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FULL PAPER

Supramolecular catalysis by β-cyclodextrin for the synthesis of kojic acid derivatives in water

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Evgeny A. Kataev,*[a] Mittapalli Ramana Reddy,[a] Gangarpu Niranjan Reddy,[b] Vemulapati Hanuman Reddy,[b] Cirandur Suresh Reddy*[c] and Basi V. Subba Reddy*[b]

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An efficient and green method has been developed for the synthesis of kojic acid derivatives employing 20 mol% β-cyclodextrin in aqueous media. The high functional group tolerance and shorter reaction times make this method suitable for the synthesis of kojic acid derivatives with a wide substitution pattern.

Introduction:

In recent years, environmental protection laws and global warming effects have impelled the researchers to utilize renewable sources for chemical processes with minimum of waste or zero discharge. Therefore, the development of eco-friendly processes is one of the great challenges for organic chemists. On the other hand, kojic acid and its analogues have emerged as promising scaffolds[1] because of their broad spectrum of biological activities such as herbicidal,[2] antimicrobial,[3] pesticidal and insecticidal behaviour.[4] In particular, kojic acid is used as skin lightening/depigmentation agent in personnel care products.[5] It is known to inhibit the tyrosinase, which is responsible for the formation of melanin in skin.[6] Furthermore, it is used as an antioxidant in food stuff.[7] In addition, it acts as a bidentate ligand to form a stable metal complex with different metal ions.[8] These metal complexes are used as drugs for the treatment of various diseases.[9,10]

In view of the importance of these heterocycles, various synthetic methods have been developed for the synthesis of kojic acid derivatives.[11] Recently our group has reported the synthesis of kojic acid derivatives through a three-component reaction of kojic acid, aldehyde and 1,3-diketone or indole in solvent-free conditions.[12] Mukherjee *et al.* reported the derivatives of kojic acid by means of the

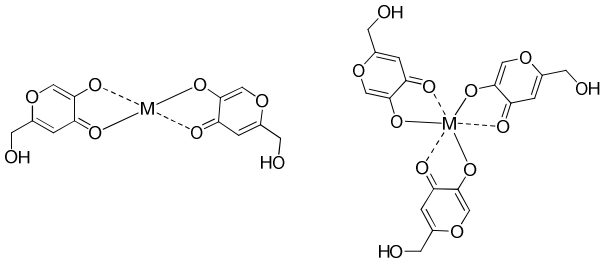


Fig. 1. Bis and tris-Kojic acid metal complexes

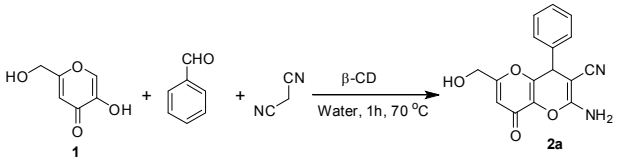
aldol reaction using alumina supported base catalyst.[13] Li *et al.* reported the synthesis of amide derivatives from aromatic aldehyde Meldrum's acid, kojic acid, and ammonium acetate using ionic liquid.[14] Imafuku *et al.* reported the formation of amino substituted kojic acid derivatives from arylidene malononitrile and kojic acid.[15] Although different approaches have been reported for the derivatization of kojic acid,[16] there are some limitations such as the use of strong basic conditions, elevated temperature, long reaction time, hazardous organic solvents and low conversions. However, the development of green, mild and simpler procedure to eliminate the use and generation of hazardous substances is the foremost goal of green chemistry. In a quest for easy and eco-friendly synthesis of amino kojic acid derivatives, we were interested to explore cyclodextrins as catalysts in aqueous medium.[17]

The most prominent feature of cyclodextrins is their capability to form inclusion complexes (host–guest complexes) with different classes of compounds.[18] Cyclodextrins contain hydrophobic cavity inside and hydrophilic hydroxyl groups outside. These macrocycles act as host molecules and form stable complexes with hydrophobic compounds.[19] Thus, by complexation they can boost a solubility in water and reduce toxicity. Cyclodextrins are cyclic oligomers of D-glucose and are named α, β and γ-cyclodextrin for the hexamer, heptamer and octamer, respectively. The cavity size of cyclodextrins determines the selectivity for a particular guest. For instance, α-Cyclodextrin can typically complex low molecular weight molecules or compounds with aliphatic side chains, β-cyclodextrin will complex aromatics and heterocycles and γ-cyclodextrin can accommodate larger molecules such as macrocycles and steroids.[20,21] Cyclodextrins are promising supramolecular catalysts in aqueous medium[22] because they are non-toxic, biodegradable and in many instances, they are recyclable.

Results & Discussion:

In this communication, we report the use of β-cyclodextrin as a catalyst in the synthesis of amino substituted kojic acid derivatives in aqueous medium (Scheme 1). Initially, we performed the three-component condensation using 20 mol% β-cyclodextrin in water at room temperature. The reaction was found to be sluggish at room temperature; however, by increasing the temperature to 70 °C, the corresponding product (**2a**) was obtained in 90% yield (Scheme 1).

Scheme 1. Synthesis of 2-amino-6-(hydroxymethyl)-8-oxo-4-phenyl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile **2a**



To optimize the catalyst, the above reaction was carried out by using different cyclodextrins. Based on screening results in Table 1, β-CD is the best catalyst than others. Low conversions were observed either by α- or by ϒ-cyclodextrins. It is clear that α -CD was not a good catalyst because the cavity of α -CD might be too small to hold three reagents. In addition, the cavity of γ-CD was too big compared to β-CD. This observation is in a good agreement with the known fact that β-CD has usually one order of magnitude higher affinity for benzene of naphthalene derivative as compared to α- and γ-CD.[23] No product formation was detected in the absence of cyclodextrin, which clearly demonstrates the catalytic role of cyclodextrin. Therefore, β-CD was preferred as a catalyst for this reaction.

Furthermore, the reaction was also performed in different solvents such as DMF, DMSO, CH_3OH, EtOH, DCM, THF and water. However, β-CD is insoluble in MeOH or EtOH.[24] After several experiments, water was found to be the best solvent due to high solubility of β-CD in water.

Table 1. Screening cyclodextrins in the formation of **2a**

Entry	Catalyst	solvent	Temp(°C)	Time(h)	Yield(%)[a]
1	-	Water	70	-	-
2	α-CD	Water	70	3	40
3	β-CD	Water	70	3	90
4	ɤ-CD	Water	70	3	35

[a] isolated yield

After the reaction, the reaction mass was cooled to RT and β-CD was filtered and washed with ice-cold water and then dried under reduced pressure. The recovered β-CD was further used in subsequent reactions with the same substrate. The catalytic activity of recovered catalyst is shown in Figure 2. The catalyst quantity and yields after two recycles were almost the same.

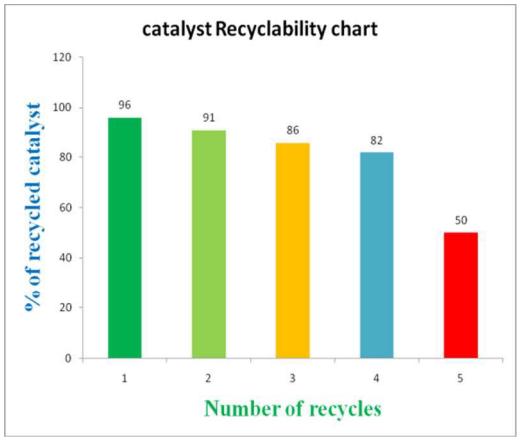
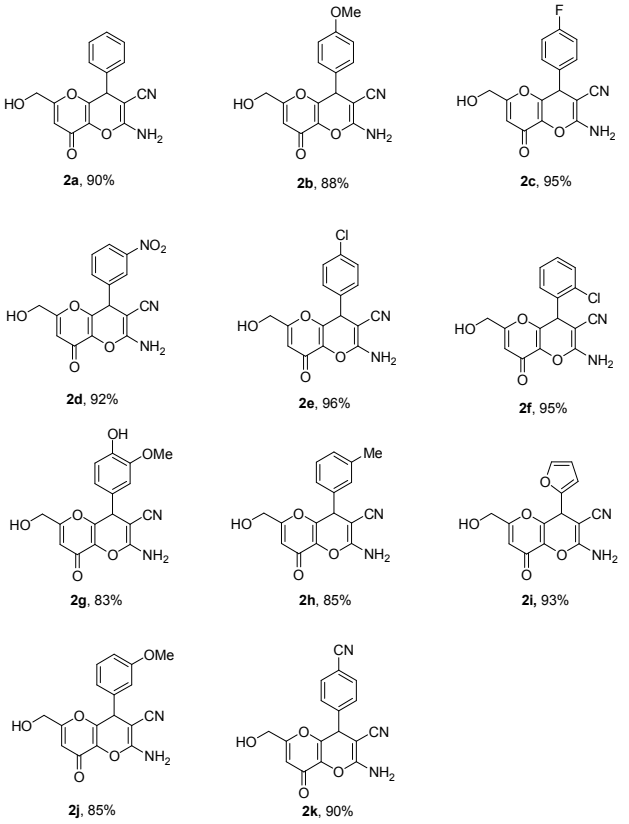


Figure 2. Recyclability of the catalyst.

After optimizing the reaction conditions, we extended this process to other substrates. The scope of the reactions is illustrated with respect to various aldehydes and the results are summarized in Table 2. Both electron-rich and electron-deficient aromatic aldehydes such as 4-cyano, 4-methoxy-, 3-methoxy, 4-hydroxy-, 3-methyl-, and 3-nitrobenzaldehydes reacted efficiently with kojic acid and malononitrile to furnish the corresponding amino substituted

kojic acid derivatives in good yields (entry **2k**, **2j**, **2g**, **2h** and **2d**, Table 2). The substituents present on the aromatic ring had shown some effect on the conversion. It was observed that both activated aromatic aldehydes (entry **2b**, **2g, 2j** and **2h**, Table 2) and deactivated aromatic aldehydes (entry **2d** and **2k**, Table 2) gave the products slightly in lower yields than halogenated aromatic counterparts (entries **c, e** and **f**, Table 2). Similarly, hetero aromatic aldehydes like furan-2-carboxaldehyde reacted well to furnish the respective amino kojic acid in good yield (entries **i**, Table 2).

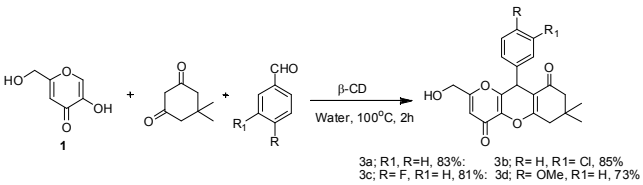
Table 2. Synthesis of amino substituted kojic acid derivatives[a,b]



[a]20 mol% β-cyclodextrin, kojic acid (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), water, 70 °C. [b]Isolated yields.

Inspired by above results, we extended this method to the condensation of kojic acid, aldehyde and 1,3-diketone. Accordingly, treatment of kojic acid (**1**) with benzaldehyde and dimedone under similar conditions afforded the cyclized product **3a** as a sole product in 83% yield (Scheme 2).

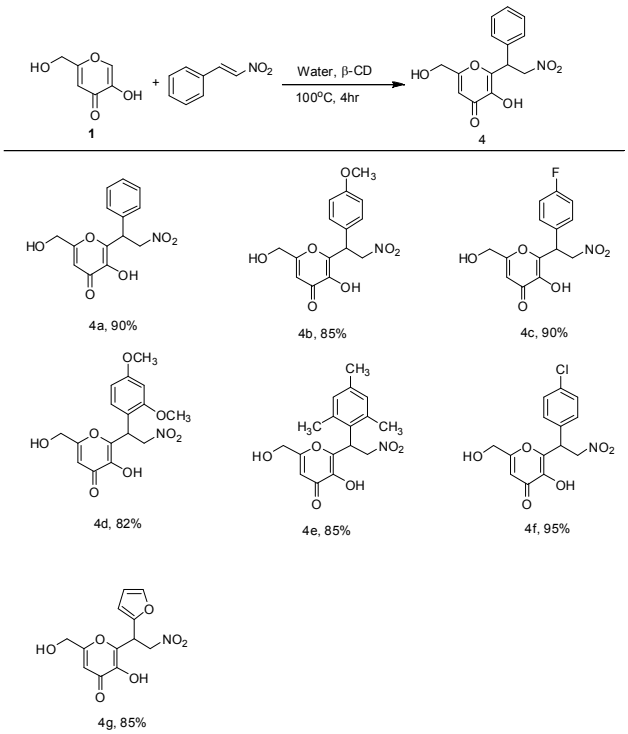
Scheme 2: Synthesis of (**3**) by three-component condensation reaction.



The scope of the reaction is illustrated with respect to various aldehydes and diketones and the results are summarized in Scheme **2**. In all cases, kojic acid reacted efficiently with diketones to furnish the desired products in good to high yields (73–85%).

Encouraged by the results obtained with aldehydes and malononitrile and diketones, we turned our attention to β-nitro styrenes. Accordingly, treatment of kojic acid with 2-(*E*)-(2-nitrovinyl)benzene under similar conditions afforded the respective nitro substituted acyclic kojic acid derivative **4a** as a sole product in 90% yield. We next extended this process for other (*E*)-(2-nitrovinyl)benzenes. The scope of the reaction is illustrated with

Table 3. Synthesis of different nitro substituted kojic acid derivatives



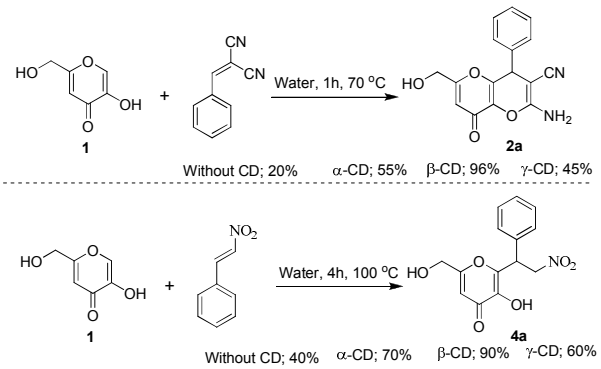
[a] Reaction condition: kojic acid 1(1 mmol), nitro styrene (1 mmol), β-CD (20 mol%) water, 100 °C. [b] Isolated yields.

respect to various nitro styrene's and the results are summarized in Table 3. In all cases, we observed good yields. Interestingly, the substituent present on the aromatic ring had shown some effect on the conversion. It was observed that halogen substituted nitro styrene gave the products in higher yields than other aromatic counterparts

(entries c and f, table 3). The reaction also works well with hetero aromatic nitro olefin. (entry g, Table 3).

Next, we studied the catalytic activity of cyclodextrins. in the reaction of Kojic acid with benzylidene malononitrile or nitro styrene in presence of α, β and γ-cyclodextrins (Scheme 3). High yields were observed when the reaction was performed using β-CD as a catalyst and lower yields were observed with α- and ϒ-cyclodextrins.

Scheme 3. Synthesis of **2a** and **4a** in the presence of different cyclodextrins.



Next, we investigated the role of *β*-cyclodextrin in the reaction with the help of ^{1}H NMR, Because it is known that *β*-cyclodextrin can encapsulate aromatic compounds, we measured spectra of *β*-cyclodextrin in the presence and in the absence of starting materials and products. Unfortunately, the products were not sufficiently solution in water to understand if they are encapsulate by cyclodextrin or not. The spectra (500MHz, D_2O) of *β*-CD-kojic acid complex, *β*-CD-benzaldehyde mixtures and free β-CD are depicted in Figure 3 and 4. An up field shifts of H3 (0.02 ppm, 0.09 ppm) and H5 (0.04, 0.16 ppm) protons of cyclodextrin in the β-CD kojic acid and *β*-CD-benzaldehyde mixtures were observed compared to the spectrum of free β-CD. These shifts indicate that the aldehyde and kojic acid are ideally located for the Knoevenagel condensation/Michael addition in the hydrophobic environment of the β-CD cavity. Thus, it is suggested that the reaction is accelerated by encapsulation and eventually activation of starting materials during the reaction.

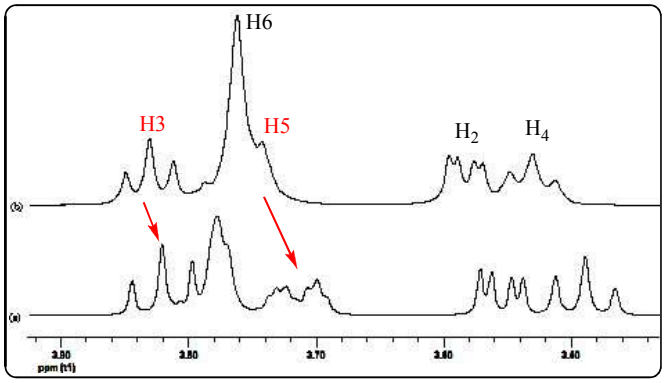


Figure 3. ^{1}H NMR spectra (500 MHz) of (a) *β*-CD- kojic acid complex and (b) *β*-CD obtained in D_2O.

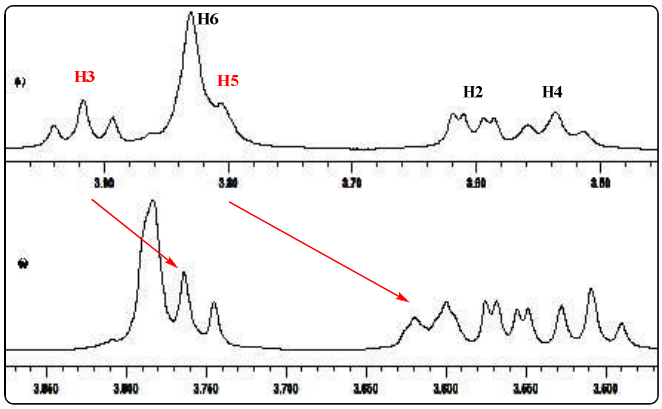
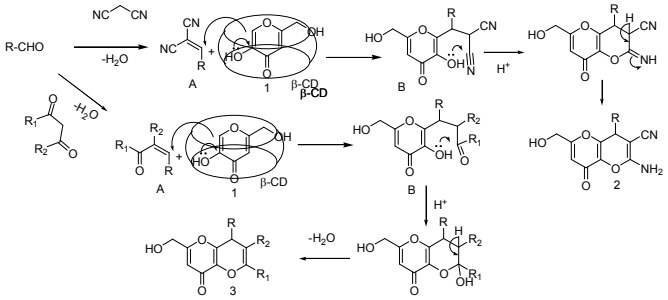


Figure 4. ^{1}H NMR spectra (500 MHz) of (a) *β*-CD- Benzaldehyde complex and (b) *β*-CD obtained in D_2O.

The catalytic activity of cyclodextrins for these reactions is documented by the fact that in the absence of cyclodextrin, the reactions were observed to proceed in very low yields even in high temperatures. Initially, the complexation of aldehyde with *β*-CD can increase the reactivity of the carbonyl group through the hydrogen bonding with *β*-CD hydroxyl groups. This activation facilitates the Knoevenagel condensation with malononitrile or diketones to form benzylidene malononitrile or dimedone derivatives. Similar activation of the kojic acid in the cavity of *β*-CD enhances its reactivity in the Michael addition

Based on experimental studies, we proposed a plausible mechanism (Scheme 4). The Knoevenagel condensation of aldehyde with malononitrile generates an intermediate **A**. Subsequent the Michael addition of the kojic acid encapsulated in β-CD on activated olefin **A** affords product **B**, which further cyclizes to give desired products **2** or **3** (Scheme 4).



Scheme 4. Proposed reaction mechanism

Conclusions:

In conclusion, an efficient method has been developed for the synthesis of biologically relevant kojic acid derivatives using β-cyclodextrin as a catalyst in aqueous medium. The operational simplicity, mild reaction conditions, short reaction time, high yields, (75–95%) and environmental friendliness are the notable features of this procedure. Reusability of the catalyst for more than two cycles without any significant loss of activity adds to the salient features of this reaction, which makes this process very useful and attractive.

Experimental:

General: All the solvents were dried according to standard procedures. Reactions were performed in oven-dried round bottom flask. The flasks were fitted with rubber septa and the reactions were conducted under nitrogen atmosphere. Glass syringes were used to transfer the solvent. Crude products were purified by column chromatography on silica gel of 60–120 or 100-200 mesh. TLC plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to acidic methanolic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporator at 35–40 °C. IR spectra were recorded on FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR (proton-decoupled) spectra were recorded on 300, 500 or 600 MHz NMR spectrometers in $CDCl_3$ and DMSO solvent. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). Mass spectra were recorded on mass spectrometer by ESI technique. Commercially available starting materials were used with out further purification.

Typical procedure for the synthesis of kojic acid derivatives:

Kojic acid (1 mmol), aldehyde (1 mmol) and malononitrile (1 mmol) were mixed in 5 mL distilled water in a 50 mL round bottom flask. To this mixture was added β-cyclodextrin (20 mol%). Then the reaction was heated to 70-100°C (70°C for 2 and 100°C for 3&4) until completion of the reaction as indicated by TLC. The reaction mixture was cooled to the room temperature and β-CD was filtered, and washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3X10 mL). The aqueous layer was cooled to 0°C and the remaining β-CD was filtered again. The combined β-CD were reused for next reaction. The organic layers were washed with water, saturated brine solution and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (8:2) as eluent to give the title compound.

Preparation of β-CD: Kojic acid Inclusion Complex.

β-CD (0.2 mmol) was dissolved in D_2O (1 mL) by warming to 50 °C until a clear solution was formed, and then kojic acid (0.2 mmol) dissolved in D_2O (1.0 mL) was added and the solution was allowed to come to room temperature. It was stirred for 3h. and solution was characterised by ^{1}H NMR.

Preparation of β-CD: Benzaldehyde Inclusion Complex.

β-CD (0.2 mmol) was dissolved in D_2O (1 mL) by warming to 50 °C until a clear solution was formed, and then benzaldehyde (0.2 mmol) was added and the solution was allowed to come to room temperature. It was stirred for 3h. and solution was characterised by ^{1}H NMR.

Notes and references

[a]Institute of Chemistry, Faculty of Natural Sciences, Technische Universität Chemnitz, 09107 Chemnitz, Germany, http://www.tu-chemnitz.de/chemie/supchem/.; Email: evgeny.kataev@chemie.tu-chemnitz.de
[b] Natural Product Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.; [c] Department of Chemistry, Sri Venkateswara University, Tirupathi 517502, AP, India.

†Electronic Supplementary Information (ESI) available: characterization data, copies of ^{1}H and ^{13}C NMR spectrum of products can be found in the online version, at. See *DOI: 10.1039/b000000x/*

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