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An Efficient Protocol for Synthesis of 2-amino-3-cyanopyridine Derivatives using Nano-modified SBA-15

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Abstract

Condensation reaction of chalcones with malononitrile and ammonium acetate in the presence of the green nano-modified SBA-15 affords the corresponding 2-amino-3-cyanopyridine derivatives in excellent yield. This approaches claimed to be an environment friendly protocol as it afforded some advantages such as excellent yields and cleaner reaction.

Keywords: *2-amino-3-cyanopyridine, Chalcone, Malononitrile, Multi-component reactions.*

Introduction

Designing for more efficient processes which allow for the rapid generation of molecular complexity and diversity from simple and readily accessible starting materials have attracted much attention of organic chemists. With the rapid developments in the field of synthetic organic chemistry, environmentally benign and eco-friendly processes such as multi-component reactions (MCRs) are becoming more and more in demand procedures [1-3]. MCRs represent a highly valuable synthetic tool for the construction of novel and complex molecular structures with a minimum number of synthetic steps [4-6]. Green chemistry principles are focusing on minimizing the hazard and maximizing the efficiency of any chemical choice. MCRs take significant advantages over conventional stepwise strategies by reducing waste production, saving energy, shortening reaction periods, rapid access to small and highly functionalized organic molecules, diversity, efficiency, high selectivity and avoiding protection and deprotection of functional groups; thus resulting in both economical and environmental benefits. MCRs have emerged as a highly valuable synthetic tool

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in the context of modern drug discovery and developing of new MCRs and improving the known MCRs are an area of considerable current interest in organic and medicinal chemistry [7-11]. Consequently, as a one-pot reaction, MCRs generally obtain good yields and are fundamentally various from two-component and permitted a rapid access to combinatorial libraries of complex organic molecules utilizing unconventional solvents (such as ionic liquid, water, and PEGs) or solvent-free conditions [12-16].

As a MCR, synthesis of 2-aminopyridine derivatives attracted enormous attention due to their wide applications. The N-heteroaromatic pyridine is incorporated into the structure of many natural products, pharmaceuticals, and functional materials. Among these compounds, 2-amino-3-cyanopyridine derivatives have been reported to possess antiviral, anticancer, antitubercular, antimicrobial, anticardiovascular, analgesic, IKK-b inhibitors, and fungicidal activities [17-19]. Moreover, 2-Amino-3-cyanopyridine is a highly reactive compound. It is extensively utilized as reactant or reaction intermediate because the cyano functions of this compound are suitably situated to enable the reaction with common mono- or bidentates to form a variety of heterocyclic compounds [20]. Therefore, the synthesis of these compounds continues to attract much interest in organic chemistry. Various preparation methods of 2-Amino-3-cyanopyridine have been reported such as [E tNH$_3$]NO$_3$, TFE, MWI, FePO$_4$, TBBDA and Ti(dpm)(NMe$_2$)$_2$ [20-22].

Recently, because of their high surface areas, large pore size, uniform pore structures, excellent thermal and mechanical stability, and high sorption capacities, mesoporous materials have attracted much attention as heterogeneous catalysts. Among those materials, SBA-15 (SBA=Santa Barbara Amorphous), a mesoporous molecular sieve with a large surface area up to 1000 (m^2/g), well-ordered hexagonal channels (5–30 nm), thick framework walls (3–6 nm), controlled pore volume (up to 2.5 cm^3/g), small crystallite size of primary particles, complementary textural porosity and excellent hydrothermal stability, well-organized array of straight channel and narrow pore size distribution [23-25]. Another special characteristic of SBA-15, abundant surface silanol groups, is then significant, which several functional groups via reacting with silanol groups can be incorporated into the surface of SBA-15 to adjust adsorption interactions with other molecules such as enzymes [9, 26].

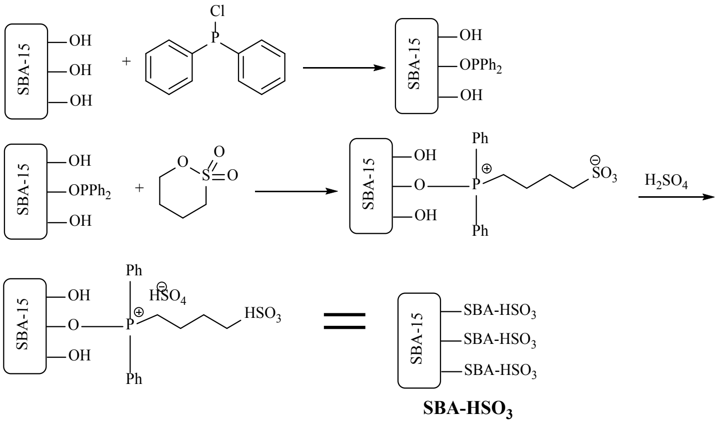
In this work and as part of our ongoing works on developing efficient green catalysts for organic synthesis [27-29], we functionalized SBA-15 by chlorodiphenylphosphine and produced a novel modification SBA-15 ionic liquid (SBA/HSO$_3$) heterogeneous catalyst. Catalytic activities were evaluated through the three-component condensation of α,β-unsaurated ketones, malononitrile and ammonium acetate (Scheme 1).

Experimental

All of the reagents and solvents used in the current study were purchased from Merck Chemical Company and used without further purification. The samples were ground into a fine powder and analyzed by XRD on a Philips X'pert X-ray diffractometer. The surface morphologies of the catalyst were studied by SEM on a Hitachi-4160 and TEM using a LEO912-AB microscope. The FT-IR spectroscopic measurements were carried out using a Nicolet FT/IR (550) spectrophotometer. The spectra were recorded in the range of 400–4000 cm^{-1} using a KBr technique.

General Procedure for Synthesis of Catalyst

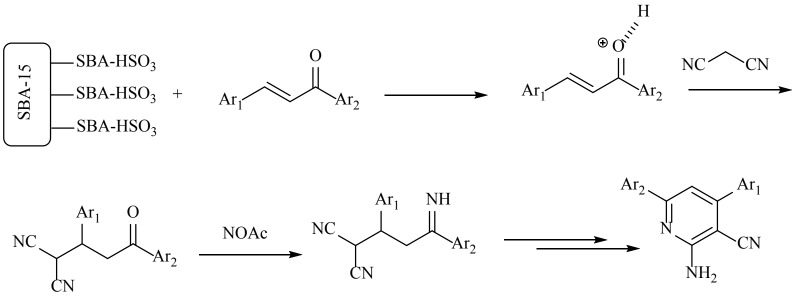
In a typical synthesis, 4 g (0.8 mmol) of $EO_{20}PO_{70}EO_{20}$ was dissolved in 150 mL of 1.6 M HCl at 35 ºC. To this solution, 8.8 g (40 mmol) tetraethylorthosilicate (TEOS) was added under vigorous stirring. After stirring for several mins, the mixture was kept in static conditions at the same temperature for one day and then the white solid product was collected by filtration, washed with acetone/ Et_2O (2×5 mL) and dried in an oven overnight. The resulting powders were calcined at 550 ºC for 6 h in order to obtain mesoporous silica materials. 1 g of produced SBA-15, 0.88 g (4 mmol) of chlorodiphenylphosphine and 0.54 g (4 mmol) of 1,4-butane sultone were dissolved in dry toluene (50 ml) refluxed for 36 h. The mixture was cooled down to room temperature, the residue was washed with MeOH/acetone and then dried in an oven overnight. Finally, 1 g of resulted solid was treated with 0.5 mL of H_2SO_4 (C) and CH_2Cl_2 (10 mL) for 24 h. After evaporation of solvent, solid nano acid catalyst ($SBA-HSO_3$) was obtained.



Scheme 1. Summary of the $SBA-HSO_3$ preparation procedure.

General Procedure for Synthesis of 2-Amino-3-cyanopyridines

Typical experimental procedure, A mixture of chalcone (0.5 mmol), malononitrile (1 mmol), ammonium acetate (2 mmol) and catalyst (6 mol%) were stirred in one-pot in EtOH (2 mL) at 50 ºC for the stipulated time. The progress of the reaction is monitored by TLC. After completion of the reaction, the reaction mixture was filtered off and the catalyst was removed. The corresponding pure solid product was obtained through recrystallized from hot EtOH affording the highly 2-amino-3-cyanopyridine derivatives. The physical data (M.p, IR, NMR) of known compounds were found to be identical with those reported in the literature.



Scheme 2. Plausible mechanistic pathway for the synthesis of 2-Amino-3-cyanopyridines.

Results and discussion

Catalyst Characterization

The effective incorporation of the organic functional groups in the structure of the synthesized materials was investigated through FTIR spectroscopy. The FT-IR spectra of the SBA-15 and SBA-HSO$_3$ are shown in Fig. 1. The FTIR analysis shows variations in the spectra caused by the organo-functionalization. SBA-15 shows the typical adsorption bands of the SBA-15 silica at 1077 cm^{-1} (asymmetric Si–O–Si stretch), 780 cm^{-1} (symmetric Si–O–Si stretch), and 452 cm^{-1} (Si–O–Si bending mode), while the adsorption bands at 3433 cm^{-1} and 1627 cm^{-1} are assigned to the hydrated silane group and the bending vibration of surface hydroxide, respectively. Besides, the peak around 955 cm^{-1} corresponds to surface Si–OH groups of SBA-15 and they could still be seen in the FT-IR spectrum of SBA-HSO$_3$. On the other hand, functionalized SBA-15 presented characteristic bands for aliphatic C–H stretching vibrations for pendant alkyl chains around 2890 cm^{-1} and weak peaks around 1441 cm^{-1} assigned to the bending vibrations of C–H bonds in aromatic ring. Compared with the FT-IR spectrum of SBA-15, the SBA-HSO$_3$ peak at 1503cm^{-1} could be ascribed to the stretching of the benzene ring from chlorodiphenylphosphine [25, 30-34]. The bands corresponding to the S=O stretching vibrations are normally found in the range of 1000–1400 cm^{-1}. Unfortunately, these bands cannot be clearly observed since they are hidden by the wide and strong band at 1077 cm^{-1} due to Si–O–Si stretching [31, 33]. This observation indicated the successful immobilization of chlorodiphenylphosphine on the surface of SBA-15.

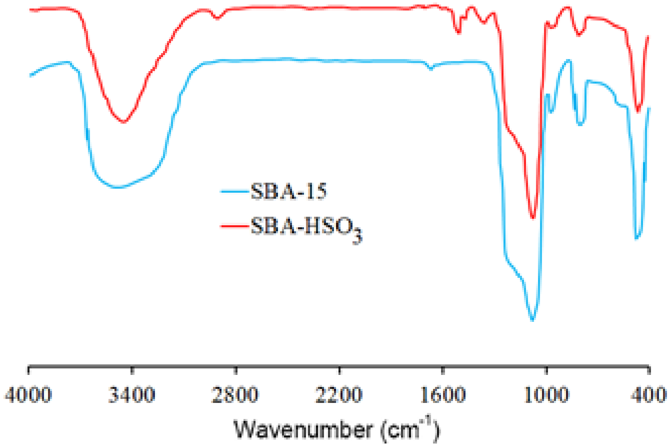


Figure 1. FT-IR spectra of the SBA-15 and SBA-HSO^3.

The XRD patterns of SBA-15 and SBA-HSO$_3$ are shown in Figure 2. The SBA-15 showed a pattern with a very strong reflection at 2θ=0.86° for d100 and two other weaker reflections at 2θ=1.46°and 2θ=1.68°for d110 and d200, respectively, associated with the quasi-regular arrangement of mesopores with hexagonal symmetry [24, 25, 35]. Though modification caused a remarkable decrease in the XRD reflection intensity for SBA-15, long range ordering and a well-formed hexagonal lattice in the structure were indicated. In addition, the intensities of all peaks diminished and shifted towards higher angle in comparison with the SBA-15, demonstrating the introduction of substrate inside the mesoporous channels of SBA-15 [35].

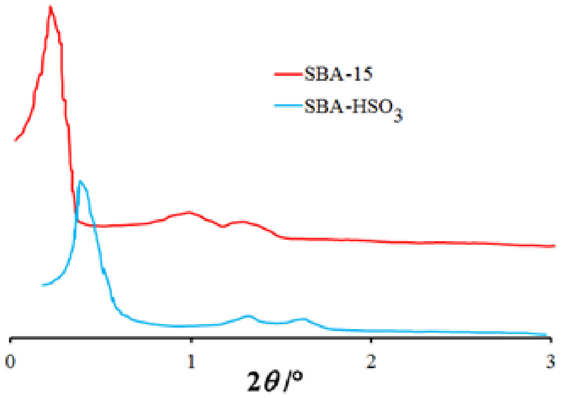


Figure 2. XRD patterns of the SBA-15 and SBA-HSO$_3$.

The SEM and TEM images are represented in Figure 3. The SEM revealed that SBA-HSO3 had some aggregation of catalyst particles in spheres, and conglomerates with uneven shapes and sizes. The TEM showed that the catalyst had long-range mesopore channels of SBA-15 highly ordered long mesochannels [26-29].

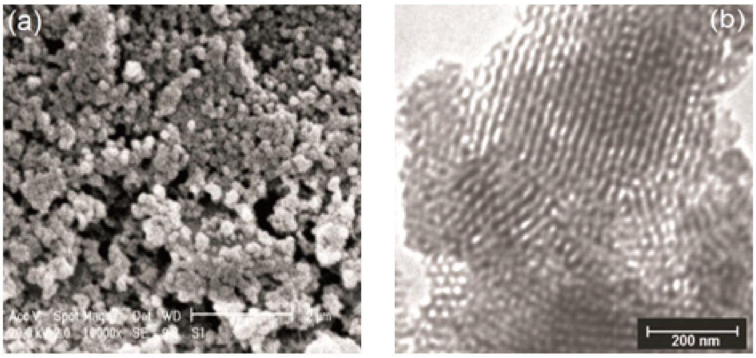


Figure 3. SEM (a) and TEM (b) of the SBA-HSO_3.

Catalytic activity

Initially, the conversion of malononitrile, ammonium acetate, and chalcone to 2-amino-4,6-diphenylnicotinonitrile was selected as the model substrate to determine the optimal conditions. The results are summarized in Table 1. As can be seen from Table 1, the best results were achieved when the reaction was performed at 50 °C for 8 h (Table 1, entry 4) with 3 mg (6 mol%) of catalyst and EtOH as solvent.

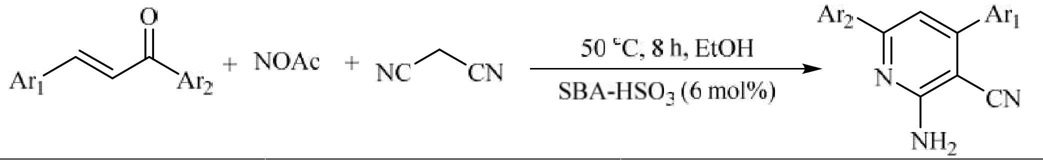
Table 1. Optimization of reaction conditions.

Entry	Solvent	T (ºC)	Catalyst (mg)	Time (h)	Tield (%)[a]
1	H_2O	R.T.	4	24	N.R.
2	H_2O	Reflux	4	12	N.R.
3	EtOH	R.T.	3	12	50
4	EtOH	50	3	8	90
5	CH_3CN	50	5	8	75
6	CH_3CN	50	3	8	70
7	Toluene	Reflux	4	8	N.R.
8	DMF	80	3	8	45

[a] Isolated yield.

To evaluate the role of our catalyst, the reaction was performed with various chalcones and the results are represented in Table 2. Chalcones with several functionalities such as Cl, Me, OMe, and NO_2 were used. Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding pyridines with good efficiency. It is seen that this procedure has the advantage of short routine, good yields, convenient work-up and being environmentally friendly.

Table 2. Synthesis of 2-amino-3-cyanopyridines.



Entry	Ar$_1$	Ar$_2$	Tield (%)[a]	M.p. (ºC)		
				Obtained	Reported	[Ref.]
1	C_6H_5	C_6H_5	91	187-189	186	[17-21]
2	C_6H_5	4-ClC_6H_5	86	18-190	190	[17-21]
3	C_6H_5	4-MeOC_6H_5	92	190-192	192-195	[17-21]
4	C_6H_5	4-MeC_6H_5	86	172-174	175-176	[17-21]
5	C_6H_5	3-$NO_2C_6H_5$	89	231-232	224-230	[17-21]
6	4-BrC_6H_4	C_6H_5	87	178-180	175	[17-21]

[a] Isolated yield.

Conclusion

In summary, we have synthesized a series of 2-amino-3-cyanopyridine derivatives by one-pot method using nano SBA-HSO_3 as a heterogeneous catalyst, thus providing a facile, efficient and environmentally friendly method.

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