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# Hexafluoroisopropanol dispersed into the nanoporous SBA-15 (HFIP/ SBA-15) as a rapid, metal-free, highly reusable and suitable combined catalyst for domino cyclization process in chemoselective preparation of alkyl rhodanines

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# 1. Introduction

In last decade, ordered mesoporous silicas as nanoreactor such as SBA-15 and its functionalized family (RX@SBA-15) with a tunable pore structure and tailored composition have received considerable interest in organic synthesis [1]. The strategy of using unfunctionalized SBA-15 as catalyst, which has advantage of porous mesochannels as nanoreactor, is typically easier than functionalization or modification of SBA-15 to RX@SBA-15 while it needs fewer synthetic steps [2]. On the other hand, fluorinated alcohols (R<sub>f</sub>OH) demonstrate their unique properties as solvents/ co-solvents or additives in the organic synthesis [3]. The availability of R<sub>f</sub>OHs has initiated a boom in their applications in the past decade [2,3]. The utilization of R<sub>f</sub>OH as a reaction medium or co-solvent was highlighted by Bégué et al. and Uneyama. Based on their unique nature acid-catalyzed organic process can be done in the fluorinated alcohols [3].

In our recent investigation, the reaction of dialkyl acetylenedicarboxylate with carbon disulfide in the presence of alkyl amine derivatives led to the formation of alkyl rhodanine derivatives [4].

# ABSTRACT

Hexafluoroisopropanol dispersed catalytically amount of SBA-15 (HFIP/SBA-15) with organic substrate was found to be an efficient, ultra-fast and waste-free approach for the synthesis of the biologically and pharmaceutically interesting alkyl rhodanines. The advantages of the present method are low catalyst loading, simple procedure, waste-free and direct synthetic entry to excellent yield of rhodanines, high reusability of the catalyst, and short reaction time. Also, the reaction can be performed without activation and modification of the substrates under the neutral conditions. The solid SBA-15 and HFIP could be recovered and reused for recycling.

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However, this method has many drawbacks such as using nonstoichiometric amount of carbon disulfide, tedious work-up, generation of large amounts of CS<sub>2</sub> waste, low yields of products, and long reaction times. The development and improvement of novel synthesis methods for 5-oxo-2-thioxo-3-thiophenecarboxylates (rhodanine) are still attractive goals because of their numerous biological and chemical activities including the inhibition of numerous targets such as PMT1 manosyl transferase [5], PRL-3 and JSP-1 phosphatases [6].

Following to our recent success in applying the TFE/SBA-15 nanoreactor in the imidazole preparation [2] an active and recyclable HFIP-medium (1,1,1,3,3,3-hexafluoro-2-propanol or hexafluoroisopropanol) catalyst was applied in the present research for synthesis of alkyl rhodanines under mild reaction conditions. While this approach showed reusability for both HFIP and SBA-15, it minimized the wastes and side products (Scheme 1).

# 2. Results and discussion

We developed synthetic methods for biologically interesting molecules *via* multicomponent reactions and nanocatalysts [7]. The challenge in this field was developed by an efficient and suitable method instead of synthesizing these heterocycles in the presence of polar solvents such as DMF, and DMSO, which lead to complex isolation and recovery procedures. In this paper, we present the results of an extended investigation on the activity of







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### Table 1

Optimization of reaction conditions for the synthesis of rhodanine 3a.<sup>a</sup>



Entry	SBA-15 (mg)	Solvent	<i>T</i> (°C)	Time (min)	Yield (%)
1	10	THF	r.t.	5	24
2	10	CyHex <sup>b</sup>	r.t.	10	23
3	20	CyHex <sup>b</sup>	r.t.	5	31
4	10	H <sub>2</sub> O	r.t.	5	26
5	10	EtOH	r.t.	5	33
6	10	TFE <sup>c</sup>	r.t.	5	71
7	10	TFE <sup>c</sup>	r.t.	10	88
8	10	<sup>i</sup> PrOH	r.t.	5	37
9	10	<sup>i</sup> PrOH	r.t.	10	45
10	10	HFIP	r.t.	5	73
11	10	HFIP	40	10	95
12	10	HFIP	r.t.	10	94
13	15	HFIP	r.t.	10	94
14	20	HFIP	r.t.	10	93
15	10	HFIP	r.t.	15	93
16	-	H <sub>2</sub> O	r.t.	10	15

<sup>a</sup> Reaction condition: allyamine (1 mmol), CS<sub>2</sub> (1 mmol), and DMAD (1 mmol) was added SBA-15 in 2 mL solvent.

<sup>b</sup> Cyclohexane.

<sup>c</sup> 2,2,2-Trifluoroethanol.

the SBA-15 [8] as a highly reusable catalyst in HFIP medium leading to the formation of rhodanine derivatives without any salts or additives. Herein, the reaction of allylamine with carbon disulfide in the presence of dimethyl acetylenedicarboxylate (DMAD) was selected as a model.

In order to investigate the catalytic activity and application of unfunctionalized SBA-15 (mesochannels of SBA-15 as reaction vessel or reactor in nano-scale) in the multicomponent synthesis of rhodanine, we examined its efficiency in the model reaction. Due to the fact that the solvent may play an important role in this process, different solvents were screened. The model reaction was examined in cyclohexane, EtOH, TFE, <sup>*i*</sup>PrOH, H<sub>2</sub>O, and HFIP using SBA-15 (Table 1).

As can be seen in Table 1 and Fig. 1, when the reaction was run in HFIP medium, the product was obtained in 94% yield at room temperature in 10 min. The results show that under the same conditions the yield decreased sharply when the reaction medium was changed from HFIP. we also used commercial SiO<sub>2</sub> containing 530 m<sup>2</sup>/g surface areas in comparison with SBA-15 mesoporous material with 915 m<sup>2</sup>/g (BET surface area). These results exhibited an exceptional behavior for HFIP (and also TFE) in the presence of SBA-15 as a high surface area silica-mesoporous nanomaterial (Fig. 1). In addition to obtained results, to demonstrate the diversity of the hexafluoroisopropanol/SBA-15 adduct (HFIP/SBA-15) as combined catalyst and to expand the scope of the process, the optimized conditions were applied to a series of substrates **1** and **2** as shown in Table 2.



**Fig. 1.** Model reaction over the SBA-15/<sup>i</sup>PrOH (blue), HFIP (red), SiO<sub>2</sub>/HFIP (green), SBA-15/HFIP (violet) and SBA-15/TFE (yellow). Reactant scales was selected 1 mmol containing SBA-15 (10 mg) or SiO<sub>2</sub> (17 mg) in 2 mL solvent. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

#### Table 2

The synthesis thioxo-thiophenecarboxylate skeleton by HFIP/SBA-15.<sup>a</sup>



<sup>a</sup> Reaction scale: 2 mmol.

<sup>b</sup> Isolated yield.



Fig. 2. Chemoselective synthesis of alkyl rhodanines in HFIP/SBA-15 catalytic system.



Fig. 3. Schematic representation of the SBA-15 and HFIP recycling.

The catalytic activity of HFIP/SBA-15 in the domino threecomponent process to synthesis of rhodanine **3c** and **4** was also studied under the optimized conditions. When we set a one-pot reaction with mixture of an aromatic amine (aniline) and aliphatic amine (benzyl amine) in the presence of the carbon disulfide and dimethyl acetylenedicarboxylate (DMAD), the yield of **3c** was 95% without any detected product of **4** (Fig. 2) after 10 min.

The possibility of recycling the HFIP/SBA-15 catalytic system was also studied. When the reaction was completed, the HFIP was easily separated from the reaction mixture by heating at the  $\sim$ 70 °C. The recovered HFIP phase was reused for consecutive reactions. The reaction mixture residue was centrifuged after adding dichloromethane (DCM) for separating the SBA-15 (Fig. 3). Finally the DCM was removed under reduced pressure, and the

remained rhodanines **3** was washed with cold diethyl ether. The SBA-15 catalyst could be reused at least for 10 runs.

Although, we have not still provided a certain mechanism for the synthesis of rhodanines **3** over the HFIP/SBA-15 adduct in an experimental manner, a possible explanation [4] is proposed in Scheme 2. In this condition, the nanochannels of the SBA-15 provide a synergistic means to input the reactants and also drive out the products for next recycles [2].

# 3. Conclusion

In conclusion, an efficient protocol for the one-step preparation of alkyl rhodanines from the three-component condensation reaction of amines, carbon disulfide, and electron deficient



Scheme 2.



Fig. 4. Schematic representation of the synthetic procedure for SBA-15 mesoporous and its SEM and TEM images.

acetylenes using a reusable HFIP/SBA-15 adduct was described. The reactions were carried out under mild condition with short reaction time and facile work-up. Fluorinated alcohol-mediated procedure, also produced the corresponding products in good yields without any CS<sub>2</sub> waste. The SBA-15 (also HFIP) could be successfully recovered and reused at least for ten runs.

# 4. Experimental

# 4.1. Chemicals and apparatus

All reagents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured by an Electrothermal 9100 apparatus. Progress of reactions was monitored by Thin Layer Chromatography (TLC). <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured (CDCl<sub>3</sub>) with a Bruker DRX-500 AVANCE spectrometer at 500.13 and 125.7 MHz, respectively. IR spectra were recorded on Shimadzu IR-460 spectrometer, absorbencies are reported in cm<sup>-1</sup>.

#### 4.2. SBA-15 synthesis and analysis

In this work, SBA-15 nanoreactor was synthesized by the procedure reported by Zhao et al. [8]. Schematic representation of the synthetic procedure for SBA-15 and HFIP/SBA-15 adduct as a combined catalyst was shown in Fig. 4. The SEM and TEM images as morphological and channels study of SBA-15 mesoporous material are also presented in the same figure.

In the FT-IR spectrum of SBA-15, the bands from 807 and  $1100 \text{ cm}^{-1}$  are assigned to the vibrations of (Si–O–Si) bond, and the band at about 960 cm<sup>-1</sup> is assigned of (Si–OH) bond and the SiO–H groups are appeared by the very broad IR absorption band in the 3100–3700 cm<sup>-1</sup> region (Fig. 5).

Diffraction peaks at the below  $2^{\circ}$  corresponding to the (1 0 0), (1 1 0), and (2 0 0) are readily recognized from the XRD pattern of SBA-15 (Fig. 6). The observed diffraction peaks agree with the 2 D-hexagonal SBA-15 [8].

# 4.3. General procedure

The alkyl amine (2 mmol) and carbon disulfide (2 mmol) were added to a dispersion of SBA-15 (20 mg) in HFIP (4 mL), and the mixture was stirred at room temperature for 30 Sec, and then



Fig. 5. FT-IR spectra of SBA-15: (a) newly prepared; (b) used 10 times.



Fig. 6. XRD patterns of SBA-15: (a) newly prepared; (b) used 10 times.

2 mmol of DMAD was added to the mixture during 30 s. After completion of the reaction (TLC), the SBA-15 and TFIP was drawn out and the crude rhodanines **3** were washed with cold diethyl ether (Fig. 3). All isolated products gave satisfactory spectral and

physical data. All the products were previously reported [4] and were characterized by comparing IR, NMR and physical data with those reported. The spectral data for selected product: *Ethyl 2-[3-*((4-chlorophenyl)methyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylide-

*n]ethanoate* (**3b**) Orange powder. IR (KBr) ( $\nu_{max}$ , cm<sup>-1</sup>): 1728 (CO), 1649 (C=C), 1310 and 1177 (C=S). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  = 3.87 (3H, s, OCH<sub>3</sub>), 5.24 (2H, s, CH<sub>2</sub>Ar), 6.84 (1H, s, C=CH), 7.28 (2H, d,  ${}^{3}J_{HH}$  = 8.4 Hz, 2 CH of Ar), 7.37 (2H, d,  ${}^{3}J_{HH}$  = 8.4 Hz, 2 CH of Ar) ppm.  ${}^{13}$ C NMR (125.7 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  = 46.62 (OCH<sub>3</sub>), 52.89 (CH<sub>2</sub>Ar), 117.16 (C=CH), 128. 86 (2 CH of Ar), 130.49 (2 CH of Ar), 132.79 (Cipso of Cl), 134.36 (Cipso of C-N), 141.82 (C=CH), 165.45 (CON), 166.46 (CO<sub>2</sub>CH<sub>3</sub>), 195.43 (C=S) [4].

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