

Silica nanoparticles as highly efficient catalyst for the one-pot synthesis of α -aminophosphonate derivatives from primary amines, quinoline-4-carbaldehyde and phosphite under solvent-free conditions

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Abstract

Kabachnik-Fields reaction between an amine, quinoline-4-carbaldehyde, and a phosphite in the presence of the prepared silica nanoparticles from rice hulls (silica NP; ca. 42 nm) proceeds smoothly to afford the corresponding α -aminophosphonates in high yields. The reactions were carried out in one pot and under solvent-free conditions at 50-80 °C.

Keywords: Kabachnik-Fields reaction; nanocatalyst; 4-quinolinecarboxaldehyde; silica- nanoparticles; α -aminophosphonate.

Introduction

Phosphorus-carbon bond formation has attracted too much attention because of its application in organic synthesis and bioorganic chemistry. The key role of naturally occurring amino acids in the chemistry of life, and as structural units in peptides, proteins and enzymes, has led to intense interest in the chemistry and biological activity of synthetic analogues. α -amino phosphonates are phosphorus analogs of amino acids [1], which have been widely used as imaging agents and as antitumor, antihypertensive, antifungal, and antibacterial agents [2]. Aminophosphonic acids are also found as the constituents of natural products [3].

Various synthetic methods for α -aminophosphonic acids and α -aminophosphonates have been reported [3a,4]. However, the most remarkable pathway to the synthesis of α -aminophosphonates is the Kabachnik-Fields reaction [5], which is a one-pot, three-component procedure using carbonyl compound, amine and dialkyl phosphite. The key step in the Kabachnik-Fields synthesis of α -aminophosphonates is the nucleophilic base- or acid- catalysed condensation of an amine with a carbonyl compound followed by the addition of phosphite to the resulting imine. A broad range of catalysts has been employed for the Kabachnik-Fields reaction. Lewis acids, such as $Mg(ClO_4)_2$, $LiClO_4$,

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InCl_3 , BF_3 , ZrCl_4 , AlCl_3 and SnCl_4 [6], and various bases, such as potassium fluoride on alumina [7], lithium diisopropylamine (LDA) [8], and magnesium oxide (MgO) [9], were also applied as catalysts.

Acids, and especially Lewis acids are effective catalysts for Pudovik reaction. However, their application in one-pot Kabachnik-Fields reaction is not straightforward, because water forming during imine formation can deactivate the Lewis acid. This problem was solved by either co-use of catalyst with dehydrating agent or by application of catalysts being stable in water, for example, some rare earth metal triflates, e.g. lanthanide triflates/ MgSO_4 [10a], TaCl_5 - SiO_2 [10b].

Nanoparticles (NPs) have recently attracted tremendous attention in catalysis due to their improved efficiency under mild and environmentally benign conditions in the context of green synthesis [11]. NPs have the potential to exhibit superior catalytic activity in comparison to bulk counterparts owing to their enormously large and highly reactive surface area [12].

Here, we report a simple procedure for the preparation of α -aminophosphonates *via* multi-component reactions in the presence of silica nanoparticles as high efficient and inexpensive catalysts.

Experimental

General

Starting materials and solvents were purchased from Merck (Germany), Fluka (Switzerland), and Acrös (USA) and were used without further purification. The reactions were monitored by TLC and NMR techniques, which indicated that there were no side products. Melting points were measured on an Electrothermal

9100 apparatus. IR spectra were recorded on a Mattson-1000 FTIR spectrophotometer. ^1H (250 MHz), ^{13}C (62.5 MHz) and ^{31}P (101 MHz) NMR measurements were recorded on a Bruker 400 spectrometer in CDCl_3 with tetramethylsilane as internal standard. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. Elemental analyses: Heraeus-CHN-O-Rapid analyzer has been used to determine the percentage of the elements.

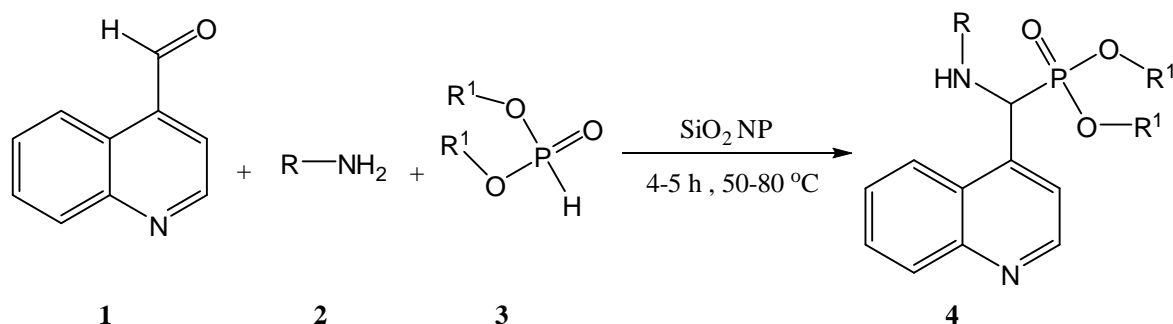
The silica-NP samples were characterized with a scanning electron microscope (SEM) (Philips XL 30) with gold coating. X-Ray powder diffraction (XRD) measurements: X_{pert} diffractometer of Philips company with monochromatized CuK α radiation. The samples were then dried and analyzed.

General procedure for the synthesis of 4a-4e

Phosphite 3 (0.5 mmol) was added dropwise to a magnetically stirred solution of 4-quinolinecarboxaldehyde 1 (0.5 mmol) and amines 2 (0.5 mmol) in the presence of nanocatalyst (silica nanoparticles, 20 mol %) at room temperature, following which the mixture was heated in an oil bath at 50-80 °C and stirred for 4-5 h (Table 1). The progress of the reaction was monitored by TLC (eluent: EtOAc/petroleum ether, 70:30). When the reaction was completely done, EtOAc (3×20 mL) was added to the mixture and the catalyst was separated by filtration. The organic solvent was removed under reduced pressure and the products were purified by preparative layer chromatography (PLC).

General procedure for the preparation of silica nanoparticles

Silica nanoparticles were prepared by the thermal decomposition of rice hulls [13a], with a modified procedure [13b]. The rice hulls, washed in water and dried at 80 °C, and then, grinded by ball milling. The powders are refluxed in HCl (1 M) for 1 h. The resulted mixture filtered and washed with deionized water for 3 times, and then dried at 80 °C for 1 h. The prepared silica- NPs was calcinated at 700 °C in the air for 3 h to remove the template.



Scheme 1. Preparation of α -aminophosphonates **4a-4e** from 4-quinolinecarboxaldehyde **1**, amines **2**, and phosphites **3**

The results from X-ray diffraction (XRD) showed that the sample was silica NP as indicated by broadened peaks around $2\theta = 22^\circ$ [13b].

In connection with our recent interest to α -aminophosphonates, here, we use Silica nanoparticles, prepared from rice hulls, as highly efficient and inexpensive catalyst for the synthesis of α -aminophosphonate derivatives. Also, In order to investigate the effects of other reaction media in this reaction, we

Results and discussion

As a part of our ongoing program to develop efficient and robust methods for the preparation of organophosphorus compounds [14-18], here we report a simple, one-pot, three-component reaction between quinoline-4-carboxaldehyde (**1**), amines **2**, and phosphites **3**, in the presence of silica NPs which leads to α -aminophosphonates after 4-5 h **4** (Scheme 1).

carry out the described three component reaction in CH_3OH and solvent-free (neat) systems without catalyst (Table 1). In absence of catalyst no product observed. The reaction in the presence of CH_3OH , and silica gel powder proceeded in fairly low to moderate yields. In comparison of previously reported nanoparticles [19], MCM-41@PEI, SiO_2 NPs gives higher yields of products.

Table 1. Optimization of the synthesis of α -aminophosphonate **4a**

Entry	Catalyst	Solvent	Temp. / °C	Reaction Time/h	Yield ^a / %
1	–	–	100	24	0
2	SiO_2 NP	CH_3OH	65	8	47
3	silica gel powder HF_{254} (Merck)	–	80	4	51
4	SiO_2 NP	–	80	4	93
5	MCM-41@PEI	–	80	5	91

^aIsolated yield

Silica nanoparticles was found to catalyze the synthesis of α -aminophosphonate derivatives **4** from quinoline-4-carboxaldehyde (**1**), amines

2 and phosphites **3** under solvent-free conditions with high efficiency (Table 2).

Table 2. Synthesis of α -aminophosphonates **4a-4e** by silica NPs

Entry	Products ^a	R	R ¹	Reaction Time/h	Temp. /°C	Yield ^b / %
1	4a	Ph	Ph	4	80	93
2	4b	4-F-C ₄ H ₆	Ph	4	80	89
3	4c	C ₆ H ₅ -CH ₂ -CH ₂	Ph	5	80	85
4	4d	Ph	Et	4	50	91
5	4e	4-F-C ₄ H ₆	Et	4	50	90

^a previously reported products [19]

^b Isolated yield

The recycling potential of silica NPs catalyst was studied in this system. The catalyst separated by simple filtration of the reaction mixture, washed with deionized water and ethanol and then dried under vacuum at

60 °C for several days. As shown in Figure 1, the yields of **4a** only decrease a little after the reuse of SiO₂ NPs for four times.

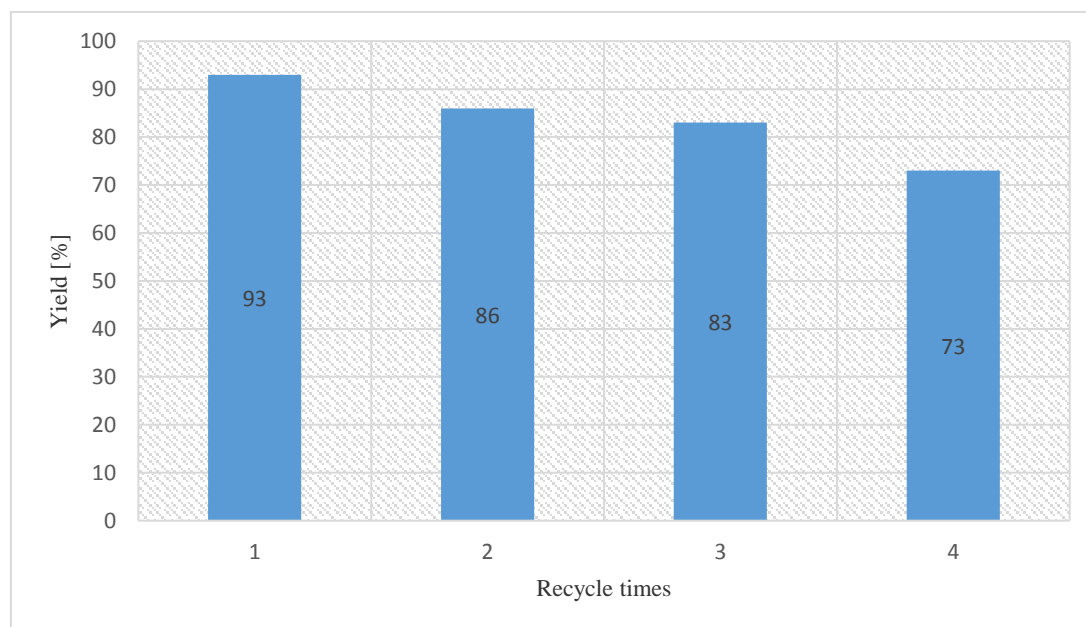


Figure 1. Reusability of the nanocatalyst

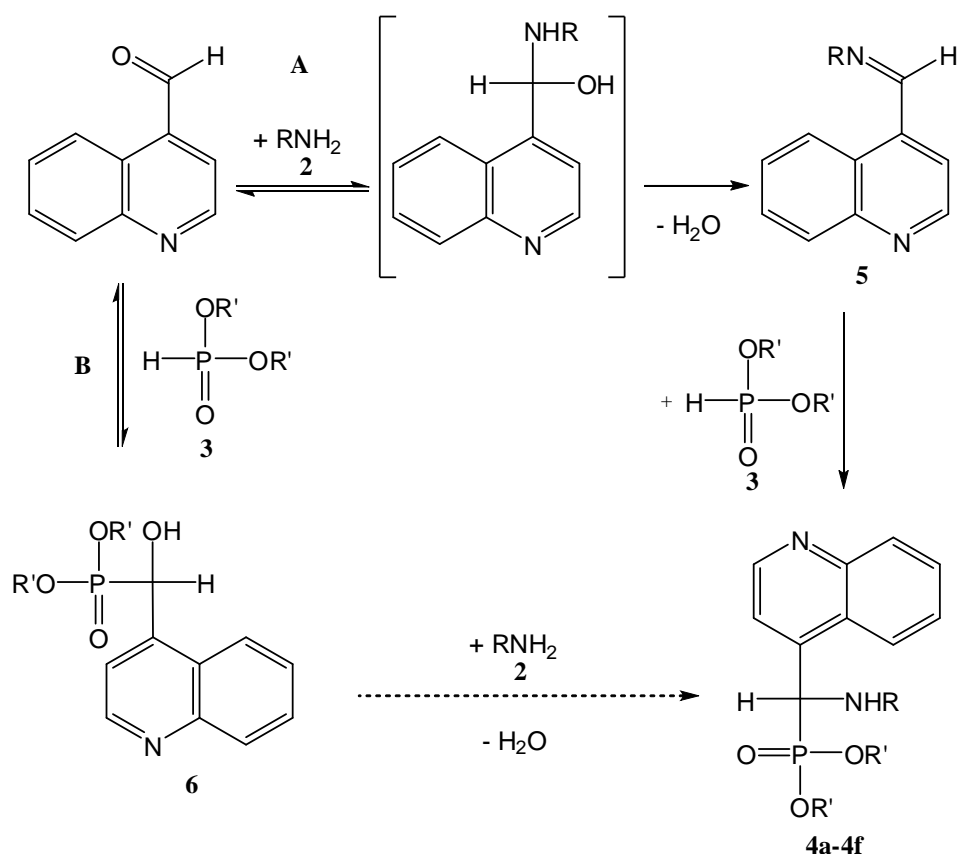
The structures of the products were deduced from their IR, Mass, ¹H NMR, ¹³C and ³¹P NMR spectra. The mass spectra of three compounds displayed molecular ion peaks at the appropriate *m/z* values. The ¹H NMR spectrum of **4a** also exhibited distinct signals from

NH ($\delta = 5.31$ - 5.38 ppm), one *dd* for CHP ($\delta = 6.01$ ppm, $J_{HP} = 25.25$) and aromatic -CH ($\delta = 6.54$ - 8.82 ppm). The ¹H decoupled ¹³C NMR spectrum of **4a** delineated one *d* for C-P ($\delta = 51.02$ ppm, $J_{CP} = 152$), and other 27 distinct resonances, the partial assignment of

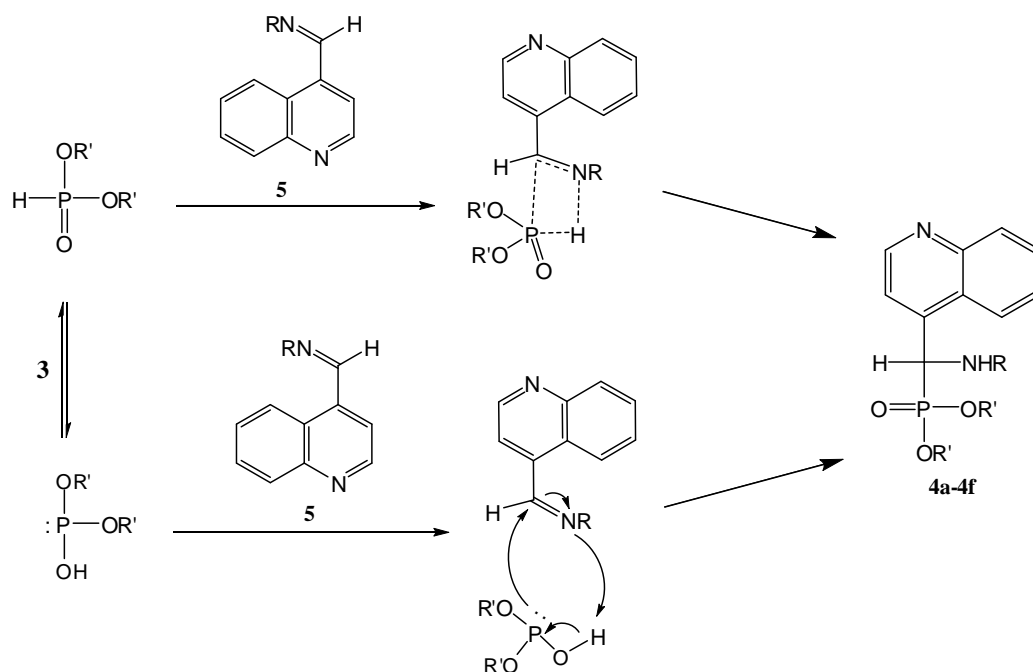
these resonances is given in the Experimental Part. The ^{31}P NMR spectrum of **4a** showed one resonance at the $\delta=13.71$ ppm that is consistent with its phosphonic acid ester structure [20].

A reasonable mechanism for the formation of compounds **4a-4f** is shown in Scheme 2. The first step is the condensation of 4-quinolinecarboxaldehyde **1** and amine **2** to form the corresponding imine **5** (Pathway A). In the second step phosphites **3** adds to the C=N bond of the transient imine **5**, and it was followed by the Pudovic type of

addition to give α -aminophosphonates **4** as the final product [20]. On the other hand, phosphites are able to undergo Abramov addition to C=O bond, giving α -hydroxyphosphonates **6** (Scheme 2, path B) [21]. It is sometimes asserted that the Abramov pathway can also lead to the product **4** of Kabachnik-Fields reaction and even considered the direct nucleophilic substitution of hydroxyl in α -hydroxyphosphonates by amino component [22]. Due to the tautomerism of phosphite, the addition to the imine **5** could occur by either a four- or five-membered transition state (Scheme 3).



Scheme 2. Proposed mechanism for the formation of compounds **4a-4e**



Scheme 3. Addition of phosphite to imine

Conclusion

In summary, herein, SiO₂ NPs prepared from rice hulls have been described as an inexpensive, economically-friendly and extremely efficient catalysts for the synthesis of α -aminophosphonates by the three-component reaction between 4-quinolinecarboxaldehyde (**1**), amines (**2**), and phosphite (**3**). This solvent-free reaction has many advantages for the synthesis of α -aminophosphonates: such as reduced pollution, low costs, high yields of products, reuse of catalyst, and simplicity in process and handling.

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