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Article

Ultrasound assisted multicomponent reactions: A green method for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines using β-cyclodextrin as a supramolecular reusable catalyst in water

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ABSTRACT

We demonstrate a superficial method for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines using β-cyclodextrin as a supramolecular, biodegradable, and reusable catalyst in aqueous medium. The reaction product is in excellent yield with moderate to excellent selectivity. The mechanistic transformation presumably proceeds *via* a one-pot, multicomponent cyclization of dimedone in the presence of aromatic aldehydes and aromatic amines/INH, undergoing a tandem Michael addition reaction. The proposed approach in this study provides a highly efficient and environmentally benign route to *N*-substituted 1,8-dioxo-decahydroacridines.

1. Introduction

Recently, the development of new processes that minimize pollution in the chemical industry has received considerable attention because of growing environmental concerns. In this regard, supramolecular catalysis using efficient heterogeneous catalysts have been used in various organic transformations. The ability of supramolecular catalysis to enhance catalytic activity provides an alternative to replace expensive catalysts with lesser quantities of inexpensive heterogeneous catalysts. Additionally, waste effluent is reduced or even absent, increasing the commercial viability. Catenanes, rotaxanes, crown ether, cyclodextrin (CD), and calixarenes are examples of emerging green and sustainable supports in heterogeneous catalysis.

Among these supramolecular catalysts, CD has drawn significant attention for the reason that, CDs [1,2] are a family of cyclic oligomers, composed of 1-4 linked β-D-glucose units. Such family members include the industrially produced α-CD (six glucose units), β-CD (seven units), and γ-CD (eight units) as well as several other oligosaccharides having increased glucose units. CDs are crystalline, homogeneous, non-hygroscopic molecules possessing a hollow truncated cone shape with all the secondary hydroxyl groups [O2)-H and O3)-H] crowning the outer edge, while all the primary hydroxyl groups [O6)-H] reside within the inner perimeter. The CD exterior, containing numerous hydroxyl groups, possesses hydrophilic characteristics, while the cavity—containing two rings of methine protons—is relatively hydrophobic.

Enormous interest in CDs lies in their unique structural topography, which enables them to form inclusion complexes with a wide variety of hydrophobic guest molecules [3]. The

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host-guest complexation exerts a profound effect on the physicochemical properties of the guest, such as solubility, stability and taste modification by masking unpleasant flavors and odors etc. Among various CDs, β-CD is an attractive conformation as a catalyst in regard to both an economical and environmental point of view. The most accessible β-CD is a cyclic oligosaccharide composed of seven α-1,4-linked glucopyranosyl units. Several members of β-CD are used industrially in pharmaceutical and associated applications [4]. The ability to use the hydrophobic cavity of β-CD to encapsulate bioactive molecules in water has drawn tremendous interest from the pharmaceutical industry because encapsulation improves the stability and bioavailability of drug molecules [5], apart from being non-toxic, metabolically safe [6], and readily recoverable and reusable.

Many biologically important molecular scaffolds can easily be synthesized from readily available starting materials with the help of multi-component reactions (MCRs) [7–10]. MCRs combine at least three simple building blocks *in situ*, and provide a diverse route to complexity in a limited number of reaction steps. MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to a large library of organic compounds with diverse substitution patterns.

The MCR of dimedone, aldehydes and aniline has produced numerous research studies since its discovery. The resulting acridine and acridine-1,8-dione derivatives are interesting heterocyclic compounds that have generated numerous publications in organic, pharmaceutical and medicinal chemistry fields because of their potential biological activities and presence in a variety of significant natural products and synthetic dye-stuffs. Such characteristics exhibit diverse pharmacological activities in areas relating to anti-malaria [11], anti-tumor [12], anti-cancer [13], fungicidal [14], cytotoxic [15], anti-multidrug-resistant [16], antimicrobial [17], and are widely prescribed as calcium β-blockers [18,19]. Additionally, 1,8-dioxo-decahydroacridines were created to act as laser dyes [20,21] and used as photoinitiators [22].

The significance of such heterocycles in chemical and biological applications has been well established, and as a result, the ready and efficient synthesis of these molecules has attracted considerable attention from the synthetic organic community with numerous reports detailing methods for the synthesis of acridine and acridine-1,8-dione derivatives. Method development has included the use of dimedone, aldehydes and various nitrogen sources, such as urea [23], hydroxylamine [24], ammonium acetate on basic alumina [25], ammonium bicarbonate [26], ammonium hydroxide and various appropriate amines or ammonium acetate [27]. Additional methods have included conventional heating of organic solvents in the presence of Amberlyst-15 [28], benzyltriethyl ammonium chloride (TEBAC) [29], the use of microwave irradiation [30,31], and using ionic liquids [32,33]. Furthermore, 9,10-diarylacridine-1,8-diones have also been prepared using *p*-dodecylbenzenesulfonic acid (DBSA) [34], $Zn(OAc)_2{\cdot}2H_2O$, ammonium chloride or *L*-proline [35], proline [36], CAN [37] and the sulfonated organic heteropoly acid salts, $[MIMPS]_3PW_{12}O_{40}$ and $[TEAPS]_3PW_{12}O_{40}$ [38]. However, these methodologies suffer from one or more shortcomings, such as low yield, prolonged reaction time, use of toxic organic solvents and employ costly and hazardous catalysts as well as cumbersome work-up procedures. Therefore, introducing clean processes and utilizing eco-friendly catalysts, which can be easily recycled at the end of the reaction, have received increasing attention.

Conversely, in comparison with conventional thermal heating, ultrasound irradiation has some important advantages: improved yields with enhanced product yield and selectivity, substantial decreases of reaction time, lower costs and easier handling and processing. At the same time, in many cases, reactions under ultrasound irradiation are considered to be environmentally friendly as they require only a limited quantity of solvent and are more energy efficient [39]. Additionally, ultrasonic irradiation provides minimal side reactions [40].

The demand for an environmentally benign procedure utilizing a heterogeneous and reusable catalyst led our investigations to develop a safe alternative method for the synthesis of acridine-1,8-dione derivatives. Bearing the above points in mind, we believe this to be the first ever report on a sonically enhanced one-pot multicomponent reaction in aqueous media using the environmentally benign β-CD as a supramolecular catalyst.

2. Experimental

2.1. General

All chemicals were purchased and used by further purification. Melting points were determined on a open capillary tube and are uncorrected. Progress of the reaction was monitored by thin layer chromatography (TLC) on Merck's silica plates. ^{1}H NMR spectra were recorded on Bruker Avance 100 MHz instruments using TMS as internal standard. ^{13}C NMR spectra were recorded on Bruker AvII-400 MHz instruments. Elemental analysis was recorded on elemental analyzers Euro-E 3000.

2.2. Reactions

All the reactions were carried out in Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath (Built-in heating, 30–80 °C there-mostatically adjustable). The reaction vessel placed inside the ultrasonic bath containing water.

General procedure for the synthesis of *N*-substituted decanhydroacridine-1,8-diones **4a**–**4k**. The mixture of 5,5-dimethylcyclohexane-1,3-dione **1a** (1.98 g, 2 mmol), aldehyde **2a** (700 mg, 1 mmol) and aniline **3a** (650 mg, 1 mmol) were added in β-cyclodextrin (10 mol%) solution containing water (20 mL). The resulting mixture was stirred under ultrasonication at 80 °C. After completion of the reaction (monitored by TLC), reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated brine solution and dried over anhydrous sodium sulphate. The combined

organic layer was evaporated under reduced pressure and thus obtained crude product was further purified by crystallization from hot ethanol. The aqueous layer was then cooled to 0 °C to recover β-CD reappeared as white solid. Thus the obtained solid mass then filtered and washed with water to recover β-CD. The recovered β-CD was reused for 3–4 consecutive runs in this reaction without any significant loss in yield and activity. The product was confirmed by melting point, ^{1}H NMR, ^{13}C NMR, elemental analysis and the results obtained are summarized in (Table 3).

General procedure for the synthesis of *N*-substituted decanhydroacridine-1,8-diones **4l–4t**. The mixture of 5,5-dimethylcyclohexane-1,3-dione **1a** (1.31 g, 2 mmol), aldehyde **2a** (500 mg, 1 mmol) and isoniazid **3a** (640 mg, 1 mmol) were added in β-cyclodextrin (10 mol%) solution containing water (20 mL). The resulting mixture was stirred under ultrasonication at 80 °C. After completion of the reaction (monitored by TLC), reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated brine solution and dried over anhydrous sodium sulphate. The combined organic layer was evaporated under reduced pressure and thus obtained crude product was further purified by crystallization from hot ethanol. The aqueous layer was then cooled to 0 °C to recover β-CD reappeared as white solid. Thus the obtained solid mass then filtered and washed with water to recover β-CD. The recovered β-CD was reused for 3-4 consecutive runs in this reaction without any significant loss in yield and activity. The product was confirmed by melting point, ^{1}H NMR, ^{13}C NMR, elemental analysis and the results obtained are summarized in Table 3.

3. Results and discussion

3.1. Synthesis

In this study, we describe for the first time, a sustainable one-pot synthesis of *N*-substituted 1,8-dioxo-decahydroacridines **4a–4t** (Scheme 1) under ultrasonication at 80 °C in aqueous conditions using β-CD as a reusable supramolecular catalyst.

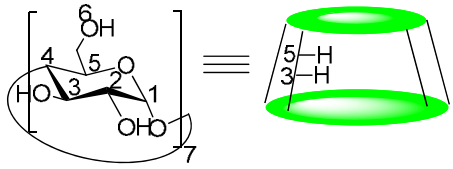
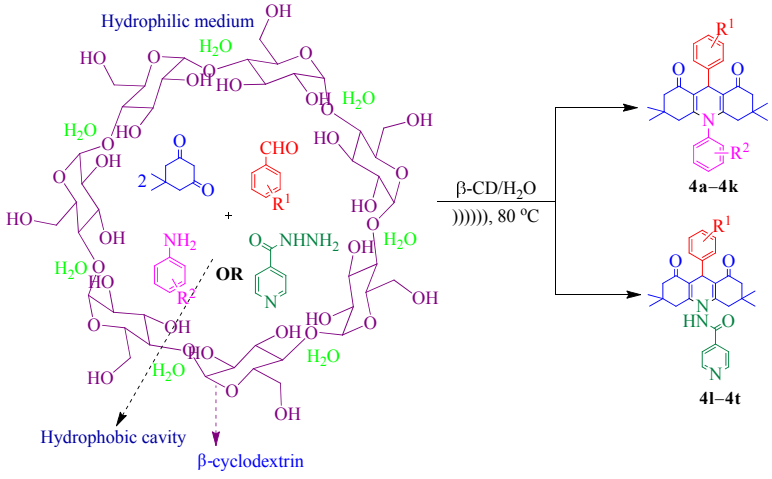


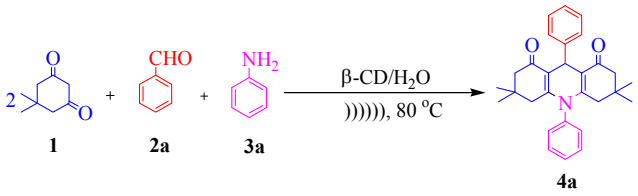
Fig. 1. Schematic of the β-CD structure.

Reaction condition matrices—with respect to solvent and catalyst—are typically governed on their environmental impact and today's environmental concerns push industrial and academic processes away from solvents to environmentally benign water. The chemical and physical properties of water enhance selectivity and reactivity in reactions, which cannot be matched using organic solvents [41–44]. However, dissolving many organic compounds in water is difficult and for this reason, the majority of reactions cannot proceed easily in aqueous media [45]. One way to improve the solubility of substrates in water is the incorporation of water-soluble macrocycles as inverse phase transfer catalysts. CDs, which encapsulate organic compounds in aqueous media have been found to enhance the rate of water mediated reactions because of hydrophobic effects. β-CD is a cyclic oligosaccharide possessing a hydrophobic cavity and several hydroxyl groups in two distinct regions (Fig. 1) [46,47]. These structural characteristics allow substrates to bind selectively through non-covalent interactions. Being soluble in water, non-toxic, and readily available, β-CD is often used as an additive for various chemical reactions in water [48–57].

In this study, a model reaction was conducted by reacting dimedone (**1**), benzaldehyde (**2a**) and aniline (**3a**) in water at room temperature in the absence of β-CD to obtain the corresponding *N*-substituted acridine-1,8-dione, albeit at lower yields (25%) and longer reaction times. The poor solubility of dimedone and aniline in water at elevated temperature resulted in the formation of undesired products. When the same reaction was performed in the presence of β-CD, at room temperature, the product was obtained in moderate yield (41%). However, the controlled experiment using β-CD as a supramolecular catalyst at 60–80 °C resulted in an excellent product yield (94%) at 10 mol% of β-CD within 62 min without column



Scheme 1. Synthesis of *N*-substituted 1,8-dioxo-decahydroacridines.



Scheme 2. Standard model reaction.

chromatographic purification (Scheme 2).

This result indicates that the catalyst plays a critical role in the reaction. Method development in this study, shows the merit of CD, as for the first time, various CDs, such as α-CD, β-CD and γ-CD were examined for their efficiency as supramolecular catalysis. The results are tabulated in Table 1.

Of these CDs (Table 1), β-CD was found to be the superior mediator and gave moderate to excellent yield of the desired substituted 1,8-dioxo-decahydroacridines. As β-CD is inexpensive and readily available, when compared with α-CD and γ-CD, β-CD was selected as the catalyst to perform the reaction.

Furthermore, we studied the three-component condensation of dimedone (2 mmol), benzaldehyde (1 mmol) and aniline (1 mmol) to optimize the reaction conditions with respect to temperature, time, catalyst/substrate molar ratio and catalyst reusability.

Temperature has an important role on product yield. At lower temperatures product formation is observed at trace concentrations and required longer reaction times. Increasing the temperature from room temperature to 80 °C resulted in increased yields along with decreasing reaction times. All proceeding reactions were performed at the elevated temperature of 80 °C (Table 2). The fixed catalyst loading was evaluated in the model reaction (Table 2, entry 1) at 80 °C in water. The optimum result was obtained at 10 mol% of β-CD affording 94% yield within 62 min under sonication in water and the use of excess catalyst had no impact on either the rate of reaction or on product yield.

The effect of solvent on the yield of 1,8-dioxo-decahydroacridines is given in Table 3. The reaction among dimedone, benzaldehyde and aniline was chosen as a model reaction for investigating the effect of solvent. Among all the solvents, water was found to play an effective role in this transformation affording the highest yields (Table 3, entry 6). Therefore, water was selected as the optimum solvent for this transformation. Another reason for this is that water is a green solvent.

After obtaining the optimized reaction conditions, thereafter the investigation studied the reaction between a series of aromatic aldehydes and aromatic amines or isoniazide with 1,3-cyclohexanediones. To assess the general applicability of this method under the given optimized reaction conditions, a wide range of divergent aldehydes and anilines possessing varying substituents, in the presence of two equivalents of 1,3-cyclohexanediones, were allowed to undergo this three-component condensation. The nature of the functional group on the aldehyde/aniline aromatic rings exerted a slight influence on the reaction time. –Cl, –F, –Me, –OMe and –NO_2 were found to be compatible under the optimized reaction conditions. Heteroaromatic aldehydes, such as 2-furan-2-carbaldehyde was equally amenable to these conditions (Table 2, entry 11). An attempt to synthesize 1,8-dioxo-decahydroacridine by reacting the aliphatic aldehyde, propionaldehyde, was not successful as the product yield was very low even after prolonged reaction time (Table 2, entry 20). On the basis of the above results, we suggest that the internal hydrophobic cavity of β-CD forms an inclusion complex with the aldehyde and dimedone more effectively and enhances the rate of reaction resulting in an increase in the product yield and a decrease in

Table 1
Optimization of reaction conditions for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines using various CD catalysts.

Catalyst	Time (h)	Isolated yield (%)
α-CD	10–12	40–50
β-CD	1	80–94
γ-CD	6–8	60–70

Reaction conditions: dimedone 2 mmol, benzaldehyde 1 mmol, aniline 1 mmol.

Table 2
Synthesis of *N*-substituted decahydroacridine-1,8-diones in the presence of β-CD in water under ultrasonication at 80 °C.

Entry	Product	R^1	R^2/INH	Time (min)	Isolated yield (%)	M.P. (°C) [37,38,58]
1	**4a**	–H	–H	62	93.57	254–257
2	**4b**	*p*-Br	–H	74	87.35	>300
3	**4c**	*p*-Cl	–H	70	80.12	242–244
4	**4d**	*p*-OMe	–H	68	82.04	219–223
5	**4e**	*p*-OH	*p*-F	70	81.02	263–265
6	**4f**	–H	*p*-OMe	77	72.36	216–218
7	**4g**	*p*-Cl	*p*-OMe	80	93.45	252–255
8	**4h**	*m*-NO_2	–H	81	91.55	278–280
9	**4i**	*p*-OMe	*p*-Me	79	85.27	280–284
10	**4j**	*p*-F	*p*-F	61	89.11	110–113
11	**4k**	2-Furan	–H	70	88.09	278–280
12	**4l**	–H	INH	65	88.77	148–150
13	**4m**	*p*-Cl	INH	62	90.18	96–98
14	**4n**	*p*-OMe	INH	68	94.56	99–102
15	**4o**	*m*-OMe	INH	63	85.12	252–254
16	**4p**	*p*-F	INH	62	88.23	109–111
17	**4q**	*p*-NO_2	INH	65	86.58	92–94
18	**4r**	*p*-Me	INH	62	88.30	85–87
19	**4s**	*m*-Me	INH	61	90.12	153–155
20	**4t**	Propionaldehyde	INH	90	56.35	280–282

Reaction conditions: dimedone 2 mmol, benzaldehyde 1 mmol, aniline 1 mmol, β-CD 10 mol%, water, ultrasonication, 80 °C, 62 min.

Table 3
Optimization of solvent for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines.

Entry	Solvent	α-Cyclodextrin		β-Cyclodextrin		γ-Cyclodextrin	
		Time (h)	Yield* (%)	Time (min)	Yield* (%)	Time (h)	Yield* (%)
1	Ethanol	7.2	38	78	86	5.3	78
2	Aq. ethanol	8	41	75	89	4.5	72
3	CH_3CN	9	48	78	78	4.0	68
4	DMF	8	40	72	67	5.0	55
5	THF	8.2	35	74	71	5.5	60
6	Water	8.8	45	62	94	5.0	75

Reaction conditions: dimedone 2 mmol, benzaldehyde 1 mmol, aniline 1 mmol, β-cyclodextrin 10 mol%, 80 °C. * Isolated yield.

reaction time. The ultrasound irradiation technique was also established to be compatible with all listed substrates (Table 2). Representative results are summarized in Table 2. Product formation was confirmed by ^{1}H NMR, ^{13}C NMR, elemental analysis and melting point data.

3.2. Catalyst recycling

The main advantages of β-CD as a catalyst were observing clean reactions without any side product formation, the ability to reuse the catalyst, and efficient recovery. Reusability was studied by three cycles, comparing back with the fresh catalyst in the synthesis of 1,8-dioxo-decahydroacridines. Each cycle showed that the catalyst was almost quantitatively recovered and after the second and third catalyst cycle product yield was 89% and 92% of the fresh cycle yield, respectively (Fig. 2).

3.3. Reaction mechanism

β-CD has a rigid conical molecular structure with a hydrophobic interior and a hydrophilic exterior. The internal hydrophobic cavity is the key structural feature of the β-CDs. It provides the ability to complex and holds a wide variety of inclusion molecules. To account for the very efficient catalysis by β-CD of this tandem reaction, wherein supramolecular catalyzed reactions are involved, it is proposed that β-CD with its seven free primary –OH groups synergistically behave as an efficient host and supramolecular β-CD catalyst (Fig. 1). In aqueous solutions, hydrophobic bonding in β-CD is accompanied by a favorable entropy change (ΔS) during the transfer of the guest molecules—dimedone, aldehyde and aniline from aqueous media to a polar media, i.e. the β-CD cavity. Large favorable ΔS and small unfavorable ΔH changes are observed during the time of transfer. The favorable change in entropy to form hydrophobic bonding is responsible for stabilization of the host-guest complex, i.e. complexation of CD with a polar guest molecule (dimedone, aldehyde or aniline). No covalent bonds are formed or broken during the complex formation and molecules in the complex were in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules

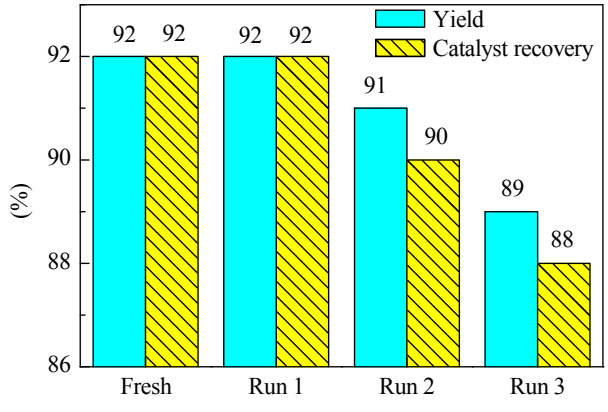
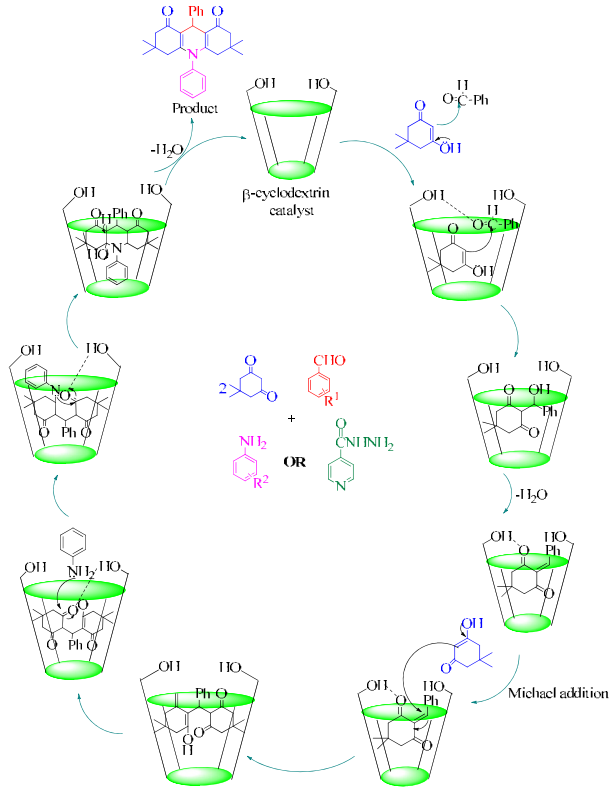


Fig. 2. Reuse and recovery of β-cyclodextrin and its effect on yield.



Scheme 3. Plausible mechanism for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines.

from the cavity, electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, release of conformational strain and charge-transfer interactions.

A plausible mechanism is detailed in Scheme 3. In the first step, the aldehyde binds to the β-CD cavity. Activation of a proton from dimedone by β-CD catalyzes a Knoevenagel condensation reaction with the carbonyl group to give the 2-arylidene dimedone. The cooperative enzyme-like binding of these intermediates ensures a tighter fit into the cavity and facilitates further reactions, namely Michael addition of a second dimedone to 2-2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)phenyl) methyl)-5,5-dimethylcyclohexane-1,3-dione activated by a dimedone proton followed by cyclization with aniline to give the final product (Scheme 3).

4. Conclusions

We have disclosed a clean and efficient procedure for the synthesis of pharmacologically significant 1,8-dioxo-decahydroacridine derivatives *via* one-pot three-component condensation of dimedone, benzaldehyde and aniline/INH using β-CD as a supramolecular catalyst in aqueous medium. This rate enhancement is preliminary because of superior hydrophobic binding of β-CD to hydrophobic substituents, which in turn enhances the reactivity of substrates. The task-specific β-CD catalyst used is biodegradable, recyclable/recoverable and purely environmentally benign. Furthermore, the catalyst is easy to prepare and does not require any harmful solvent/chemicals. Other prominent features are: shorter reaction

times, no volatile solvent effluents formed and no toxic by-products are generated during aqueous work-up. All of the above green aspects offer advantages over existing reported methods in the formation of such commercially valued products.

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Graphical Abstract

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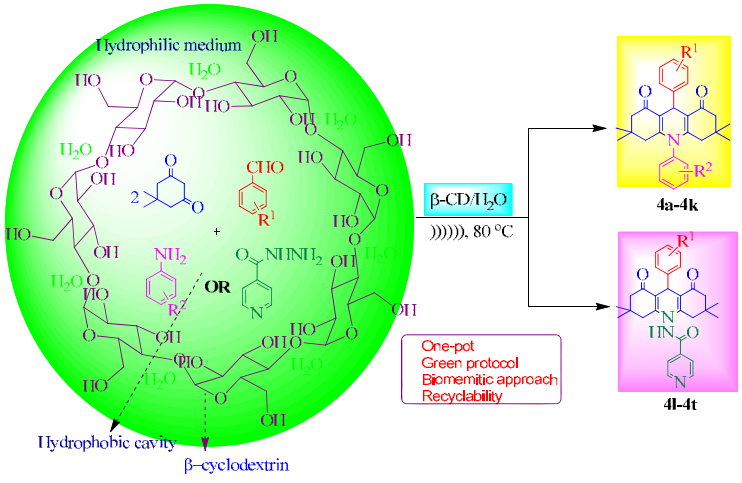

A mild and environmentally benign protocol was developed using β-cyclodextrins as a catalyst to significantly improve the yield of *N*-substituted 1,8-dioxo-decahydroacridine derivatives. The β-cyclodextrin employed in the multi-component reaction satisfies the requirements for green chemistry.

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