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2,4,6-Trichloro-1,3,5-Triazine-Promoted Synthesis of 1,8-Dioxo-Octahydroxanthenes under Solvent-Free Conditions

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A practical protocol has been developed for the synthesis of 1,8-dioxo-octahydroxanthenes from aromatic aldehydes and 5,5-dimethylcyclohexane-1,3-dione under solvent-free conditions in the presence of wet 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride). The desired products were obtained in high yields with a simple and environmentally benign procedure.

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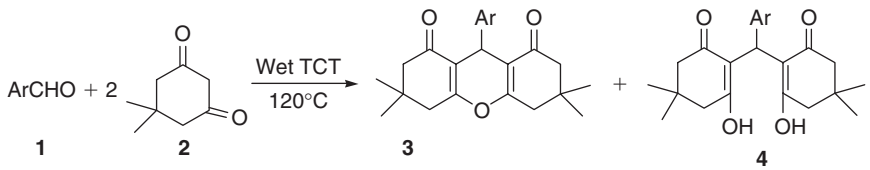
Recently, a variety of reports regarding synthesis studies of the xanthene derivatives have been presented, as these compounds were documented to exhibit a wide range of biological activities.[1,2] In addition, xanthene derivatives have been used as dyes,[3] in laser technologies,[4] and as fluorescent 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 was conducted in the presence of strong protonic acids,[7] Lewis acids such as $InCl_3 \cdot 4H_2O$,[8] $FeCl_3 \cdot 8H_2O$,[9] $NaHSO_4$,[10] and heterogeneous catalysts like Dowex-50W,[11] $NaHSO_4 \cdot SiO_2$,[12] silica sulfuric acid,[13] polyaniline-*p*-toluenesulfonate,[14] polyphosphoric acid supported on silica (PPA-SiO_2),[15] TiO_2/SO_4^{2-},[16] and Amberlyst-15.[17] Other catalysts, such as trimethylsilyl chloride,[18] *p*-dodecylbenzenesulfonic acid,[19,20] triethylbenzylammonium chloride,[21] and NH_2SO_3/sodium dodecyl sulfate,[22] have also been used for this transformation. It has also been reported that the above condensation process could proceed in ionic liquid[23] or ethylene glycol.[24,25] 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, excess catalysts, and special apparatus. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, and simple workup for the synthesis of xanthene derivatives under neutral, mild, and practical conditions is of prime interest.

2,4,6-Trichloro-1,3,5-triazine (TCT, cyanuric chloride) is a stable, non-volatile, inexpensive, commercially available, and easy-to-handle reagent. Over the past few years, there has been considerable growth in interest in using TCT or its derivatives in organic synthesis.[26] The use of this reagent has been reported for the tetrahydropyranylation of phenols and alcohols,[27] direct conversion of carboxylic acids into amides,[28] chemoselective transthioacetalization of aldehyde acetals and oxathioacetals,[29] conversion of nitronate into nitrile oxide,[30] conversion of alcohols, thiols, and trimethylsilyl ethers into alkyl nitrites,[31] chemoselective deprotection and ring-enlargement of dithioacetals and oxathioacetals,[32] and the synthesis of homoallylic alcohols and amines,[33] 4,6-diarylpyrimidin-2(1*H*)-ones,[34] thiiranes,[35] dihydropyridine glycoconjugates,[36] bis(indolyl)methanes,[37] ketoximes,[38] isonitrile,[39] and the Beckmann rearrangement.[40] These observations prompted us to explore the catalytic activity of TCT for the synthesis of 1,8-dioxo-octahydroxanthene derivatives. In continuation of our previous work on the applications of cheap and ecofriendly materials as catalysts for the development of new synthetic methodologies,[41] 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 under solvent-free conditions in the presence of wet TCT (Scheme 1).



Scheme 1.

 10.1071/CH07274 0004-9425/08/020077

Table 1. TCT-mediated synthesis of 1,8-dioxo-octahydroxanthene derivatives (3) at 120°C

Entry	Aldehyde **1**	Time [min]	Yield [%][A]	mp [°C] (lit.)
a	PhCHO	50	92	202–203 (202–204)[19]
b	4-MeC_6H_4CHO	50	94	215–216 (217–218)[19]
c	3,4,5-$(OMe)_3C_6H_2CHO$	50	93	210–212
d	4-$MeOC_6H_4CHO$	55	92	242–243 (242–244)[19]
e	3-$MeOC_6H_4CHO$	55	92	161–162 (160–162)[18]
f	3,4-$(MeO)_2C_6H_3CHO$	55	95	185–186 (184–185.5)[42]
g	3-MeO-4-OHC_6H_3CHO	50	94	225–227 (226–227)[19]
h	4-OHC_6H_4CHO	50	92	247–248 (246–248)[19]
i	3,4-$(OCH_2O)C_6H_3CHO$	50	91	224–225 (224–226)[19]
j	4-$Me_2CHC_6H_4CHO$	50	90	170–172 (172–173)[42]
k	4-FC_6H_4CHO	45	93	226–227 (225–227)[21]
l	2-ClC_6H_4CHO	70	88	226–227 (228–230)[19]
m	4-ClC_6H_4CHO	40	95	226–228 (228–230)[19]
n	3-ClC_6H_4CHO	45	93	183–185 (183–184)[19]
o	2,4-$Cl_2C_6H_3CHO$	70	87	253–254 (253–254)[19]
p	4-BrC_6H_4CHO	45	94	238–239 (240–242)[18]
q	3-$NO_2C_6H_4CHO$	45	92	165–166 (168–170)[19]
r	4-$NO_2C_6H_4CHO$	45	94	222–224 (226–228)[19]
s	Thiophene-2-carbaldehyde	50	91	163–164
t	Pyridine-2-carbaldehyde	60	90	204–205

[A] Isolated yield.

We first examined the condensation process by employing 4-chlorobenzaldehyde **1m** and 5,5-dimethylcyclohexane-1,3-dione **2** as model substrates. When **1m** (1 mmol) was treated with **2** (2 mmol) in the presence of a catalytic amount of wet TCT (10 mol-%), the desired product **3m** was obtained in 95% yield. However, only the non-cyclodehydrated intermediate 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **4m** was obtained in the absence of catalyst even after longer reaction times and high temperatures. Varying the percentage of the catalyst showed that 10 mol-% of TCT was optimum; the use of larger amounts of catalyst did not improve yields, whereas decreasing the amount of catalyst decreased yields. However, the effect of reaction temperature on the output was also investigated and the optimum temperature was found to be 120°C. It is noteworthy that the reaction did not go to completion in completely dry media; it is thus necessary to add one or two drops water for the reaction to go to completion. TCT reacted with water to release HCl and cyanuric acid (removable by washing with water). The in situ-generated HCl acts as a protic acid and activates the carbonyl oxygen and promotes the condensation to give the desired products.

With this exciting 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, nitro) or electron-donating groups (such as methyl, methoxy, 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 **1l** and **1o**). Further, the present protocol was successfully applied to heteroaromatic aldehydes such as thiophene-2-carbaldehyde (entry **1s**) and pyridine-2-carbaldehyde (entry **1t**); the corresponding 1,8-dioxo-octahydroxanthenes were obtained in high yields.

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 2,4,6-trichloro-1,3,5-triazine as catalyst. High yields of the products, short reaction times, mild reaction conditions, absence of solvent, and simple experimental procedure and product isolation make this protocol complementary to the existing methods.

Experimental

Melting points were recorded on an X-4 apparatus (Beijing Tech Instrument Co., Ltd) and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8900 spectrophotometer with KBr optics. ^{1}H NMR spectra were recorded with a Bruker AV300 spectrometer using TMS as an internal standard. Elemental analyses were carried out on a Vario EL III CHNOS Elemental Analyzer.

*General Procedure for the Synthesis of 1,8-Dioxo-Octahydroxanthene Derivatives **3***

The aldehyde (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (2 mmol), TCT (0.1 mmol), and H_2O (two drops) were mixed and stirred for 5 min at room temperature; the temperature was then raised to 120°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 purified by recrystallization from ethanol or by silica gel column chromatography (3:2 petroleum spirits/ethyl acetate). The products were characterized by IR and ^{1}H NMR data and by comparison with melting points of reported compounds.

*3,3,6,6-Tetramethyl-9-(3,4,5-trimethoxyphenyl)-1,8-Dioxo-Octahydroxanthene **3c***

White solid. (Found: C 70.7, H 7.5. $C_{26}H_{32}O_6$ requires C 70.8, H 7.3%) δ_H ($CDCl_3$, 300 MHz) 1.03 (s, 6H), 1.11 (s, 6H), 2.23

(s, 4H), 2.47 (s, 4H), 3.77 (s, 3H), 3.80 (s, 6H), 4.71 (s, 1H), 6.51 (s, 2H). ν_{max} (KBr)/cm^{-1} 2955, 2931, 2875, 2838, 2817, 1666, 1652, 1190.

3,3,6,6-Tetramethyl-9-thiophen-2-yl-1,8-Dioxo-Octahydroxanthene ***3s***

White solid. (Found: C 70.5, H 7.0. $C_{21}H_{24}O_3S$ requires C 70.8, H 6.8%) δ_H ($CDCl_3$, 300 MHz) 1.06 (s, 6H), 1.11 (s, 6H), 2.26 (s, 4H), 2.46 (s, 4H), 5.15 (s, 1H), 6.81–7.03 (m, 3H). ν_{max} (KBr)/cm^{-1} 2957, 2895, 2872, 1659, 1622, 1371, 1360, 1200.

3,3,6,6-Tetramethyl-9-pyridin-2-yl-1,8-Dioxo-Octahydroxanthene ***3t***

White solid. (Found: C 75.0, H 7.0, N 4.2. $C_{22}H_{25}NO_3$ requires C 75.2, H 7.2, N 4.0%) δ_H ($CDCl_3$, 300 MHz) 0.99 (s, 6H), 1.10 (s, 6H), 2.15 (d, *J* 16.2, 2H), 2.23 (d, *J* 16.2, 2H), 2.44 (d, *J* 17.4, 2H), 2.52 (d, *J* 17.4, 2H), 4.85 (s, 1H), 6.94–7.02 (m, 1H), 7.55–8.38 (m, 3H). ν_{max} (KBr)/cm^{-1} 2958, 2930, 2874, 1681, 1657, 1623, 1199.

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