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Facile Synthesis of Octahydroxanthenes by One-Pot Reaction under Solvent-Free Condition

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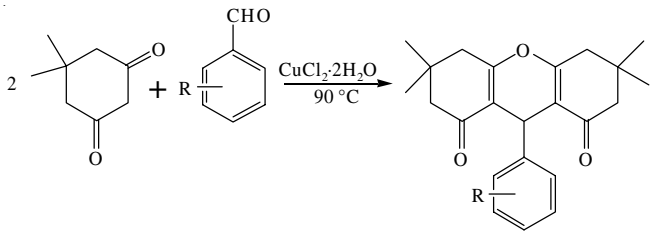
Synthesis of 1,8-dioxo-octahydroxanthenes by cyclocondensation of 5,5-dimethyl-1,3-cyclohexanedione and aromatic aldehydes using catalytic amount of $CuCl_2·2H_2O$ under solvent free condition is reported. Structures of ten compounds are characterized by spectral and analytical data.

Keywords: Tetramethyl-1,8-dioxo-octahydroxanthenes, $CuCl_2·2H_2O$, 5,5-Dimethyl-1,3-cyclohexendione, Solvent-free.

INTRODUCTION

1,8-Dioxo-octahydroxanthenes are well known heterocyclic compounds possessing xanthene units in their structural frameworks. Xanthene derivatives constitute an important class of organic compounds containing naturally occurring and synthetic heterocycles and occupy a prominent position in medicinal chemistry [1]. Xanthene-based compounds have also been investigated for agricultural bactericide activity [2], anti-inflammatory effect [3] and antiviral activity [4]. Xanthenediones constitute a structural unit in a number of natural products [5] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring [6]. Thus, the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal chemistry. Many methods are reported for the synthesis of xanthenes. Among these methods, the condensation of aldehydes with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione to the corresponding xanthenes were found to be conducted successfully 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], *p*-dodecylbenzenesulphonic acid [11], acidic ionic liquid [12], Fe^{3+} montmorilonite [13]. However, most of these methods often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product separation.

In recent years, copper compounds have been used as catalyst in organic synthesis because these compounds are easy to handle, low cost and good stability. Among these, $CuCl_2·2H_2O$ has emerged as medium and as well as catalyst in various organic transformations like carbonylation of alkylamines and heterocyclization to pyrrolidinone, pyridinones, pyrroles and dihydrofuran [14]. In continuation of our work on the application of cupric chloride in the synthesis of organic compounds [15], here we report the synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by $CuCl_2·2H_2O$ under solvent free condition (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Reagents were used without further purification. Commercial solvents were used after distillation. Melting points were determined on a "Veego MP-I" capillary melting point apparatus and are uncorrected. The IR spectra were recorded on and Shimadzu IR 408 spectrometers. Infrared spectra were recorded as thin films on KBr plates with ν_{max} in cm^{-1}. Column chromatography was performed on Merck Silica Gel 60 (230-400 mesh) using analytical reagent grade hexane and ethyl acetate as eluents.

Synthesis of octahydroxanthene derivatives: Aromatic aldehyde (**2**) (0.5 mol), 1,3-cyclohaxenedione (**1**) (1 mol) and $CuCl_2·2H_2O$ (0.4 mmol) were heated at 90 °C with stirring for 30-45 min. Then water was added and the product was

extracted with chloroform. After the organic layer was dried over sodium sulphate and evaporated, the residue was recrystallized by ethanol and chloroform to products **3**. In cases where further purification was required, the crude products were subjected to column chromatography on SiO_2, using increasing amounts of ethyl acetate in hexanes as eluent.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3a): White solid; IR (KBr, ν_{max}, cm^{-1}): 3030, 2933, 1661, 1586; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 0.98 (s, 6H) 1.65 (s, 6H), 2.24 (dd, 4H), 2.44 (dd, 4H), 4.89 (s, 1H), 7.22-7.34 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$ δ ppm) 20.2, 27.1, 31.5, 36.9, 116.8, 126.4, 128.0, 128.3, 144.3, 163.9, 196.5, Anal. calcd. for $C_{23}H_{26}O_3$: C,78.3, H,7.47. Found: C, 78.32; H, 7.3.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-*p*-tolyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3b): White solid; IR (KBr, ν_{max}, cm^{-1}): 3028, 2931, 1665, 1560; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.62 (s, 6H), 1.92 (s, 6H), 2.26 (dd, 4H), 2.34 (s, 3H), 2.47 (dd, 4H), 4.77 (s, 1H), 7.0-7.19 (aro., 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 20.2, 21.0, 27.1, 31.1, 36.9, 117.0, 128.2,, 128.8, 135.9, 141.48, 163.7, 196.6. Anal. calcd. for $C_{24}H_{28}O_3$: C, 79.09; H7.74. Found: C, 79.05; H, 7.81.

3,4,6,7-Tetrahydro-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3c): White solid; IR (KBr, ν_{max}, cm^{-1}): 3025, 2987, 1684, 1661; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.01 (s, 6H) 1.92 (s, 6H), 3.7 (s,3H), 4.7 (s, 1H), 6.74-7.22(aro.,4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 20.9, 27.1, 30.7, 32.0, 31.1, 36.9, 117.0, 128.2, 128.8, 135.9, 141.48, 163.7, 196.6. Anal. calcd. for $C_{24}H_{28}O_4$: C, 75.76; H,7.41. Found: C, 75.62; H, 7.45.

9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3d): White solid; IR (KBr, ν_{max}, cm^{-1}): 3028, 2987, 1680, 1660, 1620; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 0.98 (s, 6H) 1.23 (s, 6H), 2.45 (dd, 4H), 2.44 (dd, 4H), 7.22-7.34 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 20.9, 27.1, 30.7, 31.1, 36.9, 117.0, 128.2, 128.8, 135.9, 141.48, 163.7, 196.6. Anal. calcd. for $C_{23}H_{25}O_3Cl$: C, 71.77; H,6.55. Found: C, 71.78; H, 6.45.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3e): White solid; IR (KBr, ν_{max}, cm^{-1}): 3024, 2977, 1689, 1666, 1632; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.11 (s, 6H), 2.18 (dd, 4H), 2.49 (s, 4H), 4.82 (s, 1H), 7.47(d, 2H), 7.47 (d, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 21.9, 26.1, 31.7, 32.2, 33.9, 119.1, 127.2, 128.9, 136.9, 140.28, 161.7, 195.2. Anal. calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H,6.37. Found: C, 69.78; H, 6.45.

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3f): White solid; IR (KBr, ν_{max}, cm^{-1}): 3030, 2965, 1677, 1669, 1643; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.09 (s, 12H), 2.21 (q, 4H), 2.45 (s, 4H), 4.67 (s, 1H), 6.61 (d, 2H), 7.11 (d, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 26.1, 31.7, 32.2, 33.9, 44.6, 51.6, 119.1, 127.2, 128.9, 136.9, 140.28, 161.7. Anal. calcd. for $C_{23}H_{26}O_4$: C, 69.86; H,6.37. Found: C, 75.38; H, 7.15.

9-(2-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3g): White solid; IR (KBr, ν_{max}, cm^{-1}): 3027, 2982, 1684, 1670, 1621; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.03 (s, 6H), 1.11 (s, 6H) 2.34 (q, 4H), 2.45 (s, 4H), 4.67 (s, 1H), 7.11-7.27 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 27.1, 30.5, 33.9, 43.6, 51.6, 116.3, 127.2, 128.5, 130.7, 135.1, 143.2, 157.7, 165.3. Anal. calcd. for $C_{23}H_{25}O_3Cl$: C, 71.77; H, 6.45. Found: C, 71.83; H, 7.23.

9-(2-Bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3h): White solid; IR (KBr, ν_{max}, cm^{-1}): 3027, 2982, 1684, 1670, 1621; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.03 (s, 6H), 1.11 (s, 6H) 2.06 (q, 4H), 2.45 (s, 4H), 4.56 (s, 1H), 7.21-7.34 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 27.3, 30.6, 31.3, 44.6, 51.6, 114.3, 126.2, 127.4, 128.5, 131.8, 134.5, 144.7, 159.7, 166.7. Anal. calcd. for $C_{23}H_{25}O_3Br$: C, 71.77; H, 6.45. Found: C, 71.83; H, 7.23.

9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3i): White solid; IR (KBr, ν_{max}, cm^{-1}): 3031, 2984, 1683, 1672, 1625; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.02 (s, 6H), 1.13 (s, 6H) 2.26 (q, 4H), 2.46 (s, 4H), 7.20 (s, 1H), 7.34 (d, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 27.4, 30.3, 30.7, 44.6, 51.2, 114.3, 126.2, 128.4, 128.7, 130.8, 134.5, 146.7, 157.7, 167.3. Anal. calcd. for $C_{23}H_{24}O_3Cl_2$: C, 65.88; H, 5.77. Found: C, 65.83; H, 5.63.

9-(3-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8-(2*H*)-dione (3j): White solid; IR (KBr, ν_{max}, cm^{-1}): 3027, 2982, 1684, 1670, 1621; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 0.96 (s, 6H), 1.01 (s, 6H) 1.86 (q, 4H), 2.85 (s, 4H), 3.96 (s, 1H), 7.14-7.33 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 27.7, 30.4, 32.5, 44.6, 51.3, 113.4, 119.2, 125.4, 128.6, 133.7, 143.4, 148.7, 155.7, 169.3. Anal. calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37. Found: C, 69.83; H, 6.23.

RESULTS AND DISCUSSION

Initially, benzaldehyde (**1a**) was selected as the representative arylaldehyde to investigate the optimized reaction conditions and the results are listed in Table-1. Obviously, catalyst had important effects on the reaction. The reaction in presence of catalytic amount of $CuCl_2$ gives low yield product; the addition of a catalytic amount of $BiCl_3$ resulted in the product with high yield but with longer time (Table-1). However, the addition of a catalytic amount of $CuCl_2{\cdot}2H_2O$ resulted in the product **3a-e** with maximum yield of 80-95 % at 80-90 °C within 30-50 min. Thus we optimized experimental conditions at 90 °C using $CuCl_2{\cdot}2H_2O$ as catalyst under solvent-free condition and extended to various aldehydes (**2**). Under these optimized reaction conditions, the scope and efficiency of this reaction was explored for the synthesis of a wide variety of octahydroxanthenes (**10**) and results are summarized in Table-2. As can be seen from Table-2, aromatic aldehydes containing electron donating groups (such as methyl, methoxy) were found reacting smoothly and give higher yield.

TABLE-1
CONDENSATION REACTION OF BENZALDEHYDE AND DIMETHYL-1,3-CYCLOHEXANEDIONE UNDER DIFFERENT REACTION CONDITIONS

Entry	Catalyst	Time (min)	Yield (%)
1	$CuCl_2$	30-40	80-95
2	$BiCl_3$	120-240	70-80
3	$SnCl_2$	1-2	60-70

TABLE-2
SYNTHESIS OF 9-ARYL SUBSTITUTED 1,8-DIOXO-OCTAHYDROXANTHENES USING $CuCl_2·2H_2O$

Entry	R	Product	Time (min)	Yield (%)	m.p. (°C)
1	C_6H_5	**3a**	35	80	203-204
2	4-MeC_6H_4	**3b**	30	90	217-219
3	4-$MeOC_6H_4$	**3c**	40	84	240-241
4	4-ClC_6H_4	**3d**	38	70	228-230
5	4-$NO_2C_6H_4$	**3e**	45	69	223-224
6	4-OHC_6H_4	**3f**	35	75	243-244
7	2-ClC_6H_4	**3g**	40	72	202-203
8	2-BrC_6H_4	**3h**	43	73	207-208
9	2,4-$Cl_2C_6H_3$	**3i**	47	68	203-204
10	3-$NO_2C_6H_4$	**3j**	45	69	201-202

It was found that the reaction gave the desired octahydroxanthene product **3a** in high yield (90 %). The structure of this compound was characterized by elemental analysis and spectroscopic methods. Initially, we examined the presence of functional groups from IR spectra. The stretching frequencies at 3030, 2933, 1661, 1586, cm^{-1} correspond to the presence of C=O, C=C and aromatic C–H bonds in the compound. Then, the number of protons and carbons present in the compound were found matching with the ^1H NMR and ^{13}C NMR spectra. The ^1H NMR and ^{13}C NMR are as follows. ^1H NMR (300 MHz, $CDCl_3$, δ ppm) 0.98 (s, 6H), 1.65 (s, 6H), 2.24 (d, 4H), 2.44 (d, 4H) 4.89 (s, 1H), 7.22-7.34 (aro, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 20.2, 27.1, 31.5, 36.9, 116.8, 126.4, 128.0, 128,3, 144.3, 163.9, 196.5.

Conclusion

In summary, $CuCl_2$ is proved to be an efficient catalyst for the synthesis of 1,8-dioxooctahydroxanthene derivatives by condensation of aldehydes with 1,3-cyclohexanedione. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, solvent-free conditions and use of low cost and commercially available copper(II) chloride as catalyst.

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