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Three Component Coupling Catalyzed by Nickel (II) Chloride Hexahydrate: Synthesis of α-Amino Phosphonates

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ABSTRACT

A simple highly versatile and efficient method has been developed for the three-component coupling of aromatic aldehydes, aromatic amines and diethyl phosphate in the presence of a catalytic amount of nickel (II) chloride hexahydrate in acetonitrile. The advantages of this method are high yield, mild reaction conditions and easy work up procedure.

Keywords: nickel (II) chloride hexahydrate, green synthesis, α-amino phosphonates

1. INTRODUCTION

The synthesis of α-amino phosphonates has attracted much attention recently due to their significant in pharmaceutical chemistry [1], biological activities and structural analogy to amino acids [2]. They have been reported to act as peptidomimics, [3], antibodies [4]. Many procedures for the synthesis of α-amino phosphonate derivatives have been developed during the last two decades [5]. A number of methods for the preparation of diverse α-aminophosphonates, such as nucleophilic amination of α-hydroxy phosphonate derivatives [6], electrophonic amination of α-alkylphosphonamides [7], hydrogenation of dehydroaminophosphonate, [8] and catalyzed Mannich-type one-pot procedure, [9] have been reported.

Among the various synthetic approaches to them, nucleophilic addition of phosphites to imines is one of the most preferred methods, which is usually catalyzed by an alkali metal alkoxide, Bronsted [10] or Lewis acids, [11] natural phosphate, [12] Lanthanide triflate, [13] $TaCl_5$-SiO_2, [14] Cobalt(II) chloride, [15] $Na_2CaP_2O_7$, [16] $H_3PW_{12}O_{40}$, [17] H-beta zeolite, [18] $In(OTf)_3$, [19], $NbCl_5$, [20] ZnO nanoparticle, [21] Xanthan sulfuric acid, [22] and Amberlyst-15, [23] have been used.

In addition, ultrasonic radiations [24] and microwave-assisted solvent-free condition, [25] have also been reported. However, most of these Lewis acids are moisture sensitive and hence difficult to handle. Also their cost is considerable especially for the scale up of the reaction. Some of these reactions cannot proceed in one-pot from a carbonyl compound, an amine and a phosphite because

the water that is generated during the course of the reaction can decompose or deactivate the Lewis acid. [26]

Although, these approaches are satisfactory for synthesis of α-aminophosphonates, these methods suffer from drawbacks, such as long reaction times, low product yields, the harsh reaction conditions, expensive reagents, requirement of the stoichiometric amounts of catalysts, formation of a large amount of waste and/ or use of toxic organic solvents. The catalyst- free synthesis of α-amino phosphonates is rather limited. [27]

Although a number of different methods have been reported for the preparation of α-amino phosphonates, there is still a need to search for better catalysts with regards to their handling and economic viability.

In recent years, nickel chloride derivatives has attracted much attention because of their friendly ecological behavior and its diverse applicability as catalysts in synthesis of pyrazolophthalazinyl spirooxindoles, [28] tetra-substituted pyrroles, [29] α-aminonitriles. [30] It has been explored as powerful catalyst for different reactions, such as thioacetalization of aldehydes, [31] deprotection, [32] and coupling reaction. [33]

In continuation of our investigations on the use of heterogeneous catalysts for fine chemical preparation through multi-component procedures, [34] here we present our recent studies on the synthesis of substituted α-amino phosphonates via three-component reaction between aldehydes, secondary amines and diethyl phosphite in the presence nickel (II) chloride hexahydrate in acetonitrile.

2. MATERIALS AND METHODS

2.1 Instruments and Characterization

All the reagents and the solvents employed were commercially available and used with no further purification. Products were characterized by spectroscopy data (IR, FTIR, ^{1}H NMR and ^{13}C NMR spectra), elemental analysis (CHN) and melting points. A JASCO FT/IR-680 PLUS spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded on a Bruker 400 Ultrasheild NMR and DMSO-d6 was used as solvent. Melting points reported were determined by open capillary method using a Galen Kamp melting point apparatus and are uncorrected. Mass Spectra were recorded on a Shimadzu Gas Chromatograph Mass Spectrometer GCMS-QP5050A/Q P5000 apparatus.

2.2 General Procedure for the Synthesis of α-aminophosphonates Derivatives

To a mixture of aromatic aldehydes (1 mmol), amines (1 mmol) diethyl phosphite (114 mg, 1mmol) in acetonitrile (5 mL) was added $NiCl_2.6H_2O$ (10 mol %) and the solution were mixed and stirred at reflux temperature for appropriate time. After completion of the reaction (as monitored by TLC), the acetonitrile was removed under vacuum. The crude mixture was purified by flash column chromatography (EtOAc/ petroleum ether 1:4) to afford the pure product.

Diethyl (phenyl)-N-(phenyl)aminomethylphosphonate (2a):

Mp 88-90 °C; FTIR (KBr, cm^{-1}): 3310, 2955, 1608, 1498, 1237, 1040; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.14 (3H, t, $-OCH_2Me$), 1.34 (3H, t, $-OCH_2Me$), 3.73-4.21 (4H, m, $-OCH_2CH_3$), 4.86 (1H, d, CHP), 6.65-6.70 (2H, m, ArH), 6.90 (1H, s, -NH), 7.12-7.18 (2H, m, ArH), 7.28-7.57 (7H, m, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.4 (d, J = 5.5 Hz, OCH_2CH_3), 16.6 (d, J = 5.4 Hz, OCH_2CH_3), 58.2 (d, J = 150 Hz, CH), 62.7 (d, J = 7.0 Hz, OCH_2CH_3), 62.8 (d, J = 6.8 Hz, OCH_2CH_3), 128.9 (CH), 128.7 (CH),

128.4 (CH), 128.3 (CH), 127.9 (CH), 127.1 (CH), 136.0 (C), 140.5 (C); MS (m/z): 319.13 (M^+); Anal. Calcd for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39. Found: C, 63.71; H, 6.86; N, 4.15.

*Diethyl (4-Chlorophenyl)-N-(phenyl) aminomethyl phosphonate **(2b):***

Mp 64-66 °C; FTIR (KBr, cm^{-1}): 3315, 2965, 1608, 1498, 1233; ^1H NMR (400 MHz, DMSO-d6) δ 1.15 (3H, t, -OCH_2Me),1.26 (3H, t, -OCH_2Me), 3.71-4.17 (4H, m, -OCH_2CH_3), 4.78 (1H, d, CHP), 5.8 (1H, br s, -NH), 6.61 (2H, d, ArH), 6.72 (1H, t, ArH), 7.12 (2H, t, ArH), 7.31 (2H, dd, ArH), 7.41 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.2 (d, OCH_2CH_3), 16.4 (d, OCH_2CH_3), 54.8 (d, OCH_2CH_3), 56.4 (d, J = 150 Hz, CH), 63.5 (s, OCH_2CH_3), 114.8 (CH), 118.6 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 132.6 (CH), 134.8 (C), 146.1 (C), 147.4 (C); MS (m/z): 353.09 (M^+); Anal. Calcd for $C_{17}H_{21}ClNO_3P$: C, 57.71; H, 5.98; N, 3.96. Found: C, 57.60; H, 5.84; N, 3.75.

*Diethyl (4-nitrophenyl)-N-(phenyl) aminomethyl phosphonate **(2c):***

Mp 124-126 °C; FTIR (KBr, cm^{-1}): 3321, 2951, 1602, 1498, 1529, 1356, 1231, 1037; ^1H NMR (400 MHz, DMSO-d6) δ 1.14 (3H, t, -OCH_2Me), 1.24 (3H, t, -OCH_2Me), 3.86-4.17 (4H, m, -OCH_2CH_3), 4.90 (1H, d, CHP), 5.20 (1H, br s, -NH), 6.54 (2H, d, ArH), 6.66 (1H, t, ArH), 7.06 (2H, t, ArH), 7.67 (2H, dd, ArH), 8.12 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.4 (s, OCH_2CH_3), 16.6 (s, OCH_2CH_3), 51.4 (d, J = 158 Hz, CH), 63.6 (s, OCH_2CH_3), 115.1 (CH), 119.2 (CH), 120.6 (CH), 124.7 (CH), 129.8 (CH), 130.4 (CH), 145.6 (C), 147.6 (C), 168.8 (C); MS (m/z): 364.12 (M^+); Anal. Calcd for $C_{17}H_{21}N_2O_5P$: C, 56.04; H, 5.81; N: 7.69. Found: C, 55.81; H, 5.73; N, 7.45.

*Diethyl (4-hydroxyphenyl)-N-(phenyl) aminomethyl phosphonate **(2d):***

oil; FTIR (KBr, cm^{-1}): 3561, 3311, 2958, 1616, 1498, 1234, 1036; ^1H NMR (400 MHz, DMSO-d6) δ 0.88 (3H, t, -OCH_2 Me), 1.06 (3H, t, OCH_2Me), 3.48-3.91 (4H, m, -OCH_2CH_3), 4.52 (1H, d, JHP 23.6 Hz, CHP), 4.96 (1H, s, -PhOH), 5.44 (1H, br s, -NH), 6.40-6.50 (3H, m, ArH), 6.65 (2H, d, ArH), 6.88 (2H, d, ArH), 7.06 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.2 (d, OCH_2CH_3), 16.4 (d, OCH_2CH_3), 56.8 (d, J = 154 Hz, CH), 63.2 (s, OCH_2CH_3), 115.7 (CH), 119.4 (CH), 121.6 (CH), 125.8 (CH), 128.2 (CH), 130.6 (CH), 132.8 (C), 147.1 (C), 156.5 (C); MS (m/z): 335.13 (M^+); Anal. Calcd for $C_{17}H_{22}NO_4P$: C: 60.89, H; 6.61, N; 4.18. Found: C: 60.65, H; 6.43, N; 3.95.

*Diethyl (4-methylphenyl)-N-(phenyl) aminomethyl phosphonate **(2e):***

Mp 62-64 °C; FTIR (KBr, cm^{-1}): 3323, 2945, 1618, 1492, 1231, 1039; ^1H NMR (400 MHz, DMSO-d6) δ 0.98 (3H, t, -OCH2Me), 1.10 (3H, t, -OCH_2Me), 2.12 (3H, s, PhMe), 3.52-4.00 (4H, m, -OCH_2CH_3), 4.60 (1H, d, JHP 24.1 Hz, CHP), 5.72 (1H, br s, -NH), 6.43-6.54 (3H, m, ArH), 6.79-7.02 (4H, m, ArH), 7.23 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ ^{13}C NMR (400 MHz, DMSO-d6) δ 16.3 (d, J = 4.5 Hz, OCH_2CH_3), 16.5 (d, J = 4.2 Hz, OCH_2CH_3), 21.4 (d, CH_3), 55.6 (d, J = 150.6 Hz, CH), 63.5 (s, OCH_2CH_3), 114.3 (CH), 119.4 (CH), 128.3 (CH), 130.2 (CH), 133.8 (CH), 138.1 (C), 147.3 (C), 147.5 (C); MS (m/z): 333.15(M^+); Anal. Calcd for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.56; H, 6.96; N, 3.88.

*Diethyl (4-methoxyphenyl)-N-(phenyl) aminomethyl phosphonate **(2f):***

oil; FTIR (KBr, cm^{-1}): 3319, 2957, 1625, 1494, 1232, 1030; ^1H NMR (400 MHz,

DMSO-d6) δ 1.04 (3H, t, JHH 6.9 Hz, -OCH_2Me), 1.20 (3H, t, -OCH_2Me), 3.69 (3H, s, PhO Me), 3.61-4.07 (4H, m, -OCH_2CH_3), 4.62 (1H, d, CHP), 5.21 (1H, br s, -NH), 6.50 (2H, ArH), 6.61 (1H, t, J = 7.1 Hz, ArH), 6.76 (2H, t, ArH), 7.02 (2H, dd, ArH), 7.32 (2H, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ ^{13}C NMR (400 MHz, DMSO-d6) δ 16.2 (d, OCH_2CH_3), 16.4 (d, OCH_2CH_3), 57.4 (d, OCH_3), 57.6 (d, J = 150 Hz, CH), 62.5 (s, OCH_2CH_3), 115.3 (CH), 119.7 (CH), 121.3 (CH), 126.2 (CH), 128.8 (CH), 130.1 (CH), 133.3 (C), 147.3 (C), 158.5 (C); MS (m/z): 349.14 (M^+); Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 3.90, Found: C: 61.62, H: 6.84, N: 3.79.

Diethyl (4-chloroaniline)(phenyl)methylphosphonate (2g):

Mp 104-106 °C; FTIR (KBr, cm^{-1}): 3325, 2941, 1610, 1496, 1233, 1037; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.08 (3H, J = 6.7 Hz, t, -CH_2Me), 1.22 (3H, J = 6.7 Hz, t, –OCH_2Me), 3.52-3.62 (1H, m), 3.77-3.87 (1H, m), 4.07-4.20 (2H, m), 4.70 (1H, d), 5.16 (1H, br s, -NH), 6.45 (2H, d, ArH), 6.97 (2H, d, ArH), 7.20-7.30 (4H, m, ArH), 7.43 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.2 (d, OCH_2CH_3), 16.3 (d, OCH_2CH_3), 50.0 (d, CH_3), 56.6 (d, CH), 63.5 (s, OCH_2CH_3), 112.8 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 130.1 (CH), 134.6 (CH), 135.4 (C), 147.6 (C), 147.8 (C); MS (m/z): 353.06 (M^+); Anal. Calcd for $C_{17}H_{21}ClNO_3P$: C, 57.71; H, 5.98; N: 3.96. Found: C, 57.62; H, 5.78; N, 3.75.

Diethyl (4-nitroaniline)(phenyl)methylphosphonate (2h):

Mp 144-146 °C; FTIR (KBr, cm^{-1}): 3321, 2943, 1611, 1493, 1231, 1035; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.14 (3H, J = 7.1 Hz, t, -CH_2Me), 1.34 (3H, J = 7.1 Hz, t, –OCH_2Me), 3.58-3.68 (1H, m), 3.87-3.97 (1H, m), 4.12-4.26 (2H, m), 4.40 (1H, d), 6.30 (1H, br s, -NH), 6.41 (1H, d, ArH), 7.26–7.37 (3H, m, ArH), 7.53 (2H, d, ArH), 7.93 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.3 (d, OCH_2CH_3), 16.4 (d, OCH_2CH_3), 53.8 (d, CH_3), 56.3 (d, CH), 63.7 (s, OCH_2CH_3), 112.4 (CH), 127.7 (CH), 128.4(CH), 128.8 (CH), 129.8 (CH), 134.6 (CH), 134.4 (C), 141.3 (C), 149.4 (C); MS (m/z): 364.11 (M^+); Anal. Calcd for $C_{17}H_{21}N_2O_5P$: C, 56.04; H, 5.81; N: 7.69. Found: C, 55.87; H, 5.69; N, 7.51.

Diethyl (4-methylaniline)(phenyl)methylphosphonate (2i):

Mp 116-118 °C; FTIR (KBr, cm^{-1}): 3328, 2946, 1617, 1490, 1237, 1031; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.16 (3H, J = 7.2 Hz, t, -OCH_2Me), 1.33 (3H, J = 7.1 Hz, t, -OCH_2Me), 2.24 (3H, s), 3.62-3.72 (1H, m), 3.93-4.01 (1H, m), 4.08-4.22 (2H, m), 4.65 (1H, br s, -NH), 6.45 (2H, d, ArH), 6.84 (2H, d, ArH), 7.44-7.48 (1H, m, ArH), 7.50 (2H, t, ArH), 7.70 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.2 (d, OCH_2CH_3), 16.3 (d, OCH_2CH_3), 20.3 (CH_3). 54.2 (d, CH_3), 56.9 (d, CH), 63.4 (s, OCH_2CH_3), 113.7 (CH), 127.3 (CH), 128.4(CH), 128.8 (CH), 129.8 (CH), 129.2 (CH), 129.4 (C), 132.3 (C), 139.6 (C); MS (m/z): 333.145(M^+); Anal. Calcd for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.62; H, 6.11; N, 4.02.

Diethyl (4-methoxyaniline)(phenyl)methylphosphonate (2j):

Mp 76-78°C; FTIR (KBr, cm^{-1}): 3323, 2940, 1613, 1490, 1239, 1035; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.12 (3H, J = 6.8 Hz, t, -OCH_2Me), 1.26 (3H, J = 6.8 Hz, t, -OCH_2Me), 3.64 (3H, s), 3.64-3.74 (1H, m), 3.88-3.98 (1H, m), 4.04-4.27 (2H, m), 4.68 (1H, br s, -NH), 6.55 (2H, d, ArH), 6.67 (2H, d, ArH), 7.24-7.49 (1H, m, ArH), 7.55 (2H, t, ArH), 7.70 (2H, d, ArH); ^{13}C NMR (400 MHz, DMSO-d6) δ 16.1 (d, OCH_2CH_3), 16.2 (d, OCH_2CH_3), 29.5 (CH_3). 54.8 (d, CH_3), 56.3

(d, CH), 63.2 (s, OCH_2CH_3), 114.7 (CH), 116.7 (CH), 127.6(CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 136.41 (C), 140.4 (C), 151.6 (C); MS (m/z): 349.14 (M^+); Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 3.90, Found: C: 61.70, H: 6.88, N: 3.73.

3. RESULTS AND DISCUSSIONS

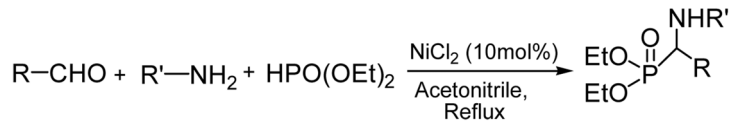
In an effort to develop an optimal catalytic system, various reaction parameters like effect of temperature, catalyst loading, time and solvent were studied for the preparation α-amino phosphonates of via reaction of benzaldehyde, aniline and diethyl phosphite in different solvents under reflux and the results are summarized in Table 1.

The control experiments for the three-component reaction conducted under identical conditions and devoid of catalyst gave no coupled product, despite prolonged reaction times. $NiCl_2.6(H_2O)$ was found to be the most effective catalyst that afforded excellent yield (Table 2, entry 5). In a systematic study, diethyl phosphite was added to a solution of benzaldehyde, aniline and $NiCl_2.6(H_2O)$ in acetonitrile and the reaction mixture was stirred for 10 h at room temperature or 5h at refluxing. Our initial experiments focused on the optimization of the amount of $NiCl_2.6(H_2O)$ by using 1 equiv of benzaldehyde, 1 equiv of aniline, 1 equiv of diethyl phosphite and variable amount of $NiCl_2.6(H_2O)$.

In the absence of catalyst, it was observed that no conversion to product was obtained even after 48 h at room temperature. To evaluate the effect of catalyst concentration, the model reaction was carried out in the presence of different amounts of catalyst (2, 5, 8, 10, 15, 20 and 25 mol%).

We observed that 10 mol % of $NiCl_2.6(H_2O)$ (based on benzaldehyde) could effectively catalyze the reaction. With 2 and 5 mol% of $NiCl_2.6(H_2O)$ a lower yield was observed under the same reaction period (Table 2, entry 2-3) and increasing the amount of $NiCl_2.6(H_2O)$ to 15, 20 and 25 mol % showed no substantial improvement in the yield (Table 2, entry 4-6).

Table 1. $NiCl_2$-catalyzed synthesis of α-amino phosphonates derivatives[a].



Entry	Product	R	R'	Time (min)/Yield (%)[a]	MP °C (lit.) [Ref.]
1	2a	Ph	Ph	60/90	88-90 (86) [17]
2	2b	4-ClC_6H_5	Ph	45/92	64-66 (57) [17]
3	2c	4-$NO_2C_6H_5$	Ph	55/95	124-126 (120) [17]
4	2d	4-OHC_6H_5	Ph	60/85	Oil
5	2e	4-$CH_3C_6H_5$	Ph	40/80	62-64 (60) [17]
6	2f	4-$OCH_3C_6H_5$	Ph	35/81	Oil
7	2g	Ph	4-ClC_6H_5	40/94	104-106 (111-113) [35]
8	2h	Ph	4-$NO_2C_6H_5$	45/80	144-146 (145-146) [35]
9	2i	Ph	4-$CH_3C_6H_5$	35/92	116-118 (117-118) [35]
10	2j	Ph	4-$OCH_3C_6H_5$	30/90	76-78 (78-80) [35]

[a] Yields after isolation of products

Table 2. Effect of catalyst type and amount of catalyst on the synthesis of compounds.

Entry	Catalyst	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	None	-	48	No reaction
2	$NiCl_2.6(H_2O)$	2	15	70
3	$NiCl_2.6(H_2O)$	5	15	75
4	$NiCl_2.6(H_2O)$	8	15	82
5	$NiCl_2.6(H_2O)$	10	15	95
6	$NiCl_2.6(H_2O)$	15	15	70
7	$NiCl_2.6(H_2O)$	20	15	65
8	$NiCl_2.6(H_2O)$	25	15	50
9	$NiCl_2$	5	15	40
10	$NiCl_2$	10	15	45
11	$NiCl_2$	15	15	40

[a] Yields after isolation of products

To check the solvent effect on the outcome of the reaction, the above model reaction was carried out with 10 mol % of $NiCl_2.6(H_2O)$ in solvents such as H_2O, EtOH, CH_3CN, DCM, DMF, THF and Toluene. (Table 3). Acetonitrile and DCM provided excellent yields and proved to be the solvent of choice. It was observed that much better yield was obtained when the reaction was carried out in acetonitrile at other solvents (Table 3, entry 2). Whereas ethanol and MeOH afforded lower yields. The reaction in THF afforded very poor yields whilst the use of DMF and toluene could not effectively catalyze the reaction.

To establish the generality, various aldehydes and amines were subjected to a one-pot three-component reaction catalyzed by $NiCl_2.6(H_2O)$. It was found that obvious electronic effects from aromatic aldehydes existed in the three-component couplings. Aromatic aldehydes with both electron-donating and withdrawing groups could be accomplished the one-pot reaction (Table 1). Various functionalities present in the aryl aldehydes, such as halogen, methoxy, hydroxyl, methyl and nitro groups were tolerated (see Table 1).

As can be seen from Table 1, each benzaldehyde containing electron-deficient or electron-releasing groups reacts efficiently with aniline for generation of the corresponding α-amino phosphonates. The presence of electron-donating groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however, aldehydes possessing electron-withdrawing groups afforded the corresponding α-amino phosphonates in shorter reaction times and in higher yields. It is important to note that the presence of the methoxy group in 4-methoxybenzaldehyde reduces the electrophilicity of the carbonyl carbon through resonance.

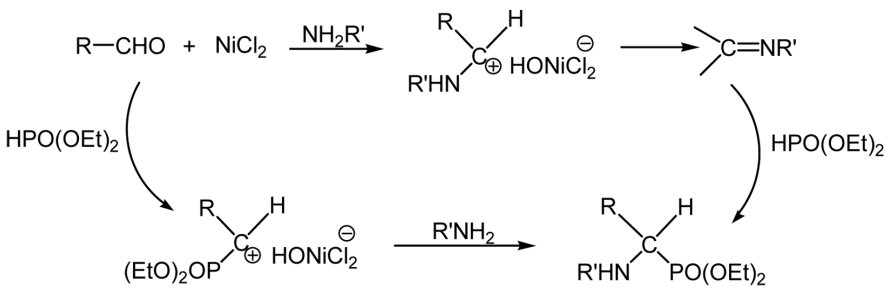
For generalization of this method, we also screened aniline, *p*-chloroaniline, *p*-methoxyaniline, *p*-methylaniline, and *p*-nitroaniline in reactions with benzaldehyde and obtained the desired α-amino phosphonates in very good yields (entries 7-10).

Also, amines possessing electron-donating groups gave the corresponding products in good yields. But the strong electron-withdrawing property of nitro group in *p*-nitroaniline decreases the nucleophilicity of the amine group.

Table 3. Solvent studies under different parameters for the model reaction catalyzed by $NiCl_2.6(H_2O)$.

Entry	Solvent	Time (h)/Yield (%)[a] Room temperature	Time (h)/Yield (%)[a] Reflux
1	H_2O	10/0	5/45
2	EtOH	10/0	5/80
3	MeOH	10/0	5/75
4	CH_3CN	10/0	5/90
5	DCM	10/0	5/65
6	DMF	10/0	5/30
7	THF	10/0	5/45
8	Toluene	10/0	5/35

[a] aromatic aldehydes (1 mmol), amines (1 mmol) and diethyl phosphite (1 mmol) in the presence of catalyst (10 mol %) at room temperature and reflux condition in various solvents.



Scheme 1. Reaction scheme for synthesis of α-aminophosphonates in the presence of catalyst.

Table 4 compares the efficiency of present method with the efficiency of other methods in the synthesis of a-amino phosphonates derivativess. As evident from Tables 4, $NiCl_2.6(H_2O)$ shows better efficiency than other methods. In addition the reaction times are lower than previously reported conditions.

Table 4. Comparison of the efficiency of $NiCl_2.6(H_2O)$ with other reported catalysts in the synthesis of α-amino phosphonates derivativess[a].

Entry	Catalyst (mol %)	Condition	Time	Yield (%)[a]	References
1	$NiCl_2.6(H_2O)$	CH_3CN/Reflux	1 h	90	This work
	Natural phosphate	Solvent-free /RT	14 h	53	12
2	$Yb(OTf)_3$	DCM/RT	5 h	89	13
3	$TaCl_5$–SiO_2	DCM/RT	20 h	90	14
4	$Na_2CaP_2O_7$	Solvent-free /RT	10 h	75	16
5	$In(OTf)_3$	THF/Reflux	21 h	79	19

[a] benzaldehyde, aniline and diethyl phosphite in the presence of catalyst.

On the basis of these results, together with the literature reports [18, 24] a reaction scheme for the $NiCl_2$-catalyzed aldehyde-amine–diethyl phosphite coupling is proposed in Scheme 1. The reaction involving the activation of the C=O bond of carbonyl group by $NiCl_2$.

4. CONCLUSIONS

We have successfully developed a simple and efficient method for the three-component coupling of aldehydes, amines and diethyl phosphite in acetonitrile to yield α-aminophosphonates in moderate to very good yields using Nickel (II) chloride hexahydrate. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst are expected to contribute to its utilization for the development of benign chemical processes and products.

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