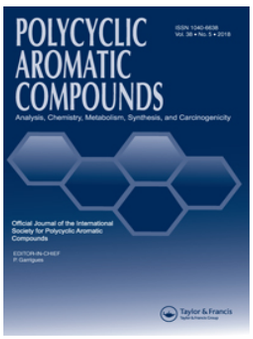

Polycyclic Aromatic Compounds

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpol20

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To cite this article: Farzaneh Mohamadpour (2020): Supramolecular β-cyclodextrin as a Biodegradable and Reusable Catalyst Promoted Environmentally Friendly Synthesis of Pyrano[2,3-*d*]pyrimidine Scaffolds *via* Tandem Knoevenagel–Michael–Cyclocondensation Reaction in Aqueous Media, Polycyclic Aromatic Compounds, DOI: 10.1080/10406638.2020.1852274

To link to this article: https://doi.org/10.1080/10406638.2020.1852274

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Supramolecular β-cyclodextrin as a Biodegradable and Reusable Catalyst Promoted Environmentally Friendly Synthesis of Pyrano[2,3-*d*]pyrimidine Scaffolds *via* Tandem Knoevenagel–Michael–Cyclocondensation Reaction in Aqueous Media

Farzaneh Mohamadpour

School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran

ABSTRACT

The catalytic activity of supramolecular β-cyclodextrin as a biodegradable and reusable catalyst was studied for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds in aqueous media. This green and eco-safe domino approach revealed simplicity, use of biodegradable and highly efficient catalyst, avoidance of toxic organic solvents, versatility and high stability of the catalyst combined with excellent yields, easy work-up procedures with no necessity of chromatographic purification steps, the reusability of the catalyst and being in agreement with the green chemistry protocols, and time-saving aspects of the reaction suggest that this method presents real alternatives over conventional reaction protocols.

ARTICLE HISTORY
Received 31 August 2019
Accepted 6 November 2020

KEYWORDS
Aqueous media; β-cyclodextrin (β-CD); pyrano[23-d]pyrimidine scaffolds; reusable catalyst; easy work-up

Introduction

Among various cyclodextrins, β-CD is attractive as a catalyst since it is useful both from an economic and environmental point of view, apart from being nontoxic, metabolically safe, and readily recoverable and reusable, β-cyclodextrin-mediated reactions in water have been found to be a useful tool for economical as well as environmental points of view.[1–3]

Most of the biologically active potential drugs used currently are synthetic organic molecules that often contain a heterocyclic ring.[4] Despite recent advances in drug-designing molecular biology and combinatorial synthetic methodology, the range of easily accessible and suitable functionalized heterocyclic motifs toward the synthesis of structurally diverse compounds is rather limited.[5] Pyrano[2,3-*d*]pyrimidine derivatives, including attached rings of a uracil and a pyran, are analogues of uracil, which have different pharmacological properties such as antiallergic,[6] antihypertensive,[7] cardiotonic,[8] bronchiodilator,[9] antibronchitic,[10] and antitumor activities.[11] Considering the importance of such compounds, many methods for synthesis of pyrano[2,3-*d*]pyrimidine scaffolds have been reported. The conventional synthesis method involves condensation of barbituric acid/1,3-dimethylbarbituric acid with aldehyde derivatives and malononitrile using different catalytic systems such as DAHP,[12] DABCO-based ionic liquids,[13] L-proline,[14] iron ore pellet,[15] nano-sawdust-OSO_3H,[16] Al-HMS-20,[17] TSA/$B(OH)_3$,[18] Mn/ZrO_2,[19] cellulose-based nanocomposite,[20] DBA,[21] TBAB,[22] Fe_3O_4@SiO_2@$(CH_2)_3$-Urea-SO_3H/HCl,[23] Et_3N-Ultrasonic,[24]

CONTACT Farzaneh Mohamadpour mohamadpour.f.7@gmail.com School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran.

Supplemental data for this article is available online at https://doi.org/10.1080/10406638.2020.1852274.

$ZnFe_2O_4$ nanoparticles,[25] microwave,[26] nickel nanoparticles,[27] $CaHPO_4$,[28] Zn[(L)proline]$_2$,[29] theophylline,[30] uric acid,[31] and Fe_3O_4@PVA-Cu nanocatalyst.[32] However, most of these synthetic approaches have restrictions, including the utilization of intense acidic or basic conditions, difficult work-up, toxic or expensive catalysts or reagents, low yields and prolonged reaction times.

Green chemistry is an increasingly important aspect of chemical research devoted to minimize the use and generation of hazardous substances, organic solvents, and toxic catalysts on the environment.[33] In continuation of our studies of efficient and eco-safe catalysts[34–37] using multi-component reactions,[38–44] preparation of various biologically active pyrano[2,3-*d*]pyrimidine scaffolds are one of considerable interest and we report herein an environmentally friendly, biodegradable and reusable *β*-cyclodextrin-catalyzed procedure for synthesis of pyrano[2,3-*d*]pyrimidine scaffolds *via* three-component Knoevenagel-Michael addition cyclocondensation reaction of aryl aldehyde derivatives, malononitrile with barbituric acid/1,3-dimethylbarbituric acid gave the expected products in excellent yields and short reaction times, which might solve some cost problems in industry. Subsequently, we studied the recyclability of the *β*-cyclodextrin for the above reaction. However, the catalyst can be recycled at least three times without significant decrease in catalytic activity, which makes it highly beneficial to address the industrial needs and environmental concerns.

Experimental

General

Melting points of all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra, was recorded on a Bruker DRX-300 Avance and Bruker DRX-400 Avance instrument with DMSO-d_6 as solvents. In this article, all reagents and solvents purchased from Merck, Fluka, and Acros chemical companies were used without further purification.

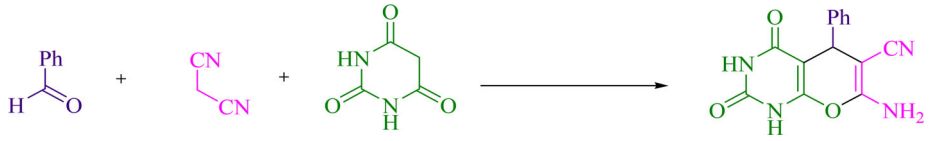
General procedure for preparation of pyrano[2,3-d]pyrimidine scaffolds (4a-s)

A mixture of aryl aldehyde derivatives (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), barbituric acid/1,3-dimethylbarbituric acid (**3**, 1.0 mmol), *β*-cyclodextrin (10 mol %), and 5 mL H_2O was heated at 80 °C for appropriate time. After completion of the reaction, as monitored by TLC using *n*-hexane:ethyl acetate (8:3) as eluent, the mixture was cooled to RT, the precipitated product was filtered and washed with ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (4a-s). The products have been characterized by melting points and ^{1}H NMR spectroscopy. Supporting information associated with this article can be found in the online version.

Results and discussion

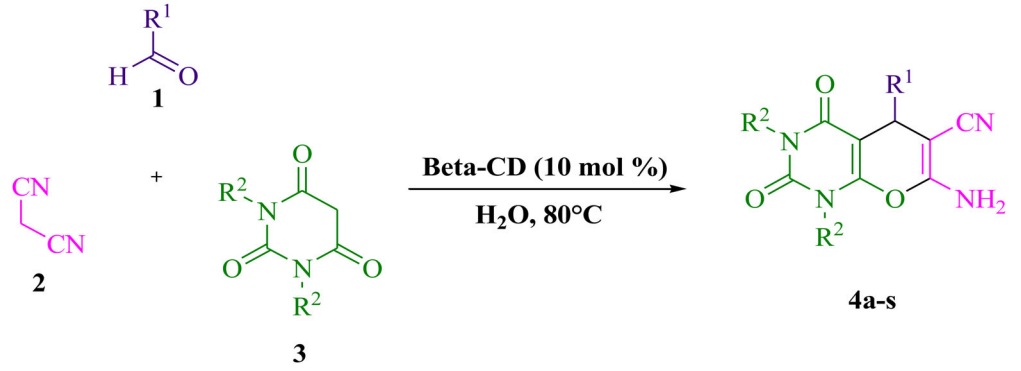
Initially, catalytic activity of supramolecular *β*-cyclodextrin was tested in a model system in the three-component reaction between a mixture of benzaldehyde (1 mmol), malononitrile (1 mmol), and barbituric acid (1 mmol). In the absence of a catalyst, only a trace of product was obtained at 80 °C and RT for a reaction time of about 360 min (Table 1, entries 1 and 2), which indicated that the catalyst should be necessary for this transformation. The optimized conditions were determined by changing the effecting parameters of the reaction such as the amount of the catalyst, solvent, and the temperature. Thereafter, for determining the optimum quantity of catalyst, the model reaction was performed in the presence of different amounts of *β*-cyclodextrin. Various loadings of catalyst, including 5, 10, and 15 mol%, were screened in our model reaction. By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower

Table 1. Optimization of the reaction condition on the synthesis of **4a**[a].



Entry	β-CD (mol %)	Solvent/conditions	Time (min)	Isolated yields (%)
1	Catalyst free	H_2O, 80 °C	360	Trace
2	Catalyst free	H_2O, rt	360	Trace
3	5	H_2O, 80 °C	20	71
4	**10**	**H_2O, 80 °C**	**10**	**93**
5	10	EtOH, reflux	30	74
6	10	H_2O/EtOH (1:1), reflux	20	80
7	10	THF, reflux	45	62
8	10	DMF, 80 °C	55	67
9	10	Solvent free, 80 °C	85	25
10	10	MeOH, reflux	60	48
11	10	H_2O, rt	480	73
12	10	H_2O, 40 °C	240	81
13	10	H_2O, 60 °C	120	85
14	10	H_2O, reflux	10	94
15	15	H_2O, 80 °C	10	93

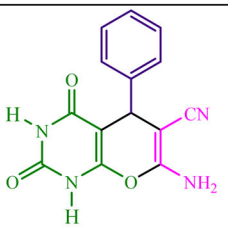
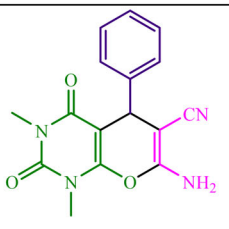
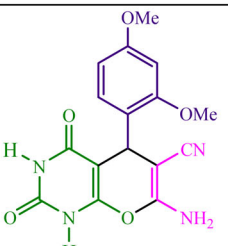
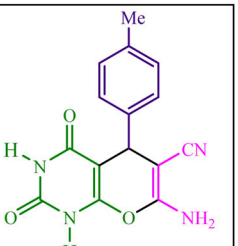
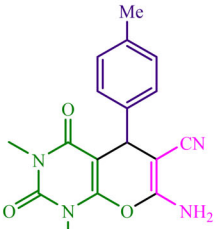
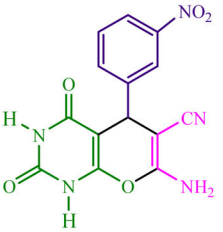
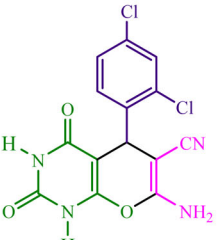
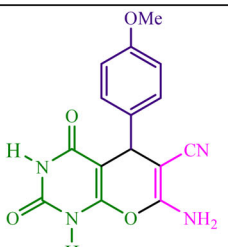
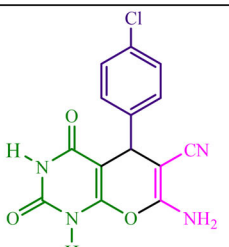
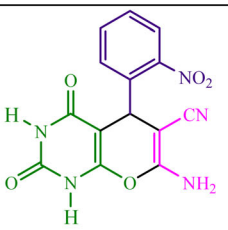
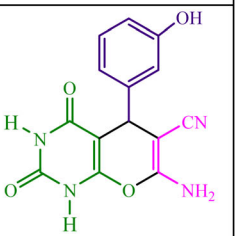
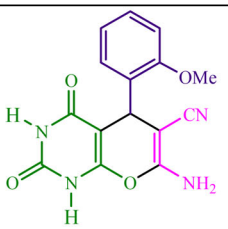
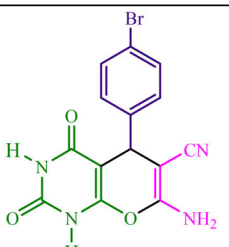
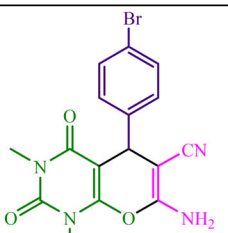
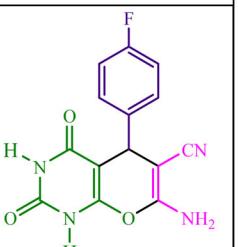
[a]Reaction conditions: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), barbituric acid (1.0 mmol), solvent (5 mL), and β-CD in various solvents and temperatures.



Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

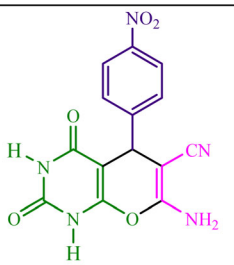
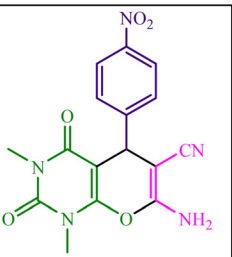
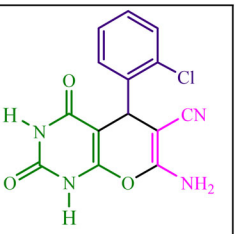
yield (Table 1, entry 3). By increasing the amount of catalyst from 5 to 10 mol%, the reaction time is reduced and the yield of the product increases (Table 1, entries 3, 4). So, among them, 10 mol % of β-CD was proven to be the most efficient catalyst for this reaction (Table 1, entry 4). The larger amount of the catalyst did not improve the yields (Table 1, entry 15). In the absence of solvent and in the presence of 10 mol% of the catalyst and at 80 °C, the reaction was investigated, which resulted in the production of a reaction product with low yield and longer reaction time, indicating that the solvent plays an effective role in the development of this reaction (Table 1, entry 9). Therefore, choosing an appropriate solvent has crucial importance for the successful synthesis. To search for the optimal solvent, the model reaction was investigated in the presence of 10 mol% of β-CD using various solvents. The results indicated that a low yield of the desired product was obtained when EtOH, H_2O/EtOH, THF, DMF and MeOH were used as solvents. The best yield was obtained when the reaction was performed in H_2O and it accelerated the reaction compared with other solvents and solvent-free condition. The results of these

Table 2. Supramolecular β-cyclodextrin catalyzed synthesis of pyrano[2,3-*d*]pyrimidine scaffolds[a].

 **4a** (10 min, 93%) Mp. 225-227 °C Lit. 224-225 °C [13]	 **4b** (10 min, 91%) Mp. 237-239 °C Lit. 237-238 °C [18]	 **4c** (20 min, 83%) Mp. 228-230 °C Lit. 227-228 °C [15]	 **4d** (15 min, 89%) Mp. 224-226 °C Lit. 226 °C [18]
 **4e** (15 min, 90%) Mp. 207-209 °C Lit. 205-207 °C [18]	 **4f** (25 min, 84%) Mp. 167-169 °C Lit. 169-170 °C [15]	 **4g** (10 min, 92%) Mp. 260-261 °C Lit. 259-261 °C [16]	 **4h** (30 min, 81%) Mp. 239-241 °C Lit. 241-242 °C [14]
 **4i** (20 min, 87%) Mp. 273-275 °C Lit. 272-274 °C [16]	 **4j** (25 min, 85%) Mp. 235-237 °C Lit. 235-237 °C [18]	 **4k** (10 min, 95%) Mp. 256-258 °C Lit. 254-256 °C [13]	 **4l** (25 min, 80%) Mp. 159-161 °C Lit. 158-160 °C [14]
 **4m** (15 min, 89%) Mp. 230-232 °C Lit. 230 °C [29]	 **4n** (30 min, 79%) Mp. 242-244 °C Lit. 240-245 °C [15]	 **4o** (30 min, 76%) Mp. 208-210 °C Lit. 210-211 °C [19]	 **4p** (10 min, 94%) Mp. 257-259 °C Lit. 256-260 °C [13]

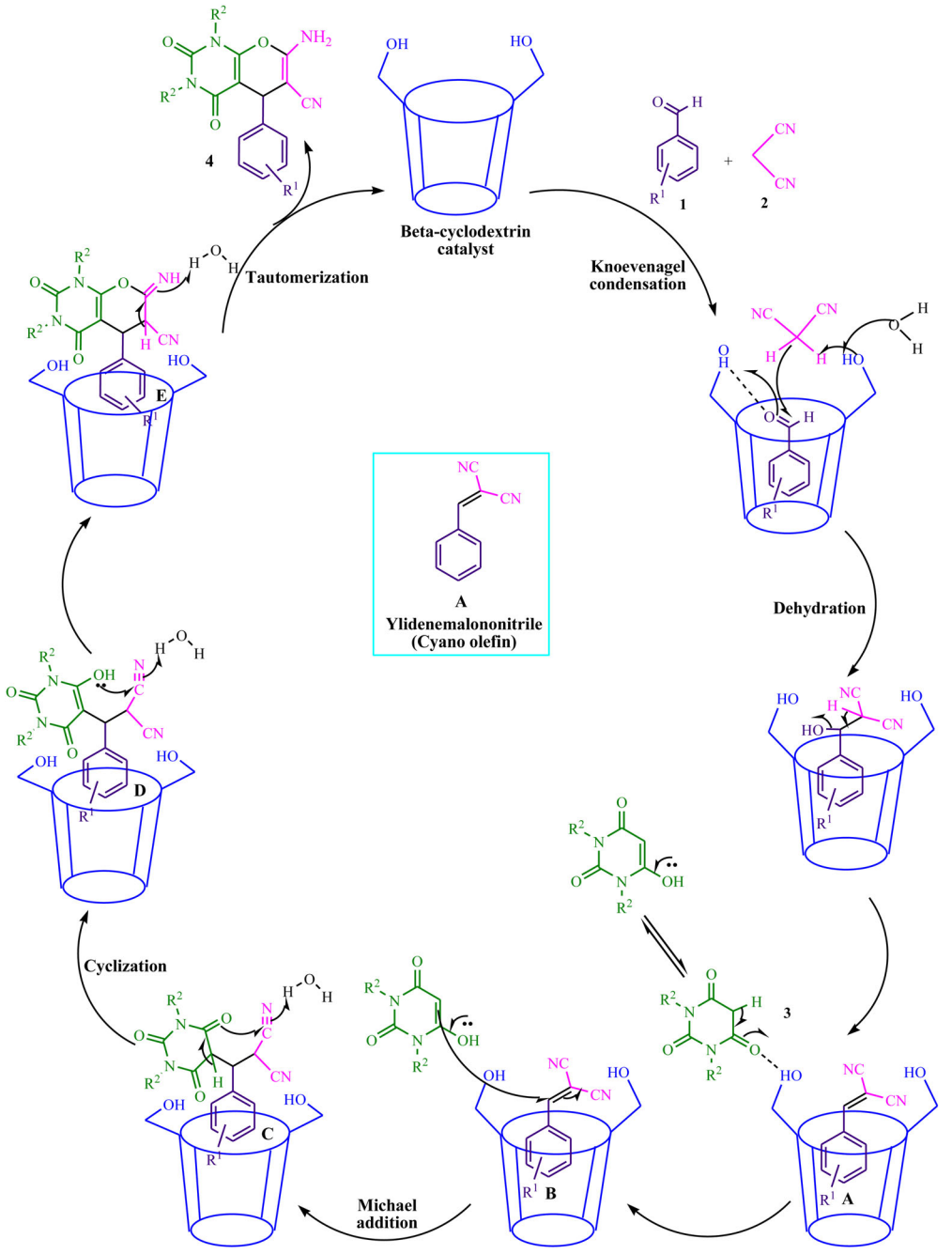
(*continued*)

Table 2. Continued.

		
4q (15 min, 88%) Mp. 237-239 °C Lit. 236-237 °C [13]	**4r** (20 min, 89%) Mp. 215-217 °C Lit. 214-216 °C [18]	**4s** (25 min, 87%) Mp. 210-212 °C Lit. 211-214 °C [18]

comparative experiments are summarized in Table 1. We also examined the influence of temperature on the reaction yield. Results indicated that when the reaction proceeded using β-CD (10 mol %) at room temperature for 480 min, the yield of the corresponding product was low (73%) (Table 1, entry 11). The reaction time was decreased from 480 min to 10 min when the reaction temperature increased from rt to 80 °C, and the yield of 93% was obtained. Therefore, we employed the optimized conditions 10 mol% of β-CD as a catalyst in 5 mL H_2O at 80 °C for the condensation reaction of aryl aldehyde derivatives **1**, malononitrile **2** with barbituric acid/1,3-dimethylbarbituric acid **3** into the corresponding pyrano[2,3-*d*]pyrimidine scaffolds (Scheme 1 and Table 2). Encouraged by the remarkable results obtained from the above conditions, and in order to show the generality and scope of this protocol, we used various aromatic aldehydes bearing either electron-withdrawing functional groups or electron-donating groups for the synthesis of corresponding pyrano[2,3-*d*]pyrimidine scaffolds. The effects of substitute on the aromatic rings were estimated strong in terms of yields under these reaction conditions. Both classes of aromatic aldehydes containing electron- donating and electron-withdrawing substituent in their aromatic rings gained the appropriate products in excellent yields and short reaction times. The reaction times of aromatic aldehydes having electron-withdrawing groups and electron-donating groups had rather same results. We also applied 1,3-dimethylbarbituric acid. In each of these substitutions, there is no significant difference in the reaction time and product yields. The results are summarized in Table 2. The attractive features of this catalyst are biodegradable, reusable and environmentally benign conditions, operational simplicity, excellent yields and short reaction times.

Proposed mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds is shown in Scheme 2. The reaction was promoted by the formation of an inclusion complex between β-CD and arylaldehyde, and the intermediate ylidenemalononitrile (cyano olefin) **A** was readily formed in situ from Knoevenagel condensation between β-CD solubilized arylaldehyde **1** and active methylene compound **2** in water. This can be evidenced by the steric effects of the arylaldehydes on the reaction efficiency (Table 2). β-CD also catalyzed the formation of the enolic form of barbituric acid/1,3-dimethylbarbituric acid **3** through hydrogen bonding stabilization, which could easily react with cyano olefin **A** and give intermediate **B**, followed by cyclization and tautomerization of **C** afford the target products **4**. In this case, the β-CD material would not only function as a protic acid but would also perform as a phase-transfer catalyst. The β-CD material would therefore catalyze the reaction and participate in the formation of stable colloidal particles in the presence of the substrates in water, which would play an important role in accelerating the rate of the



Scheme 2. Proposed mechanistic route for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

reaction. The formation of colloidal particles could be the main reason that *β*-CD exhibited such a high level of catalytic activity toward this reaction.[45–47]

Comparison of catalytic ability of some previously reported catalytic systems with *β*-CD for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds is shown in Table 3. The advantages offered by this *β*-CD versus known catalysts are as follows: (i) environmentally friendly, (ii) reusable, (iii) biodegradable, and (iv) no need chromatographic separation. In addition, simple manipulation of

Table 3. Comparison of catalytic ability of some previously reported catalytic systems with *β*-CD for synthesis of pyrano[2,3-*d*]pyrimidine scaffolds[a].

Entry	Catalyst	Conditions	Time/yield (%)	TOF	References
1	$[DABCO](SO_3H)_2(Cl)_2$	H_2O, reflux	10 min/86	0.50	[13]
2	$[DABCO](SO_3H)_2(HSO_2)_2$	H_2O, 90 °C	7 min/90	1.28	[13]
3	Nano-sawdust-OSO_3H	EtOH, reflux	15 min/94	0.31	[16]
4	Al-HMS-20	EtOH, rt	12 h/92	0.004	[17]
5	TSA	EtOH / H_2O, Reflux	90 min/88	0.04	[18]
6	$B(OH)_3$	THF / H_2O, Reflux	125 min/81	0.06	[18]
7	Theophylline	H_2O/EtOH, 50 °C	10 min/86	0.86	[30]
8	Uric acid	EtOH, 50 °C	20 min/91	0.30	[31]
9	**β-cyclodextrin**	**H_2O, 80 °C**	**10 min/93**	**0.93**	**This work**

[a]Based on the three-component reaction of benzaldehyde, malononitrile, and barbituric acid.

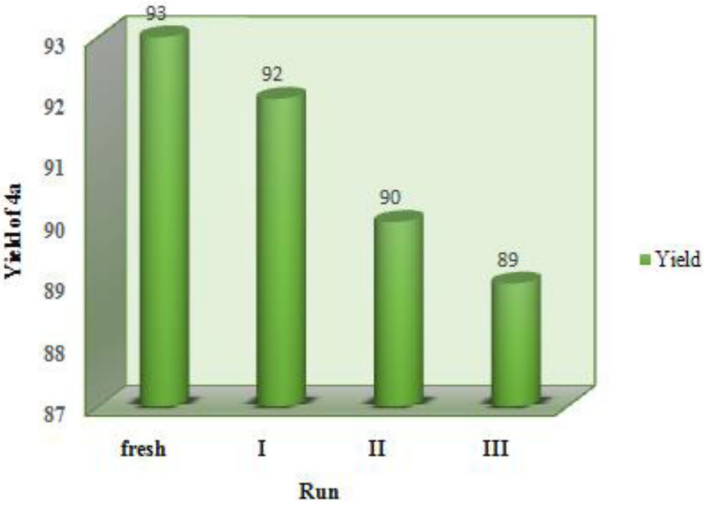


Figure 1. The recyclability of the *β*-CD in the preparation of **4a**.

the products, use of H_2O as a relatively environmentally benign solvent, excellent yields, and short reaction times in the reaction are the main benefits of this protocol.

Reusability of the catalyst

As catalyst reusability is very important from both economic and environmental points of view, the catalytic reusability of *β*-CD was investigated in several subsequent runs. The catalyst recovery and reusability were studied by three cycles, including the use of fresh catalyst for the synthesis of 7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (**4a**). The *β*-CD remains in aqueous medium after the reaction. This aqueous medium was reused to recycle for three runs while the product isolated was good with enough potential to make it cost-effective as shown in Figure 1. Slight decrease in the yield of product was observed in the first, second, and third reaction runs (92%, 90%, and 89%, respectively).

Conclusion

In conclusion, eco-safe, highly efficient, and convenient protocol has been developed for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds using supramolecular *β*-cyclodextrin as a catalyst *via*

tandem Knoevenagel–Michael–cyclocondensation reaction in aqueous media. Use of the β-CD as an environmentally friendly and biodegradable catalyst, excellent yields, short reaction times, high catalytic efficiency, avoiding the hazardous catalysts or solvents, simple experimental, straightforward work-up with no column chromatographic separation, economic availability of the catalyst, and green procedure are the notable advantages of this eco-friendly and simple protocol. Also, the catalyst was highly stable and could be reused in three successive runs with no significant structural change and loss of activity.

Acknowledgments

We gratefully acknowledge financial support from the Research Council of the Apadana Institute of Higher Education.

Disclosure statement

There are no conflict of interests.

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