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Environmentally benign synthesis of 9-aryl-1,8-dioxo-octahydroxanthene

Sandeep V.Shinde^{1*}, Wamanrao N.Jadhav¹, Rajendra P.Pawar¹, Rajesh H.Tale², Nilesh P.Tale²¹Dnyanopasak College, Parbhani-431401, Maharashtra, (INDIA)²School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, Maharashtra, (INDIA)

Fax : +91-2462-229245

E-mail : sv_shinde@rediffmail.com

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ABSTRACT

An efficient and convenient approach to the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthene derivatives using inexpensive boric acid as the catalyst (10 mol%) is described. The use of water as reaction medium is the most important feature of this reaction.

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INTRODUCTION

Xanthenes are an important class of organic compounds that find use as dyes^[1], pH-sensitive fluorescent material for visualization of biomolecules^[2] and utilized in laser technologies^[3] due to their useful spectroscopic properties. Xanthenes have also received significant attention from many pharmaceutical and organic chemists, essentially because of the broad spectrum of their biological properties such as antiviral^[4], antibacterial^[5], and anti-inflammatory activities^[6]. These are also used in photodynamic therapy^[7] and as an antagonist for the paralyzing action of zoxazolamine^[8].

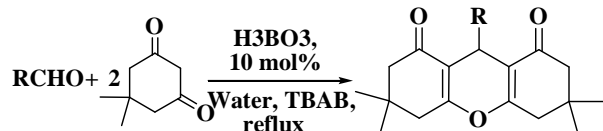
1,8-Dioxo-octahydroxanthene is usually synthesized by the one-pot three component condensation reactions of two equivalents of dimedone and aldehydes in presence of suitable catalysts. The various catalysts and the reaction conditions so far reported in the literature are as follows: (a) *p*-dodecylbenzenesulfonic acid in water^[9]. (b) tetrabutylammonium hydrogen sulphate in dioxane-H₂O system^[10]. (c) solid super acid TiO₂/SO₄²⁻ by grinding technique^[11]. (d) microwave conditions^[12] (e) HCl^[13]

Each of these methods have their own advantages

but also suffer from one or more disadvantages such as prolonged reaction time, tedious work-up processes, low yield, and hazardous reaction conditions. In addition, chemo selectivity can be a problem, if acid sensitive groups are present in the same molecule. The major disadvantage of some of the methods is that the reaction does not go to completion and stops at open chain structure 5,5-dimethyl-2-((4,4-dimethyl-2,6-dioxocyclohexyl)(phenyl)methyl)cyclohexane-1,3-dione, instead of forming the cyclized compound. The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in organic synthesis has also posed a serious threat to the environment. Consequently, methods that successfully minimize the above drawbacks are the focus of much attention.

Boric acid is the commercially available crystalline, non toxic and stable solid. It is an electron deficient compound with a low-lying vacant *p*-orbital on the boron, the property that confirms it as an efficient and mild Lewis acid catalyst. In recent years, boric acid has gained much popularity as efficient and green Lewis acid catalysts in organic synthesis^[14-16].

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RESULTS AND DISCUSSION

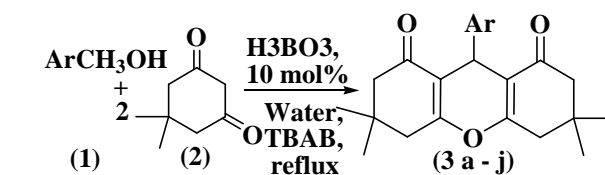
In view of the surprising lack of literature report on the truly economical and environmentally benign methods for the synthesis of 9-aryl-1, 8-dioxo-octahydroxanthene derivatives, we thought it was worthwhile to develop the practical, general, mild and environmentally benign protocol for the synthesis of 9-aryl-1, 8-dioxo-octahydroxanthene derivatives. In order to meet the objective of such a protocol, the use of catalyst which would be environmentally benign, stable to air and moisture, and inexpensive was at the forefront of our scheme of things. Thus in view of our objective of the development of environmentally benign protocol for the synthesis of titled compounds, we thought the boric acid would be prime and suitable choice to be employed as catalyst for the same. To further illustrate the utility of water as solvent and role of PTCs in organic synthesis, we chose to study the cyclocondensation reaction of aldehyde and 5,5-dimethyl-1,3-cyclohexanedione in water. In view of making the process inexpensive we preferred boric acid as an inexpensive and efficient catalyst and TBAB as a phase transfer catalyst.

As a starting point for the development of boric acid catalyzed synthesis of 9-aryl-1, 8-dioxo-octahydroxanthenes in water, cyclocondensation reaction involving benzaldehyde (3 mmol) and 5,5-dimethyl-cyclohexa-1,3-dione (3 mmol) in the presence of 10 mol% of boric acid and TBAB (1 mmol) in water under reflux was performed. We were pleased to find that the corresponding cyclocondensation reaction product was obtained in 84% isolated yield within 10 h. To check out whether there is a need for catalyst to perform the present reaction in a practical way; we repeated the above experiment under same reaction conditions as above but without using boric acid. We found that this time the corresponding cyclocondensation product was obtained only in 30 % yield despite the reaction being continued for 15h. Thus, this finding confirmed the pivotal role of the boric acid as a catalyst in

the present reaction. With good results being obtained in the reaction of benzaldehyde, next, a variety of aromatic aldehydes were examined under our optimized reaction conditions (TABLE 1).

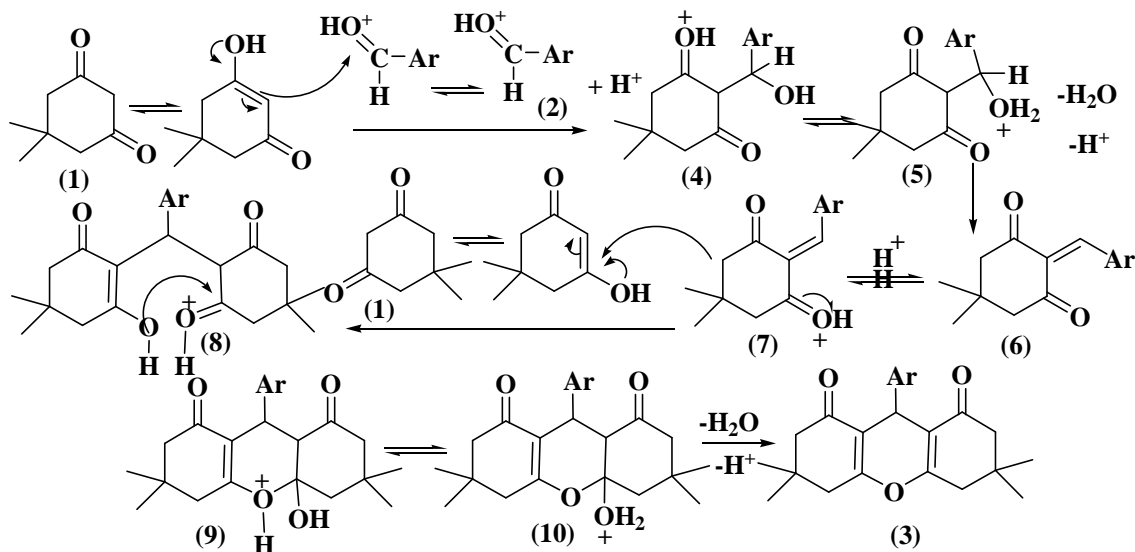
The results are summarized in TABLE 1. Thus it is seen that aromatic aldehydes possessing both electron withdrawing and electron releasing substituents underwent the cyclocondensation reaction smoothly to afford the corresponding products in high yield. It was found that the nature of the substituents on aldehydes did not have detrimental effect on the product yields. Moreover, the reaction can also be applied to α - β unsaturated aldehydes, (TABLE 1, entry 10), such as cinnamaldehyde giving the corresponding product in high yield. In all the examples, studied generally >70% yield of the corresponding 9-aryl-1,8-dioxo-octahydroxanthenes were obtained within 10 h. A broad range of functional groups such as halides, cyano, alkoxy, nitro (entries, 7-9) were tolerated under the present reaction conditions which clearly evident the functional groups compatibility of the present method. The work-up is very easy and the products can be obtained in high purity by mere washing the reaction mixture with water to remove the boric acid catalyst followed by recrystallization with ethanol. Thus this novel approach not only preserves the simplicity but consistently produced the

TABLE 1: Synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthene catalyzed by boric acid in aqueous medium



Entry	Ar	Reaction time (h)	Product	Yield (%) ^a	M. p. (°C)	
					Found	Reported ⁹
1	C ₆ H ₅	10	3a	84	202-204	202-204
2	4-CH ₃ C ₆ H ₄	12	3b	78	218-219	217-218
3	4-CH ₃ OC ₆ H ₄	11	3c	81	244-245	242-244
4	4-HOC ₆ H ₄	13	3d	78	245-246	246-248
5	4-HO-3-CH ₃ OC ₆ H ₃	12	3e	74	225-226	226-228
6	4-ClC ₆ H ₄	11	3f	77	228-229	228-230
7	4-NO ₂ C ₆ H ₄	10	3g	76	227-228	226-228
8	3-NO ₂ C ₆ H ₄	12	3h	79	168-169	168-170
9	2-NO ₂ C ₆ H ₄	14	3i	73	248-249	247-249
10	C ₆ H ₅ CH=CH	15	3j	74	175-176	175-177

^aIsolated yield



structurally diverse 9-aryl-1,8-dioxo-octahydroxanthenes in high yields in an environmentally benign and resource effective process.

Mechanistically, the reaction will proceed through Knoevenagel condensation ($1+2 \rightarrow 6$) followed by Michael addition ($1+6 \rightarrow 8$) to form 1,5-dicarbonyl compound (8) which finally undergoes cyclodehydration to form 9-aryl-1,8-dioxo-octahydroxanthene (3). The role of boric acid is to enhance enolic (nucleophilic) character of dimedone required essentially for the Knoevenagel condensation and Michael addition.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. ^1H NMR spectra were recorded at 400 MHz in CDCl_3 using TMS as internal standard. The representative spectral analysis for few of the products is given below:

General experimental procedure

The aromatic aldehyde (3 mmol), 5,5-dimethyl-1,3-cyclohexanedione (6 mmol), boric acid (10 mol%) and TBAB (1 mmol) were mixed in 20 mL of water. The resulting reaction mixture was refluxed in a 100 mL round bottom flask for the time as indicated in TABLE 1. The reaction progress was monitored by TLC. The reaction mixture was cooled to room temperature and the solid product was filtered off and dried. The crude prod-

uct was purified by recrystallization method using ethanol to afford 9-aryl-1,8-dioxo-octahydroxanthene in good to excellent yield.

(i) 3,4,6,7,-tetrahydro-3,3,6,6-tetramethyl-9-P-tolyl 2H-xanthene-1,8(5H,9H)-dione (3b)

Crystalline yellow solid, M.p. 218-219°C (Lit.⁹ melting point: 217-218°C). IR (KBr, cm^{-1}): 3016, 2958, 2924, 1680, 1664, 1510, 1357, 1195, 1165, 1020, 999, 931, 840, 765, 715.

^1H NMR (CDCl_3): δ = 1.01 (s, 6H, 2CH_3), 1.11 (s, 6H, 2CH_3), 2.20 (s, 4H, 2CH_2), 2.25 (s, 4H, 2CH_2), 2.47 (s, 3H, ArCH_3), 4.72 (s, 1H, ArCH), 7.03 (d, J = 10.4 Hz, 2H, ArH), 7.19 (d, J = 10.8 Hz, 2H, ArH).

(ii) 9-(4-chlorophenyl)3,4,6,7,-tetrahydro-3,3,6,6-tetramethyl-2H-xanthene-1,8(5H,9H)-dione (3f)

Crystalline yellow solid, M.p. 228-229°C (Lit.⁹ melting point: 228-230°C). IR (KBr, cm^{-1}): 3018, 2964, 2875, 1680, 1660, 1489, 1361, 1197, 1087, 852, 717. ^1H NMR (CDCl_3): δ = 1.00 (s, 6H, 2CH_3), 1.12 (s, 6H, 2CH_3), 2.20 (s, 4H, 2CH_2), 2.23 (s, 4H, 2CH_2), 4.73 (s, 1H, ArCH), 7.20 (d, J = 8.4 Hz, 2H, ArH), 7.25 (d, J = 8.4 Hz, 2H, ArH).

(iii) 3,4,6,7,-tetrahydro-3,3,6,6-tetramethyl-9-styryl-2H-xanthene-1,8(5H,9H)-dione (3j)

Crystalline yellow solid, M.p. 175-176°C (Lit.⁹ melting point: 175-177°C) ^1H NMR (CDCl_3): δ = 1.11 (s, 12H, 4CH_3), 2.29 (s, 4H, 2CH_2), 2.43 (s, 4H,

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2CH₂), 4.39 (s, 1H, ArCH), 6.23-6.35 (m, 2H, CH=CH), 7.14-7.27 (m, 5H, ArH).

CONCLUSION

The synthesis of 9-aryl-1,8-dioxo-octahydroxanthene is characterized by the following merits: (a) non-toxic, inexpensive and readily available nature of boric acid (b) use of aqueous medium is the most striking feature (c) easy work-up (d) preparative simplicity (e) high yields. In conclusion, we have demonstrated an environmentally benign three component condensation of aromatic aldehyde and two equivalents of dimedone to form 9-aryl-1,8-dioxo-octahydroxanthene using boric acid in aqueous medium.

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