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REGULAR ARTICLE

A new procedure for synthesis of α-aminophosphonates by aqueous formic acid as an effective and environment-friendly organocatalyst

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Abstract. Aqueous formic acid (37%) as a green organocatalyst was used to synthesis of α-aminophosphonates in one-pot, three-component Kabachnik–Fields reaction. The structures of compounds were determined by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. After optimization of the experimental conditions, the reaction was carried out at 65 °C under solvent- free condition. Use of a nontoxic effective organocatalyst, easy work up process and low-cost cleaning procedure are from the main advantages of this research.

Keywords. Organocatalyst; α-aminophosphonate; formic acid; kabachnik–fields reaction; green chemistry.

1. Introduction

The α-aminophosphonates and their derivatives are very useful compounds with wide range of applications in organic chemistry especially in medicinal chemistry.[1] A large number of α- aminophosphonate derivatives are known as antiviral,[2] antifungal,[3] antibacterial[4] and anti-tumor[5] agents. Thus, they form an important class of compounds with diverse biological activities (Figure 1).

Some other activities such as peptidomimetic,[6] enzyme inhibitors,[7] pharmacogenic agent,[8] haptens of catalytic antibodies,[9] inhibitors of UDP-galactopyranose mutase[10] and antitumor agents[11–13] have been recognized for these compounds. Some of significant studies for synthesis of α- aminophosphonate derivatives are such as: synthesis of di or tri-alkyl phosphite derivatives,[14] hydrogenation of aziridinylphosphonate,[15] aldol-type reactions of (isocyanomethyl) phosphonates with aldehydes,[16] addition of phosphites to sulphimines[17] and catalyzed Mannich-type reaction.[18] Among the versatile procedures, the Kabachnik - Fields reaction is one of the basic methods for preparation of α-aminophosphonate which was discovered in 1952 independently by Kabachnik[19] and Fields.[20] Recently some new researches have been reported for promotion of one-pot Kabachnik-Fields reaction such as microwave irradiation, heating[21] and acidic or basic catalysts. Some Lewis acid catalysts, such as $ZrOCl_2 \cdot 5H_2O$,[22] $Mg(ClO_4)_2$,[23] $FeCl_3$,[24] $Al(H_2PO_4)$,[25] $BiCl_3$,[26] $InCl_3$,[27] $YbCl_3$,[28] $In(OTf)_3$,[29] $Ce(OTf)_4$,[30] $Fe_3O_4@ZrO_2/SO_4^{2-}$,[31] CAN,[32] $TaCl_5SiO_2$,[33] SmI_2,[34] $LiClO_4$,[35] and some solid acids (montmorillonite KSF), silica sulphuric acid, and also some base catalysts like $CaCl_2$, PPh_3 and other catalysts such as ZnO, TiO_2, tosyl chloride and mesoporous aluminosilicate nanocage[36] have been used to succeed this reaction. In spite of all researches, still there are some serious limitations such as hard work up process, long reaction time and expensive and toxic catalyst in these methods. With regard to importance of removal of toxic and hazardous catalysts from organic reactions, we decided to introduce formic acid as an efficient and green organocatalyst for synthesis of α-aminophosphonates with interesting specifications in Kabachnik-Fields reaction. Formic acid is a colourless liquid with a pungent, penetrating odour and often used in an aqueous solution. Formica, is Latin word of ant and name of formic acid has been derived from its root referring to its early isolation by the distillation of ants' bodies. In nature, formic acid has been found in the stings and bites

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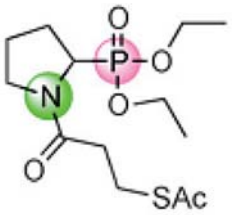
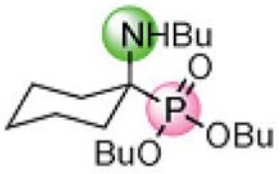


S-(3-(2-(diethoxyphosphoryl)pyrrolidin-1-yl)-3-oxopropyl)ethanethioate

Anti-hypertensive agent



Dibutyl (1-(butylamino)cyclohexyl)-phosphonate

Herbicidal activity

Figure 1. α- aminophosphonate with biological activities.

of many insects of the order Hymenoptera, including bees and ants. Furthermore formic acid is used as a preservative and antibacterial agent in livestock feed. Also it has been known as an important intermediate in chemical synthesis. In synthetic organic chemistry, it is used as a source of hydride ion which has been reported in some reactions like Eschweiler-Clarke and the Leuckart-Wallach. So its azeotrope with triethylamine is applied as a source of hydrogen in transfer hydrogenation. Sometime formic acid is employed as a volatile pH modifier in HPLC and capillary electrophoresis like acetic acid and trifluoroacetic acid. Also, formic acid can be a convenient source of carbon monoxide by being readily decomposed by sulphuric acid. Another important chemical activity of formic acid, is its useas reductant in combination with a catalyst, for the transfer hydrogenation of anilines[37] and reduction of alkynes can selectively produce cis, trans-alkenes and alkanes,[38] α-substituted acetophenones,[39] β-keto esters[40] and nitroarenes. In aspect of physical description it is a strong oxidizer, and with strong caustic properties. In our previous work, we showed formic acid as an efficient organocatalyst for synthesis of imines and α-aminonitriles in Strecker reaction.[41] In this work, in order to favour environmental considerations, we used aqueous formic acid as a green organocatalyst in the synthesis of α-aminophosphonates through kabachnik - field reaction.

2. Experimental

All of the chemicals were obtained from Merck and used without further purification. Infrared (IR) spectra were obtained on a Shimadzu FT-IR-8400S spectrophotometer using a KBr pellet. Melting points were measured by an Electro thermal 9100 apparatus. Analytical TLC was performed on Merck 0.2 mm silica gel 60 F-254 Al-plates. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker DRX-500 Avance, Bruker DRX-400 Avance and Bruker DRX-250 Avance spectrometers at ambient temperature, respectively.

2.1 *General procedure for the synthesis of α-aminophosphonate*

For synthesis of α-aminophosphonate **1c**, in a 5 mL dry balloon, a mixture of 15 μL catalyst (formic acid (37%)) and 1 mmol aldehyde was combined, after that 1 mmol amine and 1.2 mmol dimethylphosphite were added to the mixture. The reaction proceeds under solvent free condition and 65 °C temperature for a period of time on a vigorous magnetic stirrer. The progress of reaction by TLC in solvent samples 1: 1 hexane / ethyl acetate was followed. Finally, after completion of the reaction, the solid product was filtered, washed with deionized water. After recrystalization it was dried at room temperature.

2.2 *Spectral data of representative compounds*

2.2a *Dimethyl [(phenyl) (phenylamino) methyl] phosphonate* **1a**: M.p.: 90–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (d, J = 10.8 Hz, 3H), 3.89 (d, J = 11.2 Hz, 3H), 5.86 (m, 1H), 5.93 (d, 1H), 7.28-8.09 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 53.70 (d, $^2J_{P,C}$ = 6.7 Hz), 54.4 (d, $^2J_{P,C}$ = 7.6 Hz), 54.7 (d, $^1J_{P,C}$ = 152.0 Hz), 114.3, 118.7, 123.0, 128.1, 129.0 (d, $^2J_{P,C}$ = 4.4 Hz),131.0, 134.7 (d, $^2J_{P,C}$ = 2.5 Hz), 146.6 (d,$^2J_{P,C}$ = 14.9 Hz) ppm.

2.2b *Dimethyl[(2-chlorophenyl)(phenylamino) methyl]phosphonate* **1b**: M.p.: 128–129 °C, FT-IR (KBr, ν_{max} cm^{-1}); 3311(N-H), 1602, 1519, 1232, 1033; ^{1}H NMR ($CDCl_3$, 500 MHz) = 3.4 (d, J = 10.4 Hz, 3H), 3.8 (d, J = 10.7 Hz, 3H), 5.0 (br, NH, 1H), 5.36 (d, J = 24.6 Hz, 1H), 6.6 (d, J = 7.6 (m, 9H).^{13}C NMR ($CDCl_3$, 125 MHz): 51. 04, 52.26, 54.24 (m), 114. 02, 119.13, 127.87, 129.39, 129.72, 130.05, 134.18, 134.41 (d, $^2J_{P,C}$ =7.12 Hz), 145.87 (d, $^2J_{P,C}$ = 14.7 Hz).

2.2c *Dimethyl [(4-chlorophenyl) (phenylamino) methyl] phosphate* **1c**: M.p.: 139-140 °C, IR (KBr, ν_{max} cm^{-1}): 3319(N-H), 1602, 1494, 1232, 1033; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3. 55 (d, J = 10.8 Hz, 3H), 3.79 (d, J = 10.5 Hz, 3H), 4.98(d, $^1J_{P-H}$ = 24 Hz, 1H), 7.3-8.2 (m, 9H). ^{13}C NMR (125MHz, $CDCl_3$): δ = 53.8, 54.2, 56.1, 114.3,

126.8, 128.2(d, $^{3}J_{p-c} = 5.5$ Hz), 128.4 (d, $^{3}J_{p-c} = 3.0$ Hz), 131.1, 132.2, 141.0, 146.6 (d, $^{2}J_{p-c} = 14.5$ Hz) ppm.

2.2d *Dimethyl (4-Dimethyl amino phenyl) (N-phenylamino) methylphosphonate* **1d:**: M.p.: 144 °C; IR (KBr, ν_{max} cm^{-1}); 3446, 2926, 1350, 1251, 1167, 1030. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.12$ (s, 1H), 2.93 (s, 6 H), 3.51(d, $J = 10.4$ Hz, 3 H), 3.78 (d, $J = 10.4$ Hz, 3 H), 4.70 (d, $^{1}J_{P-H} = 23.6$ Hz, 2 H), 6.63(d, d, $J = 8.6$ Hz, $J = 0.8$ Hz, 2 H), 6.68 (m, 3 H), 7.12(m, 2 H), 7.32(t, t $J = 6.8$ Hz, $J = 2$ Hz, 2 H) ppm.

2.2e *Dimethyl(4- methoxy phenyl)(N-phenylamino) methylphosphonate* **1e**: M.p.: 123-124 °C; IR (KBr, ν_{max} cm^{-1}): 3290, 1602, 1508, 1240, 1024 cm^{-1}; 1H NMR ($CDCl_3$, 400 MHz): 2.93 (s 3H), 3.50 (3H, d, $J = 10.4$ Hz), 3.77 (d, $J = 10.8$ Hz 3H), 4.74 (1H, d, $^{1}J_{P-H} = 24.08$ Hz), 6.60 (d, d, $J = 8.6$ Hz, $J = 1.2$ Hz, 2H), 6.72(t, $J = 7.2$ Hz 1H),6.90(d, $J = 8.4$ Hz, 2H), 7.13(t, $J = 8.2$ Hz, 2H),7.40(t, t, $J = 2.4$ Hz, 2.4 Hz, 2H), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 54.01, 55.82, 57.52, 115.05, 115.74, 120.05, 128.87, 129.45, 129.73, 146.60, 146.90, 159.96 ppm.

2.2f *Dimethyl(4-methylphenyl)(N-phenylamino)methylphosphonate* **1f**: M.p.: 128 °C; IR (KBr, ν_{max} cm^{-1}): 3313, 1602, 1498, 1232, 1031 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 3.49 (d, $J = 10.4$ Hz, 3H), 3.79 (d, $J = 10.8$ Hz, 3H), 4.82 (d, $^{1}J_{P-H} = 23.6$ Hz, 1H), 6.60 (d,d $J = 8.6$ Hz, J=1.2 Hz, 2H), 6.71 (t, $J = 7.2$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 2H), 7.12 (t, $J = 7.8$ Hz, 2H), 7.40 (t, t, $J = 6.4$ Hz, $J = 2.4$ Hz 2H) ppm.

2.2g *Dimethyl(Terephthal)(N-phenylamino)methylphosphonate* **1g**: M.p.: 130-135 °C; IR (KBr, ν_{max} cm^{-1}): 3290, 1602, 1508, 1240, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.83 (br, s 1H), (3.51 (3H, d, $J = 10.4$ Hz), 3.77 (s, 3H), 3.80 (d, $J = 1.2$ Hz, 3H), 4.77 (1H, d, $^{1}J_{P-H} = 24.08$ Hz). 6.60-7.41 (9H, m) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz):54.01, 55.82, 57.52, 115.05, 115.74, 120.05, 128.87, 129.45, 129.73, 146.60, 146.90, 159.96 ppm.

2.2h *Dimethyl(4-chlorophenyl)(N-4-nitrophenyla-mino) methylphosphonate* **1J**: M.p.: 160-162 °C; IR (KBr, ν_{max} cm^{-1}): 3413(N-H), 3176(br O-H), 1602, 1504, 1231, 1029; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45 (d, $J = 10.5$ Hz, 3H), 3.74 (d, $J = 10.7$ Hz, 3H), 4.73 (d, $^{1}J_{P-H} = 23.8$ Hz, 1H), 5.82(br 2H) 6.60 (d, $J = 7.5$ Hz, 2H), 6.70 (t, $J = 7.2$ Hz, 1H), 6.79(d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 6.51$ Hz 1H), 7.07 (d, $J = 7.6$ Hz, 2H), 7.17(m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): 54.0, 54.1, 54.7-56.3(d, $^{1}J_{c-p} = 152$ Hz), 113.9, 114.4, 115.8, 118.7, 119.7, 129.2, 129.9, 136.7, 145.9, 146.0, 157.3 ppm.

2.2i *Dimethyl(2,6-dichlorophenyl)(4-nitrophenyla-mino)methylphosphonate 1k*: M.p.: 135 °C; IR (KBr, ν_{max} cm^{-1}): 3303, 2952, 1602, 1498, 1315, 1240, 1180, 1051, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 3.65$ (d, $J = 10.8$ Hz, 3H), 3.90 (d, $J = 11.2$ Hz, 3H), 5.90 (d d, $J = 9.2$ Hz, $J = 30.8$ Hz 2 H),5.87(s br, 1H), 6.62 (d, $J = 9.2$ Hz, 2H) 7.22 (t,d, $J = 8$Hz, $J = 2$Hz 1 H), 7.30 (d, $J = 1.2$ Hz, 1H) 7.40 (d, t, $J = 8$ Hz, $J = 1.2$ Hz, 1H), 8.1 (d, $J = 9.2$ Hz, 2H) ppm.

2.2j *Dimethyl(4-nitrophenyl)(4-nitrophenylamino) methylphosphonate* **1l**: M.p.: 123 °C; IR (KBr, ν_{max} cm^{-1}): 3310, 1602, 1498, 1237, 1027cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (d, $J = 10.5$ Hz, 3H), 3.85 (d, $J = 10.6$ Hz, 3H), 5.69 (d, $J = 24.0$, 1H), 6.58 (d, $J = 8.0$ Hz, 2H), 6.69 (t, $J = 7.6$ Hz, 1H), 7.06 (t, $J = 7.7$ Hz, 2H), 7.47 (t, 7.7 Hz, 1H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.65 (t, 7.8 Hz, 1H), 7.83 (d, $J = 7.3$ Hz, 2H), 7.94 (d, $J = 8.1$ Hz, 1H), 8.26 (d, $J = 8.7$ Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 50.96$, 52.18, 54.13 (d, $J = 7.1$ Hz), 114.04, 118.89, 123.03, 125.96 (m), 126.95, 129.10 (d. $^{3}J_{C-P} = 3.6$ Hz), 129.55, 129.66, 131.79 (d, $^{3}J_{C-P} = 4.5$ Hz), 134.30, 146.30 (d, $^{2}J_{C-P} = 14.1$ Hz) ppm.

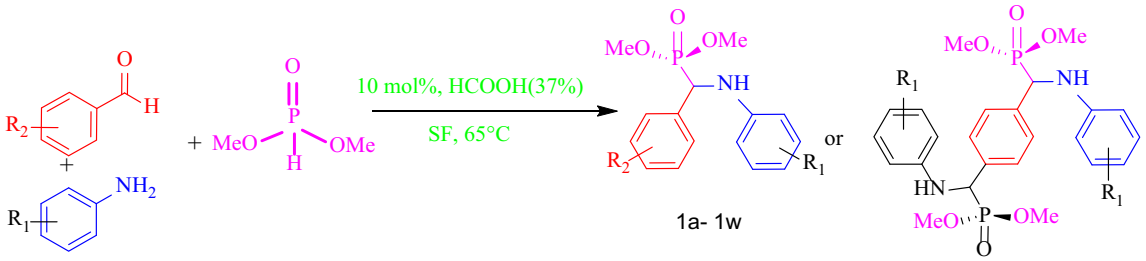
2.2k *Dimethyl (Terephthal) (N-4-nitrophenylamino) methylphosphonate* **1m**: M.p.: 237 °C, IR (KBr, ν_{max} cm^{-1}); 3446, 2926, 1350, 1251, 1167, 1030. ^{1}H NMR (DMSO, 250 MHz): $\delta = 3.45$ (m, 6H) 3.70 (m, 6H), 4.90(s br), 5.05 (dd, $J = 23.5$ Hz, $J = 5.2$ Hz 2H), 6.70 (m, 4H), 7.39 (m, 6 H), 7.94(d, $J = 8.5$ Hz 4H) ppm.

2.2l *Dimethyl (4-methylphenyl) (N-4-nitrophenylamino) methylphosphonate* **1n**: M.p.: 158 °C; IR (KBr, ν_{max} cm^{-1}) 3306, 1600, 1500, 1313, 1240, 1027. ^{1}H NMR (400 MHz, $CDCl_3$ d_6): $\delta = 2.34$(s, 3H), 3.47 (d, $J = 10.8$Hz, 2H), 3.8 (d, $J = 11.2$, 3H), 4.83(d, $J = 24$ Hz, 3H), 5.9 (s, br 1H), 6.6 (d, $J = 9.2$ Hz, 2H), 7.2 (d, $J = 8.0$ Hz, 2H), 7.35 (d d, $J = 12.4$Hz, $J = 2.0$ Hz, 2H)8.0 (d, $J = 10.8$ Hz, 2H) ppm.

2.2m *Dimethyl (3-hydroxyphenyl) (N-4-nitrophenylamino)methylphosphonate* **1p**: M.p.: 165 °C, IR (KBr, ν_{max} cm^{-1}) 3301, 2950, 1612, 1514, 1458, 1337, 1238, 1178, 1058, 1027. ^{1}H NMR($CDCl_3$, 250 MHz): δ 3.41 (d, $J = 10.5$ Hz, 3 H), 3.68 (d, $J = 14.2$ Hz, 3H), 4.71 (d, $J = 23.7$, 1H), 5.49 (s, br, 1 H), 6.52 (d, $J = 3.2$ Hz, 1H), 6.76 (d, $J = 7.7$Hz, 1H), 6.9 (m, 2 H), 7.14 (t, $J = 7.7$ Hz, 1H) 7.96 (d, $J = 7.2$Hz, 1H) ppm.

2.2n *Dimethyl(4-hydroxyphenyl)(N-4-nitrophenylamino)methylphosphonate* **1q**: M.p.: 166 °C, IR (KBr, ν_{max} cm^{-1}) 3298, 3074, 2921, 2852, 2432, 1600, 1546, 1490, 1328, 1278, 1234, 1178, 1112, 1091, 1051, 1024, ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.4 (d, $J = 10.5$ Hz, 3H), 3.70 (d, $J = 10.7$Hz, 3 H), 4.74 (d, $^{1}J_{P-H} = 23.5$ Hz, 1 H), 5.6 (s, 2H), 6.52 (d, $J = 9$Hz, 2H), 6.80 (d, $J = 8.5$Hz, 2H) 7.20 (d, $J = 9.4$, 2H), 7.96 (d, $J = 9.2$Hz, 2H) ppm.

2.2o *Dimethyl(2-chlorophenyl)(4-methylphenyla-mino) methylphosphonate* **1r**: M.p.: 158 °C, IR (KBr, ν_{max} cm^{-1}) 3271, 3070, 2954, 2923, 2848, 1483, 1182.^{1}H NMR



Scheme 1. Kabachnik-Fields reaction by aqueous formic acid as organocatalyst.

Table 1. Optimization of reaction conditions for the synthesis of α-aminophosphonate by aqueous formic acid as green organocatalyst.[a]

Entry	Temp. (°C)	Solvent	Time(min)	Catalyst(mL)	Yield (%)
1	25	-	2h	0	Trace
2	25	-	25	15	45
3	40	-	25	10	50
4	65	-	25	10	85
5	80	-	25	10	80
6	65	H_2O	25	10	-
7	65	EtOH	25	10	80
8	65	Toluene	25	10	80
9	65	n-Hexane	25	10	83
10	65	-	25	15	60
11	65	-	25	20	50
12	65	-	25	25	55

[a] 1 mmol aldehyde, 1 mmol amine and 1.2 mmol dimethylphosphate.

($CDCl_3$, 250 MHz): $\delta = 2.20$ (s, 3 H), 3.46 (d, $J = 10.5$ Hz, 3 H), 3.70 (d, $J = 11$ Hz, 3 H), 3.71 (s, 3 H), 5.40 (d, $^1J_{P-H} = 24.7$Hz, 1H), 5.86 (s, br 1H), 6.53 (d, $J = 8.3$ Hz, 2 H), 6.92 (d, $J = 8.3$ Hz, 2 H), 7.25 (m, 2 H), 7.40 (d, $J = 8.2$ Hz, 1 H), 7.60 (d, $J = 8.2$ Hz, 1 H) .^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 20.3, 50.1, 52.5, 53.8 (m), 113.7, 126.8, 127.4 (d), 127.9, 128.8 (d), 129.2 (d), 129.5 (d), 129.8 ppm.

2.2p *Dimethyl[(4-nitrophenyl)-(N-2-methylphenylamino)methyl]phosphonate* **1t**: M.p.: 146-150 °C; IR (KBr, ν_{max} cm^{-1}): 3331, 1602, 1498, 1449, 1230, 1028 cm^{-1}; ^{1}H NMR(250 MHz, $CDCl_3$): δ 2.19 (s, 3H), 3.70 (d, J == 8.0 Hz, 2H) 7.67 (d, $J = 8.5$Hz, 2H), 8.2 (d, $J = 8.2$ Hz, 2H);^{13}C NMR ($CDCl_3$, 62.9MHz): δ 20.3, 54.2(m), 57.0(d), 114.0(d), 123.8(d), 123.9, 128.6(d), 129.8, 142.9 (d), 143.7 (d), 147.8(d) ppm.

3. Results and Discussion

Aqueous formic acid was used to synthesis of α-aminophosphonate by a one-pot, three-component reaction of aldehyde, amine and dimethylphosphite under solvent-free conditions (Scheme 1).

3.1 *Optimization of synthetic conditions for kabachnik-fields reaction catalyzed by aqueous formic acid*

To determine the best experimental conditions, the reaction of, 4-chlorobenzaldehyde, aniline and dimethylphosphite was considered as the model of reaction (Table 1).

For optimization of the best condition to carry out the reaction different conditions were tested and the results summarized in Table 1.

Positive effect of aqueous formic acid in promotion of this reaction has been indicated in Table 1. Without using catalyst, No significant amount of product is obtained after 2 h. To determine the optimum amount of catalyst, we compared four diverse amounts of catalyst and the results show that 10% is the best amount for this reaction. More or lower than this range, can decrease the yield percentage. To determination the best solvent condition, some current solvent were tested and compared with solvent free (SF) condition and SF had shown the best result in this reaction. In aspect of temperature conditions, among the various temperatures, the best result was obtained at 65 °C (Table 2).

Table 2. Synthesized derivatives of α-aminophosphonate in the presence of aqueous formic acid as reaction organocatalyst[a].

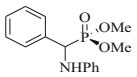
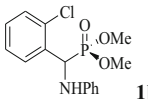
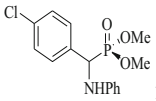
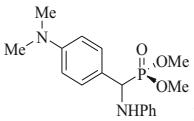
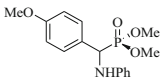
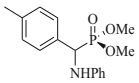
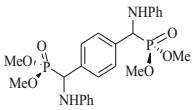
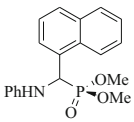
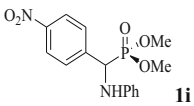
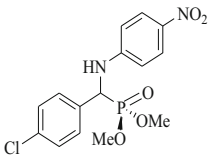
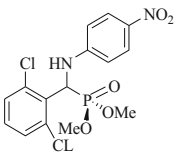
Entry	Amine	Aldehyde	Product	Time (min)	Yield (%)	M.p (°C) (found)	M.p (°C) (Ref)
1	Aniline	PhCHO	 **1a**	30	85	94	90–92[40]
2	Aniline	2-(Cl)C_6H_4CHO	 **1b**	25	80	130	128–129[41]
3	Aniline	4-(Cl)C_6H_4CHO	 **1c**	18	85	138	139–140[42]
4	Aniline	4-[N(Me)$_2$]PhCHO	 **1d**	30	87	145-150	144[43]
5	Aniline	4-(MeO)C_6H_4CHO	 **1e**	25	78	123-125	123–124[40]
6	Aniline	4-(Me)C_6H_4CHO	 **1f**	30	80	129	125–128[31]
7	Aniline	Terephthaldehyde	 **1g**	15	86	130-135	164–165[44]
8	Aniline	1-naphthaldehyde	 **1h**	30	62	144	143–145
9	Aniline	4-(NO_2)C_6H_4CHO	 **1i**	25	78	127	127–128[40]
10	4-Nitroaniline	4-(Cl)C_6H_4CHO	 **1J**	20	78	168	160–162[45]
11	4-Nitroaniline	2,6-(Cl)$_2C_6H_3$CHO	 **1k**	35	85	135	(New)

Table 2. (*contd.*)

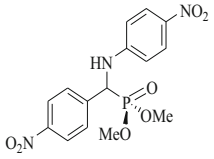
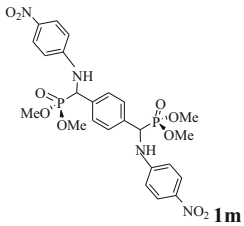
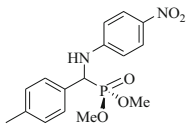
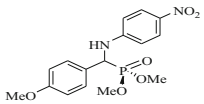
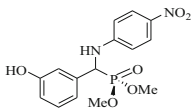
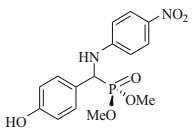
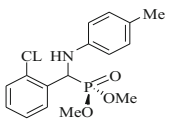
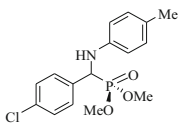
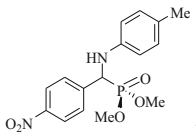
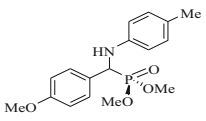
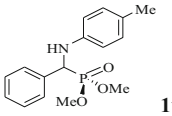
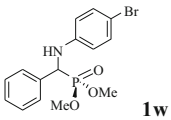
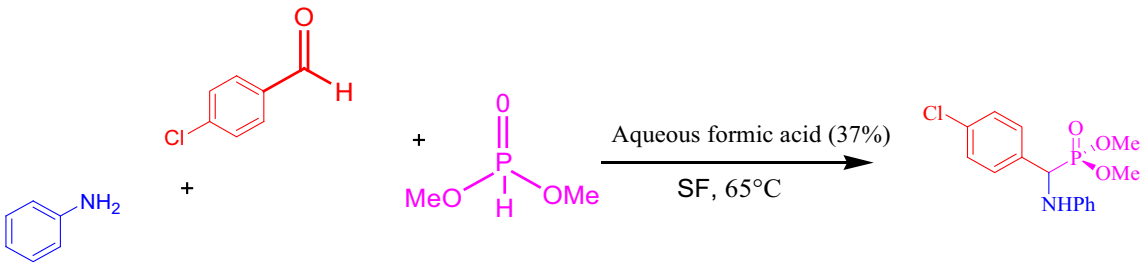
Entry	Amine	Aldehyde	Product	Time (min)	Yield (%)	M.p (°C) (found)	M.p (°C) (Ref)
12	4-Nitroaniline	4-(NO_2)C_6H_4CHO	 **1l**	25	70	123	186[46]
13	4-Nitroaniline	Terephthaldehyde	 **1m**	15	80	237	(New)
14	4-Nitroaniline	4-(Me)C_6H_4CHO	 **1n**	45	80	158	(New)
15	4-Nitroaniline	4-(OMe)C_6H_4CHO	 **1o**	35	80	153	150–152[46]
16	4-Nitroaniline	3-(OH)C_6H_4CHO	 **1p**	35	72	165	(New)
17	4-Nitroaniline	4-(OH)C_6H_4CHO	 **1q**	30	68	166	(New)
18	*p*-Toluidine	2-(Cl)C_6H_4CHO	 **1r**	25	80	158	(New)
19	*p*-Toluidine	4-(Cl)C_6H_4CHO	 **1s**	20	80	137	134–137
20	*p*-Toluidine	4-(NO_2)C_6H_4CHO	 **1t**	25	83	146–150	209–211[46]

Table 2. (*contd.*)

Entry	Amine	Aldehyde	Product	Time (min)	Yield (%)	M.p (°C) (found)	M.p (°C) (Ref)
21	*p*-Toluidine	4-(MeO)C_6H_4CHO	 **1u**	35	75	90	96–99[46]
22	*p*-Toluidine	PhCHO	 **1v**	25	77	70	68–71[46]
23	4-Bromoaniline	PhCHO	 **1w**	40	70	65	60[47]

[a]1 mmol aldehyde, 1 mmol amine and 1.2 mmol dimethylphosphate, 15 μL catalyst (formic acid (37%)), 65 °C temperature.



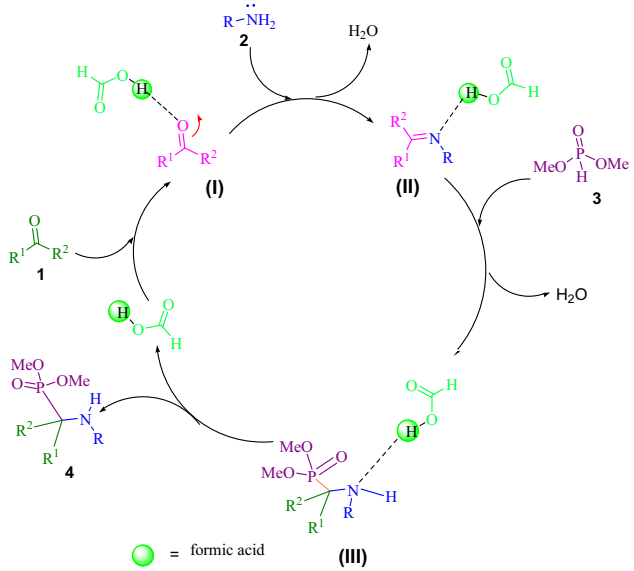
Scheme 2. The reaction of, 4-chlorobenzaldehyde, aniline and dimethylphosphite to preparation of α –aminophosphonates.

After optimization of the reaction condition, in order to generalize the method, it was expanded with versatile aldehydes and amines for synthesis of other derivatives of α-aminophosphonates and the results were summarized in (Table 2). Six derivatives including (Entry 11, 13, 14, 16, 17, 18) have been synthesized for the first time in this work.

3.2 *The proposed mechanism of the Kabachnik–Fields reaction in the presence of aqueous formic acid*

The suggested mechanism to synthesis of α-aminophosphonate by aqueous formic acid as organocatalyst is shown in Scheme 3.

As shown in Scheme 3, the first step is the activation of carbonyl groups in aldehydes by hydrogen bond interaction with HCOOH (**I**). Second, a nucleophilic addition of amine to activated carbonyl, cause



Scheme 3. The proposed mechanism of the Kabachnik—Fields reaction by aqueous formic acid as organocatalyst.

the formation of an imine intermediate (**II**). The formation of imine intermediate by formic acid was reported in our former research[41]. Also, the addition of nucleophilic phosphonate **3** to imine cause the formation of α-aminophosphonate **4**. After the separation of catalyst, the pure product can be obtained.

4. Conclusions

Aqueous formic acid was demonstrated as a green and effective organocatalyst in Kabachnik-Fields reaction to synthesize α-aminophosphonate derivatives. The eco-friendly and low cost organocatalysts and solvent free condition provide considerable advantages for this procedure. Also, this method has shown several benefits such as: easy work up process, short reaction time and lack of toxicity. Six of the reported derivatives were synthesized for the first time in this study.

Supplementary Information (SI)

Additional experimental data and spectroscopic characterization data are given in the Supplementary Information. Supplementary Information is available at www.ias.ac.in/chemsci.

Acknowledgements

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