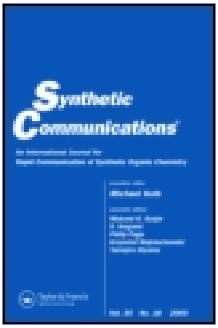

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$ZrOCl_2 \cdot 8H_2O$: An Efficient Catalyst for One-Pot Synthesis of α-Amino Phosphonates Under Solvent-Free Conditions

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$ZrOCl_2{\cdot}8H_2O$: An Efficient Catalyst for One-Pot Synthesis of α-Amino Phosphonates Under Solvent-Free Conditions

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(Autonomous), University of Mumbai, Mumbai, India

Abstract: A highly efficient protocol has been developed for the three-component reaction of an amine, an aldehyde, and diethyl phopshite catalyzed by $ZrOCl_2{\cdot}8H_2O$, an environmentally friendly catalyst, at ambient temperature. The catalyst exhibited remarkable activity and tolerated a wide variety of functional groups, providing the desired amino phosphonates in excellent yields under solvent-free conditions. Alternatively, the reaction rate can be significantly enhanced by carrying out the reaction in a monomode microwave reactor as a promoter.

Keywords: Aldehydes, amines, α-amino phosphonate, diethyl phosphite, solvent free, zirconium oxychloride

INTRODUCTION

α-Amino phosphonates constitute an important class of compounds with biological and medicinal properties. They are phosphorous analogs of amino acids that have been widely used as enzyme inhibitors, pharmacogenic agents, antithrombotic agents, and herbicides.[1] Apart from this,

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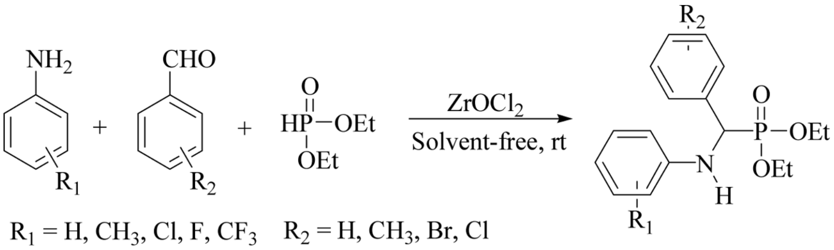
they have applications because of their antifungal and antibacterial activities.[2] There are various synthetic protocols that have been developed for the synthesis of α-amino phosphonates. The nucleophilic addition of phosphites to imines (Kabachnik–Fields reaction) represents a convenient route for their preparation. A variety of Lewis acids such as $SnCl_4$,[3] $ZrCl_4$,[4] $BF_3{\cdot}OEt_2$,[5] BrDMSBr (bromodimethylsulfonium bromide),[6] $Bi(NO_3)_3{\cdot}5H_2O$,[7] metal perchlorates,[8] metal triflates,[9] $TaCl_5$-SiO_2,[10] $InCl_3$,[11] $TiCl_4$,[12] and $SbCl_3$-Al_2O_3[13] have been reported to affect this transformation. Recently, Bhattacharya et al. have reported Amberlite-IR 120–catalyzed synthesis of α-amino phosphonates reaction under microwave irradiation.[14] Although significant advances have been made in this direction, there still exist some limitations such as use of solvents, expensive and toxic catalyst, longer reaction time, and elevated temperature, thereby limiting applications. Also, in many cases, a two-step protocol is employed wherein a preformed imine is used, which is not preferred because some imines are hygroscopic and are not stable for isolation. Thus an efficient protocol was desired for the synthesis of α-aminophosphonates that could overcome these disadvantages and facilitate the direct addition of phosphites to imines in a one-pot fashion under mild reaction conditions.

In recent years, solvent-free reactions have gained considerable attention because the method is valuable not only for ecological and economical reasons but also for simplicity in procedures and high yields of products. Emphasis is also toward the development of clean and green chemical processes, and investigations for new and less hazardous catalysts have become a priority in synthetic organic chemistry. In this context, $ZrOCl_2{\cdot}8H_2O$ is a highly water-tolerant, easy-to-handle, readily available, and inexpensive compound with low toxicity ($LD_{50} = 2950$ mg/Kg). Because of its significant advantages, $ZrOCl_2{\cdot}8H_2O$ has been widely used as a catalyst in various organic transformations such as Michael addition, β-acetamido ketones, esterification, acylation, and Fries rearrangement.[15]

Thus in continuation of our work on solvent-free organic transformations,[16] we herein report an efficient protocol for the one-pot synthesis of α-amino phosphonates using $ZrOCl_2{\cdot}8H_2O$ as a catalyst under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

Initially the one pot reaction of aniline, benzaldehyde and diethyl phosphite was chosen as a model and the role of various reaction parameters



Scheme 1. Synthesis of α-amino phosphonates.

such as catalyst, solvent and catalyst loading were studied (Table 1, entries 1–16). Lewis acid catalysts such as $La(NO_3)_3{\cdot}6H_2O$, $Y(NO_3)_3{\cdot}6H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$, $CuCl_2{\cdot}2H_2O$, and $ZrOCl_2{\cdot}8H_2O$ were investigated, and it was observed that both

Table 1. Influence of catalyst, solvent, and catalyst loading[a]

Entry	Catalyst	Solvent	Catalyst loading (mol %)	Yield (%)[b]
Influence of catalyst				
1	$La(NO_3)_3 \cdot 6H_2O$	Neat	10	23
2	$Y(NO_3)_3 \cdot 6H_2O$	Neat	10	27
3	$Cu(OAc)_2 \cdot H_2O$	Neat	10	44
4	$Cu(NO_3)_2 \cdot 3H_2O$	Neat	10	84
5	$CuCl_2 \cdot 2H_2O$	Neat	10	87
6	$ZrOCl_2 \cdot 8H_2O$	Neat	10	91
Influence of solvent				
7	$ZrOCl_2 \cdot 8H_2O$	Ethanol	10	5
8	$ZrOCl_2 \cdot 8H_2O$	Toluene	10	2
9	$ZrOCl_2 \cdot 8H_2O$	Dichloromethane	10	—
10	$ZrOCl_2 \cdot 8H_2O$	Dioxane	10	12
Influence of catalyst concentration				
11	$ZrOCl_2 \cdot 8H_2O$	Neat	12.5	91
12	$ZrOCl_2 \cdot 8H_2O$	Neat	7.5	82
13	$ZrOCl_2 \cdot 8H_2O$	Neat	5	77
14	$ZrOCl_2 \cdot 8H_2O$	Neat	2.5	61

[a] Reaction conditions: aniline (1 mmol), benzaldehyde (1 mmol), diethyl phosphite (1.1 mmol), solvent (1 ml), time (8 h).

[b] Yields determined by GC.

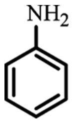
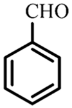
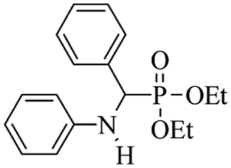
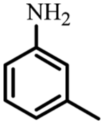
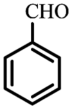
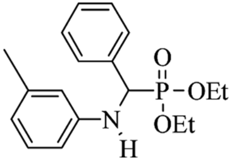
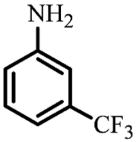
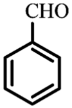
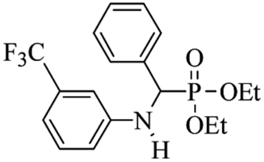
$La(NO_3)_3{\cdot}6H_2O$ and $Y(NO_3)_3{\cdot}6H_2O$ gave lower yields of desired product, whereas copper salts and $ZrOCl_2{\cdot}8H_2O$ were found to give complete conversion of the corresponding imine in 8 h (Table 1, entries 1–6). However, $ZrOCl_2{\cdot}8H_2O$ was used for further studies. The influence of various solvents such as ethanol, toluene, dichloromethane, and dioxane was investigated, and it was observed that excellent yield of the product was obtained when the reaction was carried out under solvent-free conditions (Table 1, entries 7–10). The probable reason may be that under solvent-free conditions, the concentration of catalyst leads to higher reaction rates than the same reaction in the presence of solvent. To get optimium results, the influence of catalyst loading was also studied (Table 1, entries 8–14). An increase in product yield was obtained with an increase in catalyst concentration up to 10 mol%. A further increase in catalyst concentration did not have much effect on the reaction yield.

Using $ZrOCl_2{\cdot}8H_2O$ as catalyst, the one-pot reaction of structurally and electronically different amines/aldehydes and diethyl phosphite was studied at ambient temperature under solvent-free conditions (Table 2, entries 1–16). The reaction of aniline, benzaldehyde, and diethylphosphite in the presence of $ZrOCl_2{\cdot}8H_2O$ (10 mol%) as a catalyst gave 91% yield of diethyl[anilino(phenyl)methyl]phosphonate (Table 2, entry 1). Anilines having electron-donating and electron-withdrawing groups such as CH_3, CF_3, and Cl reacted smoothly with benzaldehyde, providing good yield of the product within a short reaction time (Table 2, entries 2–5). However, activated aniline such as *o*-toluidine provided low yield of the corresponding product even after 24 h (Table 2, entry 6). Next, we also investigated variation in the aldehyde component and substituted benzaldehydes having activating and deactivating groups such as CH_3, Cl, and Br were viable partners (Table 2, entries 7–16). Benzaldehydes substituted at *ortho*, *meta*, and *para* positions were well tolerated under the present conditions, providing good yield of desired product.

To further enhance the reaction rate and yield, we carried out a parallel reaction in a monomode microwave reactor, and the results are presented in Table 1, entries 1–16, method B. A significant enhancement in reaction rate was observed, and the reactions were completed within 5 min thereby extending the scope of the methodology.

The mechanism of the reaction is similar to that reported in the literature[4,8a] and involves two steps. The first step is the reaction of an amine with aldehyde to generate an imine, which then gets activated by the Lewis acid catalyst. The second step involves the nucleophilic addition of diethyl phosphite to the activated imine, thereby affording the desired amino phosphonate.

Table 2. $ZrOCl_2 \cdot 8H_2O$-catalyzed one-pot synthesis of α-aminophosphonates[a]

				Method A		Method B	
Entry	Amine	Aldehyde	Product	Time (h)	Yield[b] (%)	Time (min)	Yield[b] (%)
1				8	91	3	92
2				7	92	2	91
3				7	91	2	92

(*Continued*)

Table 2. Continued

				Method A		Method B	
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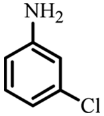
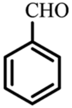
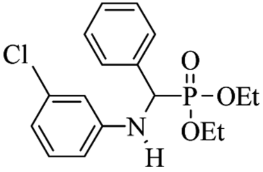
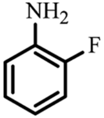
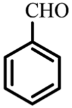
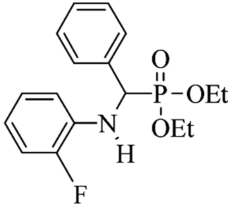
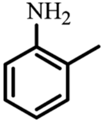
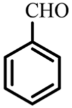
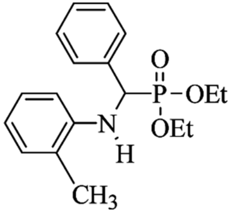
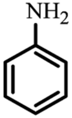
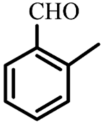
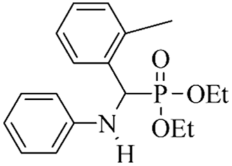
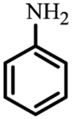
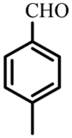
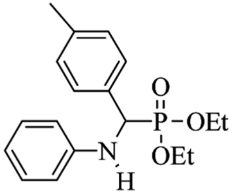
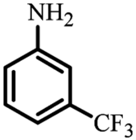
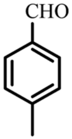
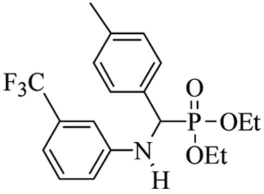
4				6	83	3	86
5				24	88	4	88
6				24	51	5	82

7				8	87	2	88
8				8	88	2	86
9				7	90	2	90

(*Continued*)

Table 2. Continued

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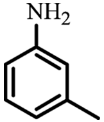
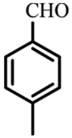
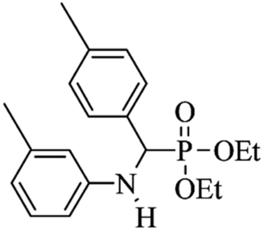
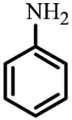
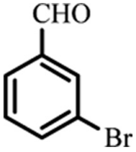
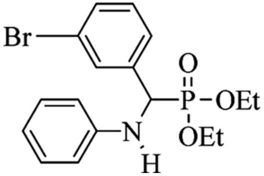
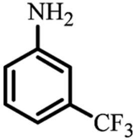
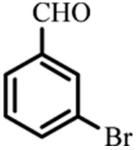
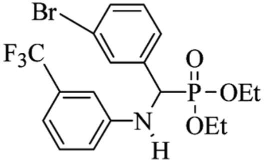
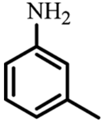
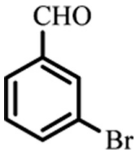
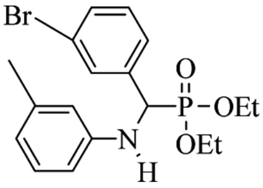
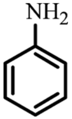
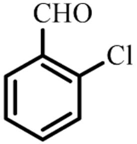
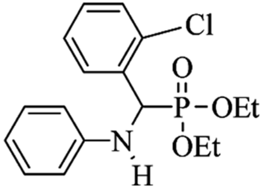
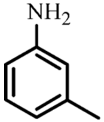
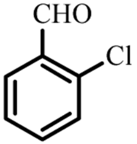
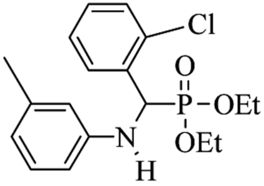
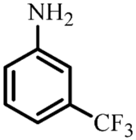
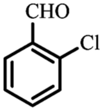
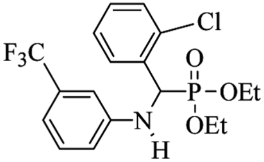
10				6	87 (83)	2	85
11				8	90 (87)	2	91
12				7	87 (85)	2	86

13				6	88 (84)	2	89
14				12	82	3	85
15				6	84 (81)	3	85

(*Continued*)

Table 2. Continued

				Method A		Method B	
Entry	Amine	Aldehyde	Product	Time (h)	Yield[b] (%)	Time (min)	Yield[b] (%)
16				7	87 (84)	3	85

[a] Reaction conditions: amine (1 mmol), aldehyde (1 mmol), diethyl phosphite (1.1 mmol), $ZrOCl_2 \cdot 8H_2O$ (0.1 mmol).
[b] Yields determined by GC. Yields in parantheses are of isolated compounds.

CONCLUSION

In conclusion, we have developed an efficient protocol for one-pot synthesis of α-amino phosphonates using $ZrOCl_2{\cdot}8H_2O$ as a catalyst under solvent-free conditions. Apart from being relatively nontoxic and environmentally friendly, the catalyst offers other advantages such as greater substrate compatibility, high reaction yields, short reaction times, solvent-free conditions, and the ability to tolerate functional groups, making it an important addition to the reported methods. The use of microwave irradiation as a promoter has also been successfully demonstrated in this methodology.

EXPERIMENTAL

General Procedure for Synthesis of α-Aminophosphonates

Method A

A mixture of an aldehyde (1 mmol), an amine (1 mmol), diethyl phosphite (1.1 mmol), and $ZrOCl_2{\cdot}8H_2O$ (10 mol%) was stirred at room temperature. The progress of the reaction was monitored on a gas chromatograph (Chemito 1000). After completion, the product was isolated by silica-gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent. The IR, ^{1}H NMR, ^{13}C NMR, and MS data of some representative α-amino phosphonates are given later.

Method B

A mixture of an aldehyde (1 mmol), an amine (1 mmol), diethyl phosphite (1.1 mmol), and $ZrOCl_2{\cdot}8H_2O$ (10 mol%) was irradiated in a monomode microwave reactor (Biotage) at 120°C using focused irradiation. The progress of the reaction was monitored on a gas chromatograph (Chemito 1000). After completion, the product was isolated by silica-gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent.

Data

Diethyl [(4-methylphenyl){(3-methylphenyl)amino}methyl]
phosphonate: Table 2, Entry 10

FT-IR (KBr): $\nu = 3287$, 2982, 1607, 1487, 1386, 1235. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.12$ (t, $J = 6.9$ Hz, 3H), 1.27 (t, $J = 6.9$ Hz, Hz, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 3.61–3.75 (m, 1H), 3.85–4.17 (m, 3H), 4.76 (d, $J = 7.3$ Hz, 1H), 6.36 (d, $J = 8.2$ Hz, Ar 1H), 6.44 (s, Ar 1H), 6.5 (d, $J = 7.3$ Hz, Ar 1H), 6.97 (t, $J = 7.9$ Hz, Ar 1H), 7.12 (d, $J = 8$ Hz, Hz, Ar 2H), 7.33 (dd, $J = 2.2$ Hz, $J = 8$ Hz, Ar 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.2$, 16.4, 21.2, 21.6, 54.7, 56.7, 63.2, 110.8, 114.8, 119.3, 127.7, 129.1, 129.3, 132.9, 137.6, 138.9, 146.3. MS (EI, 70 eV): 347 (3) (M^+), 210 (100), 118 (13), 91 (20).

Diethyl[anilino(3-bromophenyl)methyl]phosphonate: Table 2, Entry 11

FT-IR (KBr): $\nu = 3300$, 2981, 1605, 1488, 1233. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.16$ (t, $J = 6.9$ Hz, 3H), 1.29 (t, $J = 6.9$ Hz, 3H), 3.70–3.83 (m, 1H), 3.92–4.19 (m, 3H), 4.66 (d, $J = 7.3$ Hz, 1H), 6.56 (d, $J = 7.7$ Hz, Ar 2H), 6.72 (t, $J = 7.3$, Ar 1H), 7.09–7.62 (m, Ar 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.2$, 16.4, 54.7, 56.7, 63.5, 114, 118.7, 122.8, 126.4, 129.3, 130.2, 130.8, 131.1, 138.6, 145.9. MS (EI, 70 eV): 398 (8) (M^+), 260 (100), 180 (18), 104 (23).

Diethyl[(3-bromophenyl){3-(trifluoromethyl)phenylamino}methyl]phosphonate: Table 2, Entry 12

FT-IR (KBr): $\nu = 3292$, 2982, 1607, 1489, 1239. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.16$ (t, $J = 6.9$ Hz, 3H), 1.30 (t, $J = 6.9$ Hz, 3H), 3.72–3.83 (m, 1H), 3.92–4.21 (m, 3H), 4.7 (dd, $J = 7.5$ Hz, $J = 24.3$ Hz, 1H), 6.68 (d, $J = 8$ Hz, Ar 1H), 6.86 (s, Ar 1H), 6.94 (d, $J = 7.7$ Hz, Ar 1H), 7.17–7.63 (m, Ar 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.2$, 16.4, 54.5, 56.5, 63.6, 110.5, 115.1, 116.3, 122.9, 126.4, 129.8, 130.3, 130.7, 131.4, 131.8, 138, 146.3. MS (EI, 70 eV): 466 (8) (M^+), 328 (100), 172 (18), 145 (22).

Diethyl[(3-bromophenyl){(3-methylphenyl)amino}methyl] phosphonate: Table 2, Entry 13

FT-IR (KBr): $\nu = 3297$, 2981, 1603, 1498, 1232. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.15$ (t, $J = 6.9$ Hz, 3H), 1.28 (t, $J = 6.9$ Hz, 3H), 2.22 (s, 3H), 3.72–3.83 (m, 1H), 3.91–4.02 (m, 1H), 4.10–4.18 (m, 2H), 4.7 (dd, $J = 6$ Hz, $J = 24.7$ Hz, 1H), 6.35 (d, $J = 8$ Hz, Ar 1H), 6.42 (s, Ar 1H), 6.56 (t, $J = 7.6$ Hz, Ar 1H), 6.97–7.62 (m, Ar 5H). ^{13} C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.2$, 16.4, 21.6, 54.7, 56.7, 63.5, 110.7, 113.8, 114.7, 119.7, 122.8, 126.4, 129.2, 130.2, 130.8, 138.6, 139.1, 145.9. MS (EI, 70 eV): 412 (8) (M^+), 274 (100), 194 (12), 91 (30).

Diethyl[(2-chlorophenyl){(3-methylphenyl)amino}methyl] phosphonate: Table 2, Entry 15

FT-IR (KBr): $\nu = 3294$, 2983, 1615, 1496, 1346, 1236. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.06$ (t, $J = 7.1$ Hz, 3H), 1.33 (t, $J = 6.9$ Hz, Hz, 3H), 2.21 (s, 3H), 3.56–3.69 (m, 1H), 3.83–3.96 (m, 1H), 4.16–4.26 (m, 2H), 5.36 (dd, $J = 8.2$ Hz, $J = 24.7$ Hz, 1H), 6.37 (d, $J = 7.8$ Hz, Ar 1H), 6.45 (s, Ar 1H), 6.51 (d, $J = 7.3$ Hz, Ar 1H), 6.96–7.59 (m, Ar 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.1$, 16.4, 21.6, 50.5, 52.5, 63.5, 110.5, 114.6, 119.5, 127.4, 128.9, 129.1, 129.2, 129.4, 134.1, 134.3, 139.1, 145.7. MS (EI, 70 eV): 367 (3) (M^+), 230 (100), 91 (20).

Diethyl[(2-chlorophenyl)[{3-(trifluoromethylphenyl)amino}methyl] phosphonate: Table 2, Entry 16

FT-IR (KBr): $\nu = 3297$, 2927, 1728, 1614, 1342, 1236. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 1.07$ (t, $J = 6.9$ Hz, 3H), 1.34 (t, $J = 6.9$ Hz, 3H), 3.57–3.70 (m, 1H), 3.85–3.98 (m, 1H), 4.18–4.28 (m, 2H), 5.40 (dd, $J = 8.9$ Hz, $J = 24.5$ Hz, 1H), 6.71 (d, $J = 8$ Hz, Ar 1H), 6.89–7.65 (m, Ar 7H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 16.1$, 16.5, 50.3, 52.4, 63.6, 110.5, 114.8, 116, 122.4, 126, 127.5, 129.1, 129.5, 129.7, 131.3, 133.6, 134.3, 146.3. MS (EI, 70 eV): 421 (5) (M^+), 284 (100), 172 (20), 145 (30).

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