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ONE POT SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENES IN AQUASE PHASE USING B-CYCLODEXTRIN AS AN EFFICIENT AND GREEN CATALYST

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ABSTRACT

A simple and highly efficient protocol for the synthesis of biologically active 1,8-dioxo-octahydroxanthenes from various aromatic aldehydes with dimedone under catalyst ß-Cyclodextrin in water is reported. This protocol gives wide range of xanthene derivatives with high yield.

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INTRODUCTION:

Xanthene and their derivatives are unavoidable in the field of medicinal chemistry for their biologically active properties as they have been synthesized and evaluated for their potential as antiviral[1], antibacterial[2], anti-inflammatory[3], anti-depressants and antimalarial agents[4]. They have been widely used as dyes fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties[5].

Among them, xanthenediones forms the structural unit in a number of natural products[6] and santalin pigments isolated from a number of plant species[7], and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring[8]. Also, they possess a potential antimicrobial activity similar to chlotrimazole and ampicilin, against Candida albicans and Staphlococcusaureus, respectively[9]. Furthermore, these compounds have emerged as sensitizers in photodynamic therapy[10] and are used as leuco-dyes[5] and in laser technology[11].

In recent years, several methods are reported for the preparation of 1,8-dioxo octahydroxanthenes such as cyclocondensation between 2-hydroxy aromatic aldehydes and 2-tetralone[12], trapping of benzynes by phenols[13], cyclization of polycyclic aryltriflate esters[14], and intramolecular phenyl carbonyl coupling reactions of benzaldehyds and acetophenones[15].The conventional procedure involves acid- or base-catalyzed condensation of appropriate active methylene carbonyl compounds like dimedone with aldehydes[16], in the presence of p-dodecylbenzenesulphonic acid[17], Fe^{3+}-montmorilonite[18], $NaHSO_4$-SiO_2 or silica chloride[19], Amberlyst-15[20], $(NH_4)_2HPO_4$[21], Dowex-50W[22], $SbCl_3/SiO_2$[23], and $BiCl_3$[24], as well as with the assistance of ultrasound[25] or microwave irradiation[26]have been reported.

However, those methods still have some disadvantages including tedious reaction conditions,lowyield, and commercially unavailable key intermediates.Therefore to develop a simple and straightforward method is requisite.

Herein, we report new applications of β-cyclodextrinfor the one-pot synthesis of xanthene and their derivatives.The directone-pot synthesis of xanthene derivativesfrom aromatic aldehyde and dimedonewas achieved under neutral conditions using β-cyclodextrin and water.

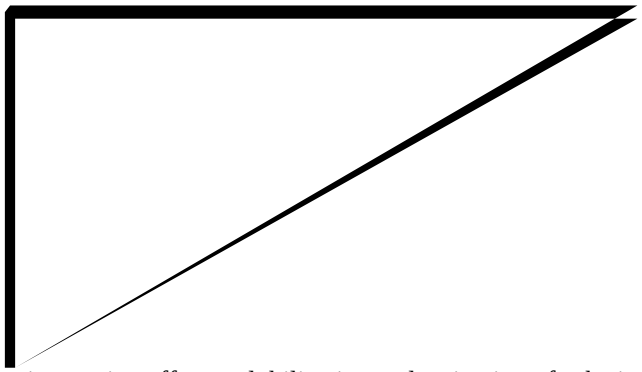
MATERIALS AND METHODS:

All liquid reagents were distilled before use. IR spectra were recorded on Bio-Rad FTS-40spectrometer (KBr). ^{1}H NMR spectra were measured on Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and DMSO as solvent.

General procedure for the preparation of 9-Aryl-1,8-dioxooctahydroxanthane derivatives:

β-cyclodextrin(10%) was dissolved in 10 ml distilled water by heating at 50-55^{0}c,to it was added an aromatic aldehyde (1.0 mmol), dimedone (2.0 mmol) dissolved in ethanol was stirred at reflux. The progress of the reaction was monitored by thin layer chromatograph. After completion of the reactions, the crude products were isolated by extracting with ethyl acetate(5ml x 3).The organic layer were separated,dried over sodium sulphate and evaporated under vacuum. The crude products were purified by recrystallization with mixture of ethanol and water.

Scheme :



Cyclodextrin by supramolecular interaction effects solubilization and activation of substituted aryl aldehyde through formation of host-guest complex during the course of reaction and thus facilitates the condensation (Figure 1).

Figure : Host-guest complex of β-cyclodextrin and substituted aryl aldehyde.

Table 1:Synthesis of various 9-aryl-1,8-dioxo-octahydroxanthane derivatives catalysed by β-cyclodextrin

Entry	Aldehydes(2)	Products	Time(min.)	Yield(%)	M.P. 0c (Reported)
1	C_7H_6O	3a	15	96	266-268 (267-269)
2	4-Br-C_7H_5O	3b	15	90	231-233 (230-232)
3	2-Cl- C_7H_5O	3c	15	92	224-226 (226-228)
4	4-C_2H_5- C_7H_5O	3d	20	89	140-142(143-147)
5	4-CH_3- C_7H_5O	3e	20	90	215-216 (217-218)
6	4-OCH_3- C_7H_5O	3f	20	93	244-245 (241-243)
7	4-OH- C_7H_5O	3g	15	90	225-227 (226) 44
8	2-Br- C_7H_5O	3h	20	89	223-224 (226-228)
9	4-NO_2- C_7H_5O	3i	20	90	222-224 (221-223)
10	2,4-Cl-C_7H_4O	3j	25	91	246-247(248-250)

RESULTS AND DISCUSSION:

The contemporary methods suffer from one or moreof the following drawbacks such as strong acidic conditions, long reaction times, low yields of theproducts, tedious work-up; need to use excessamounts of reagent and the use of toxic reagents,catalysts and solvents. Therefore, there is a strongdemand for a highly efficient and environmentally benign method for the synthesis of theseheterocycles. β-cyclodextrin mediatedcyclisation of *4*-bromobenzaldehyde with dimedoneproduces 3b with 90% yield.

Next, we examined the scope of the reaction of dimedonewitha varietyof aromaticaldehydes.Asshown inTable 1, itwasobservedthat a series of aromatic aldehydes bearing eitherelectron-donating or electron-withdrawing groups on aromatic ring were investigated. The substitutiongroups on the aromatic ring have no obvious effecton the yields and reaction time under the above optimal conditions. However, aldehydes with strongly electron-withdrawing groups on aromaticring such as 2,4-dichlorobenzaldehyde gave the productof with good yield in a long reaction time.

Characterizationof thecompounds:

9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(3b)

IR(KBr):3079,2947,2909,1702,1622,1544,1375cm-1;^{1}HNMR400MHz(CDCl3):δ1.00(s,6H),2.10(q,J=16.6Hz,4H),2.41(s,4H),4.63(s,1H),7.12(d,J=8.30Hz,2H,ArH),7.29(d,J=8.30Hz,2H, ArH);^{13}C NMR 400 MHz($CDCl_3$):δ27.5,32.3,38.9,39,51.5,113.9,120.1, 131.2,131.5,155,143.4,198.9,LC-MS (M+1) = 430.

3,3,6,6-tetramethyl-9-p-tolyl-3,4,5,6,7,9-hexahydro-1-H-xanthene-1,8(2H)-dione(3e)

IR(KBr):3101, 2924, 2829, 1666, 1600, 1529, 817,736cm-1;^{1}H NMR 400 MHz ($CDCl_3$):δ1.06(s, 12H), 2.07 (d, J = 17.1 Hz, 2H), 2.49 (d, J =16.1 Hz, 2H),2.33 (s,3H) 4.49 (s, 1H), 6.86 (d, J = 7.0Hz, 2H), 7.05 (d, J = 7.0 Hz, 2H); ^{13}C NMR 400 MHz($CDCl_3$):δ19.6, 26.9, 29.0, 38.8, 42.1, 55.6,112.1, 128.8,132.0, 137.5, 152.9, 198.2; LC-MS (M+1) = 365.

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1-xanthene-1,8(2H)-dione(3f)

IR(KBr) : 3058, 2934, 2852, 1656, 1614, 1577, 1535, 1342,1145, 814,725cm-1;
^{1}H NMR 400 MHz ($CDCl_3$):δ1.09 (s, 12H), 2.06 (d, J = 17.1 Hz, 2H),2.52-2.54(d, J = 16.1 Hz, 2H),3.72 (s,3H) 4.61 (s, 1H), 6.76(d, J = 7.0 Hz, 2H), 6.91 (d, J = 7.0 Hz, 2H);^{13}C NMR 400 MHz ($CDCl_3$):δ 27.4, 29.6, 39.7, 42.0, 50.2, 54.4, 114.2, 118.3, 128.3, 134.8, 149.4, 154.2, 197.2;LC-MS: (M+1) = 381

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(3g)
IR(KBr) : 3412, 3024, 2962, 2931, 2899, 2872, 1662,1614,1514, 1450, 1359, 1246, 1201, 1003, 839. Cm-1;^{1}H NMR 400 MHz ($CDCl_3$):δ 1.12 (s, 12 H), 2.07 (d, J = 16.4 Hz, 2H), 2.21 (d,J = 16.6 Hz, 2H), 4.53 (s, 1H), 5.12 (s, 1H)6.45 (d, J= 7.2 Hz, 2H), 6.68 (d, J = 7.0 Hz, 2H);^{13}C NMR 400 MHz($CDCl_3$):δ 23.7, 29.6, 38.3, 41.3, 51.2, 112.1, 114.8,29.4,153.8,154.5, 197.8;LC-MS (M+1) = 367.

3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(3i)
IR(KBr):3060, 2934, 2832, 1650, 1613, 1515, 1489,1366, 1035, 831,722 cm-1;
^{1}H NMR 400 MHz ($CDCl_3$):δ 1.08 (s, 12H), 2.12 (d, J =17.4 Hz,2H),2.36 (d, J = 16.5Hz,2H),4.43(s,1H),7.20(d,J=7.2Hz,2H),8.01(d,J=7.4Hz,2H); ^{13}CNMR400MHz($CDCl_3$):δ 26.2, 30.5, 38.9, 43.1 64.5,112.5,121.7,129.9,139.5,146.1, 152.3, 189.1,LC-MS : (M+1) = 395.

ANTIMICROBIAL ACTIVITY:

The antimicrobial activities of all the synthesized compounds**(3a-3j)** were performed using kirby-Bauer method against both gram-positive as well as gram negetive strains like *S.typhi,E.coli,B.subtilis and S.aureus*.The each well (diameter 10 mm) was loaded with 0.1 mL-^{1} of test compound solution in DMSO,so that concentration of each test compound was 100µg mL-^{1}.The zone of inhibition were recorded in mm after incubation for 24 h at 37^{0}c.clear inhibition zone record of the compounds indicated that **(3f)** and **(3i)** werw highly active against *E.coli* and moderately active against *S.aureus* and *B.subtilis*.Majority of the compounds werw found moderately against *S.typhi*.

To determine minimum inhibitory concentration (MIC),the serial dilution technique was followed using nutrient broth medium.The MIC values of compounds **(3f)** and **(3i)** werw determined against *E.coli* and *S.aureus* which were found to be 50 and 65µg mL-^{1} respectively.

Table 2: Antimicrobial activity of Synthesis of various 9-aryl-1,8-dioxo-octahydroxanthane derivatives.

Entry	*S.typhi* mm	*E.coli* mm	*B.subtilis* mm	*S.aureus* mm
3b	10	15	11	-
3e	11	10	-	11
3f	15	18	13	12
3g	-	12	10	-
3i	14	17	15	13
Chlorophenicol	19	22	21	23

CONCLUSION :

In Summary,An eco-friendly and economic method has been developed for synthesis of 9-Aryl-1,8-dioxooctahydroxanthane derivatives using β-cyclodextrin catalyst with moderate to good yields. This methodology also overcomes the formation of unwanted by-products, low yields, slow reaction times, high temperatures and hazardous solvents.Antimicrobial potential study of these compounds revealed that most of the compounds showed promising antibacterial activity against gram positive and gram negative bacteria.

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