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Sulfated zirconia: A novel and reusable catalyst for the one-pot synthesis of α -aminophosphonates

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ABSTRACT

A new catalytic method has been developed for the one-pot synthesis of α -aminophosphonates via three component coupling of aldehyde, amine and diethyl phosphite at room temperature in acetonitrile using sulfated zirconia as a solid super acid catalyst. The recovered catalyst could be recycled for five times with gradual decrease in activity.

Keywords: Aldehydes; amines; diethyl phosphate; solid super acid; sulfated zirconia; α -aminophosphonates.

INTRODUCTION

The phosphate group is a common structural unit in natural nucleotides, which play an important role as metabolic intermediates, as common regulatory switches for proteins, and as a backbone for the genetic information [1]. The potential of α -amino phosphonates as peptide mimics has been recognized over many years [2,3]. The chemistry of alkylphosphonates is a relatively new area of research, which has been developed mostly during the past two decades. The α -aminophosphonates are found to exhibit a diverse range of biological activities such as syntheses inhibitors, HIV protease inhibitors, rennin inhibitors, PTPases inhibitors, enzyme inhibitors and as surrogates of α -amino acids [4-7]. There are some reports in which antitumor activity of α -aminophosphonates has been investigated [8-10]. As a result, various approaches have been developed for the synthesis of organophosphorous compounds, in particular, functionalized phosphonates and phosphinates, which attract a special attention due to their biological activities [11]. Generally, α -aminophosphonates are prepared by the addition of phosphorous nucleophiles to imines in the presence of acid catalysts [12].

Recently, three-component synthesis involving the coupling of aldehyde, amine and diethylphosphite or triethylphosphite has been reported by using acid catalysts such as LiClO_4 , InCl_3 , FeCl_3 , ZrCl_4 , $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, lanthanide triflates, $\text{SbCl}_3/\text{Al}_2\text{O}_3$, $\text{TaCl}_5\text{-SiO}_2$, amberlist-15, montmorillonite clay-MW, $\text{Al}_2\text{O}_3\text{-MW}$, TiO_2 , $\text{CF}_3\text{CO}_2\text{H}$, $\text{Sc}(\text{DS})_3$, β -cyclodextrin, SDS, $\text{M}(\text{ClO}_4)$ [13-28]. However, many of these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and diethyl phosphite, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acid. To overcome these, the usage of inorganic solid acid-catalyzed organic transformations are gaining much importance due to the proven advantage of heterogeneous catalysts, like simplified product isolation, mild reaction conditions, high selectivity, easy of recovery and reuse of the catalysts and also minimization of byproducts formation [29-31]. Of various solid acids, interestingly, sulfated zirconia exhibits excellent catalytic activity for a wide range of organic transformations [32,33]. To the best of our knowledge, Kabachnik-Fields reaction has not been reported earlier by sulfated zirconia

(SO₄²⁻/ZrO₂).

MATERIALS AND METHODS

All chemicals and solvents were obtained from Aldrich and used without further purification. Column chromatographic separations were carried out on silica gel 100–200 mesh size. The ¹H NMR spectra of samples were recorded on a JEOL 300-MHz NMR spectrometer using TMS as an internal standard in CDCl₃. Mass spectra were recorded on a MALDI-MS.

General Procedure for the preparation of compound 4

To a mixture of aldehyde (2 mmol), amine (2 mmol) and diethyl phosphite (2.2 mmol), sulfated zirconia (5 mol%) was added and stirred at room temperature for the appropriate reaction time under nitrogen atmosphere. After completion of the reaction, distilled water (5 ml) was added, and the mixture was extracted with EtOAc (3 X 10 ml). The combined organic portions are washed with water (2 X 10 ml), dried over anhydrous Na₂SO₄, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel to obtain pure α-aminophosphonate.

Spectral data of principal compounds

Diethyl phenyl (phenyl amino) methyl phosphonate (4a).

IR (neat): ν_{\max} 3295, 1601, 1498, 1234, 1022, 963, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.79-7.69 (m, 3H), 7.60-7.55 (m, 1H), 7.41-7.34 (m, 2H), 7.01 (t, 2H, *J* = 7.7 Hz), 6.60 (d, 2H, *J* = 7.7 Hz), 4.89 (d, 1H, *J* = 23.9 Hz), 4.18-4.03 (m, 2H), 3.92-3.83 (m, 1H), 3.66-3.56 (m, 1H), 1.26 (t, 3H, *J* = 6.8 Hz), 1.04 (t, 3H, *J* = 6.8 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 146.2, 146.1, 133.0, 129.0, 128.2, 127.8, 127.5, 126.8, 125.9, 125.4, 118.2, 113.7, 63.3, 57.0, 55.0, 16.1; EIMS (M+H): *m/z*: 320.

Diethyl (4-bromophenyl) (phenyl amino) methyl phosphonate (4g).

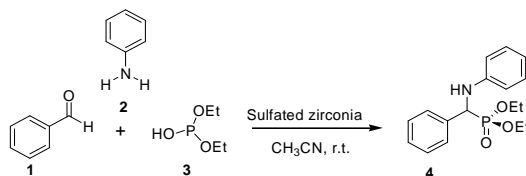
IR (neat): ν_{\max} 3302, 1601, 1495, 1235, 1021, 971, 751 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.16 (m, 4H), 6.99 (t, 2H, *J* = 7.5 Hz), 6.59 (t, 1H, *J* = 7.3 Hz), 6.44 (d, 2H, *J* = 7.7 Hz), 4.75 (brs, 1H), 4.58 (d, 1H, *J* = 24.1 Hz), 4.12-3.95 (m, 2H), 3.94-3.81 (m, 1H), 3.75-3.58 (m, 1H), 1.23 (t, 3H, *J* = 6.9 Hz), 1.10 (t, 3H, *J* = 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 145.9, 134.9, 131.6, 129.4, 129.3, 129.1, 118.5, 113.7, 63.4, 56.4, 54.4, 16.2; EIMS (M+): *m/z*: 398.

Diethyl (naphthalene-3-yl) (phenyl amino) methyl phosphonate (4h).

IR (neat): ν_{\max} 3304, 1601, 1503, 1234, 1022, 969, 750 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.9 (s, 1H), 7.76 (t, 3H, *J* = 8.3 Hz), 7.60-7.55 (m, 1H), 7.44-7.37 (m, 2H), 7.03 (t, 2H, *J* = 7.5 Hz), 6.65-6.55 (m, 3H), 4.98 (br s, 1H), 4.87 (d, 1H, *J* = 24.9 Hz), 4.18-4.04 (m, 2H), 3.95-3.81 (m, 1H), 3.67-3.53 (m, 1H), 1.29 (t, 3H, *J* = 6.7 Hz), 1.06 (t, 3H, *J* = 6.7 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 146.1, 146.0, 133.0, 128.9, 128.1, 127.7, 127.4, 126.8, 126.7, 126.0, 125.9, 125.4, 118.2, 113.7, 63.4, 57.0, 54.9, 16.1; EIMS (M+H): *m/z*: 370.

RESULTS AND DISCUSSION

In this paper, we wish to report an efficient and versatile procedure for affecting the three-component, one-pot reaction of an aldehyde, an amine, and diethylphosphite for the preparation of α-aminophosphonates in the presence of a catalytic amount of sulfated zirconia (Scheme 1).



Scheme 1. Synthesis of α-aminophosphonate 4a

Initially, we attempted the one-pot reaction of benzaldehyde (1), aniline (2) and diethylphosphite (3) in the presence of 5 mol% sulfated zirconia in acetonitrile at room temperature. The corresponding diethyl phenyl (phenylamino) methylphosphonate 4a was obtained in 95% yield (Scheme 1). At the outset, the three-component reaction was

investigated in various solvents at room temperature. To optimize the reaction conditions, the model reaction was examined in solvent-free conditions as well as in various solvents such as acetonitrile, acetone, dichloromethane and ethanol in the presence of sulfated zirconia. As a solvent, acetonitrile appeared to give the best results, when aldehyde (2 mmol), amine (2 mmol) and diethylphosphite (2.2 mmol) were treated with sulfated zirconia (5 mol%) at room temperature. Under these conditions, the reaction proceeded smoothly under mild conditions to produce the desired phosphonate in good yield. However, in the absence of sulfated zirconia, the reactions did not proceed even after 24 h at room temperature (Table 1).

Table 1. Screening of the catalyst and solvent for the synthesis of 4a

Entry	Catalyst (% mol)	Solvent	Time (h)	Yield (%)
1	-	CH ₃ CN	24	-
2	SO ₄ ²⁻ /ZrO ₂ (10)	Solvent free	24	-
3	SO ₄ ²⁻ /ZrO ₂ (10)	CH ₂ Cl ₂	24	65
4	SO ₄ ²⁻ /ZrO ₂ (10)	Ethanol	24	70
5	SO ₄ ²⁻ /ZrO ₂ (10)	Acetone	24	70
6	SO ₄ ²⁻ /ZrO ₂ (5)	CH ₃ CN	8	95

Encouraged by this result, we turned our attention to various aldehydes, amines and diethylphosphite with similar molar ratios as mentioned earlier. In all the cases, the reactions proceeded smoothly at room temperature to furnish the corresponding α -aminophosphonates in good to high isolated yields (78-95%). Next, we have studied the reaction with both electron-rich and electron-deficient aromatic aldehydes. To further evaluate the role of the substituent for this reaction, several aldehydes and amines with different substituent were subjected to the present reaction conditions (Table 2). The reactions with substrates bearing electron donating groups on the aromatic ring are faster than those that of electron-deficient substrates.

Table 2. One-pot synthesis of α -aminophosphonates using sulfated zirconia at room temperature

Entry	Aldehyde	Amine	Phosphite	Product (4) ^a	Time (h)	Yield (%) ^b	m.p. Found ^o C (Reported)	Reference
a					8	95	87(86)	[35]
b			"		11	82	57(57)	[35]
c			"		10	80	Viscous oil	[36]
d			"		12	78	120(120)	[37]
e			"		10	80	Viscous oil	[40]
f			"		8	90	108(108)	[34]
g			"		9	82	Viscous oil	[38]
h			"		9	90	Viscous oil	[38]
i			"		8	92	122(123)	[39]
j			"		11	84	Viscous oil	[38]
k			"		12	80	130(131)	[36]

^aThe products were characterized by NMR, IR and mass spectrometry^bYield refers to pure products after chromatography.

The efficiency of the sulfated zirconia was compared with other reported catalysts for the synthesis of α -aminophosphonates (Table 3). The results summarized in Table 3 clearly demonstrate the superiority of sulfated zirconia in terms of time, cost and operational simplicity. The catalyst was easily separated by simple filtration and reused after activation with gradual decrease in activity. The recovered sulfated zirconia was recycled in further reactions (Table 4).

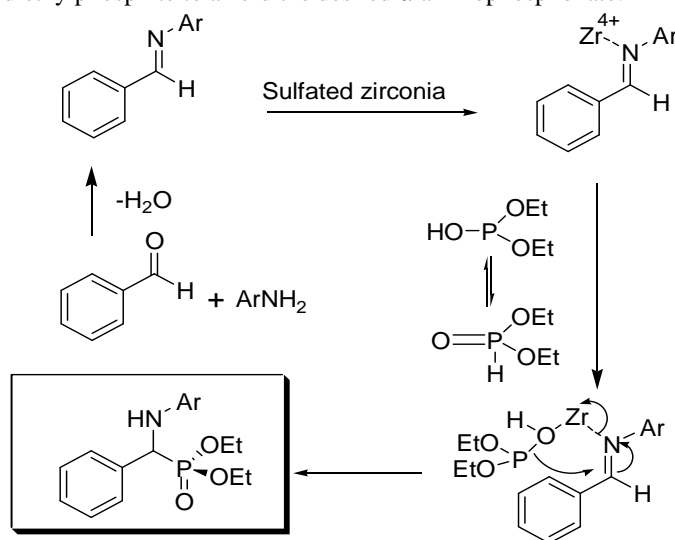
Table 3. Synthesis of α -aminophosphonates using different catalysts

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Amberlyst-15	CH ₃ CN	24	-
2	Cl-SO ₃ H	CH ₃ CN	24	10
3	PMA	CH ₃ CN	24	-
4	SO ₄ ²⁻ /ZrO ₂	CH ₃ CN	8	95

Table 4. Recycling of sulfated zirconia for the preparation of **4a**

No. of cycles	Catalyst	Solvent	Yield (%)
1	Sulfated zirconia	CH ₃ CN	95
2	Sulfated zirconia	CH ₃ CN	93
3	Sulfated zirconia	CH ₃ CN	92
4	Sulfated zirconia	CH ₃ CN	89
5	Sulfated zirconia	CH ₃ CN	85

A reasonable pathway for three component reaction of an aldehyde, amine and diethylphosphite in the presence of sulfated zirconia is presented in Scheme 2. The reaction proceeds *via* the initial formation of imine that undergoes subsequent addition with diethylphosphite to afford the desired α -aminophosphonate.

**Scheme 2.** A plausible reaction mechanism

CONCLUSION

In conclusion, we have shown that sulfated zirconia catalyzes efficiently the one-pot synthesis of biologically active α -aminophosphonates in good yields via a three-component coupling reaction of an aldehyde, amine and diethylphosphite at room temperature. This protocol has advantages of mild reaction conditions, use of recyclable, water-tolerant and environment-friendly catalyst and also involve simple work-up procedure.

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