



The Reaction of Aromatic Aldehydes and 1,3-Cyclohexanedione in Aqueous Media

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Received 10 January 2006; Accepted 14 April 2006

Abstract: The reaction of aromatic aldehyde and 1,3-cyclohexanedione in aqueous media has been catalyzed by *p*-dodecylbenzenesulfonic acid (DBSA) or sodium dodecyl sulfate (SDS) and yields two products: 9-aryl-1, 8-dioxooctahydroxanthene derivatives and 2,2'-arylmethylene bis(3-hydroxy- 2-cyclohexene-1-one). This method provides several advantages such as good yield, simple work-up procedure and environment friendly.

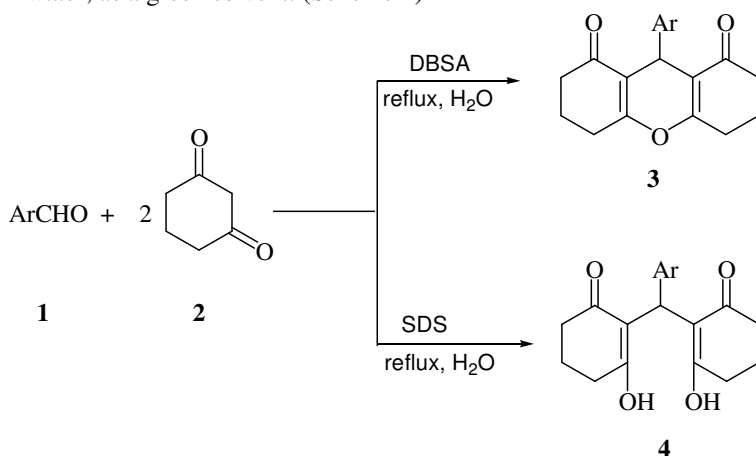
Keywords: 9-aryl-1, 8-dioxooctahydroxanthene derivatives; *p*-dodecylbenzenesulfonic acid (DBSA); sodium dodecyl sulfate (SDS); synthesis

Introduction

In recent years, polyfunctionalized benzopyrans and their derivatives have attracted strong interest due to their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, diuretic, antianaphylactin, anticancer.¹ In addition, they also constitute a structural unit of a series of natural products² and because of the inherent reactivity of the inbuilt pyran ring are versatile synthesis.³ Furthermore, these compounds can be employed as cosmetics, pigments⁴ and utilized as potential biodegradable agrochemicals.⁵ Thus, synthesis of the heterocyclic nucleus is of much current importance. Octahydroxanthene derivatives containing a structural unit of benzopyrans can be used as antispasm⁶ and fluorescent fuel⁷. The tetraketones and their enol forms are the precursors of synthesis of

acridines, xanthenes and thioxanthenes which contain structures such as dihydropyridine, pyran and thiapyran. It has been reported⁸⁻¹¹ that the reaction of aromatic aldehyde and 1,3-cyclohexanedione can yield 9-aryl-1,8-dioxo-octahydroxanthene and their derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) by many methods. However, the use of *p*-dodecylbenzenesulfonic acid (DBSA) or sodium dodecyl sulfate (SDS) as the catalyst in aqueous media for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthene and their derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) has not been reported. Herein, we wish to synthesize 9-aryl-1,8-dioxooctahydroxanthene derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) using *p*-dodecyl-benzenesulfonic acid (DBSA) or sodium dodecyl sulfate (SDS) as the catalyst in aqueous media.

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.¹² 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.¹³ 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.¹⁴ DBSA and SDS have been used in a number of organic reactions as good catalysts. In the course of our investigations to develop new synthetic methods in water using DBSA and SDS as catalysts, we examined the synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) in water, as a green solvent. (Scheme 1)



Scheme 1 Synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) in water

Experimental

Materials and Measurements

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

Procedure for the synthesis of 3 and 4 using DBSA or SDS as catalyst

A mixture of an aromatic aldehyde (1.0 mmol), 1, 3-cyclohexanedione (2.0 mmol) and DBSA (20 mol%) or SDS (10 mol%) in water (20 mL) was stirred at refluxing for three hours. 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 H₂O (40 mL) and the crude products were got. The crude products 3 and 4 were purified by recrystallization by ethanol. Data of some compounds are shown below:

Compound 3c. 9-(3-Chlorophenyl)-1, 8-dioxo-octahydroxanthene:

IR (KBr): ν_{\max} 2953, 2890, 1672, 1621, 1474, 1358, 1201, 1174, 1129, 847, 684 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ_{H} 7.13 (4H, m, ArH), 4.56 (1H, s, CH), 2.64 (4H, m, 2×COCH₂), 2.29 (4H, m, 2×CH₂), 1.95 (2H, m, CH₂), 1.88 (2H, m, CH₂).

Compound 3e. 9-(2-nitrophenyl)-1, 8-dioxo-octahydroxanthene:

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_{H} 7.77 (1H, d, J=6.8Hz, ArH), 7.56 (1H, m, ArH), 7.35 (2H, d, J=6.8Hz, ArH), 5.40 (1H, s, CH), 2.64 (4H, m, 2×COCH₂), 2.27 (4H, m, 2×CH₂), 1.95 (2H, m, CH₂), 1.86 (2H, m, CH₂).

Compound 3h. 9-(4-hydroxyphenyl)-1, 8-dioxo-octahydroxanthene:

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_{H} 9.19 (1H, s, OH), 6.95 (2H, d, J=8.4Hz, ArH), 6.59 (2H, d, J=8.4Hz, ArH), 4.48 (1H, s, CH), 2.63 (4H, m, 2×COCH₂), 2.27 (4H, m, 2×CH₂), 1.94 (2H, m, CH₂), 1.86 (2H, m, CH₂).

Compound 3j. 9-(4-methylphenyl)-1, 8-dioxo-octahydroxanthene:

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_{H} 7.00 (4H, dd, J₁=22Hz, J₂=8Hz, ArH), 4.54 (1H, s, CH), 2.60 (4H, m, 2×COCH₂), 2.25 (4H, m, 2×CH₂), 1.93 (2H, m, CH₂), 1.84 (2H, m, CH₂).

Compound 3k. 9-(3, 4-dioxymethylenephenyl)-1, 8-dioxo-octahydroxanthene:

IR (KBr): ν_{\max} 2954, 2893, 1658, 1619, 1485, 1361, 1201, 1177, 1135, 853, 794 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ_{H} 6.64 (3H, m, ArH), 5.94 (2H, s, -OCH₂O-), 4.51 (1H, s, CH), 2.61 (4H, m, 2×COCH₂), 2.29 (4H, m, 2×CH₂), 1.95 (2H, m, CH₂), 1.86 (2H, m, CH₂).

Results and Discussion

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%) or SDS (10 mol%) for a certain period of time required to complete the reaction, the corresponding 9-aryl-1,8-dioxooctahydroxanthene derivatives and 2,2'-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) were obtained in good yields. The results are summarized in Table 1.

As shown in Scheme 1, the different products were obtained using different catalyst in this reaction. In a typical general experimental procedure, aromatic aldehyde and 1,3-cyclohexanedione reacted in the presence of a catalytic amount of DBSA or SDS, the corresponding products 3 and 4 were obtained in good to excellent yields. The catalyst effect shows that acid is needed during the cyclization.

To study the generality of this process, several examples illustrating this method for the synthesis **3** and **4** were studied. As shown in Table 1. 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 reaction proceeded smoothly under refluxing water to give the corresponding products **3** and **4** in good yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxy group, alkoxy group) were employed and reacted well to give the corresponding **3** and **4** in good to excellent yields.

Table 1 Synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives and 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one) in aqueous media

Ar	Product	Yield ^a (%)	M. P. / °C	
			Found	Reported
C ₆ H ₅ 1a	3a	91	272-273	270-271 ⁸
	4a	64	210-211	205-207 ¹⁰
4-ClC ₆ H ₄ 1b	3b	84	288-290	289-291 ⁸
3-ClC ₆ H ₄ 1c	3c	80	276-277	
2-ClC ₆ H ₄ 1d	3d	78	254-255	250-251 ⁸
	4d	67	235-237	238-240 ¹⁰
2-NO ₂ C ₆ H ₄ 1e	3e	90	245-246	
3-NO ₂ C ₆ H ₄ 1f	3f	94	286-288	286-288 ⁸
4-NO ₂ C ₆ H ₄ 1g	3g	86	263-265	263 ¹²
	4g	92	195-196	191-192 ¹¹
4-HOC ₆ H ₄ 1h	3h	84	279-281	
4-CH ₃ OC ₆ H ₄ 1i	3i	88	196-197	201-202 ⁸
	4i	73	183-185	178-180 ¹¹
4-CH ₃ C ₆ H ₄ 1j	3j	67	262-263	
3,4-OCH ₂ OC ₆ H ₃ 1k	3k	84	248-249	

^a Isolated yield

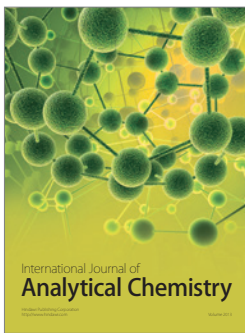
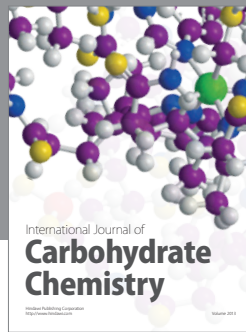
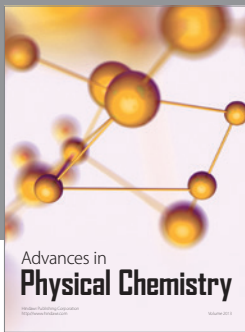
The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, 4-chlorobenzoaldehyde reacted with 1, 3-cyclohexanedione in the presence of 10mol% DBSA to give the product **3b** in modest yield (76.6%) at refluxing water after three hours of reaction time. Increasing of the catalyst to 20 and 30mol% results in accelerating the reaction yields to 83.7% and 80.3% respectively. Use of just 20mol% 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, 20mol% DBSA was chosen as a quantitative catalyst for these reactions. In addition, it must be pointed out that all of these reactions were carried out in water and those products were characterized by melting point, IR and ¹H NMR.

Conclusions

We have described a practical and efficient procedure for the preparation of 9-aryl-1, 8-dioxooctahydroxanthene derivatives and 2,2'- arylmethylene bis(3-hydroxy-2-cyclohexene-1-one). In addition, these reactions, which proceed sluggishly in organic solvents, attest to the unique property of water as a reaction medium. 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. Mostly important, water has been chosen as a green solvent for these reactions.

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