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Efficient sonochemical protocol for the facile synthesis of dipyrimido-dihydropyridine and pyrimido[4,5-*d*]pyrimidines in aqueous β-cyclodextrin

Chandrakant Jadhav, Lalit D. Khillare, and Manisha R. Bhosle

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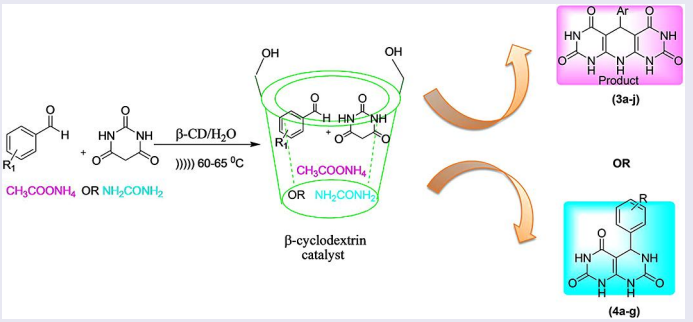
ABSTRACT

An economical and efficient synthesis of dipyrimido-dihydropyridines and pyrimido[4,5-*d*]pyrimidines is described using greener and recyclable β-cyclodextrin as a supramolecular catalyst in aqueous medium. The remarkable features of this method are mild reaction conditions, short reaction times, easy workup procedure, recyclability of the catalyst, and excellent yields of the products. The highly functional group tolerance and shorter reaction times make this method suitable for the synthesis of dihydropyridine and pyrimido [4,5-*d*]pyrimidine derivatives with a wide substitution pattern.

GRAPHICAL ABSTRACT



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β-cyclodextrin; dihydropyridines; dipyrimido-dihydropyridines; pyrimido[4,5-*d*]pyrimidines; ultrasonication

Introduction

1,4-Dihydropyridine (DHP) scaffold represents the heterocyclic unit of remarkable pharmacological efficiency.[1] Dipyrimido-dihydropyridines having DHPs as privileged pharmacophore provide important ligands for biological receptors.[2] These compounds, although described for the first time more than a century ago, have recently been recognized as vital drugs, e.g., amlodipine and felodipine (Figure 1) as antihypertensive and calcium channel blockers. Moreover, DHPs also act as nicotinamide adenine dinucleotide (NADH) mimics for the reduction of carbonyl compounds and their derivatives.[3] In human body, the main metabolic route of dihydropyridine drugs involve their oxidation to pyridines catalyzed by cytochrome P450 in liver.[4] Pyrimido[4,5-*d*]

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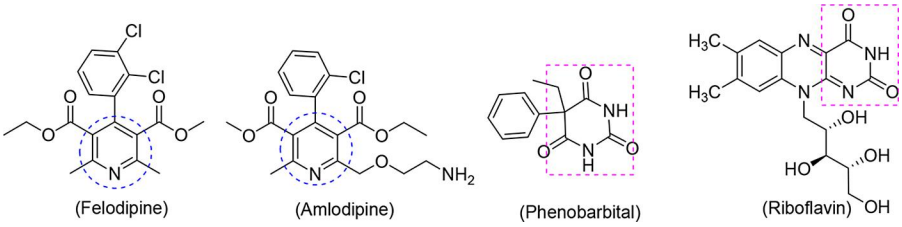


Figure 1. Biologically active molecules.

pyrimidine derivatives are also important heterocycles well recognized as bronchodilators, vasodilators, antiallergic, antihypertensive, and anticancer agents.[5]

Barbituric acid is one of the most important nitrogen-containing heterocyclic systems; it is found in various natural and synthesized compounds of anesthetics, anti-inflammatory drugs, analgesics, anxiolytics, anticancer drugs, HIV/AIDS protease inhibitors, and others.[6] Riboflavin (vitamin B2) and Phenobarbital (to treat epilepsy) are vital molecules in the market having barbituric acid as one of the pharmacophores (Figure 1).[6e] Therefore, lot of efforts have been made toward the synthetic manipulation of uracil for the preparation of dipyrimido-dihydropyridines and pyrimido[4,5-*d*]pyrimidine derivatives, using Zn^{2+}@KSF,[7a] Fe_3O_4@SiO_2,[7b] In-SiO_2 composite,[8] l-proline[9] as catalysts and MW assisted reaction[10] which usually requires forcing conditions, long reaction times and complex synthetic pathways. Therefore, there is a need to develop more efficient and sustainable chemical process for the synthesis of pyrimido[4,5-*d*]pyrimidines.

The development of green alternatives to multicomponent reactions (MCRs) has attracted much attention as these reactions produced important biological scaffolds and marketed drugs in an environment-friendly pathway.[11] The reaction parameters, such as solvent, catalyst of an MCR determine the selectivity, versatility, and environmental acceptability. Water is the greenest solvent among all and consequently it has been widely used as the reaction medium for elementary organic transformations as well as in MCRs.[12] It has also been reported that water accelerates the rate of reaction due to its high polarity, hydrogen bonding in the transition state, and hydrophobic effect.[13] Thus, the synthesis of bioactive scaffolds through MCR using a mild and inexpensive catalyst in a green solvent like water is valued.

Catalysis is also a keystone in chemical sciences supported by the improvement of known industrial reactions, the development of new reaction pathways, and the exponential burgeoning of organocatalysis.[14] Cyclodextrins are promising supramolecular catalysts in aqueous medium because they are nontoxic, biodegradable and, in many instances, they are recyclable.[15] β-Cyclodextrin (β-CD) is a cyclic oligosaccharide composed of seven α-1, 4-linked glucopyranosyl units. Cyclodextrins contain hydrophobic cavities inside and hydrophilic hydroxyl groups outside (Figure 2). The most prominent feature of cyclodextrins is their capability to form inclusion complexes (host–guest complexes) with different classes of compounds by noncovalent bonding interactions.[16,17] The internal cavity of the cyclodextrin molecule is strongly hydrophobic in nature, and this particular characteristic of the cyclodextrin molecule enables it to bind with a wide range of guest molecules.[18] Cyclodextrin binds with the substrate in its hydrophobic cavity and catalyzes reactions in a selective manner.

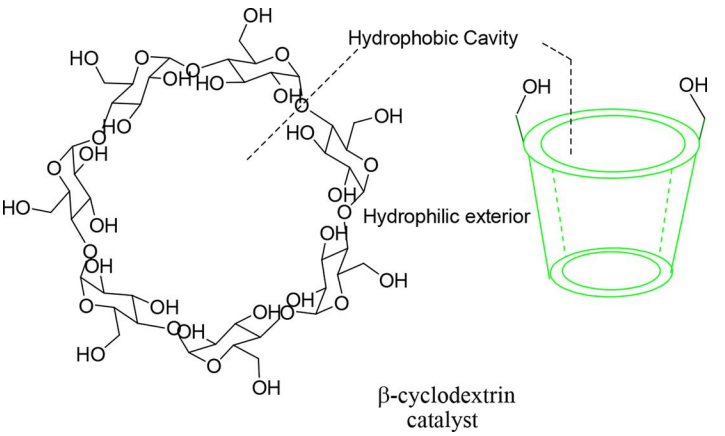


Figure 2. Chemical structure of β-cyclodextrin.

Ultrasound irradiation is a vital tool in heterocyclic chemistry, which allows reactions under mild conditions and is known to enhance yields and reduce reaction times.[19] Ultrasound also offers advantages such as minimal waste production and energy savings among others, consequently it is expedient green chemistry approach.[20] Thus, researchers attempted to use ultrasonication for improving the recognized MCRs.

In continuation of our work on β-CD,[21] we now disclose a newer methodology for the synthesis of known dipyrimido-dihydropyridines and pyrimido[4,5-*d*]pyrimidines as one-pot synthesis involving three-component annulation of substituted aldehydes, barbituric acid, and ammonium acetate/urea in the presence of β-CD as a recyclable catalyst in aqueous media at 60–65 °C.

Results and discussion

Optimization of reaction conditions and scope of the reaction

To find out the best experimental conditions for the preparation of dipyrimido-dihydropyridines, a model reaction, involving the three-component annulation between benzaldehyde (**1a**), barbituric acid (**2a**), and ammonium acetate was selected.

In this study, a model reaction was conducted by the addition of benzaldehyde (**1a**), barbituric acid (**2**), and ammonium acetate at room temperature in the presence of catalyst, *p*-toluenesulfonic acid, cetyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, β-CD to obtain the corresponding dihydropyridines (**3a**) in aqueous medium. Among all these catalysts, β-CD gives product in good yield (Table 1). This might be due to the most notable feature of cyclodextrins, i.e., their ability to form solid inclusion complexes (host–guest complexes) with a very wide range of compounds by a molecular complexation. This will result in solubility enhancement of highly insoluble guests.

Temperature has more than one effect upon cyclodextrin complexes. Heating can increase the solubility of the complex but at the same time also destabilizes the complex. These effects often need to be balanced. Therefore to check the effect of temperature on reaction rate, the model reaction was performed at different temperatures, 40, 50, 60, 70 °C. The reaction was found to be sluggish at 40 °C; however, by increasing the

Table 1. Optimization of reaction condition using different catalysts for the synthesis of 5-(phenyl)-1,3,5,7,9,10-hexahydropyrimido[5′,4′-5,6]pyridine[2,3-*d*]pyrimidine-2,4,6,8-tetraone (**3a**).[a]

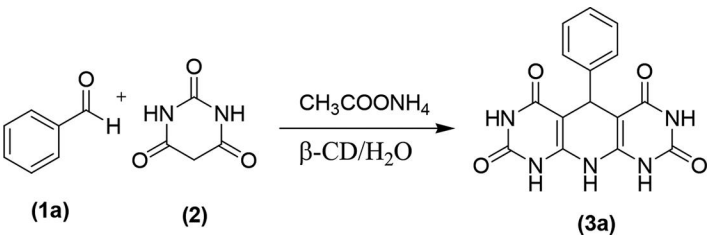
Entry	Catalyst	Solvent	Time (h)	Concentration (mol%)	Temperature (°C)	Yield (%)[b]
1	—	Water	27	—	40/stir	No condensation
2	*p*-TSA	Water	6	20	40/stir	69
3	CTAB	Water	6	20	40/stir	75
4	TTAB	Water	6	20	40/stir	71
5	β-CD	Water	1	20	40, 50, 60, 70/stir	71, 79, 85, and 86
6	β-CD	Water	1	10, 15, **20**, 25	60/US	71, 86, **90**, and 91
7	α-CD	Water	10	20	40/US	45
8	γ-CD	Water	8	20	60/US	39
9	β-CD	EtOH	1	20	60/US	84
10	β-CD	MeOH	1	20	60/US	79
11	β-CD	DCM	1	20	60/US	82

Bold values for selected catalyst concentration and its respective yield.
CTAB, cetyltrimethylammonium bromide; *p*-TSA, *p*-toluenesulfonic acid; TTAB, tetradecyltrimethylammonium bromide; US, ultrasonication.
[a]*Reaction conditions:* Benzaldehyde (**1a**) (1 mmol), barbituric acid (**2**) (2 mmol), ammonium acetate (3 mmol).
[b]Isolated yield.

temperature to 60 °C, the corresponding product (**3a**) was obtained in 85% yield within 7 h (Scheme 1).

Considering the significance of ultrasonication as it offers an alternative energy source for reactions that ordinarily require longer reaction time, we performed the model reaction using β-CD under ultrasonication, it was observed that the corresponding product was obtained in 90% yield within 1 h at 60 °C. Here, ultrasonication reduces the reaction time from 7 to 1 h. Ultrasound accelerates reaction rates by facilitating mass transfer in the microenvironment, through the process of acoustic cavitation. Cavitation occurs in an irradiated liquid, involving bubble formation, growth, and impulsive collapse. The collapsing bubbles induce high temperature and pressure, in the form of hot spots with sufficient energy to facilitate chemical reactions.[22] Therefore, all the reactions are carried under ultrasonication.

Furthermore, effort was made to perform the cyclocondensation using different cyclodextrins in water under ultrasound irradiation. Based on the screening results in Table 1, β-CD is the best catalyst among others. Low conversions were observed with either α- and γ-cyclodextrin. It is clear that α-CD was not a good catalyst because the cavity of α-CD might be too small and the cavity of γ-CD was too big compared to β-CD. β-CD has usually one order of degree, higher affinity for the benzene derivatives as compared to α- and γ-CD. No product formation was detected in the absence of cyclodextrin, which



Scheme 1. Synthesis of 5-(benzyl)-1,3,5,7,9,10-hexahydropyrimido[5′,4′-5,6]pyridine[2,3-*d*]pyrimidine-2,4,6,8-tetraone (**3a**).

clearly demonstrates the catalytic role of cyclodextrin. Therefore, β-CD was preferred as a catalyst for this reaction.

To optimize the catalyst, the model reaction was performed at different concentration of β-CD in water. As catalyst concentration is important factor that exclusively affects the reaction rate and product yield. To study this, the reaction was performed at different concentrations of β-CD, i.e., 10, 15, 20, and 25 mol%, and gave the product in 71, 86, 90, and 91% yield, respectively (Table 1). Thus, it is clear that reaction rate was positively influenced by increasing catalyst concentration up to 10 mol% and then became static on further increasing the catalyst concentration. It means that the presence of 10 mol% of β-CD was sufficient for catalyzing the reaction effectively in the forward direction.

Recycling of β-CD

The catalyst recyclability was studied thrice including the use of fresh catalyst for the synthesis of dipyrimido-dihydropyridine (**3a**). The catalyst was almost quantitatively recovered and no significant loss in yield was observed (Figure 3). The FTIR spectra of fresh and recovered β-CD were also measured (Figure 4), and no change was found in the functional groups as well as the fingerprint region, indicating that no reaction occurs with β-CD.

With this optimized result in hand, we next explored the scope of this reaction. The efficiency of the catalyst:β-CD was also checked for the coupling of diversely substituted aryl aldehydes, barbituric acid, and ammonium acetate (Scheme 2). The results (Table 2) showed that substituted aryl aldehydes containing either electron-donating or electron-withdrawing groups gave the analogous products in good yields (Table 2).

Having established by these results, we extended this process to other substrates. The scope of the reactions is illustrated with respect to urea for synthesizing pyrimido[4,5-*d*] pyrimidines (**4a**–**g**) by using number of aldehydes (**1a**–**g**), barbituric acid (**2**), and urea (Scheme 3). Under the optimized reaction conditions, we used various aromatic aldehydes to react with barbituric acid and urea and a series of functionalized pyrimido [4,5-*d*]pyrimidine derivatives were synthesized with excellent yields. The results of reactions are summarized in Table 2. As shown in Table 2, we found that all the reactions were performed smoothly, and the aromatic aldehydes, with either electron-withdrawing groups or electron-donating groups, could all be used for the synthesis of functionalized pyrimido[4,5-*d*]pyrimidine derivatives with excellent yields.

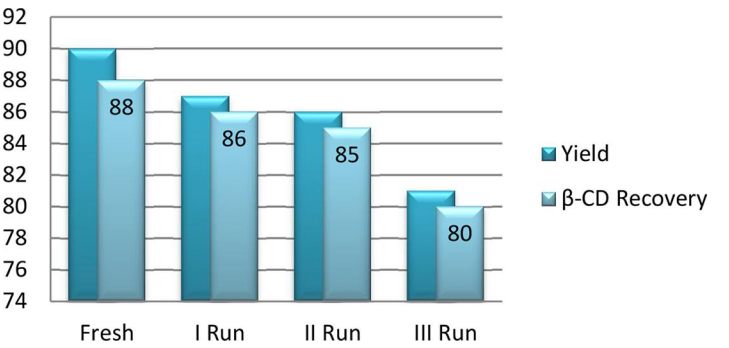


Figure 3. Reuse and recovery of β-CD and its effect on yield.

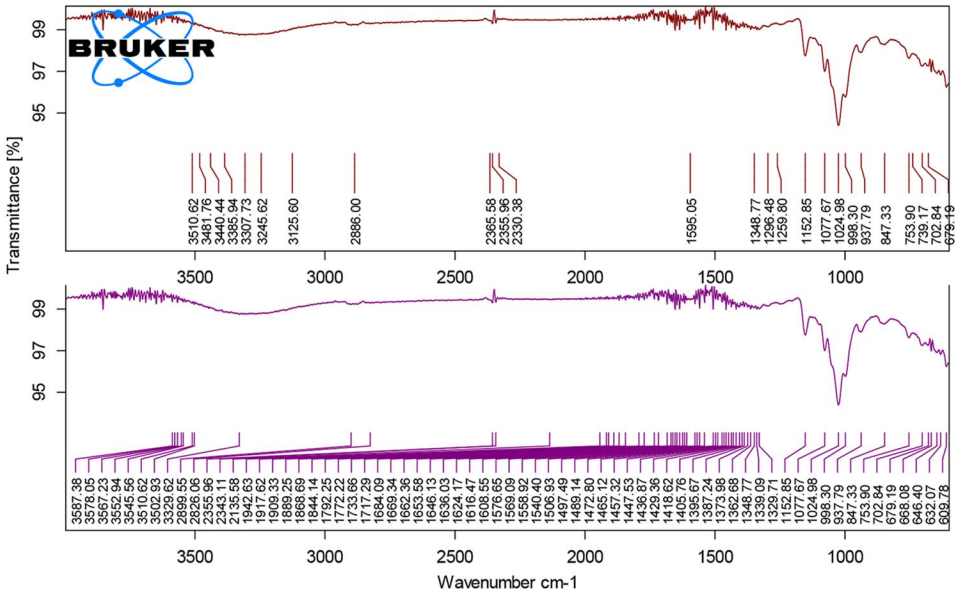
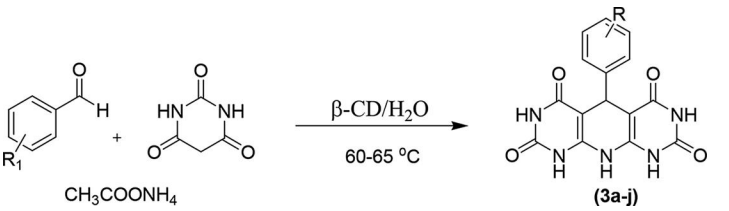


Figure 4. FTIR spectra of β-CD before reaction (upper red curve) and third run (lower pink curve).

Plausible reaction mechanism for the synthesis of dipyrimido-dihydropyridines

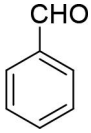
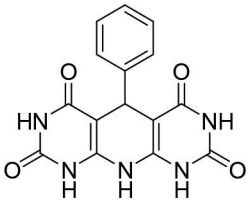
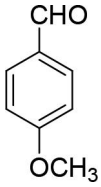
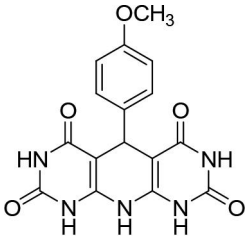
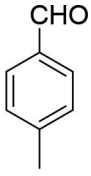
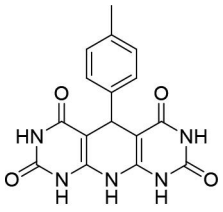
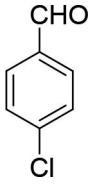
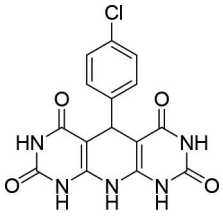
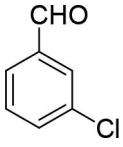
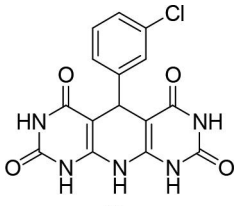
The process represents a typical cascade of Knoevenagel condensation followed by Michael addition and cyclization in the cavity of β-CD.[23] Subsequent Michael addition takes place by sequential addition of ammonium acetate on benzylidine barbiturate resulting into intermediate, which is also stabilized by H-bonding with the secondary hydroxyl groups of β-CD.

The rate acceleration of this condensation can be attributed to (1) aqueous β-CD which provides a unique hydrophobic truncated cone-shaped cavity and hydrophilic outwardly hydroxyl groups.[23] The aldehydes and barbituric acid might be forming noncovalent reversible supramolecular complexes with β-CD in the cavity, enhancing the localized concentration of the aldehydes and barbituric acid resulting in the dissolution in aqueous medium. Because of this, aldehydes become readily available to interact with barbituric acid and (2) the electrophilic behavior of carbonyl carbon of the aldehydes would have been enhanced because of intermolecular hydrogen bonding between outwardly hydroxyl groups of β-CD and carbonyl oxygen of the aldehydes and resulting into benzylidine barbiturate. Then followed by



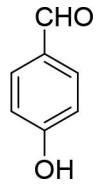
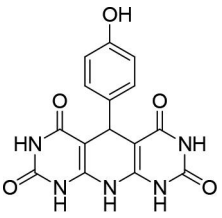
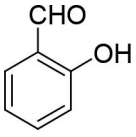
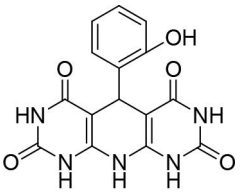
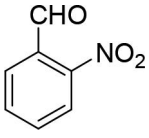
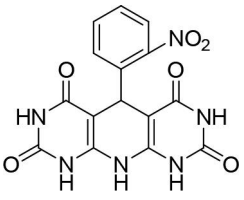
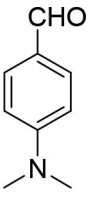
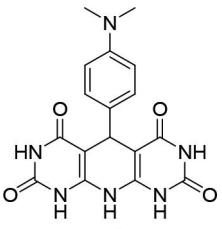
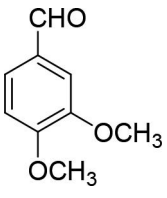
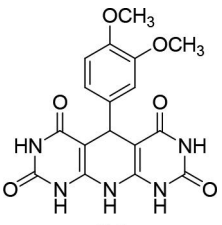
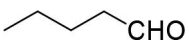
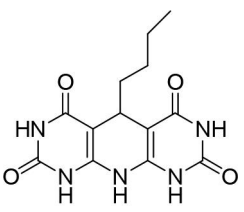
Scheme 2. General scheme of the synthesis of dihydropyridines (**3a–j**).

Table 2. Synthesis of 5-(substituted)-1,3,5,7,9,10-hexahydropyrimido[5′,4′-5,6]pyridine[2,3-*d*]pyrimidine-2,4,6,8-tetraones (**3a**–**k**) and 5,6-dihydro-5-(substituted phenyl)pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-triones (**4a**–**g**).[a]

S. no.	Substrates		Structure of products	Yield[b] (%)	Melting point (°C)[c]	
					Found	Reported
1		CH_3COONH_4	 **3a**	90	294–296	295–297
2		CH_3COONH_4	 **3b**	87	>300	>300
3		CH_3COONH_4	 **3c**	79	>300	>300
4		CH_3COONH_4	 **3d**	81	300–302	300–301
5		CH_3COONH_4	 **3e**	80	>300	>300

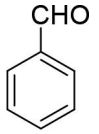
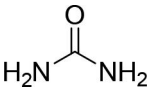
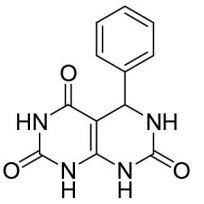
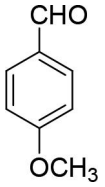
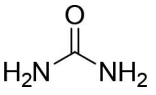
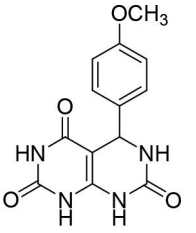
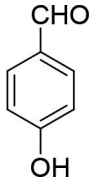
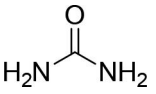
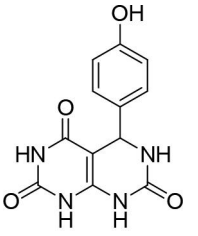
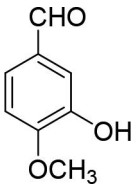
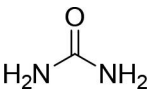
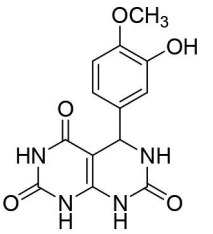
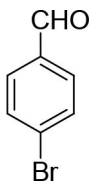
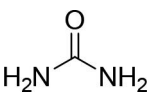
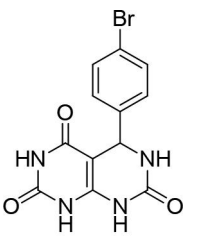
(*Continued*)

Table 2. Continued.

S. no.	Substrates		Structure of products	Yield[b] (%)	Melting point (°C)[c] Found	Reported
6		CH_3COONH_4	 **3f**	84	>300	>300
7		CH_3COONH_4	 **3g**	72	260–262	261–263
8		CH_3COONH_4	 **3h**	78	257–258	255–257
9		CH_3COONH_4	 **3i**	73	287–289	287–288
10		CH_3COONH_4	 **3j**	84	295–297	293–295
11		CH_3COONH_4	 **3k**	72	230–232	233–234

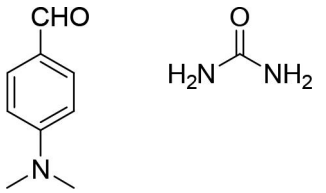
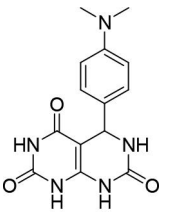
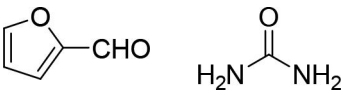
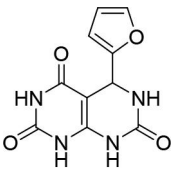
(*Continued*)

Table 2. Continued.

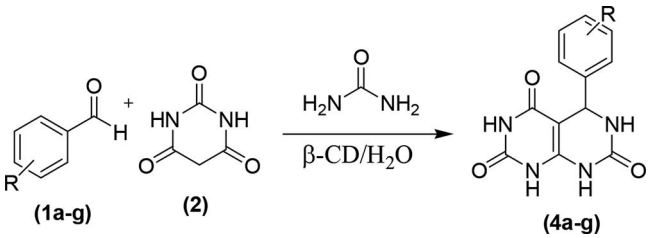
S. no.	Substrates		Structure of products	Yield[b] (%)	Melting point (°C)[c] Found	Reported
12			 **4a**	89	243–245	244–246
13			 **4b**	86	285–286	284–286
14			 **4c**	81	210–211	210–212
15			 **4d**	77	276–278	275–277
16			 **4e**	76	212–214	210–212

(*Continued*)

Table 2. Continued.

S. no.	Substrates	Structure of products	Yield[b] (%)	Melting point (°C)[c] Found	Reported
17		 **4f**	82	255–257	256–257
18		 **4g**	75	272–274	273–275

[a]*Reaction conditions:* Substituted aldehydes (**1a–k**) (1 mmol), (**2**) barbituric acid (2 mmol), ammonium acetate (2 mmol), or urea (1 mmol), β-cyclodextrin (20 mol%), at 60–65 °C.
[b]Isolated yield.
[c]Melting points, IR, ^{1}H NMR and ^{13}C NMR are in good agreement with those reported in the literature.[10,24]



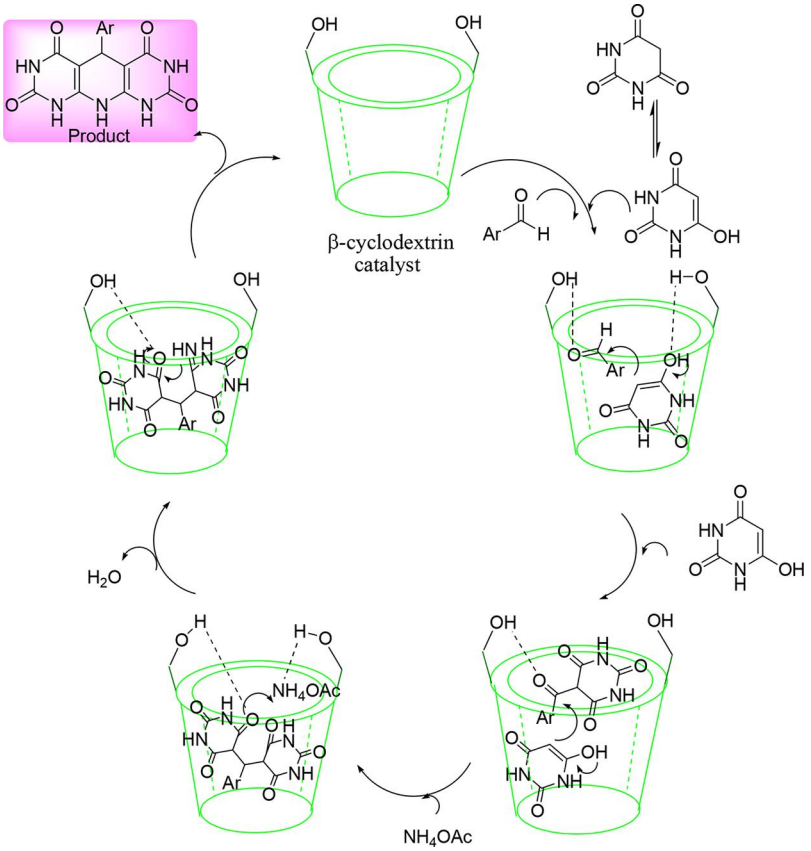
Scheme 3. Synthesis of pyrimido[4,5-*d*]pyrimidines (**4a–g**).

intramolecular cyclization, loss of CO_2 molecule and hydrolysis, there is formation of desired product. After the formation of the product, the escape from the CD cavity occurs readily (Scheme 4).

Experimental

General

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 and 100 MHz using DMSO-d_6 solvent and tetramethylsilane as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Sciex, Model; API 3000 LC–MS/MS Instrument. The progress of reaction was checked by TLC using silica gel, $60F_{254}$ aluminum sheets as adsorbent and visualization was accomplished by



Scheme 4. Plausible mechanism for the synthesis of dihydropyridine.

iodine/ultraviolet light. The ultrasonic-assisted reactions were performed in Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath built in heating, 30–80 °C thermostatically adjustable. The reaction flask was located in the cleaner, where the surface of reactants is slightly lower than the level of the water.

All compounds were known and IR, ^{1}H, ^{13}C NMR spectra were found to be identical to the ones described in the literature.[10,24]

General procedure for the synthesis of 5-(substituted phenyl)-1,3,5,7,9, 10-hexahydropyrimido[5′,4′-5,6]pyridine[2,3-d]pyrimidine-2,4,6,8-tetraones (3a–k)

A mixture of substituted aldehydes (**1a–k)** (1 mmol), barbituric acid (**2a)** (2 mmol), and ammonium acetate (2 mmol) was added in β-CD (20 mol%) solution containing water. The resulting mixture was stirred under ultrasonication at 60–65 °C. The progress of the reaction was monitored by thin-layer chromatography. After 1 h of ultrasound irradiation, the reaction mixture was cooled to room temperature, filtered, and washed with hot water to remove β-CD. Dried product was crystalized from ethanol to afford the purified desired product. All synthesized compounds were characterized by IR, ^{1}H, ^{13}C NMR spectra and were found to be identical to the ones described in the literature.[10,24]

Spectral data of selected compound

5-(Benzyl)-1,3,5,7,9,10-hexahydropyrimido[5′,4′-5,6]pyridine[2,3-d]pyrimidine-2,4,6,8-tetraone (3a)

White solid, yield 90%; mp 294–296 °C; IR (ATR, υ cm^{-1}): 3551 (CONH stretching), 3478 (CONH stretching) 3196 (N–H stretching), 2820 (C–H stretching), 1676, 1611 (C=O stretching), 1442, 1288, 1031, 861, 799. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.39 (s, 2H, NH), 11.23 (s, 2H, NH), 10.59 (s, 1H, NH), 7.08–7.54 (m, 5H, Ar–H), 5.21 (s, 1H, pyrimidine).[10,24] ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 162.41 (2C), 157.78 (2C), 152.50, 151.51, 149.46, 146.32, 128.67, 123.37 (2C), 118.74 (2C), 87.43, 40.09. Mass (LC–MS): *m/z* 326 $[M+H]^+$. Anal. calcd. for $C_{15}H_{11}N_5O_4$: N, 21.53; C, 55.39; H, 3.41. Found: N, 21.49; C, 55.40; H, 3.47%.

General procedure for the synthesis of pyrimido[4,5-d]pyrimidine (4a–g)

A mixture of aldehyde (**1a)** (1 mol), barbituric acid (**2a)** (1 mol), and urea (1 mol) was added in β-CD (20 mol%) solution containing water. The resulting mixture was stirred under ultrasonication at 60–65 °C. The progress of the reaction was monitored by thin-layer chromatography. After 1 h of ultrasound irradiation, the reaction mixture was cooled to room temperature, filtered, and washed with hot water to remove β-CD. Dried product was crystallized from ethanol to afford the purified desired product. The rest of the substrates (**4b**–**g**) were prepared by a procedure similar to that for **4a.** The known compounds (**4a**–**g**) were characterized by IR, ^{1}H, ^{13}C NMR spectra and showed satisfactory spectroscopic data in agreement with those reported in the literature.[10,24]

Spectral data of selected compound

5,6-Dihydro-5-(benzyl)pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4a)

Off-white solid, yield 89%; mp 243–245 °C; IR (ATR, υ cm^{-1}): 3525 (CONH stretching), 2372 (C–H stretching), 1672, 1623 (C=O stretching), 1453, 1227, 1063, 827, 793. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.28 (s, 1H, NH), 11.25 (s, 1H, NH), 8.39 (s, 1H, NH), 7.23–7.35 (m, 5H, A-H), 5.47 (s, 1H).[10,24] ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 163.69, 157.24, 154.57, 143.35, 138.75, 128.23 (2C), 127.41 (2C), 124.13, 90.71, 47.28. Mass (LC–MS): *m/z* 259 $[M+H]^+$. Anal. calcd. for $C_{12}H_{10}N_4O_3$: N: 21.70; C: 55.81; H: 3.90. Found: N, 21.69; C, 55.85, H: 3.90%.

Conclusion

In conclusion, an efficient method has been developed for the synthesis of biologically relevant dipyrimido-dihydropyridines (**3a**–**k**) and pyrimido[4,5-*d*]pyrimidine (**4a**–**g**) derivatives using β-CD as a catalyst in aqueous medium. The operational simplicity, mild reaction conditions, short reaction time, high yields (72–90%), and environmental friendliness are the notable features of this procedure. Indeed, a wide range of aldehydes were converted to the corresponding known dipyrimido-dihydropyridines (**3a**–**k**) and pyrimido[4,5-*d*]pyrimidine (**4a**–**g**) in aqueous β-CD.

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