



## Tetrabutylammonium Bromide: An Efficient Catalyst for the Synthesis of Xanthenediones under Solvent-free Conditions

ALI EZABADI\*, RAMO NAZARIAN and MINA GHOLAMI

Department of Chemistry, Faculty of Sciences, Central Tehran Branch,  
Islamic Azad University, Sanat Square, Iran.

\*Corresponding author E-mail: aliezabadi@yahoo.com

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### ABSTRACT

TBAB was found to be an effective catalyst for the synthesis of xanthenediones in good to excellent yields under solvent-free conditions. This method has many advantages such as avoiding the use of harmful solvents and catalysts, high yields and simple work-up.

**Key words:** Xanthenediones, Tetrabutyl ammonium bromide,  
Solvent free conditions, Aromatic aldehydes, 5,5-Dimethyl-1,3-cyclohexanedion.

### INTRODUCTION

Xanthene derivatives especially xanthenediones have been attracting great interest because of their importance in synthetic organic chemistry. Many products that contain the subunit of xanthene exhibit useful and diverse biological activities such as analgesic<sup>1</sup>, antiviral<sup>2</sup>, antibacterial<sup>3</sup>, and anti-inflammatory activities<sup>4</sup>. Some of them have been used as antagonist for paralyzing the action of zoxazolamine,<sup>5</sup> and in photodynamic therapy.<sup>6</sup> Moreover, they can be used as dyes<sup>7</sup> and are used extensively in laser technology<sup>8</sup> and pH sensitive fluorescent materials for visualization of biomolecules.<sup>9</sup> Many synthetic procedures for preparing xanthenediones have

been reported by the condensation of aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione in the presence of alumina-sulfuric acid,<sup>10</sup> Fe<sub>3</sub>O<sub>4</sub> nanoparticles,<sup>11</sup> Fe<sup>3+</sup>-montmorillonite,<sup>12</sup> ZrOCl<sub>2</sub>.8H<sub>2</sub>O,<sup>13</sup> succinimide-N-sulfonic acid,<sup>14</sup> [Et<sub>3</sub>NH][HSO<sub>4</sub>],<sup>15</sup> PMA-SiO<sub>2</sub>,<sup>16</sup> silica sulfuric acid,<sup>17</sup> nano Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-SO<sub>3</sub>H,<sup>18</sup> DSIMHS,<sup>19</sup> and zinc oxide nanoparticles.<sup>20</sup>

Although most of these methods offer distinct advantages, they suffer from certain drawbacks such as high cost, unsatisfactory yields, the use of volatile organic solvents, stoichiometric amount of catalyst, and also environmentally toxic catalyst. Therefore, the search for green and readily available catalyst is still being actively pursued.

In recent years, tetrabutylammonium bromide (TBAB) has emerged as an extremely useful homogeneous catalyst in various organic transformations,<sup>21</sup> including conjugate addition of thiols to electron deficient alkenes,<sup>22</sup> transthioacetalisation of acetals<sup>23</sup>, trimethylsilylation of alcohols,<sup>24</sup> synthesis of aryl-14H-dibenzo[a, j]xanthenes,<sup>25</sup> synthesis of biscoumarin and 3,4-dihydropyrano[c]chromene derivatives,<sup>26</sup> synthesis of quinazolin-4(3H)-ones,<sup>27</sup> synthesis of tetrahydrobenzo [b]pyran derivatives,<sup>28</sup> and synthesis of optically active polyamides.<sup>29</sup> TBAB is an inexpensive readily available ionic liquid with inherent properties like environmental compatibility, greater selectivity, operational simplicity, non-corrosive nature and ease of reusability. Herein, we wish to report a simple and efficient method for the synthesis of xanthenediones from aromatic aldehydes, 5,5-dimethyl-1, 3-cyclohexane-dione and TBAB as a catalyst under solvent-free conditions (Scheme 1).

## EXPERIMENTAL

### Material and Methods

All chemical compounds have been purchased from Fluka, Romill and Merck companies and used without further purifications. The progress of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined using Buchi B-540 melting point apparatus. FT-IR were recorded by JACSO FT-IR410 spectrophotometer with KBr plates and <sup>1</sup>H NMR spectra were recorded by Bruker DRX-500 MHz in CDCl<sub>3</sub>. Chemical shifts were expressed in  $\delta$  ppm.

### General procedure for the synthesis of xanthenediones under solvent-free conditions

A mixture of aromatic aldehydes (1 mmol), 5,5-dimethyl-1, 3-cyclohexanedione (2.2 mmol) and TBAB (40 mol%) under solvent-free conditions was heated at 120 °C and stirred for the required time (Table 2). After completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crude product was recrystallized from hot ethanol to afford pure product.

### Spectral data

3,3,6,6-Tetramethyl-9-(phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3a): <sup>1</sup>H NMR

(CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 1.00 (s, 6H), 1.14 (s, 6H), 2.16-2.26 (q, 4H), 2.47 (s, 4H), 4.76 (s, 1H), 7.09-7.30 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2954, 1661, 1364, 1198.

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3b): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 0.98 (s, 6H), 1.09 (s, 6H) 2.14-2.24 (q, 4H), 2.45 (s, 4H), 4.7 (s, 1H), 7.16-7.25 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2956, 2877, 1662, 1364, 1197, 845.

3,3,6,6-Tetramethyl-9-(3-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3c): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 0.99 (s, 6H), 1.09 (s, 6H) 2.15-2.24 (q, 4H), 2.46 (s, 4H), 4.71 (s, 1H), 7.06-7.25 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2958, 2877, 1670, 1361, 1192, 1139.

3,3,6,6-Tetramethyl-9-(2-chlorophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3d): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 1.00 (s, 6H), 1.09 (s, 6H) 2.13-2.23 (q, 4H), 2.43 (s, 4H), 4.98 (s, 1H), 7.04-7.41 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2961, 1665, 1526, 1353, 1202.

3,3,6,6-Tetramethyl-9-(4-bromophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3e): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 0.97 (s, 6H), 1.09 (s, 6H) 2.01-2.21 (q, 4H), 2.45 (s, 4H), 4.68 (s, 1H), 7.15-7.32 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2955, 1662, 1363, 1196.

3,3,6,6-Tetramethyl-9-(3-bromophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3f): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 1.00 (s, 6H), 1.1 (s, 6H) 2.16-2.26 (q, 4H), 2.46 (s, 4H), 4.7 (s, 1H), 7.08-7.35 (m, 4H), 8.07-8.09 (d, 2H) IR (KBr) cm<sup>-1</sup>: 2953, 1668, 1362, 1201.

3,3,6,6-Tetramethyl-9-(2-bromophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3g): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 1.01 (s, 6H), 1.09 (s, 6H) 2.13-2.22 (q, 4H), 2.44 (s, 4H), 5.01 (s, 1H), 6.94-7.44 (m, 4H). IR (KBr) cm<sup>-1</sup>: 2954, 1668, 1359, 1202, 1014, 742.

3,3,6,6-Tetramethyl-9-(4-nitro-Phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3h): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 0.98 (s, 6H), 1.11 (s, 6H) 2.14-2.26 (q, 4H), 2.44 (s, 4H), 4.81 (s, 1H),

7.46-7.48 (d, 2H), 8.07-8.09 (d, 2H). IR (KBr)  $\text{cm}^{-1}$ : 1660, 1363, 1200. 2957, 1660, 1518, 1353, 1201.

3, 3, 6, 6-Tetramethyl-9-(3-nitro-Phenyl)-1, 8- dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3i):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.99 (s, 6H), 1.11 (s, 6H) 2.01-2.26 (q, 4H), 2.50 (s, 4H), 4.83 (s, 1H), 7.25-8.00 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 2960, 1664, 1526, 1353, 1200.

3, 3, 6, 6-Tetramethyl-9-(2-nitro-Phenyl)-1, 8- dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3j):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.99 (s, 6H), 1.08 (s, 6H) 2.13-2.23 (q, 4H), 2.45 (s, 4H), 5.5 (s, 1H), 7.21-7.75 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 2957, 1660, 1518, 1353, 1201.

3,3,6,6-Tetramethyl-9-(3-methoxy phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3k):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.99 (s, 6H), 1.07 (s, 6H) 2.11-2.26 (q, 4H), 2.44-2.46 (q, 4H), 3.71 (s, 3H), 4.81 (s, 1H), 6.69-7.35 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 2956, 1664, 1366, 1199.

3,3,6,6-Tetramethyl-9-(2-methoxy phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3l):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.93 (s, 6H), 1.07 (s, 6H) 2.09-2.21 (q, 4H), 2.44-2.46 (q, 4H), 3.76 (s, 3H), 4.84 (s, 1H), 6.73-7.41 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 2951, 1666, 1361, 1197, 754.

3,3,6,6-Tetramethyl-9-(4-fluoro phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3m):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.98 (s, 6H), 1.09 (s, 6H) 2.14-2.24 (q, 4H), 2.45 (s, 4H), 4.71 (s, 1H), 6.86-7.25 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 2958, 1660, 1527, 1365, 1197, 845.

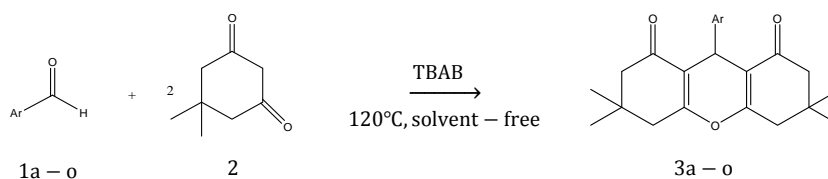
3,3,6,6-Tetramethyl-9-(4-hydroxy phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3n):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.98 (s, 6H), 1.08 (s, 6H) 2.14-2.24 (q, 4H), 2.44 (s, 4H), 4.66 (s, 1H), 6.58-7.25 (m, 4H). IR (KBr)  $\text{cm}^{-1}$ : 3358, 2960, 2868,

3,3,6,6-Tetramethyl-9-(2-thienyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (3o):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 1.99 (s, 6H), 1.02 (s, 6H) 2.25 (s, 4H), 2.44 (s, 4H), 5.14 (s, 1H), 6.81-7.25 (m, 3H). IR (KBr)  $\text{cm}^{-1}$ : 2956, 2875, 1665, 1363, 1199.

## RESULTS AND DISCUSSION

During initial exploratory reaction, condensation of benzaldehyde and 5,5-dimethyl-1, 3-cyclohexanedione were taken as a model reaction to establish the feasibility of our strategy and to optimize reaction conditions, the results of which are summarized in Table 1. As expected, the catalytic system is influenced by various reaction parameters such as amounts of the catalyst employed (entries 1-4), effect of temperature (entries 4,5), amount of 5,5-dimethyl-1, 3-cyclohexanediones (entries 6) and solvent system (entries 7-11). Through thorough investigation, the best result in 92% yield was obtained by carrying out the reaction with 1:2.2 mol ratios of benzaldehyde and 5,5-dimethyl-1, 3-cyclohexanedione at  $120^\circ\text{C}$  and the dosage of 40 mol% catalyst for 8h under solvent-free conditions.

Encouraged by the remarkable results obtained with the above reaction conditions and in order to show the generality and scope of this new protocol, we performed the reaction with a variety of aromatic aldehydes with different substituents. The results are shown in Table 2. From the results, we found that all aromatic aldehydes carrying either electron-donating or electron-withdrawing group substituents reacted efficiently to give excellent yields. The high yield was also obtained in the case of the heterocyclic aldehyde (Table 2, entry 16). The desired products were characterized by  $^1\text{H}$  NMR, infrared (IR), melting points and also, by comparison with authentic samples.



**Scheme 1: TBAB catalyzed synthesis of xathenediones**

**Table 1: The reaction of benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione under different reaction conditions<sup>a</sup>**

Entry	Solvent	Amount of catalyst (mol%)	Temperature (°C)	Yield <sup>b</sup>
1	None	10	120	-
2	None	20	120	-
3	None	30	120	82
4	None	40	120	85
5	None	40	100	-
6	None	40	120	92 <sup>c</sup>
7	H <sub>2</sub> O	40	Reflux	-
8	CHCl <sub>3</sub>	40	Reflux	-
9	CH <sub>2</sub> Cl <sub>2</sub>	40	Reflux	-
10	EtOH	40	Reflux	20
11	EtOAc	40	Reflux	50

<sup>a</sup>Reaction conditions: benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol)

<sup>b</sup>Isolated yield

<sup>c</sup>Reaction conditions: benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2.2 mmol), 8h

**Table 2: The synthesized of xanthenediones catalyzed by TBAB**

Entry	Ar	Product	Time (h)	Yield (%)	M.P. (°C)	
					Found	Reported <sup>ref</sup>
1	C <sub>6</sub> H <sub>5</sub>	3a	8	92	202-204	205-206 <sup>30</sup>
2	4-ClC <sub>6</sub> H <sub>4</sub>	3b	5	96	228-230	231-233 <sup>19</sup>
3	3-ClC <sub>6</sub> H <sub>4</sub>	3c	6	97	180-182	179-181 <sup>13</sup>
4	2-ClC <sub>6</sub> H <sub>4</sub>	3d	8	92	226-228	227-228 <sup>19</sup>
5	4-BrC <sub>6</sub> H <sub>4</sub>	3e	4.5	94	238-239	240-242 <sup>19</sup>
6	3-BrC <sub>6</sub> H <sub>4</sub>	3f	8	97	188-190	189-191 <sup>19</sup>
7	2-BrC <sub>6</sub> H <sub>4</sub>	3g	8	90	226-228	226-229 <sup>31</sup>
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3h	5	97	225-227	222-224 <sup>19</sup>
9	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3i	9	97	167-169	171-172 <sup>18</sup>
10	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3j	8	70	256-258	250-256 <sup>18</sup>
11	3-MeOC <sub>6</sub> H <sub>4</sub>	3k	10	96	164-166	161-163 <sup>32</sup>
12	2-MeOC <sub>6</sub> H <sub>4</sub>	3l	12	85	253-255	257-258 <sup>33</sup>
13	4-FC <sub>6</sub> H <sub>4</sub>	3m	10	95	223-225	221-223 <sup>19</sup>
14	4-OHC <sub>6</sub> H <sub>4</sub>	3n	18	90	243-245	245-247 <sup>19</sup>
15	C <sub>4</sub> H <sub>3</sub> S	3p	15	90	158-161	163-165 <sup>10</sup>

<sup>a</sup> Isolated yield

## CONCLUSION

In conclusion, we have explained an efficient method for the synthesis of xanthenediones catalyzed by TBAB as an inexpensive and readily available ionic liquid. The methodology has the advantages of high yield, lack of organic solvent,

and easy work up for separation of products.

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