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## Chitosan/ionic liquid forms a renewable and reusable catalyst system used for the synthesis of highly functionalized spiro derivatives<sup>†</sup>

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Chitosan, a reusable heterogeneous catalyst, can be combined with an ionic liquid as a green solvent to generate a highly efficient catalyst system for our densely functionalised and diversified target molecule. The reaction is completed with a good to excellent yield. This procedure demonstrates an eco-friendly catalyst system and eliminates the use of toxic transition metal catalysts, bases and volatile organic solvents, which adversely affect the environment and human beings.

## Introduction

Creating a highly efficient, selective, eco-friendly, and reusable catalyst is an interesting target in synthetic chemistry. Catalysis is at the centre of many chemical procedures. Catalysts are not only required in organic syntheses, but are also used in fine chemical industries. The chemical nature and form of a catalyst play an important role in a reaction. A strong relationship between heterogeneous catalysis and the practices and principles of eco-friendly synthesis could potentially result in an environmentally benign society.<sup>1</sup> Replacement or elimination of toxic reagents or volatile organic solvents in chemical processes is one of the main goals of green chemistry.<sup>2</sup> During the past ten years, room temperature ionic liquids have been described as very efficient green reaction media to replace traditional volatile organic solvents.3 They display many advantages, such as excellent ability to dissolve organic compounds, negligible vapour pressure, ease of separation from products and recyclability.<sup>4</sup> Additionally, one of the most important features of ionic liquids is their tendency to form solvophobic interactions that generate an internal pressure, encouraging better involvement of the reactants in a reaction medium and promoting multicomponent reactions more efficiently, as compared to traditional solvents.5 Their broad liquid range and solvating ability also establish them as suitable reaction media for multi component processes.<sup>6</sup> During the last decade, a number of organic syntheses have been performed using ionic

liquids as environmentally friendly solvents, e.g. hydrogenation, the Suzuki reaction, Aldol condensation, Diels-Alder reactions, alkylation, Michael addition and the Schmidt reaction.<sup>4</sup> Room temperature ionic liquids have found particular application in materials science, electrochemistry and separation technology.<sup>7</sup> Since the use of the first ionic liquid as a reaction medium for organic synthesis, researchers have mostly concentrated on homogeneous catalysis in ionic liquids.8 However, homogeneous catalysis has many drawbacks, such as multistep separation of the catalyst by extraction, distillation, chromatography etc., costly metal complexes and the extraction of metal ions, which involves a difficult procedure.9 Heterogeneous catalysis, on the other hand, produces less waste, thus making the procedure easier, results in less adulteration of the products with the active catalytic species, allows reuse and separation of the catalysts, and does not involve the use of toxic solvents.<sup>10,11</sup> The crisis of the reduction in non-renewable resources has created and encouraged chemists to use biomass, such as polymers present in nature, in place of fossil resources. For instance, polysaccharides, which exist widely in nature, have been used as supports in heterogeneous catalytic systems.<sup>12</sup>

In recent years, the application of small synthetic or natural organic scaffolds has provided an interesting substitute for conventional metal-catalyzed reactions in some asymmetric syntheses. In this respect, chitosan can play an important role as a renewable, biocompatible, natural polymer which is physiologically inert and stable to air and moisture.<sup>13</sup> In fact, chitosan is a polysaccharide obtained from chitin, which is present in nature (Fig. 1). It is a linear polyamine and a polar biopolymer, which is available in ample amounts in nature throughout the world.<sup>14</sup> It is insoluble in most organic compounds. Chemists have described the greater performance of chitosan than that of chitin in many areas of industry that involve heterogeneous catalysis. Since chitosan has both amino and hydroxyl groups,



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Fig. 1 Applications of chitosan in different fields

it can be altered chemically into different forms and can take part in various types of reactions as an appropriate support for various catalytic species.<sup>15</sup> Hence, chitosan, as a natural polyglucosamine, can be examined as a heterogeneous catalyst in organic transformation.<sup>16,17</sup> The indole nucleus is a highly versatile heterocyclic scaffold present in different types of medicinal agents and natural products. Molecules with indole nuclei display antifungal and antibacterial activities.<sup>18</sup> Moreover, it has been reported that C-3 spiroindoline derivatives have high biological activity.<sup>19</sup> The oxindole moiety is the core structure of various natural alkaloids and pharmacological agents.<sup>20</sup> Dihydropyrano[2,3-c]pyrazoles also play an important role in biologically active molecular scaffolds, and hence are an attractive moiety in medicinal chemistry. They have been broadly applied as medicinal intermediates because of their important biological and pharmaceutical properties. They are an attractive synthetic moiety with a high level of bioactivity that involves antiinflammatory and antimicrobial properties. Fig. 2 shows some important bioactive spiro moieties.21 Due to environmental



Fig. 2 Some important bioactive molecules containing a spiro-oxindole moiety.



Scheme 1 General reaction scheme.

concerns and the important features of dihydropyrano[2,3-*c*]pyrazoles and spiro moieties, we wish to demonstrate the combination of an ionic liquid as a green reaction medium and chitosan as a reusable heterogeneous catalyst for this protocol (Scheme 1).

#### Results and discussion

A number of protocols have been demonstrated for the synthesis of dihydropyrano[2,3-*c*]pyrazole and its related derivatives.

These transformations involve a base- or an acid-catalyzed reaction between a hydrazine, a  $\beta$ -ketoester, an isatin and an active methylene compound. Several methods have been reported for the synthesis of dihydropyrano[2,3-*c*]pyrazole, involving the application of L-proline,<sup>22</sup> Aspergillus niger,<sup>23</sup> ultrasound waves,<sup>24</sup> triethylamine (TEA)<sup>25</sup> and meglumine.<sup>26</sup> Previously examined methods have long reaction times and multistep work-up procedures, and use catalysts and toxic solvents. Keeping these aspects in mind, we tried to develop an eco-friendly approach for the synthesis of our target molecule. We selected ethylacetoacetate (1a), phenylhydrazine (2a), isatin (3a) and malononitrile (4a) as reactants, based on the disconnection approach (Fig. 3).

A series of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'carbonitriles were prepared using ethylacetoacetate (1 mmol), phenylhydrazine (1 mmol), malononitrile (1 mmol) and isatin (1 mmol) in the absence of a catalyst.

We discovered that only trace amounts of the products were formed after a long time. In order to optimize the reaction conditions, test reactions were performed using model reactants under different reaction conditions to investigate the effect of different solvents and varying amounts of catalyst in terms of the amount of product and the reaction time. We observed that commonly used bases (entries 2–5 of Table 1)



Fig. 3 Disconnection approach for the target molecule (5a)

Table 1 Optimization of the catalyst

Entry	Catalyst	Time (h)	Yield <sup>a</sup> (%)
1	None	3	Trace
2	NaOH	3	40
3	КОН	3	42
4	DEA	3	45
5	TEA	3	48
6	SDS	3	50
7	CTAB	3	60
8	Chitosan	3	76

Reaction conditions: ethylacetoacetate (1 mmol), phenylhydrazine (1 mmol), malononitrile (1 mmol) and isatin (1 mmol). <sup>*a*</sup> Yield of product.

could catalyze the reaction, with a moderate yield (40-50%) of the product. In addition, a number of by-products were formed. In the next step, we used surfactants, for example SDS (sodium dodecyl sulfate) and CTAB (cetyltrimethylammonium bromide) to carry out this protocol, but again, the yield of the product was not satisfactory (entries 6 and 7 of Table 1). In order to develop an eco-efficient approach and in continuation of our previous work<sup>27</sup> on the development of a green protocol, we examined the potential of chitosan by performing the model reaction with it. The reaction proceeded smoothly, resulting in the formation of the corresponding products in good yields and reaching completion within 3 hours. Chitosan has a high concentration of both primary and secondary hydroxyl groups and amino groups. Hence, it can increase the activity of the nucleophilic and electrophilic centres of the reactants during the reaction via lone pairs and hydrogen bonding. The activity of the chitosan catalyst was optimized for the synthesis of the desired product. The results showed that when we increased the amount of chitosan to 20 mol%, the yield of the product continuously increased from 76 to 85% (entry 3 of Table 2). Using amounts of chitosan less than 20 mol% (5 mol%, 10 mol% and 15 mol%), the desired product was obtained in a moderate yield with a longer reaction time, while with a further increase in the amount of chitosan, there was no increase in the yield of the target molecule (entries 4 and 5 of Table 2). From this result, we concluded that 20 mol% chitosan is the optimum amount for obtaining the desired product. Corma and coworkers previously demonstrated that the reaction rate of the Knoevenagel condensation, in which solid catalysts are used, decreased in a non-polar reaction medium, and a higher yield was obtained on increasing the polarity of the solvents.<sup>28</sup> Gascon and co-workers reported a similar result, in which polar solvents increased the reaction rate of the heterogeneous Knoevenagel condensation, and the reaction was completed with difficulty in non-polar solvents.<sup>29</sup> A literature survey showed that ionic liquids can act as a substitute reaction medium, connecting various types of polymers that are present in nature and resulting in an improvement in their reusability. In order to increase the basicity of the catalyst, we used ionic liquids. We found that ionic liquids form good combinations with chitosan. After examining chitosan-catalyzed reactions in the presence of an ionic liquid as a reaction medium, there are a number of points that need to be discussed.

In the next step, we investigated the effect of various types of ionic liquids on the model reaction, using chitosan as a reaction promoter. The reaction was performed using 20 mol% chitosan

Table 3 Optimization of the ionic liquid

Entry	Ionic liquid	Time (h)	Yield <sup>a</sup> (%)
1	(Bmim)BF <sub>4</sub>	3	Trace
2	(Hmim)HSO <sub>4</sub>	3	25
3	(Hmim)H <sub>2</sub> PO <sub>4</sub>	3	28
4	(Bmim)PF <sub>6</sub>	3	65
5	(Bmim)OH	3	92

Reaction conditions: ethylacetoacetate (1 mmol), phenylhydrazine (1 mmol), malononitrile (1 mmol) and isatin (1 mmol).  $^a$  Yield of product.

in different types of ionic liquid, such as  $(Bmim)BF_4$ ,  $(Hmim)HSO_4$ ,  $(Hmim)H_2PO_4$  and  $(Bmim)PF_6$  (Table 3). The interaction of the ionic liquid with chitosan results in enhancement of the basicity of the medium, thereby increasing the rate of the reaction. This catalyst system increases the yield of the product when the reaction is carried out at room temperature.

The recyclability of the catalyst system using chitosan (20 mol%) and (Bmim)OH (5 ml) was also examined for the test reaction. After completion of the reaction, the reaction medium, products and reactants were separated from the reaction mixture by extraction with ethylacetate and water. The mixture of chitosan catalyst and ionic liquid reaction medium was then washed several times with water and further applied in the conversion under similar conditions to those used in the first run. It was observed that the catalyst and solvent system could be reused six times. In the first three cycles, the system did not show a significant decrease in catalyst activity (Table 4).

After optimization of the reaction conditions, the method was evaluated using different types of  $\beta$ -ketoesters (1), hydrazines (2), isatins (3) and active methylene compounds (4). Two ethylacetoacetates (1), four substituted hydrazines (2), two malononitriles (4) and many substituted isatins (3) were used for the synthesis of a library of 6'-amino-3'-methyl-2-oxo-1'-phenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'-

carbonitriles in good yields at room temperature in the presence of chitosan as a catalyst and an ionic liquid as a reaction medium. The results are shown in Table 5. From Table 5, it is obvious that this protocol works with a broad range of reactants.

A plausible mechanism for the reaction is shown in Scheme 2. In the first step, the hydroxyl group of chitosan activates the carbonyl group of the  $\beta$ -ketoester (1), which undergoes a condensation reaction with the hydrazine (2),

Table 2         Optimization of the amount of catalyst			
Entry	Amount of chitosan (mol%)	Time (h)	Yield <sup>a</sup> (%)
1	10	3	65
2	15	3	76
3	20	3	85
4	30	3	85
5	40	3	85

Reaction conditions: ethylacetoacetate (1 mmol), phenylhydrazine (1 mmol), malononitrile (1 mmol) and isatin (1 mmol). <sup>*a*</sup> Yield of product.

Table 4	Reusability	of the	catalyst	system
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Entry	Cycle	Catalyst system	Yield <sup>a</sup> (%)	
1	1	Catalyst system	92	
2	2	Catalyst system	80	
3	3	Catalyst system	70	
4	4	Catalyst system	65	
5	5	Catalyst system	58	
6	6	Catalyst system	56	

Reaction conditions: ethylacetoacetate (1 mmol), phenylhydrazine (1 mmol), malononitrile (1 mmol) and isatin (1 mmol).  $^a$  Yield of product.

Ethylacetoacetate (1)	Hydrazine (2)	Isatin (3)	Active methylene compound (4)	Yield <sup>b</sup> (%)	Time (h)
5a 0 0 0C <sub>2</sub> H <sub>5</sub>	NH-NH <sub>2</sub>	€ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	< <sup>CN</sup> CN	92	3
5b 0 0C <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> -NH <sub>2</sub>	F C S S S S S S S S S S S S S S S S S S		89	4
5c 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	NH <sub>2</sub> -NH <sub>2</sub>	↓↓↓ ₽		86	5
5d OC <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> -NH <sub>2</sub>			85	4.5
5e OC <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> -NH <sub>2</sub>	C↓ ₽°	SCN COOC₂H₅	87	4.5
5f OC <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> -NH <sub>2</sub>	C↓ NH °		87	5
5g 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	NH <sub>2</sub> -NH <sub>2</sub>			86	6
5h OC <sub>2</sub> H <sub>5</sub>	NH-NH <sub>2</sub>			88	4
5i OC <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> -NH <sub>2</sub>	CI C		91	3
5j OC <sub>2</sub> H <sub>5</sub>	$\stackrel{\rm NH_2}{\underset{\rm NH_2}{\overset{\rm I}}}$	Br		91	2.5
5k OC <sub>2</sub> H <sub>5</sub>	$\stackrel{\rm NH_2}{\underset{\rm NH_2}{\overset{\rm I}}}$	Br		93	2.5
51 0 0 0C <sub>2</sub> H <sub>5</sub>	$_{\rm NH_2}^{\rm NH_2}$	F		93	2.5
5m 0 0 0C <sub>2</sub> H <sub>5</sub>	$_{\rm NH_2}^{\rm NH_2}$	↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓		89	3.5
$5n$ $O$ $O$ $OC_2H_5$	NH <sub>2</sub> -NH <sub>2</sub>	€ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓		90	3.5
50 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	NH-NH <sub>2</sub>			91	3

<sup>*a*</sup> Reaction conditions: Stoichiometric amount of β-ketoester, hydrazines, isatin and active methylene compound. <sup>*b*</sup> Yield of product.

leading to the formation of intermediate (A). A Knoevenagel condensation between the isatin (3) and the active methylene compound (4), leading to the formation of intermediate (B), is facilitated by the amine group of chitosan. Finally, Michael addition between intermediate (A) and intermediate (B) occurs to form intermediate (C), which undergoes intramolecular cyclization followed by tautomerization to form the desired product (5). Isatins with electron withdrawing groups show

higher reactivity towards malononitrile as compared to isatins with electron donating groups. Here, we demonstrate an ecofriendly and efficient protocol for a four-component synthesis of pyrano[2,3-*c*]pyrazoles in ionic liquids in the presence of chitosan as a catalyst. The chitosan as reaction promoter and the ionic liquid as reaction medium could be reused in their original pure forms after being used in the model reaction. Both the reaction medium and the catalyst could be recycled



Scheme 2 Plausible mechanism for the synthesis of the library of compounds (5).

many times without a convincing decrease in performance. We hope that this protocol finds wide use in the areas of drug discovery and combinatorial chemistry.

#### Typical experimental procedure

#### Materials and method

All chemicals were reagent grade, purchased from Aldrich and Alfa Aesar, and used without purification. NMR spectra were recorded on a Bruker Avance II-400FT Spectrometer (400 MHz for <sup>1</sup>H NMR, 100 MHz for <sup>13</sup>C NMR) using CDCl<sub>3</sub> as a solvent and TMS as an internal reference. All the reactions were monitored by TLC using pre-coated G/UV-254 silica gel sheets of 0.25 mm thickness (Merck 60F254).

(A) General procedure. A general experimental procedure for the reaction of the  $\beta$ -ketoester (1), hydrazine (2), isatin (3) and active methylene compound (4) is described below:

A mixture of isatin (1.0 mmol), malononitrile or its derivative (1.0 mmol) and the catalyst system (5 ml Bmim(OH) and 20 mol% chitosan) was stirred at room temperature for 0.5 h in a 20 ml round bottom flask. Then, a hydrazine (1 mmol) and a  $\beta$ -ketoester (1 mmol) were added to the mixture. The whole solution was stirred at room temperature for the time indicated in Table 5. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was purified by column chromatography using hexane and ethyl acetate in silica gel. Upon completion of the reaction, the catalyst system (chitosan and ionic liquid) was removed and reused.

(B) Recycling of the catalyst system (chitosan and ionic liquid). After completion of the reaction, ethylacetate and water

were added to the reaction mixture in a separating funnel. The chitosan and the ionic liquid separated from the organic layer. The chitosan was recovered after centrifugation of the water layer, and was used in further reactions. Recovery of the ionic liquid was also investigated. The water layer was dried under vacuum at 90  $^{\circ}$ C to afford (Bmim)OH, which was used in subsequent runs without purification.

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