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Chinese Chemical Letters 23 (2012) 419–422

CHINESE CHEMICAL LETTERS

www.elsevier.com/locate/cclet

Highly efficient and easy synthesis of 2,4,6-triarylpyridines catalyzed by pentafluorophenylammonium triflate (PFPAT) as a new recyclable solid acid catalyst in solvent-free conditions

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Received 2 November 2011
Available online 3 March 2012

Abstract

Pentafluorophenylammonium triflate (PFPAT) was found to be a highly efficient catalyst for the preparation of 2,4,6-triarylpyridines from the reaction of acetophenone derivatives, aromatic aldehydes and ammonium acetate. Present methodology offers several advantages, such as short reaction time, high yields, simple procedure with an easy work-up and the absence of any volatile and hazardous organic solvent. In addition, this catalytic system can act as an active, inexpensive, metal-free, recoverable and recyclable catalyst.

Keywords: Pentafluorophenylammonium triflate; 2,4,6-Triarylpyridines; Solvent-free conditions; Organocatalyst; Multi-component reaction

Multicomponent reactions (MCRs) have manifested as a powerful tool for the rapid introduction of molecular diversity. The design and development of MCRs for the generation of heterocycles receive growing interest [1]. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption, and waste production. Therefore, discovery for new MCRs and improving already known MCRs are of substantial interest. One such reaction is the synthesis of 2,4,6-triarylpyridines. Pyridines play a key role in catalyzing both biological and chemical systems. In many enzymes of living organisms there is the prosthetic pyridine nucleotide (NADP) that is involved in various oxidation–reduction processes [2]. The pyridine ring is also ubiquitous in agrochemicals such as fungicides, and herbicides [3]. In view of different biological and chemical applications of pyridine derivatives, the development of suitable synthetic methodologies for their generation has been a topic of great interest in recent times. The general method for synthesis of 2,4,6-triarylpyridines (Kröhnke pyridine) involves the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate [4]. Recently, much effort has been devoted to developing more efficient methods for the synthesis of 2,4,6-triarylpyridines, for example reaction of chalcones with ammonium acetate [5], solvent-free reaction between acetophenones, benzaldehydes, and ammonium acetate in the presence of various catalyst, for example cyanuric chloride [6], $HClO_4$–SiO_2 [7], Brønsted-acidic ionic liquid [8], and I_2 [9]. However, many of these methods suffer

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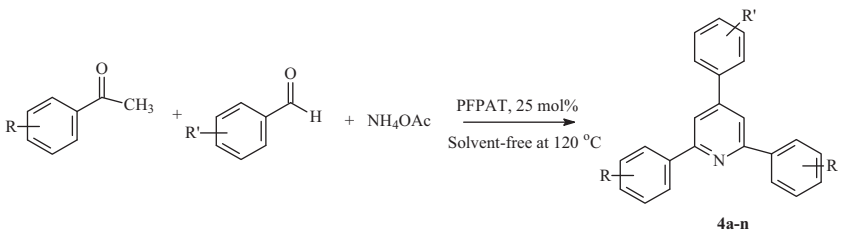
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2012.01.035



Scheme 1.

from drawbacks such as expensive catalyst, long reaction time, special care in handling and storing the reagents, undesired side products in reaction with harsh reagents, using metal oxidants, cumber some product isolation procedure and environmental pollution. Therefore, a need still exists for further development of versatile reaction conditions in synthesis of 2,4,6-triarylpyridine using an efficient, reusable, inexpensive, eco-friendly, green, great selectivity and metal-free catalyst. Tanabe *et al.* reported the application of pentafluorophenylammonium triflate (PFPAT) as a novel organocatalyst in organic transformation such as esterification of carboxylic acids with alcohols [10], C-acylations of enol silyl ethers or ketene silyl (thio)acetals with acid chlorides [11], and Mukaiyama aldol and Mannich reactions using ketene silyl acetals with ketones and oxime ethers [12]. However, to the best of our knowledge the use of PFPAT as a catalyst in the synthesis of 2,4,6-triarylpyridines has not been reported yet. Recently, we reported our research findings on the application of PFPAT as catalyst in the synthesis of coumarins via von pechmann condensation [13]. In continuation, herein, we report the first example of the PFPAT-catalyzed, one-pot three-component synthesis of 2,4,6-triarylpyridines from a solvent-less reaction of acetophenones, aryl aldehydes, and ammonium acetate in high yields (Scheme 1).

1. Experimental

1.1. Typical procedure

A mixture of an acetophenone derivative (2 mmol), aryl aldehyde (1 mmol), ammonium acetate (1.3 mmol), and PFPAT (25 mol% based on aryl aldehyde) was heated on the oil bath at 120 °C for the indicated time. The progress of the reaction was monitored by TLC. After completion of the reaction mixture was cooled to room temperature and water was added. The precipitated solid was collected by filtration under suction, washed with cold water, and then recrystallized from *n*-hexane to afford pure products **4a**–**n** (Table 2) in high yields. The filtrate was evaporated under reduced pressure and then washed with *n*-hexane, dried at 50 °C under vacuum for 1 h and reused in another reaction with only slight reduction in the catalytic activity. All the products were identified by comparison of spectral data (IR and ^{1}H NMR), and m.p. with those reported [5a,8].

2. Results and discussion

Solvent-free conditions are especially important for providing an eco-friendly system. The number of publications reporting solvent-free condition for the heterocyclic synthesis has increased rapidly in recent years [14]. One advantage of solvent-free reaction, in comparison to the reaction in molecular solvent, is that the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography. Therefore, due to the increasing demand in modern organic processes for avoiding expensive purification, we decided to investigate the efficiency of PFPAT as catalyst in the synthesis of 2,4,6-triarylpyridines under solvent-free conditions. Initially, to optimize the reaction conditions such as temperature, solvent and amount of catalyst (PFPAT), the reaction between acetophenone, benzaldehyde, and ammonium acetate was selected as a model. The results are collected in Table 1. Increasing the reaction temperature and amount of the catalyst up to 120 °C and 25 mol%, respectively under solvent-free conditions, increased the yield of product **4a** (entries 3–7), whereas further increase in both temperature and catalyst amount was found to have an inhibitory effect on formation of the product (entries 8–11). Interestingly, in the absence of the catalyst (entry 1) or in the presence of the catalyst at room temperature (entry 2), **4a** was obtained in a very trace amount after 12 h which indicated that the catalyst and temperature should be absolutely necessary for this reaction.

Table 1
Effect of PFPAT amount, temperature, and solvent on the synthesis of 2,4,6-triphenylpyridine (model reaction).[a]

Entry	Catalyst (mol%)	T (°C)	Solvent	Time (h)	Yield (%)[b]
1	None	120	None	12	Trace
2	25	r.t.	None	12	Trace
3	20	100	None	3	54
4	20	120	None	3	66
5	20	140	None	2	65
6	25	100	None	3	85
7	25	120	None	2	89
8	25	140	None	2	85
9	30	100	None	3	63
10	30	120	None	2	87
11	30	140	None	3	85
12	25	Reflux	EtOH	10	Trace
13	25	Reflux	MeCN	6	60
14	25	Reflux	CH_2Cl_2	8	63
15	25	Reflux	$CHCl_3$	8	55
16	25	Reflux	Toluene	5	72

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

On the contrary, lower catalytic activity is observed for various organic solvents such as EtOH, MeOH, MeCN, CH_2Cl_2, $CHCl_3$, and toluene under reflux condition and in the presence of 25 mol% of catalyst (Table 1, entries 12–16).

In order to show generality and scope of this new protocol, we used various substituted acetophenones and benzaldehydes and the results obtained are summarized in Table 2. All the reaction with substituted benzaldehydes preceded very cleanly at optimized reaction conditions and no undesirable side-reaction were observed, although the yields were dependent on the substituent. The results in Table 2 show that electron-withdrawing groups such as nitro, and chloro at the phenyl ring of benzaldehyde favored the formation of product (Table 2, entries 2 and 3). In contrast, electron-donating groups gave slightly lower yields (Table 2, entries 4–7). To check the versatility of this method, we had also studied the various substituted acetophenones and results obtained are summarized in Table 2 (entries 8–14). All the reaction with substituted acetophenones proceeded very cleanly and no undesirable side-reaction was observed. Compared to other methodologies reported for the synthesis of 2,4,6-triarylpyridines via one-pot reaction,

Table 2
PFPAT catalyzed synthesis of 2,4,6-triarylpyridines **4a**–**n**.[a]

Entry	R	R′	Time (h:min)	Product[b]	Yield [Ref][c]	m.p. (°C)
1	H	H	2	**4a**	89	130–131
2	H	4-NO_2	2	**4b**	92	192–193
3	H	4-Cl	2:15	**4c**	91	123–124
4	H	4-Me	2:40	**4d**	87	127–128
5	H	2-Me	2:30	**4e**	88	122–124
6	H	4-OMe	2:50	**4f**	86	100–101
7	H	4-OH	3	**4g**	84	193–195
8	4-Br	H	2:45	**4h**	85	103–105
9	4-Me	4-Me	2:30	**4i**	87	178–179
10	4-Me	4-Cl	2:10	**4j**	92	199–201
11	4-Me	2-Cl	2:30	**4k**	88	186–187
12	4-NO_2	4-OMe	2:40	**4l**	86	155–157
13	4-OMe	4-Cl	2	**4m**	93	175–177
14	4-OMe	4-NO_2	2	**4n**	94	143–144

[a] *Reaction condition*: acetophenone 2 mmol, benzaldehyde 1 mmol, ammonium acetate 1.3 mmol, and PFPAT 25 mol% at 120 °C under solvent-free conditions.
[b] All products were characterized by use of IR, and ^{1}H NMR spectral data, and comparison of their melting points with those of authentic samples.
[c] Isolated yields based on aromatic aldehyde.

Table 3
Comparison of efficiency of various catalysts in the synthesis of 2,4,6-triphenylpyridine **4a**.

Catalyst	Conditions	Time (h)	Yield (%)	Ref.
Cyanuric chloride	Solvent-free; 130 °C	4	70	[6]
$HClO_4$–SiO_2	Solvent-free; 120 °C	4	80	[7]
Brønsted-acidic ionic liquid	Solvent-free; 120 °C	3	88	[8]
I_2	Solvent-free; 120 °C	6	56	[9]
PFPAT	Solvent-free; 120 °C	2	89	This work

the present methodology offers suitable conditions with respect to reaction times and yields. Some of the results are summarized in Table 3.

The reusability of the catalyst is one of the most important benefits and makes them useful for commercial applications, thus the recovery and reusability of PFPAT was investigated. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the catalyst was easily 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 (89% for 1st use; 87% for 2nd use; 84% for 3rd use).

3. Conclusion

In conclusion, we have developed a new method for the one-pot three-component synthesis of 2,4,6-triarylpyridines from aromatic aldehydes, acetophenones, and ammonium acetate using PFPAT as an efficient organocatalyst in good to excellent yields. Simple experimental procedure, nontoxic, noncorrosive, metal-free, inexpensive solid acid catalyst, recyclability of the catalyst with no loss in its activity, short reaction times, eco-friendly, great selectivity, and solvent-free reaction conditions have made this approach distinctly superior over to many other protocols reported earlier.

Acknowledgment

This research has been supported by the Islamic Azad University, Tonekabon Branch.

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