An efficient synthesis of 1, 8-dioxo-octahydroxanthenes using tetrabutylammonium hydrogen sulfate

Hitendra N. Karade, Manisha Sathe, and M. P. Kaushik*

Process Technology Development Division, Defence R & D Establishment, Jhansi Road, Gwalior-474002 (MP), India
E-mail: mpkaushik@rediffmail.com

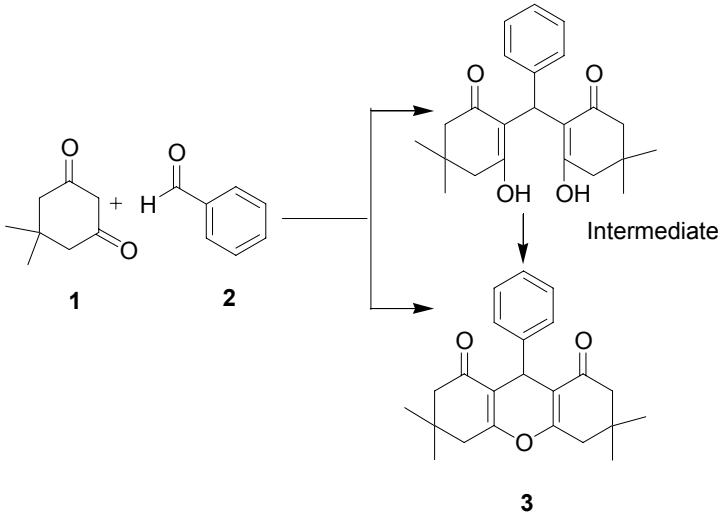
Abstract
A general synthetic route to 1,8-dioxo-octahydroxanthenes has been developed using tetrabutylammonium hydrogen sulfate in semi-aqueous media. The union of two fragments was accomplished by an efficient and convenient protocol enabling the synthesis of 1,8-dioxo-octahydroxanthenes in excellent yields. This method provides several advantages such as simple work-up, environmental friendliness and shorter reaction time along with high yields.

Keywords: Tetrabutylammonium hydrogen sulfate, 1,8-dioxo-octahydroxanthenes, eco-friendly

Introduction

Xanthenes are an important class of organic compounds that find use as dyes, fluorescent material for visualization of biomolecules and in laser technologies due to their useful spectroscopic properties.[1] Xanthenes have also received significant attention from many pharmaceutical and organic chemists essentially because of the broad spectrum of their biological and pharmaceutical properties such as antiviral,[2] antibacterial,[3] anti-inflammatory activities[4] as well as efficiency in photodynamic therapy[5] and antagonist for the paralyzing action of zoxazolamine.[6] There are several reports in the literature for the synthesis of 1,8-dioxo-octahydroxanthene derivatives employing aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione, these include $InCl_3 \cdot 4H_2O$ in ionic liquid,[7] solid-state condensation by grinding at room temperature,[8] NH_2SO_3H in aqueous media,[9] $FeCl_3 \cdot 6H_2O$ in ionic liquid,[10] microwave-induced synthesis in solid or liquid phase,[11] *p*-dodecylbenzenesulfonic acid in water.[12] 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, lack of easy availability/preparation of starting materials 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

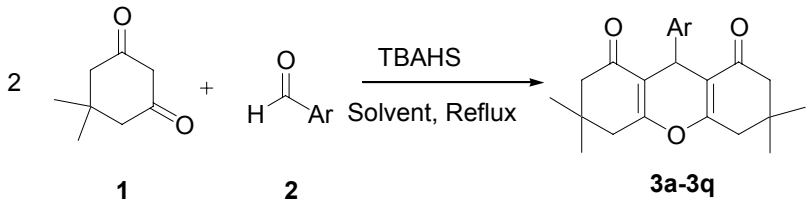
and stops at open chain structure [2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)] [13], instead of forming the cyclized compound. This was overcome by an acid catalyzed cyclization reaction (Scheme 1).



Scheme 1. Synthesis of 1,8-dioxo-octahdroxanthene (**3**) *via* open chain 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one).

Tetrabutylammonium hydrogen sulfate (TBAHS) is an acid catalyst[14] that has been employed for dehydration and the ring closing step of Hantzsch dihydropyridine like transformations.[15] This observations inspired us to use the acidic reagent for the synthesis of 1,8-dioxo-octahydroxanthenes. 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 their use are the focus of much attention.[16]

Herein, we report on the synthesis of 1,8-dioxo-octahydroxanthene using TBAHS in semi-aqueous media where 1,4-dioxane acts as co-solvent (8 mL of H_2O + 2 mL of 1,4-dioxane) (Scheme 2).

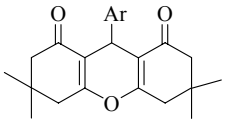


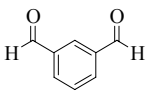
Scheme 2. Synthesis of 1,8-dioxo-octahydroxanthene using TBAHS in semi-aqueous media.

Results and Discussion

Under the given reaction conditions several aromatic aldehydes containing electron donating as well as electron withdrawing groups with diverse substitution pattern were effectively cyclized to give 1,8-dioxo-octahydroxanthenes (Table 1).

Table 1. Synthesis of 9-aryl substituted 1,8-dioxo-octahydroxanthenes using TBAHS

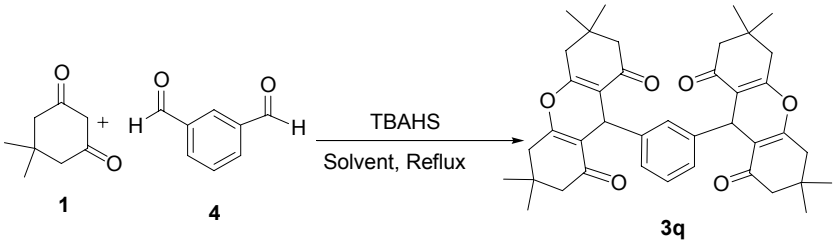


Entry	Ar	Product[a]	Time (hr)	Yield (%)	M.p.°C	
					Found	Reported [8,12]
1.	C_6H_5	**3a**	3.5	88	204-206	204-205
2.	4-(CH_3O)-C_6H_4	**3b**	3.0	93	240-242	241-243
3.	4-(NMe_2)-C_6H_4	**3c**	3.5	90	221-223	220-222
4.	4-(Cl)-C_6H_4	**3d**	3.0	92	229-230	230-231
5.	2-(Cl)-C_6H_4	**3e**	3.5	90	225-227	224-226
6.	3-(Cl)-C_6H_4	**3f**	3.0	94	182-184	183-184
7.	2,4-$(Cl)_2$-C_6H_3	**3g**	3.0	91	251-253	253-254
8.	4-NO_2-C_6H_4	**3h**	3.0	94	221-223	222
9.	3-$NO_2C_6H_4$	**3i**	3.0	94	170-172	171.5-172.5
10.	2-$NO_2C_6H_4$	**3j**	3.5	92	248-249	246-248
11.	4-HOC_6H_4	**3k**	3.0	92	247-248	246-247
12.	4-$CH_3C_6H_4$	**3l**	3.5	91	217-218	217-218
13.	3,4-$OCH_2OC_6H_3$	**3m**	3.0	92	219-220	218.5-220
14.	C_6H_5CH=CH	**3n**	3.0	90	176-78	175-177
15.	3-OEt-4-OH-C_6H_3	**3o**	3.0	92	194-96	-
16.	2-OCH_3-5-Br-C_6H_3	**3p**	3.5	90	204-06	-
17.		**3q**	3.0	90	236-238	-
18.	2-Pyridinyl	**3r**	3.5	88	188-190	

[a] Experimental data are in supplementary material.

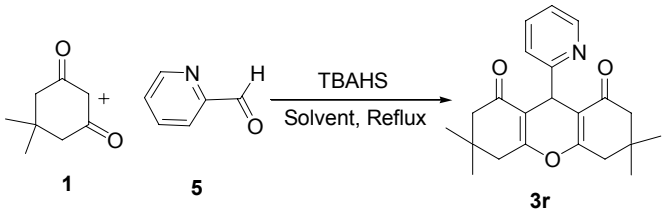
This is a new method for the synthesis of these compounds. By using this method, four new compounds have been synthesized and characterized by all the spectroscopic data. The

advantage of semi-aqueous solvent system lies in the solubility difference of the starting material and the final product. Hence, during the course of the reaction the product precipitates out and the product was isolated simply by filtration. The practical synthetic efficiency of this reaction was highlighted by the reaction of isophthalaldehyde (**4**) with dimedone (**1**) to give a structurally complex xanthenone derivative (**3q**) (Scheme 3).



Scheme 3. Synthesis of bis (1,8-dioxo-octahdroxanthene).

An important feature of this method is that the acid sensitive functionality present in the molecule remains unaffected. This fact was amply demonstrated by the reaction of pyridine-2-carboxaldehyde (**5**) with dimedone (**1**), which gave 9-(pyridin-2-yl)-1,8-dioxo-octahydroxanthene (**3r**) in excellent yield (Scheme 4).



Scheme 4. Synthesis of 9-(pyridin-2-yl)-1,8-dioxo-octahydroxanthene.

Experimental Section

General experimental procedure. The aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**1**) (2 mmol), TBAHS (10 mol %) were mixed in 20 mL of aqueous 1,4-dioxane (20 mL of 1,4-dioxane + 80 mL of water) at room temperature. The reaction mixture was refluxed for the time indicated in Table 1. Completion of the reaction was monitored by TLC (Hexane: EtOAc 8: 2). The reaction mixture was cooled to room temperature and the solid product was filtered off and dried. Purity was checked by TLC and all the compounds described gave satisfactory spectroscopic data.

For the typical synthesis of (**3q**) isopthalaldehyde (**4**) (1 mmol), dimedone (**1**) (4 mmol) and TBAHS (10 mol %) were mixed in the given solvent system and refluxed for 3 hrs. After the

completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature. Solid product precipitated out and was filtered under suction, washed with cold water (20 mL) and dried to give the pure product.

3,3,6,6-Tetramethyl-9-(3-ethoxy-4-hydroxyphenyl)-1,8-dioxo-octahydroxanthene (3o). Mp 194-196ºC; IR (KBr, cm^{-1}) ν_{max} 3431, 2950, 1669, 1515, 1441, 1363, 1278, 1194 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (6H, s, 2 × CH_3), 1.02 (6H, s, 2 × CH_3), 1.28 (3H, t, J = 6.9Hz, -OCH_2CH_3), 2.05-2.09 and 2.23-2.27 (4H, 2 × d, J = 16.00 Hz, 16.00 Hz, 2 × CH_2, H-4, H-5), 2.50-2.53 (4H, d, 12.00 Hz, 2 × CH_2, H-2, H-7), 3.90 (2H, q, J = 6.9 Hz, -OCH_2CH_3), 4.40 (1H, s, H-9), 6.59-6.66 (3H, m, Ar-H), 8.69 (1H, s, -OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.70 (CH_3, -CH_2CH_3), 26.31 (2 × CH_3), 28.69 (2 × CH_3), 30.33 (C-3, C-6), 31.80 (C-9), 38.87 (C-4, C-5), 50.05 (C-2, C-7), 63.84 (CH_2, -CH_2CH_3), 114.00 (Ar-C), 114.68 (Ar-C), 115.01 (2C, C=C), 120.32 (Ar-C), 135.28 (Ar-C), 145.22 (C-OH), 145.87 (C-OEt), 162.55 (2C, C=C), 196.05 (2 × C=O); ESI-MS *m/z*: 433 (M+Na, 5%), 273 (M^+-$C_8H_9O_2$, 100%), 843 (2M+23) .

3,3,6,6-Tetramethyl-9-(2-methoxy-5-bromophenyl)-1,8-dioxo-octahydroxanthene (3p). Mp 204-206ºC; IR (KBr, cm^{-1}) ν_{max} 2947, 2875, 1663, 1483, 1359, 1248, 1198, 883; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (6H, s, 2 × CH_3), 1.02 (6H, s, 2 × CH_3), 1.997-2.037 and 2.268-2.228 (4H, 2 × d, J = 16.00 Hz, 16.00 Hz, 2 × CH_2, H-4, H-5), 2.54 (4H, s, H-2, H-7), 3.67 (s, 3H, -OCH3), 4.49 (1H, s, H-9), 6.83-7.31 (3H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.67 (2 × CH_3), 29.03 (2 × CH_3), 29.84 (2C, C-3, C-6), 31.90 (OCH_3), 38.87 (C-9), 50.03 (2C, C-4, C-5), 55.52 (2C, C-2, C-7), 111.27 (Ar-C), 111.52 (Ar-C), 113.39 (2C, C=C), 130.25 (Ar-C), 132.29 (Ar-C), 134.10 (Ar-C), 156.94 (Ar-C), 163.91 (2C, C=C), 196.24 (2C, C=O); ESI-MS *m/z*: 459(M+H, 68%), 273 (M^+-C_7H_6BrO, 100%).

Bis (1,8-dioxo-octahdroxanthene) (3q). Mp 236-238ºC; IR (KBr, cm^{-1}) ν_{max} 2957, 2879, 1664, 1457, 1368, 1203, 1158, 779; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 1.00 (12H, s, 4 × CH_3), 1.08 (12H, s, 4 × CH_3), 2.10-2.14 and 2.16-2.20 (8H, 2 × d, J = 16.00 Hz, 16.00 Hz, 4 × CH_2), 2.398-2.442 and 2.511-2.555 (8H, 2 × d, J = 17.6 Hz, 17.6 Hz, 4 × CH_2), 4.68 (2H, s,), 7.04-7.26 (4H, m, Ar-H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.68 (4 ×CH_3), 29.35 (4 × CH_3), 31.42 (2 × C-3, 2 × C-6), 32.32 (2 × C-9), 40.92 (4 × C-4, C-5), 50.91 (4 × C-2, C-7), 115.66 (4 × C=C), 126.55 (Ar-C), 127.95 (Ar-C), 128.39 (Ar-C), 143.74 (2 × Ar-C), 162.53 (C=C), 196.60 (4 × C=O); ESI-MS *m/z*: 623(M+H, 100%), 645 (M+Na, 40%), 661 (M+K, 20%), 273 (M^+-$C_{23}H_{25}O_3$, 100%).

3,3,6,6-Tetramethyl-9-(pyridin-2-yl)-1,8-dioxo-octahydroxanthene (3r). Mp 188-190ºC; IR (KBr, cm^{-1}) ν_{max} 3053, 3007, 2957, 1656, 1467, 1364, 1199, 1156, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (6H, s, 2 × CH_3), 1.10 (6H, s, 2 × CH_3), 2.13-2.17 and 2.22-2.26 (4H, 2 × d, J = 16.00 Hz, 16.00 Hz, 2 × CH_2, H-4, H-5), 2.435-2.479 and 2.508-2.552 (4H, 2 × d, J = 17.6 Hz, 17.6 Hz, 2 × CH_2, H-2, H-7), 4.86 (1H, s, H-9), 6.99 (1H, t, J = 5.3 Hz, Ar-H), 7.54 (1H, t, J = 6.1 Hz Ar-H), 7.60 (1H, d, J = 7.6 Hz), 8.38 (1H, d, J = 4.52 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.26 (2C, CH_3), 29.47 (2C, CH_3), 32.42 (2C C-3, C-6), 34.57 (C-9), 41.00 (2C, C-4, C-5), 50.90 (2C, C-2, C-7), 114.47 (2C, C=C), 121.49 (Ar-C), 125.04 (Ar-C), 135.78 (Ar-C), 149.03

(Ar-C), 161.88 (2C, C=C), 163.47 (C=C), 197.05 (2C, C=O); ESI-MS *m/z*: 352 (M+H, 100%), 374 (M+23), 725 (2M+23).

Conclusions

In summary, we have described a general and efficient procedure for the synthesis of structurally complex and diverse 1,8-dioxo-octahydroxanthenes catalyzed by TBAHS in semi-aqueous media. Moreover, the procedure offers several advantages including high yield, operational simplicity, cleaner reaction and minimal environmental impact, which makes it a useful and attractive process for the synthesis of these compounds.

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