

Silica Sulfuric Acid: An Efficient Heterogeneous Catalyst for the One-Pot Synthesis of 1,4-Dihydropyridines under Mild and Solvent-Free Conditions

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Abstract: A series of 1,4-dihydropyridines have been prepared by a one-pot condensation of aldehydes, ethyl acetoacetate, and ammonium acetate in the presence of a heterogeneous catalyst silica sulfuric acid at room temperature under solvent-free condition. This new protocol has the advantage of short reaction time and excellent yields, and is an environmentally benign route to the synthesis of 1,4-dihydropyridines.

Key words: aldehyde; ethyl acetoacetate; ammonium acetate; silica sulfuric acid; 1,4-dihydropyridine

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In synthetic organic chemistry a one-pot synthesis has become a blue print to improve the efficiency of a reaction wherein a reactant is subjected to successive chemical reactions in one vessel [1]. The advantage of this strategy involves: i) use of commercially available starting materials; ii) avoiding a lengthy separation of the intermediates; iii) saving time and resources; iv) achieving increase in the chemical yield, and one such one-pot synthesis is of 1,4-dihydropyridines.

1,4-Dihydropyridine (DHP) scaffold has been shown to possess remarkable pharmacological activities [2]. 1,4-Dihydropyridines (DHPs) such as nifedipine, nitrendipine, and nimodipine, have been proved to be an important class of calcium-channel modulators [3,4] and have been introduced as potential drugs for the treatment of congestive heart failure [5]. DHPs act as potent vasodilators, anti-hypertensives, bronchodilators, antiatherosclerotics, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents [6]. They are also useful as cognition enhancers, neuroprotectants, and platelet antiaggregatory agents [7-9]. DHP esters serve as biomimetic reducing agents such as NADPH and NADH models also [10,11].

In 1881, Arthur Rudolf Hantzsch was the first to report the synthesis of DHPs by a one-pot reaction of an aldehyde, a β -ketoester, and aqueous ammonium hydroxide in ethanol [12]. Since then a series of procedures have been developed for the synthesis of DHPs. The reported procedures involve the use of reagents and catalysts such as Montmorillonite K10 [13], TBAB [14], $\text{HClO}_4 \cdot \text{SiO}_2$ [15], I_2 [16], silica gel/ NaHSO_4 [17], $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ [18], 2,4,6-trichloro[1,3,5]-

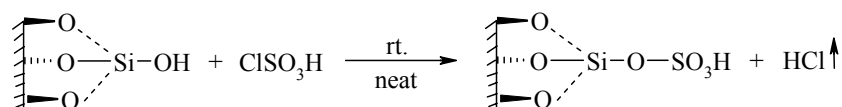
triazines (TCT, cyanuric chloride) [19], ionic liquid/3,4,5-trifluorobenzeneboronic acid [20], sulfonic acid [21], and fermenting bakers' yeast [22] under various conditions such as ultrasound [23], microwave irradiation [24], and high temperature in refluxing solvent [25]. Moreover, procedures involving use of β -enaminones [26] as substrates have also been reported for the synthesis of DHPs. Recently, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [27], PW/SiO_2 [28], and PPh_3 [29] have been employed for this condensation reaction.

In the 19th century considering economic and environmental aspects, heterogeneous catalysts have gained a lot of importance [30-32], and silica sulfuric acid has been widely used as a stable and an efficient heterogeneous catalyst. Silica sulfuric acid produces little waste with excellent activity and selectivity. Silica sulfuric acid can be prepared facilely by treating chlorosulfonic acid with silica gel [33,34] and is a better reagent when compared to a solely homogeneous acid such as chlorosulfonic acid or sulfuric acid (Scheme 1).

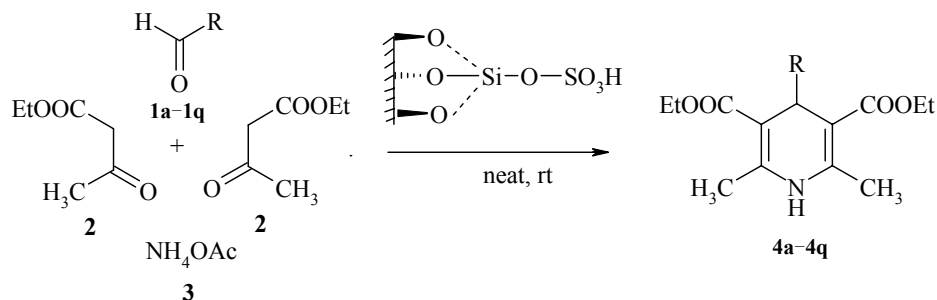
Herein, we report an efficient and convenient procedure for the synthesis of DHPs from ethyl acetoacetate, aldehyde, and ammonium acetate using silica sulfuric acid as catalyst (Scheme 2). Once the reaction goes to completion, the catalyst can be filtered, washed with warm ethanol, and reused without decrease in activity for four runs.

1 Experimental

All reagents were commercial available and used without further purification. The products were characterized by ^1H



Scheme 1. Preparation of silica sulfuric acid.



Scheme 2. Synthesis of DHPs from ethyl acetoacetate, aldehyde, and ammonium acetate.

NMR and mass spectral analyses. The melting points were measured on a Raaga (Chennai) melting point apparatus. NMR spectra of the products were recorded on Bruker AMX 400-MHz spectrophotometer. LC-MS and GC-MS were performed on an Agilent Technologies 1200 series instrument and on a Shimadzu GC-MS QP 5050A instrument, respectively.

In a general experimental procedure for the synthesis of DHPs, a mixture of ethyl acetoacetate (10 mmol), aldehydes (5 mmol), ammonium acetate (5 mmol), and silica sulfuric acid (0.1 g, 0.26 mmol of H^+) [27] were mixed in a round-bottom flask and stirred at room temperature (for a stipulated time as indicated in Table 1) under solvent-free condition. After completion of the reaction (detected by TLC), ethyl acetate (5 ml) was added to the reaction mixture and the catalyst was filtered, washed with warm ethanol for reuse. The filtrate was then washed with water (5 ml) followed by brine solution (10 ml) and dried over $MgSO_4$. The solution was concentrated in vacuum to afford the crude product. Then, the crude product was further purified by silica gel column chromatography. Yields of all the products prepared by this procedure are presented in Table 1.

2 Results and discussion

In continuation of our ongoing studies towards the development of new environmentally friendly protocols for the synthesis of biologically active molecules through solid-supported catalyst in a one-pot synthesis [35–40], we report a simple and efficient procedure for the synthesis of 1,4-dihydropyridines using non-toxic, environmental friendly, and reusable silica sulfuric acid as a catalyst herein.

In an initial endeavor, ethyl acetoacetate (10 mmol) was treated with benzaldehyde (5 mmol) and ammonium acetate (5 mmol) in methanol and stirred for 24 h to get the desired product in 10% yield. To optimize the reaction conditions, we added silica sulfuric acid to the reaction mixture and allowed to stir for 30 min, which produced 70%–80% of the product. In order to further increase the yield, we treated ethyl acetoacetate (10 mmol) with benzaldehyde (5 mmol) and ammonium acetate (5 mmol) in the presence of silica sulfuric acid under solvent-free condition to get the product in 96% yield. It was also found that, this high yield was obtained with 100 mg of the catalyst and use of excess of the catalyst did not remarkably increase the yield. With the optimal conditions on hand, further investigations were carried out to expand the scope of use of other aldehydes and the results are summarized in Table 1.

A series of aromatic aldehydes and formaldehyde have been investigated, and it can be seen from Table 1 that, aromatic aldehydes bearing both electron-donating and electron-withdrawing groups have no obvious effect on the yields and reaction time under the above optimal conditions. We also examined the said reaction with heteroaromatic aldehydes like furfural (**1j**) to get the corresponding product (**4j**) in high yield.

Finally, under optimized conditions the recycling of the catalyst for the reaction was carried out. As silica sulfuric acid is a heterogeneous catalyst, it was separated by simple filtration and reused after washing with ethyl acetate and warm ethanol (Fig. 1). In every case, >90% of silica sulfuric acid was recovered. The results showed that the catalyst could be used 5 times without major loss of activity.

On the basis of our experimental results and together with literature reports [22], we have proposed a plausible mecha-

Table 1 Synthesis of 1,4-dihydropyridines from ethyl acetoacetate, aldehyde, and ammonium acetate

Product ^a	R	Time (min)	Yield ^b (%)	Melting point ^c (°C)
4a	H	15	97	182 (183–185)
4b	C ₆ H ₅	20	96	155 (155–157)
4c	4-CH ₃ OC ₆ H ₄	30	95	156 (158–160)
4d	3-CH ₃ O,4-HOC ₆ H ₃	27	91	163 (163–164)
4e	3,4-(CH ₃ O) ₂ C ₆ H ₃	40	90	161 (163–164)
4f	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	45	93	140 (140–142)
4g	4-NO ₂ C ₆ H ₄	45	92	128 (129–130)
4h	3-NO ₂ C ₆ H ₄	40	97	160 (162–164)
4i	2-NO ₂ C ₆ H ₄	37	91	170 (171)
4j	2-C ₄ H ₉ O	35	95	163 (164)
4k	4-HOC ₆ H ₄	25	95	227 (227–28)
4l	2-HOC ₆ H ₄	30	91	121 (122)
4m	4-ClC ₆ H ₄	27	96	143 (145–146)
4n	3-ClC ₆ H ₄	35	92	141 (142)
4o	2-ClC ₆ H ₄	30	93	216 (216–218)
4p	4-(CH ₃) ₂ NC ₆ H ₄	40	90	201 (203)
4q	3,4-(OCH ₂ O) ₂ C ₆ H ₃	25	94	163 (164)

^aAll the products are known and **4b**, **4c**, and **4g** are characterized by ¹H NMR spectral analysis. Mass spectral data and IR spectra of all the products (**4a–4q**) matched with the reported data.

^bIsolated yields.

^cThe numbers in brackets are melting points of the samples prepared by the reported method [17].

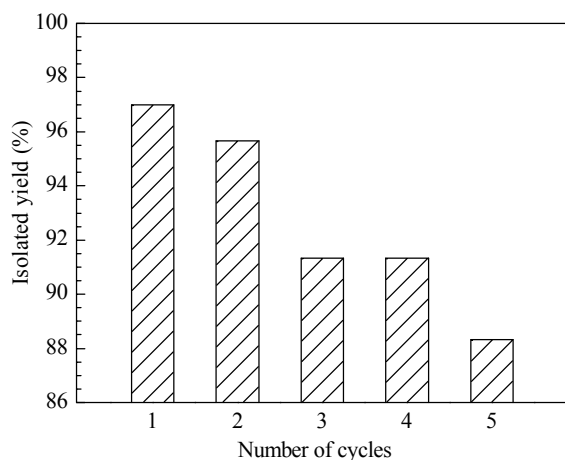


Fig. 1. Repeated use of silica sulfuric acid for the synthesis of 1,4-dihydropyridines under solvent-free condition at 25 °C.

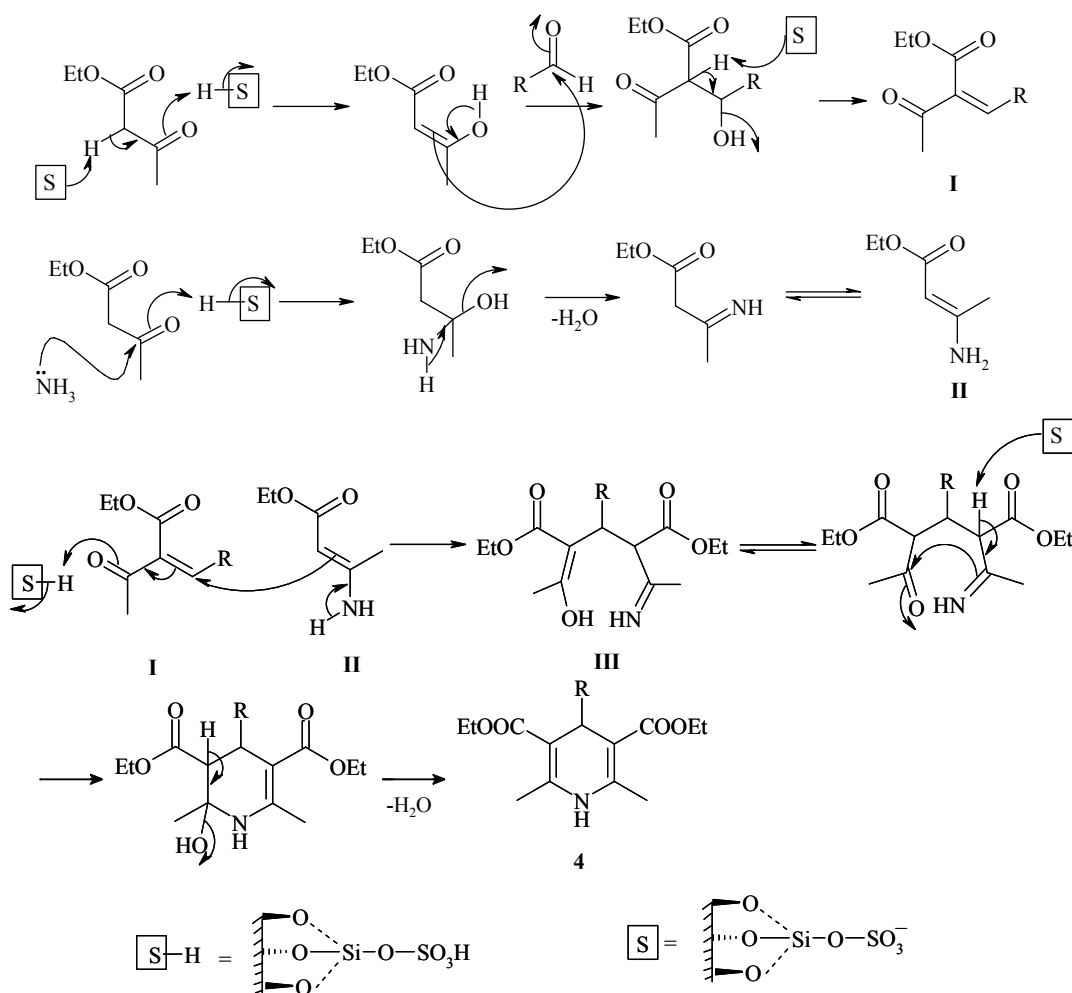
nism for the formation of 1,4-dihydropyridines on silica sulfuric acid (Scheme 3). The reaction is supposed to proceed via two steps. The first step involves silica sulfuric acid-catalyzed formation of Knoevenagel product **I** from 1 equivalent of ethyl acetoacetate and aldehyde. The next step comprises of formation of β -enaminoesters **II** from the second equivalent of ethyl acetoacetate and ammonia (generated 'in situ' from ammonium acetate). Condensation of fragments **I** and **II** may give intermediate **III**, which in a subsequent step gets converted to 1,4-dihydropyridine by cyclization followed by dehydration.

3 Conclusions

A simple and efficient methodology for a one-pot synthesis of 1,4-dihydropyridines from ethyl acetoacetate, aldehyde, and ammonium acetate in the presence of heterogeneous catalyst silica sulfuric acid has been developed. This new protocol has advantages including: (i) the use of small amount (0.1 g) of inexpensive, easy to handle, and reusable catalyst; (ii) short reaction times (15–45 min); and (iii) high yields (90%–97%). We believe that use of a heterogeneous catalyst and a solvent-free reaction set up in this protocol is environment-friendly and can be applied for large-scale operations.

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Scheme 3. A plausible mechanism for the formation of 1,4-dihydropyridines.

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