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Magnetic Solid Sulfonic Acid Decorated with Hydrophobic Regulators: A Combinatorial and Magnetically Separable Catalyst for the Synthesis of α-Aminonitriles

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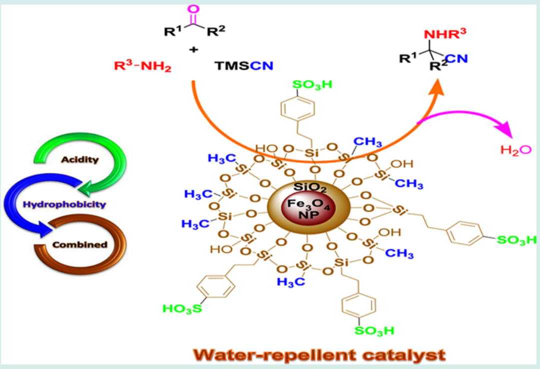
Ⓢ *Supporting Information*

ABSTRACT: A three-component, Strecker reaction of a series of aldehydes or ketones, amines, and trimethylsilyl cyanide for the synthesis of α-aminonitriles in the presence of a catalytic amount of a magnetic solid sulfonic acid catalyst, $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ under solvent-free conditions have been investigated. This catalyst, with a combination of hydrophobicity and acidity on the $Fe_3O_4@SiO_2$ core−shell of the magnetic nanobeads, as well as its water-resistant property, enabled easy mass transfer and catalytic activity in the Strecker reaction. The catalyst was easily separated by an external magnet and the recovered catalyst was reused in 6 successive reaction cycles without any significant loss of activity.



KEYWORDS: *heterogeneous catalyst, core−shell magnetic solid acid, hydrophobicity, Strecker reaction*

■ INTRODUCTION

Because of their potential applications for replacing liquid mineral acids in industry, solid acid catalysts have received significant attention;[1] they exhibit the advantages of easy separation of the catalyst from the liquid reaction medium, minimal corrosion, good recyclability, green chemical process, and enhanced product selectivity.[2] Among the solid acids, magnetic nanoparticles have currently been actively investigated.[3]

The three-component Strecker reaction (S-3CR) using an aldehyde or ketone, an amine and a cyanide source to synthesize α-aminonitriles is a well-established process and is a useful way to form C−C bonds in organic synthesis.[4] α-Aminonitriles are regarded as possible precursors to corrins, porphyrins, nucleic- and nicotinic acids,[5] and have an immense number of applications in the synthesis of a wide variety of pharmacologically relevant molecules of interest.[6] They are also regarded as versatile intermediates for the preparation of sulfur- and nitrogen-containing heterocycles, such as thiadiazoles and imidazoles.[7] Furthermore, α-aminonitriles are the key precursors of diverse α-amino acids for synthesizing proteins,[8] and are also chiral building blocks in the pharmaceutical industry.[4a] For instance, the (*R*)-phenylglycinol derivative (**a**) plays a key role in the synthesis of 7-methoxybenzolactam-V8, an intermediate of a potent activator of protein kinase C (Figure 1).[9] Also, compounds **b** and **c** serve as precursors to biologically active manzacidins[10] and cytotoxin and mitosis inhibitor (−)-hemiasterlin,[11] respectively (Figure 1).

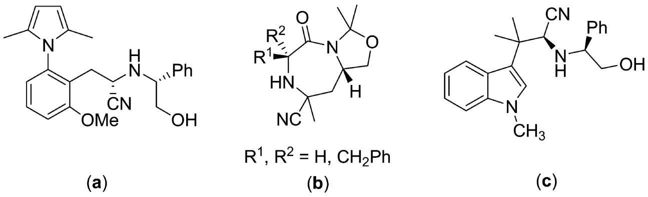


Figure 1. Chemical structure of three pharmaceutically important α-aminonitriles synthesized by Strecker type reaction as the basic step.

The classical Strecker reaction is generally carried out with hydrogen cyanide or alkaline cyanides in aqueous solution[4b,12] which has some limitations. To manage these limitations, several modifications of the Strecker reaction have been reported. These modifications use other alternative cyanating sources, such as TMSCN,[13] $K_4[Fe(CN)_6]$,[14] $(EtO)_2P(O)CN$,[15] Bu_3SnCN,[16] and Et_2AlCN.[17] Among these cyanating agents, TMSCN has proven to be an effective, relatively safe, and easily handled cyanide anion source. However, many of the TMSCN-based methods involve the use of expensive reagents, extended

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reaction times, harsh conditions, and a tedious aqueous work-up generating large amounts of toxic waste. Additionally, many of these catalysts are deactivated or decomposed by amines or the water produced during imine formation. Although a variety of profound modifications have been made to the original conditions,[18−20] the development of simple, efficient and general multicomponent procedures, utilizing ketones remains an unsolved challenge.[21]

In many acid-catalyzed reactions by solid sulfonic acids, particularly the S-3CR involving hydrophobic and hydrophilic substrates, the water produced as a byproduct is coadsorbed on the surface of the catalyst poisoning the surface and producing a more hydrophilic environment, resulting in reduced catalytic activity.[3d,22,23] On the other hand, the polarities of the reactants and products, hydrophobic−hydrophilic balance on catalyst's surface, and the acidity of the catalyst have considerable effect on the progress of the reaction. Further research studies addressed the design, synthesis and utilization of the catalytic applications of surface modified $-SO_3H$ solid materials in order to optimize these properties, and the performance of catalysts overall.[23e,24,25] Because of the inherent properties of silica-coated magnetic nanoparticles ($Fe_3O_4@SiO_2$), such as biocompatibility, easy renewability, and recovery by magnetic separation, thermal stability against degradation, large surface area and higher loading of active sites, these magnetic particles have emerged as a useful group of heterogeneous catalysts. Many investigations have been conducted on the synthesis and characterization of acidic magnetic nanoparticles.[3] However, no attention has been paid to combining hydrophobicity with acidity of materials for providing bifunctional $Fe_3O_4@SiO_2$ core−shell magnetic nanoparticles bearing both sulfonic acid and terminal organic groups as hydrophobicity regulators on the surface of nanocomposites. The introduction of sulfonic acid and organic groups onto the surface of $Fe_3O_4@SiO_2$ core−shell is interesting since the combination of both functionalities[26] allows creation of a less polar organic environment with a relatively strong acidity for acid-catalyzed reactions. As part of our efforts to explore novel heterogeneous catalysts for organic reactions,[24] we have recently reported the results obtained for the Biginelli reaction using hydrophobic organosulfonic acid-functionalized silica-coated magnetic nanoparticle catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ (Figure 2).[24a] To further establish other water-generating reactions with our catalyst, we herein report the S-3CR of various aldehydes and ketones with amines and TMSCN (Figure 3).

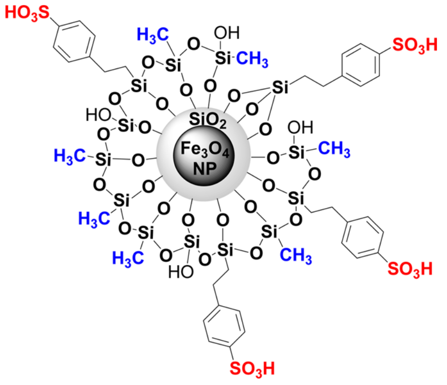


Figure 2. Hydrophobic magnetic solid sulfonic acid catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$.

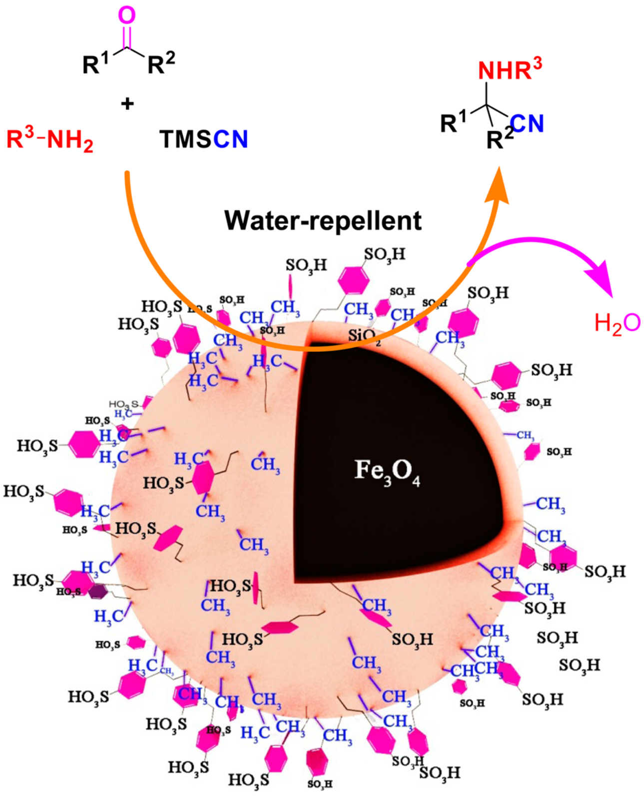


Figure 3. Water-generating S-3CR in the presence of the catalyst in solvent-free condition.

RESULTS AND DISCUSSION

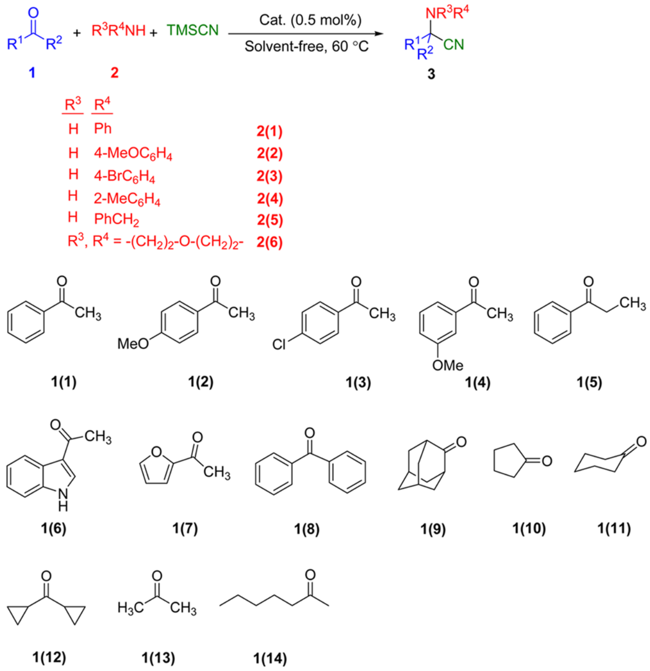
To find the best reaction conditions, we first examined the effect of different temperatures and amounts of the catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ for the Strecker reaction of acetophenone (2 mmol), aniline (2 mmol), and TMSCN (2.4 mmol) under solvent-free condition as a model reaction. It was found that at higher temperature and mol %, the catalyst performed in shorter reaction times (Table 1, entries 1−5). Also, we have shown that reducing the amount of the catalyst decreased the product yield at 60 °C (Table 1, entries 5−7). We also examined the effect of higher temperatures (80 °C) and lower amounts of the catalyst (Table 1, entries 8 and 9). These results showed the significant effect of the catalyst in the

Table 1. Effects of Temperature and the Amount of Catalyst for the S-3CR[a]

entry	amount of catalyst (mol %)	temperature (°C)	time (h)	yield (%)[b]
1	0.5	25	48	82
2	1	25	36	81
3	0.5	40	15	80
4	1	40	15	88
5	**0.5**	**60**	**9**	**91**
6	0.35	60	9	83
7	0.25	60	9	75
8	0.35	80	9	90
9	0.25	80	9	83

[a] Reaction conditions: acetophenone (2 mmol), aniline (2 mmol), TMSCN (2.4 mmol), $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ at various temperatures under solvent-free condition. [b] Yields refer to the isolated pure products.

Table 2. S-3CR of Various Ketones and Amines Catalyzed by Catalyst Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$[a]



entry	ketone	amine	product	time (h)	yield (%)[b]
1	1(1)	2(1)	3{1(1),2(1)}	9	91
2	1(2)	2(1)	3{1(2),2(1)}	9	85
3	1(3)	2(1)	3{1(3),2(1)}	9	94
4	1(4)	2(1)	3{1(4),2(1)}	7	89
5	1(5)	2(1)	3{1(5),2(1)}	20	87
6	1(6)	2(1)	3{1(6),2(1)}	24	81
7	1(7)	2(1)	3{1(7),2(1)}	24	76
8	1(8)	2(1)	3{1(8),2(1)}	32	78[c]
9	1(9)	2(1)	3{1(9),2(1)}	0.75	92
10	1(10)	2(1)	3{1(10),2(1)}	20	83
11	1(11)	2(1)	3{1(11),2(1)}	20	81
12	1(12)	2(1)	3{1(12),2(1)}	23	90
13	1(13)	2(1)	3{1(13),2(1)}	2	92[d]
14	1(3)	2(2)	3{1(3),2(2)}	20	89
15	1(4)	2(2)	3{1(4),2(2)}	20	78
16	1(5)	2(2)	3{1(5),2(2)}	20 (24)[e]	40 (72)[e]
17	1(8)	2(2)	3{1(8),2(2)}	32 (48)[f]	21 (50)[f]
18	1(9)	2(2)	3{1(9),2(2)}	1.5	91
19	1(11)	2(2)	3{1(11),2(2)}	20	62 (79)[g]
20	1(13)	2(2)	3{1(13),2(2)}	2	79[d] (90)[d,g]
21	1(1)	2(3)	3{1(1),2(3)}	8	90
22	1(5)	2(3)	3{1(5),2(3)}	20	88
23	1(8)	2(3)	3{1(8),2(3)}	32	57 (80)[c]
24	1(10)	2(3)	3{1(10),2(3)}	20	86
25	1(11)	2(3)	3{1(11),2(3)}	20	84
26	1(12)	2(3)	3{1(12),2(3)}	23	91
27	1(13)	2(3)	3{1(13),2(3)}	2	91[d]
28	1(14)	2(3)	3{1(14),2(3)}	24	86
29	1(1)	2(4)	3{1(1),2(4)}	9	88
30	1(1)	2(5)	3{1(1),2(5)}	10	70
31	1(5)	2(6)	3{1(5),2(6)}	24	<5

[a] Reaction conditions: ketones (2 mmol), amine (2 mmol), TMSCN (2.4 mmol), catalyst (0.5 mol %), at 60 °C under solvent-free condition. [b] Isolated yields. [c] 1.5 mol % of the catalyst was used. [d] Reactions were performed at room temperature. [e] 1.75 mol % of the catalyst was used. [f] 1.5 mol % of catalyst at 80 °C was used. [g] 1 mol % of the catalyst was used.

reaction and gave the expected product in a good yield. It was concluded that solvent-free conditions at 60 °C in the presence of 0.5 mol % of the catalyst was the optimized condition for the S-3CR (Table 1, entry 5).

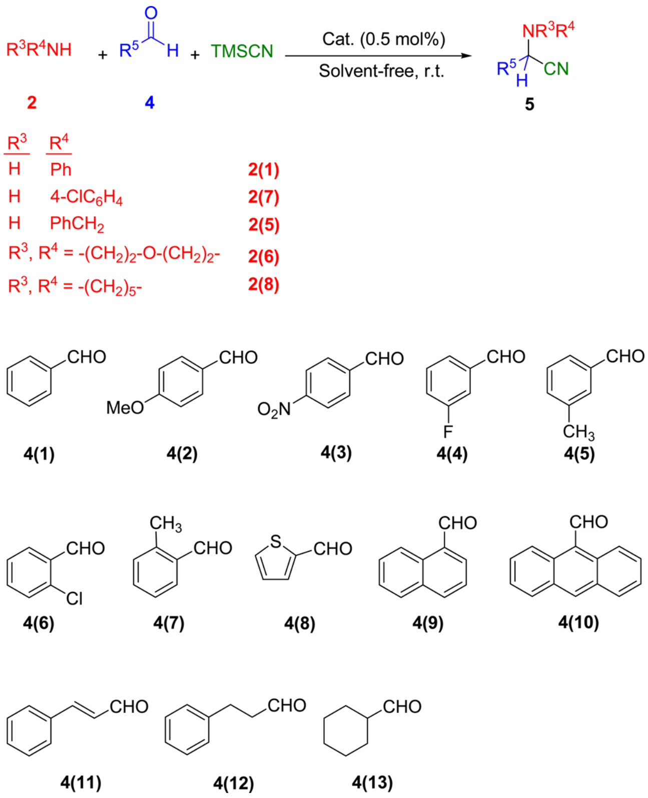
To survey the generality of the procedure, we studied the S-3CR of ketones with amines and TMSCN under solvent-free conditions. Representative results are listed in Table 2. A wide range of ketones, such as alicyclic, strained cyclic, aliphatic and aromatic, as well as enolizable ketones smoothly reacted with primary amines to give the corresponding α-aminonitriles in good to high yields.

The reaction was almost equally facile with acetophenone derivatives (Table 2, entries 1−4, 14, 15, and 21); as expected, the reaction of acetophenone substituted with electron-withdrawing group occurred in higher yield and shorter reaction time than its electron-donating counterpart (Table 2, entries 2 and 3).

The obtained results reveal that the strained and rigid 2-adamantanone gave the corresponding products in short reaction times and higher yields than other ketones (Table 2, entries 9 and 18). Heteroaryl ketones, such as 3-acetylindole and 2-acetylfuran, provided good to high yields of the desired α-aminonitriles (Table 2, entries 6 and 7). Acetone, with a relatively low boiling point, rapidly underwent the condensation within 2 h in high yield despite the fact that its reaction took place at room temperature (Table 2, entries 13, 20, and 27). Sterically hindered ketones, such as benzophenone, also reacted with anilines and TMSCN to give the corresponding products in moderate to good yields although the reactions proceeded rather slowly and needed 1.5 mol % of the catalyst (Table 2, entries 8 and 23) or even higher temperature (80 °C, Table 2, entry 17). To assess the effect of the lower reactivity of aliphatic ketones in the reaction and also to study the possibility of the formation of TMS enol ethers, the reaction of 2-heptanone, as an enolizable ketone with 4-bromoaniline was investigated; in fact, the high yield of this reaction showed the superiority of the imine formation and S-3CR as opposed to the TMS enol ether formation (Table 2, entry 28). Also, sterically hindered 2-methylaniline **2(4)**, gave a high yield of the corresponding α-aminonitrile in an appropriate time (Table 2, entry 29). Aliphatic amines were also screened; while the reaction of acetophenone with benzylamine provided the desired product in a good yield, the reaction of propiophenone with morpholine resulted in a mixture of products, with very poor yield of the corresponding α-aminonitrile (Table 2, entries 30 and 31).

Inspired by these results, the optimized conditions were also applied to the S-3CR with aldehydes at room temperature. Therefore, different aliphatic, aromatic and heteroaromatic aldehydes reacted with a range of amines, such as piperidine, morpholine, and benzylamine as well as aniline derivatives, all at room temperature in a solvent-free environment. Table 3 shows the results of these reactions, using the hydrophobic solid acid catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ at 0.5 mol %. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields (81−95%) in a reaction time ranging from 10 to 150 min. The treatment of various aldehydes and anilines with TMSCN in the presence of the catalyst afforded the corresponding products (Table 3, entries 1−9 and 15) in excellent yields within short reaction times (10−40 min). This method is equally effective with aldehydes bearing electron-withdrawing, electron-donating, and sterically hindered substituents in the aromatic ring (**4(2)**, **4(3)**, **4(6)**, and **4(7)**). Moreover, an acid sensitive aldehyde, cinnamaldehyde, reacted well without any polymerization under these reaction conditions.

Table 3. S-3CR of Various Aldehydes and Amines Catalyzed by Catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H^a$



entry	aldehyde	amine	product	time (min)	yield (%)^b
1	4(1)	2(1)	5{4(1),2(1)}	13	95
2	4(2)	2(1)	5{4(2),2(1)}	20	90
3	4(4)	2(1)	5{4(4),2(1)}	10	94
4	4(5)	2(1)	5{4(5),2(1)}	15	91
5	4(6)	2(1)	5{4(6),2(1)}	20	91
6	4(7)	2(1)	5{4(7),2(1)}	20	89
7	4(8)	2(1)	5{4(8),2(1)}	30	87
8	4(10)	2(1)	5{4(10),2(1)}	30	90
9	4(12)	2(1)	5{4(12),2(1)}	40	89
10	4(1)	2(5)	5{4(1),2(5)}	120	89
11	4(3)	2(5)	5{4(3),2(5)}	120	90
12	4(8)	2(5)	5{4(8),2(5)}	120	83
13	4(13)	2(5)	5{4(13),2(5)}	150	81
14	4(1)	2(6)	5{4(1),2(6)}	150	89
15	4(11)	2(7)	5{4(11),2(7)}	25	92
16	4(9)	2(8)	5{4(9),2(8)}	150	85

[a] Reaction conditions: aldehyde (2 mmol), amine (2 mmol), TMSCN (2.4 mmol), catalyst (0.5 mol %), at room temperature under solvent-free condition. [b] Isolated yields.

Also, an enolizable aldehyde, such as 3-phenylpropionaldehyde produced the corresponding α-aminonitrile in high yield (**5{4(12),2(1)}**), Table 3, entry 9). However, primary and secondary aliphatic amines reacted with aldehydes but with relatively slow reaction rate due to the unstable nature of the formed aliphatic imines (Table 3, entries 10−14 and 16). If the reaction time was prolonged to 120−150 min, high yields of the products could be obtained.

The catalytic activity and reusability of this hydrophobic magnetic solid acid catalyst was also studied for the S-3CR coupling reaction of adamantanone (2 mmol) with aniline (2 mmol) and TMSCN (2.4 mmol) for 45 min at 60 °C under

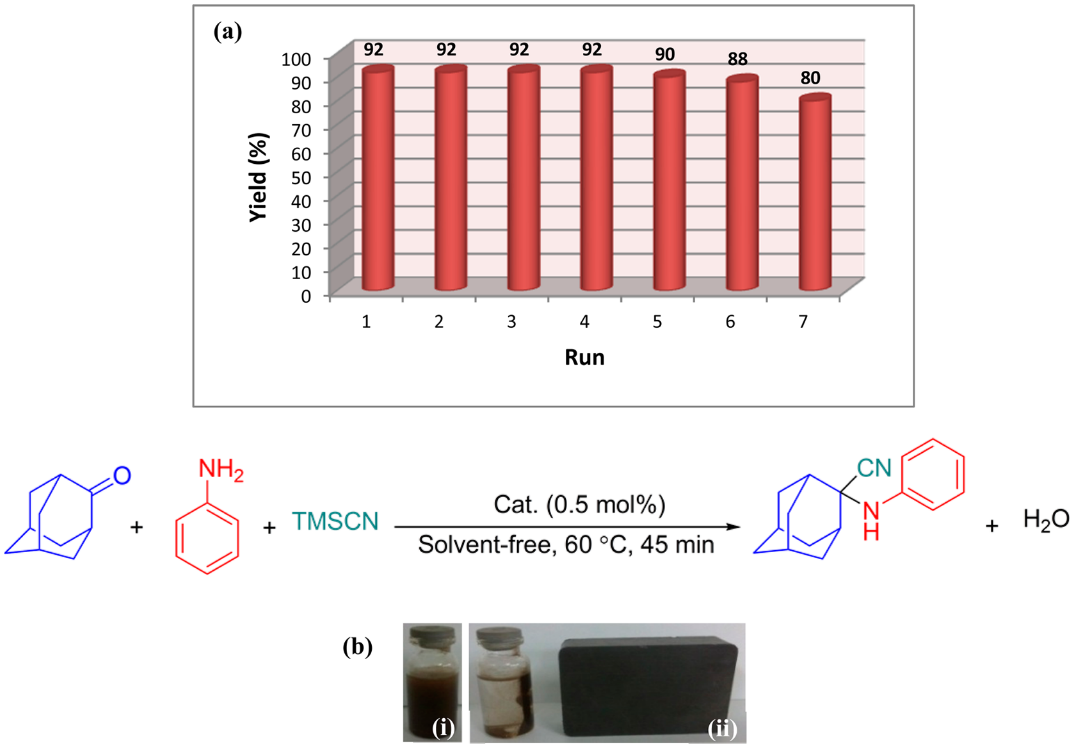


Figure 4. (a) Recyclability of the catalyst $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ for the S-3CR of adamantanone with aniline in the presence of trimethylsilyl cyanide. (b) The catalyst in a typical reaction mixture in the absence (i) and the presence (ii) of a magnetic field.

solvent-free condition. Upon completion of the reaction, the mixture was diluted with EtOAc and the catalyst was easily separated and recovered by an external magnet and washed with EtOAc and EtOH and finally dried at 100 °C for 30 min prior to the next run. The crude product was recrystallized from EtOAc/*n*-hexane for further purification. During the recycling experiment with fresh reactants, under the same reaction conditions, no considerable change in the activity of the catalyst was observed for at least 6 successive runs which clearly demonstrate the stability of the catalyst for these conditions in the S-3CR (Figure 4).

Finally, we compared the catalytic performance of our catalyst with other catalytic systems reported in the literature for the S-3CR of benzaldehyde, aniline, and TMSCN (Table 4). Table 4 clearly demonstrates the advantages of the present work over the other reported protocols, in terms of the product yield, reaction temperature, and time.

■ CONCLUSIONS

In summary, we have presented a magnetic solid sulfonic acid modified with hydrophobic regulators, $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$, which was efficiently used as a combinatorial and heterogeneous catalyst for the three-component Strecker reaction for the synthesis of α-aminonitriles under solvent-free condition. This catalyst, with its hydrophobic surface, resulting from the methyl groups bounded on the surface, enabled the repulsion of water; otherwise, the sulfonic acid sites would have been deactivated. The catalyst was readily separated by an external magnet and the recovered catalyst was reused for at least 6 reaction cycles without any significant loss of activity. The clean reaction conditions and high selectivity affording exclusively α-aminonitriles in high yields, no observation of undesired side products, and utilizing a green and magnetically separable heterogeneous catalyst were the advantages of this work. These results expand the capability of the catalyst and antedate further progress by creative research to explore the surface hydrophobicity of magnetic catalysts and magnetic materials in other fields.

Table 4. Comparison of Different Catalytic Systems with the Present Work

entry	catalyst	solvent	*T* (°C)	time	yield (%)
1	Nafion-Fe (100 mg)	CH_2Cl_2	60	4 h	95[27a]
2	Nafion-SAC-13 (200 mg)	CH_2Cl_2	60	6 h	87[27b]
3	Nafion-H (200 mg)	CH_2Cl_2	60	6 h	80[27b]
4	MCM-41-SO_3H (5 mg)	EtOH	rt	70 min	97[22b]
5	Silica-based Sc (III) interphase (5 mol %)	CH_2Cl_2	rt	14 h	94[27c]
6	Silica-supported $H_3PW_{12}O_{40}$ (7 mol %)	CH_3CN	rt	5 min	98[27d]
7	SBA-15-Ph-PrSO_3H (1 mol %)		50	5 min	100[25b]
8	Montmorillonite KSF clay (1 g)	CH_2Cl_2	rt	3.5 h	90[27e]
9	β-Cyclodextrin (0.1 mmol)	H_2O	rt	1 h	98[19c]
10	$NiCl_2$ (5 mol %)	CH_3CN	rt	12 h	92[27f]
11	[Bmim]BF_4 (1 mL)		rt	5 h	92[27g]
12	[Bmim]PF_6 (1 mL)		rt	6 h	87[27g]
13	$Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ (0.5 mol %)		rt	13 min	95[a]

[a] Present work.

■ EXPERIMENTAL PROCEDURES

All chemicals were purchased from Merck and Aldrich Chemical Companies. Melting points were determined on a

Büchi melting point B-540 apparatus. NMR spectra were recorded at 400, 300, and 250 (^{1}H), and 100.6, 75.4, and 62.9 (^{13}C) MHz, respectively, on commercial Bruker DMX-400, Bruker DMX-300, and Bruker DPX-250 instruments using $CDCl_3$ as solvent. IR spectra were recorded on an ABB Bomem Model FTLA 2000 spectrophotometer using KBr discs.

Preparation of Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$ Catalyst. The synthesis of the Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$ catalyst was conducted according to the procedure previously reported.[24a] In a typical preparation procedure, 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane (CSPETS, 0.2 g, 0.62 mmol) and trimethoxymethylsilane (TMMS, 0.2 g, 1.47 mmol) were added to dry toluene (35 mL) containing silica-coated magnetic nanoparticles (Fe_3O_4@SiO_2, 1.0 g). The resulting mixture was stirred for 24 h and then washed with toluene (2 × 15 mL) and distilled water. Finally, the solid was suspended in H_2SO_4 (1 M) solution for 2 h, washed several times with water and dried at room temperature under vacuum overnight to give the desired catalyst. The catalyst was also characterized by FT-IR, VSM, XRD, SEM, TEM, TG-DTA, and elemental analysis data, as well as water adsorption−desorption, and N_2-sorption isotherms. The concentration of sulfonic acid groups was quantitatively estimated by ion-exchange pH analysis and the acid amount was determined to be 0.7 mmolg^{-1}.[24a]

General Procedure for the One-Pot Preparation of α-Aminonitriles. A mixture of aldehyde/ketone (2 mmol), amine (2 mmol), trimethylsilyl cyanide (2.4 mmol), and catalyst (14.2 mg, 0.5 mol %) were stirred in a sealed tube at rt/60 °C, respectively for an appropriate time in solvent-free condition (Tables 2 and 3). The progress and completion of the reaction was monitored by thin layer Chromatography (TLC). After the completion of the reaction, the mixture was diluted with ethyl acetate and the catalyst was separated by magnetic decantation. The crude product was either recrystallized from EtOAc/*n*-hexane or subjected to preparative TLC (silica gel) for further purification. All compounds were characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, melting points, ^{1}H NMR, ^{13}C NMR spectra, and Dept-135 spectra of selected α-aminonitriles. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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