

## Sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester as a recyclable solid acid catalyst for the synthesis of $\alpha$ -amino nitriles

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### ABSTRACT

Sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE) is employed as a recyclable catalyst for the synthesis of  $\alpha$ -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. The catalyst could be recycled and reused several times without any loss of efficiency.

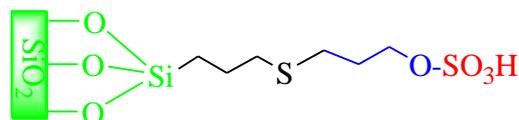
**Keywords:** Sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester,  $\alpha$ -Amino nitriles, Catalyst, Aldehydes, Amines, Synthesis.

### 1. Introduction

The addition of cyanide anion to imines (the Strecker reaction) [1] provides one of the most important and straightforward methods for the synthesis of  $\alpha$ -aminonitriles, which are useful intermediates for the synthesis of amino acids [2] and nitrogen containing heterocycles such as thiadiazoles and imidazoles, etc [3,4]. The classical Strecker reaction is usually 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 [5], such as diethyl phosphorocyanidate and  $\alpha$ -trimethylsiloxy nitriles, as well as catalysts such as  $\text{InCl}_3$  [6],  $[\text{bmim}]\text{BF}_4$  [7], montmorillonite KSF clay [8], silica sulfuric acid [9],  $\text{I}_2$  [10],  $\text{Fe}(\text{Cp})_2\text{PF}_6$  [11], xanthene sulfuric acid [12], hydrophobic sulfonic acid based nanoreactors [13], silica-bonded *S*-sulfonic acid [14], sulfamic acid-functionalized magnetic  $\text{Fe}_3\text{O}_4$  nanoparticles [15], silica-based ionic liquid [16], silica-bonded *N*-propylpiperazine sulfamic acid [17], silica-bonded *N*-propyldiethylenetriamine sulfamic acid [18], Mitsunobu's reagent [19], Choline chloride.2ZnCl<sub>2</sub> [20], L-proline [21], 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 [22,23]. 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. Furthermore, many of these catalysts are deactivated or sometimes decomposed by amines and the water that exist during imine formation. In order to overcome these problems, recently one-pot procedures have been developed for this transformation [24].

Recently we prepared sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE) and used as a catalyst for the formylation and acetylation of hydroxyl groups [25], 1,2-diarylimidazoles [26], 4,4'-alkylmethylene-bis(3-methyl-5-pyrazolones) [27], and silylation of hydroxyl groups [28] (Scheme 1).



(SASPSPE)

**Scheme 1.** The proposed structure for sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester (SASPSPE).

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## 2. Experimental

### 2.1. General

Chemicals were purchased from Fluka, Merck and Aldrich. IR spectra were run on a Shimadzu Infra Red Spectroscopy FT-IR-8000. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR was run on Bruker Avance (DRX 500 MHz and 400 MHz) instruments in  $\text{CDCl}_3$ . Results are reported in ppm. Melting points were recorded on a SMP1 Melting Point apparatus in open capillary tubes and are uncorrected. Reaction progress was followed by TLC using silica gel SILG/UV 254 plates. All the products were characterized by comparison of their IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopic data and their melting points with reported values [5-18].

### 2.2. General procedure for the synthesis of $\alpha$ -amino nitrile derivatives

A mixture of aldehyde (1 mmol), amine (1.2 mmol), trimethylsilyl cyanid (TMSCN, 1.2 mmol) and SASPSPE (0.1 g, 3.3 mol%) in EtOH (2 mL) was stirred at room temperature for appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and the remaindered was washed with warm ethanol ( $3 \times 5$  mL). After cooling, the corresponding  $\alpha$ -amino nitrile products were obtained and purified by recrystallization from hot ethanol. The recovered catalyst was dried and reused for subsequent runs.

*2-(N-Anilino)-2-(2,4-dichlorophenyl)acetonitrile (1d)*:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.05 (brs, 1H, NH), 5.70 (s, 1H), 6.79 (dd, 2H,  $J_1 = 8.6$  Hz,  $J_2 = 0.8$  Hz, Ar), 6.94 (t, 1H,  $J = 7.4$  Hz, Ar), 7.27-7.32 (m, 2H, Ar), 7.39 (dd, 1H,  $J_1 = 8.3$  Hz,  $J_2 = 2.1$  Hz, Ar), 7.53 (d, 1H,  $J = 2.1$  Hz, Ar), 7.70 (d, 1H,  $J = 8.5$  Hz, Ar).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  47.69, 114.41, 117.39, 120.76, 128.14, 129.66, 129.89, 130.42, 134.35, 136.54, 144.32.

*2-[N-(4-Methylanilino)]-2-(3,4,5-trimethoxyphenyl)acetonitrile (1f)*: IR (KBr): 3360, 3320, 2990, 2943, 2843, 2220, 1600, 1520, 1130, 820  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR

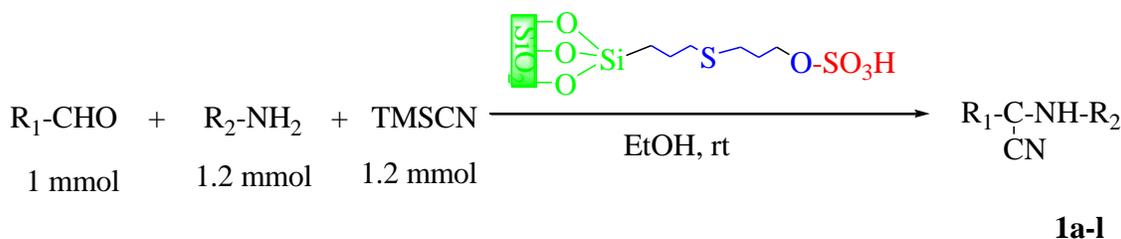
(500 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.32 (s, 3H,  $\text{CH}_3$ ), 3.78 (s, 1H, CH), 3.90 (s, 9H,  $\text{OCH}_3$ ), 5.37 (s, 1H, NH), 6.75 (d, 2H,  $J = 7.3$  Hz, Ar), 6.84 (s, 2H, Ar), 7.12 (d, 2H,  $J = 7.3$  Hz, Ar).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.94, 51.39, 56.72, 61.32, 104.74, 115.02, 118.71, 130.51, 139.32, 154.22. Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 69.21; H, 6.45; N, 8.97. Found: C, 69.02; H, 6.49; N, 8.70.

## 3. Results and Discussion

Based on our studies in order to develop new routes for the synthesis of highly substituted heterocycles and using solid acid catalysts [25-32], herein, we wish to report a valid and an efficient procedure for the synthesis of  $\alpha$ -amino nitriles *via* one-pot three-component condensation of aldehydes, amines and trimethylsilyl cyanide in the presence of SASPSPE as an inexpensive solid acid catalyst (Scheme 2).

To study the effect of catalyst loading on these reactions, the reaction of benzaldehyde and aniline with TMSCN was chosen as a model reaction (Table 1). To illustrate the need of SASPSPE for these reactions, we examined the Strecker reaction of benzaldehyde with aniline and TMSCN in the absence of this catalyst. In this case, the reaction did not proceed even after 24 h (Table 1, entry 1). Obviously, SASPSPE is an important component of the reaction. As indicated in Table 1, the best result has been obtained with 0.1 g (3.3 mol%) of SASPSPE in terms of reaction time and isolated yield.

Next, we prepared a range of  $\alpha$ -amino nitriles under the optimized conditions (Table 2). Both aromatic and aliphatic aldehydes reacted with amines and TMSCN in the presence of SASPSPE to afford excellent yields of the corresponding  $\alpha$ -amino nitriles. Aldehydes with electron-withdrawing groups or electron-donating, i.e. 3-nitrobenzaldehyde or 4-methoxybenzaldehyde, and 3,4,5-trimethoxy-benzaldehyde were converted into the corresponding  $\alpha$ -amino nitriles **1e-1g** in high yields (Table 2, entries 5-7).



$\text{R}_1 =$  aliphatic, aromatic

**Scheme 2.** Condensation of aldehydes, amines and trimethylsilyl cyanide catalyzed by SASPSPE.

**Table 1.** The reaction of benzaldehyde, aniline and TMSCN in the presence of different amounts of SASPSPE.<sup>a</sup>

Entry	The amounts of catalyst (g)	Time (min)	Yield (%) <sup>b</sup>
1	-	24 h	0
2	0.03	210	55
3	0.05	180	75
4	0.1	100	92
5	0.12	90	92

<sup>a</sup>Reaction conditions: benzaldehyde (1 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), EtOH (2 ml), room temperature.

<sup>b</sup>Isolated Yield.

The acid sensitive substrate thiophene-2-carbaldehyde gave the expected  $\alpha$ -amino nitrile **1h** in very good yield (Table 2, entry 8). Aliphatic aldehydes such as pentanal and 2-methylpropanal gave the corresponding products **1i** and **1j** in 75% and 78% yields respectively (Table 2, entries 9,10).

The possibility of recycling the catalyst was examined. For this reason, the reaction of benzaldehyde and aniline with TMSCN was studied 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 SASPSPE was observed (Figure 1).

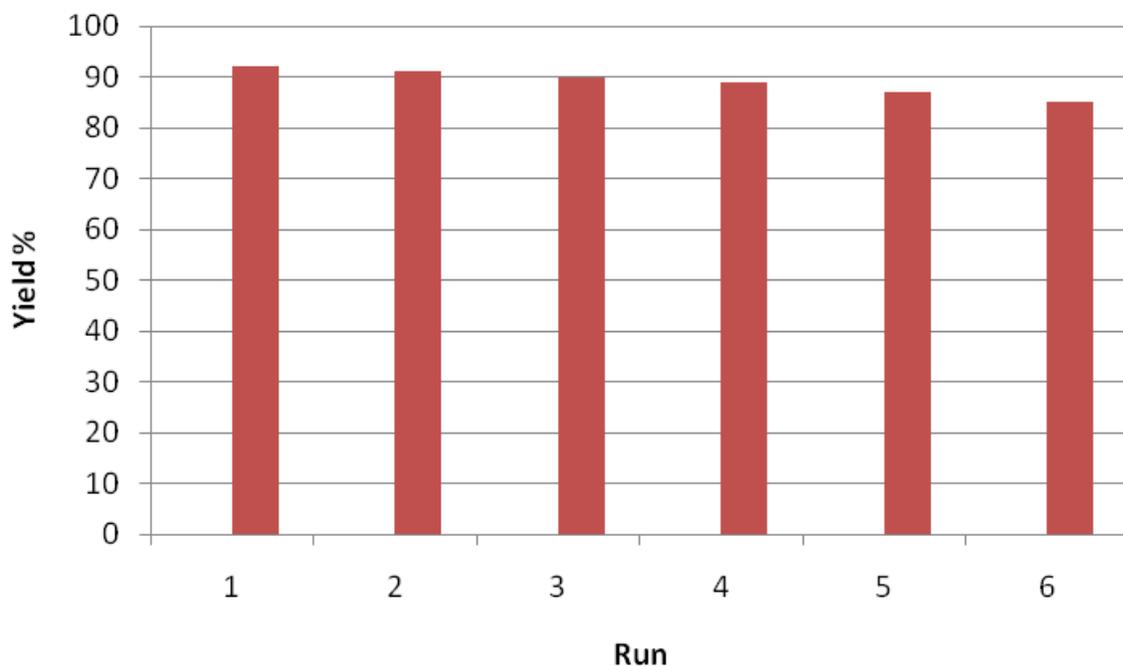
Finally, a comparative study of SASPSPE with other recently reported catalysts for condensation of benzaldehyde and aniline with TMSCN as a model compound was made which revealed that SASPSPE is an equally efficient and reusable catalyst (Table 3).

**Table 2.** Preparation of various  $\alpha$ -amino nitriles in the presence of SASPSPE in EtOH at room temperature.<sup>a</sup>

Entry	R <sub>1</sub> -CHO	R <sub>2</sub> -NH <sub>2</sub>	Product	Time (min)	Yield (%) <sup>b</sup>	m.p. (°C)	Lit. m.p. (°C)
1	C <sub>6</sub> H <sub>5</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1a</b>	100	92	80-82	81-83 [12]
2	4-ClC <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1b</b>	70	91	112-114	111-112 [8]
3	4-BrC <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1c</b>	70	88	101-103	99-100 [5]
4	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1d</b>	100	80	115-117	115-117 [14]
5	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1e</b>	120	92	95-97	94-95 [8]
6	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> -	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>1f</b>	100	91	149-152	149-152 [16]
7	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1g</b>	120	87	89-92	89-92 [14]
8	2-Thionyl-	C <sub>6</sub> H <sub>5</sub> -	<b>1h</b>	150	82	100-102	98-100 [11]
9	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> -	<b>1i</b>	210	75	55-57	56-58 [10]
10	(CH <sub>3</sub> ) <sub>2</sub> CH-	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> -	<b>1j</b>	210	78	Colorless oil	Colorless oil [6]
11	C <sub>6</sub> H <sub>5</sub> -	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> -	<b>1k</b>	100	90	Colorless oil	Colorless oil [12]
12	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> -	<b>1l</b>	100	91	86-88	86-88 [14]

<sup>a</sup>Reaction conditions: aldehyde (1 mmol), amine (1.2 mmol), TMSCN (1.2 mmol), SASPSPE (0.1 g), EtOH (2 mL).

<sup>b</sup>Isolated yield.



**Fig. 1.** Recyclability of SASPSPE (0.1 g) in the reaction of benzaldehyde (1 mmol) and aniline (1.2 mmol) with TMSCN (1.2 mmol) in ethanol at room temperature. Time = 100 min.

#### 4. Conclusions

In conclusion, we have shown that sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE), which can be prepared from commercially available and cheap starting materials, catalyzed efficiently the synthesis of  $\alpha$ -amino nitriles. Green solvent, easy and clean work-up, high yields, heterogeneous solid acid

and recovery of the catalyst makes this method practical for the synthesis of  $\alpha$ -amino nitriles

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**Table 3.** Comparison of the result of condensation reaction of benzaldehyde, aniline and TMSCN in the presence of different catalysts based on silica at room temperature.

Entry	Catalyst	Catalyst loading (g)	Time (min)	Yield (%) <sup>a</sup>	Ref.
1	Montmorillonite KSF clay	1.0	210	90	[8]
2	Silica sulfuric acid	0.095 (0.25 mmol)	360	88	[9]
3	Xanthene sulfuric acid	0.1 (0.06 mmol)	65	97	[12]
4	SBA-15 supported sulfonic acid	0.031 (0.017 mmol)	5	100 <sup>b</sup>	[13]
5	SBSSA	0.2 (0.066 mmol)	30	94	[14]
6	Sulfamic acid Fe <sub>3</sub> O <sub>4</sub> nanoparticles	0.02 (0.006 mmol)	10	97	[15]
7	SASPSPE	0.1 (0.033 mmol)	100	92	Present work

<sup>a</sup>Isolated Yield.

<sup>b</sup>The reaction was accomplished at 50 °C.

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