



Research Article

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## SiO<sub>2</sub>-OSbCl<sub>2</sub> as highly effective and reusable heterogeneous catalyst for Mannich condensation in Solvent or under Solvent-Free Conditions

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### ABSTRACT

*An easy operational protocol, for the synthesis of  $\beta$ -aminocarbonyl compounds using silica-supported Antimony (III) Chloride (SiO<sub>2</sub>-OSbCl<sub>2</sub>) as catalyst, has been developed. The use of (SiO<sub>2</sub>-OSbCl<sub>2</sub>) as an inexpensive, highly active, and easy to prepare and handle as a recyclable heterogeneous catalyst, makes this method an environmentally acceptable synthetic tool for Mannich reaction.*

**Keywords:** Recyclable heterogeneous catalyst, One-pot, Three-component, Mannich reaction,  $\beta$ -aminocarbonyl, Solid supported reagents, SiO<sub>2</sub>-O SbCl<sub>2</sub>, SbCl<sub>3</sub>/SiO<sub>2</sub>

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### INTRODUCTION

Lewis acids are the most widely used catalysts in organic synthesis, unfortunately, most of them suffer from high toxicity, moisture sensitive, air intolerance and expensive, thus, recently the use of Lewis acids supported on "inert" carriers has received considerable importance. The ease of handling, enhanced reaction rates, greater selectivity, improved activity, simple workup, and recyclability of the catalysts are other common features that make the use of supported Lewis acids as attractive alternatives to conventional individual reagents [1].

Antimony (III) chloride is among the most widely used Lewis acids due to its accessibility as an inexpensive commercial reagent and easier handling as compared to other metal halides [2], lately, it has emerged as an efficient catalyst in promoting various organic transformations including Knoevenagel condensation [3], bis(indolyl)methanes synthesis [4], Michael addition of indoles to  $\alpha,\beta$ -unsaturated ketones [5], ring opening of epoxides [6], and Biginelli reaction [7]. Due to the high toxicity of SbCl<sub>3</sub> [8], supported antimony (III) chloride has recently received considerable attention [9, 10]. In this context and in continuation of our studies on the applications of Lewis acids as catalysts in the development of new synthetic methodologies [11], and for environmental pollution control and cleaner processes, we wish to describe, in the present research, a mild and efficient approach for the synthesis of  $\beta$ -aminocarbonyl compounds, using a catalytic amount of silica-supported SbCl<sub>3</sub> as a heterogeneous catalyst which, to the best of our knowledge, this has not been used earlier in Mannich reaction (Scheme 2).

### EXPERIMENTAL SECTION

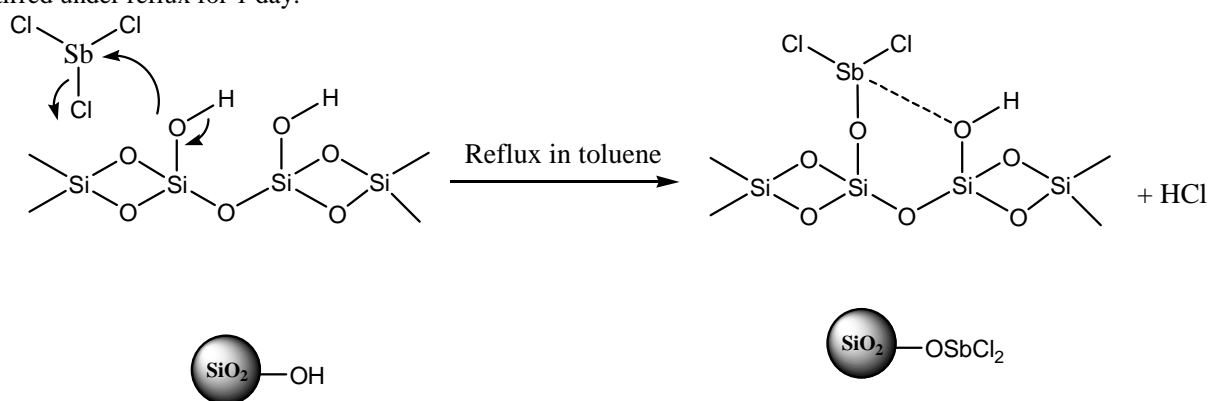
All products were characterized by mp, IR and <sup>1</sup>H and <sup>13</sup>CNMR. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>CNMR spectra were recorded on a BRUKER AVANCE DPX spectrometer at 250 and 62.9 MHz respectively as solutions in CDCl<sub>3</sub>. Chemical shifts are reported in parts of million ( $\delta$ .ppm) relative to TMS ( $\delta$ .0.0) as internal standard and coupling constants (*J*) are reported in hertz

(Hz). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR 8201 PC spectrometer. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254, was used to monitor the progress of reactions.

#### Catalyst preparation

Catalyst was prepared according to literature method [12].

Twenty grams of silica gel (80–200 mesh) was washed with 150 ml of 1 mol/l hydrochloric acid, followed by deionized water, 30% H<sub>2</sub>O<sub>2</sub>, and then again deionized water to neutral. The obtained silica was dried overnight at 70°C in vacuum to give preconditioned silica gel. The preconditioned silica (1.54 g) was first refluxed in toluene (50 ml) for 2 h, and then antimony (III) chloride (1.99 g) was added to the stirring suspension. The resulting mixture was stirred under reflux for 1 day.



Scheme 1. Reaction of SbCl<sub>3</sub> with silica gel to form a highly active catalyst.

The solvent was removed, and the residue was washed three times with absolute ethanol and heated at 100°C under vacuum for 5 h to furnish silica-supported antimony (III) chloride (2.83 g) as a white free-flowing powder (Scheme 1).

#### General procedure for the acid-catalyzed Mannich reaction

To the mixture of acetophenone (10 mmol), aromatic aldehyde (10 mmol) and aniline (10 mmol) in ethanol (3ml), SiO<sub>2</sub>-OSbCl<sub>2</sub> (2 mol %) was added. The mixture was stirred at room temperature for an appropriate time until the reaction was completed as monitored by TLC (Table 4). The resulting mixture was filtered to recover the catalyst, and the filtrate was evaporated to give the crude product. The analytical sample was obtained by recrystallization from ethanol. All of the products are known and were characterized by nuclear magnetic resonance and melting points.

#### Selected spectroscopic data

##### 3-(4-Methylphenyl)-1-phenyl-3-(phenylamino)propan-1-one (4b)

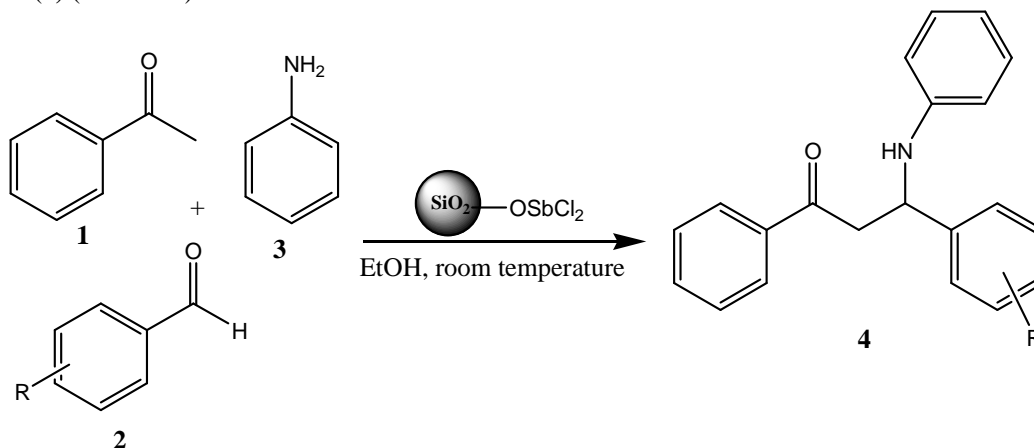
90%. Mp: 134–135 °C. IR (KBr, cm<sup>-1</sup>) 1446.5, 1512.1, 1658.7 (C=C, aromatic), 1743.5 (C=O, carbonyl), 3394.5 (NH, amine). <sup>1</sup>H RMN (CDCl<sub>3</sub>): δ (ppm) = 2.4 (s, 3H, CH<sub>3</sub>), 3.46 (dd, *J*<sup>2</sup> = 3.89Hz, *J*<sup>3</sup> = 8.74Hz, 1H, CH<sub>2</sub>), 3.58 (dd, *J*<sup>2</sup> = 3.85Hz, *J*<sup>3</sup> = 9.26Hz, 1H, CH<sub>2</sub>), 5.05 (dd, *J*<sup>3</sup> = 5.52Hz, 1H, CH), 6.65 (dd, *J*<sub>o,m</sub> = 7.58Hz, 1.09Hz, 2H, CH), 6.73 (tt, *J*<sub>o,m</sub> = 7.32Hz, 1Hz, 1H, CH), 7.15 (dd, *J*<sub>o,m</sub> = 5.44Hz, 1.18Hz, 2H, CH), 7.2 (dd, *J*<sub>o,m</sub> = 6.28Hz, 0.95Hz, 2H, CH), 7.29 (s, 1H, N-H), 7.41 (t, *J*<sub>o</sub> = 8.07Hz, 2H, CH), 7.49 (t, *J*<sub>o</sub> = 7.65Hz, 2H, CH), 7.61 (tt, *J*<sub>o,m</sub> = 7.19Hz, 1.31Hz, 1H, CH), 7.98 (dd, *J*<sub>o,m</sub> = 7.02Hz, 1.48Hz, 2H, CH). <sup>13</sup>C RMN (CDCl<sub>3</sub>): δ (ppm) = 198.3, 146.9, 139.9, 136.6, 133.4, 129.5, 129.1, 128.7, 128.2, 126.35, 117.8, 116.4, 113.9, 54.5, 46.3, 21.11.

##### 3-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (4c)

87%. Mp: 147–148 °C. IR (KBr, cm<sup>-1</sup>) 744.5 (disubstitution ortho), 1149.5 (C-O, ether), 1450.4, 1512.1, 1643.2 (C=C, aromatic), 1743.5 (C=O, carbonyl), 3390.6 (NH, amine). <sup>1</sup>H RMN (CDCl<sub>3</sub>): δ (ppm) = 3.41 (dd, *J*<sup>2</sup> = 2.88Hz, *J*<sup>3</sup> = 8.88Hz, 1H, CH<sub>2</sub>), 3.55 (dd, *J*<sup>2</sup> = 0.89Hz, *J*<sup>3</sup> = 6.55Hz, 1H, CH<sub>2</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 5 (dd, *J*<sup>3</sup> = 5.86Hz, 1H, CH), 6.61 (dd, *J*<sub>o,m</sub> = 10Hz, 1.08Hz, 2H, CH), 6.72 (tt, *J*<sub>o,m</sub> = 6.31Hz, 0.99Hz, 1H, CH), 6.88 (dd, *J*<sub>o,m</sub> = 8.81Hz, 2.11Hz, 2H, CH), 7.13 (dd, *J*<sub>o,m</sub> = 6.5Hz, 1.11Hz, 2H, CH), 7.29 (s, 1H, N-H), 7.40 (t, *J*<sub>o</sub> = 5.02Hz, 2H, CH), 7.47 (t, *J*<sub>o</sub> = 5.33Hz, 2H, CH), 7.6 (tt, *J*<sub>o,m</sub> = 6.27Hz, 1.44Hz, 1H, CH), 7.95 (dd, *J*<sub>o,m</sub> = 5.07Hz, 1.52Hz, 2H, CH). <sup>13</sup>C RMN (CDCl<sub>3</sub>): δ (ppm) = 198.3, 158.7, 146.6, 136.6, 134.6, 133.4, 129.1, 128.6, 128.2, 127.5, 117.9, 114.1, 114.2, 55.2, 54.4, 46.2.

## RESULTS AND DISCUSSION

In the initial experiments, we screened different common Lewis acids for their ability to catalyze the three-component Mannich type reaction. To study their feasibility, the reaction of acetophenone (**1**), 4-chlorobenzaldehyde (**2**, R = 4-Cl) and aniline (**3**) was selected as a model for the preparation of  $\beta$ -aminocarbonyl compounds (**4**) (Scheme 2).



Scheme 2. Silica-supported Antimony (III) chloride catalyzed one-pot Mannich reaction of acetophenone, aromatic aldehydes and aniline

According to the obtained data, the common Lewis acids  $\text{FeCl}_3$ ,  $\text{ZnCl}_2$  and  $\text{AlCl}_3$  did not furnish the desired products even after 24 h stirring (Table 1, experiments 1–3).

Table 1 Mannich reaction of acetophenone, 4-chlorobenzaldehyde and aniline catalyzed by different catalysts<sup>a</sup>

Experiment	Catalyst	Amount of catalyst (%)	Time (h)	Yield <sup>b</sup> (%)
1	$\text{FeCl}_3$	2	24	0
2	$\text{ZnCl}_2$	2	24	0
3	$\text{AlCl}_3$	2	24	0
4	neat	---	24	traces
5	$\text{SiO}_2$	2	24	trace
6	$\text{SbCl}_3$	2	5	84
7	$\text{SbCl}_3/\text{SiO}_2$	2	5	89.8
8	$\text{SiO}_2\text{-OSbCl}_2$	2	5	95.5

<sup>a</sup> All reactions of acetophenone (1 mmol), 4-chlorobenzaldehyde (1 mmol) and aniline (1 mmol) were carried out in ethanol at room temperature.

<sup>b</sup> Yields refer to the isolated product.

In the case of neat  $\text{SbCl}_3$ , 84% of desired product was obtained (Table 1, experiment 6) while with neat  $\text{SiO}_2$  no product was formed even after 24 h stirring (Table 1, experiment 5). However, silica supported antimony (III) chloride could efficiently catalyze Mannich reaction to afford the desired product in high yield (Table 1, experiment 8). In contrast, the physical mixture of silica and antimony (III) chloride (Table 1, experiment 7) exhibited an intermediate level of activity, which was lower than the silica supported antimony (III) chloride. This reveals that  $\text{SiO}_2\text{-OSbCl}_2$  is presumably acting in a synergistic fashion to catalyze the reaction. The controlled three component reaction conducted under identical conditions and devoid of catalyst gave no coupled product, despite prolonged reaction time (Table 1, experiment 4) which indicates that the catalyst is obviously necessary for the reaction.

Table 2: Optimization of amount of  $\text{SiO}_2\text{-SbCl}_2$  for the synthesis of **4a**

Experiment	Catalyst (mol %)	Yield (%)
1	2	95.5
2	5	90
3	10	89
4	15	88

Mannich reaction was very sensitive to reaction temperature. The high temperature could improve the reaction rate and shorten the reaction time, but favor side reactions and the oxygenolysis of aldehyde and amine; therefore, it was found that the room temperature was an appropriate condition for the silica supported antimony (III) chloride catalyzed Mannich reaction.

The solvents also played an important role in the Mannich reaction catalyzed by silica supported antimony (III) chloride. Several solvents were tested for the reaction, such as toluene, EtOH, MeCN, H<sub>2</sub>O and THF. The reaction in water, toluene and tetrahydrofuran resulted in 20–45% yield of the product (Table 3, experiments 1–3). Acetonitrile gave 70 % yield of **4a** (Table 3, experiment 4). Under free-solvent conditions, the product was obtained in 80% yield (Table 3, experiment 6); whereas in ethanol the product was obtained in 95.5% yield (Table 3, experiment 5). Therefore, EtOH was selected as the reaction solvent in the following investigations.

**Table 3: Silica-supported antimony (III) chloride catalyzed Mannich-type reaction in different Solvents<sup>a</sup>**

Experiment	Solvent	Yield (%)
1	H <sub>2</sub> O	20
2	Toluene	40
3	THF	45
4	MeCN	70
5	EtOH	95.5
6	Neat	80

<sup>a</sup> All reactions of acetophenone (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol) and aniline (1.0 mmol) were carried out at room temperature for 5 h.

<sup>b</sup> Yields refer to the isolated product.

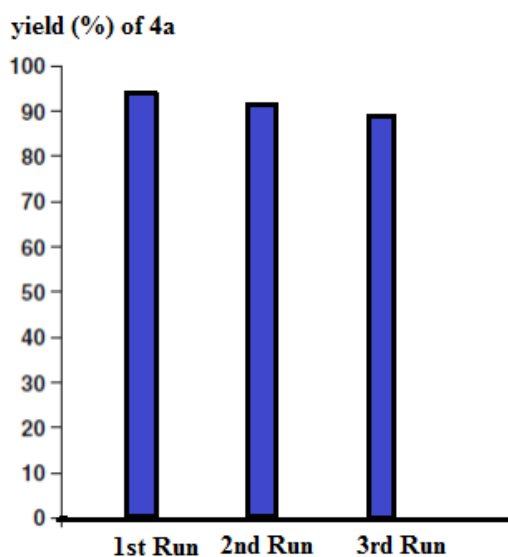
Having established the optimized reaction conditions, and in order to show the general applicability of this method, different substituted aromatic aldehydes were reacted with acetophenone and aniline affording the corresponding products (**4a-h**) in good to excellent yields (Table 4).

**Table 4 Silica-supported Antimony (III) chloride catalyzed Mannich reaction of acetophenone, aromatic aldehydes and aniline**

Entry	R	Time (h)	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Mp (°C)	
					Found	reported
1	4-Cl	5	4a	95	114 -115	114-115 <sup>[13]</sup>
2	4-CH <sub>3</sub>	5	4b	90	134-135	134-135 <sup>[13]</sup>
3	4-OCH <sub>3</sub>	5	4c	87	147 -148	142-143 <sup>[13]</sup>
4	H	4	4d	93	169-170	169-171 <sup>[14]</sup>
5	4-F	4	4e	60	110-111	111-112 <sup>[16]</sup>
6	4-NO <sub>2</sub>	4	4f	75	104-105	104-106 <sup>[15]</sup>
7	3-NO <sub>2</sub>	5	4g	84	131-132	131-132 <sup>[13]</sup>
8	4-N(CH <sub>3</sub> ) <sub>2</sub>	3	4h	92	200-201	202-203 <sup>[13]</sup>

<sup>a</sup> All products were characterized by comparison of their melting points, IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra with those of authentic samples.

<sup>b</sup> Yields refer to the isolated products.



**Figure 1 Catalyst reusability**

Interestingly, the results showed that the reaction worked well in the presence of electron donating as well as electron withdrawing substitution in different positions of the benzene ring such as *para*-MeO, Me, F, Cl, Me<sub>2</sub>N and *meta*-NO<sub>2</sub>.

Furthermore, the silica supported antimony (III) chloride could be easily separated from the reaction mixture only by filtration and reused three times without obvious loss of activity (figure1).

#### *Evaluation of Catalyst Stability*

The catalyst stability was assessed to evaluate if the dispersed SbCl<sub>3</sub> from catalyst could be leached out by solvent or not. In control experiment, the catalyst was subjected to reaction condition in the absence of substrates for 1 h. The SiO<sub>2</sub>-OSbCl<sub>2</sub> catalyst was filtered and the filtrate was used as reaction medium in the reaction of 4-Chlorobenzaldehyde, aniline and acetophenone. No transformation of substrates was noticed this, confirms that SbCl<sub>3</sub> is immobilized on silica surface as stable O–Sb–Cl species.

### CONCLUSION

The operational simplicity, low catalyst loading, reusability, and the applicability to various substrates render this approach an interesting alternative to previously applied procedures. From the environmental standpoint, SiO<sub>2</sub>-OSbCl<sub>2</sub> is stable, highly active and minimal waste generation. These features make this procedure a valuable contribution to the existing processes in the field of β- aminocarbonyl compounds syntheses.

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