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Hypervalent iodine catalysed synthesis of 1, 8-dioxo-octahydroxanthenes in aqueous media

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ABSTRACT

A general synthetic route has been developed for the synthesis of 1, 8-Dioxo-octahydroxanthenes from 5, 5-dimethyl-1, 3-cyclohexadione and aromatic aldehydes by using Diacetoxy iodobenzene (DIB) as a catalyst in aqueous media. The experimental procedure is very simple, environmentally friendliness, which requires shorter reaction time with good to excellent yields.

Keywords: 1,8-Dioxo-octahydroxanthenes, Dimedone, aromatic aldehydes, Diacetoxy iodobenzene.

INTRODUCTION

The multi component coupling reactions are emerging as a useful source for building – up of complex molecules with maximum simplicity and several levels of structural diversity. One example of the multicomponent coupling is the synthesis of xanthenes. Xanthenes have attracted the attention of organic chemists due to their wide range of biological and therapeutic properties like antiviral [1], antibacterial [2] and anti-inflammatory [3]. Many procedures have been reported for the synthesis of xanthenes and benzoxanthenes, including cyclodehydration [4], trapping of benzynes by phenol [5], as well as the cyclocondensation of 2- hydroxyl aromatic aldehydes with 2- tetralone [6].

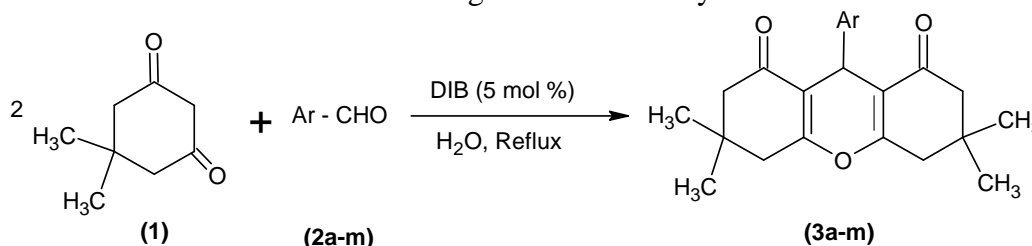
The synthesis of xanthenediones usually condenses appropriate active methylene carbonyl compounds with aldehydes catalysed by sulfuric acid or hydrochloric acid [7]. Recently, many procedures have been reported for the synthesis of 1, 8- Dioxo- octahydroxanthene derivatives by condensation of dimedone and aldehydes using silica sulfuric acid[8], Dowex-50W[9], HClO₄ – SiO₂ and PPA – SiO₂[10] silica chloride and NaH SO₄– SiO₂[11], P- dodecylbenzene sulphonic acid[12], Fe³⁺ - montmorillonite[13] Amberlyst -15[14], Diammonium hydrogen phosphate[15], TMSCl[16], Ionic liquids[17], PEG[18], SelectofurTM[19], Silica sulphate[20],

NBS[21], Ferric Hydrogen Sulphate[22], Cellulose sulphonic acid[23], and hydrochloric acid[24] as catalyst.

Most of these methods are suffered by several drawbacks such as use of expensive and hazardous catalysts, low yields, prolonged reaction time, and tedious work-up processes. Herewith, we report a more realistic Diacetoxy iodobenzene (DIB) catalyzed condensation between active methylene carbonyl compound and aldehyde in aqueous media under reflux conditions which is needed for contemporary chemical synthesis with less waste and eco-friendly procedure (*Scheme 1*).

The development of environmentally friendly procedures in chemical and pharmaceutical industries has become a crucial and demanding research area in modern organic chemistry [25]. Therefore there has been considerable interest in green synthesis involving environmentally benign catalyst and solvent. When water is used as a solvent then the procedure is acceptable in terms of cost and environmental impact. However, despite its large liquid range and extremely high specific heat capacity, it is frequently overlooked as a solvent for organic reactions. Most of catalysts and reagents are deactivated or decomposed in water. Therefore organic reactions in water possess important challenges in the area of reactions to design.

We reports the hypervalent iodine catalyzed synthesis of 1, 8-dioxo-octahydroxanthenes in aqueous media with short reaction time and good to excellent yields.



MATERIALS AND METHODS

All reagents were purchased from s d fine and Qualigens and were used without further purification. All yields were referring to isolated products after purification. The products were characterized by comparison of their spectral (IR, ^1H NMR) and physical data with those reported in the literature. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded in KBr discs on a Jasco FT/IR-4100 typeA, ^1H NMR spectra were recorded on a Varian mercury YH-300 using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by TLC using silica gel-G (Merck).

General procedure for the synthesis of 1,8-Dioxo-octahydroxanthenes. A mixture of aldehyde (2.0 mmole), 5, 5-dimethyl-1, 3 – cyclohexanedione (4.0 mmole) and Diacetoxy iodobenzene (5 mol %) in water (10 ml) was refluxing for time given in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and solid was filtered off and washed with H_2O (20ml) and the crude product recrystallized using ethyl alcohol to afford the pure product.

3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxo-octahydroxanthene(3a).

White solid, M.P.: 196-198 °C, IR(KBr)(ν_{max}): 3350, 2980, 1795, 1725, 1699, 1640, 1520, 1360, 1345, 1260, 1233, 1201, 1195, 850, 843 cm^{-1} . ^1H NMR(CDCl_3): δ_{H} 300 MHz 1.09(s, 6H), 1.23(s, 6H), 2.27-2.49(m, 8H), 5.54(s, 1H), 7.08-7.28 (m, 5H).

3,3,6,6-Tetramethyl-9-(4-Hydroxyphenyl)-1,8-dioxo-octahydroxanthene(3b).

White solid, M.P.: 180-184 °C, IR (KBr)(V_{\max}): 3498, 3078, 2933, 2929, 1719, 1645, 1577, 1384, 1166, 850, 840 cm^{-1} . ^1H NMR (CDCl_3): δ_{H} 300 MHz 0.99(s,6H), 1.09(s,6H), 2.21(s,4H), 2.46(s,4H), 4.66 (s,1H), 6.57(dd,2H), 7.08(dd,2H).

3,3,6,6-Tetramethyl-9-(4-Chlorophenyl)-1,8-dioxo-octahydroxanthene(3c).

White solid, M.P.: 150-152 °C, IR (KBr) (V_{\max}): 3028, 2980, 1680, 1660, 1620, 1490, 1480, 1360, 1200, 1170, 1140, 1090, 1010, 1000, 850, 840 cm^{-1} . ^1H NMR(CDCl_3): δ_{H} 300 MHz 1.12(s,6H),1.27(s,6H),2.33-2.49(m,8H), 5.54(s,1H), 7.01(dd,2H),7.26(dd,2H).

3,3,6,6-Tetramethyl-9-(4-Methoxyphenyl)-1,8-dioxo-octahydroxanthene(3d).

White solid, M.P.: 210-212 °C, IR (KBr) (V_{\max}):3025, 2980, 1685, 1660, 1620, 1513, 1450, 1375, 1360, 1260, 1235,1170, 1142,1032,1003,840 cm^{-1} . ^1H NMR (CDCl_3): δ_{H} 300 MHz 1.09(s, 6H),1.22(s, 6H),2.33-2.63(m, 8H), 3.76(s, 3H),5.48(s, 1H),6.82(d, 2H),7.01(d, 2H).

3,3,6,6-Tetramethyl-9-(3-Nitrophenyl) -1,8-dioxo-octahydroxanthene (3e).

White solid, M.P.:176-178 °C, IR(KBr)(V_{\max}): 2960, 2873, 1680, 1675, 1593, 1529, 1377, 1311, 1251, 1157, 1042, 842, 763, 732, 665 cm^{-1} . ^1H NMR (CDCl_3) : δ_{H} 300 MHz 1.12(s,6H),1.27(s,6H),2.36-2.53(m,8H),5.54 (s,1H),7.42(dt,2H),8.00(d,2H).

3,3,6,6-Tetramethyl-9-(4-Hydroxy-3-Methoxyphenyl)-1,8-dioxo-octahydroxanthene(3f).

White solid,M.P.:198-200 °C, IR (KBr) (V_{\max}): 3694, 3565, 3151, 2972, 1665, 1508, 1355, 1169, 842, 760, 730, 690 cm^{-1} . ^1H NMR(CDCl_3): δ_{H} 300 MHz 1.10(s,6H), 1.23(s,6H), 2.35-2.45(m,8H), 3.75(s,3H), 5.49 (s,1H), 5.60(s,1H), 6.60(dd,2H), 6.78(dd,2H).

3,3,6,6-Tetramethyl-9-(3,4,5-Trimethoxyphenyl)-1,8-dioxo-octahydroxanthene(3g).

White solid, M.P.:192-194 °C, IR(KBr)(V_{\max}): 2990, 1662, 1593, 1454, 1411, 1373, 1238, 1128, 885 cm^{-1} . ^1H NMR(CDCl_3): δ_{H} 300 MHz 1.12(s, 6H), 1.24(s, 6H), 2.35(s, 4H), 2.41(s, 4H), 3.75(s, 6H), 3.81(s, 6H), 5.49(s, 1H), 6.34 (s, 2H).

3,3,6,6-Tetramethyl-9-(4-Hydroxy-3,5-Dimethoxyphenyl)-1,8-dioxo-ctahydroxanthene(3h).

White solid, M.P.:204-206 °C, IR (KBr) (V_{\max}):3694,3565,3151,2972,1665,1508,1355,1169,842, 760,730,690 cm^{-1} . ^1H NMR(CDCl_3): δ_{H} 300 MHz 1.11(s,6H),1.24(s,6H),2.35(s,4H),2.42(s,4H), 3.77 (s,6H),5.45(s,1H),5.49(s,1H),6.34(s,2H).

3,3,6,6-Tetramethyl-9-(4(Dimethylamino)phenyl)-1,8-dioxo-octahydroxanthene(3i).

White solid, M.P.: 182-184 °C, IR (KBr) (V_{\max}): 3087, 3010, 2923, 2901, 1709, 1643, 1573, 1376, 1133, 841, 835 cm^{-1} . ^1H NMR(CDCl_3) : δ_{H} 300 MHz 1.09(s,6H), 2.28-2.38(m,8H), 2.89(s,6H), 5.47(s,1H), 6.67 (dd,2H), 6.92(dd,2H).

3,3,6,6-Tetramethyl-9-(2-chlorophenyl)-1,8-dioxo-octahydroxanthene(3k).

White solid, M.P.: 200-204 °C, IR (KBr) (V_{\max}): 3392, 3064, 2960, 2929, 1719, 1664, 1595, 1380, 1166, 850, 690, 650 cm^{-1} . ^1H NMR (CDCl_3) : δ_{H} 300 MHz 1.05(s,6H), 1.15(s,6H), 2.20-2.51(m,8H), 5.60(s,1H), 7.11-7.39 (m,4H).

RESULTS AND DISCUSSION

The present protocol was examined with substituted and non substituted aldehydes. It was observed that the electronic effect, steric effect and substituent on aromatic ring of aldehyde did not show considerable effect on product in terms of reaction time, yield and reaction conditions.

The reaction proceeded smoothly in water under refluxing condition to offer good yields of products (3a-m).

Table 1: - DIB Catalysed synthesis of 1, 8 – dioxo octahydroxanthenes in aqueous media

Entry	Ar	Product ^(a)	Time Min.	Yield % ^(b)	M.P. ^o C found ^(c)
1.	C ₆ H ₅ -	3a	30	94	196-198
2.	4 -OH C ₆ H ₄ .	3b	60	85	180-184
3.	4 -Cl C ₆ H ₄ .	3c	60	90	150-152
4.	4- MeO C ₆ H ₄ .	3d	60	89	210-212
5.	3 -NO ₂ C ₆ H ₄ .	3e	20	80	176-178
6.	4-(OH), 3-(MeO) C ₆ H ₃ .	3f	30	94	198-200
7.	3,4,5 -(OCH ₃) ₃ C ₆ H ₂ .	3g	25	85	192-194
8.	4-(OH),3,5-(MeO) ₂ C ₆ H ₂ .	3h	35	95	204-206
9.	4 - NMe ₂ C ₆ H ₄ .	3i	20	84	182-184
10.	2 Furyl	3j	30	92	148-150
11.	2 -Cl C ₆ H ₄ .	3k	60	84	200-204
12.	2 -OH C ₆ H ₄ .	3l	60	85	201-204
13.	2 -NO ₂ C ₆ H ₄ .	3m	25	85	256-258

a) All the products were well characterized by ¹H NMR. And IR spectral data.

b) Isolated yields.

c) After recrystallisation.

To optimize the amount of catalyst, the present protocol was examined with 0 mol% to 10 mol% of catalyst taking benzaldehyde and dimedone as model to produce the product 3a. The results obtained are summarized in Table 2. It was found that without catalyst very trace amount of product was formed by refluxing for 6 hours and more the reaction time reduced and yield increased as the amount of catalyst increased up to 5 mol%. No reduction in time and increment in yield were observed for further increase of amount from 5 mol% to 10 mol%.

We also examined the effect of solvent on the model reaction (Table 3).

Table 2. Optimization of the quantity of catalyst (reflux, aqueous media) in the reaction of dimedone and benzaldehyde

Entry	Catalyst Mole %	Time Hr.	Yield. %
1	0	6.00	tr
2	2.5	1:00	94
3	5.0	0:30	94
4	10.0	0:30	95

Table 3. Optimization of reaction condition for the synthesis of (3e)

Entry	Condition	Time min.
1	Reflux/ Ethyl acetate	30
2	Reflux/ THF	30
3	Reflux/Acetonitrile	30
4	Reflux/ Alcohol	20
5	Reflux/ Water	20

CONCLUSION

We have developed a simple rapid and most efficient green protocol for the synthesis of 9-aryl-1, 8-dioxo- octahydroxanthene derivatives using Diacetoxy iodobenzene in aqueous medium.

The short reaction time, simple work- up in isolation of the products, good yields with high purity, and mild reaction conditions are features of the present procedure.

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