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Alum-promoted Synthesis of 1,8-Dioxo-octahydroxanthenes in Water

Balaji R. Madje[a,*], **Milind B. Ubale**[a], **Jagdish V. Bharad**[a] **and Murlidhar S. Shingare**[b]

[a]*Department of Chemistry, Vasantrao Naik Mahavidyalaya, Aurangabad 431 003, M.S., India.*

[b]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, M.S., India.*

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ABSTRACT

A new and efficient method to synthesize a 3,3,6,6,9-aryl-1,8-dioxo-octahydroxanthene derivative using alum as catalyst was performed in aqueous media. This method has several advantages such as environmental friendliness, high yields and simple workup procedure.

KEYWORDS

Alum, aqueous media, 3,3,6,6,9-aryl-1,8-dioxo-octahydroxanthene, condensation reaction.

1. Introduction

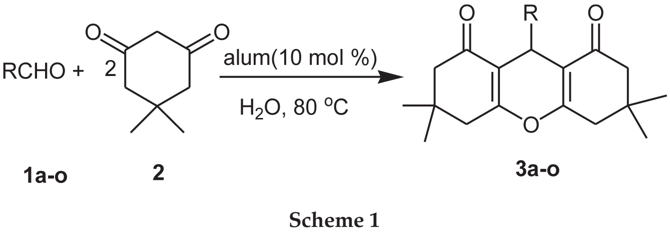
The development of simple, efficient and general synthetic methods for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Recently, a variety of reports regarding synthetic studies on xanthene derivatives has been presented, as these compounds were documented to exhibit a wide range of biological activities.[1,2] In addition, xanthene derivatives have been used as dyes,[3] in laser technologies,[4] and as fluorescent materials for visualization of biomolecules.[5] They are also valuable synthons because of the inherent reactivity of the inbuilt pyran ring.[6] Many syntheses of xanthene derivatives have been published; one of them is the condensation of aldehydes with cyclohexane-1,3-dione or 5,5-dimethylcyclohexane-1,3-dione to give 1,8-dioxo-octahydroxanthene derivatives. This reaction has been conducted in the presence of strong protonic acids,[7] Lewis acids such as $InCl_3.4H_2O$,[8] $FeCl_3.8H_2O$,[9] $NaHSO_4$[10] and heterogeneous catalysts like Dowex-50W,[11] $NaHSO_4.SiO_2$,[12] silica sulphuric acid,[13] polyaniline-*p*-toluenesulphonate,[14] polyphosphoric acid supported on silica (PPA-SiO_2),[15] TiO_2/SO_4^{2-},[16] Amberlyst-15[17] and Wet TCT.[18] Other catalysts, such as trimethylsilyl chloride,[19] *p*-dodecylbenzenesulphonic acid,[20,21] triethylbenzylammonium chloride,[22] NH_2SO_3/sodium dodecyl sulphate[23] and HPWA/MCM-41[24] have also been used for this transformation. It has also been reported that the above condensation process could proceed in ionic liquids[25] and ethylene glycol.[26,27] However, some of these methodologies have not been entirely satisfactory, with disadvantages such as low yields, long reaction times, harsh reaction conditions and the requirement of expensive catalysts and special apparatus. Therefore, to avoid these limitations, the discovery of a new and efficient process for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in aqueous media is of prime interest.

Organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheap and environmentally friendly solvents, but also because it exhibits unique reactivity and selectivity, which is different from those of conventional organic solvents.[28] In this respect, the development of water-tolerant catalysts has rapidly become an area of intense research. These findings prompted us to investigate the synthesis of 1,8-dioxo-octahydroxanthene derivatives in aqueous media catalyzed by alum.

Alum, $KAl(SO_4)_2.12H_2O$, was found to be effective in the synthesis of *cis*-isoquinolic acids,[29a] mono- and di-substituted 2,3-dihydroquinazolin-4(1H)-ones,[29b] dihydropyrimidines *via* the Biginelli reaction,[29c] coumarins,[29d] 1,3,4-oxadiazoles,[29e] dibenzoxanthenes,[29f] 1,5-benzodiazepines,[29g] trisubstituted imidazoles,[29h] etc. However, there are no examples of the use of alum as a catalyst for the synthesis of 1,8-dioxo-octahydroxanthene derivatives.

2. Results and Discussion

In continuation of our previous work on the applications of cheap and ecofriendly materials as catalysts for the development of new synthetic methodologies,[30] in the present paper we report a simple and facile synthesis of 1,8-dioxo-octahydroxanthene derivatives by treatment of aryl aldehydes with 5,5-dimethylcyclohexane-1,3-dione catalyzed by alum in aqueous media (Scheme 1, Table 1). We first examined the condensation process by employing 4-chlorobenzaldehyde (**1h)** and 5,5-dimethylcyclohexane-1,3-dione (**2)** as model substrates. When **1h** (1 mmol) was treated with **2** (2 mmol) in the presence of a catalytic amount of alum (10 mol %), the desired product **3h** was obtained in 96 % yield. Varying the percentage of the catalyst showed that 10 mol % of alum was optimal (Table 2, entry 4); the use of larger amounts of catalyst did not improve yields (Table 2, entries 5, 6), whereas decreasing the amount of catalyst decreased yields (Table 2, entries 1–3). However, the effect of reaction temperature was also investigated on yield and reaction time and the optimum temperature was found to be 80 °C (Table 3, entry 2). To demonstrate the merit of the present work in



Scheme 1

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* To whom correspondence should be addressed. E-mail: balumadje@yahoo.com.

Table 1 Alum-catalyzed synthesis of 1,8-dioxo-octahydroxanthene derivatives [a].

Compound [b]	R	Time/min	Yield/% [c]	M.p./°C	
				Found	Reported
3a	Ph	30	92	200–202	(202–204)[20]
3b	4-Me-C_6H_4	30	95	214–216	(217–218)[20]
3c	4-MeO-C_6H_4	40	92	242–244	(242–244)[20]
3d	3-MeO-C_6H_4	40	92	162–164	(160–162)[20]
3e	4-OH-C_6H_4	30	94	248–250	(246–248)[20]
3f	4-F-C_6H_4	25	94	226–227	(225–227)[22]
3g	2-Cl-C_6H_4	60	90	226–228	(228–230)[20]
3h	4-Cl-C_6H_4	25	96	226–228	(228–230)[20]
3i	3-Cl-C_6H_4	30	93	182–184	(183–184)[20]
3j	2,4-Cl_2-C_6H_3	60	90	252–254	(253–254)[20]
3k	4-Br-C_6H_4	25	94	238–240	(240–242)[19]
3l	3-NO_2-C_6H_4	30	92	166–168	(168–170)[20]
3m	4-NO_2-C_6H_4	25	94	222–224	(226–228)[20]
3n	Thiophene	30	92	164–166	(163-164)[18]
3o	Pyridine	40	92	204–206	(204-205)[18]

[a] Reaction conditions: aldehyde (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (2 mmol) were stirred in the presence of alum (0.1 mmol) in H_2O (10 mL) at 80 °C.

[b] Compounds were characterized by IR, ^{1}H NMR and mass spectrometry and compared with reported methods.

[c] Isolated yield based upon starting aldehyde.

comparison with previously reported results in the synthesis of 1,8-dioxo-octahydroxanthene derivatives, see Table 4. It is thus evident that alum can act as an effective catalyst with respect to reaction times and yields.

With this result, we extended this method to a variety of aldehydes to investigate its scope and generality. The results are summarized in Table 1. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as halide and nitro) or electron-donating groups (such as methyl, methoxy and hydroxyl) were treated with 5,5-dimethylcyclohexane-1,3-dione (**2**) to give the corresponding 1,8-dioxo-octahydroxanthene derivatives in good to excellent yields. Generally, *ortho*-substituted benzaldehydes required longer reaction times, owing to steric hindrance (Table 1, entries **3g** and **3j**). Further, the present protocol was successfully applied to heteroaromatic aldehydes such as thiophene-2-carbaldehyde (Table 1, entry **3n**) and pyridine-2-carbaldehyde (Table 1, entry **3o**); the corresponding 1,8-dioxo-octahydroxanthenes were obtained in high yields.

A role of alum has been proposed to activate the aldehyde by binding of alum with the oxygen atom[29a] which ultimately enhances the electrophilicity of the aldehyde and leads to a decrease in reaction time. The proposed mechanism is shown in Scheme 2.

Table 2 Optimization of molar ratio of catalyst for the model reaction.

Entry	Mole %	Yield/% [a]
1	0	trace
2	2	30
3	5	50
4	10	96
5	15	95
6	20	94

[a] Yields refer to pure isolated products.

Table 3 Effect of temperature on yield and reaction time for the model reaction.

Entry	Temperature/°C	Reaction time/min	Yield/%[a]
1	25	120	trace
2	50	120	42
3	60	120	75
4	**80**	**25**	**96**
5	80	90	96
6	90	25	95
7	100	25	95

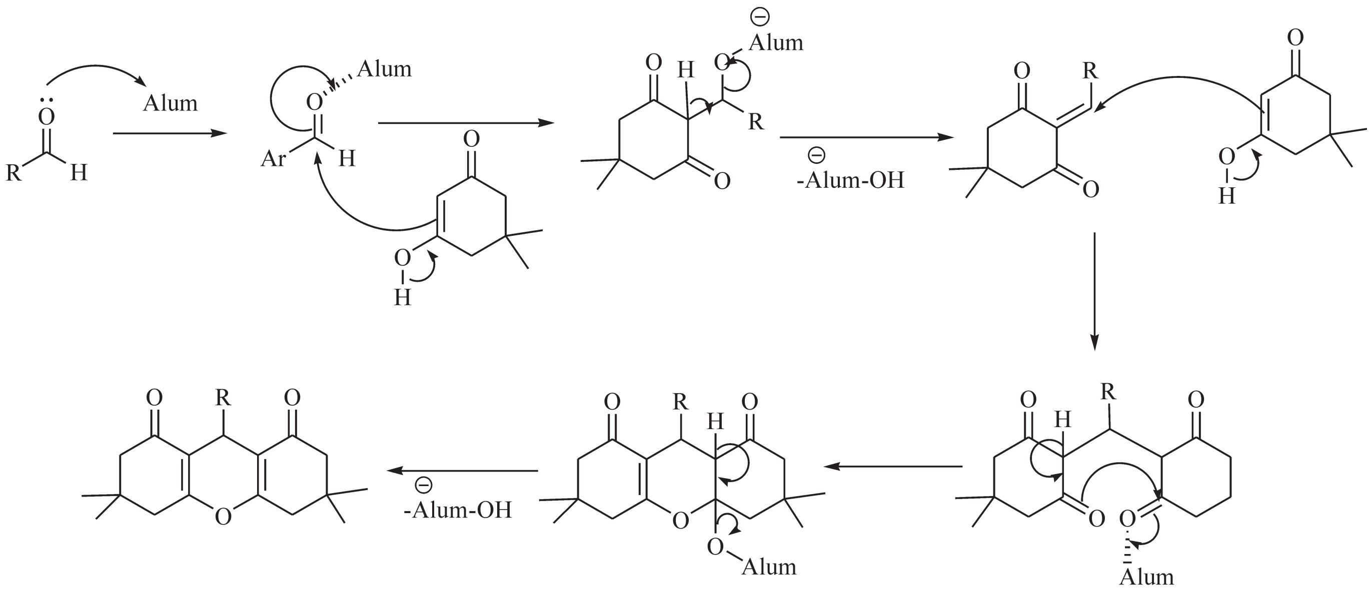
[a] Yields refer to pure isolated products.

3. Experimental

All the reagents and aromatic aldehydes were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on KBr matrices with a Perkin-Elmer 1430 spectrophotometer (Manasquan, NJ, USA). ^{1}H NMR spectra were recorded on a Varian Model Mercury Plus 200 MHz NMR spectrometer (Lake Forest, CA, USA). Mass spectra [ES-MS] were

Table 4 Comparison of the results of alum with those of other catalysts reported in the literature in the synthesis of 1,8-dioxo-octahydroxanthene derivatives.

Entry	Catalyst	Reaction conditions (catalyst)	Time	Yield/%
1	Alum	H_2O, 80 °C (10 mol %)	25–60 min	90–96
2	Wet TCT	H_2O, 120 °C (0.1 mmol)	40–75 min	87–95 [18]
3	$InCl_3.4H_2O$	IL, 80 °C (0.1 mmol)	4–10 h	76–95 [8]
4	TiO_2/SO_4^{2-}	Solvent free, r.t. (100 mg)	30 min	87–92 [16]
5	Dowex-50W	Solvent free, 80 °C (0.1 g)	2–5 h	78–91 [11]
6	TMSCl	CH_3CN, reflux (2 mmol)	8–10 h	72–84 [19]
7	Amberlyst-15	CH_3CN, reflux (0.2 g)	5 h	90–96 [17]



Scheme 2
Proposed mechanism for the synthesis of 1,8-dioxooctahydroxanthenes.

recorded on a Water-Micro Mass Quattro-II spectrometer (Welltech Enterprises, Inc., Capitol Heights, MD, USA).

3.1. General Procedure for the Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives (3a–o)

In a 50 mL round-bottom flask, aldehyde (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (2 mmol) were stirred in the presence of alum (0.1 mmol) in H_2O (10 mL) for 5 min at room temperature; the temperature was then raised to 80 °C and maintained for an appropriate time (monitored by TLC). After completion of the reaction, the mixture was diluted with H_2O (2 × 10 mL), stirred for 5 min, and the resulting solid product was collected by filtration. The crude product was then purified by recrystallization from ethanol. The products were characterized by IR, ^{1}H NMR and mass spectral data and by comparison with the melting points of reported compounds.

3.2. Spectral Data of Representative Compounds

3.2.1. *3,3,6,6-Tetramethyl-9-(4-methylphenyl)-1,8-dioxo-octahydro-xanthene* (**3b**)

IR (KBr, ν_{max}): 2980, 1680, 1665, 1630, 1510, 1470, 1360, 1200, 1170, 1140, 790, 770 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 0.98 (6H, s, 2 × CH$_3$), 1.10 (6H, s, 2 × CH$_3$), 2.07–2.20 (8H, m, 4 × CH$_2$), 2.42 (3H, s, CH$_3$–Ar), 4.69 (1H, s, CH), 6.95 (2H, d, 2 × ArH), 7.28 ppm (2H, d, 2 × ArH). LC-MS: 387 (M+23).

3.2.2. *3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,8-dioxo-octahydro-xanthene* (**3h**)

IR (KBr, ν_{max}): 2980, 1680, 1660, 1620, 1490, 1480, 1360, 1200, 1170, 1140, 1090, 1010, 1000, 850, 840 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 0.98 (6H, s, 2 × CH$_3$), 1.10 (6H, s, 2 × CH$_3$), 2.03–2.14 (8H, m, 4 × CH$_2$), 4.64 (1H, s, CH), 7.12 (2H, d, 2 × ArH), 7.26 ppm (2H, d, 2 × ArH). LC-MS: 406 (M+23).

4. Conclusion

In conclusion, we have developed a general and efficient protocol for the synthesis of 1,8-dioxo-octahydroxanthene derivatives by condensation of aldehydes with 5,5-dimethylcyclohexane-1,3-dione by using commercially available and inexpensive alum as catalyst. High yields of the products, short reaction times, mild reaction conditions, a simple experimental procedure and product isolation make this protocol complementary to the existing literature methods.

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