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Short Communication

Chitosan: An efficient biodegradable and recyclable green catalyst for one-pot synthesis of 3,4-dihydropyrimidinones of curcumin in aqueous media

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ABSTRACT

An efficient procedure for the synthesis of curcumin 3,4-dihydropyrimidinones has been developed by simple one-pot condensation of curcumin, aromatic aldehydes and urea/thiourea in the presence of commercially available chitosan in 2% acetic acid in aqueous media at 60 °C for 80–90 min. In the reaction, curcumin: a potential biologically active molecule has been used as a component of multi-component synthesis using chitosan as an efficient biodegradable and recyclable green catalyst. The resultant product curcumin 3,4-dihydropyrimidinone is formed in excellent yield (97%). The chitosan catalyst can be reused for without loss of catalytic activity.

1. Introduction

Curcumin is a naturally occurring 1,3-dicarbonyl compound isolated as a yellow pigment from turmeric of the herb *Curcuma longa* rhizomes. It is commonly used as a food colorant spice and as traditional medicine in India and China. Literature review shows that curcumin and its derivatives have various biological activities such as anti-oxidant, anti-microbial, anti-HIV, anti-inflammatory, anti-Alzheimer's, wound healing, anticancer as well as hydrogen-peroxide-induced oxidative stress [1–8]. In recent decade, one-pot multi-component reactions [9] (MCRs) are considered as the most powerful tool in organic synthesis because of the significant advantages they offer, such as the synthesis of complex molecules from readily available building blocks, easy workup procedure, higher yield, a single purification step and diversity can be achieved simply by varying reaction substrates. In multi-component reaction at least three reaction substrates are required. Biginelli condensation or reaction involving a ternary cyclocondensation of substituted aldehydes, β-ketoester and urea is the most recognized and widely employed multi-component reaction for the preparations of dihydropyrimidinones. These dihydropyrimidinones have been found to possess various pharmacological activities such as anti-oxidant, anti-tubercular, anti-bacterial as well as anti-inflammatory [10–13].

In recent years, Biginelli reaction has been performed under a wide variety of conditions, and several improvements for the experimental procedures have been made, although, it has been traditionally catalyzed by acids and bases [14]. Such type of reactions has been successfully catalyzed by various other catalysts such as hydrotalcites etc. [15]. Looking into the biological activities of curcumin and the resultant 3,4-dihydropyrimidinone analogs, we describe herein the synthesis of a new class of 3,4-dihydropyrimidinone analogs of curcumin (Table 1) in one-pot three component cyclocondensation of curcumin **1**, substituted aromatic aldehydes **2**, and urea/thiourea **3** in the presence of commercially available chitosan as biodegradable and recyclable green catalyst in 2% aqueous acetic acid solution at 60 °C.

In recent years, to minimize waste and the atom economy in the use of raw materials, the target of science and technology has been shifting towards more environment friendly, sustainable resources and reusable catalyst. In this direction every contribution to the development of new "green" techniques, whether small or large, is important if we are to minimize the production of waste. Thus, biopolymers are attractive candidates in the search for such biodegradable and non-toxic catalyst. Chitosan is a deacetylated product of the naturally abundant and renewable polymer. It is easily prepared from the treatment of inexpensive chitin with alkali [16]. Chitosan offers a unique set of environmentally benign properties such as biodegradability to harmless products, non-toxicity, biocompatibility, recyclability [17–19], physiological inertness, stability to air and moisture, and inexpensiveness or cheapness. It can be quantitatively recovered by adding aqueous solution of alkali, filtered and reused without drying. It gives excellent yield of the targeted product (**4**).

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Table 1
Synthesis of curcumin 3,4-dihydropyrimidinones.[a]

Entry	R	X	Time (min)	Yield (%)[b]	Mp. (°C)
1	C_6H_5	O	80	97	207–208
2	4-OCH_3-C_6H_4	O	80	94	211–212
3	4-OH-C_6H_4	O	80	96	152–153
4	4-Cl-C_6H_4	O	90	95	202–203
5	4-HO-3-OCH_3-C_6H_3	O	80	94	225–227
6	4-NO_2-C_6H_4	O	80	95	199–200
7	4-CH_3-C_6H_4	O	90	94	159–161
8	C_6H_5	S	80	94	218–219
9	4-HO-3-OCH_3-C_6H_3	S	80	96	295–296
10	4-CH_3-C_6H_4	S	80	94	262–263

[a] Curcumin (1 mmol), aromatic aldehyde (1 mmol) and urea/thiourea (1.2 mmol) in the presence of chitosan at 60 °C for 80–90 min.
[b] Isolated yield.

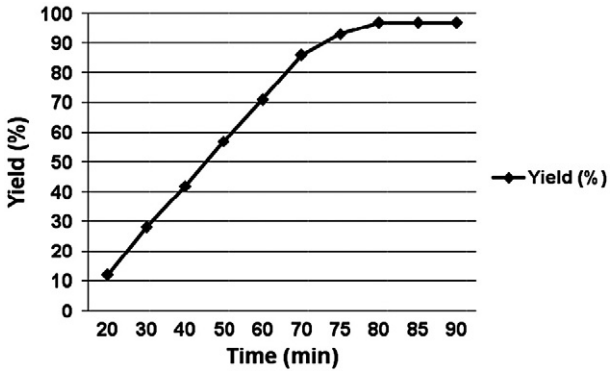


Fig. 1. Effect of reaction time on product yield.

In continuation with our previous work [20], commercially available chitosan has been utilized as a biodegradable, biopolymeric catalyst for the synthesis of 3,4-dihydropyrimidinone analogs of curcumin. To the best of our knowledge, chitosan has not been reported as catalyst in multi-component synthesis in aqueous media (Scheme 1).

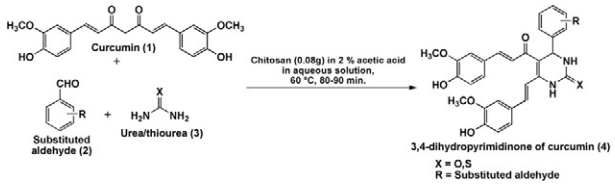
The present study has the following advantages:

- Using chitosan reaction has been carried out in aqueous medium, thus making heat and mass transfer more efficient in water medium.
- Chitosan is a naturally occurring material.
- Recyclability is more efficient (goes up to 98% recovery) as chitosan is a biopolymer.

2. Experimental

2.1. General remarks

^{1}H NMR spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer. Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass spectrometer. HPLC analysis of curcumin was carried out using Varian 920 instrument with RI detector, column C_{18} (250 mm × 4.6 mm × 5 μ), solvent system 80% CH_3CN + 20% H_2O, flow rate 1 mL/min. HPLC purity was reported by area%.



Scheme 1. Synthesis of curcumin 3,4-dihydropyrimidinones.

Table 2
Effect of molecular weight of chitosan on product yield.[a]

Entry	Type of chitosan[b]	Time (min.)	Temp. (°C)	Yield (%)[c]	Recovery of catalyst (%)
1	High molecular weight (310 > 375 kDa, > 75% DDA, viscosity 800–2000 cps)	80	60	97	98
2	Medium molecular weight (190–310 kDa, 75–85% DDA, viscosity 200–800 cps)	90	60	92	91
3	Low molecular weight (50–190 kDa, 75–85% DDA, viscosity 20–200 cps)	90	60	86	86

[a] Curcumin (1 mmol), benzaldehyde (1 mmol) and urea (1.2 mmol) in the presence of chitosan at 60 °C for 80–90 min.
[b] Purchased from Sigma Aldrich.
[c] Isolated yield.

Table 3
Optimization of chitosan catalyst.[a]

Entry	Solvent	Yield (%)[b]
1	0.5% Acetic acid in water	81
2	1% Acetic acid in water	89
3	2% Acetic acid in water	97
4	2.5% Acetic acid in water	86
5	3% Acetic acid in water	72
6	5% Acetic acid in water[c]	27
7	Water	–
8	No catalyst[d]	–
9	Solvent free[c]	36

[a] Curcumin (1 mmol), benzaldehyde (1 mmol) and urea (1.2 mmol) in the presence/absence of chitosan at 60 °C for 80 min.
[b] Isolated yield.
[c] Not easy to workup.
[d] In 2% acetic acid alone (without catalyst).

2.2. Isolation of curcumin

Took 10 g turmeric (*Curcuma longa*) powder in a 100 mL beaker and to this distilled water was added to wet turmeric powder. To this potassium hydroxide solution was added till its pH reaches to 10–11. After stirring for about 15 min the contents were filtered.

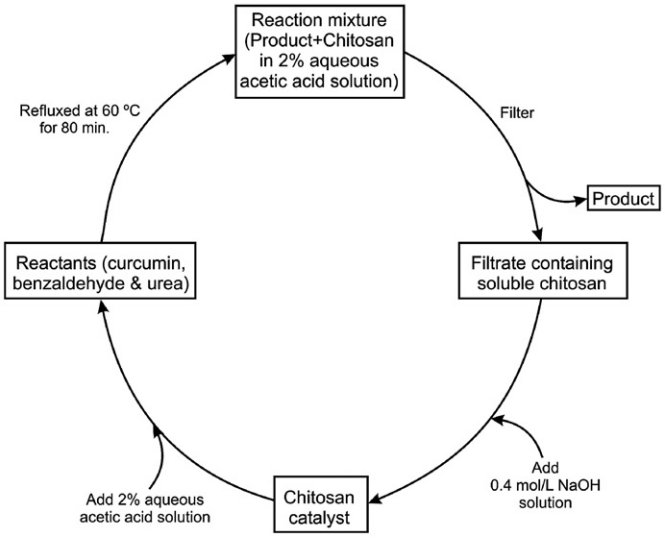


Fig. 2. Recyclability and reusability of the catalyst.

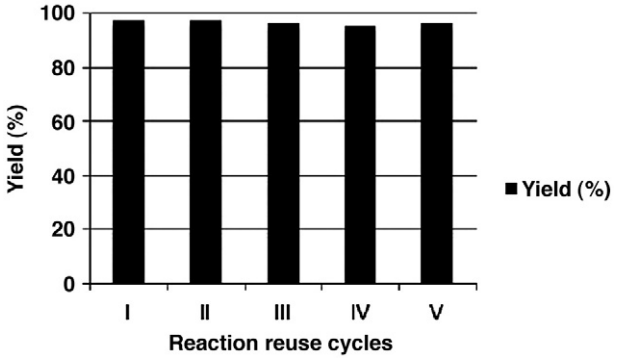


Fig. 3. Reuse of chitosan catalyst.

Few drops of acetic acid were added to the filtrate until the yellow color precipitate persists and its pH was maintained between 4 and 6 for precipitation of curcumin; the precipitate was filtered using Whatman filter paper No. 1, and the residue was washed with distilled water until the smell of acetic acid was removed. The product was dried at room temperature and recrystallized from acetone to get solid product. The isolated curcumin was found to have 99.86% purity using HPLC analysis.

2.3. Synthesis of 3,4-dihyrdopyrimidinone analogs of curcumin under aqueous media

In a 100 mL round bottom flask, chitosan catalyst (0.08 g) was dissolved in 10 mL 2% aqueous acetic acid solution and to it curcumin **1** (1 mmol), aromatic aldehydes **2** (1 mmol) and urea/thiourea **3** (1.2 mmol) were added and heated at 60 °C on a magnetic stirrer for 80–90 min (based on substituted aldehydes). The reaction was monitored by TLC using acetone/hexane (4:6) ratio as eluent. After completion of the reaction, contents were filtered to get synthesized product **4** (Table 1). The residue thus obtained was purified by silica gel column chromatography (acetone/hexane, v:v = 4:6) to afford their respective pure title products and filtrate was treated with 0.4 mol/L NaOH solution to recover the chitosan catalyst. The catalyst was washed with water and reused.

3. Results and discussion

In the present communication, curcumin 3,4-dihydropyrimidinones in 2% aqueous acetic acid solution have been synthesized. After the success of the reaction, the effect of various solvents viz. methanol, ethanol, propanol, acetonitrile, toluene, DMF, DMSO, mixture of ethanol and DMF, ethanol and DMSO were studied. The yield of the desired product was very poor in all the organic solvents studied up to 10 h. This observation can be attributed to the insolubility of chitosan catalyst in the organic solvents. Chitosan is soluble in minimum 1% aqueous acetic acid solution.

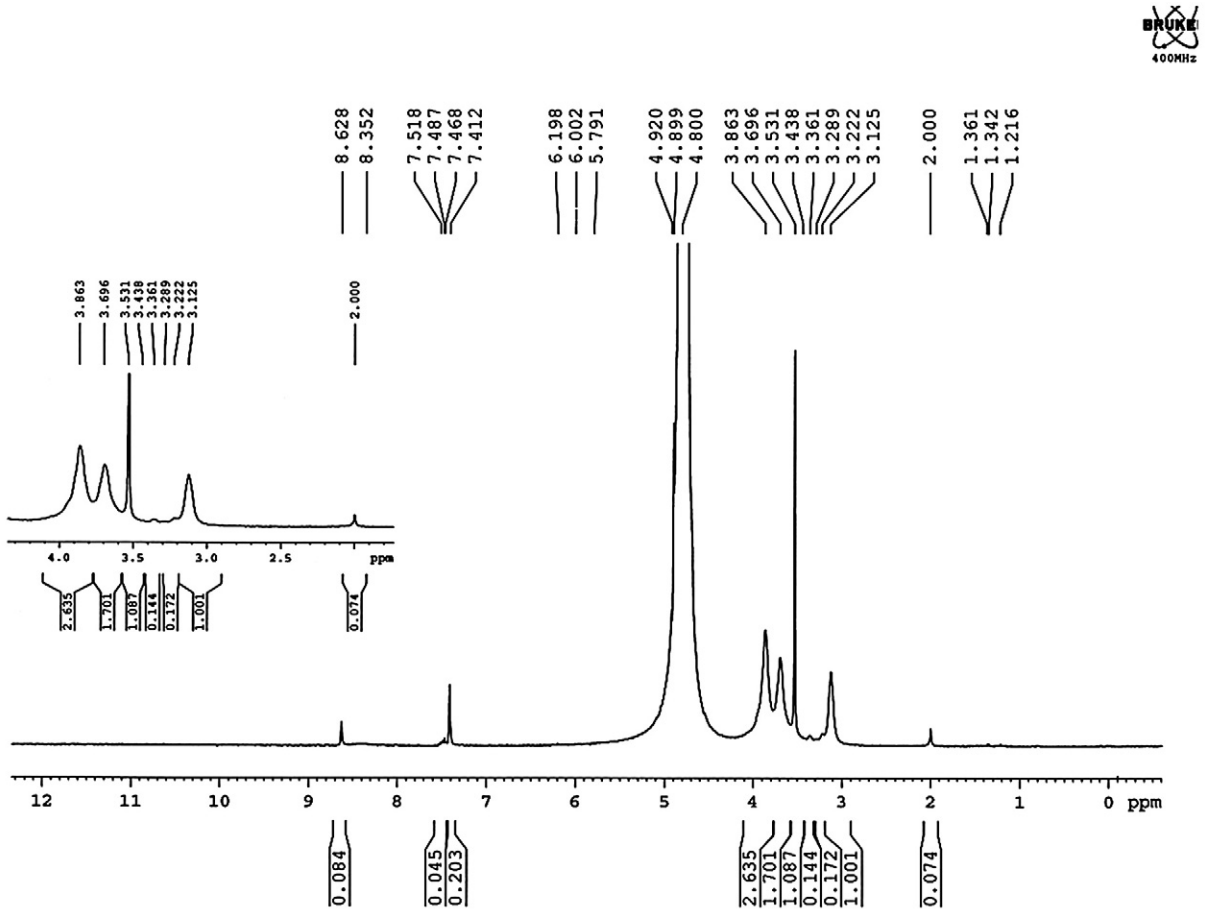


Fig. 4. ^{1}H NMR spectra of chitosan catalyst before applying for the reaction.

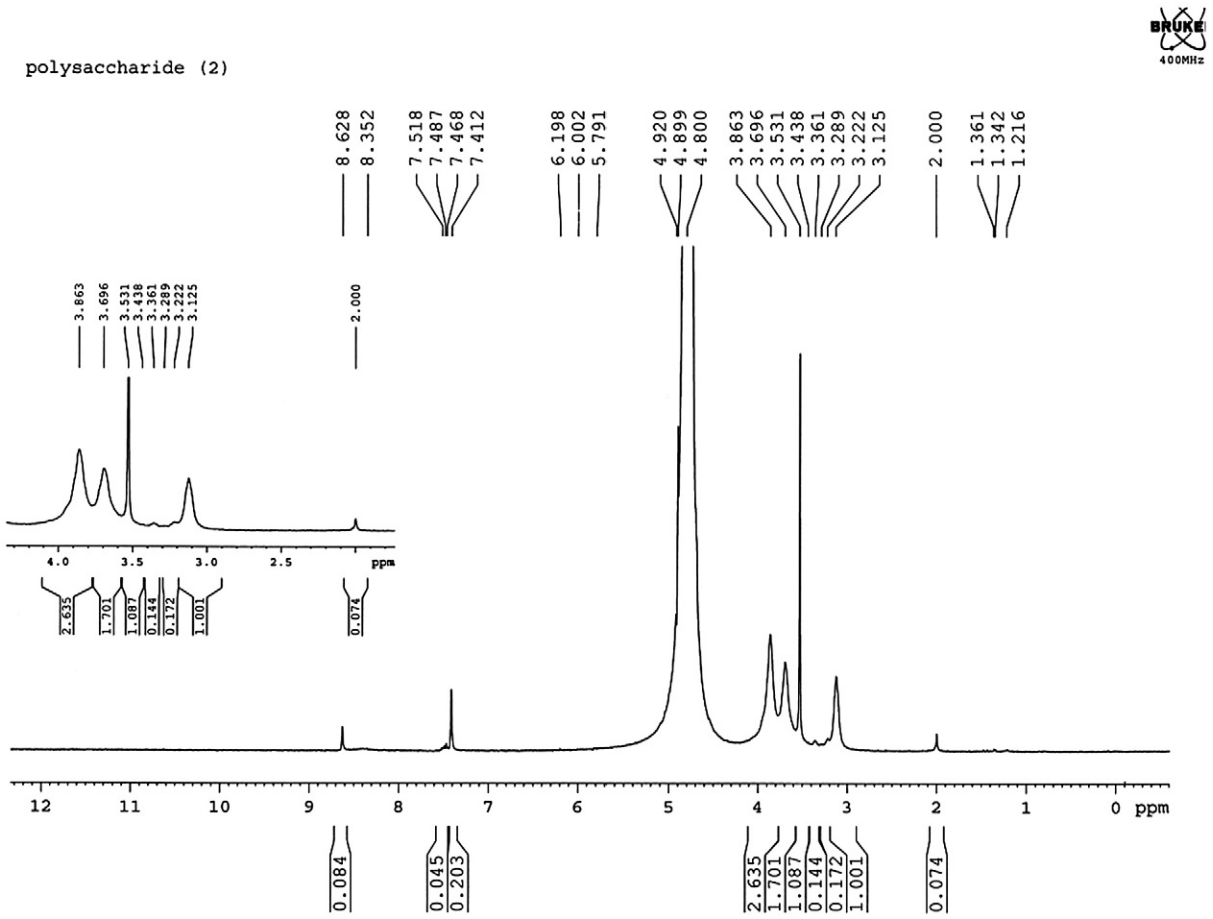


Fig. 5. ^{1}H NMR spectra of chitosan catalyst after recycling.

Substituted aromatic aldehydes containing both electron donating and withdrawing groups afforded high yields of the desired products with high purity, (Table 1). This shows that substitution of benzaldehyde has no significant effect. Similar results were observed for the synthesis of 3,4-dihydropyrimidinones of curcumin using thiourea. Catalyst was recovered from the filtrate after completion of the reaction.

3.1. Catalytic studies

3.1.1. Effect of molecular weight of chitosan on product yield

In order to test the appropriate molecular weight of chitosan catalyst, three types of chitosan were used for the study and it was concluded that chitosan of high molecular weight gives maximum yield of the desired product. The yield decreases with decrease in molecular weight of chitosan (Table 2).

3.1.2. Effect of reaction time

In order to study the effect of reaction time on the yield of the product, the reaction was studied at different times (20, 30, 40, 50, 60, 70, 75, 80, 85 and 90 min), for the model reaction between curcumin (1 mmol), benzaldehyde (1 mmol) and urea (1.2 mmol) in the presence of 0.08 g chitosan in 2% aqueous acetic acid solution (10 mL) at 60 °C. It was observed that there is a sharp increase in the yield from 70 to 80 min. After 80 min the yield of the product reached its maximum level and no further enhancement was observed if a longer reaction time was applied. So, reaction time 80 min was chosen as the optimum reaction time for the reaction (Fig. 1).

3.1.3. Optimization of chitosan catalyst

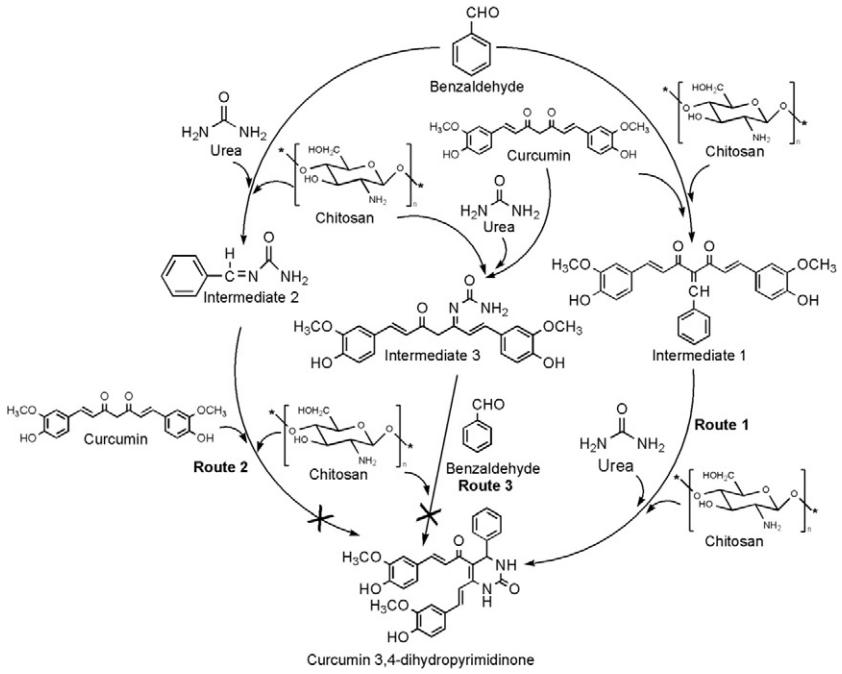
For the synthesis of curcumin 3,4-dihydropyrimidinones, curcumin (1 mmol), benzaldehyde (1 mmol) and urea (1.2 mmol) were used using amount of acetic acid (0.5, 1.0, 2.0, 2.5, 3.0 and 5.0 mL) respectively in 100 mL aqueous medium. Best yield (97%) was obtained in 2% aqueous acetic acid solution. It was observed that increase in acetic acid concentration from 2 to 5% resulted in viscous gel formation thus retarding the yield of the product (Table 3, entry 6). No final product was formed in the presence of only 2% acetic acid (without catalyst), Table 3, entry 8.

3.1.4. Substrate scope study

Chitosan 0.08 g in 2% aqueous acetic acid solution was used for the condensation of curcumin (1 mmol), aromatic aldehyde (1 mmol) and urea/thiourea (1.2 mmol) (Table 1). Seven substituted aromatic aldehydes were tested in the reaction; the yield of the condensation products is about 97% indicating that 0.08 g chitosan in 2% aqueous acetic acid solution has a high level of activity for the reaction.

3.2. Recyclability and reusability of chitosan catalyst

The recyclability and reusability of the chitosan catalyst were tested upon the reaction of curcumin (1 mmol), benzaldehyde (1 mmol) and urea (1.2 mmol) employing 0.08 g chitosan catalyst in 2% aqueous acetic acid solution (Fig. 2), chitosan can be recovered after completion of the reaction from filtrate by the treatment of 0.4 mol/L aqueous solution of NaOH. It is interesting to note that here aqueous solution of NaOH is being added to neutralize aqueous acetic acid



Scheme 2. Mechanistic routes for the synthesis of curcumin 3,4-dihydropyrimidinones.

solution, as chitosan is soluble in aqueous acetic acid solution and precipitated out on addition of NaOH solution. The pH at the end is neutral. Recovered catalyst can be reused directly. The catalytic activity of the recovered catalyst was investigated (Fig. 3) for five consecutive times. The results show that there is no significant decrease in reaction yield. The structural changes in chitosan were evaluated using ^{1} NMR spectra of chitosan catalyst before applying in the reaction (Fig. 4) and after recycling (Fig. 5) and observed that both the spectra of chitosan (before applying and after recycling) were the same which clearly indicates that, catalyst is stable during the reaction.

3.3. Mechanistic investigations

For the reaction under investigation three mechanistic routes are possible (Scheme 2) via intermediate 1, route 1, intermediate 2, route 2 and intermediate 3, route 3. According to route 1 the intermediate 1 reacts with urea giving target product. When intermediates 2 and 3 were reacted with their respective components (route 2 and route 3) i.e. curcumin and benzaldehyde respectively, target product was not formed which clearly supports that target product is possible via Knoevenagel condensation mechanism i.e. route 1. All the reactions were possible only in the presence of chitosan in aqueous conditions. The primary amino ($-NH_2$) group present in chitosan can be considered to be responsible for catalyzing the above reaction, similar to that reported by Debache et al. [21].

4. Conclusions

In conclusion, curcumin was isolated from turmeric (*Curcuma longa*), characterized and used as 1,3-dicarbonyl moiety in the synthesis of curcumin 3,4-dihydropyrimidinones in a single operation by cyclocondensation reaction with substituted aromatic aldehyde, urea/thiourea and curcumin in aqueous media using chitosan as catalyst. The remarkable merits offered by this methodology are short reaction time, environment friendly, simple workup procedure with excellent yield. The catalyst used in the procedure is recyclable, non-toxic, and biodegradable.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.06.017.

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