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β-Cyclodextrin: a green supramolecular catalyst assisted eco-friendly one-pot three-component synthesis of biologically active substituted pyrrolidine-2-one†

Subhankar Paul,[a] Sharmistha Das,[a] Bijeta Mitra,[a] Gyan Chandra Pariyar[b]
and Pranab Ghosh *[a]

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A green, novel and eco-efficient synthetic route towards the synthesis of highly substituted bio-active pyrrolidine-2-one derivatives was demonstrated using β-cyclodextrin, a water-soluble supramolecular solid as a green and eco-benign catalyst at room temperature under water–ethanol solvent medium. The exploration of the green catalyst β-cyclodextrin for the metal-free one-pot three-component synthesis of a wide range of highly functionalized bio-active heterocyclic pyrrolidine-2-one moieties from easily available aldehydes and amines explains the superiority and uniqueness of this protocol.

1. Introduction

A significant amount of research work is dedicated towards the development of novel nitrogen-based heterocyclic molecules. Not only are they present in abundance in nature, but their unique structural skeleton also demonstrates their importance in the biological system and medicinal chemistry. Among them, the five-membered ring systems with a pyrrolidine moiety have gained increased attention lately due to their diverse medicinal properties, which include antibacterial, antibiotics, antitumor and cytotoxic effects.

The pyrrolidine ring system that includes nicotine,[1] tryptamine and vinblastine possesses considerable biochemical, pharmaceutical, agricultural importance. These natural compounds may have hydroxyproline, 2-pyrrolidone, streptopyrrolidine or diphenylprolinol rings as a component in their well-defined conformations. The pyrrolidinone nucleus is rated as one of the most important heterocyclic compounds, featuring notable pharmaceutical effects and acting as a versatile precursor in the design of powerful bio-active agents and intricate medicinally important compounds. Polysubstituted 3-hydroxy-2-pyrrolidinones are an important part of the framework in many biologically active compounds and have found wide applications in pharmaceutical and agricultural sectors.[2] Some of the biologically active compounds and natural products containing the pyrrolidinone moiety are aniracetam, doxapram,[3] cotinine, clausenamide, lactacystin,[4] ethosuximide, codonopsinine, pyrrolidinone quercetin,[5] azaspirene[6] and salinosporamide A[7] (Fig. 1). This fascinating group of compounds has diverse pharmacological activities, such as antidepressant, anti-malarial, antibacterial, antifungal, anti-cancer and anti-convulsant. Substituted 3-pyrrolin-2-ones with a 2-pyrrolidinone[8] moiety are also used in medicinal chemistry, as many derivatives show significant pharmacological and biological activities, such as anti-cancer agents,[9] anti-tumour,[10] HIV-1 integrase inhibitors,[11] anti-microbial,[12] antibacterial[13] and anti-inflammatory.[14]

Nowadays, there is a rising interest towards using supramolecular chemistry and homogeneous catalysts, as they play an important role in synthesizing organic heterocyclic compounds[15] and pharmaceutically important compounds. β-Cyclodextrin, a major class of cyclodextrins, is a family of cyclic oligosaccharides consisting of a macrocyclic ring of 7 glucose subunits joined by α-1,4 glycosidic bonds and is an important enzyme model.[16] As with other cyclodextrins, β-cyclodextrin also uses its internal hydrophobic cavity to encapsulate biologically active molecules from aqueous solution and to selectively bind the organic substrates. β-Cyclodextrin catalyzes the organic transformations with high selectivity[17] by non-covalent supramolecular bonding with the reversible formation of host–guest complexes as seen in enzymes, which gradually increases the bioavailability and stability of drug molecules. β-Cyclodextrin activates a variety of organic compounds like aldehydes, ketones, anhydride, oximes, amines, nitriles and increases the rate of reactions.[18] These properties of β-CD recognises it as an

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[a] Department of Chemistry, University of North Bengal, District-Darjeeling, West Bengal, India. E-mail: pizy12@yahoo.com; Fax: +91 0353 2699001; Tel: +91 0353 2776381

[b] Department of Food Technology, University of North Bengal, District-Darjeeling, West Bengal, India

† Electronic supplementary information (ESI) available: All of the experimental details and the spectroscopic details, *i.e.*, spectroscopic data and all the scanned copies of ^{1}H, ^{13}C &^{19}F NMR spectra of the synthesised derivatives. See DOI: https://doi.org/10.1039/d2ra08054k

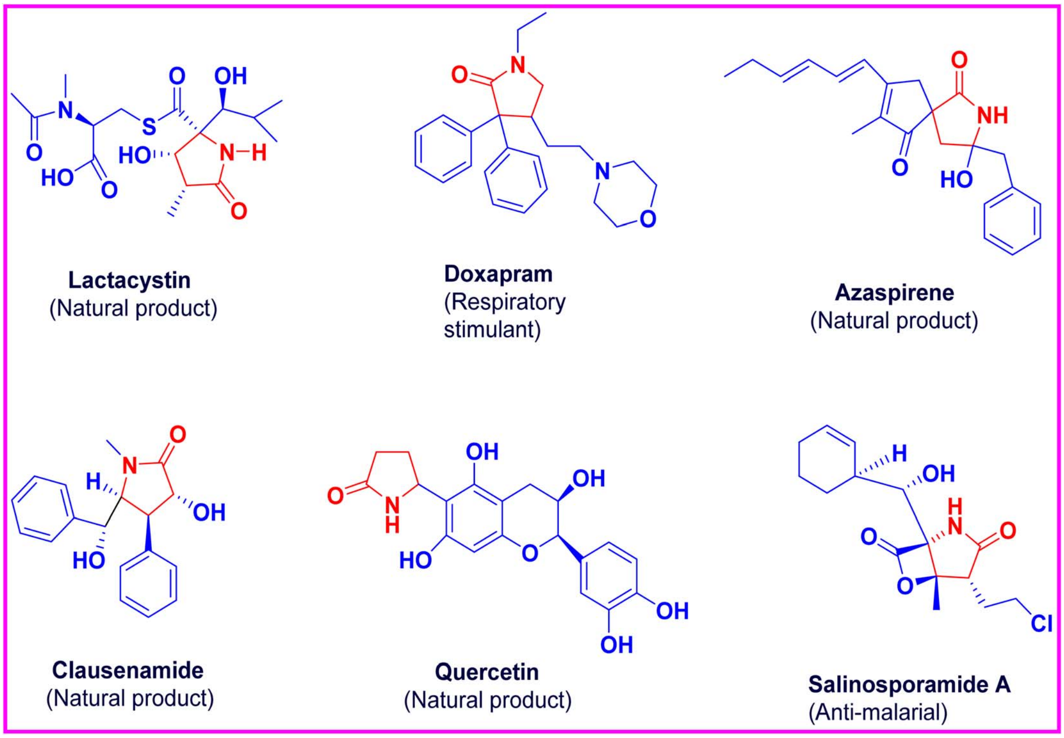


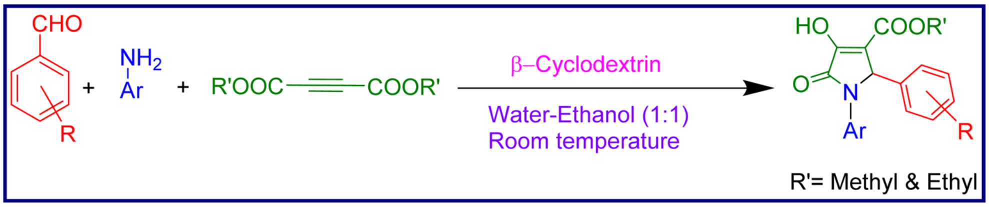
Fig. 1 Biologically active compounds and natural products containing the pyrrolidinone motif.

important asset for pharmaceutical industries, as well as for synthetic chemistry. Moreover, β-CD is easily available, recyclable, inexpensive, and water-soluble due to the presence of a hydrophilic external part, and is a mild and non-toxic supramolecule.[19] This account summarises our efforts in designing an important organic transformation using β-cyclodextrin, as well as a greener synthetic route to a variety of biologically relevant organic molecules.

In the last few decades, many research works for the synthesis of biologically active heterocyclic compounds have been empowered by one-pot multi-component reactions (MCRs).[20] These reactions have considerable importance in organic synthesis, as well as in the medicinal and pharmacological sectors. In comparison with multi-step reactions, a multi-component synthesis involves three or more starting materials that react together in the same reaction vessel to exclusively produce the desired product molecule without the need of separating the intermediates. This makes the reaction time shorter, reduces the wastage of solvents, and completes the reaction with low consumption of energy.

In organic synthesis using the MCR strategy, the catalyst and solvents play a very pivotal role. Use of highly volatile solvents or transition metal and lanthanide metal catalysts may have detrimental environmental effects. Furthermore, the catalysts might be associated with drawbacks such as high cost, low compatibility, difficulty in handling, and being easily ruined by impurities. These limitations of metal catalysts and organic solvents can be overcome by using any green organo-catalyst and green eco-friendly solvent, which will be beneficial to our environment. Water and ethanol are versatile solvents, and the water–ethanol system is now broadly used from the view of a greener approach. The aqueous–ethanol mixture as a reaction medium has been greatly beneficial in many instances.[21] This not only offers a homogenous medium for many reactions, but also provides rate accelerations in several others. The water–ethanol reaction medium has been demonstrated to be an efficient system for the multi-component synthesis of biologically potent heterocyclic derivatives.[22–24]

Numerous examples of multi-component synthesis of pyrrolidinone derivatives using a variety of catalysts, such as the



Scheme 1 β-Cyclodextrin-mediated synthesis of functionalised pyrrolidine-2-ones.

ionic liquids [BBSI][HSO_4] and [BBSI][Cl],[25] magnetic solid acid catalysts [Fe_3O_4@SiO_2@NMPs], [Fe_3O_4@SiO_2@Cl NMPs] and [Fe_3O_4@SiO_2@propyl-ANDSA],[26] metal catalyst [$Cu(OAc)_2$],[27] metal–organic framework [UiO-66-SO_3H],[28] TiO_2-nanoparticle in aqueous CTAB solution,[29] tetragonal-ZrO_2 nanocatalyst,[30] ethanolic citric acid under US condition,[31] ionic liquid [bmim] BF_4 in PEG-400,[32] photocatalyst Rose Bengal in CH_3CN–H_2O under visible light,[33] acid catalyst PTSA,[34] and carbocatalyst graphene oxide,[35] have been reported in the literature. These working routes for synthesising pyrrolidinones include the condensation of aryl anilines, aromatic aldehydes and dialkylacetylenedicarboxylates using various metal catalysts, lanthanide catalysts, ionic liquids, nanoparticles, and acids. Although these synthetic routes of pyrrolidinone derivatives may have advantages, they still suffer from limitations such as the use of hazardous solvents, harsh reaction conditions, high temperature, long reaction time, complex synthetic pathways, low yield, limited structural diversity, functional group tolerability and metal contamination at the end of the reaction. Synthesising and characterising the metal catalysts, magnetic nanoparticles, lanthanide metal catalysts, and ionic liquids make these processes expensive, complex, time-consuming, and difficult to carry out under mild conditions or separate the products in a simple way. Consequently, better quality approaches for synthesising pyrrolidinone derivatives with a precise, straightforward, green, eco-efficient one-pot multicomponent reaction in the absence of transition metal or lanthanide metal catalyst and harmful organic solvents are still unknown, and will be well accepted in synthetic organic chemistry.

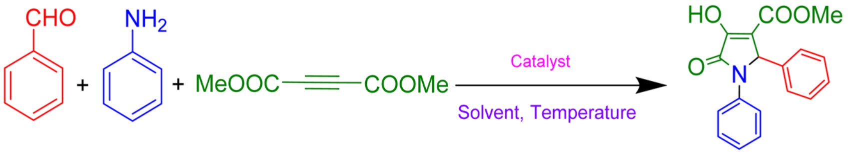
Taking into consideration all the above mentioned factors, we have succeeded in employing a combination of water–ethanol and β-cyclodextrin at room temperature for a greener synthesis of substituted pyrrolidinone derivatives (Scheme 1).

2. Experimental section

2.1 General procedure for the synthesis of methyl/ethyl 2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate and methyl/ethyl 1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

β-Cyclodextrin (10 mg) and 2 ml of water–ethanol (1 : 1 ratio) were added to the mixture of aldehydes (1 mmol), amines (1 mmol) and dimethylacetylenedicarboxylate (1.2 mmol) or diethylacetylenedicarboxylate (1.2 mmol) contained in a reaction vessel. The resulting reaction mixture was then stirred in a magnetic stirrer at room temperature for 8 h in open air. The progress of the reaction was monitored by TLC using petroleum ether and ethyl acetate as the eluent solvent in a silica bed on an aluminium sheet. After completion of the reaction as indicated by TLC, a large amount of water and ethyl acetate were added to the reaction mixture, and the product was extracted thrice by ethyl acetate with the help of a separating funnel. The extracted ethyl acetate solution was then passed through the bed of anhydrous sodium sulphate (Na_2SO_4) to make it a completely water-free organic solution, and evaporated to achieve a significant volume reduction. The crude product or crystal product obtained was then purified by filtering and washing with ethyl acetate and petroleum ether mixture. The products obtained

Table 1 Screening of the reaction conditions[a,b]



Entry	Solvent	Catalyst loading (mg)	Temperature (°C)	Time (h)	Yield[c] (%)
1	Neat	30	100	24	45
2	Acetonitrile	30	Reflux	24	Trace
3	DMF	30	100	24	Trace
4	Methanol	30	Reflux	12	60
5	Ethanol	30	Reflux	12	65
6	Water	30	Reflux	12	70
7	Water + ethanol (1 : 1)	30	Reflux	12	75
8	Water + ethanol (1 : 1)	20	Reflux	12	75
9	Water + ethanol (1 : 1)	10	Reflux	12	75
10	Water + ethanol (1 : 1)	5	Reflux	12	40
11	Water + ethanol (1 : 1)	—	Reflux	12	—
12	Water + ethanol (1 : 1)	10	70	12	77
13	Water + ethanol (1 : 1)	10	50	12	79
14	Water + ethanol (1 : 1)	10	r.t.	12	80
15	**Water + ethanol (1 : 1)**	**10**	**r.t.**	**8**	**82**

[a] The bold numbers represent the optimised condition. [b] Reaction of benzaldehyde (1 mmol), aniline (1 mmol), and dimethylacetylenedicarboxylate (1.2 mmol). [c] Isolated yield after purification.

were known compounds, and identified through ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectroscopies.

2.2 Spectroscopic data of the synthesized compounds

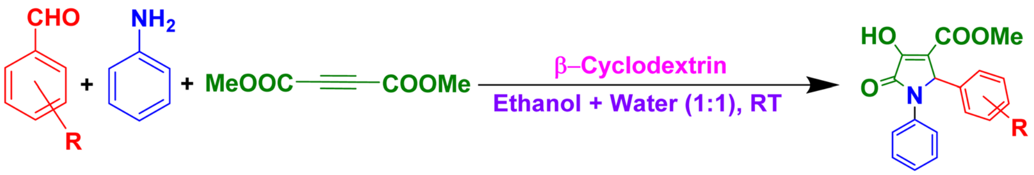
2.2.1. Methyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4a). Pale white solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.562 (s, 3H), 6.048 (s, 1H), 7.194–7.261 (m, 8H), 7.541 (d, 2H, $J = 7.6$ Hz), 11.746 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 51.570, 61.003, 112.399, 122.976, 125.816, 128.107, 128.381, 128.730, 129.127, 136.695, 136.943, 152.996, 162.920, 164.403.

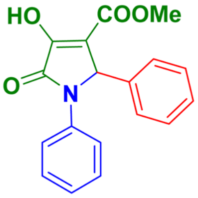
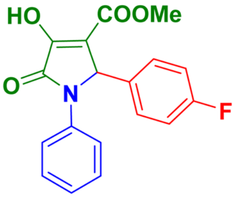
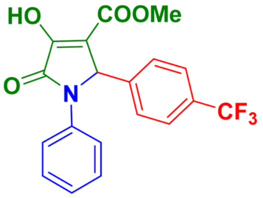
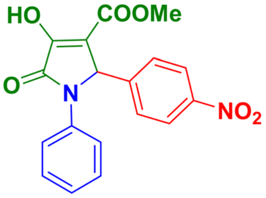
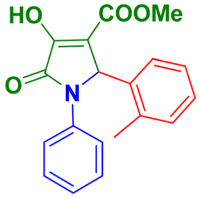
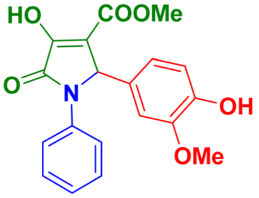
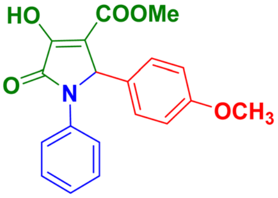
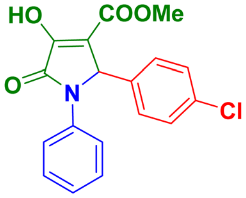
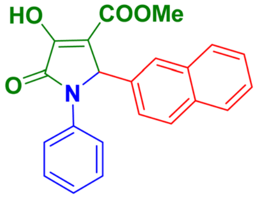
2.2.2. Methyl 4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4d). Pale yellow solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.483 (s, 3H), 6.098 (s, 1H), 7.026–7.063 (m, 1H), 7.236–7.275 (m, 2H), 7.516–7.599 (m, 4H), 8.040 (d, 2H, $J = 8.4$ Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 50.621, 59.853, 122.489, 123.629, 125.467, 129.145, 129.395, 137.246, 147.135, 147.950, 164.154.

2.2.3. Methyl 4-hydroxy-5-oxo-1-phenyl-2-(*o*-tolyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4e). Pale yellow solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 2.555 (s, 3H), 3.579 (s, 3H), 6.260 (s, 1H), 7.000–7.109 (m, 5H), 7.266–7.305 (m, 2H), 7.416–7.561 (m, 2H), 11.684 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 19.520, 51.592, 57.046, 113.167, 123.287, 125.276, 126.133, 126.617, 128.007, 129.228, 130.859, 134.953, 136.881, 137.810, 153.269, 163.106, 164.732.

2.2.4. Methyl 4-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4f). Pale yellow solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.335 (s, 3H), 3.657 (s, 3H), 5.946 (s, 1H), 6.574–6.642 (m, 2H), 6.768 (d,

Table 2 Synthesis of methyl 2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4a–4i**)[a]



 4a, 82%	 4b, 88%	 4c, 90%
 4d, 85%	 4e, 68%	 4f, 70%
 4g, 72%	 4h, 87%	 4i, 67%

[a] Reaction with aldehydes (1 mmol), aniline (1 mmol), dimethylacetylenedicarboxylate (1.2 mmol) with 10 mg of β-CD in 1 : 1 ratio of water–ethanol at room temperature for 8 h.

1H, $J = 8$ Hz), 7.091 (t, 1H, $J = 7.2$ Hz), 7.269–7.308 (m, 2H), 7.552 (d, 2H, $J = 8$ Hz), 8.911 (s, 1H), 11.558 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 51.535, 56.100, 60.642, 112.224, 112.506, 115.700, 120.689, 121.478, 123.234, 125.759, 127.270, 128.495, 129.043, 136.840, 146.638, 147.686, 152.715, 163.023, 164.299.

2.2.5. Methyl 4-hydroxy-2-(naphthalen-2-yl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4i). White solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.539 (s, 3H), 6.228 (s, 1H), 6.997–7.034 (m, 1H), 7.216–7.274 (m, 3H), 7.426–7.448 (m, 2H), 7.597 (d, 2H, $J = 7.6$ Hz), 7.720–7.785 (m, 2H), 7.831–7.854 (m, 1H), 11.848 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 51.589, 61.185, 112.229, 123.072, 124.878, 125.871, 126.691, 127.940, 128.197, 128.473, 129.127, 133.052, 134.415, 136.703, 153.224, 162.991, 164.485.

2.2.6. Methyl 4-hydroxy-5-oxo-2-phenyl-1-(1*H*-1,2,4-triazol-3-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (5c). White solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.526 (s, 3H), 6.350 (s, 1H), 7.209–7.369 (m, 5H), 7.718 (s, 1H), 11.689 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 52.253, 53.656, 59.317, 98.725, 127.375, 128.854, 129.135, 139.934, 141.102, 146.795, 151.028, 163.670, 164.415.

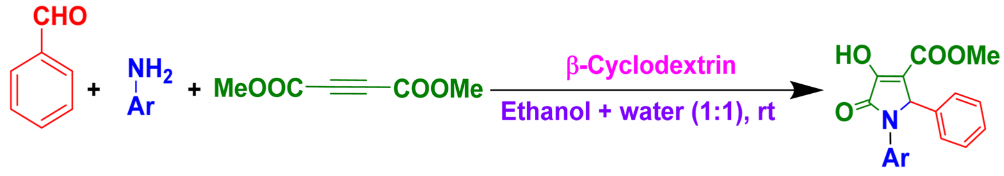
2.2.7. Methyl 4-hydroxy-5-oxo-2-phenyl-1-(1*H*-tetrazol-5-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (5d). White solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 3.535 (s, 3H), 6.761 (s, 1H), 7.300–7.415 (m, 5H), 12.232 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 52.487, 53.848, 58.784, 99.918, 127.622, 129.452, 139.429, 139.940, 148.604, 163.304, 163.931.

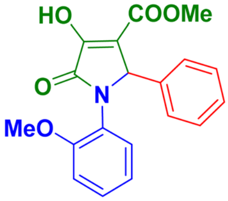
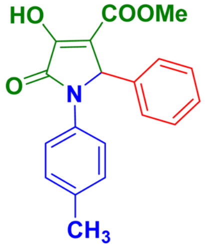
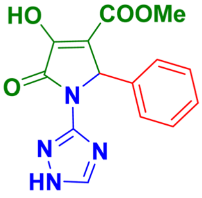
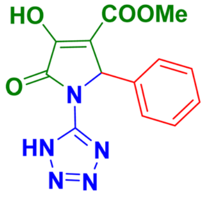
2.2.8. Ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (6a). White solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 1.028 (t, 3H, $J = 7$ Hz), 3.893–3.951 (m, 2H), 5.876 (s, 1H), 7.025–7.258 (m, 8H), 7.555 (d, 2H, $J = 8$ Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 14.601, 58.834, 60.255, 60.781, 122.594, 125.173, 127.690, 128.075, 128.310, 128.969, 137.538, 139.488, 163.745, 166.990.

2.2.9. Ethyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (6e). Pale white solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 1.037 (t, 3H, $J = 7$ Hz), 3.622 (s, 3H), 3.887–3.937 (m, 2H), 5.813 (s, 1H), 6.709 (d, 2H, $J = 8.4$ Hz), 6.995–7.032 (m, 1H), 7.091–7.115 (m, 2H), 7.210–7.249 (m, 2H), 7.542 (d, 2H, $J = 8.4$ Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 14.749, 55.310, 58.708, 60.224, 113.676, 122.605, 125.021, 128.913, 129.157, 131.310, 137.637, 158.690, 163.866, 167.060.

2.2.10. Ethyl 4-hydroxy-1-(3-nitrophenyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (7a). Pale white crystal, ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 1.068 (t, 3H, $J = 7$ Hz), 3.951–4.089 (m, 2H), 6.206 (s, 1H), 7.135–7.238 (m, 3H), 7.315 (d, 2H, J

Table 3 Synthesis of methyl-1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (5a–5d)[a]



 5a, 74%	 5b, 75%
 5c, 65%	 5d, 64%

[a] Reaction with benzaldehyde (1 mmol), aryl amines (1 mmol), dimethylacetylenedicarboxylate (1.2 mmol) with 10 mg of β-CD in 1 : 1 ratio of water–ethanol at room temperature for 8 h.

= 7.6 Hz), 7.533–7.574 (m, 1H), 7.895–7.963 (m, 2H), 8.606 (s, 1H), 11.877 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 14.421, 60.284, 60.950, 113.338, 116.765, 120.142, 128.271, 128.633, 128.858, 130.581, 136.381, 137.839, 148.268, 152.542, 162.277, 164.976.

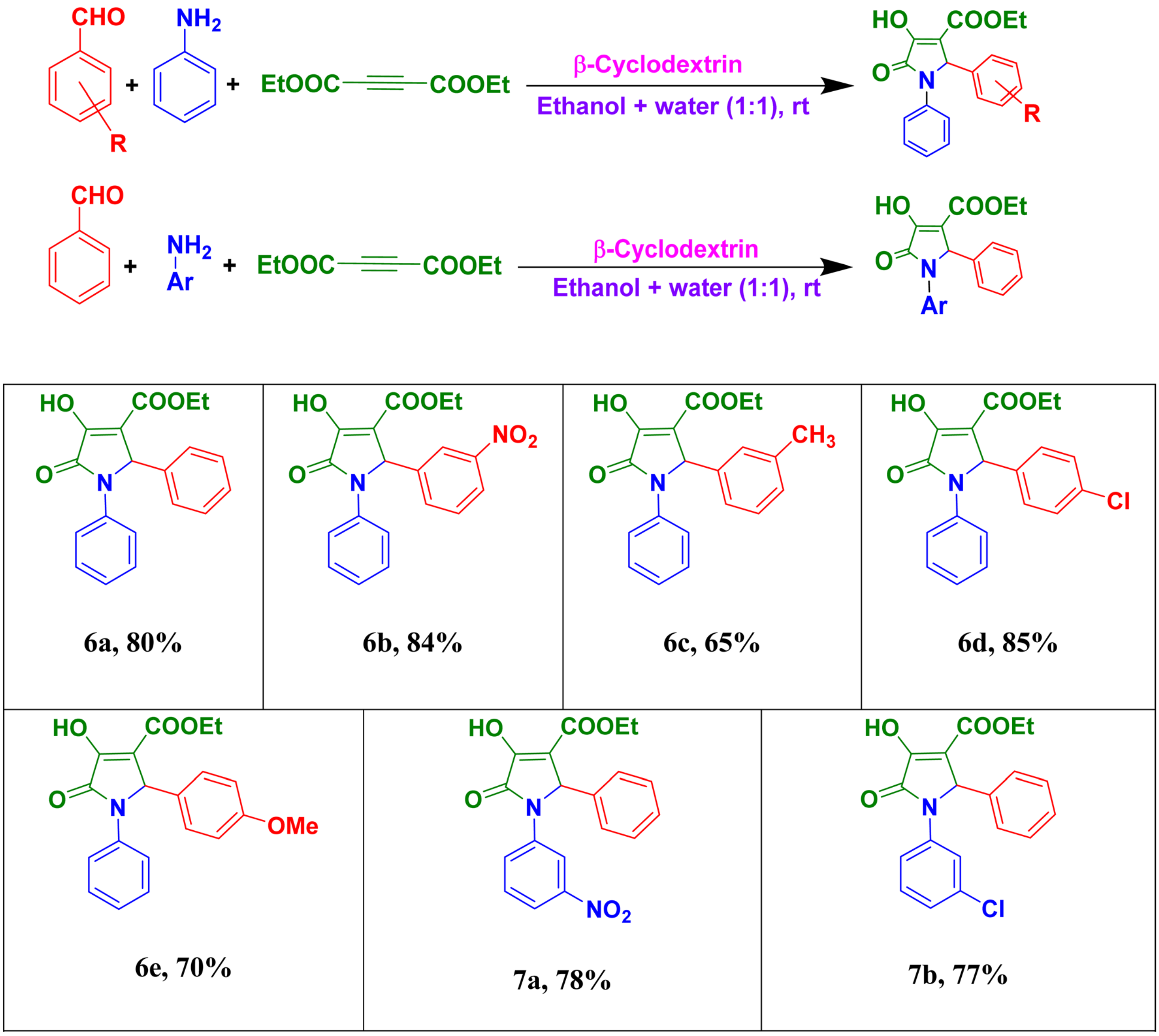
3. Result and discussion

3.1 Optimisation of reaction conditions

For the optimisation of the reaction conditions, reaction parameters such as the solvent, temperature, time and amount of catalyst used were observed to have a wide influence on the reaction, and also on the yield of the desired product. To begin our study, we have taken benzaldehyde, aniline and dimethylacetylenedicarboxylate in 1 : 1 : 1.2 ratios as a model reaction. We have performed the reaction in various solvents, such as acetonitrile, DMF, methanol, ethanol, water, water–ethanol mixture, as well as in solvent-free condition, and all the experimental results are summarised in Table 1.

At first, the reaction was carried out in solvent-free condition with 30 mg of the β-CD at 100 °C for 24 h. It was observed that only a small amount of the desired product (Table 1, entry 1) was formed. Then, the same reaction was performed in various aprotic solvents, such as acetonitrile and DMF, with 30 mg β-CD under reflux condition and 100 °C, respectively. Under such reaction conditions, only a trace amount of the desired product was formed even after 24 h (Table 1, entries 2 and 3). After that, various polar protic solvents such as methanol and ethanol were

Table 4 Synthesis of ethyl-2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**6a–6e**)^a and synthesis of ethyl-1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**7a** and **7b**)^b



[a] Reaction with aldehydes (1 mmol), aniline (1 mmol), diethylacetylenedicarboxylate (1.2 mmol) with 10 mg of β-CD in 1 : 1 ratio of water–ethanol at room temperature for 10 h. [b] Reaction with benzaldehyde (1 mmol), aryl amines (1 mmol), diethylacetylenedicarboxylate (1.2 mmol) with 10 mg of β-CD in 1 : 1 ratio of water–ethanol at room temperature for 10 hours.

screened with 30 mg β-CD under reflux condition for 12 h, and we were happy to observe a good amount of the desired product formation. With ethanol, the yield was quite high (Table 1, entries 4 and 5). Then, we carried out the same reaction in aqueous medium under reflux condition for 12 h, where an excellent amount of the expected product was formed (Table 1, entry 6). From this observation, it was concluded that water was necessary to perform the reaction perfectly with better conversion since β-CD is highly water-soluble. Then, we tried the same reaction with water and ethanol in a 1 : 1 ratio under reflux condition for 12 h with 30 mg catalyst, and the expected product was formed in high yield (Table 1, entry 7). From this, it was clear that water–ethanol in a 1 : 1 ratio is the ideal solvent for this organic transformation.

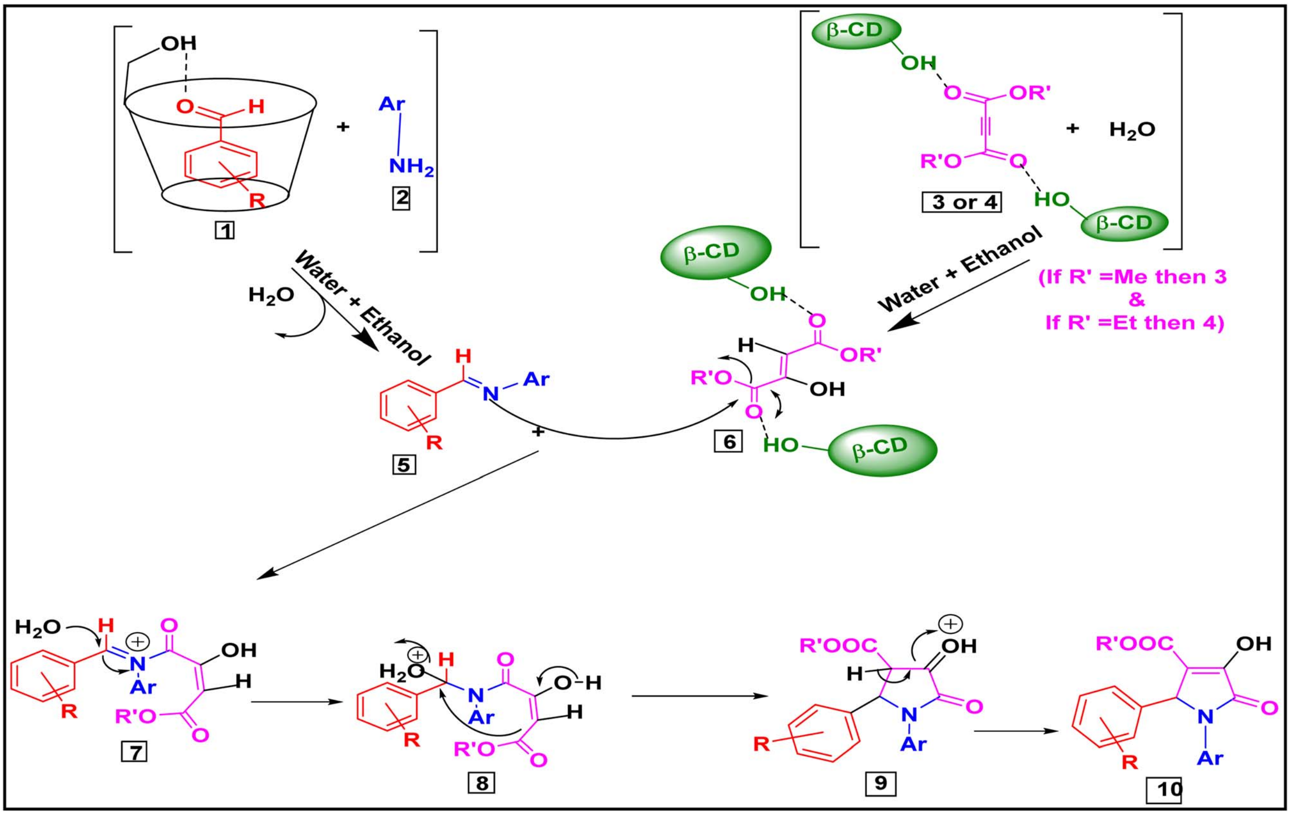
We then reduced the amount of the catalyst to 20 mg and 10 mg, where almost the same amount of the desired product was obtained (Table 1, entries 8 and 9). Since 30 mg, 20 mg and 10 mg of the catalyst gave nearly the same amount of the desired product under the same reaction condition, it can be concluded that 10 mg of the catalyst was sufficient for the reaction. After that, on further reducing the amount of catalyst to 5 mg, a low amount of the product was obtained (Table 1, entry 10). No desired product was obtained without any catalyst (Table 1, entry 11). Now, from these observations, it can be concluded that for our reaction, 10 mg β-CD was adequate enough to get good yield of the products.

After that, we started optimizing the temperature and time. The reaction was carried out in a solvent mixture containing 1 : 1 ethanol–water ratio for 12 h with 10 mg of β-CD at different temperatures, such as 70 °C, 50 °C and room temperature (Table 1, entries 12–14). It was observed that the best result was obtained at room temperature (Table 1, entry 14). Furthermore, the expected product separation became easier for the reaction carried out at room temperature since the side product formation was minimized. Now, when the time was reduced to 8 h, it was found that the yield of the desired product was almost the same (Table 1, entry 15). Hence, from these above-mentioned observations during the screening of the reaction conditions, it can be concluded that the reaction with 10 mg of β-CD and 1 : 1 ratio of water–ethanol solvent at room temperature for 8 h was the best condition for our work.

3.2 Investigating products

For the summary of this research scheme, numerous aldehydes and amines were treated with dialkylacetylenedicarboxylate (alkyl = methyl & ethyl) under the optimised reaction condition to project a versatile range of alkyl-2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate and alkyl-1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (alkyl = methyl &ethyl) derivatives (Tables 2–4). Here, all the pure solid products were isolated without column chromatography.

In Table 2, from the result of investigation, it was detected that aldehydes with electron-withdrawing groups on the benzene ring, *e.g.*, 4-fluorobenzaldehyde (Table 2, **4b**), 4-



Scheme 2 Plausible mechanism for β-cyclodextrin-mediated synthesis of functionalised pyrrolidine-2-ones.

trifluoromethylbenzaldehyde (Table 2, **4c**), 4-nitrobenzaldehyde (Table 2, **4d**) and 4-chlorobenzaldehyde (Table 2, **4h**) gave good yield of the desired product, whereas the aldehydes with electron-donating groups on the benzene ring, *e.g.*, *o*-tolubenzaldehyde (Table 2, **4e**), vanillin (Table 2, **4f**), 4-methoxybenzaldehyde (Table 2, **4g**) and 2-naphthaldehyde (Table 2, **4i**) offered quite low yields of the desired product. It was also found that benzaldehyde itself (Table 2, **4a**) gave high yield of the desired product.

We further extended our protocol for the synthesis of methyl-1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives using various aryl amines with benzaldehyde and dimethylacetylenedicarboxylate (Table 3). Here, aromatic amines having electron-donating groups on the benzene ring (like before) also gave good yield of the product. With heterocyclic amines, *e.g.*, triazole (Table 3, **5c**) and tetrazole (Table 3, **5d**) amines, a low yield of the desired products was observed.

We further used the protocol for the synthesis of ethyl-2-aryl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate and ethyl-1-aryl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives using various aromatic aldehydes, aniline and diethylacetylenedicarboxylate and various aryl amines, benzaldehyde and diethylacetylenedicarboxylate, respectively (Table 4). These procedures needed 10 h to complete under the optimized conditions.

3.3 Mechanism

A plausible mechanism for the synthesis of various 1,2,3-functionalised 4-hydroxy pyrrolidine-5-ones is shown in Scheme 2. The supramolecular catalyst β-CD synergistically behaves as an effective host molecule for various types of organic compounds due to the presence of its seven free primary –OH groups. Our catalyst β-CD possibly activates both aryl aldehyde (1) and di(methyl/ethyl) acetylene dicarboxylate (3, 4) derivatives simultaneously as the active electrophilic species, and hence facilitates the further reaction. The condensation reaction of aryl amines (2) with these activated electrophilic aldehydes with the loss of water, along with the reaction of water with activated electrophilic di(methyl/ethyl) acetylene dicarboxylate derivatives, may then generate the corresponding intermediates (5) and (6), respectively. After that, the reaction between these two intermediates (5) and (6) will yield the corresponding intermediate (7). Finally, a series of tautomerization, cyclization and aromatisation reactions generate the intermediates (8), (9), and finally the product molecule (10).

4. Conclusion

In conclusion, we present a straightforward, vigorous, simplistic, eco-friendly and green approach for the synthesis of 1,2,3-functionalised 4-hydroxy pyrrolidine-5-one derivatives using a bio-degradable, eco-benign, green, supramolecular catalyst β-cyclodextrin, in water–ethanol medium. Furthermore, the reaction was carried out without using any additional metal catalyst or metal salt, volatile organic solvent under mild reaction conditions which boosts the benefits of the procedure. The replacement of toxic and costly metal catalysts with an eco-friendly, bio-degradable, green and inexpensive organo-catalyst is the unique benefit of this synthetic procedure. This environmentally-benign approach is likely to reach widespread applications in the pharmaceutical industry, organic synthetic chemistry and natural product synthesis.

Author contributions

S. Paul and S. Das have completed the whole experimental work, and contributed equally to these methodologies. Dr B. Mitra and Dr G. C. Pariyar helped them in the selection of work and preparation of manuscript under the supervision of Prof. P. Ghosh.

Conflicts of interest

The authors declare no conflict of interest.

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