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One-Pot Multicomponent Solvent-Free Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans Catalyzed by Per-6-amino-β-cyclodextrin

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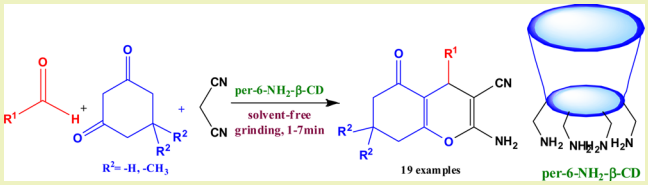
Supporting Information

ABSTRACT: An efficient three-component reaction of aromatic aldehyde, 1,3-cyclohexanedione/dimedone, and malononitrile was developed, for the first time, using per-6-amino-β-cyclodextrin, as a supramolecular host for aldehydes and an efficient base catalyst, which produced various substituted 2-amino-4*H*-benzo[*b*]pyrans in good to excellent yields, under solvent-free conditions. The catalyst can be reused at least three times without any marked change in its catalytic activity. Other remarkable features include a much milder procedure, a shorter reaction time, a wide range of functional group tolerance, and absence of any tedious workup or purification. This procedure also avoids hazardous reagents/solvents and is thus an eco-friendly alternative to the existing methods.



KEYWORDS: *Multicomponent reaction, Solvent-free synthesis, Aminocyclodextrin, Tetrahydrobenzo[b]pyrans, Supramolecular reusable catalyst*

INTRODUCTION

The efficiency of a chemical synthesis can be measured nowadays, not only by parameters like selectivity and overall yield but also by its raw material, time, human resources, and energy requirements, as well as the toxicity and hazards of the chemicals and the protocols involved.[1] Multicomponent reactions (MCRs) have been refined in recent years into powerful and useful tools in synthetic organic chemistry and have attracted increasing attention because complex molecules and drugs can be prepared from cheap and easily available starting materials.[2−6] In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and "green" chemistry.[7,8] With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water and solvent-free reactions represents very powerful green chemical protocols from both the economic and synthetic point of view. They have many advantages, such as reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment.[9] In recent years solventless (or minimal-solvent) mechanochemistry, i.e., reactions conducted by grinding solid reactants together, offers some advantages, such as greater efficiency with regard to time, materials, and energy usage, as well as the discovery of new or improved reactivity and products, as an alternative approach to synthesis.[10]

4*H*-Pyran and its derivatives occur frequently in numerous natural compounds,[11] exhibiting important biological activities and wide applications in pharmaceutical use such as antiallergic, antitumor, and antibacterial agents.[12−14] Furthermore, these compounds exhibit unique pharmacological activities including treatment of human inflammatory TNF-mediated diseases, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[15,16] Moreover, functionally substituted 4*H*-pyrans have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[17,18] For example, 2-amino-4*H*-pyran derivatives bearing nitrile functionality exhibit potential applications in the treatment of psoriatic arthritis and rheumatoid arthritis, as well as in cancer therapy.[19−22] The 4*H*-pyran ring can be transformed to pyridine systems, which relate to pharmacologically important calcium antagonists of the dihydropyridine (DHP) type.[23,24] 2-Amino-3-cyano-4*H*-pyrans possess photochemical activity.[25] Because of their important use in organic synthesis, the synthetic methodologies for 4*H*-pyran have been studied for many years. The known procedure for the synthesis of 4*H*-pyran derivatives uses a three-component reaction of cyclic 1,3-diketones, arylaldehydes, and malononitrile and is performed under various reaction conditions. The conventional reported synthesis of 4*H*-pyran derivatives uses piperidine and triethylamine in organic solvents. A variety of other reagents, such as HMTAB,[26] TEBA, $Re(PFO)_3$,[27] NaBr,[28] *S*-proline,[29] and L-proline,[30] the use of microwave irradiation,[31] infrared radiation,[32] KF-basic alumina in dimethylformamide (DMF),[33] ultrasound irradiation[34] and aminofunctionalized ionic liquids[35] were found to catalyze this reaction. However, these methods show varying degrees of success as well as limitations such as prolonged reaction times, low yields, and use of toxic solvents.

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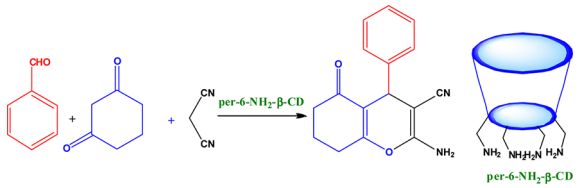
Thus, the development of an alternate milder and cleaner procedure, which surpasses those limitations, is very much relevant for the synthesis of 2-amino-4*H*-pyrans.

Cyclodextrins (CDs) are cyclic oligosaccharides that can bind substrates and catalyze chemical reactions with high selectivity through reversible formation of host−guest complexes.[36] Aminocyclodextrins are homogeneous CD derivatives modified by persubstitution at the primary face with amino pendant groups, and this manifests combined hydrophobic and electrostatic binding of guest molecules relative to native CDs. In addition they can also act as ligands for various metal ions.[37−40] As part of our continuing interest in developing newer methods for the synthesis of useful compounds, we have recently successfully utilized per-6-amino-*β*-cyclodextrin (per-6-NH_2-*β*-CD) as an useful catalyst as well as host.[41−45] Encouraged by these efforts and aiming to demonstrate the efficiency and generality of these aminocyclodextrins as catalysts further, we have utilized this novel catalyst for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans from simple and easily available starting materials under much milder reaction conditions.

RESULTS AND DISCUSSION

Preliminary studies were mainly focused on the optimization of reaction conditions. The yields of 2-amino-4*H*-benzo[*b*]pyrans derivatives obtained by reacting 1,3-cyclohexanedione, malononitrile, and benzaldehyde are given in Table 1. This three-component cyclocondensation reaction proceeds smoothly in the presence of per-6-NH_2-*β*-CD to give the desired product 2-amino-3-cyano-4-phenyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]-pyran (**4a**) in high to excellent yields in both water and solventless conditions. Although the reaction carried out in water shows similar results, the solvent-free approach facilitates higher reaction rates and yields in a very short period (1 min). The catalyst plays a crucial role in ensuring very efficient reaction rate and excellent yields. The catalytic activity of per-6-NH_2-*β*-CD is established by the fact that no product formation is observed in the absence of per-6-NH_2-*β*-CD even after longer reaction times (Table 1, entry 1). The reaction is also carried out using *β*-CD, and here too, no product formation is observed (Table 1, entry 2). When carried out in conventional bases such as piperidine and proline (Table 1, entries 3−6), decreased yield and longer reaction time are noticed in both water and solventless conditions, and an additional handicap is that the product separation from the reaction mixture is difficult. With triethylamine and ethylenediamine (Table 1, entries 7−9), no product is formed. When mono-6-amino-*β*-CD, prepared as per reported procedure,[46] is used as the catalyst, the reaction proceeds with reduced yield (Table 1, entry 10), and this highlights a more significant role for per-6-NH_2-*β*-CD particularly its role as multi/cooperative catalysts.

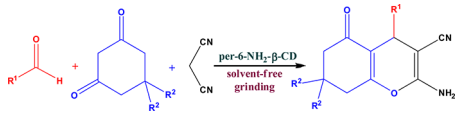
Table 1. Optimization of Reaction Conditions in the Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans from Benzaldehyde and Cyclohexanedione[a]



entry	catalyst	medium	time	yield (%)[b]
1	Nil	EtOH	24 h	Nil
2	*β*-CD	water	24 h	Nil
3	piperidine	water	5 h	78[c]
4	piperidine		30 min	65[c]
5	L-proline	water	5 h	81[c]
6	L-proline		30 min	70[c]
7	triethylamine	water	24 h	Nil[c]
8	ethylenediamine	water	24 h	Nil[d]
9	ethylenediamine		24 h	Nil[d]
10	mono-6-NH_2-*β*-CD	water	1 h	69[e]
11	per-6-NH_2-*β*-CD	water	1 h	90[e]
12	per-6-NH_2-*β*-CD	DMSO	1h	76[e]
13	per-6-NH_2-*β*-CD	DMF	1 h	81[e]
14	per-6-NH_2-*β*-CD	EtOH	1 h	86[e]
15	per-6-NH_2-*β*-CD		1 min	95[e,f]
16	per-6-NH_2-*β*-CD		1 min	29[f,g]
17	per-6-NH_2-*β*-CD		1 min	53[f,h]

[a]Reactions are performed on a 1 mmol scale of all reactants. [b]Isolated yield. [c]30 mol % catalyst. [d]4 equiv of catalyst used and bisimine of aldehyde obtained. [e]9 mol % catalyst. [f]Grinding. [g]3 mol % catalyst. [h]6 mol % catalyst.

Table 2. Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans with Various Substituted Aldehydes and 1,3-Cyclohexanedione/Dimedone[a]



sample no.	R^1	R^2	product	time (min)	yield
1	C_6H_5−	H	**4a**	1	95
2	4-NO_2−C_6H_4−	H	**4b**	2	92
3	4−Cl-C_6H_4−	H	**4c**	1	97
4	4-OH-C_6H_4−	H	**4d**	5	90
5	4-OCH_3−C_6H_4−	H	**4e**	7	90
6	2−Cl-C_6H_4−	H	**4f**	3	95
7	3,4-di−Cl-C_6H_3−	H	**4g**	3	73
8	4-Cl-3-NO_2−C_6H_3−	H	**4h**	3	71
9	4−Br-C_6H_4−	H	**4i**	2	93
10	3,5-di-OCH_3−C_6H_3−	H	**4j**	7	67
11	C_6H_{11}−	H	**4k**	4	91
12	C_6H_5-	CH_3	**4l**	3	89
13	4-OCH_3−C_6H_4-	CH_3	**4m**	5	87
14	4−Cl-C_6H_4−	CH_3	**4n**	3	85
15	4-CH_3−C_6H_4−	CH_3	**4o**	7	84
16	4-OH-C_6H_4−	CH_3	**4p**	7	88
17	3,4-di−Cl-C_6H_3−	CH_3	**4q**	4	83
18	C_5H_4N−	CH_3	**4r**	2	93
19	C_6H_{11}−	CH_3	**4s**	4	88

[a]Reaction Conditions: reactants 1 mmol; catalyst 0.09 mmol; grinding.

Table 3. Reusability of Per-6-NH_2-*β*-CD as a Catalyst in Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans from C_6H_5CHO[a]

	run		
	first	second	third
yield (%)	95	94	94

[a]Reactions were performed on a 1 mmol scale of all reactants in solvent-free conditions for 1 min at room temperature. After completion of the reaction, per-6-NH_2-*β*-CD was filtered, washed with distilled ethanol three times, dried in vacuum, and reused.

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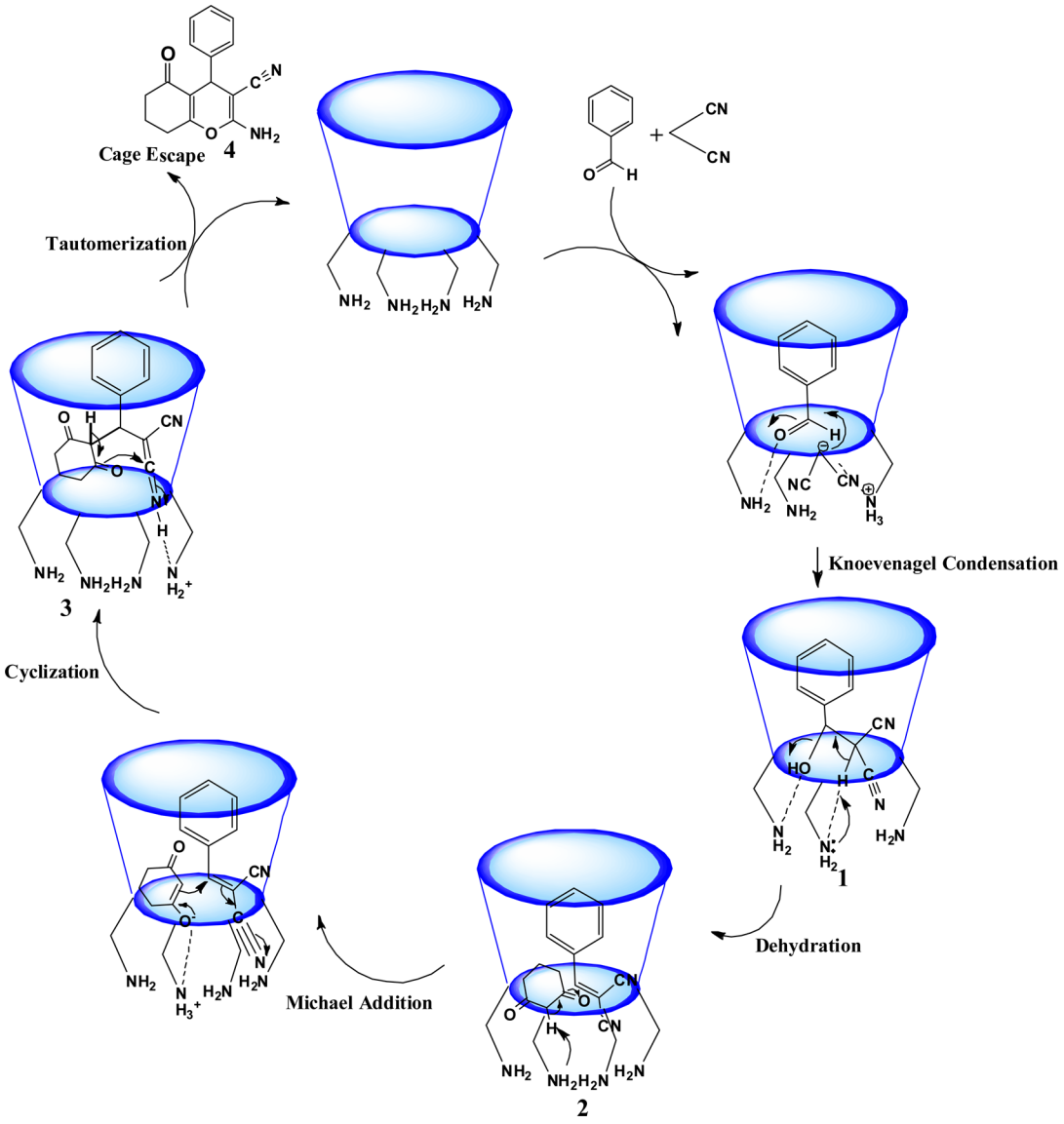
Scheme 1. Proposed Mechanism for Per-6-NH_2-β-CD Catalyzed Synthesis of 2-Amino-4*H*-benzo[*b*]pyrans



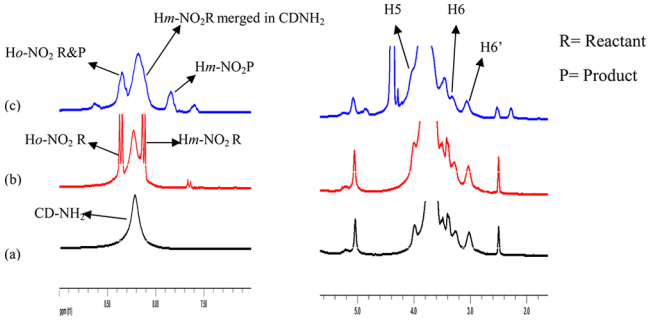


Figure 1. ^{1}H NMR spectra of (a) per-6-NH_2-β-CD, (b) per-6-NH_2-β-CD-4-nitrobenzaldehyde complex, and (c) mixture of per-6-NH_2-β-CD-4-nitrobenzaldehyde after the addition of malononitrile and dimedone. (Note: H*o*-NO_2 R-proton ortho- to nitro group in 4-nitrobenzaldehyde; H*m*-NO_2 R-proton meta- to nitro group in 4-nitrobenzaldehyde; H*o*-NO_2 P-proton ortho- to nitro group in product; H*m*-NO_2 R-proton meta- to nitro group in product.)

These significant results prompted us to propose that the presence of seven amino groups in per-6-NH_2-β-CD plays an important role in the above reaction. Among the various solvents used, the reaction works well when polar solvents such as water, dimethylsulfoxide (DMSO), DMF, and ethanol are used (Table 1, entries 11−14). On the other hand, to our surprise, when the catalyst is mixed with the reactants under solvent-free conditions, 95% yield is obtained (entry 15) in 1 min. However, lowering the mole percentage of per-6-NH_2-β-CD decreases the overall yield significantly (entries 16 and 17).

To explore the scope of the reaction further, the present study is extended to various aromatic aldehydes carrying electron-withdrawing/releasing substituents. All the reactions have proceeded efficiently and resulted in higher yields without the formation of any side products and the observed results are presented in Table 2. This very simple and convenient experimental procedure tolerates a variety of other functional groups such as methoxy, nitro, hydroxyl, and halides as well under the present reaction conditions. Aliphatic aldehydes and cyclohexanecarboxaldehyde are also investigated (Table 2, entries 11 and 19), and the final products are obtained in good yields.

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The catalyst is also found to be reusable (Table 3). After completion of the reaction, per-6-NH_2-β-CD is filtered, washed with ethanol three times, dried in vacuum, and reused. Up to three runs, there is no change in its catalytic efficiency.

To account for this very efficient multi/cooperative catalysis by per-6-NH_2-β-CD, wherein base-catalyzed reactions are involved, it is proposed that per-6-NH_2-β-CD (with its seven primary amino groups acting synergistically) behaves as an efficient supramolecular host and base catalyst (Scheme 1). In the first step, ylidemalononitrile is formed by Knoevenagel condensation between malononitrile and aldehyde. In the second step, Michael addition of 1,3-cyclohexanedione/dimedone to ylidemalononitrile takes place followed by cyclization and tautomerization to give the 2-amino-4*H*-benzopyrans.

To gain further evidence for the proposed mechanism, ^{1}H NMR spectra of the reaction mixture is recorded in DMSO-d_6, as per-6-NH_2-β-CD is insoluble in deuterium oxide. (Only the protonated form (per-6-NH_3^+-β-CD) is soluble in D_2O, which does not catalyze the reaction.) ^{1}H NMR spectra for per-6-NH_2-β-CD (Figure1a), per-6-NH_2-β-CD-4-nitrobenzaldehyde inclusion complex (Figure 1b), and the mixture of per-6-NH_2-β-CD-4-nitrobenzaldehyde after the addition of malononitrile and dimedone (Figure 1c) are recorded and are given in Figure 1. The chemical shifts of cyclodextrin protons in DMSO-d_6 were reported previously.[47] From Figure 1, it is clear that there is a downfield shift from 3.988 to 3.998 (0.01 ppm) of H5 protons of per-6-NH_2-β-CD-4-nitrobenzaldehyde complex compared to per-6-NH_2-β-CD, indicating complex formation.[48] The inclusion of the aldehyde side of the phenyl ring inside the CD cavity is evident from energy-minimization studies (Figure S4, Supporting Information). This mode of inclusion has lower complexation energy (ΔE = −55.64 kcal·M^{-1}) than the other mode (ΔE = −52.98 kcal·M^{-1}), in which the nitro group is inside the CD cavity.

When malononitrile and dimedone are added, the proton meta- to the nitro group of 4-nitrobenzaldehyde ("H*m*-NO_2 R") is merged in the −NH_2 protons of CD. The new signal that arises at δ7.84 ppm is due to proton meta- to the nitro group of product ("H*m*-NO_2 P"), indicating that the product formation occurs as soon as the reactants are added. The ortho-proton of the product is merged with the ortho-proton of the 4-nitrobenzaldehyde. After the addition of malononitrile and dimedone, an upfield shift of −NH_2 protons by 0.038 ppm and downfield shift of H6′ proton by 0.014 ppm are observed, indicating that the reaction proceeds by complexation of malononitrile and dimedone from the primary side of cyclodextrin, which is also in accordance with the previous observation by Rama Rao and co-workers.[49] These observations clearly demonstrate that the arylaldehyde is ideally located for the condensation with malononitrile and dimedone in the CD cavity. The complexation with amino β-CD increases the reactivity of the aldehyde group due to intermolecular hydrogen bonding with the amino groups in per-6-NH_2-β-CD, evident from energy-minimization studies, facilitating the proposed sequence of reactions, namely, Knoevenagel condensation between malononitrile and aldehyde and Michael addition of 1,3-cyclohexanedione/dimedone to ylidemalononitrile followed by cyclization and tautomerization to give the 2-amino-4*H*-benzopyrans.

The proposed mechanism is also supported by energy-minimization studies. The ΔE for the intermediates 1, 2, 3, and 4 are −29.40, −39.53, −29.03, and −86.58 kcal·M^{-1}, respectively (Figures S5−S8, Supporting Information). These values indicate that, when the reaction takes place, the ΔE increases for the formation of intermediates 1−4 as proposed in Scheme 1. The change in energy is very significant in step 4, which results in formation of the final product. To ensure that the reaction involves inclusion of all the reactants inside the CD cavity, control experiments are carried out with adamantanol included per-6-NH_2-β-CD (binding constant 2248 M^{-1}). As adamantanol competes with aldehyde to complex with CD, a decrease in conversion (46%) is noticed. This is also evident from the decrease in yield for disubstituted aldehydes (Table 2, entries 7, 8, and 10).

The atom economy observed in the reaction is excellent with only water as the eliminated product. This study thus demonstrates the efficiency of per-6-NH_2-β-CD as an excellent supramolecular host as well as a reusable base catalyst.

In summary, we have developed an environmentally benign technique for the synthesis of 2-amino-4*H*-benzo[*b*]pyrans in excellent yields and purities with very short reaction times, less than 5 min (in most cases), from readily available starting materials by using a minimum amount of per-6-amino-β-cyclodextrin as a reusable catalyst, in solventless conditions. This novel, environmentally friendly methodology with excellent green chemistry credentials, such as use of the minimum amount of reusable, nontoxic supramolecular catalyst and shorter reaction time without any byproduct in solvent-free conditions, may find a wide range of applications. This attractive atom-economical protocol can also be efficient on a multigram scale and thus has promising industrial applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, experimental procedures, characterization data for compounds, and copies of ^{1}H, ^{13}C NMR, and ESI-MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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