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Application of PVPP-OXA as an Efficient Catalyst for the Synthesis of Mono and Bulky 1,8-dioxooctahydroxanthenes

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Abstract

An efficient method for the synthesis of mono and bulky 1,8-dioxooctahydroxanthenes was developed by the reaction of dimedone or 1,3-cyclohexadione and aldehydes or some bisaldehydes in the presence of polyvinylpolypyrrolidone supported oxalic acid (PVPP-OXA) as a new polymeric catalyst in ethanol at room temperature. Polyvinylpolypyrrolidone supported oxalic acid was characterized by FT-IR, and TGA analysis. Clean methodologies, simple preparation of the catalyst, high yields, environment-friendly and reusable catalyst are some advantages of this work.

***Keywords*: Polyvinylpolypyrrolidone, Oxalic acid, Xanthenediones, Bisaldehyde.

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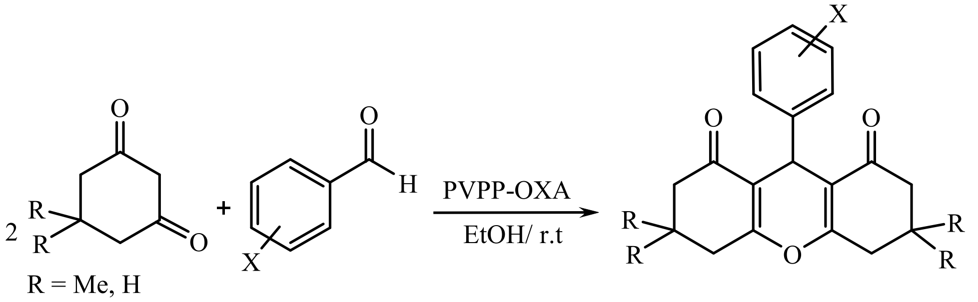
Introduction

Xanthenes show a broad biological activities, such as trypanothione reductase enzyme inhibition [1], antiviral activity [2], antibacterial [3-5], antiplasmodial [6, 7], anticancer [8-11], antimalarial [12], antifungal [13], and antihypertensive [14] activities, and also have industrial usage [15] and applications such as use as fluorescent dyes [16]. Due to these important biological properties, many synthetic methods for xanthenes have been described in the literature. One of the commonly used methods reported for the synthesis of xanthene derivatives involves the condensation of aldehydes with dimedone. This reaction can be carried out in the presence of diammonium hydrogen phosphate [17], $InCl_3.4H_2O$ [18], $FeCl_3.6H_2O$/[Hmim]BF_4 [19], silica sulfuric acid [20], amberlyst-15 [21], Fe^{3+}–montmorillonite [22], $SbCl_3/SiO_2$ [23], SiO_2-R-SO_3H [24], L-proline [25], PVPP-BF_3 [26], TPA/PAA [27], $[H\text{-}NMP]^+[HSO_4]^-$ [28], [DDPA][HSO_4] [29], SBNPSA [30], CAN/HY-zeolite [31], HOSA [32], $SnCl_2.2H_2O$ [33], $FeCl_3$-rice husk [34], TiO_2 NPs [35], nano-$ZnFe_2O_4$ [36], and nano-$CuFe_2O_4$@SO_3H [37]. In connection of our interest in the utilization of polyvinylpolypyrrolidone as support for preparation of new polymeric catalyst in some organic reactions [38-40], herein, an efficient method for the synthesis of some mono and bulky 1,8-dioxooctahydroxanthenes was developed by the reaction of 1,3-dicarbonyl compounds with aledydes in the presence of polyvinylpolypyrrolidone supported oxalic acid (PVPP-OXA) as a new polymeric catalyst in ethanol at room temperature (Scheme 1).



X = H, *p*-Cl, *m*-NO_2, *p*-OH, *o*-OH, *p*-O-$(CH_2)_4$-O-C_6H_5-CHO, *o*-O-$(CH_2)_4$-O-C_6H_5-CHO, *p*-C_6H_5-CHO, *m*-O-$(CH_2)_2$-O-

Scheme 1. Synthesis of xanthenedione derivatives catalyzed by PVPP-OXA.

Experimental

General

All chemicals were purchased from the Merck. Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. NMR spectra were determined in $CDCl_3$ on a Bruker Avance DRX-300 MHz apparatus spectrometer by TMS as internal standard. FT-IR spectra were provided with potassium bromide pellets in the range 400–4000 cm^{-1} with an SP-1100, Shimadzu instrument. The thermal stability was determined by thermogravimetric analysis (TGA, Mettler Toledo). The TGA thermogram was recorded at a heating rate of 10 °C/min in the temperature ranging from the room temperature to 600 °C in an inert atmosphere.

The catalyst preparation

To a suspension of PVPP (1 g) in acetonitrile (25 mL), a solution of oxalic acid (1.89 g, 10 mmol) in acetonitrile (5 mL) was added dropwise and the mixture stirred for 2 h at 80 °C. The resulting resin was filtered and washed with ethanol (2×10 mL) and dried at 70 °C to give PVPP-OXA as a stable powder.

General procedure for the synthesis of functionalized 1,4-dihydropyridines

A mixture of dimedon or 1,3-cyclohexadione (2 mmol), aromatic aldehyde (1 mmol) and PVPP-OXA (0.05 g) was stirred at room temperature in ethanol (5 mL) for the appropriate time, as shown in Table 2. After completion of the reaction, the reaction mixture was cooled to ambient temperature, and the PVPP-OXA was filtered off. The crude solid residue was recrystallized from ethanol to afford pure crystals of the proper xanthenediones in good yields. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and by comparison with authentic samples reported in the literature.

Spectroscopic data for new compounds as follows:

*9-(1H-indol-3-yl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3i**)*

Yellow solid; m.p. 173-175 °C; FT-IR (KBr): $\bar{\nu}$ = 730, 1203, 1454, 1544, 1656, 1676, 2891, 2943, 3055, 3409; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77-1.86 (m, 2H, CH_2), 1.92-2.00 (m, 2H, CH_2), 2.24-2.31 (m, 4H, 2CH_2), 2.62-2.69 (m, 4H, 2CH_2), 4.89 (s, 1H, CH), 6.93-7.04 (m, 3H, Ar), 7.26 (d, J = 7.5 Hz, 1H, Ar), 7.56 (d, J = 7.5 Hz, 1H, Ar), 10.80 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 22.3, 26.9, 36.9, 111.8, 116.2, 118.5, 118.8, 119.4, 120.9, 124.2, 126.1, 136.6, 164.7, 196.8.

*4-(4-(4-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)butoxy)benzaldehyde (**3j**)*

Yellow solid; m.p. 165-167 °C; FT-IR (KBr): $\bar{\nu}$ = 831, 1255, 1575, 1598, 1670, 2720, 2869, 2947; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94-2.08 (m, 8H, 4CH_2), 2.33-2.39 (m, 4H, 2CH_2), 2.58-2.67 (m, 4H, 2CH_2), 3.95-4.01 (m, 2H, CH_2), 4.11-4.17 (m, 2H, CH_2), 4.78 (s, 1H, CH), 6.75-6.79 (m, 2H, Ar), 7.00-7.04 (m, 2H, Ar), 7.20-7.25 (m, 2H, Ar), 7.84-7.88 (m, 2H, Ar), 9.91 (s, 1H, CHO); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 20.3, 25.8, 27.1, 30.7, 37.0, 67.1, 114.0, 114.8, 117.0, 129.3, 132.0, 136.6, 157.4, 163.8, 164.1, 190.9, 196.7.

2-(4-(2-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)phenoxy)butoxy)benzaldehyde ***(3k)***

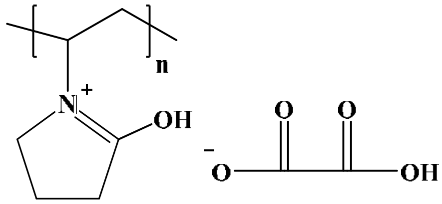
Yellow solid; m.p. 221-223 °C; FT-IR (KBr): $\bar{\nu}$ = 754, 1288, 1598, 1618, 1676, 2710, 2873, 2950; ^1H NMR (300 MHz, $CDCl_3$): δ 1.78-2.02 (m, 8H, $4CH_2$), 2.19-2.26 (m, 4H, $2CH_2$), 2.52-2.57 (m, 4H, $2CH_2$), 3.96-4.02 (m, 2H, CH_2), 4.25 (m, 2H, CH_2), 4.67 (s, 1H, CH), 6.77-6.82 (m, 1H, Ar), 6.88-6.92 (m, 1H, Ar), 7.05 (t, J = 7.5 Hz, 2H, Ar), 7.20-7.29 (m, 2H, Ar), 7.43-7.63 (m, 2H, Ar), 10.40 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 25.9, 27.0, 30.3, 36.9, 56.5, 67.6, 68.5, 112.5, 114.0, 114.5, 119.8, 121.0, 124.7, 127.9, 128.0, 131.0, 132.9, 136.9, 157.7, 161.5, 164.9, 165.0, 189.5, 196.5.

9,9'-((ethane-1,2-diylbis(oxy))bis(1,3-phenylene))bis(3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione) ***(3l)***

Yellow solid; m.p. 156-158 °C; FT-IR (KBr): $\bar{\nu}$ = 696, 1195, 1595, 1662, 2682, 2873, 2956; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 12H, $4CH_3$), 1.12 (s, 12H, $4CH_3$), 2.23 (d, J= 2.7 Hz, 8H, $4CH_2$), 2.49 (d, J= 2.1Hz, 1H), 4.28(s, 4H, $2CH_2$), 4.77 (s, 2H, 2CH), 6.70- 6.73 (m, 2H, Ar), 6.91-6.96 (m, 2H, Ar), 7.13-7.18 (m, 2H, Ar), 7.29 (s, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ27.5, 29.1, 32.2, 40.8, 50.7, 66.3, 112.4, 114.9, 115.5, 121.4, 128.9, 145.7, 158.5, 162.3, 196.4.

Results and discussion

In this study, PVPP-OXA is obtained by simple reaction of oxalic acid with the polyvinylpolypyrrolidone (Scheme 2).



Scheme 2. The chemical structure of PVPP-OXA.

Characterization of the polyvinylpolypyrrolidone supported oxalic acid was performed by recording the Fourier transform infrared spectroscopy (FT-IR) of PVPP-OXA. According to FT-IR analysis of PVPP-OXA, the stretching vibrations of amidic and acidic C=O were observed at 1649 cm^{-1}, and 1757 cm^{-1} respectievly. Also, the hydroxyl stretching vibrations was observed at 3425 cm^{-1}. The results showed that oxalic acid was successfully attached to the polyvinylpolypyrrolidone. Also, the pH of the catalyst solution (0.01 g) in water (2.5 mL) was equal to 2.3. The thermal behavior of PVPP-OXA was shown in Fig. 1. The thermal analysis PVPP-OXA showed two main decreasing peaks. The thermal analysis data of the PVPP-OXA showed that the catalyst was stable up to 150 °C. With a rise in temperature up to 200 °C, due to the loss of the oxalic acid group from the polymer surface, there has been a significant reduction in the thermal stability of the catalyst. Also, decomposition of the polymer could be observed starting around 240 °C.

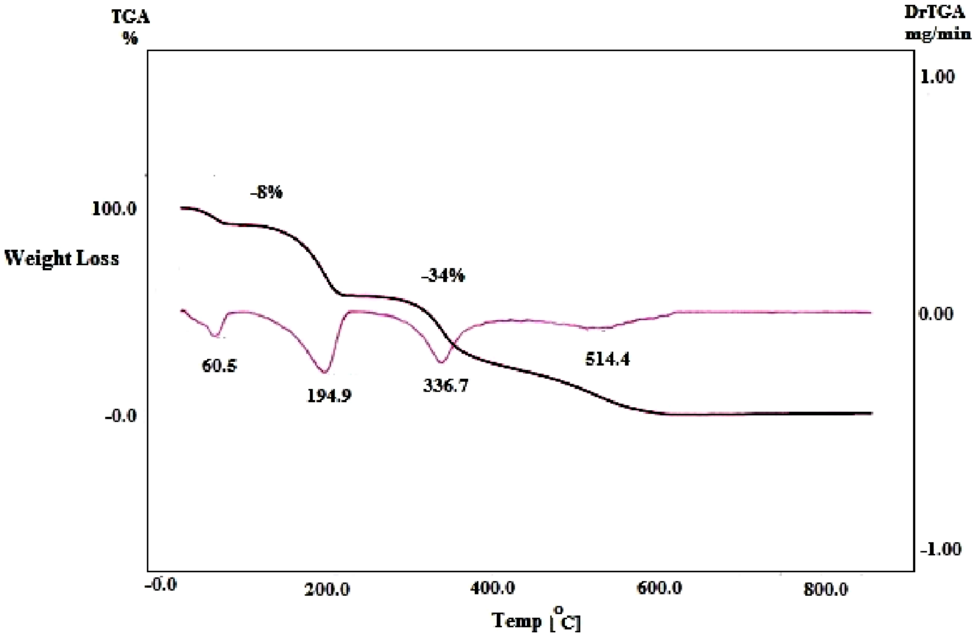


Figure 1. The thermal analysis diagram of PVPP-OXA.

In order to optimize the reaction conditions and get the best catalytic activity, the reaction of dimedone and 4-chlorobenzaldehyde was examined as a model reaction in the several solvents. In this study, it was observed that PVPP-OXA in ethanol at room temperature is more efficient with respect to reaction time and yields of the desired product (Table 1).

Table 1. Synthesis of **3b** in different solvents[a].

Entry	Solvent	Yield (%)[b]
1	MeCN	75
2	EtOH (96%)	97
3	MeOH	76
5	H_2O	70
6	$CHCl_3$	60

[a] Reaction conditions: Dimedone (2 mmol), *p*-Cl-benzaldehyde 1 mmol), PVPP-OXA (0.05 g) at room temperature after 1 h.

[b] Isolated yields.

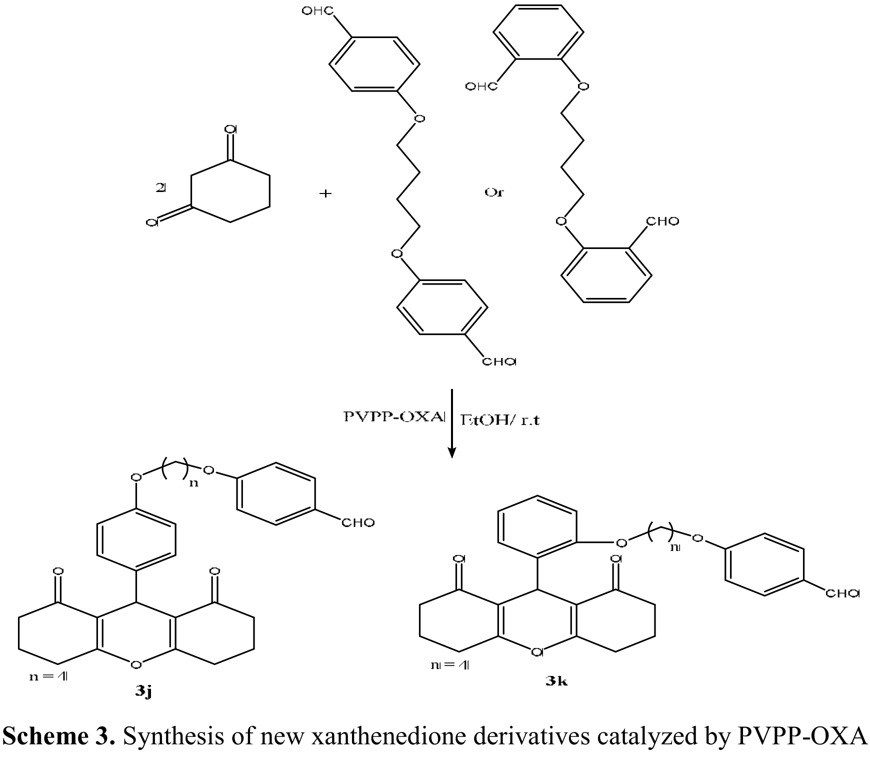
To investigate the effect of the catalyst, the model reaction was also carried out by different amounts of PVPP-OXA. It was considered that the variation of the catalyst had an effective influence on the reaction yields. The result showed the best amount of PVPP-OXA is 0.05g which afforded the required product in excellent yields (Table 2).

Table 2. Synthesis of **3o** in different amounts of the catalyst[a].

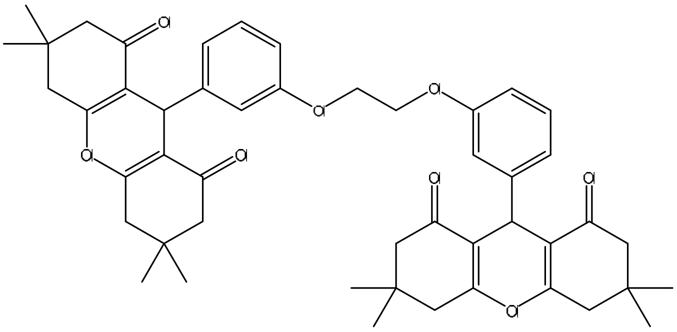
Entry	PVPP-OXA (g)	Yield (%)[b]
1	0.02	46
2	0.03	64
3	0.04	86
4	0.05	97

[a]Reaction conditions:*p*-Cl-benzaldehyde (1 mmol) and dimedon (2 mmol) in ethanol (5 mL) at room temperature after 1 h.
[b]Isolated yields.

After optimizing the reaction conditions, a diversity of xanthenediones was synthesized using PVPP-OXA in high yields (Table 3, entries 1-9). The reactions worked well with all aldehyds bearing electron-donating or electron-withdrawing substituent. Furthermore, PVPP-OXA has been successfully applied to perform the reaction of 4,4'-(butane-1,4-diylbis(oxy)) dibenzaldehyde or 4,4'-(ethane-1,2-diylbis(oxy)) dibenzaldehyde and 1,3-cyclohexadione in ethanol at room temperature to provide bulky xanthenedione derivatives **3j**, **3k** after 2h with 96 % and 94% yields respectively (Scheme 3). Also, a new bulky bisxanthenedione **3l** has been successfully prepared by the reaction of 3,3'-(ethane-1,2-diylbis(oxy))dibenzaldehyde and dimedone (1:4) in ethanol at room temperature after 2h with 95% yields (Scheme 4).



Scheme 3. Synthesis of new xanthenedione derivatives catalyzed by PVPP-OXA.



3l

Scheme 4. The chemical structure of bis xanthenedione.

Table 3. Synthesis of xanthenediones catalyzed by PVPP-OXA[a].

R	X	Product	Time (h)	Yields (%)[b]	Mp °C	
					Found	**Reported**
Me	H	**3a**	1	96	201-202	201-202 [26]
Me	4-Cl	**3b**	1	97	229-231	230-232 [26]
Me	4-Br	**3c**	1	98	242-243	242-244 [26]
Me	3-NO_2	**3d**	1	94	165-167	166-168 [26]
Me	4-NO_2	**3e**	1	97	225-226	226-228 [26]
Me	2-OH	**3f**	1.5	89	204-206	203-206 [35]
Me	4-CHO-Ph	**3g**	1.5	90	210-212	211-213 [27]
Me	3-Br	**3h**	2	93	192–194	190–192 [26]
H	Indole	**3i**	1.5	91	173-175	-------

[a]Reaction conditions: Dimedone or 1,3-cyclohexadione (2 mmol), aldehyde (1 mmol), PVPP-OXA (0.05 g), ethanol (5 ml) at room temperature. [b]All yields refer to isolated products.

To check the reusability of the catalyst, it was employed in the synthesis of **3b**, four cycles under the optimum conditions. The catalyst powder was recovered by easy filtration and washed with dichloromethane. Then, according to the amount of catalyst the required amount of fresh dimedone or 2-thionaphthol and benzaldehyde were added. The results showed that the catalyst can be reused four consecutive times without significant loss of its catalytic activity (Table 4).

Table 4. The recycling of PVPP-OXA for the synthesis of **3b**.

Run	1	2	3	4
Yield (%)	97	95	93	90

In order to explore the efficiency of the present method for the synthesis of xanthenediones compound **3a** was compared with some of those reported in the literature (Table 5). As one can see, our results show a very good comparison with previously reported data when all terms, including yields, reaction times, and reaction conditions are taken into account.

Table 5. Comparison of PVPP-OXA with some other catalysts for synthesis of **3a**.

Catalyst	**Reaction conditions**	**Time/h**	**Yield (%)**	**Ref.**
SiO_2-R-SO_3H	80 °C	4.5	75	[24]
Amberlyst-15	CH_3CN/reflux	5	86	[21]
Fe^{3+}-montmorillonite	EtOH/reflux	6	94	[22]
PVPP-BF_3	CH_3CN/rt	4	94	[26]
$FeCl_3.6H_2O$/[Hmim]BF_4	80 °C	6	92	[19]
$SbCl_3/SiO_2$	120 °C	50 min	93	[23]
TPA/PAA	100 °C	30 min	93	[27]
HOSA	90 °C	35 min	92	[32]
TiO_2 NPs	80 °C	20 min	92	[35]
$[H\text{-}NMP]^+[HSO_4]^-$	H_2O/))))	50 min	86	[28]
$SnCl_2.2H_2O$	100 °C	1	96	[33]
$FeCl_3$-rice husk	100 °C	1	91	[34]
DDPA[HSO_4]	H_2O/100 °C	1	93	[29]
SBNPSA	EtOH/reflux	2	93	[30]
CAN/Zeolite	80 °C	1.5	88	[31]
PVPP-OXA	EtOH/rt	1	96	This work

Conclusions

In summary, we have extended one-pot protocol for the synthesis of mono and bulky xanthenediones in the presence of PVPP-OXA as a stable and reusable catalyst in ethanol at room temperature. The high efficiency and simple procedure are some of the advantages of this method.

Acknowledgements

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