



Silica-bonded *S*-sulfonic acid: an efficient and recyclable solid acid catalyst for the three-component synthesis of α -amino nitriles

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ABSTRACT

Silica-bonded *S*-sulfonic acid (SBSSA) is employed as a recyclable catalyst for the synthesis of α -amino nitriles. These syntheses were performed via a one-pot three-component condensation of aldehydes, amines, and trimethylsilyl cyanide under mild reaction conditions at room temperature.

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1. Introduction

The addition of cyanide anion to imines (the Strecker reaction)¹ provides one of the most important and straightforward method for the synthesis of α -aminonitriles, which are useful intermediates for the synthesis of amino acids^{2,3} and nitrogen containing heterocycles such as thiadiazoles and imidazoles, etc.^{4,5} The classical Strecker reaction usually is carried out in aqueous solution and the work-up procedure is also tedious. Thus several modifications of Strecker reaction have been reported using a variety of cyanide reagents,^{6–8} such as diethyl phosphorocyanidate and α -trimethyl-

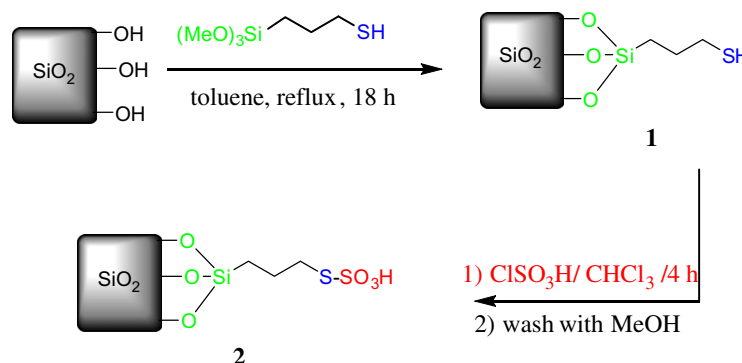
Table 1

Condensation of benzaldehyde, aniline and TMSCN in the presence of different amounts of SBSSA^a

Entry	Catalyst loading (g)	Time (min)	Yield ^b
1	No catalyst	24 h	0
2	0.05	100	80
3	0.1	60	90
4	0.2	30	94
5	0.3	30	95

^a Reaction conditions; benzaldehyde (1 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), EtOH (2 ml), room temperature.

^b Isolated yield.



Scheme 1. Preparation of silica-bonded *S*-sulfonic acid (SBSSA).

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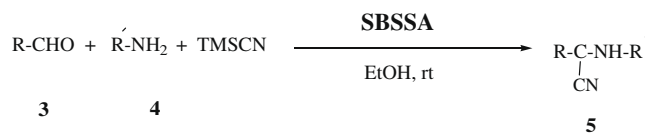
Table 2

Condensation of benzaldehyde, aniline and TMSCN in different solvents and under solvent-free conditions in the presence of SBSSA (0.2 g)

Entry	Solvent ^a	Time (min)	Yield ^b
1	EtOH	30	94
2	H ₂ O	120	75
3	CH ₂ Cl ₂	120	70
4	<i>n</i> -Hexane	120	30
5	MeCN	60	90
6	Solvent-free	120	90

^a The reaction was carried out in 2 mL of solvent at rt.

^b Isolated yield.



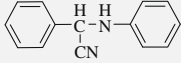
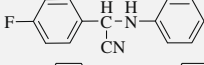
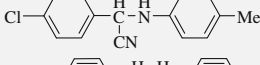
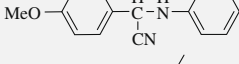
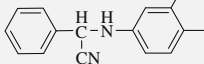
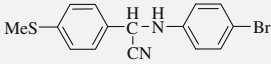
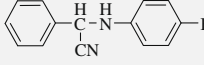
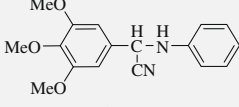
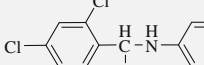
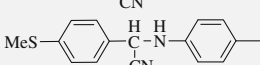
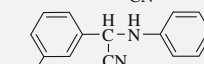
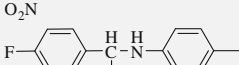
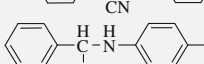
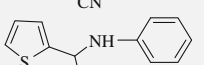

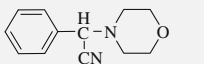
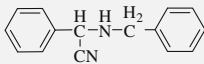
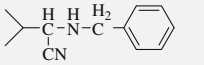
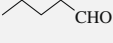
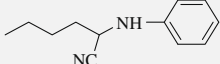
R = aliphatic, aromatic

R' = primary, secondary

Scheme 2. Synthesis of α -amino nitrile derivatives catalyzed by SBSSA.

Table 3

Preparation of various α -amino nitriles in the presence of SBSSA in EtOH at room temperature^a

Entry	R	R'	Product (5)	Time (min)	Yield (%) ^b	Mp (°C)	Lit. Mp (°C)
a	C ₆ H ₅ -	C ₆ H ₅ -		30	94	80–82	81–83 ²²
b	4-F-C ₆ H ₄ -	C ₆ H ₅ -		40	90	99–101	98–100 ¹⁵
c	4-Cl-C ₆ H ₄ -	4-Me-C ₆ H ₄ -		90	92	85–87	84–85 ⁸
d	4-MeO-C ₆ H ₄ -	C ₆ H ₅ -		25	93	95–97	94–95 ¹¹
e	C ₆ H ₅ -	3,4-(Me) ₂ -C ₆ H ₃ -		25	88	92–94	—
f	4-MeS-C ₆ H ₄ -	4-Br-C ₆ H ₄ -		30	91	122–124	—
g	C ₆ H ₅ -	4-Br-C ₆ H ₄ -		40	85	91–93	—
h	3,4,5-(MeO) ₃ -C ₆ H ₂ -	C ₆ H ₅ -		25	95	147–149	—
i	2,4-(Cl) ₂ -C ₆ H ₃	C ₆ H ₅ -		80	78	115–117	—
j	4-MeS-C ₆ H ₄ -	4-Me-C ₆ H ₄ -		40	86	102–104	—
k	3-O ₂ N-C ₆ H ₄ -	C ₆ H ₅ -		80	91	89–92	—
l	4-F-C ₆ H ₄ -	4-Me-C ₆ H ₄ -		60	94	101–103	—
m	C ₆ H ₅ -	4-Me-C ₆ H ₄ -		25	90	102–104	—
n	2-Thienyl-	C ₆ H ₅ -		60	81	100–102	98–100 ¹⁵
o	C ₆ H ₅ -			180	82	69–71	68–69 ⁹
p	C ₆ H ₅ -	Ph-CH ₂ -		90	78	Colorless oil	Colorless oil ²²
q	<i>i</i> -C ₃ H ₇ -	Ph-CH ₂ -		100	80	Colorless oil	Colorless oil ⁹
r		C ₆ H ₅ -		100	78	55–57	56–58 ¹⁷

^a Reaction conditions: aldehyde (1 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), SBSSA (0.2 g), room temperature, EtOH.

^b Isolated yield.

Table 4

Comparison of the result of condensation reaction of benzaldehyde and aniline with TMSCN in the presence of different catalysts based on silica

Entry	Catalyst	Catalyst loading (g)	Conditions	Time (min)	Yield ^a	Ref.
1	SBSSA	0.2 (0.066 mmol)	rt	30	94	Present work
2	Montmorillonite KSF clay	1.0	rt	210	90	11
3	Silica-based scandium(III)	0.1 (0.03 mmol)	rt	840	94	12
4	Xanthene sulfuric acid	0.1 (0.06 mmol)	rt	65	97	22
4	Silica sulfuric acid	0.095 (0.25 mmol)	rt	360	88	24
5	SBA-15 supported sulfonic acid	0.031 (0.017 mmol)	50 °C	5	100	25

^a Isolated yield.

siloxyl nitriles, as well as catalysts such as InCl_3 ,⁹ BiCl_3 ,¹⁰ montmorillonite KSF clay,¹¹ silica-based scandium(III),¹² $\text{SO}_4^{2-}/\text{ZrO}_2$,¹³ ferric perchlorate,¹⁴ $\text{Fe}(\text{Cp})_2\text{PF}_6$,¹⁵ InI_3 ,¹⁶ I_2 ,¹⁷ $\text{K}_5\text{CoW}_{12}\text{O}_{40}\cdot 3\text{H}_2\text{O}$,¹⁸ vanadyl triflate,¹⁹ Fe_3O_4 ,²⁰ guanidine hydrochloride,²¹ xanthan sulfuric acid,²² $[\text{bmim}]\text{BF}_4$,²³ silica sulfuric acid,²⁴ hydrophobic sulfonic acid based nanoreactors²⁵ under various reaction conditions. The use of trimethylsilyl cyanide is a safer and more effective cyanide anion source for the nucleophilic addition reactions of imines under mild conditions.^{26–28} However, many of these methods involve the use of expensive reagents, harsh conditions, extended reaction times, and also require tedious workup leading to the generation of a large amount of toxic waste. Further more many of these catalysts are deactivated or sometimes decomposed by amines and water that exist during imine formation. In order to overcome these problems, recently one-pot procedures have been developed for this transformation.^{29–31}

In continuation of our work to develop new catalysts for organic transformations, here we report mild, efficient and environmentally benign catalyst for the preparation of α -aminonitriles from aldehydes, amines and trimethylsilyl cyanide in the presence of silica bonded *S*-sulfonic acid (SBSSA) in ethanol at room temperature.

Recently, we have reported the preparation of silica-bonded *S*-sulfonic acid (SBSSA) and used it as a catalyst for the synthesis of 1,1-diacetates,³² quinoxaline,³³ coumarin derivatives,³⁴ 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols),³⁵ and silyl ethers³⁶ (Scheme 1).

To study the effect of catalyst loading on the condensation of aldehydes, amines, and trimethylsilyl cyanide as the corresponding α -amino nitriles, the reaction of benzaldehyde and aniline with TMSCN was chosen as a model reaction (Table 1). To illustrate the need of SBSSA for this condensation we examined the model reaction in the absence of SBSSA. In this case the reaction did not proceed even after 24 h (Table 1, entry 1). Obviously, SBSSA is an important component of the reaction.

The model reaction was also examined in various solvents as well as under solvent-free conditions in the presence of 0.2 g (0.066 mmol/g) of SBSSA (Table 2).

The results showed that the efficiency and the yield of the reaction in EtOH were higher than those obtained in other solvents or under solvent-free conditions. Therefore, we employed the optimized conditions [aldehyde (1 mmol), amine (1.2 mmol), TMSCN (1.2 mmol), SBSSA (0.2 g) and EtOH (2 mL)] for the synthesis of α -amino nitriles in this one-pot three-component condensation (Scheme 2).

Next, we prepared a range of α -amino nitriles under the optimized conditions (Table 3). Both aromatic and aliphatic aldehydes reacted with amines and TMSCN in the presence of SBSSA in this one-pot condensation to afford excellent yields of corresponding α -amino nitriles. Moreover, aldehydes with electron-donating or electron-withdrawing groups, that is, 4-methoxybenzaldehyde **3d**, and 3,4,5-trimethoxybenzaldehyde **3h**, or 3-nitrobenzaldehyde **3k**, were converted into the corresponding α -amino nitriles **5d**, **5h**

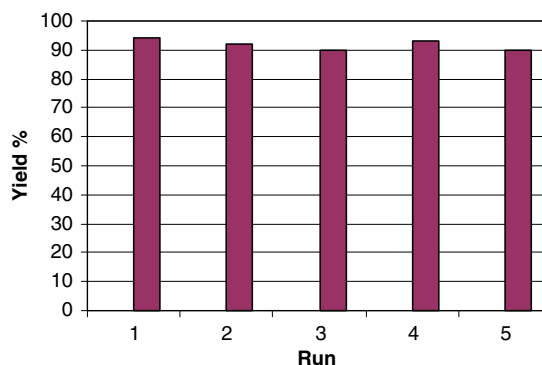


Figure 1. Recyclability of SBSSA (0.2 g) in the reaction of benzaldehyde (1 mmol) and aniline (1.2 mmol) with TMSCN (1.2 mmol) in 2 mL EtOH at room temperature. Reaction time = 30 min.

and **5k** in high yields. The acid sensitive substrate thiophene-2-carbaldehyde **3n** gave the expected α -amino nitrile **5n** in very good yield (Table 3, entry n). Most of primary and secondary amines are easily reacted in these condensations (Table 3).

To show the efficiency of the SBSSA in comparison with previously reported procedures in the literature, Table 4 compares some of our results with montmorillonite KSF clay,¹¹ silica-based scandium(III),¹² xanthan sulfuric acid,²² silica sulfuric acid,²⁴ and hydrophobic sulfonic acid based nanoreactors²⁵ with respect to reaction times, yields of obtained products. It is clear from the results shown in Table 4, which condensation reaction carried out with SBSSA requires shorter reaction time and higher yield.

The possibility of recycling the catalyst was examined using the reaction of benzaldehyde and aniline with TMSCN under the optimized conditions. Upon completion, the reaction mixture was filtered and washed with warm ethanol. The product was recrystallized from hot ethanol. The recovered catalyst was dried and reused for subsequent runs. The recycled catalyst could be reused five times without any additional treatment. No observation of any appreciable loss in the catalytic activity of SBSSA was observed (Fig. 1).

In conclusion, we have shown that silica-bonded *S*-sulfonic acid catalyzed efficiently the synthesis of α -amino nitriles by a one-pot three-component condensation of aldehydes, amines, and trimethylsilyl cyanide. The mild reaction conditions, simplicity of the procedure and the recovery of the catalyst are the advantages of this method.

All the products were characterized by comparison of their IR, ¹H NMR and ¹³C NMR spectroscopic data and their melting points with reported values.³⁷ Silica-bonded *S*-sulfonic acid (SBSSA) was prepared according to our previously reported procedure.^{32–36}

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2010.03.093.

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37. *pH Analysis of the SBSSA.* To an aqueous suspension of 0.1 g SBSSA, NaOH (1.8 mL, 0.1 M) was added. This is equal to a loading of 1.8 mmol SO₃H g⁻¹. So, all of the SH functional groups in 3-mercaptopropylsilica **1** were sulfonated. According to our previous reports,^{33–36} the loading of 3-mercaptopropylsilica **1** is 0.33 mmol/g.
General procedure: A mixture of aldehyde (1 mmol), amine (1.2 mmol), trimethylsilyl cyanid (1.2 mmol), and SBSSA (0.2 g) in EtOH (2 mL) was stirred at room temperature for appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and the remaining washed with warm ethanol (3 × 5 mL). After cooling, the corresponding α-amino nitrile products were obtained which were purified by recrystallization from hot ethanol. The recovered catalyst was dried and reused for subsequent runs.