



Efficient one-pot synthesis of new fused pyridines and bis-pyridines catalyzed by triazine diphosphonium hydrogen sulfate ionic liquid supported on functionalized nano-silica



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ABSTRACT

The efficient synthesis of novel fused pyridines via the three component condensation of aldehydes, kojic acid, and 6-amino-1,3-dimethyluracil, catalyzed by the ionic liquid aminopropyl-1,3,5-triazine-2,4-diphosphonium hydrogen sulfate supported on functionalized nano-silica, under solvent-free conditions is reported. Additionally, bis-derivatives of these compounds were smoothly synthesized from dialdehydes. This method has the advantages of mild conditions, high yields, short reaction times, easy work-up, and being environmentally friendly. Moreover, the catalyst can be easily separated from the reaction mixture, recycled, and reused several times without a noticeable decrease in catalytic activity.

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Introduction

Among nitrogen containing heterocycles, fused pyridines possess interesting bioactivities and act as a fundamental part of many natural products and synthetic pharmaceuticals.^{1,2} Compounds containing the pyridine moiety show a wide range of important biological activities such as antibacterial,³ antitumor,⁴ anti-inflammatory,⁵ anticancer,⁶ antioxidant,⁷ antiviral,⁸ antifungal,⁹ antidiabetic,¹⁰ antihypertensive,¹¹ tyrosine kinase,¹² and analgesic¹³ properties, and can also be used as chiral ligands in organic synthesis.¹⁴ Consequently, the syntheses of these important compounds has remained a hot topic of organic chemistry. Several synthetic protocols such as Hantzsch,¹⁵ Bohlmann-Rahtz,¹⁶ Friedlaender,¹⁷ Vilsmeier-Haack,¹⁸ hetero Diels–Alder reactions,¹⁹ Kröhnke annulations,²⁰ Mannich reaction of aldehydes and iminium salts,²¹ reactions of vinyl azides with monocyclic cyclopropanols,²² and various multicomponent reactions²³ have been reported for the synthesis of pyridine derivatives.

In an ideal synthetic pathway, the desired compound is prepared from readily available starting materials in a single facile, safe, and environmentally acceptable operation that proceeds rapidly in high yield. In this regard, multicomponent reactions (MCRs), in which starting materials are combined in a one-step process, have attracted much attention in organic chemistry. Such processes are highly flexible, chemoselective, and convergent methods that minimize solvent consumption, maximize atom efficiency, and avoid the isolation and purification of intermediates.^{24–26}

Ionic liquids (ILs) have been used as green reaction media and catalysts due to their negligible volatility, excellent thermal stability, nontoxicity, nonflammability as well as tunable physicochemical properties such as density, viscosity, surface tension, and thermal conductivity.^{27,28} Compared to ammonium based ILs, the phosphonium congeners possess favorable characteristics, including lower viscosity, higher thermal stability, higher ionic conductivity, and wider electrochemical windows.^{29–31} These encouraging properties make phosphonium based ILs a good choice for catalysis. However, the practical applications of these homogeneous ILs have been restricted because of the need for relatively large amounts of ILs as well as difficulties in product isolation and catalyst recovery. These restrictions can be overcome by the immobilization of ILs on solid supports, which provides the

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advantages of heterogeneous catalysts such as high interfacial surface area, and ease of handling, separation, and recycling, as well as lowering the amount of catalyst required.³²

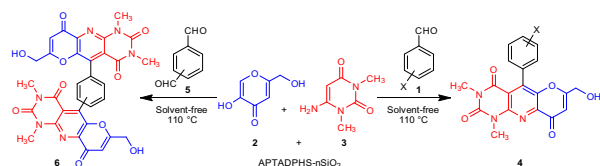
Due to importance of pyridine derivatives as privileged medicinal scaffolds,³³ the significance of nanostructure supported ILs as catalysts,³⁴ and in continuation of our previous works on the synthesis of heterocyclic compounds,³⁵ we herein report the synthesis of new fused pyridines and bis-pyridines through the three-component condensation of aldehydes **1**, kojic acid **2**, and 6-amino-1,3-dimethyluracil **3** and related compounds in the presence of a reusable catalyst, aminopropyl-1,3,5-triazine-2,4-diphosphonium hydrogen sulfate supported on nano-silica (APTADPHS-*n*-SiO₂) under solvent-free conditions (Scheme 1).

Results and discussion

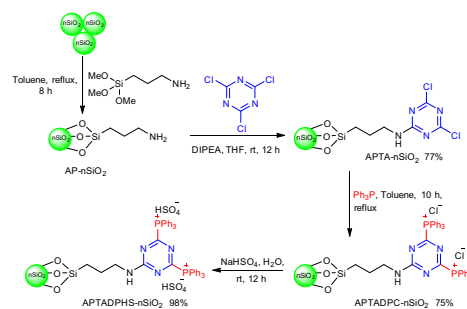
First, nano-silica was treated with 3-aminopropyltrimethoxysilane (APTS) according to the reported procedure³⁶ to afford aminopropyl-functionalized nano-silica (AP-*n*-SiO₂), which upon reaction with 2,4,6-trichlorotriazine in the presence of diisopropylethylamine produced aminopropyl-1,3,5-triazine supported on nano-silica (APTA-*n*-SiO₂). Then, APTA-*n*-SiO₂ was reacted with triphenylphosphine to provide aminopropyl-1,3,5-triazine-2,4-diphosphonium chloride supported on nano-silica (APTADPC-*n*-SiO₂). The desired catalyst, APTADPHS-*n*-SiO₂, was prepared by the reaction of APTADPC-*n*-SiO₂ with NaHSO₄ (Scheme 2) and characterized by FT-IR, SEM, TGA, and ICP (ESI).

The scanning electron micrograph (SEM) was recorded to examine the surface morphology of the nano-silica and the APTADPHS-*n*-SiO₂ catalyst (ESI, Fig. S2). The micrograph for APTADPHS-*n*-SiO₂ clearly differed from that of nano-silica, demonstrating that incorporation of the ionic liquid significantly changes the morphological structure of the nano-silica surface. To examine the catalyst stability, thermogravimetric analysis (TGA) was carried out (ESI, Fig. S3). The main weight loss was observed from 210 to 610 °C which is related to decomposition of the covalently attached IL and the organic structure from the nano-silica surface. Therefore, the catalyst is stable below about 210 °C. The phosphorous content of the catalyst was determined as 15.97 mg/L by ICP indicating that the amount of HSO₄⁻ was 1.288 mmol/g.

Initially, we optimized the reaction conditions using 3,4-dimethoxybenzaldehyde (1.0 mmol), kojic acid (1.0 mmol), and 6-amino-1,3-dimethyluracil (1.0 mmol) as model substrates (Table 1). The reaction was first examined in the absence of catalyst at 110 °C under solvent-free conditions; no product was detected after 5 h (Table 1, entry 1). Next, the reaction was carried out in the presence of 3 mol % of various Lewis and Brønsted acids as well as ionic liquids (Table 1, entries 2–12). No reactions were observed using ZnCl₂, AlCl₃, and BiCl₃, while in the presence of FeCl₃, Zn(OTf)₂, I₂, TBATB, *p*-TSA, H₃PW₁₂O₄₀, [Hmim]HSO₄⁻, and APTADPHS-SiO₂ the desired product was obtained in 10–68% yield. Significant improvements were observed by replacing APTADPHS-SiO₂ with APTADPHS-*n*-SiO₂ (Table 1, entries 12 and 13) which could be attributed to the high surface area of nano-silica which increases the catalytic activity of APTADPHS-*n*-SiO₂. Further



Scheme 1. Synthesis of fused pyridines and bis-pyridines catalyzed by APTADPHS-*n*-SiO₂.



Scheme 2. Synthesis of APTADPHS-*n*-SiO₂.

Table 1

Optimization of the reaction conditions for the synthesis of fused pyridines

Entry	Catalyst (mol %)	T (°C)	Time (min)	Yield ^a (%)
1	—	110	5 h	—
2	ZnCl ₂ (3)	110	30	—
3	AlCl ₃ (3)	110	30	—
4	BiCl ₃ (3)	110	30	—
5	FeCl ₃ (3)	110	30	10
6	Zn(OTf) ₂ (3)	110	45	57
7	I ₂ (3)	110	45	28
8	TBATB (3)	110	45	40
9	<i>p</i> -TSA (3)	110	45	30
10	H ₃ PW ₁₂ O ₄₀ (3)	110	40	40
11	[Hmim]HSO ₄ ⁻ (3)	110	50	55
12	APTADPHS-SiO ₂ (3)	110	50	68
13	APTADPHS- <i>n</i> -SiO ₂ (3)	110	30	96
14	APTADPHS- <i>n</i> -SiO ₂ (2)	110	30	82
15	APTADPHS- <i>n</i> -SiO ₂ (2.5)	110	30	96
16	APTADPHS- <i>n</i> -SiO ₂ (4)	110	30	96
17	APTADPHS- <i>n</i> -SiO ₂ (2.5)	120	30	95
18	APTADPHS- <i>n</i> -SiO ₂ (2.5)	80	30	72
19	APTADPHS- <i>n</i> -SiO ₂ (2.5)	100	30	83

^a Isolated yield.

optimization was performed by varying the amount of catalyst and temperature. The model reaction was examined using 2–4 mol % of catalyst which showed that 2.5 mol % was sufficient to carry out the reaction (Table 1, entry 15). It was also found that increasing the temperature higher than 110 °C did not lead to an improvement in yield (Table 1, entry 17), while decreasing the temperature reduced the yield (Table 1, entries 18, 19).

With optimized conditions established, the scope and generality of the reaction were examined (Scheme 3). Aldehydes bearing electron-donating and electron-withdrawing groups were treated with kojic acid and 6-amino-1,3-dimethyluracil in the presence of catalytic APTADPHS-*n*-SiO₂ at 110 °C under solvent-free conditions to afford the corresponding fused pyridines **4a–h** in 90–97% yields within 20–30 min. Polycyclic aldehydes such as naphthalene-2-carbaldehyde and anthracene-9-carbaldehyde as well as heteroaryl aldehydes such as pyridine-3-carbaldehyde and 5-methylfuran-2-carbaldehyde also participated in this reaction affording the desired fused pyridines **4i–l** in high yields. Similarly, reactions with sterically hindered aldehydes, 3-(bis(3,4-dimethoxyphenyl)methyl)benzaldehyde, and 4-(bis(3,4-dimethoxyphenyl)methyl)benzaldehyde proceeded smoothly to provide the desired products **4m,n** in excellent yields.

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