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ORIGINAL PAPER

Highly efficient, one-pot, solvent-free synthesis of 2,4,6-triarylpyridines using a Brønsted-acidic ionic liquid as reusable catalyst

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Abstract A simple, efficient, and green method for synthesis of 2,4,6-triarylpyridines by one-pot three-component reaction of acetophenones, aryl aldehydes, and ammonium acetate using 3-methyl-1-(4-sulfonylbutyl)imidazolium hydrogen sulfate $[HO_3S(CH_2)_4MIM][HSO_4]$, a Brønsted-acidic ionic liquid, as an effective and reusable catalyst under solvent-free conditions is described. This method has several advantages, for example simple procedure with an easy work-up, shorter reaction times, and high yields.

Keywords Brønsted-acidic ionic liquids · Multi-component reactions · 2,4,6-Triarylpyridines · Solvent-free conditions

Introduction

Multicomponent reactions (MCRs) have recently received the attention of organic chemists because of the many advantages these reactions over conventional multi-step synthesis and their potential applications in medicinal chemistry for generation of diverse scaffolds and combinatorial libraries for drug development [1–3]. 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.

The presence of the pyridine ring system in a number of natural products, vitamins, and pharmacologically significant molecules [4] has made it a prime target for scientific research. Literature reports have already established pyridines as antimalarials, vasodilators, anesthetics, anticovulsants, antiepileptics, and agrochemicals such as fungicides, pesticides, and herbicides [5–8]. Also, because of their π-stacking ability, some pyridines are used in supramolecular chemistry [9].

2,4,6-Triarylpyridines (Kröhnke pyridines) are structurally related to symmetrical triaryl-thiopyrylium, triaryl-selenopyrylium, and triaryl-telluropyrylium photosensitizers, which have been recommended for photodynamic cell-specific cancer therapy [10]. These compounds have already been synthesized by reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate [11, 12]. 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 α-ketoketene dithioacetals with methyl ketones in the presence of NH_4OAc [13], reaction of *N*-phosphinylethanimines with aldehydes [14], solvent-free reaction of chalcones with ammonium acetate [15], solvent-free reaction between acetophenones, benzaldehydes, and NH_4OAc in the presence of various catalysts, for example Preyssler type heteropolyacid [16], $HClO_4$-SiO_2 [17], and I_2 [18], and the one-pot reaction of acetophenones, benzaldehydes, and NH_4OAc without catalyst under microwave irradiation [19].

Ionic liquids (ILs) are salt-type compounds which are liquid at room temperature and have low vapor pressure. Because of the lack of evaporation, they are regarded as promising “green solvents” for replacing the volatile—

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therefore flammable and harmful—conventional solvents. ILs are also known as environmentally benign catalysts and much attention has currently been focused on organic reactions in the presence of these compounds as catalysts or solvents [20–23]. The introduction of Brønsted-acidic functional groups into the cations or anions of the ILs, especially SO_3H functional groups, obviously enhanced their acidities and water solubilities [24–26]. Therefore, Brønsted-acidic ILs can be used as highly efficient acid catalysts and have been attracting extensive interest as green substitute for H_2SO_4, HF, and $AlCl_3$ catalysts in chemical processes [27]. In fact, use of Brønsted-acidic ILs as catalysts is an area of ongoing activity; however, development and exploration of Brønsted-acidic ILs are currently in a preliminary stage. To the best of our knowledge, there are no examples of the use of Brønsted-acidic ILs as catalysts for synthesis of 2,4,6-triarylpyridines.

Because of the important pharmacological activity of the Kröhnke pyridines, and in line with our research program on synthesis of heterocycles [28–31] and using Brønsted-acidic ILs as novel catalysts in organic reactions [32–34], herein we would like to report an efficient procedure for preparation of 2,4,6-triarylpyridines by a one-pot three-component reaction including acetophenones, aryl aldehydes, and NH_4OAc in the presence of 3-methyl-1-(4-sulfonylbutyl)imidazolium hydrogen sulfate $[HO_3S(CH_2)_4MIM][HSO_4]$ (Fig. 1), a Brønsted-acidic IL, under solvent-free conditions (Scheme 1).

Results and discussion

For our investigations, $[HO_3S(CH_2)_4MIM][HSO_4]$ was prepared according to the literature procedure [35]. Initially, in order to optimize the reaction conditions, synthesis of 2,4,6-triphenylpyridine (**4a**) was used as a model reaction. Therefore, a mixture of acetophenone (2 mmol), benzaldehyde (1 mmol), and NH_4OAc (1.3 mmol) was heated under various reaction conditions. The efficiency of the reaction is mainly affected by the amount of the catalyst (Table 1). In the absence of the catalyst, **4a** was obtained in a trace amount after 4 h (entry 1), whereas good results were obtained in the presence of $[HO_3S(CH_2)_4MIM][HSO_4]$ (entries 2–6). The optimum amount of $[HO_3S(CH_2)_4MIM][HSO_4]$ was 20 mol% (entry 5), a higher amount of the catalyst did not increase the yield noticeably (entry 6).

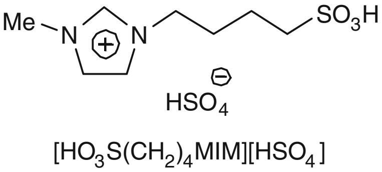


Fig. 1 Brønsted-acidic IL structure

Also, the reaction was carried out in various solvents and under solvent-free conditions (Table 2). As shown in Table 2, in comparison with conventional methods the yields of the reaction under solvent-free conditions are higher and the reaction time is shorter.

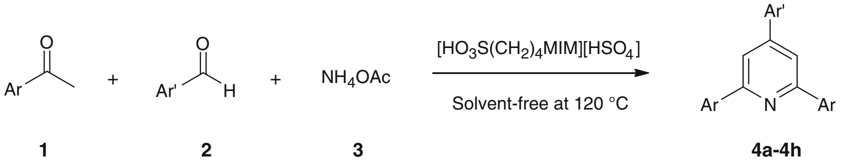
The effect of temperature was investigated by carrying out the same model reaction at different temperatures under solvent-free conditions. The yield increased as the reaction temperature was raised and at 120 °C the product was obtained in high yield. Higher temperatures did not increase the yield noticeably (Table 3).

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 4.

Reusability of the catalyst was also investigated. For this purpose, the same model reaction was again studied under the optimized conditions. After completion of the reaction, the reaction mixture was cooled to room temperature and then water was added. The precipitated solid was isolated by filtration, the catalyst was recovered from the filtrate by evaporation of the water, and reused for the similar reaction. As shown in Fig. 2, the catalyst could be reused at least three times with only slight reduction in catalytic activity.

In conclusion, we have developed a very simple and efficient method for synthesis of 2,4,6-triarylpyridines by one-pot three-component reaction of acetophenones, aryl aldehydes, and NH_4OAc in the presence of $[HO_3S(CH_2)_4MIM][HSO_4]$, a Brønsted-acidic IL, as an efficient,

Scheme 1



reusable, and eco-friendly homogeneous catalyst under solvent-free conditions. The catalyst can be reused after simple work-up, with a slight decline of its activity being observed. Other advantages of this procedure are high yields, short reaction times, easy work-up, and absence of any volatile and hazardous organic solvents.

Table 1 Effect of the amount of $[HO_3S(CH_2)_4MIM][HSO_4]$ on the model reaction

Entry	Catalyst (mol%)	Time (h:min)	Yield (%)[a]
1	None	4:00	Trace
2	5	4:00	23
3	10	3:30	42
4	15	3:10	68
5	20	3:00	88
6	25	3:00	89

2 mmol acetophenone, 1 mmol benzaldehyde, and 1.3 mmol NH_4OAc at 120 °C

[a] Isolated yields

Table 2 Synthesis of 2,4,6-triphenylpyridine **4a** in the presence of $[HO_3S(CH_2)_4MIM][HSO_4]$ (20 mol%) in different solvents

Entry	Solvent	Temperature (°C)	Time (h:min)	Yield (%)[a]
1	EtOH	78	5:00	Trace
2	CH_3CN	81	4:00	60
3	CH_2Cl_2	40	3:30	55
4	$CHCl_3$	61	4:00	36
5	Solvent-free	120	3:00	88

[a] Isolated yields

Table 3 Synthesis of 2,4,6-triphenylpyridine **4a** in the presence of $[HO_3S(CH_2)_4MIM][HSO_4]$ (20 mol%) at different temperatures under solvent-free conditions

Entry	Temperature (°C)	Time (h:min)	Yield (%)[a]
1	50	5:00	Trace
2	100	4:00	62
3	120	3:00	88
4	150	3:30	89

[a] Isolated yields

Experimental

All chemicals were commercially available and used without further purification. The Brønsted-acidic ionic liquid $[HO_3S(CH_2)_4MIM][HSO_4]$ was synthesized according to Ref. [35]. Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^1H NMR spectra (500 MHz) were recorded on a Bruker DRX500 spectrometer.

*General procedure for synthesis of 2,4,6-triarylpyridines **4a–4h***

A mixture of 2 mmol acetophenone derivative **1**, 1 mmol aryl aldehyde **2**, 100 mg NH_4OAc (1.3 mmol), and 63 mg $[HO_3S(CH_2)_4MIM][HSO_4]$ (0.2 mmol, 20 mol% based on aryl aldehyde) was heated on the oil bath at 120 °C for the time indicated. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and water was added. The precipitated solid was isolated by filtration, washed with water, and recrystallized from *n*-hexane to give pure products **4a–4h**. The structures of the products were confirmed by ^1H NMR and IR spectroscopy, and comparison with authentic samples prepared by reported methods [15–18].

Table 4 Synthesis of 2,4,6-triphenylpyridines **4a–4h**

Entry	Ar	Ar′	Products[a]	Time (h:min)	Yield[b] (%)	M.p. (°C)	
						Found	Reported
1	C_6H_5	C_6H_5	**4a**	3:00	88	136–137	134–135 [15]
2	C_6H_5	$4\text{-}ClC_6H_4$	**4b**	2:30	91	125–127	124–126 [18]
3	C_6H_5	$4\text{-}O_2NC_6H_4$	**4c**	2:00	93	198–200	195–196 [18]
4	C_6H_5	$2\text{-}MeC_6H_4$	**4d**	3:20	84	122–124	120–122 [15]
5	C_6H_5	$4\text{-}MeC_6H_4$	**4e**	3:10	87	124–125	123–124 [15]
6	C_6H_5	$4\text{-}HOC_6H_4$	**4f**	3:40	82	193–195	197 [16]
7	C_6H_5	$4\text{-}MeOC_6H_4$	**4g**	3:20	89	99–101	98 [16]
8	$4\text{-}BrC_6H_4$	C_6H_5	**4h**	1:30	86	103–105	101–102 [17]

[a] All products were characterized by use of ^1H NMR and IR spectral data, and comparison of their melting points with those of authentic samples

[b] Isolated yields

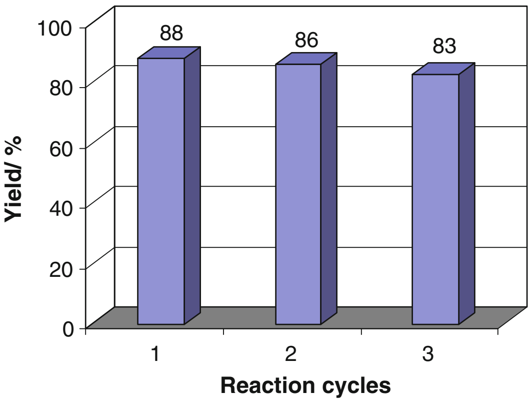


Fig. 2 Reusability of $[HO_3S(CH_2)_4MIM][HSO_4]$ for model reaction

Recycling of the catalyst

The catalyst is soluble in water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water, washed with diethyl ether, dried at 50 °C under vacuum for 1 h, and reused in another reaction with only slight reduction in the catalytic activity.

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