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A highly efficient green synthesis of 1,8-dioxo-octahydroxanthenes using β-Cyclodextrin as an environmentally compatible catalyst

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Abstract: A clean, simple, and efficient synthetic protocol for the synthesis of 1,8-dioxo-octahydroxanthenes derivatives using β-Cyclodextrin as a supramolecular catalyst in water as an environmentally benign solvent has been developed. This method provides several advantages such as environmental friendliness, low cost, excellent yields, and simple workup procedure, without using column chromatography, all of the compounds were isolated in analytically pure form. The reusability of the β-Cyclodextrin was examined up to three times without losing the catalytic activity.

Keywords: Aldehydes; 5,5-dimethylcyclohexane-1,3-dione; 1,8-dioxo-octahydroxanthene; β-cyclodextrin; green synthesis

Introduction

In recent years, use of sustainable catalysts and benign solvents are considered as key points from a green chemistry point of view for the development of sustainable protocols [1,2] Therefore, organic reactions in green solvents using green catalyst have attracted much attention; especially from the viewpoints of green chemistry [3]. Green chemistry approaches can lower energy costs, waste chemicals and reduce byproducts. The possibility of carrying out multi-component reactions under green solvents using green catalyst can improve their ecological value [4]. Reactions in aqueous media are environmentally safe, devoid of carcinogenic effects due to other solvents have simple work up, and are especially suited for [5,6]. Thus, there is a need for the development of multicomponent reactions (MCRs) in water, without the use of any harmful organic solvents and hazardous catalysts. Also the recovery and reusability of the catalyst easier and avoids loss of catalyst, therefore supporting the green chemistry principles in terms of eco-benign and economical needs for sustainability.

In organic chemistry the synthesis of biologically and pharmaceutically active compounds are considered as a pivotal theme. In the past decade, synthesis of xanthenes derivatives has been of considerable interest to organic chemists; because xanthenes are common natural products and an important motif in a variety of biologically active and useful compounds [7,8]. Compounds carrying the xanthene moiety exhibit promising biological activities, such as anticancer [9], analgesic [10], anti-inflammatory [11], and antibacterial [12] activities. In addition, xanthenes derivatives can be used as pH sensitive fluorescent materials for the visualization of bio-molecular assemblies [13], as bactericides in agriculture [14] and in laser technologies [15]. Some of the xanthenes based compounds have found applications as antagonists of zoxalamine and in photodynamic therapy [16,17]. In particular, naphtha-pyranopyrimidines have been reported to be antagonists for the neuropeptide S receptor (NPSR) [18] that is a novel drug target for the treatment of respiratory, sleep, anxiety, and addiction disorders [19]. Interestingly, this structurally complex molecule can be synthesized by a simple one pot tandem reaction between an aldehyde (1 mole) and dimedone (2 mole) or cyclohexane-1,3-dione by using different catalyst which includes $NaHSO_4$-SiO_2 or silica chloride [20], polyphosphoric acid–SiO_2 [21], $In(OTf)_3$ [22], H_2SO_4 [23], $InCl_3$ or P_2O_5 [24], cerric ammonium nitrate (CAN) under ultrasound irradiation [25], succinimide-*N*-sulfonic acid [26], $CaCl_2$ [27], Fe_3O_4 nanoparticles [28], CAN supported HY-zeolite [29], Fe_3O_4@SiO_2-Imid-$H_3PMo_{12}O_{40}$ nanoparticles [30], piperidine [31], Mg-Al hydrotalcite [32], thiourea dioxide [33], and ZnO nanoparticles [34], nanotube-supported (MWCNT–$BuSO_3H$) [35], β-CD-BSA [36]. However, in the absence of a catalyst, the reaction stops just after Knoevenagel type adduct formation [37-39], to give an open chain intermediate, 2,20-aryl/alkyl methylene-bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one). However, many of the reported methods are not effective for the synthesis of the desired compounds and suffer from drawbacks such as toxic solvents, long reaction times, use of excessive catalysts, low yields, tedious workup procedures, complex reaction pathways, harsh reaction conditions, cost effective reagents/ catalysts, unrecyclable catalyst and formation of side products. Thus, value of a synthetic method for this important class of compounds depends mainly on identifying a simple, cost effective, and eco-friendly catalyst and a simple work-up procedure.

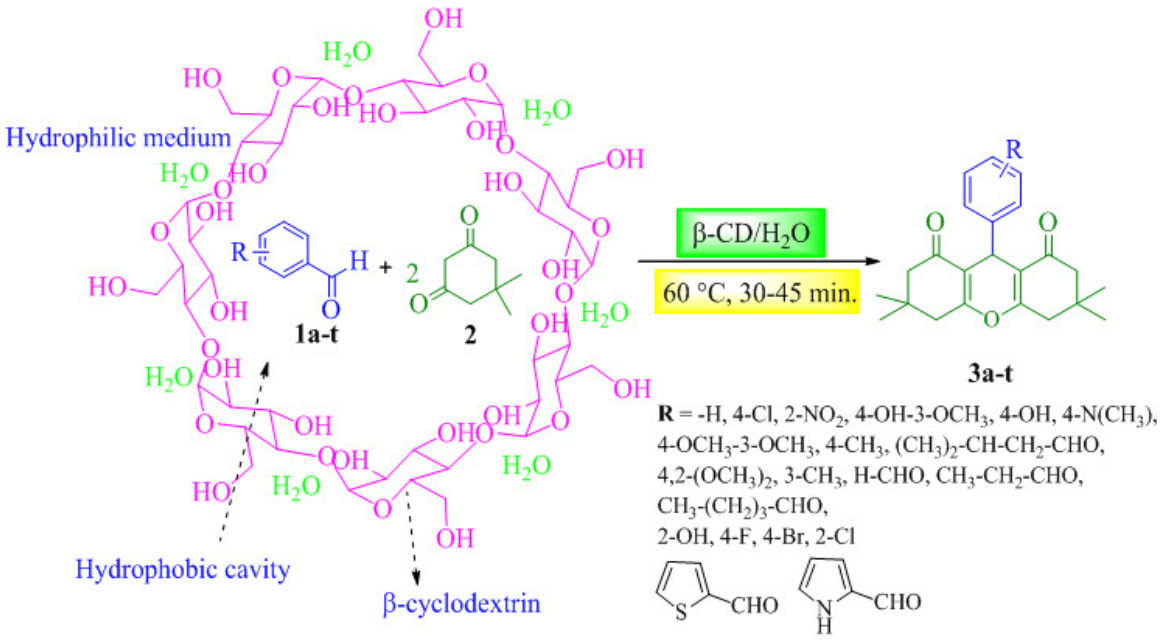
Thus, based on the above findings that there is a need for the use of more useful greener catalyst we examined β-CD, a water soluble, reusable, biodegradable, environmentally benign supramolecular catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes. Our continuing interest in multicomponent reaction using environmentally benign catalysts [40-42], Here in we report a highly efficient and clean synthesis of 1,8-dioxo-octahydroxanthenes using β-CD in excellent yields.

Result and discussion

In our initial finding, a typical one-pot three component for the synthesis of 1,8-dioxo-octahydroxanthene reactions were carried out upon treating a mixture of the readily available benzaldehyde **1a** (1 mole) and 5,5-dimethylcyclohexane-1,3-dione **2** (2 mole) was chosen as model substrates and extensive investigations were carried out to define the optimal reaction conditions in various solvents, temperatures, reactions times and catalyst loadings. The results of these optimization experiments are summarized in **(Table 1)**. These results showed that none of the desired 1,8-dioxo-octahydroxanthene product was detected when a mixture of benzaldehyde and dimedone was heated at 100 °C for 140 min in the absence of

the catalyst. When β-CD was used as the catalyst, the product was obtained in its pure form with 91% yield, simply by filtration **(Scheme 1)**. As for solvent study different solvent such as DMF, CH_3CN, THF, H_2O: EtOH (9:1), H_2O: EtOH (1:9) (**Table 1**, entries 1-6**)** and water were used some of them are polar protic solvent and some are polar aprotic and some are non-polar solvent but polar protic solvent *i.e.* water gives good yield (**Table 1**, entry 7) other than polar aprotic and nonpolar solvents given the lower yield with high reaction time as compare to water. Water represents very powerful green chemical technology procedures from both the economical and synthetic point of view. The use of water not only reduces the burden of organic solvent disposal, but also enhances the rate of reaction. The workup procedure is very simple and the products do not require further purification. So to be known as a unique solvent in many useful organic transformations.

To optimize catalyst concentration, reaction was carried out at different mole %, increasing the amount of catalyst can improve the reaction yield. Whereas using (10 mol%) catalyst the yield of was 91% (**Table 1,** entry 7). With the increasing of amount of catalyst (15 mol%) the yield decreased from 91% to 63.95%. Further increase of the amount of catalyst (20 mol%) yield also increases but time was consumed, It is well known that β-CD play crucial roles in this organic reaction. Among α-CD, β-CD and γ-CD, β-CD was found to efficiently promote the reaction and afforded the product in 92% yield when using valeraldehyde. In contrast, this reaction did not entirely work using other cyclodextrin such as α-CD and γ-CD (**Table 1**, entries 8 & 9). Finally, a brief screen of β-CD showed that commonly used β-CD catalysts affected the yields of the reaction to some extent on -OH, -F, -Br, and -Cl substituent's on benzaldehyde. β-CD exhibited the highest catalytic reactivity with 91% yield, but α-CD and γ-CD did not work complete conversion in this reaction. The desired product was observed in higher reaction time period.



Scheme 1. General scheme for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives

The effect of reaction temperature on the yield was observed. With the increasing of temperature from 30 ˚C to 100 ˚C, the higher yield (91%) was obtained in later case within the shorter time 40 min, and we choose 60 ˚C as the appropriate temperature, hence all the reactions were performed at the temperature of 60 ˚C.

To study the synthetic utility and scope, optimized reaction condition was applied to various aldehydes. All the substituted aromatic and heterocyclic aldehydes with dimedone, reacted well to afford good to excellent yields of the corresponding 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione in shorter reaction time **(Table 2**, entries 1–20**)**. Variation of the electronic properties of the substituents at o, m, or *p*-benzaldehyde was tolerable with excellent yields ranging from 74% to 95% **(Table 2**, entries 2-8, 11-12, 17-20**)**. It is worth noting that the reaction between dimedone **2** and aldehyde **1k** proceeded cleanly for only 30 min. and afforded the corresponding 1,8-dioxo-octahydroxanthenes product **3k** in 95% yield **(Table 2**, entry 11**)**. Electron-withdrawing group on the aldehyde as compare to electron-donating groups also proved to be amenable to this procedure with very high yields. On the basis of the above results, this process was then extended to heterocyclic and aliphatic aldehydes. The Thiophene-2-carbaldehyde and 1*H*-pyrrole-2-carbaldehyde afforded the corresponding product in 80-83 % yield (Table 2, entry 3j & 3p), also fortunately the chemistry is worked well with aliphatic aldehydes (92%, 80%, and 82% respectively). **(Table 2**, entries **3i, 3n** & **3o**). Compared with aromatic aldehydes, aliphatic aldehydes afforded relatively good yields of the corresponding 1,8-dioxo-octahydroxanthenes. By having this successful result in our hand, we had tried reaction of benzaldehyde and 1,3-cyclohexanedione which given the product 9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione also within short time period.

Experimental Section

Materials and methods

All chemicals were purchased and used without any further purification. Melting points were determined on a open capillary tube and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck's silica plates. IR spectra were obtained on a Bruker ALPHA (Eco-ATR) spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 MHz instruments using TMS as internal standard. ^{13}C NMR spectra were recorded on Bruker Avance 100 MHz using $CDCl_3$ as the solvent with TMS as internal standard. Mass spectra were recorded on Shimadzu QP-2000 ESI mass spectrometer. Elemental analyses were obtained on a Thermofischer EA 1112 SERIES CHNS elemental analyzer.

General procedure for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione 3a-t

The mixture of 5,5-dimethyl cyclohexane (2 mole), and benzaldehyde (1 mole) were added in β-CD (10 mole %) solution containing water (10 ml). The resulting mixture was heated at 60 ˚C. After completion of the reaction (monitored by TLC), The reaction mixture was cooled and β-cyclodextrin was filtered. The solid obtained was filtered and washed by hot water and dried. The resulting crude product was purified by crystallized from ethanol to afford the desired product. The recovered β-CD was reused for 1-3 consecutive runs in this reaction without any significant loss in yield and activity. The product was confirmed by melting point, ^{1}H NMR, ^{13}C NMR and Mass spectrum, and elemental analysis. the results obtained are summarized in supplementary materials. The rest of substrates **3b-t**, were prepared by a procedure similar to

that for **3a**. The known compounds **3b-t**, showed satisfactory spectroscopic data in agreement with those reported in the literature [43-47].

Spectral Data of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3a): Time: 30 min.; Yield: 91%; IR (ATR): 2961, 2952, 1660, 1491, 1388, 1252, 848 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.98 (s, 6H, 2 x CH_3), 1.10 (s, 6H, 2 x CH_3), 2.15–2.28 (q, 4H, 2 x CH_2), 2.48 (s, 4H, 2 x CH_2), 4.75 (s, 1H, CH), 7.09–7.13 (t, 1H, Ar), 7.19-7.26 (t, 2H, Ar), 7.27-7.29 (d, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.35, 29.28, 31.85, 32.12, 40.89, 50.76, 115.69, 126.38, 128.08, 128.39, 144.10, 162.26, 196.39; Mass spectra: m/z: 350.20 (M^{+1}). m.p. 202-205 ˚C; Anal. calcd. for $C_{23}H_{26}O_3$: C 78.83, H 7.48, Found: C, 78.79; H, 7.45.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3b): Time: 50 min.; Yield: 88%; IR (ATR): 3031, 2960, 2950, 1675, 1659, 1460, 1364, 1196, 1164, 1005, 850 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.98 (s, 6H, 2 x CH_3), 1.11 (s, 6H, 2 x CH_3), 2.16–2.26 (q, 4H, 2 x CH_2), 2.47 (s, 4H, 2 x CH_2), 4.72 (s, 1H, CH), 7.19–7.28 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 27.31, 29.30, 31.48, 32.22, 40.86, 50.70, 115.28, 128.21, 129.75, 132.05, 142.70, 162.43, 196.38; Mass spectra: m/z: 385.10 (M^{+1}), 387.40 (M^{+3}). m.p. 229-231 ˚C; Anal. calcd. for $C_{23}H_{25}ClO_3$: C 71.77, H 6.55; Found: C 71.88, H 6.65.

3,3,6,6-tetramethyl-9-(2-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3c): Time: 45 min.; Yield: 84%; IR (ATR): 2960, 2933, 2873, 1733, 1665, 1603, 1353, 1190, 862 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.01 (s, 6H, 2 x CH_3), 1.19 (s, 6H, 2 x CH_3), 2.13–2.22 (q, 4H, 2 x CH_2), 2.47 (s, 4H, 2 x CH_2), 5.55 (s, 1H, CH), 7.24–7.27 (d, 2H, Ar), 7.39-7.48 (m, 2H, Ar), 7.55-7.78 (d, 1H, Ar) ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.33, 29.22, 32.11, 32.29, 40.86, 50.66, 114.57, 121.71, 122.50, 135.81, 146.33, 148.35, 163.05, 196.45; Mass spectra: m/z: 395.12 (M^+). m.p. 249-251 ˚C; Anal. calcd. for $C_{23}H_{25}NO_5$: C 69.86, H 6.37, N 3.54; Found: C 69.65, H 6.42, N 3.48.

9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3d): Time: 50 min.; Yield: 86%; IR (ATR): 3410, 3026, 2951, 1669, 1620, 1516, 1434, 1363, 1283, 1225, 1198, 1132, 1030, 622, 574 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.00 (s, 6H, 2 x CH_3), 1.12 (s, 6H, 2 x CH_3), 2.17–2.27 (q, 4H, 2 x CH_2), 2.47 (s, 4H, 2 x CH_2), 3.90 (s, 3H, OCH_3), 4.68 (s, 1H, CH), 5.48 (s, 1H, OH), 6.58–6.60 (d, 1H, Ar), 6.73-6.76 (d, 1H, Ar), 7.01 (s, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): 27.30, 29.33, 31.33, 32.23, 40.89, 50.79, 55.89, 112.28, 113.93, 115.83, 120.03, 136.49, 144.02, 145.77, 162.60; Mass spectra: m/z: 397.15 (M^{+1}). m.p. 225-227 ˚C; Anal. calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12; Found: C, 72.80; H, 7.20

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3e): Time: 30 min.; Yield: 85%; IR (ATR): 3460, 2955, 2878, 2832, 1658, 1593, 1361, 1222, 1130, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 6H, 2 x CH_3), 1.10 (s, 6H, 2 x CH_3), 2.15–2.29 (q, 4H, 2 x CH_2), 2.42 (s, 4H, 2 x CH_2), 4.65 (s, 1H, CH), 5.71 (s, 1H, OH), 6.61–6.64 (d, 2H, Ar), 7.11-7.14 (d, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.39, 29.21, 30.98, 32.28, 40.88, 50.78, 115.20, 115.82, 129.34, 135.85, 154.55, 162.35, 197.18; Mass spectra: m/z: 367.23 (M^{+1}). m.p. 247-250 ˚C; Anal. calcd. for $C_{23}H_{26}O_4$: C 75.38, H 7.15; Found: C 75.01, H 7.24.

9-(4-(dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3f): Time: 40 min.; Yield: 78%; ^{1}H NMR (400 MHz, DMSO): δ

= 0.98 (s, 6H, $C(CH_3)_2$); 1.10 (s, 6H, $C(CH_3)_2$); 2.11–2.15 (d, 4H, CH_2); 2.31–2.50 (q, 4H, CH_2); 2.56-2.66 (q, 4H, 2 x CH_2); 3.08 (s, 6H, $N(CH_3)_2$); 4.58 (s, 1H, CH); 7.13–7.27 (m, 4H, Ar); ^{13}C NMR (100 MHz, DMSO): δ 27.40, 29.29, 32.25, 40.85, 50.74, 129.80, 162.49, 196.68; Mass spectra: m/z: 395.25 (M^{+1}). m.p. 223-225 ˚C; Anal. calcd. for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56; Found: 76.41; H, 7.86; N, 3.66

9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3g): Time: 40 min.; Yield: 79%; IR (ATR): 3003, 2959, 1669, 1630, 1469, 1365, 1260, 1223, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 6H, 2 x CH_3), 1.13 (s, 6H, 2 x CH_3), 2.15–2.30 (q, 4H, 2 x CH_2), 2.48 (s, 4H, 2 x CH_2), 3.80 (3H, OCH_3), 3.87 (3H, OCH_3), 4.72 (s, 1H, CH), 6.71–6.79 (m, 2H, Ar), 6.91 (s, 1H, Ar). ^{13}C NMR (100 MHz,$CDCl_3$): δ 27.25, 29.33, 31.23, 32.15, 40.90, 50.76, 55.77, 55.89, 110.85, 112.31, 115.78, 120.13, 136.99, 147.44, 148.45, 162.14, 196.54; Mass spectra: m/z: 411.24 (M^{+1}). m.p. 169-172 ˚C; Anal. calcd. for $C_{25}H_{30}O_5$: C 73.15, H 7.37; Found: C 72.94, H 7.45.

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3h): Time: 32 min.; Yield: 80%; IR (ATR): 2942, 2889, 2830, 1655, 1620, 1360, 1201, 1136, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 6H, 2 x CH_3), 1.16 (s, 6H, 2 x CH_3), 2.18–2.20 (q, 4H, 2 x CH_2), 2.26 (s, 3H, CH_3), 2.47 (s, 4H, 2 x CH_2), 4.77 (s, 1H, CH), 7.03 (d, 2H, Ar), 7.18-7.21 (d, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.08, 27.41, 29.29, 31.45, 32.02, 40.90, 50.78, 115.79, 128.27, 128.79, 135.78, 141.21, 162.11, 196.44; Mass spectra: m/z: 365.11 (M^{+1}). m.p. 213-215 ˚C; Anal. calcd. for $C_{24}H_{28}O_3$: C 79.09, H 7.74; Found: C 79.21, H 7.60.

9-(2,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3k): Time: 35 min.; Yield: 95%; IR (ATR): 3004, 2955, 1663, 1622, 1460, 1365, 1230, 1228, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 6H, 2 x CH_3), 1.14 (s, 6H, 2 x CH_3), 2.23–2.25 (m, 8H, 4 x CH_2), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.73 (s, 1H, CH), 6.53 (s, 2H, Ar), 7.26 (s, 1H, Ar).^{13}C NMR (100 MHz, $CDCl_3$): δ 27.21, 29.39, 31.09, 32.21, 40.05, 50.75, 56.11, 60.71, 105.71, 115.59, 136.59, 139.79, 152.91, 162.39, 196.55; Mass spectra: m/z: 411.22 (M^{+1}). m.p. 177-180 ˚C; Anal. calcd. for $C_{25}H_{30}O_5$: C 70.89, H 7.32; Found: C 70.65, H 7.41

9-butyl-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3o): Time: 40 min.; Yield: 82%; IR (ATR): 2823, 1672, 1575, 1355, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.45 (d, *J* = 11.4 Hz, 1H, CH), 2.97–2.89 (m, 1H, CH), 2.33–2.24 (m, 8H, 4 x CH2), 1.00 (6H, s, 2 x CH_3), 1.05 (6H, s, 2 x CH_3), 0.84 (d, *J* = 6 Hz, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.59, 116.69, 47.24, 46.50, 38.30, 31.33, 30.19, 27.09, 25.95, 22.52. Mass spectra: m/z: 331.21 (M^+). m.p. 147-150 ˚C; Anal. calcd. for: $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; O, 14.52 Found: C, 76.41; H, 9.25.

9-(2-bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3s): Time: 35 min.; Yield: 86%; IR (ATR): 3462, 2961, 2883, 2830, 1660, 1598, 1365, 1226, 1135, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 6H, 2 x CH_3), 1.10 (s, 6H, 2 x CH_3), 2.14–2.25 (q, 4H, 2 x CH_2), 2.46 (s, 4H, 2 x CH_2), 5.06 (s, 1H, CH), 6.93–6.97 (t, 1H, Ar), 7.18-7.20 (t, 1H, Ar), 7.35 (s, 1H, Ar), 7.45-7.49 (d, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 27.75, 29.72, 31.95, 32.65, 41.30, 51.15, 115.66, 120.69, 130.64, 131.59, 143.67, 162.89, 196.71. Mass spectra: m/z: 428.12 (M^+) & 430.19 (M^{+1}). m.p. 236-238 ˚C; Anal. calcd. for $C_{23}H_{25}BrO_3$: C 64.34, H 5.87; Found: C 64.45, H 5.79.

9-(2-chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3t): Time: 45 min.; Yield: 82%; IR (ATR): 2952, 2879, 2820, 1660, 1591, 1360, 1206, 1160, 845, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 6H, 2 x CH_3), 1.13 (s, 6H, 2 x CH_3), 2.15–2.23 (q, 4H, 2 x CH_2), 2.48 (s, 4H, 2 x CH_2), 4.97 (s, 1H, CH), 7.02–7.09 (t, 1H, Ar), 7.16-7.21 (t, 1H, Ar), 7.24-7.29 (d, 1H, Ar), 7.46-7.49 (d, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.37, 29.32, 32.02, 40.87, 50.70, 113.70, 126.35, 127.85, 130.15, 133.45, 162.95, 196.55; Mass spectra: m/z: 385.10 (M^{+1}) & 387.12 (M^{+3}). m.p. 226-228 ˚C; Anal. calcd. for $C_{23}H_{25}ClO_3$: C 71.77, H 6.55; Found: C 71.52, H 6.68.

Table 1. Optimization of the solvent for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione[a]

Entry	Solvent	Catalyst	Mole (%)	Temp (˚C)	Time (min)	Yield[b] (%)
1.	DMF	β-CD	10	100	135	75
2.	$CHCl_3$	β-CD	10	70	150	17
3.	CH_3CN	β-CD	10	80	135	77
4.	THF	β-CD	10	80	150	69
5.	H_2O:EtOH (9:1)	β-CD	10	70	170	75
6.	H_2O:EtOH (1:9)	β-CD	10	70	120	78
7.	Water	β-CD	10	70	30	91
8.	H_2O	α -CD	15	80	90	75
9.	H_2O	γ-CD	15	80	110	70

[a a] Reaction conditions: benzaldehyde (1 mmol), and dimedone (2 mmol), β-CD (10 mol %) and solvent at 60 ˚C, [b] Isolated yield

Table 2. Synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione[a]

Entry	R	Product	Time (min.)	Melting point (°C)		Yield[b] (%)
				Found	Reported [31,24]	
1.	-Ph	**3a**	30	202-205	204-206	91
2.	4-Cl-Ph	**3b**	40	229-231	230-232	88
3.	2-NO_2-Ph	**3c**	45	249-251	248-252	84
4.	4-OH, 3-OCH_3-Ph	**3d**	50	225-227	225-228	86
5.	4-OH-Ph	**3e**	30	247-250	248-251	85
6.	4-N(CH_3)-Ph	**3f**	40	223-225	224-227	78
7.	4-OCH_3, 3-OCH_3-Ph	**3g**	40	169-172	168-172	79
8.	4-CH_3-Ph	**3h**	32	213-215	211-214	80
9.	$(CH_3)_2$-CH-CH_2-CHO	**3i**	35	147-149	146-148	92
10.	Thiophene-2-carbaldehyde	**3j**	35	197-200	198-202	83
11.	4,2-$(OCH_3)_2$-Ph	**3k**	35	177-180	178-181	95
12.	3-OCH_3-Ph	**3l**	45	164-166	164-166	90
13.	H-CHO	**3m**	30	180-183	-	80
14.	CH_3-CH_2-CHO	**3n**	40	144-147	-	74
15.	C_4H_9- CHO	**3o**	40	147-150	146-150	82
16.	1*H*-pyrrole-2-carbaldehyde	**3p**	45	240-243	-	80
17.	2-OH-Ph	**3q**	40	206-208	205-208	74
18.	4-F-Ph	**3r**	40	226-230	227-231	80
19.	4-Br-Ph	**3s**	35	236-238	234-238	86
20.	2-Cl-Ph	**3t**	45	226-228	223-227	82

[a] Reaction conditions: benzaldehyde (1 mmol), and dimedone (2 mmol), β-CD (10 mol %) and solvent at 60 ˚C, [b] Isolated yield

Catalyst Recovery

The ability of a catalyst to be recovered and reused is becoming increasingly important for the development of green processes. With this in mind, we evaluated the reusability of β-CD using benzaldehyde and dimedone as model substrates. After the separation of the products, the filtrate containing the catalyst was cooled at 5 ˚C temp. the solid obtained was directly filtered, dried and used directly in the next run. To our delight, the catalyst was highly reusable

under the investigated conditions, preserving almost unaltered its initial catalytic activity after three uses which are graphically explained in **Fig. 1**. The purification of β-CD catalyst after the recycling was confirmed by IR spectra shown in **Fig. 2**.

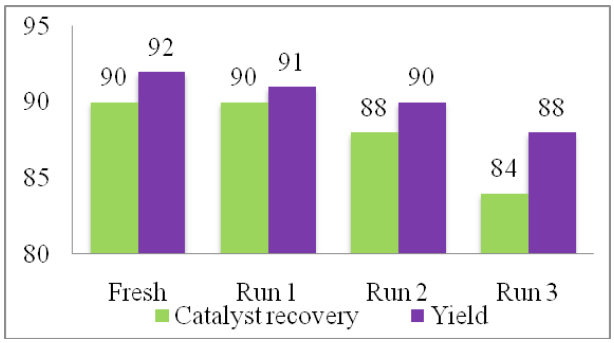


Figure 1. Reuse and recovery of β-CD and its effect on yield

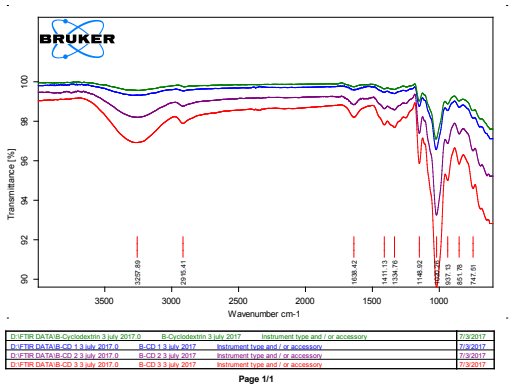
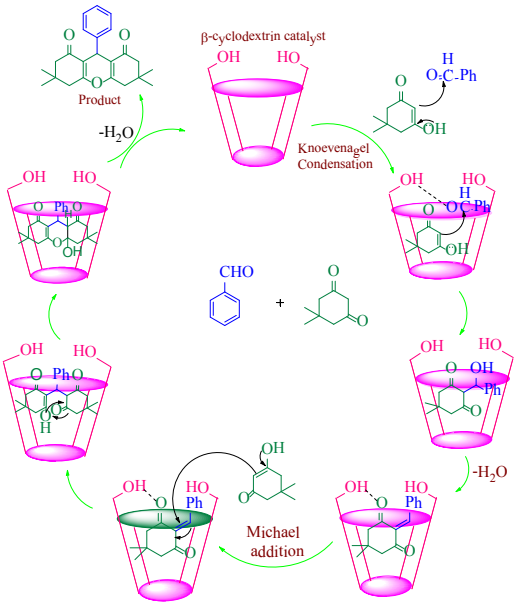


Figure 2. FTIR spectral analysis of recycling of a) β-cyclodextrin fresh (Red); b) β-CD first run (Maroon); c) β-CD second run (Blue); d) β-CD third run (Green)

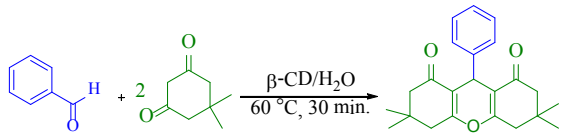
Reaction mechanism

To account for the very efficient catalysis by β-CD of this multicomponent reaction, wherein supramolecular catalyzed reactions are involved, it is proposed that β-CD with its seven free primary –OH groups acting synergistically behaves as an efficient host and supramolecular catalyst **Scheme 2**. In the first step, of plausible mechanism, the aldehyde binds to the β-CD cavity. Activation of a proton from dimedone by β-CD catalyzes its knoevenagel condensation with the carbonyl group to give the 2-arylidene dimedone. The cooperative enzyme-like binding of these intermediates which ensure their tighter fit into the cavity facilitates further reactions, i.e. the second molecule of second dimedone to 2-((2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)(phenyl)methyl)-5,5-dimethylcyclohexane-1,3-dione (by activation and of a proton from dimedone) further attacks the double bond of Knoevenagel product and subsequently undergoes Michael addition reaction to form with another molecule of dimedone to form intermediate after facilitated dehydration reaction to give the cyclised tandem 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione product **3a** and regenerates β-CD.



Scheme 2. Proposed reaction pathway for the synthesis 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

Calculation of green chemistry metrics [48]
Calculation of E-factor and atom economy (AE) for compound (3a)



1a **MW** 106.04 g/mole (1 mmole) + 2 **2** 140.08 g/mole (2 mmole) → **3a** 337.43 g/mole

Atom economy (AE): Atom economy (atom efficiency) is the conversion efficiency of a chemical reaction in terms of how many atoms from the starting materials reside within the product. AE has an ideal value of 100%, *i.e.*, all atoms from the starting materials reside in the product [49].

AE = [MW of product] ÷ Σ (MW of stoichiometric reactants) X 100

AE of compound **3a** = [337.43 (**3a**)] ÷ [386.20] X100

Atom economy AE = 87.37 %

Conclusion

In conclusion, we developed an efficient, simple, green method for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives **3a-t** using β-cyclodextrin as a inexpensive, biodegradable and recyclable catalyst. The merits of the present work are as follows: 1) high efficiency, clean reaction, simplicity,shortreactiontime,andversatility,high yields i.e. atom economic, non-chromatography technique. 2) Separation and recrystallisation of product occurs simultaneously, which reduces the use of organic solvents. 3) The catalyst is efficient, sustainable, stable and recyclable. 4) The catalyst is cheap. These features make the present work useful from industrial, economical and environmental points of view.

Supplementary Materials

The supplementary information gives the ^{1}H NMR and ^{13}C NMR data for the synthesized 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives.

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