An Efficient and Green Procedure for the Synthesis of 2,4,6-Triarylpyridines Using PPA-SiO₂ as a Reusable Heterogeneous Catalyst Under Solvent-Free Conditions

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Abstract: Silica gel-supported polyphosphoric acid (PPA-SiO₂) was found to be highly efficient, eco-friendly and recyclable heterogeneous catalyst for the synthesis of 2,4,6-triarylpyridines through one-pot three-component reaction of acetophenone, aryl aldehydes, and ammonium acetate under solvent-free conditions. This method has several advantages, such as simple procedure with an easy work-up, short reaction times, and high yields. Furthermore, the catalyst could be recycled after a simple work-up, and used at least three times without substantial reduction in its catalytic activity.

Keywords: PPA-SiO₂, Heterogeneous catalysis, 2,4,6-Triarylpyridines, Multicomponent reactions, solvent-free conditions.

Introduction

Multicomponent reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate¹⁻³. Therefore, developing new MCRs and improving known MCRs are popular areas of research in current organic chemistry. One such reaction is the synthesis of 2,4,6-triarylpyridines.

Pyridines are of interest because of occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B₆) and pyridine alkaloids⁴. Literature reports have already established pyridines as antimalarials, vasodilators, anesthetics, anticonvulsants, antiepileptics, and agrochemicals such as fungicides, pesticides, and herbicides⁵⁻⁸. 2,4,6-Triarylpyridines (Kröhnke pyridines) are structurally related to symmetrical triaryl-thiopyrylium, triarylselenopyrylium, and triaryl-telluopyrylium photosensitizers, which have been recommended for photodynamic cell-specific cancer therapy⁹. These compounds have already been synthesized by reaction of N-phenacylpyridinium salts with α,β -unsaturated

ketones in the presence of ammonium acetate^{10,11}. However, the pyridinium salts and the unsaturated ketones have to be synthesized first, so this method is relatively expensive. More recently, several new improved methods and procedures for preparation of 2,4,6-triarylpyridines have been reported, for example reaction of N-(diphenylphosphinyl)-1-phenylethanamine with aldehydes¹², solvent-free reaction of chalcones with ammonium acetate¹³, and solvent-free reaction between acetophenones, benzaldehydes, and NH₄OAc in the presence of various catalysts, for example HClO₄-SiO₂¹⁴, Brønsted-acidic ionic liquid¹⁵, and I₂¹⁶.

Recently, solid-supported reagents, such as silica gel-supported acids, 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 handling¹⁷⁻²⁰. Although, the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no report in the literature on the use of silica gel-supported polyphosphoric acid (PPA-SiO₂) in the synthesis of 2,4,6-triarylpyridines.

As part of our current studies on the development of new routes for the synthesis of organic compounds using reusable catalysts,²¹⁻²⁷ herein we wish to report an efficient, and green method for the synthesis of 2,4,6-triarylpyridines by one-pot three-component reaction of acetophenone, aryl aldehydes, and ammonium acetate using PPA-SiO₂ as a solid acid supported catalyst under solvent-free conditions (Scheme 1).

Scheme 1. Synthesis of 2,4,6-triarylpyridines catalyzed by PPA-SiO₂.

Experimental

All chemicals were available commercially and used without additional purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ¹H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer.

Preparation of PPA-SiO₂

The PPA-SiO₂ was prepared following the procedure reported by Aoyama and co-workers²⁸. PPA (2.1 g) was transferred into a round-bottom flask and CHCl₃ (100 ml) was added. After the mixture was stirred at 50 °C for 1 h, SiO₂ (200-400 mesh, 4.9 g) was added to the solution, and the mixture was stirred for a further 1 h. The CHCl₃ was removed using a rotary evaporator and the resulting solid was dried in vacuum at laboratory temperature for 3 h. The amount of H⁺ in the PPA-SiO₂ determined by acid-base titration was 0.50 mmol g⁻¹.

General procedure for the synthesis of 2,4,6-triarylpyridines 4a-j using PPA/SiO₂ as catalyst

A mixture of acetophenone **1** (2 mmol), aryl aldehyde **2a-j** (1 mmol), NH₄OAc **3** (1.3 mmol) and PPA-SiO₂ (0.05 g, 0.025 mmol of H⁺) was heated on the oil bath at 120 °C for 30-80 min. During the procedure, the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and then boiling ethanol was added. The catalyst was removed by filtration under hot conditions. After cooling the filtrate, the

precipitated solid was filtered and recrystallised from ethanol to give compounds **4a-j** in high yields.

Recycling and reusing of the catalyst

Due to the fact that the catalyst was insoluble in hot ethanol, it could therefore be recycled by a simple filtration. The separated catalyst was washed with cold ethanol, dried at 100 °C under vacuum for 2 h and reused in another reaction. The results show that there is not any significant loss of activity in using recycled catalyst after three times in the model reaction.

Results and Discussion

The use of heterogeneous catalysts especially under solvent-free conditions presented itself as a remarkable technique toward environmentally clean synthesis of organic compounds. Therefore, we decided to investigate the efficiency of PPA-SiO₂ as a solid acid supported catalyst for the synthesis of 2,4,6-triarylpyridines under solvent-free conditions.

At first, the synthesis of compound **4d** was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by heating a mixture of acetophenone **1** (2 mmol), 4-chlorobenzaldehyde **2d** (1 mmol), and NH₄OAc **3** (1.3 mmol) in the presence of PPA-SiO₂ in different solvents and under solvent-free conditions (Table 1). As can be seen from Table 1, the shortest time and best yield was achieved in solvent-free conditions (entry 7). It was also found that the yield of compound **4d** was strongly affected by the catalyst amount and reaction temperature in solvent-free conditions. Only a trace amount of the 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 0.05 g and 120 °C, respectively, increased the yield of the product **4d**, whereas further increase in both catalyst amount and temperature was found to have an inhibitory effect on the formation of the product (entries 8-12).

Table 1. Effect of PPA-SiO₂ amount, solvent and temperature on the model reaction^a.

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Yield (%) ^b
1	None	Solvent-free	120	120	Trace
2	0.05	Solvent-free	r.t	120	Trace
3	0.02	Solvent-free	100	60	43
4	0.02	Solvent-free	120	45	81
5	0.02	Solvent-free	140	45	76
6	0.05	Solvent-free	100	60	71
7	0.05	Solvent-free	120	45	90
8	0.05	Solvent-free	140	45	87
9	0.08	Solvent-free	100	60	63
10	0.08	Solvent-free	120	45	86
11	0.08	Solvent-free	140	45	82
12	0.10	Solvent-free	120	45	83
13	0.05	EtOH	Reflux	240	30
14	0.05	CHCl ₃	Reflux	100	52
15	0.05	CH ₃ CN	Reflux	90	68
16	0.05	CH ₂ Cl ₂	Reflux	70	73

^a2 mmol acetophenone, 1 mmol 4-chlorobenzaldehyde, and 1.3 mmol NH₄OAc

^bThe yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

To evaluate the generality of this model reaction we then prepared a range of 2,4,6-triarylpyridines 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 high yields. It was found that aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups, as would be expected. The results are shown in Table 2.

Table 2. PPA-SiO₂ catalyzed synthesis of 2,4,6-triarylpyridines **4a-j**^a.

Entry	Ar	Products ^b	Time (min)	Yields (%) ^c	m.p. (°C)	
					Found	Reported
1	C ₆ H ₅		60	82	136-137	134-135 ¹³
		4a				
2	4-BrC ₆ H ₄		50	77	166-168	166-167 ¹⁴
		4b				
3	2-ClC ₆ H ₄		50	80	114-115	113-114 ¹³
		4c				
4	4-ClC ₆ H ₄		45	90	125-126	125-127 ¹⁵
		4d				
5	4-HOC ₆ H ₄		80	74	192-194	193-195 ¹⁵
		4e				

6	4-MeOC ₆ H ₄		80	80	99-101	100-103 ¹³
		4f				
7	2-MeC ₆ H ₄		70	79	122-124	120-122 ¹³
		4g				
8	4-MeC ₆ H ₄		70	80	124-126	124-125 ¹⁵
		4h				
9	4-O ₂ NC ₆ H ₄		30	91	199-202	195-197 ¹³
		4i				
10	2-thienyl		60	85	165-167	162-163 ¹³
		4j				

^a2 mmol acetophenone, 1 mmol aryl aldehyde, 1.3 mmol NH₄OAc, and 0.05 g PPA-SiO₂ at 120 °C under solvent-free conditions.

^bAll the products were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ¹H NMR spectral data.

^cThe yields were calculated based on aryl aldehyde and refer to the pure isolated product.

The principle advantage of the use of heterogeneous catalysts in organic transformations is their reusability. Hence, we decided to study the catalytic activity of recycled PPA-SiO₂ in the synthesis of compound **4d** under the optimized conditions. After the completion of the reaction, the catalyst was recovered according to the procedure mentioned in experimental section and reused for a similar reaction. The catalyst could be used at least three times with only slight reduction in the catalytic activity (90% for 1st use; 89% for 2nd use; 87% for 3rd use).

Conclusions

PPA-SiO₂, a solid acid supported catalyst, showed high catalytic activity in the synthesis of 2,4,6-triarylpyridines *via* a one-pot three-component reaction of acetophenone, aryl aldehydes, and ammonium acetate under solvent-free conditions. This procedure offers several advantages including mild reaction conditions, high yields, ease of workup, which makes it a useful and attractive protocol for the synthesis of these compounds. Furthermore, the catalyst could be recycled after a simple work-up, and used at least three times with only slight reduction in its catalytic activity. It has also all advantages devoted to solvent-free reactions namely environmentally friendly conditions.

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