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One-step, three-component synthesis of highly substituted pyridines using silica nanoparticle as reusable catalyst

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ABSTRACT

One-step synthesis of 'privileged medicinal scaffolds', 2-amino-3,5-dicarbonitrile- 6-sulfanylpyridines, has been demonstrated via a multicomponent reaction of aldehydes, malononitrile, and thiols using silica nanoparticle (NP) as catalysts. The silica NP catalysts are very mild (nearly neutral in nature), effective, environmentally benign, and retain most of their activities after being reused for three times.

The synthesis of 'privileged medicinal scaffolds' is highly important as these compounds often act as ligands for a number of functionally and structurally diverse biological receptors, and consequently, serve as a platform for developing pharmaceutical agents for diverse applications.[1] An example of a 'privileged scaffold' is a substituted pyridine of general structures **A**–**C** (Fig. 1). Among them, 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines (i.e., pyridines **A**) exhibit various pharmacological activities and are useful as antihepatitis B virus,[2] antiprion,[3] antibacterial,[4] and anticancer[5] agents, and as potassium channel openers for treatment of urinary incontinence.[6] Moreover, some of these compounds were found to be highly selective ligands for adenosine receptors, implicated Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, and epilepsy.[7]

These vast applications have inspired the development of a number of methods[8] for the preparation of pyridine derivatives; however, literature studies reveal that most of the methods involve multistep sequences and low isolated yields, use of toxic and expensive catalysts, and lack generality. The synthesis of pyridines **A** through multicomponent reaction (MCR) of aldehydes, malononitrile, and thiols has recently attracted much attention owing to excellent synthetic efficiency, intrinsic atom economy, high selectivity, procedural simplicity, and environmental friendliness. This strategy for the preparation of pyridines **A** was first reported by Evdokimov et al.[9a,b] using triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst; however, yields of the pyridines were not satisfactory (20–48%) due to the formation of a significant amount of a side product, enaminonitrile. A basic ionic liquid 1-methyl-3-butylimidazolium hydroxide, ([bmIm]OH),[9c] piperidine/microwave,[9d] and a Lewis acid, $ZnCl_2$,[9e] have been very recently exploited to improve the yields of the pyridines **A**. All these above-mentioned procedures[9] involved either a strong base such as triethylamine, piperidine, DABCO, or [bmIm]OH or a Lewis acid as a catalyst. This catalyst is toxic and corrosive in nature. Thus development of efficient protocol involving a very mild (nearly neutral in nature), effective, and environmentally benign catalyst for the synthesis of highly substituted pyridines **A** would significantly increase the availability of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines for medicinal applications.

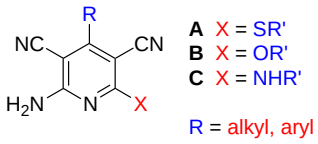

Figure 1. Substituted pyridines **A**–**C**.

Recent reports indicate that in addition to extensive use as a supporting matrix, mesoporous silica in its nanoparticulate exhibits remarkable catalytic activity.[10] Native silica nanoparticles (average size 50–100 nm) efficiently catalyzed the anti-Markovnikov addition of thiols to inactivated alkenes[10a] and bis-Michael addition of active methylene compounds to conjugated alkenes.[10b]

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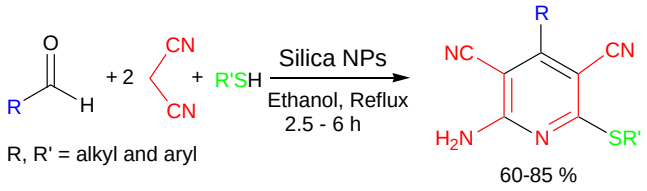


Scheme 1. Synthesis of highly substituted pyridines.

In this study, we report the use of nearly monodispersed 50 nm silica NPs as a catalyst for the synthesis of 'privileged scaffolds', 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines, through one-step, three-component condensation of aldehydes, malononitrile, and thiols (Scheme 1).

The silica NPs were synthesized by water in oil microemulsion method[11] and were found to be neutral in water (pH ~ 7.0). Briefly, ammonium hydroxide was added to a stirred solution of Triton X-100, cyclohexane, and water, and stirred for 24 h at room temperature. Methanol was added to the microemulsion, which was next centrifuged for 15 min; the precipitate was subsequently washed with methanol and water to remove the Triton X-100. The prepared nanoparticles were characterized by transmission electron microscopy (TEM) (Fig. 2) and utilized in the MCR for the synthesis of pyridines **A**.

Initially, we have explored and optimized different reaction parameters for the synthesis of pyridine derivatives using MCR of anisaldehyde, malononitrile, and thiophenol (Table 1, entry 1) as a model reaction. First, we found that the reaction outcome does not significantly depend on the size of silica NPs. Thus, 150–200 nm NPs led to slightly lower yields (by ~10%), comparing with their 50 nm counterparts, used in this study. We have observed that 10 wt % of catalyst (with respect to 1 mmol of aldehyde) efficiently catalyzed the reaction leading to 2-amino-5-cyano-4-(4-methoxy-phenyl)-6-phenylsulfanylnicotinic acid in excellent yield (85%). The same reaction was not successful in the absence of the catalyst, even after refluxing for 24 h in ethanol (Table 1, entry 3). The catalyst showed best activity in ethanol compared to other organic solvents such as DMF, toluene, and tetrahydrofuran.[10b] The above-mentioned reaction proceeded marginally in toluene (Table 1, entry 5). Surprisingly, iron oxide NPs were found to be inactive in catalyzing this MCR for the synthesis of pyridines **A** (Table 1, entry 2). Briefly, in a general experimental procedure,[12] refluxing of a mixture of aldehyde, malononitrile, thiophenol, and silica NPs in ethanol for a particular time period, followed by cooling to room temperature resulted in the precipitation of pyridines **A**.

To investigate the scope and general applicability of this procedure, we have carried out the synthesis of pyridines **A** using different aldehydes and thiols (Table 2). We have found that a series of

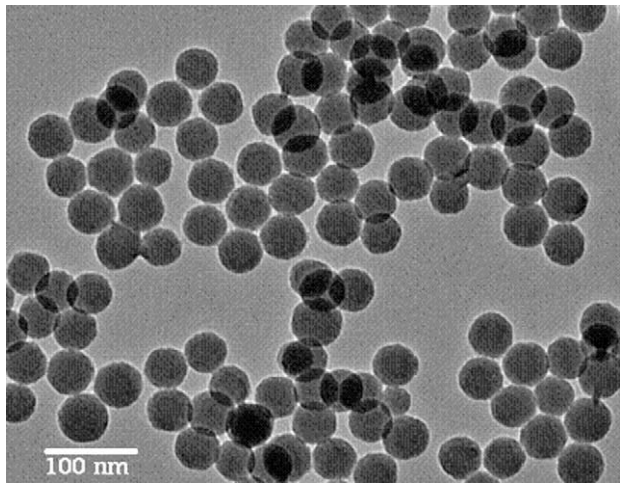
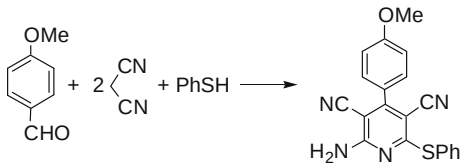


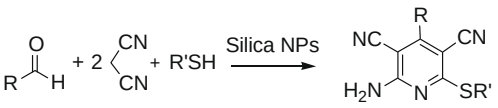
Figure 2. TEM image of silica NPs.

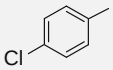
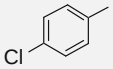
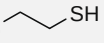
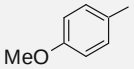
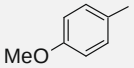
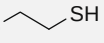
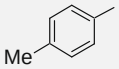
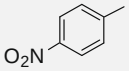
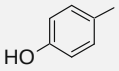
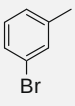
Table 1
Optimization of reaction parameters for the synthesis of pyridines **A**



Entry	Catalyst	Solvent/condition	Time (h)	Yield (%)
1	Silica NPs	EtOH/reflux	2.5	85
2	Iron oxide NPs	EtOH/reflux	2.5	0
3	None	EtOH/reflux	24	0
4	Silica NPs	EtOH/rt	24	0
5	Silica NPs	Toluene/reflux	24	20
6	Silica NPs	DMF/reflux	3	45

Table 2
Silica NP-catalyzed synthesis of substituted pyridines **A**



Entry	R	R′SH	Time (h)	Yield (%)[a]	Ref.
1	Me	PhSH	6	60	9a
2	$^{n}C_4H_9$	PhSH	6	60	13
3		PhSH	3	70	9a
4		PhSH	2.5	74	9c
5			6	60	9a
6		PhSH	2.5	85	9c
7			6	65	13
8		PhSH	2.5	75	9c
9		PhSH	2.5	84	9c
10		PhSH	3	71	9a
11		PhSH	3	73	9c
12		PhSH	3	77	9a

[a] Yield refers to those pure isolated products characterized by spectroscopic (^{1}H NMR, ^{13}C NMR, and IR) data.

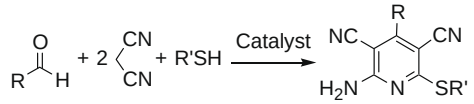
various substituted aromatic aldehydes produced 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines in good to excellent yields (60–85%). Interestingly, silica NPs also efficiently catalyzed the synthesis of pyridines **A** using aliphatic aldehydes (Table 2, entries 1 and 2) and thiols (Table 2, entries 5 and 7), whereas other reported reagents[9c,d] were unsuccessful. However, aliphatic aldehydes or thiols afforded relatively lower yields of pyridines. For comparison, the most representative reported results for the synthesis of pyridines **A** via MCR of aldehydes, malononitrile, and thiols using different reagents or catalysts are outlined in Table 3. The observed significant improvement of yields of the pyridine derivatives for the silica NPs catalyst compared to other catalysts brings up the question of a possible reaction mechanism. We believe that the presence of the reactive –OH groups on the surface of the silica NPs plays the major role in its catalytic activity.

In accordance with the mechanism outlined by Evdokimov et al.,[9a] the reaction proceeds through silica NP/base-catalyzed Michael addition of the second molecule of malononitrile to the Knoevenagel adduct (**2**), and an aldehyde with first molecule of malononitrile followed by thiolate addition to C≡N of the adduct and cyclization to dihydropyridine (**3**), which upon aromatization and oxidation (air) under the reaction conditions leads to pyridine **A** (Scheme 2).

It may be speculated that the polar amphoteric surface hydroxyl groups of the silica NPs facilitate the interaction of absorbed weak acidic and basic components due to stabilization of the corresponding transition states and intermediates by hydrogen bonding. This interaction with the neighboring silanol groups of the catalyst is shown in Scheme 2 for the first reaction step. These surface hydroxyl groups also polarized the S–H bond of the thiols (R′SH) and facilitated the formation of $R'S^-$ nucleophiles. Participation of two proximate silanol groups (one as a hydrogen bond donor and another one as an acceptor) in the reaction mechanism also seems to be plausible.

In conclusion, we have demonstrated an efficient and general procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines via multicomponent reaction of aldehydes, malononitrile, and thiols using silica NPs as a very mild (nearly neutral in nature), effective, environmentally benign, and reusable catalyst. Surprisingly, this mild catalyst efficiently catalyzed the condensation of both aromatic and aliphatic aldehydes with thiols and malononitrile leading to pyridines **A** in practical yields. Moreover, this observation demonstrated the efficacy of silica NPs in the synthesis of 'privileged medicinal scaffolds' via multicomponent reaction. These findings will stimulate further research on the applications of silica nanoparticles in organic synthesis.

Table 3
Synthesis of pyridines **A** by using different catalysts or reagents



Catalyst/ reagent	R	R′	Yield (%)	Reusability	Ref.
Et_3N or DABCO[a]	Aryl or alkyl	Aryl or alkyl	20–48	No	9a
[bmIm]OH[a]	Aryl	Aryl	62–92	yes	9c
Piperidine[b]	Aryl or alkyl	Aryl	60–81	No	9d
$ZnCl_2$[a]	Aryl or alkyl	Aryl	45–67	No	9e
Silica NPs[a]	Aryl or alkyl	Aryl or alkyl	60–85	Yes	—

[a] Reactions were carried out in ethanol at refluxing conditions.
[b] Reactions were performed in microwave heating at 90 °C.

Acknowledgment

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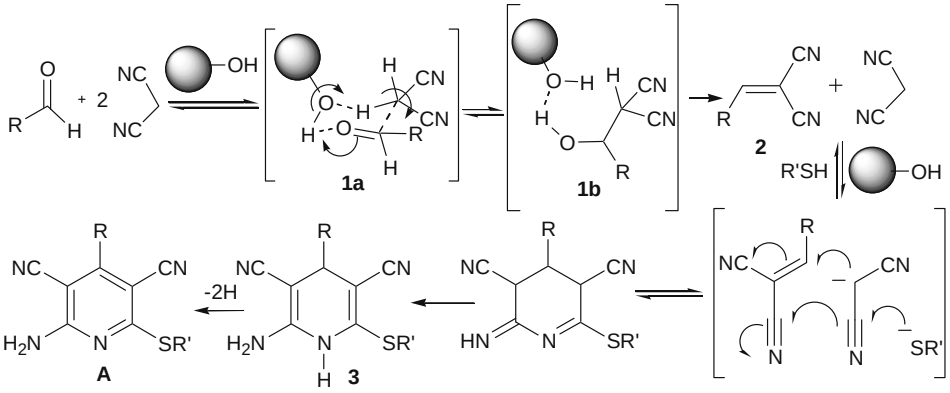

Scheme 2. Plausible mechanism for the synthesis of pyridine **A**.

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