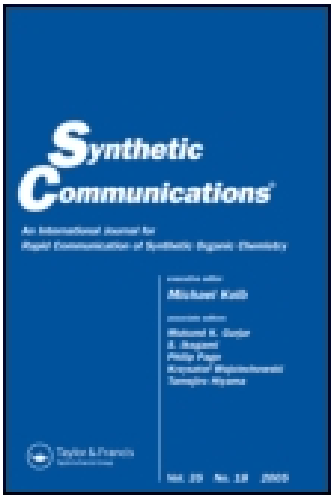

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Green Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives Using Catalytic Amount of H_2SO_4 in Water

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GREEN SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENE DERIVATIVES USING CATALYTIC AMOUNT OF H_2SO_4 IN WATER

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An green and convenient approach to the synthesis of 3,6,9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene derivatives from appropriate aromatic aldehydes and 5-aryl-1,3-cyclohexanedione in the presence of two drops of concentrated H_2SO_4 as a catalyst in water is described. This method provides several advantages such as environmental friendliness, low cost, excellent yields, and simple workup procedure.

Keywords: 5-Aryl-1,3-cyclohexadione; octahydroxanthene derivatives; water

INTRODUCTION

With increasing environmental concerns and the regulatory constraints faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.[1] 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.[2–4] In the course of our investigations to develop new synthetic methods in water, we examined the synthesis of 3,6,9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene derivatives in water, a green solvent.

It is known that 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene and its derivatives are very useful compounds. The derivatives occupy a prominent position in medicinal chemistry,[5] and they have also been used as laser technology,[6] pH-sensitive fluorescent materials,[7] and dyes.[8]

It has been reported that the reaction of aromatic aldehyde and 5,5-dimethyl-1,3-cyclohexanedione can obtain 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene and their derivatives in many methods.[9–13] However, the use of 5-aryl-1,3-cyclohexanedione as a reactant and two drop of concentrated H_2SO_4 as a catalyst for the one-pot synthesis of the 3,6,9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene and their derivatives in water has not been reported.

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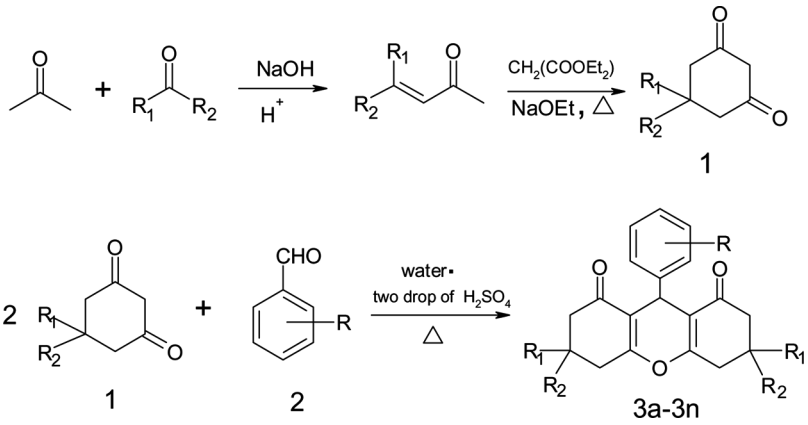

Scheme 1. Compounds **a–f:** R_1 = phenyl; R_2 = H; R=H, 2-Cl, 4-Cl, 3-OMe, 4-OMe; **g–l**: R_1 = 4-methoxyphenyl, R_2 = H; R=H, 2-Cl, 4-Cl, 3-OMe, 4-OMe, 4-N$(CH_3)_2$; and **m** and **n:** R_1 = Me; R_2 = Me; R=H, 4-Cl.

In this article, we report a clean and highly efficient route for the one-pot synthesis of their products and derivatives using inexpensive and commercially available concentrated H_2SO_4 as a catalyst in water. This a novel one-pot combination using water as a green solvent not only preserves the simplicity but also consistently gives the corresponding products in good to excellent yields (Scheme 1).

RESULTS AND DISCUSSION

The synthetic pathway is shown in Scheme 1. The 5-aryl-1,3-cyclohexanediones **1** were prepared as building blocks from aromatic aldehyde, acetone, and dimethyl molanate. The 3,6,9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene and their derivatives **3a–n** were obtained by condensation reaction of 5-aryl-1,3-cyclohexanediones **1** with appropriate aromatic aldehydes using two drops of concentrated H_2SO_4 as a catalyst in water.

The data of ^{1}H NMR, mass spectra (MS), and infrared (IR) shown in the experimental section are in accordance with the chemical structures of the target compounds. In the ^{1}H NMR spectrum of compound **3a**, the single proton peaks at δ 4.90 were the characteristic absorption proton peak of the 9-H. The structures of these compounds were further supported by their IR spectra. Typical absorption bands at 1701 cm^{-1} for (C=O) and 1120 cm^{-1} for (C-O) were observed.

As shown in Table 1, a series of aromatic aldehydes **2** were reacted with 5-aryl-1,3-cyclohexanedione **1** in the presence of two drops of concentrated H_2SO_4 in water at 70–80 °C, and the reaction proceed smoothly to afford the corresponding products **3** in good yields. All aromatic aldehydes containing electron-withdrawing groups (such as halide) or electron-donating groups (such as methoxy, *N,N*-dimethyl) were employed and reacted well to give the corresponding product **3** in good to excellent yield under these reaction conditions, so we conclude that no obvious effects of electrons and nature of substituents on the aromatic ring were observed.

Taking the reaction of 4-chlorobenzaldehyde as an example, we investigated the effect of the amount of catalyst on the reaction, which plays a crucial role in

Table 1. Synthesis of 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene in water

Entry	R_1	R_2	R	Mp (°C)	Yield (%)
3a	C_6H_5	H	H	212–213	84
3b	C_6H_5	H	2-Cl	199–200	88
3c	C_6H_5	H	4-Cl	189–190	93
3d	C_6H_5	H	3-OMe	187–188	91
3e	C_6H_5	H	4-OMe	207–208	93
3f	C_6H_5	H	4-$N(CH_3)_2$	216–217	92
3g	4-$OCH_3C_6H_4$	H	H	238–239	88
3h	4-$OCH_3C_6H_4$	H	2-Cl	240–241	89
3i	4-$OCH_3C_6H_4$	H	4-Cl	266–268	94
3j	4-$OCH_3C_6H_4$	H	3-OMe	196–198	92
3k	4-$OCH_3C_6H_4$	H	4-OMe	236–238	95
3l	4-$OCH_3C_6H_4$	H	4-$N(CH_3)_2$	228–229	94
3m	Me	Me	H	194–196	90
3n	Me	Me	4-Cl	226–228	94

the success of the reaction in terms of the rate and the yields. For example, the reaction could not be carried out in absence of the catalyst. It was found that two drops of concentrated H_2SO_4 (about 0.1 mL) in 40 mL water at 70–80 °C for 3 h can give the corresponding product in good to excellent yields. When the amount of catalyst was increased, it gave very poor yield (less than 65%). These data indicated that the two drops of concentrated H_2SO_4 is suitable for this reaction.

CONCLUSION

In summary, we have described a general and highly efficient procedure for the one-pot preparation of 3,6,9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene catalyzed by two drops of concentrated H_2SO_4 in water. It is possible to apply tenets of green chemistry to the generation of interesting products using aqueous media methods that are less expensive and less toxic than those with organic solvents. The catalyst is very cheap and nontoxic, and we used a very small amount. Moreover, the procedure offers several advantages including excellent yields, low cost, operational simplicity, clean reactions, and minimal environmental effects, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus, and the temperature was not calibrated. Microanalysis was performed on a Perkin-Elmer 2400 microanalytical instrument. IR spectra were recorded as thin films on KBr using a Perkin-Elmer 1700 spectrophotometer. The NMR spectra were recorded on a Bruker ARX-300 spectrometer. Sample solutions were prepared in $CDCl_3$ or dimethylsulfoxide (DMSO) containing tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a JMS-DX300 at 70 eV.

All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled.

5-Aryl-1,3-cyclohexanedione **1** were obtained from aromatic aldehyde, acetone, and dimethyl malonate according to the literature[14] method with slight modifications.

General Procedure

A mixture of an 5-aryl-1,3-cyclohexanedione (1.10 mmol), aromatic aldehyde (2.5 mmol), and H_2SO_4 (0.1 mL) in water (40 mL) was stirred at 70–80 °C for 2 h. Then the mixture was cooled to room temperature; the solid was filtered off and washed with water. The crude products were purified by recrystallization by ethanol (95%).

Data of Compounds

Compound 3a. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.69–2.89 (m, 4H, 4-H + 5-H), 2.91–3.04 (m, 4H, 2-H + 7-H), 3.27 (m, 2H, 3-H + 6-H), 4.90 (s, 1H, 9-H), 7.11–7.42 (m, 15H, Ph-H); IR (KBr) υ: 1701, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 447.25 ($M^+ + 1$, 100). Anal. calcd. for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.41; H, 5.85.

Compound 3b. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.51–2.63 (m, 4H, 4-H + 5-H), 2.83–2.97 (m, 4H, 2-H + 7-H), 3.30 (m, 2H, 3-H + 6-H), 5.13 (s, 1H, 9-H), 7.09–7.49 (m, 14H, Ph-H); IR (KBr) υ: 1705, 1643, 1570, 1512, 1127 cm^{-1}; MS (70 eV) m/z (%): 481.05 ($M^+ + 1$, 100), 369.16 (86). Anal. calcd. for $C_{31}H_{25}ClO_3$: C, 77.41; H, 5.24. Found: C, 77.45; H, 5.23.

Compound 3c. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.60–2.76 (m, 4H, 4-H + 5-H), 2.82–2.91 (m, 4H, 2-H + 7-H), 3.32 (m, 2H, 3-H + 6-H), 4.88 (s, 1H, 9-H), 7.12–7.42 (m, 14H, Ph-H); IR (KBr) υ: 1752, 1624, 1590, 1505, 1122 cm^{-1}; MS (70 eV) m/z (%): 480.98 ($M^+ + 1$, 100). Anal. calcd. for $C_{31}H_{25}ClO_3$: C, 77.41; H, 5.24. Found: C, 77.44; H, 5.22.

Compound 3d. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.59–2.75 (m, 4H, 4-H + 5-H), 2.81–2.99 (m, 4H, 2-H + 7-H), 3.43 (m, 2H, 3-H + 6-H), 3.82 (s, 3H, OCH_3), 5.53 (s, 1H, 9-H), 6.92–7.42 (m, 14H, Ph-H); IR (KBr) υ: 1753, 1625, 1513, 1118 cm^{-1}; MS (70 eV) m/z (%): 477.50 ($M^+ + 1$, 100). Anal. calcd. for $C_{32}H_{28}O_4$: C, 80.65; H, 5.92. Found: C, 80.68; H, 5.91.

Compound 3e. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.58–2.70 (m, 4H, 4-H + 5-H), 2.84–2.94 (m, 4H, 2-H + 7-H), 3.29 (m, 2H, 3-H + 6-H), 3.77 (s, 3H, OCH_3), 4.85 (s, 1H, 9-H), 6.78–6.86 (m, 2H, 9-Ph-H), 7.18–7.39 (m, 12H, Ph-H); IR (KBr) υ: 1708, 1625, 1511, 1121 cm^{-1}; MS (70 eV) m/z (%): 475.29 (M^- – 1, 100), 219.64 (48). Anal. calcd. for $C_{32}H_{28}O_4$: C, 80.65; H, 5.92. Found: C, 80.69; H, 5.90.

Compound 3f. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.52–2.65 (m, 4H, 4-H + 5-H), 2.71–2.80 (m, 4H, 2-H + 7-H), 2.92 (s, 3H, N-CH_3), 2.93 (s, 3H, N-CH_3), 3.28 (m, 2H, 3-H + 6-H), 4.82 (s, 1H, 9-H), 6.67–6.73 (m, 2H, 9-Ph-H), 7.11–7.39 (m, 12H, Ph-H); IR (KBr) υ: 1708, 1611, 1543, 1503, 1119 cm^{-1}; MS (70 eV) m/z (%): 490.44 ($M^- + 1$, 100). Anal. calcd. for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 80.98; H, 6.39; N, 2.84.

Compound 3g. ^{1}H NMR (DMSO, 300 MHz): 2.47–2.49 (m, 4H, 4-H + 5-H), 2.78–2.79 (m, 4H, 2-H + 7-H), 2.82 (m, 2H, 3-H + 6-H), 3.68 (s, 6H, OCH_3), 4.76 (s, 1H, 9-H), 6.82 (m, 13H, Ph-H); IR (KBr) υ: 1683, 1625, 1512, 1129 cm^{-1}; MS (70 eV) m/z (%): 506.11 (M, 100). Anal. calcd. for $C_{33}H_{30}O_5$: C, 78.24; H, 5.97. Found: C, 78.27; H, 5.93.

Compound 3h. ^{1}H NMR (DMSO, 300 MHz): 2.49–2.59 (m, 4H, 4-H + 5-H), 2.80 (m, 4H, 2-H + 7-H), 2.89 (m, 2H, 3-H + 6-H), 3.71 (s, 6H, OCH_3), 4.92 (s, 1H, 9-H), 6.79 (m, 12H, Ph-H); IR (KBr) υ: 1748, 1683, 1618, 1504, 1131 cm^{-1}; MS (70 eV) m/z (%): 540.50 (M, 100). Anal. calcd. for $C_{33}H_{29}ClO_5$: C, 73.26; H, 5.40. Found: C, 73.29; H, 5.36.

Compound 3i. ^{1}H NMR (DMSO, 300 MHz): 2.52–2.56 (m, 4H, 4-H + 5-H), 2.79 (m, 4H, 2-H + 7-H), 2.87 (m, 2H, 3-H + 6-H), 3.73 (s, 6H, OCH_3), 4.59 (s, 1H, 9-H), 6.91 (m, 12H, Ph-H); IR (KBr) υ: 1750, 1671, 1624, 1507, 1127 cm^{-1}; MS (70 eV) m/z (%): 540.5 (M, 100). Anal. calcd. for $C_{33}H_{29}ClO_5$: C, 73.26; H, 5.40. Found: C, 73.28; H, 5.38.

Compound 3j. ^{1}H NMR (DMSO, 300 MHz): 2.59–2.63 (m, 4H, 4-H + 5-H), 2.74–2.76 (m, 4H, 2-H + 7-H), 2.76 (m, 2H, 3-H + 6-H), 3.64 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3), 4.62 (s, 1H, 9-H), 6.70 (m, 12H, Ph-H); IR (KBr) υ: 1732, 1681, 1621, 1509, 1107 cm^{-1}; MS (70 eV) m/z (%): 536 (M, 100). Anal. calcd. for $C_{34}H_{32}O_6$: C, 76.10; H, 6.01. Found: C, 76.15; H, 6.00.

Compound 3k. ^{1}H NMR (DMSO, 300 MHz): 2.51–2.57 (m, 4H, 4-H + 5-H), 2.72–2.75 (m, 4H, 2-H + 7-H), 2.79 (m, 2H, 3-H + 6-H), 3.65 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3), 4.59 (s, 1H, 9-H), 6.73 (m, 12H, Ph-H); IR (KBr) υ: 1747, 1688, 1619, 1510, 1125 cm^{-1}; MS (70 eV) m/z (%): 535.33 ($M^- - 1$, 100). Anal. calcd. for $C_{34}H_{32}O_6$: C, 76.10; H, 6.01. Found: C, 76.17; H, 5.99.

Compound 3l. ^{1}H NMR (DMSO, 300 MHz): 2.49–2.61 (m, 4H, 4-H + 5-H), 2.81–2.96 (m, 4H, 2-H + 7-H), 2.99 (s, 6H, $N(CH_3)_2$), 3.02 (m, 2H, 3-H + 6-H), 3.71 (s, 6H, OCH_3), 4.53 (s, 1H, 9-H), 6.82 (m, 12H, Ph-H); IR (KBr) υ: 1710, 1685, 1617, 1506, 1132 cm^{-1}; MS (70 eV) m/z (%): 549 (M, 100). Anal. calcd. for $C_{35}H_{35}NO_5$: C, 76.48; H, 6.42; N, 2.55. Found: C, 76.51; H, 6.41; N, 2.53.

Compound 3m. ^{1}H NMR (DMSO, 300 MHz): 0.87 (s, 6H, 2-CH_3), 1.08 (s, 6H, 2-CH_3), 2.09 (m, 2H, 4-H), 2.21 (m, 2H, 5-H), 2.52 (m, 2H, 2-H), 2.61 (m, 2H, 7-H), 4.63 (s, 1H, 9-H), 7.20 (m, 5H, Ph-H); IR (KBr) υ: 1745, 1621, 1506, 1126 cm^{-1}; MS (70 eV) m/z (%): 351.09 ($M^+ + 1$, 100). Anal. calcd. for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.89; H, 7.45.

Compound 3n. ^{1}H NMR (DMSO, 300 MHz): 0.89 (s, 6H, 2-CH_3), 1.03 (s, 6H, 2-CH_3), 2.05 (d, $J = 16.20$ Hz, 2H, 4-H), 2.23 (d, $J = 16.20$ Hz, 2H, 5-H), 2.49 (m, 4H, 2-H + 7-H), 4.49 (s, 1H, 9-H), 7.16 (m, 4H, Ph-H); IR (KBr) υ: 1726, 1622, 1508, 1128 cm^{-1}; MS (70 eV) m/z (%): 383.28 ($M^- - 1$, 100). Anal. calcd. for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.55. Found: C, 71.81; H, 6.51.

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