

An Efficient Catalytic Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives with Anti-oxidant Scanning

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ECO-FRIENDLY one pot synthesis is developed for 1,8-dioxo-octahydroxanthenes from aldehydes and dimedone using non-toxic, easily prepared and recyclable catalyst ($\text{Sm}_2\text{O}_3/\text{SiO}_2$) as a silica supported rare earth element under solvent-free conditions. Four of the synthesized compounds showed promising ABTS (**3i**, 68.7; **3b**, 59.2; **3h**, 50.2 inhibition%) compared with ascorbic acid.

Keywords: Xanthene, Aldehydes, Sm_2O_3 , Silica, Anti-oxidant.

Introduction

Heterocyclic rings are often the structural core responsible of the biological activities in natural products and synthetic compounds. Xanthene derivatives have broad spectrum of pharmaceutical and biological activities such as anti-inflammatory, antiviral, antibacterial as well as antagonist and phototoxicity activity [1-3]. Uses in industry as dyes [4] and as fluorescent material for conception of biomolecules [5] in laser technologies, because of their useful spectroscopic properties [6] are known. Xanthenedione derivatives are found as a core unit in many natural compounds [7] and they are valuable symptoms due to the presence of inbuilt pyran ring [8].

Literature has several preparation methods for xanthenes. This is due to the wide range of pharmaceutical activity, industrial and synthetic applications. The catalytic condensation reaction of dimedone and variable aldehydes considered as one of the most important methods for synthesis of 1, 8-dioxo-octahydroxanthenes. To accomplish this transformation a variety of reagents such as PPA- SiO_2 [9], $\text{SbCl}_3\text{-SiO}_2$ [10], silica sulfate [11], $\text{NaHSO}_4\text{-SiO}_2$ [12] and $\text{ZrOCl}_2\cdot 8\text{H}_2\text{O}$ [13] have been used. Most of the available methods have more than one disadvantages, like the use of corrosive, expensive and unavailable reagents also the drastic conditions like refluxing, strong acidic medium and fatiguing reaction work-up to get products. To overcome these disadvantages, we suggested the following catalytic reaction

using available, efficient and recyclable catalyst ($\text{Sm}_2\text{O}_3/\text{SiO}_2$) which prepared by our group [14] in the synthesis of 1,8-dioxo-octahydroxanthenes derivatives under solvent-free conditions.

Experimental

The IR spectra were recorded with Mattson FTIR spectrometer 5000. Absorption maxima were measured in cm^{-1} . $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were obtained in CDCl_3 on Bruker with a 400 MHz Instruments using TMS as an internal standard. Chemical shift is reported in ppm. Mass spectra were recorded on a Agilent LC-MS spectrometer (pump quaternary 1200 Series, quadruple MSD 6110). LC column into multimode (ESI+APCI) ion source of MSD. Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm) and all chemical were purchased from Sigma-Aldrich.

(i) Catalyst preparation

The catalyst was prepared by mixing SiO_2 (3 g) and Sm_2O_3 (0.5 g) in 50 mL chloroform (CHCl_3). After vigorous stirring for 2h, at room temperature, the suspension was left until the solvent was evaporated whereas a white solid was obtained. ($\text{Sm}_2\text{O}_3/\text{SiO}_2$) catalyst has been identified using scanning electron microscopic investigation (SEM), X-ray diffraction analysis (XRD) and Fourier transforms infrared (FTIR) spectra [14a]. The recovery and recycling of ($\text{Sm}_2\text{O}_3/\text{SiO}_2$) were investigated.

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General synthetic procedure

The mixture of aldehydes (1 mmole), dimedone (2 mmole) and $\text{Sm}_2\text{O}_3/\text{SiO}_2$ (20 mol %) was stirred at 60-70°C. The reaction mixture was followed using thin layer chromatography (TLC) till the substrates disappeared. Chloroform (20 mL) was used to extract the organic product, and then the pure products were obtained after recrystallization.

Analytical data of new compounds 3,3,6,6-Tetramethyl-9-[2-chloro-2(4-chlorophenyl)vinyl]3,4,5,6,7,9-Hexahydro-2H-xanthene-1,8-dione (3k)

IR (KBr): 1670 (C=O), 1663 (C=O) cm^{-1} , $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm: 1.09 (s, 2 CH_3), 1.12 (s, 2 CH_3), 2.24 (s, 2 CH_2), 2.43 (s, 2 CH_2), 4.48 (d, $J = 8$ Hz, CH), 6.54 (d, $J = 8.8$ Hz, CH=), 7.24 (d, $J = 8.8$ Hz, Ar(2H)), 7.42 (d, $J = 8.8$ Hz, Ar(2H)); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) $\delta = 197.84$ (2CO), 163.47 (2 C=C), 137.10, 135.75, 134.24, 129.63, 128.18, 127.86 (2 C=C, 6 ArC), 112.96 (2 C=C), 50.62, 40.69, 32.06, 28.31, 27.36, 26.29, 24.27 (11 aliphatic C); MS (EI) m/z ,

$\% = 445, 30 [\text{M}]^+$; 430, 80; 415, 72; 346, 43; 333, 40; 273, 100; 111, 60. Anal. calcd. for $\text{C}_{25}\text{H}_{26}\text{Cl}_2\text{O}_3$ (445): C, 67.42; H, 5.88; Cl, 15.92. Found: C, 67.38; H, 5.82; Cl, 15.85

3,3,6,6-Tetramethyl-9-[3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl]3,4,5,6,2,9-hexahydro-8-hydroxyxanthene-1-one (3l)

IR (KBr): 1673 (C=O), 1597 (C=C) cm^{-1} , $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm: 0.979 (s, 2 CH_3), 0.996 (s, 2 CH_3), 1.95 (d, CH), 1.99 (d, CH), 2.10 (s, 2 CH_2), 5.67 (s, CH), 7.29-7.67 (m, 9ArH, 1 H-pyrazol, 1H-enolic), 12.09 (s, OH) (Fig.1); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) $\delta = 189.40$ - 189.37 (2 CO), 150.16 (O-C=C), 139.93 (C=N), 132.09, 131.31, 130.49, 129.76, 128.14, 128.14, 127.33, 121.91, 119.77, 118.19, 118.19 (12Ar+2pyrazole C), 46.89, 46.25, 31.67, 28.22, 25.66 [2 C of CH_2 + 4 C of 4 CH_3 + C of pyran + 2 quaternary (C)]. MS (EI) m/z ($\%$) = 570, 572 [M^+ , M^{+2}]; 493, 65; 491, 60; 465, 80; 403, 50; 273, 100; 166, 45. Anal. Calcd. For $\text{C}_{32}\text{H}_{31}\text{BrN}_2\text{O}_3$ (570.15): C, 67.25; H, 5.47; Br, 13.98; N, 4.90. Found: C, 67.20; H, 5.41; Br, 13.90; N, 4.87.

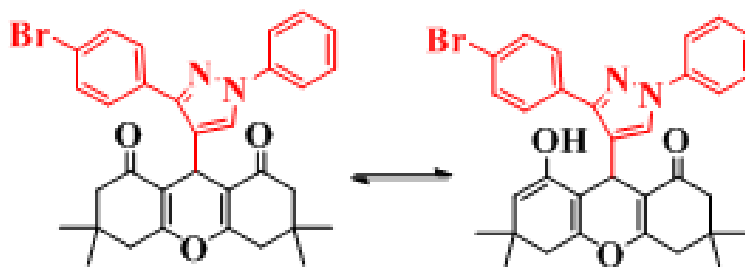


Fig.1. Tautomeric structure for (3l).

iv) Anti-oxidants was made for all compounds by using (ABTS) 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) method and using Ascorbic acid as standard.

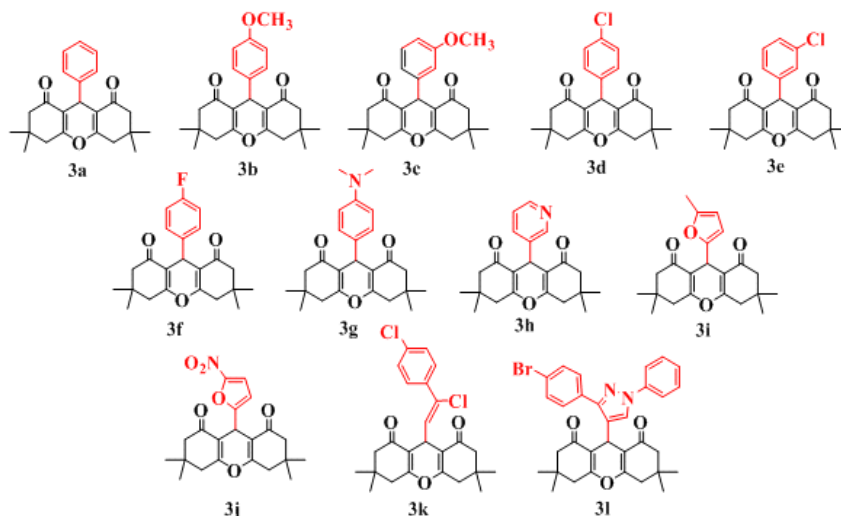


Fig. 2. Structures of synthesized 1, 8-dioxo-xanthenes.

Results and Discussion

As a model example the reaction between benzaldehyde and 2 moles of dimedone was running, at the appropriate time then the reaction was worked-up as follows: The reaction mixture was cooled to room temp and the catalysts were filtered off, washed with chloroform and dried at 100°C for one hour before being used with fresh benzaldehyde. As indicated in Table 1, we noticed that after repeating this recycling process four times, there was no significant change of efficiency of reaction time and loss of yield and this reflects the stability and efficacy of the prepared catalyst.

The proposed mechanism for the catalytic synthesis of octahydroxanthenediones is presented in Scheme 1. The aldehyde carbonyl group was polarized by the catalyst which facilitates the nucleophilic attack of C-2 of

TABLE 1. Catalyst recyclization.

Recyclization (times)	Yield (%)
1	80
2	80
3	77
4	75

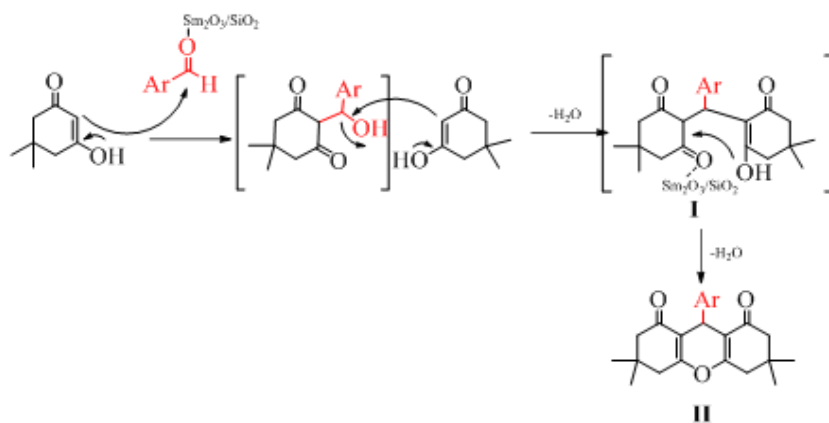
the enolized dimedone molecule, followed by another dimedone molecule to form the intermediate I, which was then activated by the catalyst to inter in another nucleophilic attack by the lone pair of electrons of OH group, after which dehydration occurred to produce the 1,8-dioxo-octahydroxanthene II.

The reaction was explored to explain the prospective of this catalytic reaction for the preparation of octahydroxanthenediones in high yield. See (Fig. 2, Table 2 and Scheme 2) summarize the products structures, melting points, yield percentages and time of reactions for compounds 3a-3l.

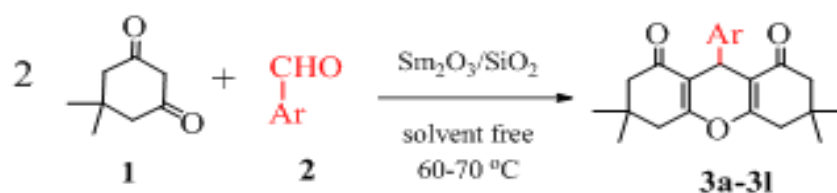
Pharmacology

In the last period, especially after the emergence of so-called cancer, due to the oxidation of molecules within the organism cells, scientists are looking for compounds acting as antioxidants to slow or prevent the oxidation of these molecules, which lead to the destruction of cells. The anti-oxidation means the use of chemical compounds to prevent the lack of oxygen inside the cells. These are dealt with the latest research in the so-called bio anti-oxidants

The following table shows the antioxidant activity of the prepared compounds:



Scheme 1. The proposed reaction mechanism.



Scheme 2. Synthesis of 1,8-dioxo-octahydroxanthenes.

TABLE 2. Synthesis of 1, 8- Dioxo-octahydronxanthenes using various aldehydes.

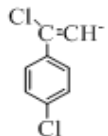
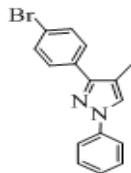
Entry	Ar	Time (min)	Yield (%)	Found (mp) ·C	Reputed (mp)
1	Phenyl	20 min	80	205-7	203–205 [15]
2	4-methoxyphenyl	60	60	235-238	242–245 [15]
3	3-methoxyphenyl	60	80	166-168	164-165 [17]
4	4-chlorophenyl	90	60	220-225	230–233 [15]
5	3-chlorophenyl	30	80	178-180	(185-187) [16]
6	4-fluorophenyl	90	70	180-183	(185-187) [16]
7	4-N,N-dimethylaminophenyl	30	90	215-217	220 –221 [17]
8	3-pyridyl	120	60	184-186	185-186 [18]
9	5-methyl-2-furyl	60	65	160-162	158-160 [19]
10	5-nitro-2-furyl	60	70	150-152	148-150 [20]
11		180	90	169	
12		210	70	160	

TABLE 3. anti-oxidant study of 1, 8- dioxo-octahydronxanthenes (3a-3l).

Entry	Method	Absorbance of samples	ABTS (Inhibition %)
	Control of ABTS	0.566	0
	Ascorbic acid	0.064	88.7
1	3a	0.300	47
2	3b	0.231	59.2
3	3c	0.293	48.2
4	3d	0.361	36.2
5	3e	0.322	43.1
6	3f	0.315	44.3
7	3g	0.086	84.6
8	3h	0.282	50.2
9	3i	0.330	41.7
10	3j	0.177	68.7
11	3k	0.398	29.7
12	3l	0.361	45.2

Comments on Table 2: For compound 3g, which gave the best results, it contains nitrogen atom containing lone pair of electrons

The other promising outputs are:

- Compound 3i, it has oxygen atom, of furan ring beside a nitro group and the result was 68.7%
- Compound 3b, it has methoxy group and the result was 59.2%
- Compound 3h, It has nitrogen atom of pyridine and the result was 50.2%

Conclusion

1,8-dioxo-octahydroxanthenes was successfully synthesized using Eco-friendly one pot catalytic reaction from aldehydes and dimedone using non-toxic, easily prepared and recyclable catalyst ($\text{Sm}_2\text{O}_3/\text{SiO}_2$) as a silica supported rare earth element under solvent-free conditions. **three** of the synthesized compounds showed promising ABTS (**3i**, **68.7**; **3b**, **59.2**; **3h**, **50.2** inhibition%) compared with ascorbic acid.

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طريقة فعالة للتحضير الحفزي لمشتقات ٨-١ داي اوكسو اوكتاهيدروزانسين مع المسح كمضادات للاكسدة

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تطوير تحضير صديق للبيئة لمركبات ٨-١ داي اوكسو اوكتاهيدروزانسين عن طريق تفاعل الالدهيدات مع الدايمدون باستخدام حفاز غير سام وسهل التحضير ويقلل اعادة التدوير (Sm_2O_3/SiO_2) وهذا عن طريق تحميل اكسيد لعنصر نادر على السيليكا وذلك في عدم وجود مذيب. ومن المسح البيولوجي كمضادات للاكسدة وجد ان هناك اربع مشتقات تعطي نتيجة واعدة مقارنة ب الاسكوريبيك اسيد.