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One-pot Synthesis of 9-Aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes Catalyzed by *p*-Dodecylbenzene Sulfonic Acid in Aqueous Media

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An efficient and convenient approach to the synthesis of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydro-xanthenes using *p*-dodecylbenzene sulfonic acid (DBSA) as the catalyst (20 mol %) in aqueous media is described. This method provides several advantages such as environment friendly, high yields and simple work-up procedure. In addition, water was chosen as a green solvent.

Key Words: Synthesis, Octahydroxanthenes, Aromatic aldehyde, 1,3-Cyclohexanedione.

INTRODUCTION

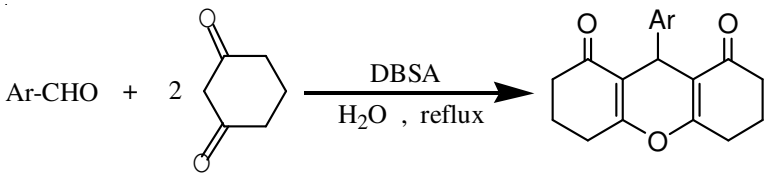
At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials using non-toxic reagents, solvents and catalysts[1]. Recently, ideal synthesis was defined as one in which the target compound is generated in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process[2]. Recently organic reactions in water without use of harmful organic solvents have attracted much attention, because water is a cheap, safe and environmentally benign solvent[3-5].

p-Dodecylbenzene sulfonic acid (DBSA) has been used in a number of organic reactions as a good catalyst. While DBSA used as a good phase transfer catalyst is a new field, it can also been used in many organic reactions[6].

Octahydroxanthene derivatives containing a structural unit of benzopyrans can be used as antispasm[7] and fluorescent fuel[8]. The reported synthesis of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes was various such as the cyclocondensation reaction between aromatic aldehydes and 1,3-cyclohexanedione under microwave irradiation in glycol[9] or catalyzed by TsOH under the reflux benzene for 24 h[10]. However, each of above methods has its own merit, while these methods are suffered by the

limitation of low yield, prolonged reaction time (24 h), use of toxic organic solvent, requirement of excess of reagents/catalysts, special apparatus and harsh reaction conditions.

We have completed a series of organic synthesize the research of the reaction with water as solvent recently[11-20]. In the course of our investigations to develop new synthetic methods in water using DBSA as catalyst, we examined the synthesis of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8- octahydroxanthenes in water, as a green solvent. This is an efficient synthesis in aqueous media, not only preserves the simplicity but also gives the corresponding products in good to excellent yields (**Scheme-I**).



1 **2** **3**

Scheme-I

In a typical general experimental procedure, a solution of an aromatic aldehyde and 1,3-cyclohexanedione in water was heated under reflux water in the presence of a catalytic amount of DBSA (20 mol %) for a certain period of time required to complete the reaction, resulting in the formation of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes, the reaction mixture was filtered off and washed with H_2O and filtrate was recycled to reuse. The crude product was purified by recrystallization from ethanol to afford the pure product.

EXPERIMENTAL

All liquid reagents were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on Bruker Avance 400 (400 MHz) spectrometer using TMS as internal standard. Elemental analyses were determined using Perkin-Elmer 2400 II elemental analyzer.

Procedure for the preparation of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes: A mixture of an aromatic aldehyde (1.0 mmol), 1,3-cyclohexanedione (2.0 mmol) and DBSA (20 mol %) in water (20 mL) was stirred at refluxing for 3 h. The progress of the reaction was monitored by thin layer chromatograph. After completion of the reactions, the mixture was cooled to room temperature and solid was filtered off and washed with H_2O (40 mL). The crude products were purified by recrystallization by ethanol (95 %). Data of some compounds are shown below:

3a: IR (KBr): ν_{max} = 2949, 2887, 2371, 1653, 1491, 1451, 1418, 1236, 1203, 1176, 1132, 1006, 958, 907, 830, 779, 702, 614, 538 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.81-1.90 (m, 2H, CH_2), 1.92-1.98 (m, 2H, CH_2), 2.26-2.31 (m, 4H, 2 × CH_2), 2.61-2.68 (m, 4H, 2 × $COCH_2$), 4.59 (s,1H, CH), 7.12-7.22 (m, 5H, ArH).

3b: IR (KBr): ν_{max} = 3078, 2960, 2879, 1650, 1652, 1619, 1457, 1431, 1356, 1236, 1200, 1178, 1135, 1051, 1010, 959, 839,767, 740, 702, 611, 538 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.78-1.87 (m, 2H, CH_2), 1.91-2.00 (m, 2H, CH_2), 2.16-2.32 (m, 4H, 2 × CH_2), 2.61-2.64 (m, 4H, 2 × $COCH_2$), 4.84 (s, 1H, CH), 7.10-7.14 (m, 4H, ArH), 7.18-7.26 (m, 3H, ArH). Anal. Calcd. for $C_{19}H_{17}ClO_3$: C 69.41, H 5.21; found C 69.46, H 5.17.

3c: IR (KBr): ν_{max} = 2953, 2890, 1672, 1621, 1474, 1358, 1201, 1174, 1129, 847, 684 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.13 (m, 4H, ArH), 4.56 (s, 1H, CH), 2.64 (m, 4H, 2 × $COCH_2$), 2.29 (m, 4H, 2 × CH_2), 1.95 (m, 2H, CH_2), 1.88 (m, 2H, CH_2). Anal. Calcd. for $C_{19}H_{17}ClO_3$: C 69.41, H 5.21; found C 69.48, H 5.27.

3d: IR (KBr): ν_{max} = 3301, 3089, 3048, 2950, 2923, 2889, 2866, 2361, 1669, 1618, 1487, 1421, 1359, 201,1173, 1128, 1011, 958, 907, 836, 767, 740, 689, 608, 533 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.83-1.90 (m, 2H, CH_2), 1.93-1.99 (m, 2H, CH_2), 2.25-2.34 (m, 4H, 2 × CH_2), 2.61-2.70 (m, 4H, 2 × $COCH_2$), 4.56 (s, 1H,CH), 7.20 (d, 2H, *J* = 8.4 Hz, ArH), 7.26 (d, 2H, *J* = 8.4 Hz, ArH).

3e: IR (KBr): ν_{max} = 3087, 2955, 2887, 2812, 1654, 1621, 1523, 1418, 1350, 1202, 1173, 1131, 1074, 1015, 960, 908, 860, 815, 717, 669, 624, 535 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.79-1.89 (m, 2H, CH_2), 1.91-1.99 (m, 2H, CH_2), 2.19-2.33 (m, 4H, 2 × CH_2), 2.55-2.70 (m, 4H, 2 × $COCH_2$), 4.78 (s, 1H, CH), 7.19-7.22 (m, 1H, ArH), 7.25-7.31 (m, 2H, ArH). Anal. Calcd. for $C_{19}H_{16}Cl_2O_3$: C 62.83, H 4.44; found C 62.87, H 4.41.

3f: IR (KBr): ν_{max} = 3077, 2964, 2945, 2896, 2873, 1678, 1619, 1520, 1335, 1202, 1178, 1130, 823, 787 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 7.77 (d, 1H, *J* = 6.8 Hz, ArH), 7.56 (m, 1H, ArH), 7.35 (d, 2H, *J* = 6.8 Hz, ArH), 5.40 (s, 1H, CH), 2.64 (m, 4H, 2 × $COCH_2$), 2.27 (m, 4H, 2 × CH_2), 1.95 (m, 2H, CH_2), 1.86 (m, 2H, CH_2). Anal. Calcd. for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found C 67.31, H 5.10, N 4.23.

3g: IR (KBr): ν_{max} = 3087, 2955, 2887, 2812, 2372, 1654, 1621, 1523, 1418, 1350, 1202, 1173, 1131, 1074, 1015, 960, 908, 860, 815, 717, 669, 624, 535 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.83-1.92 (m, 2H, CH_2), 1.95-2.01 (m, 2H, CH_2), 2.23-2.37 (m, 4H, 2 × CH_2), 2.64-2.75 (m, 4H, 2 × $COCH_2$), 4.69 (s, 1H, CH), 7.52-7.56 (m, 1H, ArH), 7.65-7.67 (m, 1H, ArH), 7.99-8.03 (m, 2H, ArH).

3h: IR (KBr): ν_{max} = 3295, 3113, 3081, 3043, 2948, 2895, 2870, 2818, 2446, 1665, 1607, 1521, 1422, 348, 1202, 1174, 1128, 1008, 958, 906, 818, 720, 688, 604, 533 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.82-1.92 (m, 2H, CH_2), 1.95-2.01 (m, 2H, CH_2), 2.22-2.37 (m, 4H, 2 × CH_2), 2.59-2.74 (m, 4H, 2 × $COCH_2$), 4.68 (s, 1H, CH), 7.49 (d, 2H, *J* = 8.8 Hz, ArH), 8.09 (d, 2H, *J* = 8.8 Hz, ArH).

3i: IR (KBr): ν_{max} = 3057, 3031, 2953, 2892, 2820, 1658, 1616, 1510, 1360, 1201, 1175, 1126, 819, 785 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 7.00 (dd, 4H, *J* 1 = 22 Hz, *J* 2 = 8 Hz, ArH), 4.54 (s, 1H, CH), 2.60 (m, 4H, 2 × $COCH_2$), 2.25 (m, 4H, 2 × CH_2), 1.93 (m, 2H, CH_2), 1.84 (m, 2H, CH_2). Anal. Calcd. for $C_{20}H_{20}O_3$: C 78.90, H 6.54; found C 78.86, H 6.50.

3j: IR (KBr): ν_{max} = 3027, 2956, 2896, 2830, 2368, 1663, 1660, 1510, 1466, 1361, 1239, 1176, 1131, 1033, 955, 904, 839, 758, 672, 612, 534 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.80-1.90 (m, 2H, CH_2), 1.95-1.98 (m, 2H, CH_2), 2.27-2.30 (m, 4H, 2 × CH_2), 2.61-2.65 (m, 4H, 2 × $COCH_2$), 3.68 (s, 3H, OCH_3), 4.53 (s, 1H, CH), 6.77 (d, 2H, *J* = 8.4 Hz, ArH), 7.08 (d, 2H, *J* = 8.4 Hz, ArH).

3k: IR (KBr): ν_{max} = 3379, 3021, 2949, 2921, 2892, 1662, 1612, 1515, 1361, 1207, 1173, 1131, 835, 762 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 9.19 (s, 1H, OH), 6.95 (d, 2H, *J* = 8.4 Hz, ArH), 6.59 (d, 2H, *J* = 8.4 Hz, ArH), 4.48 (s, 1H, CH), 2.63 (m, 4H, 2 × $COCH_2$), 2.27 (m, 4H, 2 × CH_2), 1.94 (m, 2H, CH_2), 1.86 (m, 2H, CH_2). Anal. Calcd. for $C_{18}H_{17}O_4$: C 73.53, H 5.85; found C 73.41, H 5.80.

3l: IR (KBr): ν_{max} = 3340, 2949, 2832, 2344, 1666, 1645, 1512, 1359, 1274, 1173, 1125, 1038, 951, 907, 852, 808, 735, 625, 538 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.80-1.91 (m, 2H, CH_2), 1.92-2.10 (m, 2H, CH_2), 2.28-2.31 (m, 4H, 2 × CH_2), 2.5-2.71 (m, 4H, 2 × $COCH_2$), 3.71 (s, 3H, OCH_3), 4.51 (s, 1H, CH), 6.50-6.53 (m, 1H, ArH), 6.59-6.61 (m, 1H, ArH), 6.74-6.75 (m, 1H, ArH), 8.71 (s, 1H, OH). Anal. Calcd. for $C_{20}H_{20}O_5$: C 70.57, H 5.92; found C 70.63, H 5.86.

3m: IR (KBr): ν_{max} = 2954, 2893, 1658, 1619, 1485, 1361, 1201, 1177, 1135, 853, 794 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.64 (m, 3H, ArH), 5.94 (s, 2H, -OCH_2O-), 4.51 (s, 1H, CH), 2.61 (m, 4H, 2 × $COCH_2$), 2.29 (m, 4H, 2 × CH_2), 1.95 (m, 2H, CH_2), 1.86 (m, 2H, CH_2). Anal. Calcd. For $C_{20}H_{18}O_5$: C 71.00, H 5.32; found C 71.11, H 5.28.

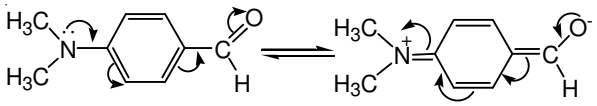
RESULTS AND DISCUSSION

To study the generality of this process, several examples illustrating this method for the synthesis those polyfunctionalized 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes were studied. The results are summarized in Table-1.

TABLE-1
SYNTHESIS OF 9-ARYL-1,8-DIOXO-1,2,3,4,6,7,8-OCTAHYDROXANTHENES CATALYZED BY DBSA IN AQUEOUS MEDIA

Entry	Ar	Product	Yield (%)	m.p. (ºC)	
				Found	Reported[9,10]
1	C_6H_5 **1a**	**3a**	91	272-273	270-271
2	2-ClC_6H_4 **1b**	**3b**	88	254-255	250-251
3	3-ClC_6H_4 **1c**	**3c**	86	276-277	–
4	4-ClC_6H_4 **1d**	**3d**	88	288-290	289-291
5	2,4-$Cl_2C_6H_3$ **1e**	**3e**	87	230-231	231-232
6	2-$NO_2C_6H_4$ **1f**	**3f**	90	245-246	–
7	3-$NO_2C_6H_4$ **1g**	**3g**	94	286-288	286-288
8	4-$NO_2C_6H_4$ **1h**	**3h**	86	263-265	263
9	4-$CH_3C_6H_4$ **1i**	**3i**	87	262-263	–
10	4-$CH_3OC_6H_4$ **1j**	**3j**	88	196-197	201-202
11	4-HOC_6H_4 **1k**	**3k**	84	279-281	–
12	3-CH_3O-4-HOC_6H_3 **1l**	**3l**	85	244-246	245-246
13	3,4-$OCH_2OC_6H_3$ **1m**	**3m**	86	248-249	–
14	4-$(CH_3)_2NC_6H_4$ **1n**	**3n**	No reaction	–	–

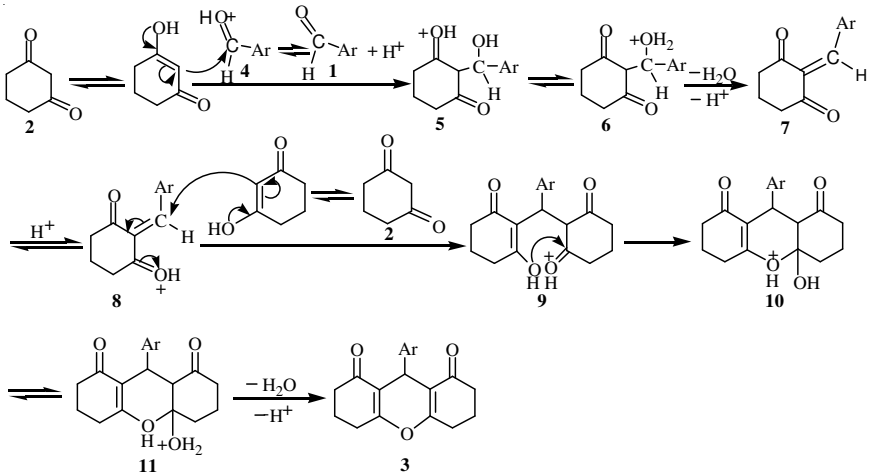
The effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under this reaction conditions. The cyclocondensation reaction proceeded smoothly under refluxing water to give the corresponding products **3** in high yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as methyl group, alkoxy group, hydroxy group) were employed and reacted well to give the corresponding 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes in good to excellent yields. 4-Dimethylaminobenzaldehyde (**1n**) failed to give the corresponding 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthene and the starting materials were quantitatively recovered under the same conditions. The explanation for this result may be due to the strong electron donating dimethylamino group in **1n** which will reduce the reactivity. A degree of tautomerization may occur in **1n** with formation of quinonoid structure and thus decreased reactivity of the aldehyde group (**Scheme-II**).



Scheme-II

The catalyst plays a significant role in the reaction in terms of the rate and the yields. For example, 4-chlorobenzoaldehyde reacted with 1,3-cyclohexanedione in the presence of 10 mol % DBSA to give the product **3d** in modest yield (76.6 %) at refluxing water after 3 h of reaction time. Increasing amount of the catalyst to 20 and 30 mol % results in accelerating the reaction yields to 88 and 80 %, respectively. The use of 20 mol % DBSA in refluxing water is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Thus, 20 mol % DBSA was chosen as a quantitative catalyst for these reactions.

The possible mechanism (**Scheme-III**) is accounted for the reaction. One molecule of aromatic aldehyde **1** was firstly condensed with 1,3-cyclohexanedione **2** to afford **8**. The step (**1** → **4** + **2** → **5** → **6** → **7** → **8**) can be regarded as a fast Knoevenagel addition. The active methylene of another molecule of 1,3-cyclohexanedione **2** by reaction with the electrophilic C=C double bond giving the intermediate **9**. Then the intermediate **9** was cyclized by the nucleophilic attack of OH group on the carbonyl (C=O) moiety and gave the intermediate **10**. Finally the expected products 3 were afforded by elimination of water (**10** → **11** → **3**). In this process, DBSA is not only a protonic acid but also an emulsifying agent, which catalyzes this reaction by the acid and forms the stable colloidal particles in the presence of the substrates in water and this colloid formation plays an important role in acceleration of the reactions.



Scheme-III

In summary, a novel and efficient procedure for the synthesis of 9-aryl-1,8-dioxo-1,2,3,4,6,7,8-octahydroxanthenes through the reaction of aromatic aldehydes and 1,3-cyclohexanedione using a catalytic amount of DBSA as catalyst is reported. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and isolated procedure which makes it a useful and attractive process for the synthesis of these compounds. Water has been chosen as a green solvent for these reactions.

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