

# $[(C_3H_7)_3N-SO_3H]Cl$ : A efficient ionic liquid catalyst for the synthesis of Spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] in aqueous medium

Shivaji Sawant<sup>1</sup>, Pradeep Patil<sup>2</sup>, Govind Salunke<sup>1,3</sup>, Sandeep Sankpal<sup>1</sup> and Shankar Hangirgekar<sup>1\*</sup>

<sup>1</sup>Department of Chemistry, Shivaji University, Kolhapur 416004, India

<sup>2</sup>Department of Chemistry, DKTE Society's Textile and Engineering Institute, Ichalkaranji, MS 416115, India

<sup>3</sup>Department of Chemistry, Raje Ramrao Mahavidyalaya, Jath 416404, India

## Abstract

A Bronsted acidic ionic liquid  $[(C_3H_7)_3N-SO_3H]Cl$  was synthesized by simple method and further its structure was confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass analysis. The catalytic efficiency of Bronsted acidic ionic liquid (BAIL) was evaluated in the environmentally benign synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] via one-pot reaction of ethyl acetoacetate, hydrazine, isatin and malononitrile in an aqueous medium. The present metal free approach using BAIL catalyst shows important significance such as ease of preparation of the catalyst, high yields, shorter reaction times, inexpensive catalyst and simple work-up procedure and reusability of the catalyst. The desired pyrano-pyrazoles were obtained in excellent yields and further purified by simple recrystallization.

**Keywords:**  $[(C_3H_7)_3N-SO_3H]Cl$ ; Bronsted acidic ionic liquid; Pyrano[2,3-c]pyrazoles, Aqueous medium, Reusability of catalyst

## \*Correspondence

Author: Shankar Hangirgekar

Email: sph.chem@unishivaji.ac.in

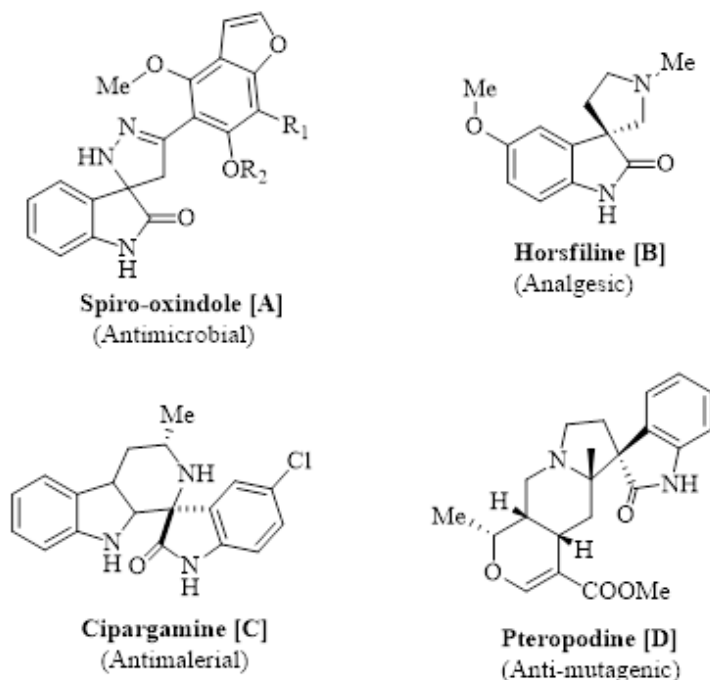
## Introduction

Owing to rigid environmental sentiments, scientific communities have concentrated their attention to introduce greener chemical processes to protect environment and human health [1]. As part of this scenario scientist directed their effort to eliminate toxic solvents and catalysts that are immensely used during chemical processes. In this context, ionic liquids become a promising solution as they work solvent as well as catalyst in variety of chemical transformations [2]. Ionic liquids (ILs) are ionic salts that possess high thermal stability, negligible vapour pressure, nonflammability and ability to dissolve both organic and inorganic compounds [3, 4]. Among these, Bronsted acidic ionic liquids (BAILs) have received substantial interest due to efficient catalytic activities and it is good substitute to corrosive acid catalysts [5, 6]. Different types Brønsted acid catalysts based on pyrrolidinium, long-chain tertiary amine, pyridinium, and imidazolium or triphenylphosphine have been tested in a variety of reactions [7].

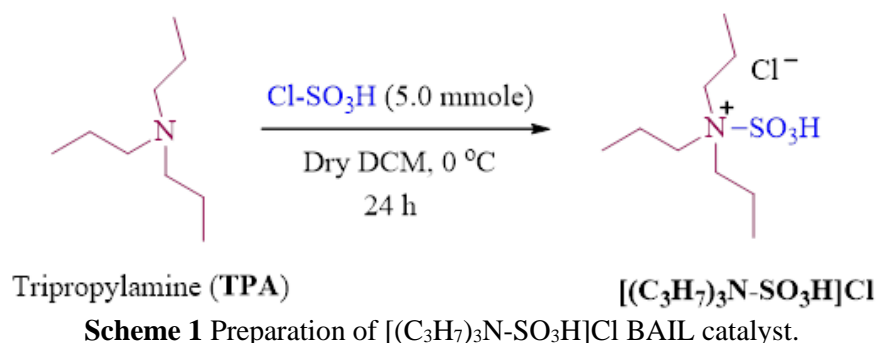
Recently multicomponent reactions (MCRs) have become a promising tool for generating library of structurally simple and complex molecular skeleton to identify most potent biologically active molecule [8, 9]. Especially, MCRs extensively used for the synthesis of fused heterocyclic derivatives. Among these, spirooxindole is one of the important nitrogen heterocyclic motifs have been studied for different properties [10-12]. Spirooxindole analogues engrafted with pyrazole nucleus have been explored in several fields such as material sciences, agriculture, medicine, etc. [13]. Particularly, spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] exhibit potent biological activities such as anti-microbial [14], anti-cancer [15], anti-inflammatory [16], antitubercular and hypoglycemic [17, 18] etc. The alkoxy substituted spirooxindole derivative (**Figure 1**) exhibits an interesting antimicrobial [**A**] [19] properties. The oxindole core Horsfiline [**B**] [20] and Cipargamine [**C**] [21] are privileged scaffolds showed analgesic and antimalarial potencies. Furthermore, drug molecule, Pteropodine [**D**] [22] has been proven to possess interesting anti-mutagenic property. Some synthetic bioactive structures of spirooxindole are shown in Figure 1.

Several synthetic methodologies have been developed for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] such as LDH/SBA/HPA [23], Glucose [24], I<sub>2</sub> [25],  $[Fe_3O_4@SiO_2@PrDABCO-SO_3H]Cl_2$  [26], and PANI/Fe<sub>3</sub>O<sub>4</sub>/CNT [27]. In addition, SBA-Pr-NHQ [28] and Et<sub>3</sub>N [29] have been employed for synthesis of pyrano[2,3-c]pyrazoles] starting from substituted isatins, pyrazolone and -CH active compound. However, some of the methods are associated with limitations of expensive precursors, leaching behavior of catalyst, harsh reaction conditions, and longer reaction time, low yield of the products, etc. Thus, there is considerable scope to develop greener methodology to eliminate aforementioned drawbacks to synthesize spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] using an environmentally friendly approach. In continuation of research activities focused on the development of eco-friendly methodologies for the bioactive heterocycles, we report Bronsted acidic  $[(C_3H_7)_3N-$

SO<sub>3</sub>H]Cl IL as a catalyst for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] in aqueous medium at room temperature.



**Figure 1** Biological potent spirooxindoles.



**Scheme 1** Preparation of [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H]Cl BAIL catalyst.

## Materials and Method

Analytical grade chemicals and solvents were availed from commercial sources and used in the experiments as received. The melting points were not corrected, and they were specified on a DBK programmed melting point apparatus (Temp. increment 2-5 °C/min.). Silica gel coated aluminium plates of Merck make were used in thin layer chromatography (TLC) analysis. The structures of synthesized compounds were investigated by FT-IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass spectrometry (MS). IR (ATR) spectra were taken from Bruker alpha spectrometer and absorptive frequency was reported in cm<sup>-1</sup>. NMR spectra were recorded on a Bruker Advance spectrophotometer at 500 MHz (<sup>1</sup>H) and 125 MHz (<sup>13</sup>C), respectively, in DMSO-d<sub>6</sub> and chemical shifts are expressed in parts per million (ppm) as δ units. Mass analysis (Q-TOF) was accomplished using water instrument, using mass spectrometer under ESI-MS mode.

### Synthesis of [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H]Cl BAIL catalyst

In typical procedure, a round bottom flask containing solution of tripropylamine (0.94 g, 5 mmol) in dry dichloromethane (DCM) was placed in ice bath. Then, a steady addition of solution of chloro-sulfonic acid (0.36 mg, 5.0 mmol) in dry DCM was allowed in the solution of tripropylamine for one hour. After completion of the reaction, the resultant Bronsted acidic ionic liquid was washed with dry DCM and dried in oven to get [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H]Cl as a viscous brown ionic liquid (**Scheme 1**). The structure of ionic liquid was identified by ATR, <sup>1</sup>H and <sup>13</sup>C NMR and mass analysis.

$[(C_3H_7)_3N-SO_3H]Cl$ ; viscous brown liquid; IR (FT-IR): 852, 1042, 1096, 1159, 1460, 1716, 2881, 2971, 3402  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  0.99 (9H, t,  $-CH_3$ ), 1.59-1.66 (6H, m,  $-CH_2$ ),  $\delta$  2.96-3.00 (6H, m,  $-CH_2$ ), 5.34 (1H, s,  $-SO_3H$ );  $^{13}C$  NMR (125 MHz, DMSO- $d_6$ ):  $\delta$  10.83, 16.61, 53.64; MS (ES+):  $m/z$ = 260.

### General procedure for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] (5a-f)

First a aqueous solution of ethyl acetoacetate (1 mmole) and hydrazine hydrate (1 mmole) was stir for 15 minute, subsequently malononitrile (1 mmole) and substituted isatin (1 mmole) were added into the same flask. After allowing the reaction mixture to agitate for ten minutes, 15 mol % of  $[(C_3H_7)_3N-SO_3H]Cl$  IL were added as a catalyst and extent of conversion was monitored using TLC (pet ether-ethyl acetate, 7:3). After end of the process, the isolated products (**5a-f**) were purified through recrystallization method in ethanol. The tools like FT-IR,  $^1H$  and  $^{13}C$  NMR, and mass analysis were employed to confirm the structures of the desired compounds.

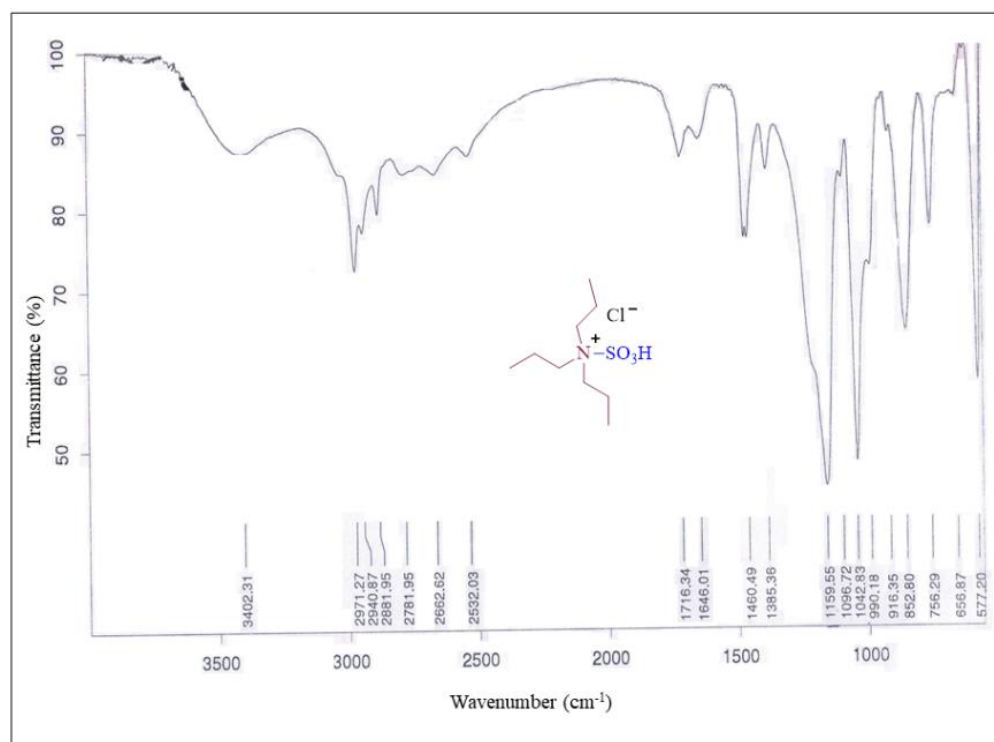
## Results and Discussion

First,  $[(C_3H_7)_3N-SO_3H]Cl$  IL was synthesized from tripropylamine and chloro-sulfonic acid as per reported method [30]. After attaining room temperature, resultant Bronsted acidic IL (BAIL) named  $[(C_3H_7)_3N-SO_3H]Cl$  was separated and washed with dry DCM and finally dried under vacuum.

### Characterization of $[(C_3H_7)_3N-SO_3H]Cl$ IL

As synthesized  $[(C_3H_7)_3N-SO_3H]Cl$  was subjected to structural interpretation by using FT-IR,  $^1H$  and  $^{13}C$  NMR,  $D_2O$  exchange and mass analysis. The FT-IR spectrum of  $[(C_3H_7)_3N-SO_3H]Cl$  showed a characteristic bands appeared at 1096  $cm^{-1}$  and 2971  $cm^{-1}$  due to C-N and C-H stretching of tripropylamine. Two intense bands at 1042  $cm^{-1}$  and 1159  $cm^{-1}$  attributed symmetric and asymmetric stretching frequency of  $-SO_3H$  group. Another broad band at 3402  $cm^{-1}$  corresponds to  $-OH$  group of acidic moiety [31] (**Figure 2**).

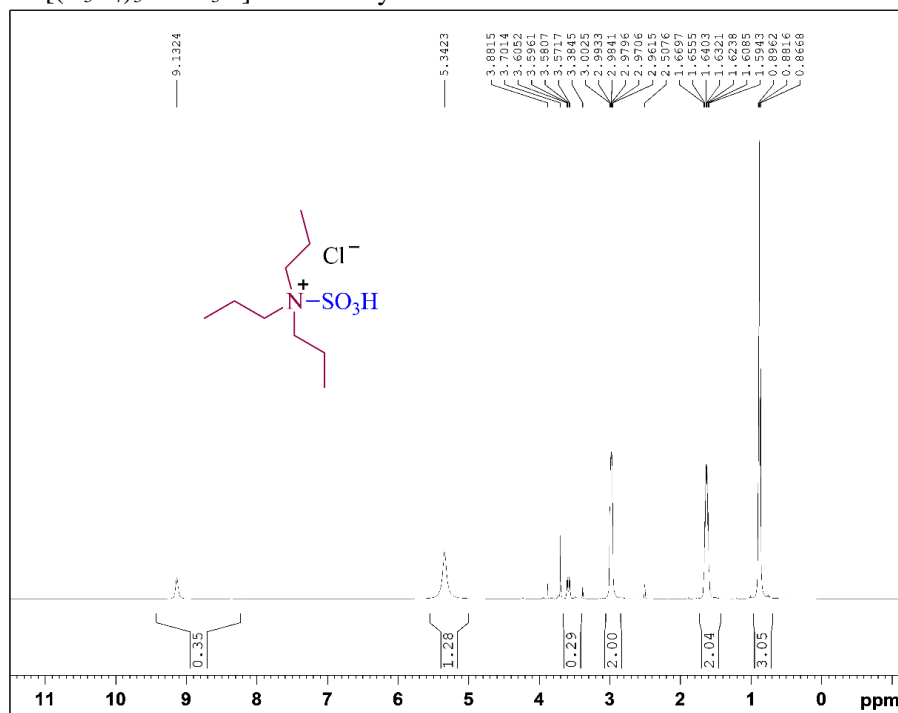
The  $^1H$  NMR result of  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst is shown in **Figure 3**. The  $^1H$  NMR spectrum exhibits one multiplet resonated at  $\delta$  0.88 ppm assigned to the three methyl ( $-CH_3$ ) protons. Another six methylene group ( $-CH_2$ ) protons displayed in two multiplets at  $\delta$  1.59-1.66 and 2.96-3.0 ppm respectively. The singlet peak at  $\delta$  5.34 ppm indicates proton of  $-SO_3H$  group from the  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst.



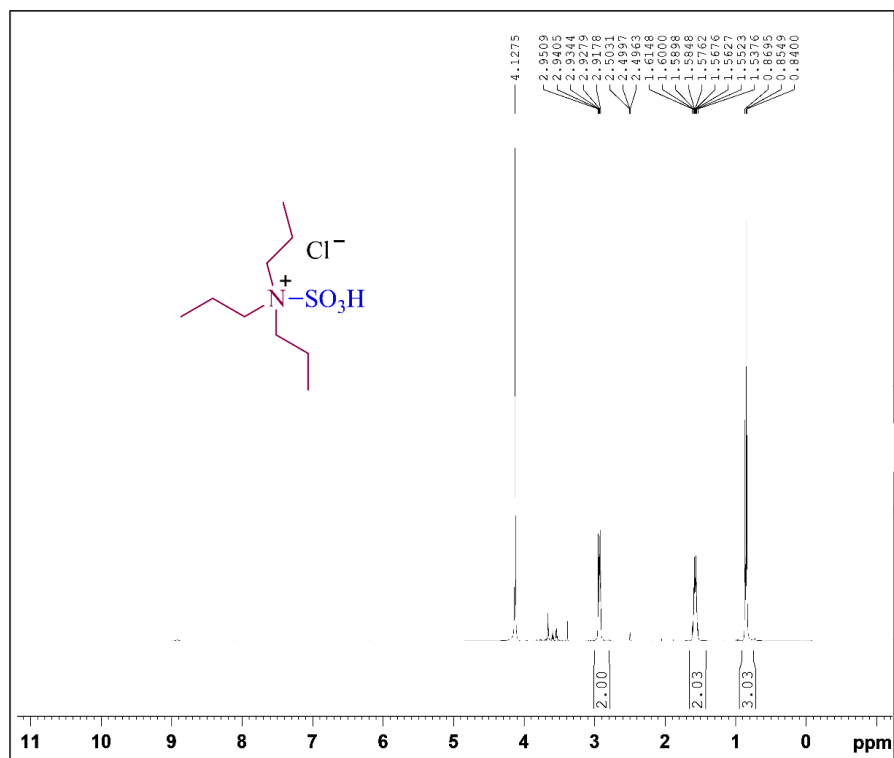
**Figure 2** IR spectrum of  $[(C_3H_7)_3N-SO_3H]Cl$  ionic liquid

$D_2O$  exchange was carried out to check the presence of sulfonic acid ( $-SO_3H$ ) functionality in the prepared  $[(C_3H_7)_3N-SO_3H]Cl$  BAIL catalyst. So, the disappearance of broad peak at  $\delta$  5.34 ppm, confirms the successful

grafting of sulfonic acid group through quarternization reaction of tripropylamine (**Figure 4**). The  $^{13}\text{C}$  NMR spectrum (**Figure 5**) of  $[(\text{C}_3\text{H}_7)_3\text{N-SO}_3\text{H}]\text{Cl}$  displayed signals at  $\delta$  10.83 for methyl carbon and  $\delta$  16.61 and 53.64 ppm for methylene carbon. Mass spectrum (**Figure 6**) exhibited molecular ion peak at (m/z) 260 which confirms the successful formation of  $[(\text{C}_3\text{H}_7)_3\text{N-SO}_3\text{H}]\text{Cl}$  IL catalyst.



**Figure 3**  $^1\text{H}$  NMR spectrum of  $[(\text{C}_3\text{H}_7)_3\text{N-SO}_3\text{H}]\text{Cl}$  ionic liquid



**Figure 4**  $\text{D}_2\text{O}$  exchange of  $[(\text{C}_3\text{H}_7)_3\text{N-SO}_3\text{H}]\text{Cl}$  ionic liquid

To evaluate the thermal stability of  $[(\text{C}_3\text{H}_7)_3\text{N-SO}_3\text{H}]\text{Cl}$  catalyst, the technique thermogravimetric analysis (TGA) and differential thermal analysis (DTA) was employed and the results are shown in **Figure 7**. The observed initial weight loss curve below  $150^\circ\text{C}$  in TGA, due to the dehydration of absorbed water, begins above ambient temperature. Water evaporates until  $150^\circ\text{C}$ , releasing most of the free water molecules. The second abrupt weight loss was seen between  $250\text{--}300^\circ\text{C}$  in TGA and a deep endothermic peak at  $290^\circ\text{C}$  in DTA due to the complete degradation of

organic and inorganic sulfonic acid moieties. After 300 °C, a constant plateau was observed, which indicates the formation residue by removal of gaseous molecules. Finally it is concluded that, prepared  $[(C_3H_7)_3N-SO_3H]Cl$  BAIL catalyst displayed good thermal stability up to 250 °C (Figure 7).

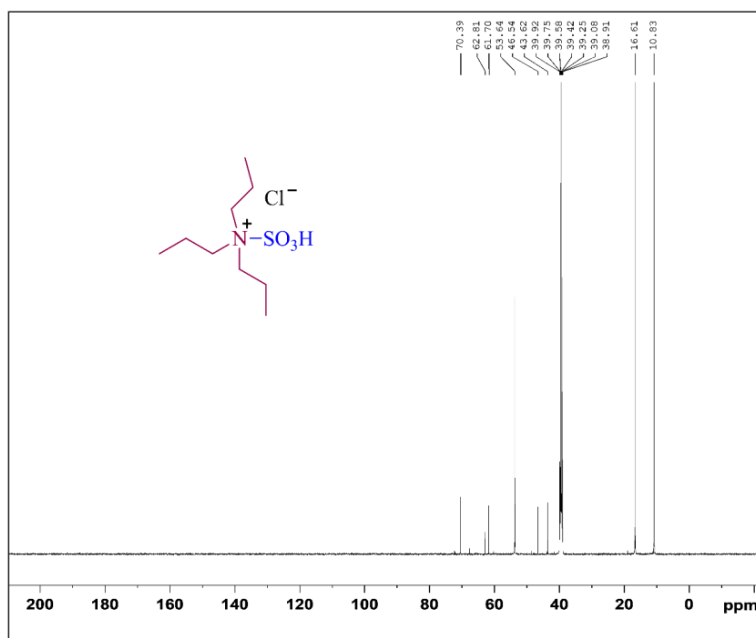


Figure 5  $^{13}C$  NMR spectrum of  $[(C_3H_7)_3N-SO_3H]Cl$  IL catalyst

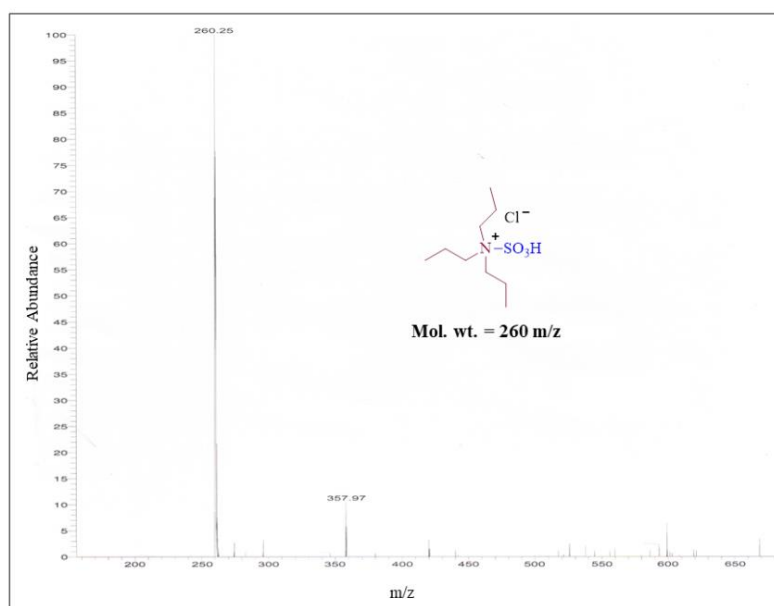
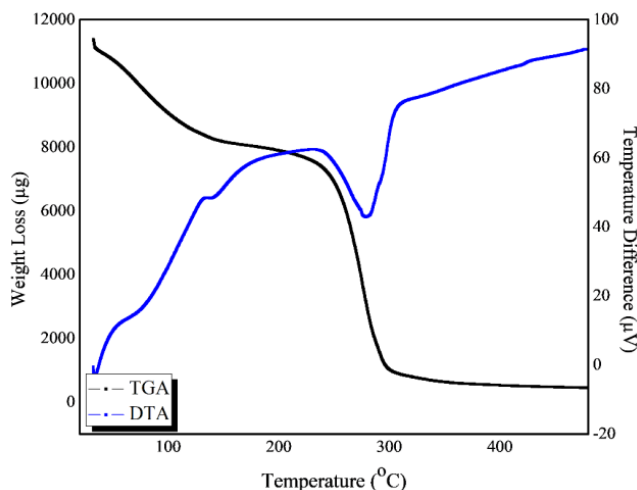


Figure 6 Mass spectrum of  $[(C_3H_7)_3N-SO_3H]Cl$  IL catalyst.

### Catalytic activity of $[(C_3H_7)_3N-SO_3H]Cl$ IL catalyst

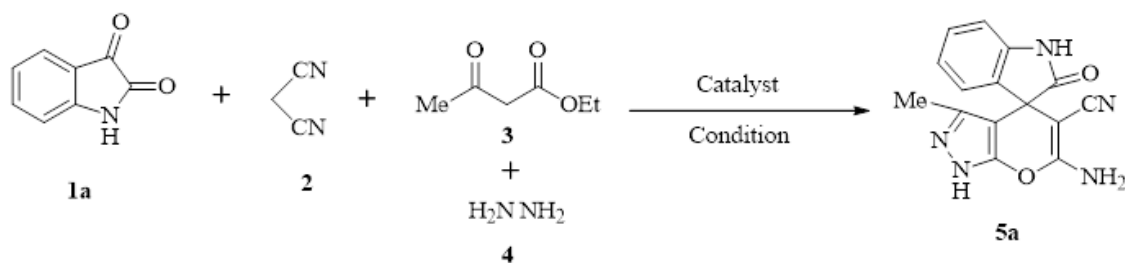
The catalytic ability of  $[(C_3H_7)_3N-SO_3H]Cl$  was examined by performing model reaction of ethyl acetoacetate, hydrazine hydrate, isatin and malononitrile. The reaction parameters for achieving excellent yield was scrutinized by changing solvent, catalyst quantity, and temperature respectively. Initially, model reaction run without catalyst in aqueous solvent didn't produce **5a** (Table 1, entry 1). Next, addition of 10 mol % catalyst in the reaction mixture furnished high yield of **5a** (Table 1, entry 2). We further modified reaction condition by increasing catalyst quantity to 15 mol %, to our delight model reaction furnished excellent yield of **5a** in short period (Table 1, entry 3). However, increasing the amount of  $[(C_3H_7)_3N-SO_3H]Cl$  to 20 mol % did not change the yield of product **5a** considerably (Table 1, entry 4). Next, model reaction performed in protic solvents such as EtOH, MeOH and aqueous ethanol (EtOH:H<sub>2</sub>O; 50:50 v/v) showed no improvement in the product yield (Table 1, entries 5-7). Model reaction gave low yield of **5a**

using organic solvents such as DCM, THF and chloroform at room temperature (entries 8-10). As shown in Table 1, 15 mol % of  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst in an aqueous solvent showed best outcome at room temperature.



**Figure 7** TGA-DTA analysis of  $[(C_3H_7)_3N-SO_3H]Cl$  IL catalyst

**Table 1** Scrutiny of reactions conditions for **5a**.



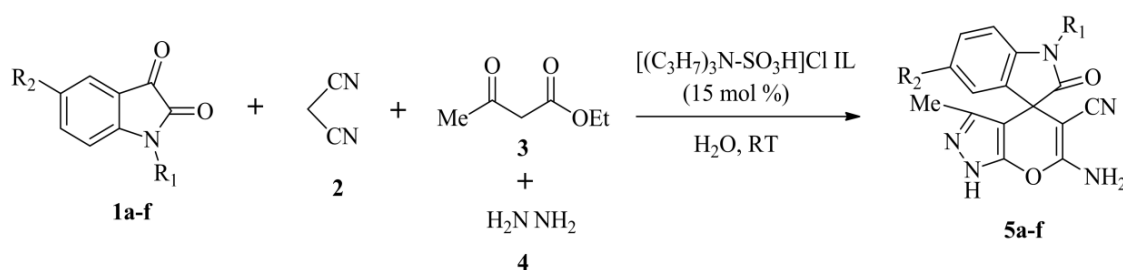
Entry	Catalyst (mol %)	Conditions	Time (min.)	Yield <sup>b</sup> (%)
1	----	H <sub>2</sub> O/ RT	180	--
2	$[(C_3H_7)_3N-SO_3H]Cl$ IL (10)	H <sub>2</sub> O/RT	24	80
3	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	H <sub>2</sub> O/RT	18	94
4	$[(C_3H_7)_3N-SO_3H]Cl$ IL (20)	H <sub>2</sub> O/RT	18	95
5	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	EtOH:H <sub>2</sub> O (50:50 v/v)/ RT	28	85
6	$[(C_3H_7)_3N-SO_3H]$ IL (15)	EtOH/RT	43	74
7	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	MeOH/RT	60	49
8	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	DCM/RT	120	Trace
9	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	THF/RT	90	Trace
10	$[(C_3H_7)_3N-SO_3H]Cl$ IL (15)	CHCl <sub>3</sub>	90	Trace

<sup>a</sup>Reaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol), isatin (1 mmol) in 5 mL solvent. <sup>b</sup>Isolated yields.

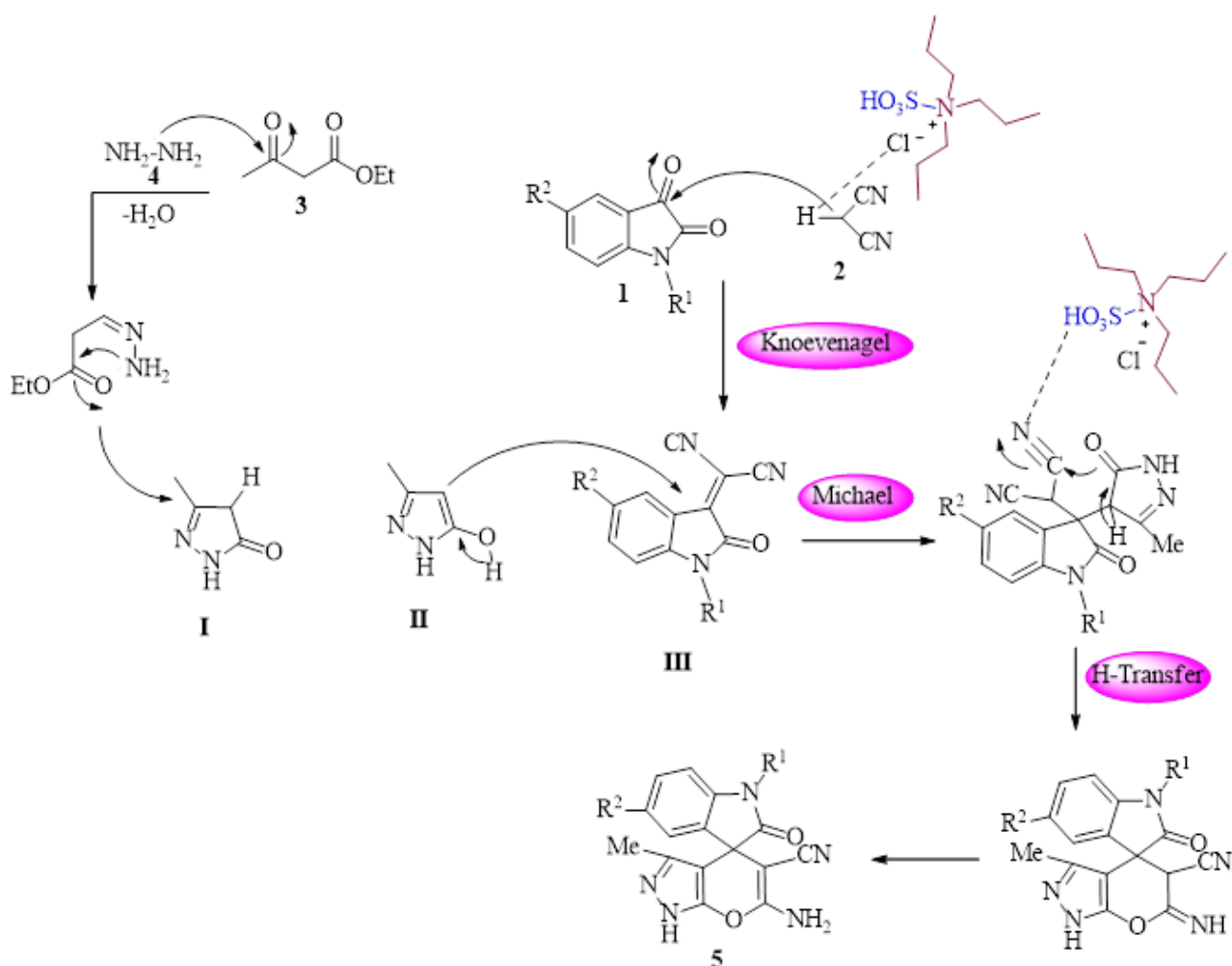
After setting optimal reaction parameters, series of pyrano[2,3-*c*]pyrazoles were synthesized by performing reactions of ethyl acetoacetate, hydrazine, substituted isatin and malononitrile and the results are given in **Table 2**. The reactions progressed very smoothly, and produced desired pyrano[2,3-*c*]pyrazoles in good to excellent yields from a diverse range of substrates. The isatin with electron releasing group gave higher yields than electron withdrawing group (Table 2, entries 1-6).

### Plausible reaction mechanism

Based on the spectroscopic results and previous reports, a plausible reaction mechanism catalyzed by  $[(C_3H_7)_3N-SO_3H]Cl$  BAIL catalyst for the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles] is depicted in **Scheme 2**. The reaction was supposed to continue *via* formation of pyrazolone intermediate (**I**) from ethyl acetoacetate (**3**) and hydrazine hydrate (**4**). Further reaction between isatin (**1**) with malononitrile (**2**) in the presence of  $[(C_3H_7)_3N-SO_3H]Cl$  resulted adduct (**III**). In the final step, Michael addition reaction between **II** and **III** followed by intramolecular cyclization produced desired product **5a**.

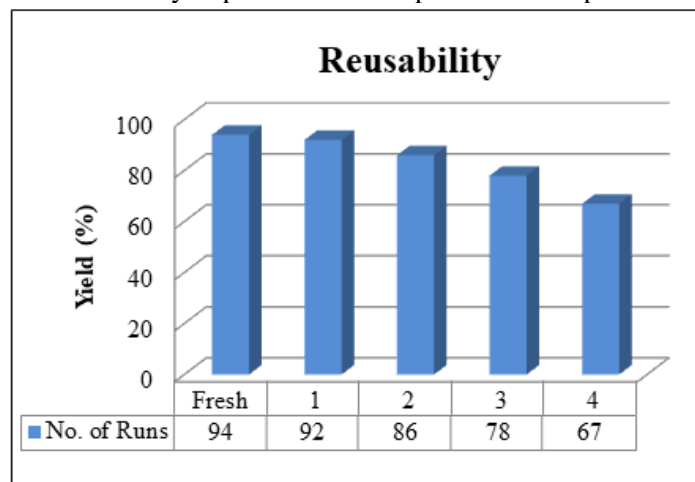
**Table 2** Synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]<sup>a</sup> derivatives using [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H] BAIL catalyst.

Entry	R <sub>1</sub>	R <sub>2</sub>	Product	Time (min.)	Yield <sup>a</sup> (%)
1	H	H	5a	18	94.14
2	H	Br	5b	20	94.97
3	-CH <sub>2</sub> -Ph-4-Cl	H	5c	16	80.26
4	-CH <sub>2</sub> -Ph-4-OMe	H	5d	14	91.06
5	-CH <sub>2</sub> Ph	Cl	5e	24	79.17
6	-CH <sub>2</sub> -Ph-2-Cl	Cl	5f	28	78.17

**Scheme 2** Plausible mechanism for the synthesis of Spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles]

One of the most crucial factors from an economic and environmental standpoint is the reusability of the catalyst. The reusability study of [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H]Cl catalyst was carried out using model reaction for the synthesis of **5a**. After accomplishment of model reaction (as monitored by TLC), by applying reduced pressure reaction solvent was removed from the catalyst. The isolated [(C<sub>3</sub>H<sub>7</sub>)<sub>3</sub>N-SO<sub>3</sub>H]Cl was further rinsed with diethyl ether (2x2 mL) to remove organic impurities. The recovered ionic liquid was again utilized to catalyze same model reaction which afforded **5a** with 92 % yield. The ionic liquid was then recovered and recycled three more times with minimal change in the yield of **5a** under optimized reaction conditions (Figure 8).

The superiority of the  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst was determined by comparing previously reported catalysts for the synthesis of spiro pyrano-pyrazoles (Table 3, entries 1-8). As revealed from the Table 3, the prepared  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst exhibits excellent catalytic potential as compared to the reported catalytic systems.



**Figure 8** Reusability study of  $[(C_3H_7)_3N-SO_3H]Cl$  IL in the synthesis of **5a**

**Table 3** Comparison of catalytic activity of  $[(C_3H_7)_3N-SO_3H]Cl$  BAIL catalyst with other reported catalysts for the synthesis of **5a**

Entry	Catalyst	Reaction Conditions	Time (min)	Yield (%) <sup>a</sup> [Ref.]
1	Fe <sub>3</sub> O <sub>4</sub> @l-arginine (15 mol %)	Neat/RT	60	96 [32]
2	I <sub>2</sub> (20 mol %)	EtOH/ RT	45	92 [33]
3	nano-SiO <sub>2</sub> /DABCO (0.05 g)	Neat/grinding	12	91 [34]
4	SDS (8 mol %)	H <sub>2</sub> O/RT	15	91 [35]
5	Et <sub>3</sub> N (20 mol %)	DCM/RT	15	62-83 [29]
6	TBBDA (0.06 mmol)	CH <sub>3</sub> CN/RT	4h	80 [36]
7	γ-Fe <sub>2</sub> O <sub>3</sub> @cellulose-OSO <sub>3</sub> H (0.01 g)	EtOH/RT	40	93 [37]
<b>8</b>	<b><math>[(C_3H_7)_3N-SO_3H]Cl</math> (15 mol %)</b>	<b>H<sub>2</sub>O/RT</b>	<b>18</b>	<b>94 [This work]</b>

## Conclusion

In conclusion, we have introduced a simple and efficient procedure for synthesis of a tripropylamine (TPA) based protic ionic liquid  $[(C_3H_7)_3N-SO_3H]Cl$  catalyst and its characterization is described in this paper. The important advantage of the present method for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] includes use of water as greener solvent, ambient temperature condition, shorter reaction times, excellent yield, no use of chromatographic as well as elevated temperature procedures and reusability of the catalyst.

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