1 mmol), aniline (1 mmol) and triethyl phosphate (1.2 mmol).

[b]Isolated yield.

Table 2. One-pot synthesis of α-aminophosphonate catalyzed by Fe_3O_4@SiO_2-imid-PMA[n].[a]

Entry	R_1	R_2	Product	Solvent free/rt		Ultrasonic/Solvent free/rt		Ref.
				Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]	
1	C_6H_5	C_6H_5	**1a**	20	96	2	98	[32]
2	C_6H_5	*p*-MeC_6H_4	**1b**	20	93	3	96	[33]
3	C_6H_5	*p*-$NO_2C_6H_4$	**1c**	30	90	8	93	[48]
4	C_6H_5	$C_6H_5CH_2$	**1d**	20	92	5	95	[49]
5	*p*-HOC_6H_4	C_6H_5	**1e**	30	91	4	92	[32]
6	*p*-$MeOC_6H_4$	C_6H_5	**1f**	40	94	5	94	[32]
7	*o*-MeC_6H_4	C_6H_5	**1g**	40	92	7	95	[50]
8	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**1h**	20	95	3	97	[32]
9	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	**1i**	60	92	9	94	[49]
10	*p*-MeC_6H_4	*n*-Butyl	**1j**	20	93	3	92	[50]
11	*p*-MeC_6H_4	*p*-MeC_6H_4	**1k**	30	91	5	95	[51]
12	*p*-MeC_6H_4	C_6H_5	**1l**	30	89	6	92	[32]
13	*p*-ClC_6H_4	C_6H_5	**1m**	15	95	2	97	[32]
14	*o*-ClC_6H_4	C_6H_5	**1n**	30	92	4	91	[32]
15	*p*-BrC_6H_4	C_6H_5	**1o**	20	95	7	95	[51]
16	*p*-BrC_6H_4	*p*-MeC_6H_4	**1p**	15	95	4	97	[51]
17	*p*-$NO_2C_6H_4$	C_6H_5	**1q**	15	96	2	95	[32]
18	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	**1r**	30	88	6	91	[48]
19	*m*-$NO_2C_6H_4$	C_6H_5	**1s**	20	94	2	96	[48]
20	Furfuryl	C_6H_5	**1t**	40	86	8	91	[48]
21	2-Thiophene	C_6H_5	**1u**	45	91	8	93	[32]
22	*n*-Propyl	*p*-$MeOC_6H_4$	**1w**	45	76	12	85	[52]

[a]Reaction condition: aldehyde (1 mmol), amine (1 mmol), triethyl phosphite (1.2 mmol), Fe_3O_4@SiO_2-imid-PMA^n (0.015 g), solvent free, room temperature or ultrasonic irradiation (30 kHz), Fe_3O_4@SiO_2-imid-PMA^n (0.005 g).

[b]Isolated yield.

Table 3. Comparison of the catalytic activity of Fe_3O_4@SiO_2-imid-PMA^n with the reported catalysts in the preparation of diethyl (phenyl)(phenylamino)methanephosphonate (**1a**).

Entry	Catalyst	Condition	Time (min)	Yield (%)[a]	Ref.
1	$NbCl_5$	Solvent-free/50°C	30	95	[53]
2	TiO_2	Solvent-free/50°C	3.5h	98	[32]
3	Choline chloride·2$ZnCl_2$	Solvent-free/r.t	60	96	[54]
4	MNP@DSO_3H	Solvent-free/rt	25min	91	[48]
5	$CeCl_3.7H_2O$	Solvent-free/rt	5h	95	[55]
6	Nano-Fe_3O_4	Solvent-free/50°C	48	94	[56]
7	[Cu(3,4-tmtppa)]$(MeSO_4)_4$	H_2O, 80^{o}C	30	96	[52]
8	Sodium 1-hexanesulfonate	Solvent-free/rt	60	75	[57]
		Ultrasonic/Solvent-free/rt	15	94	
9	CeO_2	Ultrasonic/Solvent-free/rt	5	99	[58]
10	Fe_3O_4@SiO_2-imid-PMA^n	Solvent free/r.t	20	96	This work
		Ultrasonic/Solvent-free/rt	2	98	

[a]Isolated yield

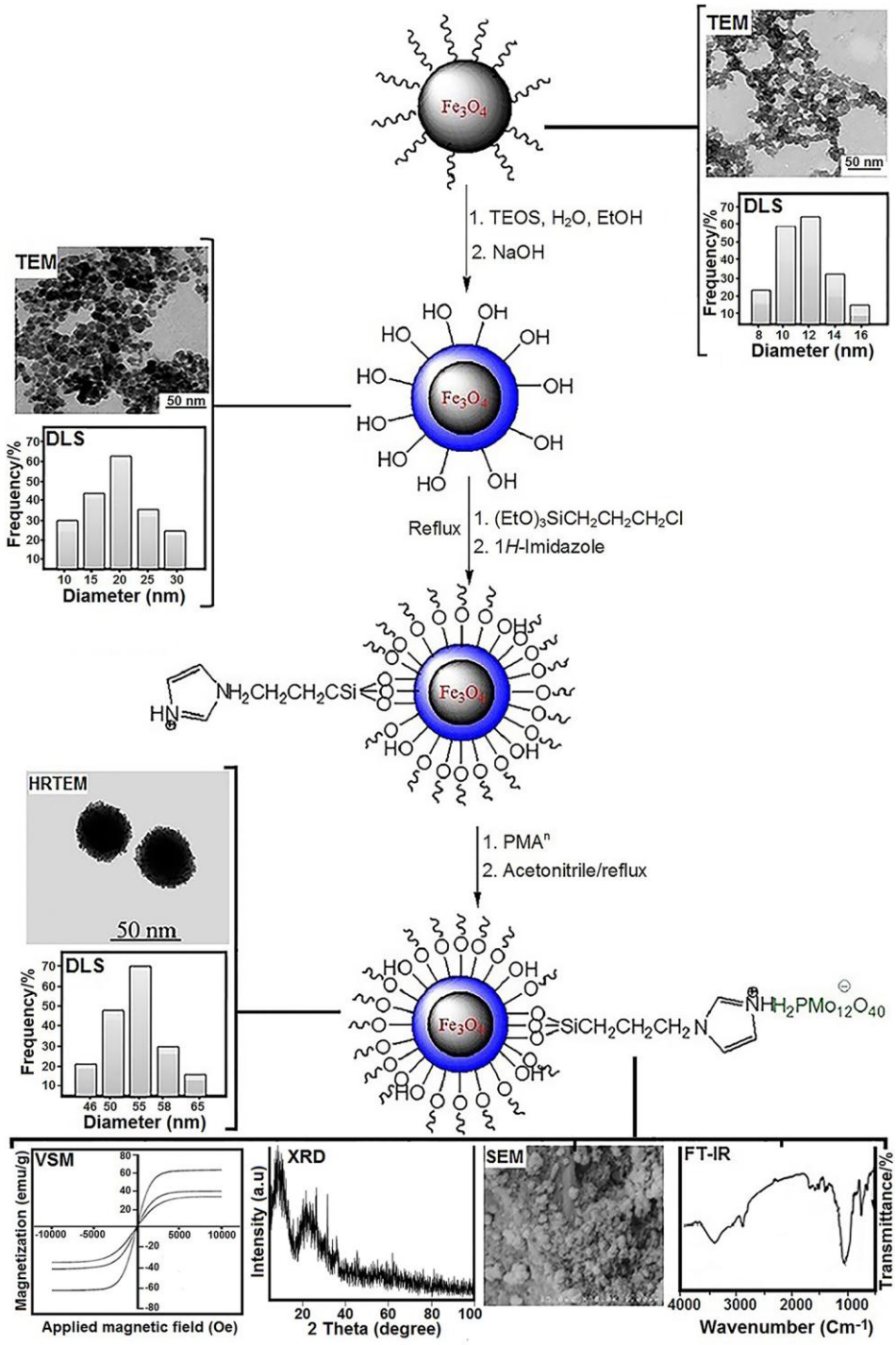


Fig 1. Process for the preparation and immobilization of $H_3PMo_{12}O_{40}$ nanoparticles (PMA^n) on imidazole functionalized $Fe_3O_4@SiO_2$ nanoparticles.

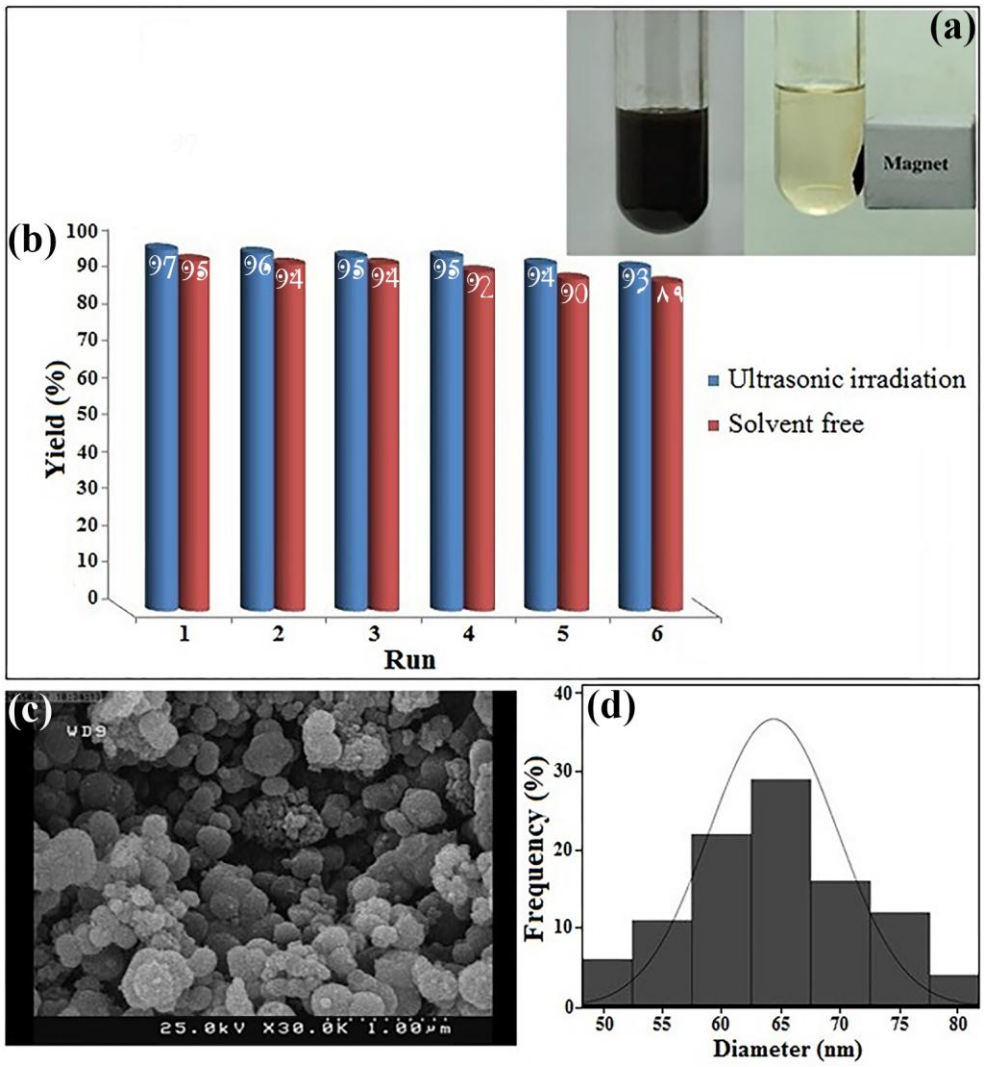
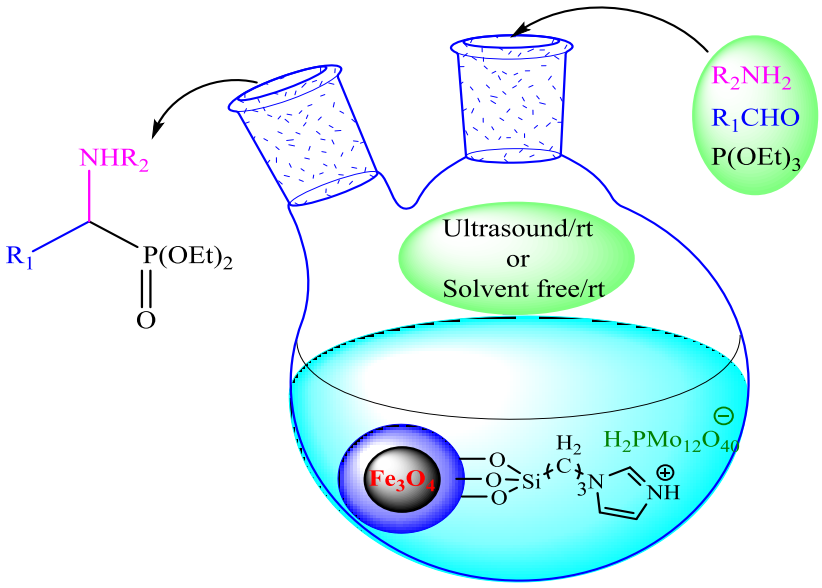


Fig 2. (a) Recyclability of Fe_3O_4@SiO_2-Imid-PMA^n in the synthesis of **1a**; **(b)** Photographs of the separation and re-dispersion processes of Fe_3O_4@SiO_2-Imid-PMA^n without external magnetic field and with external magnetic field; **(c)** and **(d)** SEM and DLS images of Fe_3O_4@SiO_2-imid-PMA^n nanoparticles after six reaction cycles.



Scheme 1. Fe_3O_4@SiO_2-imid-PMA^n catalyzed synthesis of α-aminophosphonates.