Catalysis Letters
https://doi.org/10.1007/s10562-018-2484-3

β-Cyclodextrin Based Nanosponge as a Biodegradable Porous Three-Dimensional Nanocatalyst in the One-Pot Synthesis of N- Containing Organic Scaffolds

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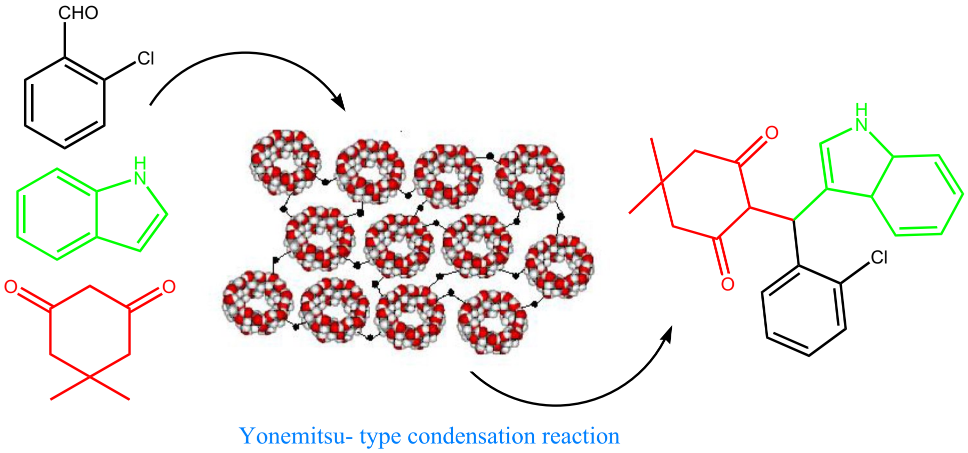
Received: 11 March 2018 / Accepted: 7 July 2018

Abstract

The motivation behind the present study was to develop an application of β-cyclodextrin-based nanosponges with the tiny mesh-like structure as porous three-dimensional nanocatalyst in the one-pot three component condensations of various aromatic aldehydes with activated methylene compounds such as dimedone, thiobarbituric acid, 4-hydroxycoumarin, 4-hydroxy-6-methyl-2-pyrone and nucleophiles including indole and amines. This nanosponge catalyst afforded the privileged N- containing organic scaffolds as key intermediates in pharmaceutical chemistry in very short reaction times.

Graphical Abstract



Keywords Nanosponges · β-Cyclodextrin · β-Cyclodextrin based nanosponges · 3-Substituted indole derivatives · N-containing heterocyclic

1 Introduction

During these last years, cyclodextrins (CDs) have greatly contributed to the development of innovative homogeneous or heterogeneous catalytic processes. More than simple molecular platforms aiming at designing new ligands or interfacial additives, CDs have been employed to generate unconventional reaction media such as nanosponges capable of stabilizing active catalytic species [1, 2]. The β-cyclodextrin-based nanosponges (βCD.NS) as new age

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branched cyclodextrin polymeric systems with tiny mesh and sponge-like structures can be obtained by crosslinking different types of cyclodextrin using the crosslinkers like dialdehydes, epoxides, epichlorohydrin, carbonyl diimidazole, dimethyl carbonate, diphenyl carbonate and etc [3–5]. Due to their inner hydrophobic cavities and external hydrophilic branching, these biocompatible nanoporous supramolecular materials are able to form stable inclusion complexes with both hydrophilic and hydrophobic molecules and thereby exhibiting tremendous potential in the pharmaceutical, biomedical, food, photo chirogenesis and catalytic applications [6–16].

Indole frameworks are one of the most widely distributed classes of heterocyclic compounds, which constitute the key core of various natural products [17, 18]. They have been widely considered as target pharmacophores for the development of therapeutic agents. Among this exceptionally elite class of heterocyclic scaffold, 3-substituted indole moieties have been known as outstanding agents in compounds of high biological, agrochemical and pharmacological relevance [19, 20].

In view of their significance, various multicomponent protocols have been recently developed for the construction of indole incorporating heterocyclic frameworks [21–23]. However, research along this line often encountered some notorious difficulty such as use of expensive or toxic metal-based catalysts, using a large quantity of volatile and toxic organic solvents, harsh reaction conditions, and contamination of media by undesired products such as bisindole, biscoumarin, xanthine and crossed adducts, and therefore the development of simple, efficient and environmentally benign synthetic approaches remains a challenging task [23–27].

In the current study, we would like to report efficient catalytic activity of β-cyclodextrin-based nanosponge for one-pot and regioselective synthesis of 3-substituted indole moieties using three component condensations of various aromatic aldehydes and indole with activated methylene compounds such as dimedone, thiobarbituric acid, 4-hydroxycoumarin, 4-hydroxy-6-methyl-2-pyrone. In the other part of this study, amines such as *N, N*-dimethylaniline, 2,4-dimethylaniline or pyrrolidine were used instead of indole, resulting the privileged N- containing organic scaffolds with medicinal value.

2 Experimental

2.1 Materials

Anhydrous β-cyclodextrin was purchased from Sigma–Aldrich Company and used with no additional purification. The known products were recognized by comparison of their melting points and spectral data with their announced authentic samples in the articles. Reactions were routinely checked with thin-layer chromatography (TLC) using Merck silica gel 60 F 254 plates. Melting points recorded in the Electro thermal IA9200 apparatus. Fourier transmission infrared (FT-IR) spectra of the powders (as pellets in KBr) were obtained using a Fourier transmission infrared spectrometer (Perkin Elmer BX-II). X-ray diffraction (XRD) pattern of the sample was obtained on a Philips X-ray diffraction model PW 1840. The particle morphology was studied with SEM (Philips XL30 scanning electron microscope. Thermogravimetric analysis (TGA) of the catalyst was performed on a BAHR SPA 503 system under an N_2 atmosphere at a heating rate of 10 °C min^{-1}, over the temperature range of 25–750 °C.

2.2 Preparation of Nanosponges Based β-Cyclodextrin

β-Cyclodextrin based Nanosponge, βCD.NS was prepared as previously reported in the literature [24]. Briefly, to a solution of anhydrous β-CD (0.871 gr, 1 mmol) in anhydrous DMF (4 ml), anhydrous carbonyl diimidazole (0.498 gr, 4 mmol) was added and the clear solution stirred at 100 °C for 4 h. After completion of the reaction, an excess of distilled water was added to the mixture, the product separated by filtration and purified by SOXHLET extraction with ethanol. The white powder βCD.NS was dried in an oven at 60 °C overnight.

2.3 General Procedure for the Synthesis of 3-Substituted Indole

A 50 ml flask was charged with aromatic aldehyde (1 mmol), indole (0.117 gr, 1 mmol), βCD.NS (0.01 g) and activated methylene compound such as dimedone (0.14 gr, 1 mmol), thiobarbituric acid (0.144 gr, 1 mmol) or 4-hydroxycoumarin (0.162 gr, 1 mmol) in ethanol (3 ml). The reaction mixture was stirred under reflux conditions and monitored by TLC. After completion of the reaction, βCD.NS was filtered off and washed with hot ethanol (2 × 10 ml). Evaporation of solvent under reduced pressure was produced crude product. The crude product was further purified by recrystallization in ethanol to offer pure 3-substituted indole product (4a–h).

2.4 General Procedure for Three-Component Reaction of Aromatic Aldehyde, with Two Different Nucleophiles

To the suspension of aromatic aldehyde (1 mmol) and βCD.NS (0.01 g) in ethanol (3 ml), activated methylene compounds [dimedone (0.14 gr, 1 mmol), thiobarbituric acid (0.144 gr, 1 mmol), 4-hydroxy-6-methyl-2-pyrone (0.126 gr, 1 mmol) or 4-hydroxy coumarin (0.162 gr, 1 mmol)] and different amines [*N, N* dimethylaniline (0.121 gr, 1 mmol), 2,4 dimethylaniline (0.121 gr, 1 mmol) or pyrrolidine (0.71 gr, 1 mmol)] was added. The reaction mixture was stirred under reflux conditions and monitored by TLC. After completion of the reaction, βCD.NS was filtered off and washed with hot ethanol (2×10 ml). Evaporation of solvent under reduced pressure was produced crude product. The crude product was further purified by recrystallization in ethanol to offer a pure product (5a–f) and (6a–e).

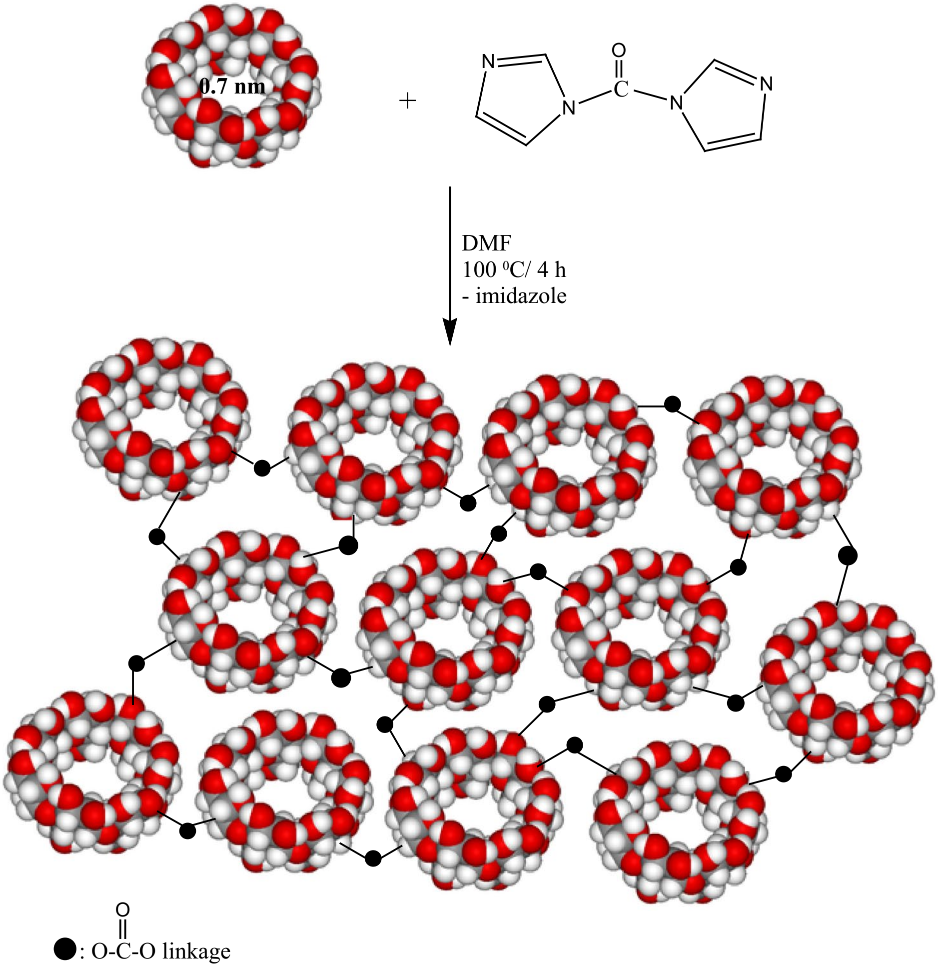
3 Results and Discussion

Recent advances in nanotechnology have demonstrated the applications of β-cyclodextrin-based nanosponges as nanometric biomaterials with a close relationship between molecular status and supramolecular properties for housing organic molecules. They are encapsulating the type of nanoparticles, which encapsulate the organic molecules within their cores [28]. Keeping all facts in our mind, firstly, porous insoluble nanoparticles of β-cyclodextrin-based nanosponges prepared as shown in Scheme 1 by the reaction of the β-cyclodextrin monomer with 1, 1′-carbonyl diimidazole [29].

The chemical characteristics of β-cyclodextrin-based nanosponge are studied by employing FT-IR spectrometer (Perkin Elmer, USA). The FT-IR spectra of βCD and βCD.NS at wavelength 400–4000 cm^{-1} were shown in Fig. 1. In the βCD.NS spectrum (b), the stretching modes of carbonate groups in the polymer can be observed at 1740 cm^{-1}.

Scanning electron microscopic (SEM) images of β-cyclodextrin-based nanosponge are shown in Fig. 2 which showed the nanosponge has relatively smooth and regular surface with mean particle size of about 300 nm and cavities with a size of 40–200 nm.

The thermal behavior and stability of the β-cyclodextrin-based nanosponge was examined by thermogravimetric analysis (Fig. 3). According to TGA thermogram, the nanosponge was thermal stable below 300 °C. The chemical stability of nanosponge was also evaluated at 78 °C (boiling point of ethanol) under both basic and acidic conditions. Although in acidic conditions (0.1 N HCl), nanosponage was stable, but under basic environment (0.1 N NaOH), a limited release of cyclodextrin units was observed after 2 h due to degradation of the nanosponge structure.



Scheme 1 β-cyclodextrin based nanosponges preparation

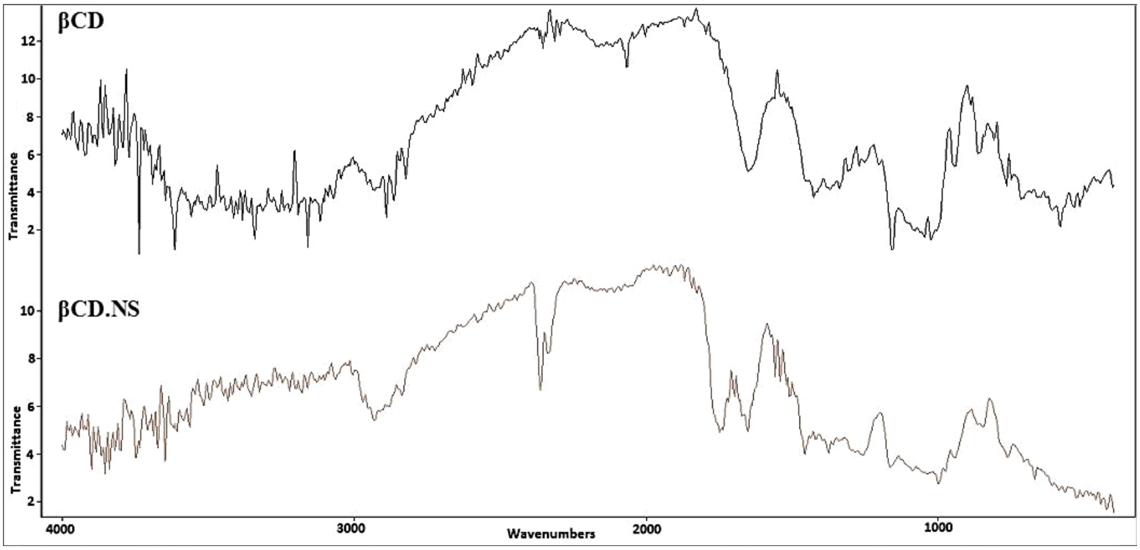
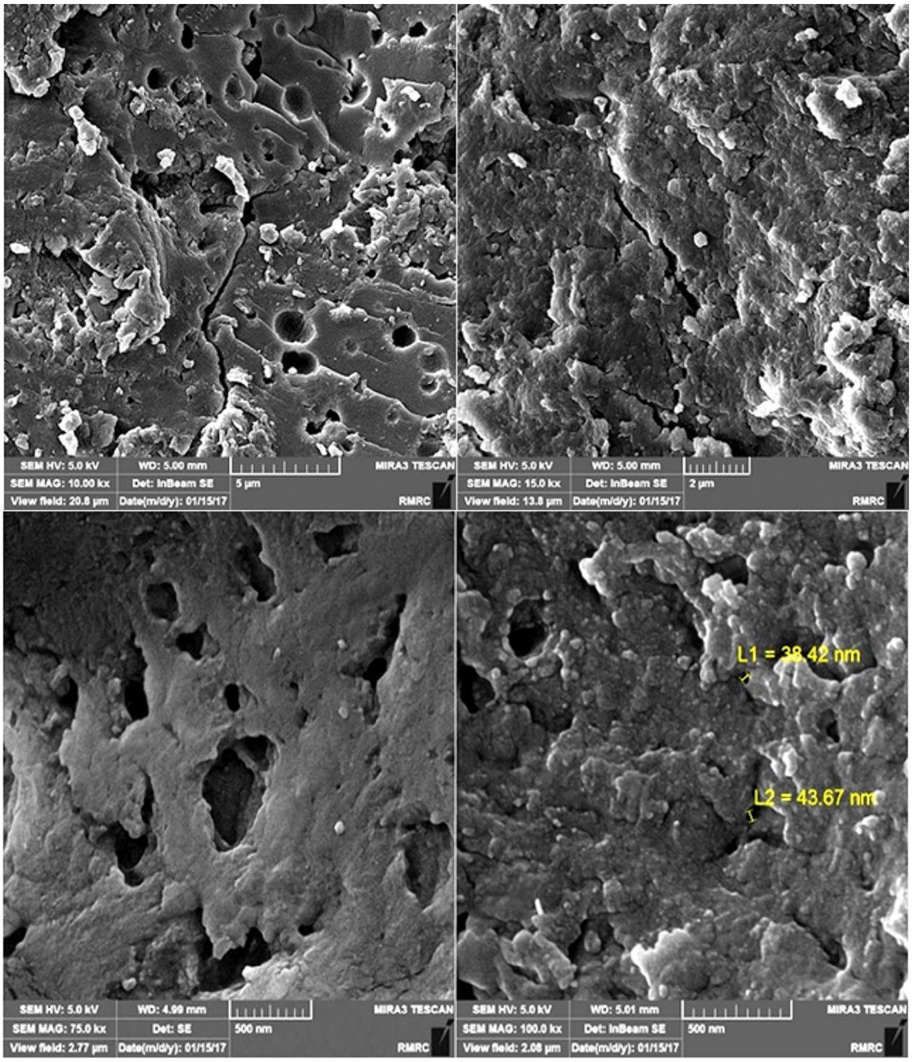


Fig. 1 The FT-IR spectra of βCD and βCD.NS

Fig. 2 SEM images of β-cyclodextrin-based nanosponge



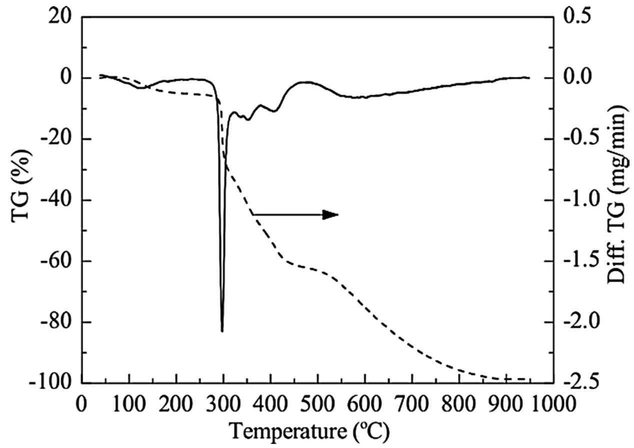


Fig. 3 TGA thermogram of β-cyclodextrin based nanosponge

The extent of solvent absorption by nanosponge was carried out by its swelling in ethanol at room temperature. The average equilibrium EtOH uptake by nanosponge (0.5%) was calculated by the following equation.

$$SW = (Wt - W0)/W0$$

SW is the swelling degree at a certain time,

Wt is the weight of the nanosponge after immersion in EtOH at time t,

W0 is the weight of the nanosponge at the beginning of testing.

The mesoporous nature of the synthesized nanosponge was studied by N_2 adsorption–desorption isotherms (Fig. 4). The Nitrogen adsorption–desorption isotherm exhibit the typical IV adsorption (according to the IUPAC classification). It presents a sharp adsorption step in the P/P0, which implies that the β-cyclodextrin-based nanosponge possesses a large pore size with narrow distributions. This was further confirmed by pore area and specific pore volume calculated by the Barrett–Joyner–Halenda (BJH) method from the adsorption branches (Fig. 4). The characteristic data on the sample are summarized in Table 1.

After successful characterization of the βCD.NS, its catalytic activity as a host catalyst was checked for the synthesis of 3-substituted indole moieties via Yonemitsu- type condensation reaction. In order to optimize the reaction conditions and attain the best catalytic activity, the reaction of 2-choloro benzaldehyde (0.14 gr, 1 mmol), indole (0.117gr, 1 mmol) and dimedone (0.14 gr, 1 mmol) was used as a model reaction (Scheme 2). The impression of solvent and the weight of the catalyst, on the rate of the reaction, were examined (Table 2). As can be discerned, 0.01 g catalyst, in ethanol under reflux conditions was beneficial for this reaction (Table 2, entry 6) and the use of the higher loading of the catalyst (0.02 or 0.03 g) did not have a discernible impact on the time and yield of the condensation reaction.

To prove the beneficial effect of the porous property of the nanocatalyst in the synthesis of the title compounds, the reaction was also done in the present of unpolymerized

Table 1 Adsorption/desorption data of βCD.NS

Pore structure parameters	BET	BJH
Surface area (m^2g^{-1})	10.9	12.07
Average pore diameter (nm)	4.86	1.21
Total pore volume ($cm^3\ g^{-1}$)	0.013	0.016

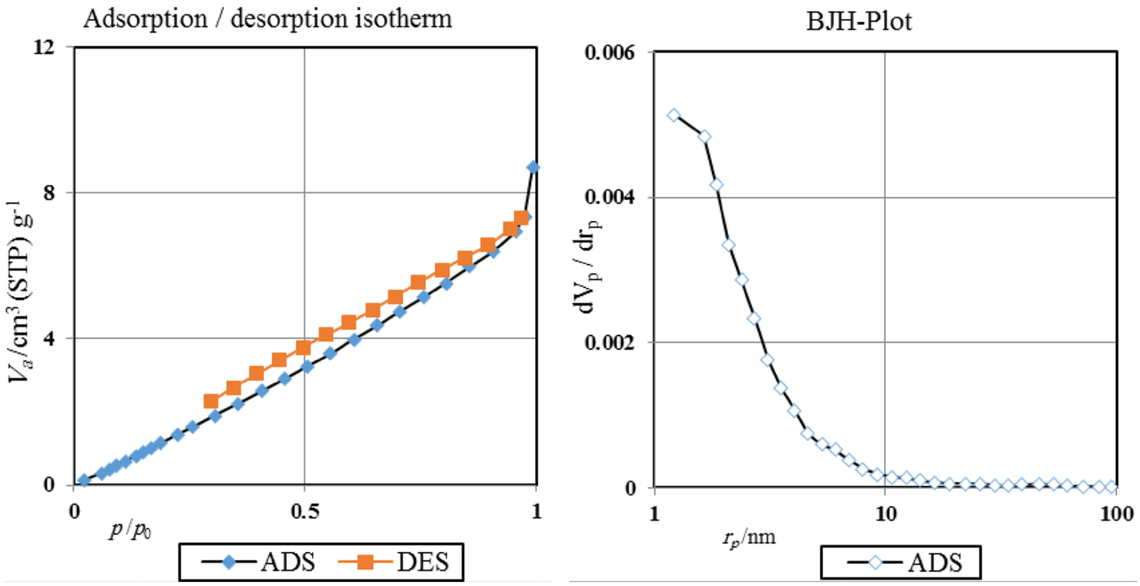
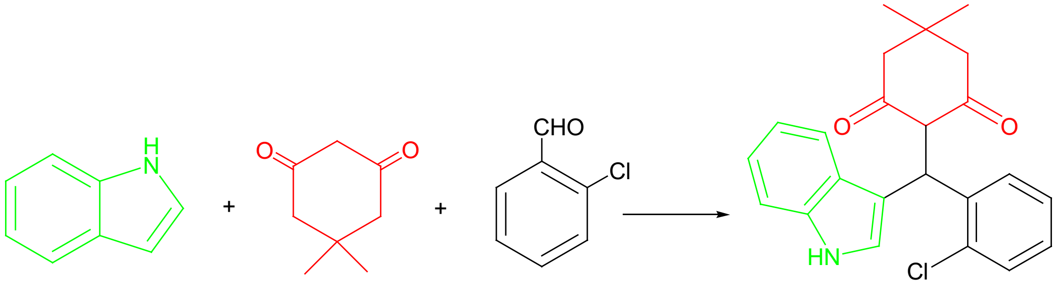


Fig. 4 Adsorption/desorption isotherm and BJH-Plot of βCD.NS



Scheme 2 Model Yonemitsu- type condensation reaction

Table 2 Optimization the reaction conditions

Entry	βCD.NS catalyst (%)	Condition (solvent/tem)[a]	Time (min)	Yield (%)
1	–	SF/100 °C	360	No reaction
2	0.01	SF/100 °C	360	Trace
3	–	EtOH/reflux	360	Trace
4	0.005	EtOH/reflux	15	56
5	0.01	H_2O/reflux	360	30
6	0.01	EtOH/reflux	5	97
7	0.02	EtOH/reflux	5	98
8	0.03	EtOH/reflux	5	98

SF solvent free

[a] Reaction conditions: 2-choloro benzaldehyde (0.14 gr, 1 mmol), indole (0.117 gr, 1 mmol) and dimedone (0.14 gr, 1 mmol)

beta-cyclodextrin in ethanol under reflux conditions. TLC analysis of the reaction mixture was shown that the reaction proceed in very poor yield (15%) even after long reaction time (360 min).

With the optimal reaction conditions in hand, consisting of a 1:1:1 molar ratios of an aromatic aldehyde, indole, activated methylene compounds (dimedone, thiobarbituric acid or 4-hydroxy coumarin), in the presence of βCD.NS (0.01 g) in ethanol under reflux conditions, the generality and synthetic scope of this coupling protocol were demonstrated through the synthesis of a series of 3-substituted indole moieties (Scheme 3).

The time is taken for efficiently one-pot multicomponent synthesis in 3-substituted indole derivatives as well as the isolated yields are recorded in Table 3.The purity determination of the products and reaction monitoring were accomplished by TLC and the 3-substituted indole products were

Scheme 3 Synthesis of 3-substituted indole moieties

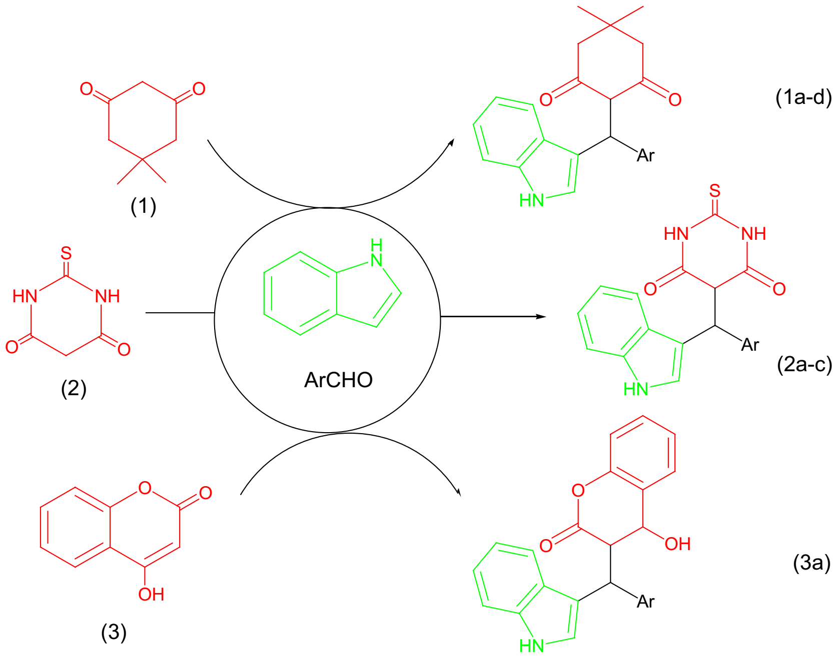
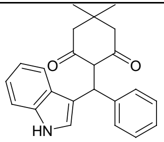
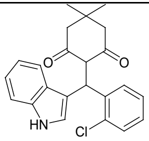
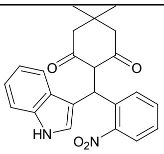
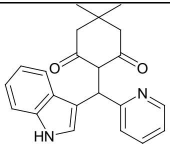
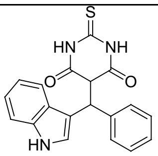
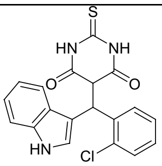
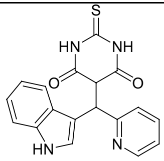
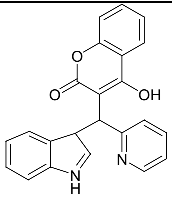
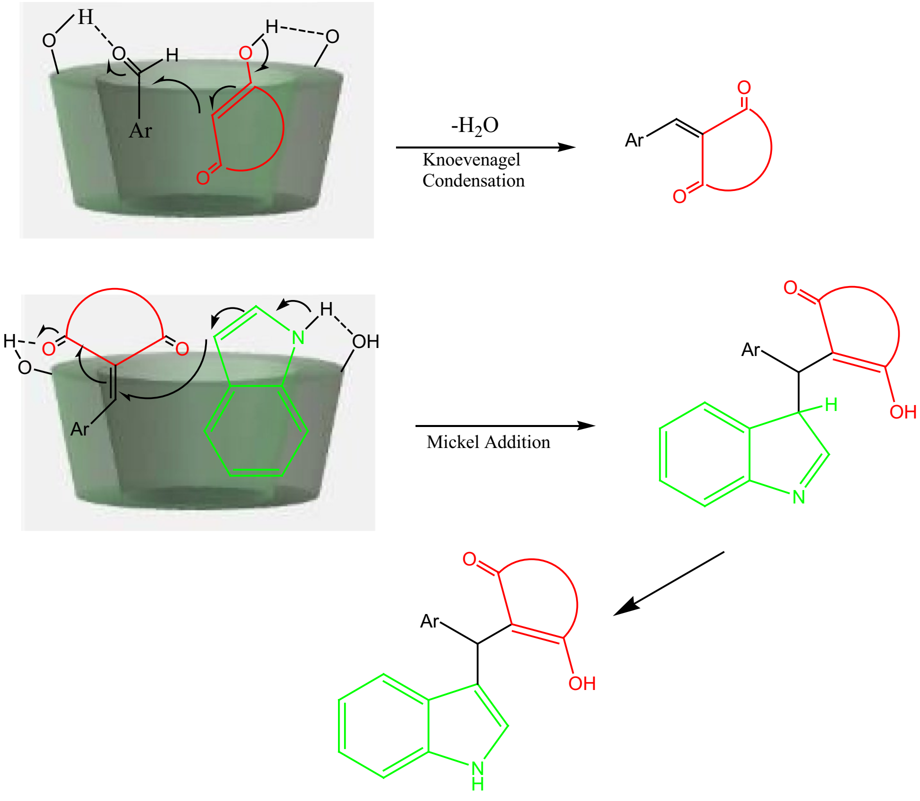


Table 3 Preparation of 3-substituted indole moieties catalyzed by βCD.NS in EtOH

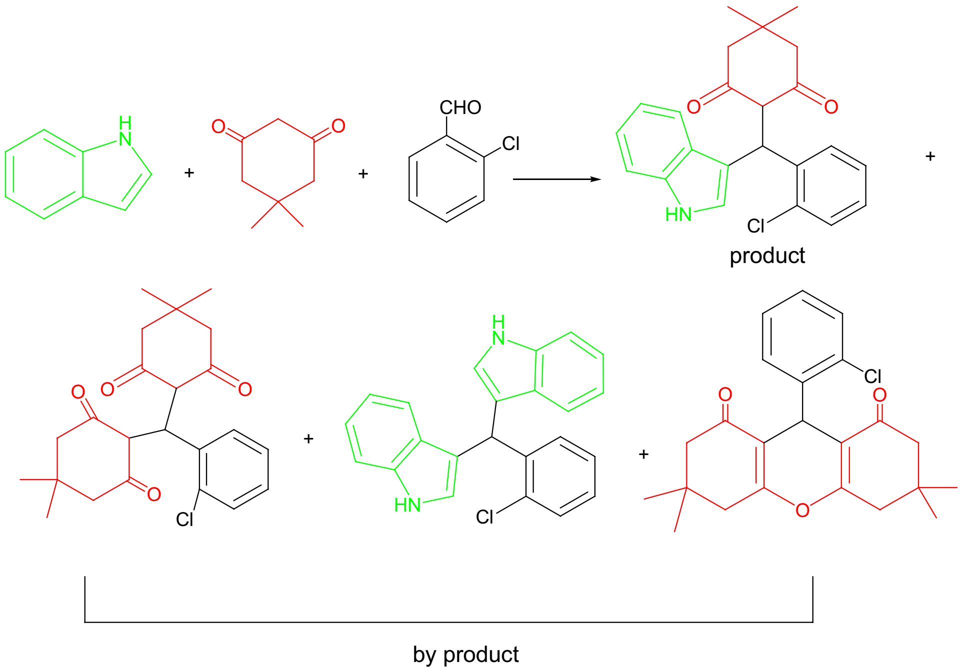
Product			
 1a Starting aldehyde: benzaldehyde Physical properties: white solid, m.p: 185-187 ^{0}C Time: 30 min, Yield: 82%	 1b Starting aldehyde:2-chloro benzaldehyde Physical properties: white solid, m.p: 225-227 ^{0}C Time: 5 min, Yield: 96%	 1c Starting aldehyde:2-nitro benzaldehyde Physical properties: white solid, m.p:190-192 ^{0}C Time: 15 min, Yield: 89%	 1d Starting aldehyde:pyridine-2-carbaldehyde Physical properties: white solid, m.p:217-220 ^{0}C Time: 10 min, Yield: 90%
 2a Starting aldehyde: benzaldehyde Physical properties: ted solid, m.p: 187-190 ^{0}C Time: 15 min, Yield: 85%	 2b Starting aldehyde:2-chloro benzaldehyde Physical properties: white solid, m.p: 218-220 ^{0}C Time: 30 min, Yield: 95%	 2c Starting aldehyde:pyridine-2-carbaldehyde Physical properties: brown solid, m.p:218220 ^{0}C Time: 5 min, Yield:90%	 3a Starting aldehyde:pyridine-2-carbaldehyde Physical properties: white solid, m.p:210-212 ^{0}C Time: 15 min, Yield: 95%

Reaction condition: aldehyde (1.0 mmol), activated methylene compounds (1.0 mmol), indole (1.0 mmol, 0.117 gr), and βCD.NS (0.01 gr) in EtOH (3.0 ml) under reflux conditions

Scheme 4 The proposed mechanism for one-pot three-component condensation of various aromatic aldehydes with activated methylene compounds and indole



3-substituted indole moieties



Scheme 5 The electrophilic reaction of aldehydes with two different nucleophiles in the absence of the catalyst

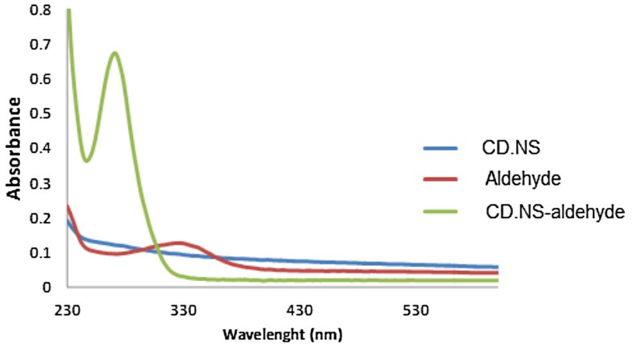


Fig. 5 The UV spectra of βCD.NS, aldehyde, and βCD.NS-aldehyde inclusion complex

characterized by comparison of their physical data, FT-IR, and ^{1}H and ^{13}CNMR spectra with known samples.

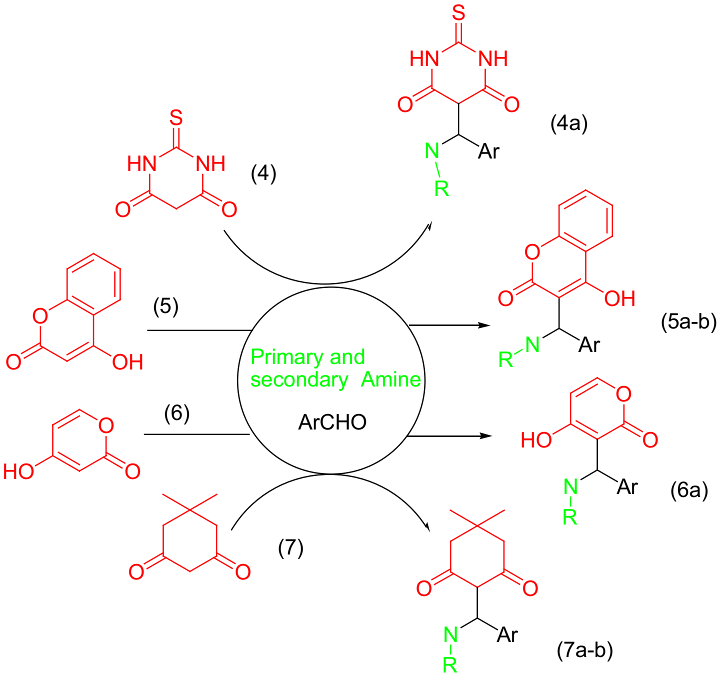
The regioselectivity and high reaction rate observed in the present method could be attributed to the fact that the hydrophobic central cavities of β-CD units and carbonate linkages in the βCD.NS polymer acted as micro-vessels and accommodated the nonpolar compounds. In addition, the hydrophilic exterior due to the outer OH of the β-CD cavity promoted the reaction via hydrogen bonding (Scheme 4).

The catalytic activity and selectivity of βCD.NS in the electrophilic reaction of aldehydes with two different nucleophiles, indole and dimedone, is established by the fact that in the absence of catalyst, the reaction was observed to proceed in very poor yields even after long reaction time and reaction media contaminated by side reactions of the aldehyde with the same nucleophiles (Scheme 5).

The host–guest interaction of βCD.NS with starting substrate, aromatic aldehyde, in EtOH has been investigated by UV spectroscopy. As shown in Fig. 5, by addition of βCD.NS to the reaction mixture, the observed spectral band (λ_{max}) for benzaldehyde at 327 nm was shifted to 267 nm. Similar changes were also reported by other authors [30, 31]. It should be point out that although the nanosponage is not soluble in ethanol, but due to its host–guest interaction with benzaldehyde in ethanol, the clear and gel type suspension is formed. The UV spectrum of this clear suspension was without any noise.

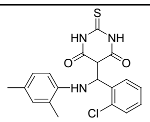
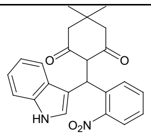
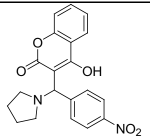
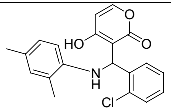
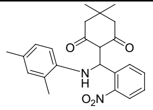
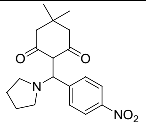
To extend the scope of the methodology, the indole was replaced by primary or secondary amines (Scheme 6). As shown in Table 4, pyrrolidine and 2,4 dimethylaniline reacted well with aromatic aldehydes and activated methylene compounds with the aid of βCD.NS to give the corresponding N- containing organic scaffold products in good to excellent yields ranging from 60 to 95%.

In the following, we were examined tertiary aromatic amine as a nucleophile with various activated methylene compounds and benzaldehyde, 2-nitro, and 2-chlorobenzaldehyde under optimized reaction conditions (Scheme 7). As shown in Table 5, *N, N*- dimethylaniline reacted well with aromatic aldehydes and activated methylene compounds by the attacker from a para position of the aromatic



Scheme 6 Three components reaction of an aromatic aldehyde activated methylene compound and primary or secondary amine

Table 4 Yonemitsu- type condensation catalyzed by βCD.NS in EtOH

Product		
 4a Starting aldehyde: 2-chloro-benzaldehyde Physical properties: white solid, m.p: 178-180 °C Time: 20 min, Yield: 95%	 1c Starting aldehyde:2-nitro benzaldehyde Physical properties: white solid, m.p:190-192 ^{0}C Time: 15 min, Yield: 91%	 5b Starting aldehyde: 4-nitro-benzaldehyde Physical properties: yellow solid, m.p: 212-215°C Time: 30 min, Yield: 86%
 6d Starting aldehyde: 2-chloro-benzaldehyde Physical properties: white solid, m.p: 78-80°C Time: 20 min, Yield: 78%	 7a Starting aldehyde: 2-nitro-benzaldehyde Physical properties: yellow solid, m.p: 192-194°C Time: 20 min, Yield: 90%	 7b Starting aldehyde: 4-nitro-benzaldehyde Physical properties: yellow solid, m.p: 200-202°C Time: 15 min, Yield: 85%

Reaction condition: aldehyde (1.0 mmol), activated methylene compounds (1.0 mmol), amines (1.0 mmol), and βCD.NS (0.01gr) in EtOH (3.0 ml) under reflux conditions

ring in the presence of βCD.NS and give the corresponding products in high to excellent isolated yields.

We believed that CD units of nanosponges not only forms the inclusion complex with starting materials and control the reaction selectivity but is also involved in the intermolecular hydrogen bonding with the guest to promote the condensation.

4 Conclusion

In the present study, the application of β-cyclodextrin-based nanosponges with a tiny mesh-like structure as porous three-dimensional nanocatalyst in the one-pot three component condensations of various aromatic aldehydes with activated methylene compounds and N- containing

Scheme 7 Three component condensation reaction of an aromatic aldehyde, activated methylene compound and *N, N*-dimethylaniline

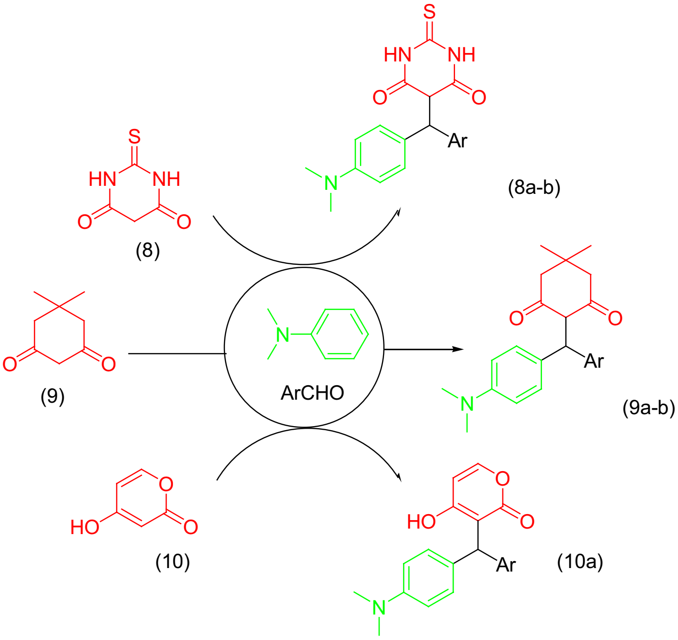
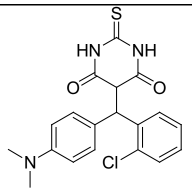
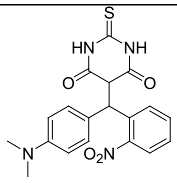
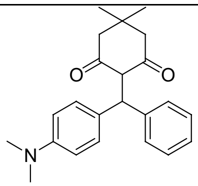
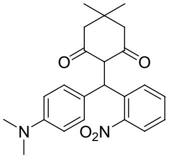
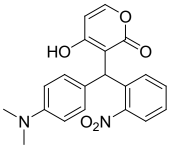


Table 5 Preparation of *N, N*- dimethylaniline containing organic scaffolds catalyzed by βCD.NS in EtOH

Product		
 8a Starting aldehyde: 2-chloro- benzaldehyde Physical properties: white solid, m.p: 260-262 °C Time: 20 min, Yield: 89%	 8b Starting aldehyde: 2-nitro- benzaldehyde Physical properties: green solid, m.p: 220-222 °C Time: 10 min, Yield: 93%	 9a Starting aldehyde: benzaldehyde Physical properties: white solid, m.p: 190-192 °C Time: 35 min, Yield: 92%
 9b Starting aldehyde: 2-nitro- benzaldehyde Physical properties: white solid, m.p: 171-173 °C Time: 15min, Yield: 95%	 10a Starting aldehyde: 2-nitro- benzaldehyde Physical properties: white solid, m.p: 235-237 °C Time: 20min, Yield: 90%	

Reaction condition: aldhyde (1.0 mmol), activated methylene compounds (1.0 mmol), *N, N*- dimethylaniline (1.0 mmol, 0.121 gr) and βCD.NS (0.01 gr) in EtOH (3.0 ml) under reflux conditions

nucleophiles was developed. This nanosponge catalyst afforded the privileged N- containing organic scaffolds in high isolated yields and in very short reaction times.

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