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Silica Sulfuric Acid as a Efficient and Recyclable Solid Acid Catalyst for the One-Pot Synthesis of 2,4,6-Triaylpyridines Under Solvent Free Conditions

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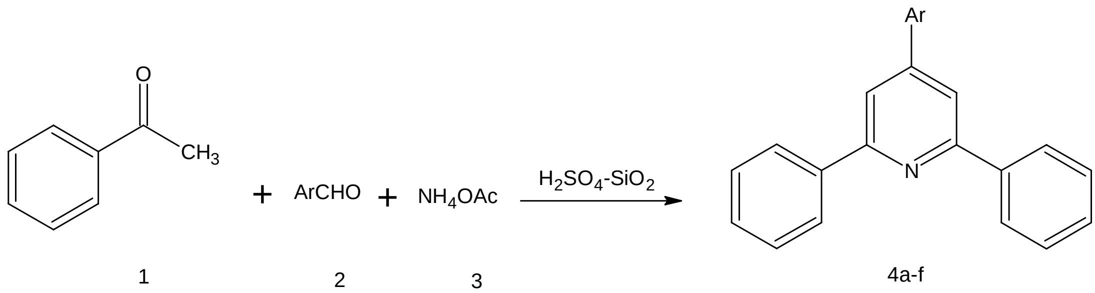
ABSTRACT

An efficient synthesis of 2,4,6-triarylpyridines is achieved via a three-component reaction of acetophenone, aryl aldehydes and ammonium acetate in one-pot under solvent-free conditions. The reaction work-up is very simple and the catalyst can be easily separated from the reaction mixture and reused three times in subsequent reactions.

Key words: Silica Sulfuric Acid, Solvent-free, 2,4,6-Triarylpyridines, Three-Component.

INTRODUCTION

Pyridines possess a broad spectrum of biological activity. In many enzymes of living organisms it is the prosthetic pyridines nucleotide (NADP) that is involved in various oxidation-reduction processes[1]. Other evidence of the potent activity of pyridine in biological system is its presence in the important vitamins niacin and pyridoxine (vitamin B_6)[2]. Also, pyridines are very useful intermediates for the development of molecules of pharmaceutical and biological interest. Substituted pyridines derivatives have found applications in diverse therapeutic areas including anti-tuberculosis, anti-bacterial, anti-inflammatory, anti-asthmatic, anti-depressant, and potent HIV protease inhibitor[3-7]. In addition to the pyridine ring is ubiquitous in agrochemicals such as fungicides[8], bactericides and herbicides[9]. The general method for synthesis of 2,4,6-triarylpyridines (krohke pyridine) involves the reaction of N-phenacylpyridinium salts with α-ϖ-unsaturated ketones in the presence of ammonium acetate[10,11]. Many procedures have been developed for the synthesis of 2,4,6-triarylpyridines, which include solvent-free reaction of chalcones with ammonium acetate[12], reaction of α-ketoketene dithioacetals with methyl ketones in the presence of ammonium acetate[13,14], reaction of N-phosphinylethanimines with aldehydes[15], solvent-free reaction between acetophenones, benzaldehydes, and ammonium acetate in the presence of various catalyst, for example $HClO_4$-SiO_2[16], sodium hydroxide[17], I_2[18], preyssler type hetero polyacid[19] and ionic liquid[20]. However most of the traditional processes suffer from a variety of disadvantages, such as pollution, high cost, excess reagents, prolonged reaction times, and harsh reaction conditions. Therefore, there is a increasing demand for a simple, highly efficient, and versatile method for the synthesis of 2,4,6-triarylpyridines. Recently, solvent-free reactions using either organic or inorganic solid supports have received increasing attention. There are several advantages to performing synthesis in dry media are short reaction times , increased safety, economic advantages due to the absence of solvent[21]. In green chemistry, elimination of volatile organic solvents in organic synthesis is also a most important goal. Solvent-free organic reaction also make procedures simpler, save energy, and prevent solvent wastes, hazards, and toxicity. The higher concentration of reaction media under solvent-free conditions usually leads to more favorable kinetics than in solution[22,23]. Solid-supported reagent, such as silica gel-supported acid have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling[24-26]. In continuation of our efforts to develop novel synthetic routes using solid acid catalysts in organic reactions[27-31], and due to our interest in the synthesis of heterocyclic compounds[32-33], herein we wish to report an efficient and solvent-free synthesis of 2,4,6-triarylpyridines by cyclocondensation reaction of acetophenones, aryl aldehydes, and ammonium acetate using H_2SO_4-SiO_2 as a solid acid catalyst (scheme 1).



Scheme 1: Synthesis of 2,4,6- triarylpyridines

EXPERIMANTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300-shimadzu spectrophotometer in KBR disks. The ^1H NMR (500 MHz) spectra were recorded on a Bruker DR×500 spectrometer. The materials were obtained from commercial suppliers and were used without further purification. The H_2SO_4-SiO_2 was prepared according to literature[27].

Preparation of the catalyst (H_2SO_4-SiO_2)

A solution of cone. H_2SO_4(2ml) in acetone (20ml) is added to a dispersion of silica gel 60 (70-230mesh) (100g) in acetone (200ml) and stirred at room temperature for 1h. The solvent is removed under reduced pressure. A yellow-brown powder is obtained, which can be stored in a desicator for long periods of times without any appreciable loss of activity[27].

General procedure for the synthesis of 2,4,6-triarylpyridines 4a-f using H_2SO_4-SiO_2 as a catalyst

A mixture of acetophenone derivative **1** (2mmol), arylaldehydes **2** (1mmol), ammonium acetate **3** (1.3mmol), and H_2SO_4-SiO_2 (3mg) as catalyst was heated at 120°C with stirring for 3h, and the solid product gradually formed. After completion of the reaction as indicated by TLC, the resulting solid product was cooled to room temperature and boiling ethanol was added. The catalyst was filtrated and the filtrate was concentrated to give the solid product that was washed with water, and recrystallized from n-hexane to give pure products **4a-f**. The structure of the products were confirmed by ^1H NMR, IR spectroscopy, and comparison with authentic samples prepared by reported methods[12,20].

Recycling and reusing of the catalyst

At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst washed with ethanol, dried at 80°C under vacuum for 1h and reused in another reaction without appreciable reduction in the catalytic activity.

RESULTS AND DISCUSSION

The uses of solid acids as heterogeneous catalysts have received tremendous attention in different areas of organic synthesis[26]. Heterogeneous solid acids are advantageous over conventional homogeneous acid catalyst as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation thereby making the process economically more viable. During the course of our studies on the development of solid acid catalyst for the heterocyclic compounds, we found that H_2SO_4-SiO_2 an inexpensive and recyclable catalyst, can efficiently catalyze a one-pot synthesis of 2,4,6-triarylpyridine via a three-component condensation of acetophenones, arylaldehydes, and ammonium acetate under solvent-free conditions(scheme 1). Initially, the one-pot three-component condensation of acetophenone, benzaldehyde, and ammonium

Table 1: Effects of H_2SO_4-SiO_2 and temperature on the model reaction[a]

Entry	Catalyst (mg)	T(°C)	Time (h)	Yield(%)[b]
1	-	120	5	Trace
2	5	r.t.	5	Trace
3	2	100	3	57
4	2	120	3	83
5	2	140	3	77
6	3	100	3	68
7	3	120	3	87
8	3	140	3	84
9	4	100	3	54
10	4	120	3	80
11	4	140	3	78

[a]2mmol acetophenone, 1mmol benzaldehyde, and 1.3 mmol ammonium acetate, under solvent- free conditions. [b]Isolated yields.

Table 2 : H_2SO_4-SiO_2 catalyzed synthesis of 2,4,6-triarylpyridines 4a-f[a]

Entry	Ar	Products[b]	Time (h)	Yield(%)[c]	m.p.(°C)	
					Found	Reported
1	C_6H_5	4a	3	87	134-135	136-137[20]
2	4-MeO-C_6H_4	4b	3	84	193-195	195-197[12]
3	3-NO_2-C_6H_4	4c	3	88	96-98	99-101 [20]
4	4-Cl-C_6H_4	4d	3	89	124-126	125-127[12]
5	4-Me-C_6H_4	4e	3	86	126-128	123-124[12]
6	2-Me-C_6H_4	4f	3	85	118-121	120-122[12]

[a] 2mmol acetophenone, 1mmol aryldehyde, 1.3 mmol ammonium acetate, and 3mg H_2SO_4-SiO_2 under solvent-free conditions at 120°C. [b]All products were characterized by use of IR, ^1H NMR spectral data, and comparison of their melting points with those of authentic samples. [c] Isolated yields.

acetate as a simple model substrate was investigated to established the feasibility of the strategy and optimize the reaction conditions. Thus, a mixture of acetophenone (2mmol), benzaldehyde (1mmol), and ammonium acetate (1.3mmol) was heated on the oil bath at different temperature in the presence of various amount of H_2SO_4-SiO_2 as solid acid catalyst under solvent-free conditions (Table 1).

It was found that the yield of compound 4a was affected by the catalyst amount and reaction temperature. Trace product was obtained in the absence of the catalyst (Entry 1) or in the presence of the catalyst at room temperature (Entry 2) indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of the catalyst and reaction temperature up to 3mg and 120°C, respectively, increased the yield of the product 4a. Further increase in both catalyst amount and temperature did not increase the yield noticeably (Entries 8-11). The model reaction was also examined in various solvents and under solvent- free conditions in the presence of 3mg of catalysts at 120°C. The yield of the reaction under solvent- free conditions was the highest and the reaction time was shortest. To evaluate the generality of this model reaction we then prepared a range of 2,4,6-triarypyridines under the optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. As expected, presence of an electron-withdrawing group in the arylaldehydes improved the rate and yield of the reaction due to enhanced electrophilic reactivity of the carbonyl group (Entries 3,4 Table 2). Whereas arylaldehydes processing electron-donating groups afforded the corresponding 2,4,6-triarylpyridines in slightly lower yields (Entries 2,5,6, Table 2).

The reusability of the catalyst is one of the most important benefits, thus the recovery and reusability of H_2SO_4-SiO_2 was investigated. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature and boiling ethanol was added. The catalyst was filtrated and recycled catalyst washed with ethanol, dried and reused for the same reaction process. The catalyst could be reused at least three times with only slight reduction in the catalyst activity (87% for 1 set use; 85% 2nd use; 82% for 3rd use).

CONCLUSIONS

In conclusions, we have successfully demonstrated a important catalyst activity of H_2SO_4-$SiO\text{-}_2$ as an inexpensive, effective, reusable and non-corrosive catalyst for the synthesis of 2,4,6-triarylpyridines in good yields. The availability and stability of the catalyst, the simple work-up procedure, good yields, and recyclable catalyst, make this method a valid contribution to the existing methodologies.

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