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Silica Sulfuric Acid as a Recyclable Catalyst for a One-Pot Synthesis of α-Aminophosphonates in Solvent-Free Conditions

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Abstract: A simple and efficient method has been developed for the synthesis of α-aminophosphonates by a one-pot three-component condensation of aldehydes, amines and diethyl phosphite in the presence of a catalytic amount of silica sulfuric acid under solvent-free reaction conditions. The major advantages of the present method are good yields, inexpensive, ecofriendly and reusable catalyst, short reaction times, mild and solvent-free reaction conditions.

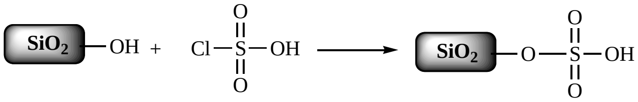
Keywords: α-Aminophosphonates, aldehydes, amines, alkyl phosphite, three-component reaction.

INTRODUCTION

α-Aminophosphonates and other related derivatives have been valuably involved in the preparation of medicinal compounds and synthetic intermediates [1]. The utilities of α-aminophosphonates as peptide mimics [2], haptens of catalytic antibodies [3], antibiotics and pharmacological agents [4], and herbicides [5] have been reported. Hence, greater attentions has been attracted to these compounds due to their wide biological activity.

Recently many synthetic methods for α-aminophosphonates have been reported. Among these, the classical method is the nucleophilic addition of phosphites with imines, that was one of the most preferred methods in the presence of Lewis acids [6] $SnCl_2$, $SnCl_4$, $BF_3.Et_2O$, $ZnCl_2$, $MgBr_2$, and $InCl_3$. However, these reactions cannot proceed in one-pot manner from a carbonyl compound, an amine, and a phosphite because the water generated during the course of the reaction can decompose or deactivate the Lewis acid [7]. Although three-component α-aminophosphonate syntheses starting from aldehydes, amines, and diethyl phophite or triethyl phosphite catalyzed by Lewis acids [8] have been reported, these new developments also suffer from stoichiometric amount of catalysts, expensive reagents, longer reaction times, and use of harmful organic solvents. Hence, there is still a need to develop a more efficient, practical, and environmentally benign method for the synthesis of α-aminophosphonic esters.

Recently, the use of solid acidic catalysts in organic synthesis has attracted much attention since they possess many advantages, for example operational simplicity, nontoxicity, recyclability, low cost, and ease of isolation after completion of the reaction. Silica sulfuric acid has emerged as a powerful solid acidic catalyst in synthetic methodology [9]. The silica sulfuric acid could easily be prepared by the reaction of silica gel and chlorosulfonic acid (Scheme **1**) [9b]. Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, we considered silica sulfuric acid to be an ideal heterogeneous acid catalyst for the synthesis of α-aminophosphonates.



Scheme 1.

Also, it is widely reported in the literature [10] that application of microwave (MW) irradiation enables realization of reactions, otherwise requiring harsh conditions and too slow for practical purposes. Moreover, MW assisted reactions are believed to satisfy the demands of ‘green chemistry’ allowing for solvent-free conditions to be employed.

Herein, we report an efficient, practical, and high yielding method for a three-component, one-pot synthesis of α-aminophosphonic esters using silica sulfuric acid under solvent-free reaction conditions.

RESULTS AND DISCUSSION

An initial study was conducted by the treatment of benzaldehyde (**1**), aniline (**2**), and diethyl phosphite in methanol in the presence of a catalytic amount of silica sulfuric acid [11] (20 mol%) and irradiating with MWs for 3 min to afford the corresponding aminophosphonate **3a** in 85 % yield. Under these conditions, we attempted to prolong reaction time to improve the yield, but no relevant effect has not been observed (Entry 2 in Table **1**). It is exciting that the removing of methanol as solvent can wonderfully improve the yield (94%) (Entry 5 in Table **1**). Rise in MW power has not led to better yield in 3 min. When water was used as solvent, although all of the substrates did not dissolve well in it, the yield has not been remarkably decreased (Entry 3 in Table **1**). After that, the amount of the catalyst was optimized. It was found that, under solvent-free conditions, silica sulfuric acid can effectively catalyze α-aminophosphonate formation under MW irradiation. The above results are summarized in Table **1**.

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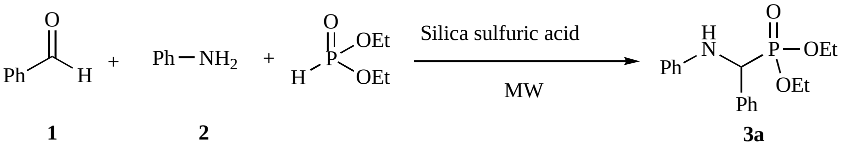
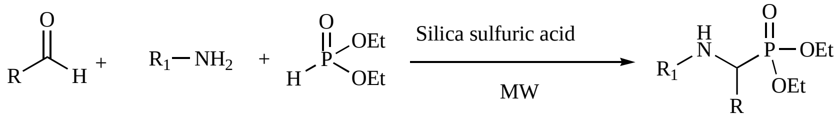
Table 1. Synthesis of α-Aminophosphonate 3a under Different Conditions[a]

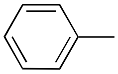
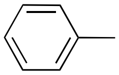
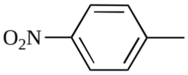
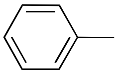
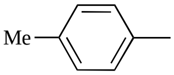
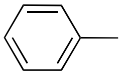
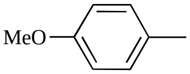
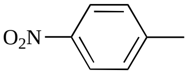
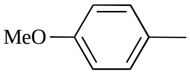
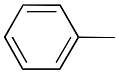
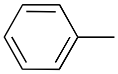
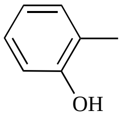
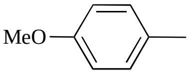
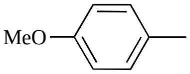


Entry	Solvent	Amount of Catalyst (mol %)	Time (min)	Yields (%)[b]
1	Methanol	20	3	85
2	Methanol	20	5	86
3	Water	20	3	90
4	No solvent	20	2	88
5	No solvent	20	3	94
6	No solvent	20	5	93
7[c]	No solvent	20	3	83
8[d]	No solvent	20	3	90
9	No solvent	10	3	85

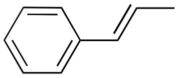
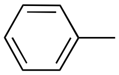
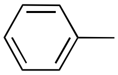
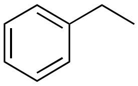
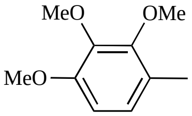
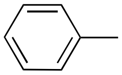
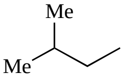
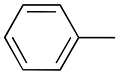
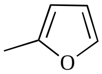
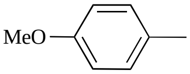
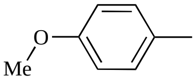
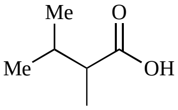
[a] All the reactions were performed on aldehyde **1** (1 mmol), amine **2** (1 mmol) and diethyl phosphite (1 mmol) in the presence of silica sulfuric acid (20 mol%) for 3 min under MW irradiation (power 1000 W) unless otherwise specified.
[b] Isolated yield.
[c] MW irradiation power 1200 W.
[d] MW irradiation power 800 W.

Table 2. Synthesis of α-Aminophosphonates Catalyzed by Silica Sulfuric Acid[a]



Entry	R	R₁	Product	Time (min)	Yields[b]
1			**3a**	3	94
2			**3b**	2	96
3			**3c**	2	93
4			**3d**	5	97
5			**3e**	3	94
6			**3f**	4	85
7			**3g**	4	97

(Table 2). Contd…..

Entry	R	R_1	Product	Time (min)	Yields^b
8			**3h**	3	89
9			**3i**	3	96
10			**3j**	5	88
11			**3k**	4	79
12			**3l**	5	97
13			**3m**	4	91

[a] Reaction conditions: aldehyde (1 mmol), amine (1 mmol), diethyl phosphite (1 mmol), silica sulfuric acid (20 mol%), 1000 W.
[b] Isolated yield.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used a variety of aldehydes and amines, which were subjected to the one-pot three-component operation in the presence of a catalytic amount of silica sulfuric acid to furnish the corresponding α-aminophosphonates in moderate to high yields [12]. The results are summarized in Table **2**. Table **2** demonstrates that there were not obvious electronic effects from differently substituted aromatic aldehydes. Benzaldehydes with both electron-donating and -withdrawing groups could be accomplished the one-pot reaction. The reaction was compatible with various substitutents such as OMe, NO_2 and Me. Lower yields were observed for aliphatic aldehydes, including cinnamaldehyde (Entries 8 and 11 in Table **2**). Morever, no conjugate addition product was obtained for cinnamaldehyde (Entry 8 in Table **2**). When anilines with electron-withdrawing substituents were used, the reactions needed to be carried out for longer periods (Entry 4 in Table **2**). In the case of aliphatic amines, such as benzylamine, the corresponding α-aminophosphonates were obtained in good yields (Entry 9 in Table **2**). In order to estimate the efficiency of this catalyst system, an amino acid was used as starting product under the selected conditions (Entry 13 in Table **2**): the reaction proceeded smoothly, and the yield was good.

The ability to recover and recycle silica sulfuric acid and its catalytic activity was studied (Table **3**). The catalyst can be easily separated by addition of CH_2Cl_2 and filtration. Thus, the recovery and recycle of silica sulfuric acid could be very convenient. The reaction of benzaldehyde (**1**), aniline (**2**), and diethyl phosphite, under the present reaction conditions reported in Table **3**, furnished the α-aminophosphonates in good yields over four cycles.

Table 3. The Investigation of Recovering and recycling the Catalyst[a]

Run	Yield^b (%)	Recovery of catalyst (%)
1	94	99
2	94	98
3	93	98
4	94	97

[a] Reaction conditions: aldehyde(**1**) (1 mmol), amine (**2**) (1 mmol), diethyl phosphite (1 mmol), silica sulfuric acid (20 mol%), 1000 W.
[b] Isolated yield.

In conclusion, silica sulfuric acid was found to be an efficient catalyst for the one-pot reaction of aldehydes, amines, and diethyl phosphite to obtain α-aminophosphonates in good to excellent yields. With the increasing need of green synthetic procedures, the advantages such as high yields, solvent-free condition, and ease of product isolation make the present methodology environmentally benign.

ACKNOWLEDGEMENT

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[11] Silica sulfuric acid was prepared by adding chlorosulfonic acid (11.66 g, 100 mmol) to the silica gel (30.00 g) dropwise at r.t. After the addition was complete, the resulting mixture was stirred until no HCl gas was evolved from the vessel. After the addition was complete, the resulting mixture was stirred until no HCl gas was evolved from the vessel. The crude product was washed with CH_2Cl_2(2×10 mL).The product (silica sulfuric acid, 36.00 g) was obtained.

[12] The required carbonyl compound (1 mmol), amine (1 mmol), diethyl phosphite(1 mmol) and silica sulfuric acid (100 mg) were taken in a test tube and exposed to MW irradiation for the appropriate time. The reactions was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and CH_2Cl_2 (25 mL) was added, followed by the filtration and washing with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, concentrated under reduced pressure, and purified by passing through a column of silica gel using ethyl acetate / *n*-hexane(1: 4) as the eluent to afford the corresponding pure α-aminophosphonates. All the products were characterized from their spectral parameters which resulted consistent with the literature data for the known compounds **3a-i**, **k**, **l**. Compound **3j**: Colorless liquid. IR (KBr): ν 3341, 1236, 1112 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 8.6 Hz, 1H), 6.77-6.61 (m, 6H), 4.95-4.88 (d, 1 H, J = 23.8 Hz), 4.20-383 (m, 13 H), 1.31-1.15 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.0, 147.3, 140.4, 132.5, 122.0, 117.5, 113.7, 113.3, 108.4, 64.4, 56.9, 55.8, 16.8, 15.4 ppm. MS (EI) m/z 409 (M^+). Elem. Anal. Calcd. for $C_{20}H_{28}NO_6P$: C, 58.67; H, 6.89; N, 3.42. Found: C, 58.76; H, 7.01; N, 3.49. **Compound 3m**: White solid, mp 115 °C. IR (KBr): ν 3379, 3335, 1698, 1238, 1108 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J=6.4 Hz, 2H), 6.67 (d, J= 6.4 Hz, 2H), 4.68 (d, J= 22.0 Hz,1H), 4.18-3.80 (m, 7 H), 3.54 (s, 1H), 2.42 (m, 1H), 1.29-1.09 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 160.2, 130.3, 124.1, 115.2, 63.1, 62.2, 56.8, 51.3, 31.2, 18.3, 15.2 ppm. MS (EI): m/z 373 (M^+). Elem. Anal. Calcd. for $C_{17}H_{28}NO_6P$: C, 54.68; H, 7.56; N, 3.75. Found: C, 54.73; H, 7.48; N, 3.80.