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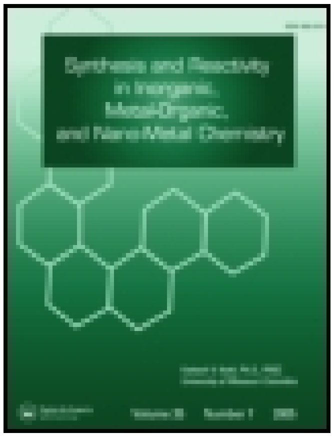

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Sulfonic Acid Supported Phosphonium Based Ionic Liquid Functionalized SBA-15 for the Synthesis of 2-Amino-3-cyano-4,6-diarylpyridines

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The surface of SBA-15 was functionalized using diphenylphosphine and then it was treated with butane sultone and sulfuric acid to obtain Brønsted acid HO_3S-phosphonium based ionic liquid functionalized SBA-15 with 4-methylbenzenesulfonate (*p*-TS^-) as a counteranion. [HO_3S-PhospIL@SBA-15], efficiently catalyzed synthesis of 2-amino-3-cyano-4,6-diarylpyridine derivatives through the reaction of chalcones, malononitrile, and ammonium acetate in good yields at 50 °C in EtOH.

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Keywords 2-amino-3-cyano-4,6-diarylpyridine, chalcones, functionalized SBA-15, malononitrile, supported ionic liquid

INTRODUCTION

Pyridine and its derivatives are one the most the important *N*-heterocycles and have considered as versatile precursors for the preparation of agrochemicals and pharmaceuticals.[1] Among them, 2-amino-3-cyano-4,6-diarylpyridine derivatives have aroused significant interest over the past decades due to a wide variety of pharmacological properties. They are known as IKK-ϐ inhibitors,[2] A_{2A} adenosine receptor antagonists[3] and potent inhibitor of HIV-1 integrase[4]

In spite of the fact that various methods have been reported for the synthesis of 2-amino-3-cyano-4,6-diarylpyridine derivatives in the literature,[5-12] development of a facile, mild, inexpensive, green and efficient approaches to access these compounds is still desirable.

Since the first report on the use of ionic liquids (ILs) as a catalyst in Friedel-Crafts acylation,[13] they have attracted lots of attention because of their remarkable catalytic properties as well as other applications such as using as a reaction medium.[14] Immobilization of ILs on the solid supports[15] particularly mesoporous silica nanoparticles (MSNs) is highly desirable for their versatile advantageous caused by heterogeneous support. It has been revealed that using supported IL catalysts offer different advantageous such as convenient separation from reaction mixture and easily use in gas-phase reaction.[16]

Recently, MSNs have been the center of attention due to well-defined pores possessing a narrow diameter distribution, high pore volume, silanol functionalization opportunity, and specific surface area.[17] Among the various MSNs, SBA-15 material has shown important textural properties such as large specific surface areas (above 1000 $m^2 \cdot g^{-1}$), uniform-sized pores (in range 4-30 nm), small crystallite size of primary particles, thick framework walls, and complementary textural porosity.[18] These advantages have made SBA-15 a useful support with high surface-to-volume ratio, variable framework compositions, and high thermal stability.[19]

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^1H NMR spectra were recorded on Bruker FT-400 using TMS as an internal standard.

Synthesis of ordered mesoporous SBA-15 silica

2D hexagonal SBA-15 was synthesized according to the literature.[20] The synthesis of SBA-15 is briefed as follows: pluronic P123 (13.9 g) was dissolved in distilled water (252 g) and concentrated HCl (7.7 g). After complete dissolution, TEOS (25.0 g) was added at once. The mixture was left under stirring at 35 °C for 24 h, followed by hydrothermal treatment at 100 °C for 48 h under static conditions. For template removal, the as-synthesized silica powders were first shortly slurried in a mixture of ethanol-HCl and subsequently calcined at 550 °C for 2 hours.

Synthesis of phosphine functionalized SBA-15

It was synthesized according to literature.[21] . SBA-15 (1 g) and triethylamine (4 mmol) were added to a solution of chlorodiphenylphosphine (4 mmol) in dry CH_2Cl_2 (100 mL). The mixture was refluxed under argon atmosphere for 12 h, then separated by filtration or centrifuge, washed with CH_2Cl_2 (3×10 ml), and dried in vacuum at 60 °C for 12 h.

Synthesis of sulfonic acidic supported phosphonium ionic liquid functionalized SBA-15

[HO_3S-PhospIL@SBA-15]

A solution of phosphine functionalized SBA-15 (1 g) and 1,4-butane sultone (4 mmol) in toluene (50 mL) was refluxed overnight. The obtained solid was separated by filtration, washed potently with methanol and acetone to remove the unreacted 1,4-butane sultone, and dried in vacuum. Then, equivalent amounts of the later solid and *p*-TSA was heated at 70 °C for 24 h to obtain the acidic catalyst with 4-methylbenzenesulfonate (*p*-TS^-) counteranion.[22]

pH-analysis of [HO_3S-PhospIL@SBA-15]

To an aqueous solution of NaCl (1 M, 25 mL) with an initial pH 5.93, the [HO_3S-PhospIL@SBA-15] (50 mg) was added and the resulting mixture stirred for 3 h when the pH of solution decreased to ~1.0. This is equal to a loading of 1.97 mmol SO_3H g^{-1} of catalyst. Additionally, this result was confirmed by back-titration analysis of the catalyst.

General procedure for the synthesis of 2-amino-3-cyano-4,6-diarylpyridines derivatives 4

A mixture of chalcone derivative (1 mmol), malononitrile (1 mmol), ammonium acetate (2 mmol), and [HO_3S-PhospIL@SBA-15] (3 mg, 0.6 mol%) in EtOH (2 mL) was stirred at 50 °C. After completion of reaction (checked by TLC), the mixture was filtered off, washed with boiling EtOH, and allowed to be recrystallized.

All compounds were known and their physical data were found to be identical compared with those of reported in the literature.

2-Amino-4,6-diphenyl-nicotinonitrile 4a

mp 187-189 °C (186 °C [5]); ^{1}H NMR ($CDCl_3$, 400 MHz,): δ_H 5.21 (s, 2H, NH_2), 7.22 (s, 1H, H_5), 7.30-7.48 (m, 6H, Ph), 7.60-7.65 (m, 2H, Ph), 8.12 (d, *J* = 7.6 Hz, 2H, Ph).

RESULTS AND DISCUSSION

The [HO_3S-PhospIL@SBA-15] was characterized by different techniques including X-ray powder diffraction (XRD), N_2 adsorptionï desorption analysis, FT-IR, transmission electron microscopy (TEM), pH analysis, and back titration. The ion-exchange pH-analysis and back titration demonstrated a loading of 1.97 mmol SO_3H g^{-1} for the obtained [HO_3S-PhospIL@SBA-15]. XRD utilizes as a sensitive technique for the determination of ordered mesoporous structures. As shown in Figure **1 a**, the XRD pattern can be indexed to the reflections of the SBA-15 structure. In SBA-15, the sharp peak related to the (100) diffraction has appeared at $2\theta=0.97^o$ along with two distinct shoulder peaks of (212) and (200) reflections at 1.47 and 1.70 º.

The aforementioned reflections in the XRD pattern confirm the 2*D* symmetry. Except for the anticipated decrease in XRD peaks intensity, no significant changes were observed during the functionalization. This confirms that the functionalization mainly accomplished inside of the meso-channels. As it has been mentioned the positions of XRD peaks remained virtually fixed which proved the retention of the meso-structure after functionalization. TEM were applied to recognize the structural order of the extracted mesoporous solid SBA-15 (Figure **1b**). In FTIR Figure **1 c**, characteristic absorption bands due to the stretching of Si-O-Si bond appear at 1090 cm^{ï1} which overlapped with SïO and PïO stretching peaks. The stretching of S=O and C=C groups in organic group appear at 1370 and 1679 cm^{ï1}, respectively. The stretching and out of plane bending of acidic OïH group are observed at 3400ï3500 and 800 cm^{ï1}, respectively.

As shown in Figure **1d** the specific surface areas of the extracted SBA-15 and [HO_3S-PhospIL@SBA-15] are calculated by the multiple-point BrunauerïEmmettïTeller (BET) around 690.04 and 355.23 m^2 g^{ï1}, respectively. Also the pore diameter distributions are determined using BJH (BarrettïJoynerïHalenda) averaged ~3.2 and 1.8 nm, respectively. These results show that the surface area and pore size have decreased after functionalization. Despite these decreases, the shape of the hysteresis loop was typically identical. This observation confirms that the pore shape does not significantly change during the modification process to prepare [HO_3S-PhospIL@SBA-15].

In continuation of our ongoing program on the design and synthesis of proficient catalysts [23, 24] and also novel heterocycles;[25-27] herein, we have developed a user-friendly, high yield, and economically and environmentally benign procedure for the synthesis of 2-amino-3-

cyano-4,6-diarylpyridines **4** through the reaction of different chalcones **1**, malononitrile **2,** and ammonium acetate **3** using [HO_3S-PhospIL@SBA-15] as a recyclable and environmentally benign catalyst (Scheme 1).

In this context, we prepared SBA-15 material according to literature.[23] Subsequently, its surface was modified through the reaction of the corresponding silica and chlorodiphenylphosphine in the presence of triethyl amine in dry dichromethane. The later compound was refluxed with a toluene solution of butane sultone leading to the formation of the heterogenized zwitterion. To obtain the desired HO_3S-Phosphonium based ionic liquid functionalized SBA-15, it was treated with *p*-TSA. TEM image and the structure of the catalyst were shown in Figure 2.

Next, we focused on the reaction of various chalcones **1**, malononitrile **2,** and ammonium acetate **3** (Scheme 1). For this purpose, we selected the reaction of chalcone **1a** malononitrile **2,** and ammonium acetate **3** as a model reaction to obtain the best reaction conditions. For the accurate screening, the model reaction was conducted in various solvents and temperature in the presence of different amount of catalyst. Some results are summarized in Table 1. AS can be seen in Table 1, the best result was obtained in EtOH at 50 °C in the presence of 3 mg (0.6 mol%) catalyst. Under the optimized conditions, the related product **4a** was obtained in 90% yield.

At the end of the reaction, the catalyst was filtered, washed with hot diethyl ether, dried at 50 °C under vacuum for 1 h, and reused in another reaction. It is worth to mention that the catalyst could be used for five times without an important change in its activity.

With these results in hand, we investigated the scope of our reaction with utilizing a variety of chalcones bearing different substituents on the aromatic ring (Table 2). It was found that chalcones possessing electron-donating as well as electron-withdrawing substituents afforded high yields of products **4**.

A proposed mechanism is depicted in Scheme 2. Probably, the Michael addition of malononitrile **2** to activated chalcone derivative **1** leads to the formation of intermediate **5** which tolerates reaction with ammonium acetate to form **6**. Intramolecular cyclization reaction following oxidation affords the title compounds **4**. It is clear that all steps including increasing the electrophilicity of the carbonyl groups as well as nitrile are catalyzed by the acidic catalyst.

CONCLUSION

In conclusion, various 2-amino-3-cyano-4,6-diarylpyridine derivatives were prepared through the reaction of different chalcones, malononitrile, and ammoniumacetate in the presence of green, recyclable, and efficient [HO_3S-PhospIL@SBA-15] in EtOH at 50 °C. The important advantages offered by this protocol are high yields of products, user-friendly procedure including simple isolation and purification of the products, using environmentally friendly solvent and recyclability of catalyst. It should be noted that the catalyst could be easily separated and reused free times without significant reduction in activity.

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TABLE 1 Optimization of the reaction conditions[a]

Entry	Solvent	Temperature (°C)	Amount of catalyst (mg)	Time (h)	Yield (%)[b]
1	H_2O	rt	4	24	NR
2	H_2O	reflux	4	12	NR
3	EtOH	rt	3	12	50
4	**EtOH**	**50**	**3**	**8**	**90**
5	CH_3CN	50	5	8	75
6	CH_3CN	50	3	8	70
7	PhMe	reflux	4	8	NR
8	DMF	80	3	8	45

[a] Carried out with chalcone **1a**, malononitrile **2,** and ammonium acetate **3** in the presence of [HO_3S-PhospIL@SBA-15].

[b] Isolated yields.

TABLE 2 Synthesis of 2-amino-3-cyano-4,6-diarylpyridines **4**

Entry	Ar	Ar'	Product **4**	Yield (%)[a]	mp (°C)	
					Observed	Reported
1	C_6H_5	C_6H_5	**4a**	90	187-189	186[5]
2	C_6H_5	4-Cl-C_6H_4	**4b**	85	188-190	190[5]
3	C_6H_5	4-MeO-C_6H_4	**4c**	90	190-192	192-195[6]
4	C_6H_5	4-Me-C_6H_4	**4d**	85	172-174	175-176[7]
5	C_6H_5	3-NO_2-C_6H_4	**4e**	88	231-232	227-230[7]
6	4-F-C_6H_4	4-F-C_6H_4	**4f**	90	205-208	204-206[12]
7	4-Cl-C_6H_4	C_6H_5	**4g**	82	183-185	182[5]
8	4-Cl-C_6H_4	4-MeO-C_6H_4	**4h**	80	180-181	177[5]
9	4-Cl-C_6H_4	4-F-C_6H_4	**4i**	82	179-180	181[5]
10	4-BrC_6H_4	C_6H_5	**4j**	85	178-180	175[5]
11	4-BrC_6H_4	4-F-C_6H_4	**4k**	85	174-176	172[5]
12	4-BrC_6H_4	4-MeO-C_6H_4	**4l**	83	183-185	181[5]
13	4-MeO-C_6H_4	4-MeO-C_6H_4	**4m**	80	155-157	159-160[7]
14	4-MeO-C_6H_4	4-Cl-C_6H_4	**4n**	80	194-195	195-196[7]

[a] Isolatd yields.

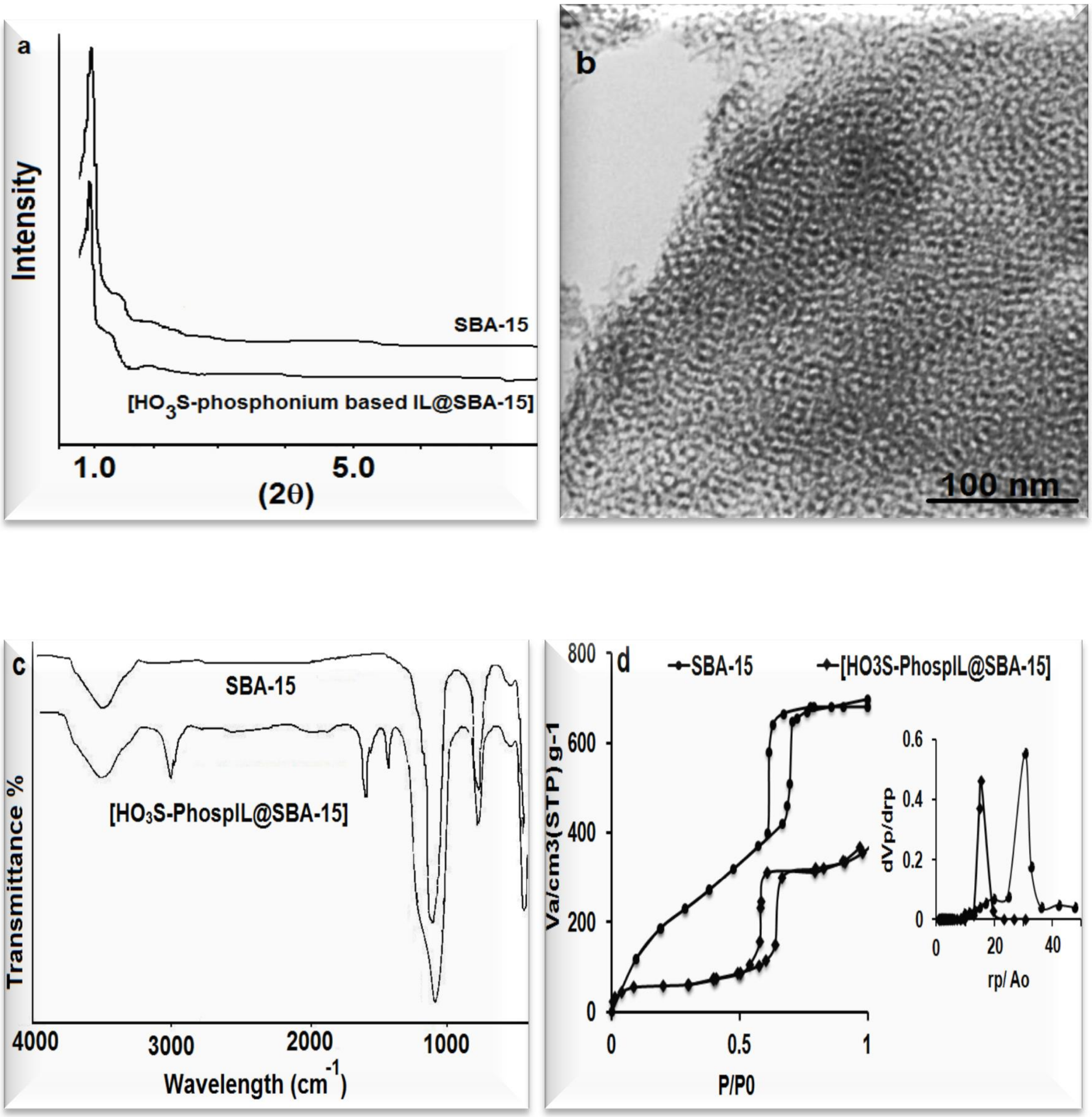


Fig. 1. XRD pattern (a), TEM (b), FTIR spectra (c), and N_2 adsorption-desorption analysis of SBA-15 and [HO_3S-PhospIL@SBA-15].

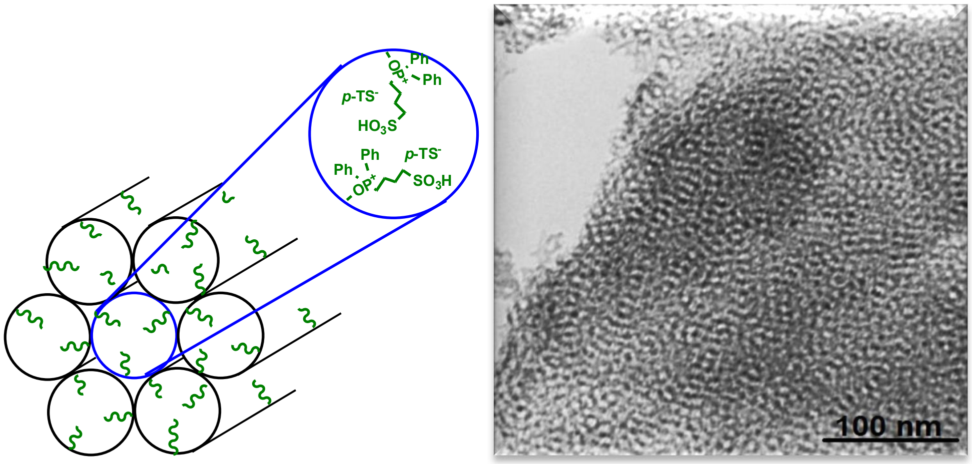
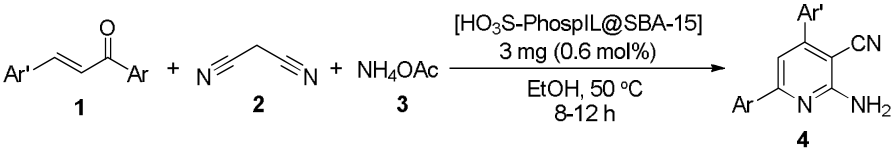
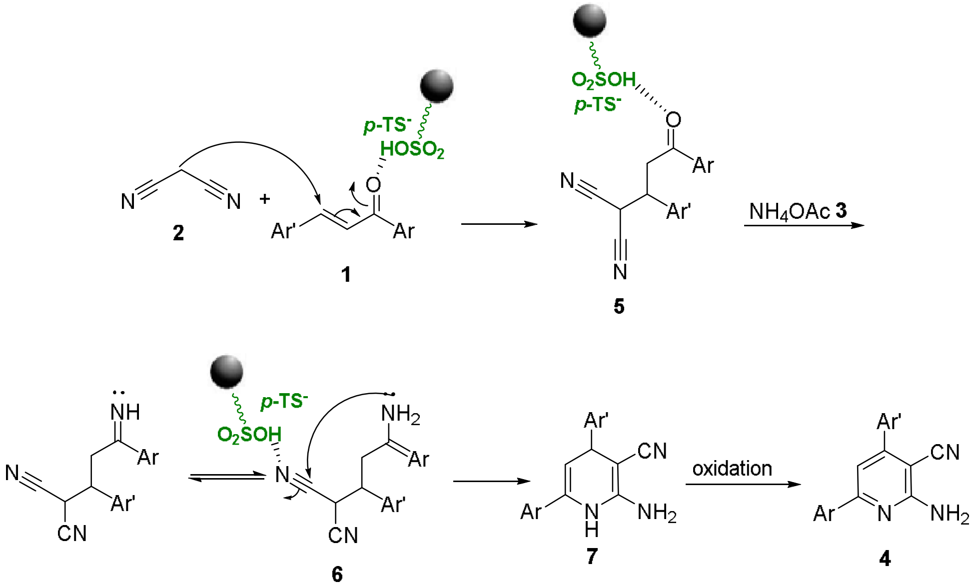


Fig. 2. Sulfonic acid supported phosphonium based ionic liquid functionalized SBA-15 [HO_3S-PhospIL@SBA-15].



Scheme 1. Synthesis of 2-amino-3-cyano-4,6-diarylpyridines **4**.



Scheme 2. Proposed mechanism for the formation of 2-amino-3-cyano-4,6-diarylpyridines **4**.