Vanadatesulfuric Acid Nanorod Particles: A Novel and Eco-Benign Catalyst for Rapid and Green Synthesis of 1,8-Dioxooctahydroxanthenes under Solvent-Free Conditions

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Abstract- **Biologically active 1,8-dioxooctahydroxanthenes were prepared by a one-pot condensation reaction of 1,3-cyclohexanediones and aldehydes in presence of Vanadatesulfuric acid nanorods (VSA NRs) as a novel, recyclable and eco-benign catalyst under solvent-free conditions in high to excellent yields (75–93%) and in short reaction times (10-60 min). The catalyst was characterized by FT-IR, XRD, TEM and SEM analysis. The present method offers several advantages such as simple procedure, short reaction times, high yields, simple workup, reusability of the catalyst and simple purification of the products.**

Keywords- 1,8-Dioxooctahydroxanthenes; Heterogeneous Aatalysis; Vanadatesulfuric Acid; Solvent-Free; Acid Catalysis; Nanorod Particles

I. INTRODUCTION

Xanthene and their derivatives are unavoidable in the field of medicinal chemistry for their biologically active properties as they have been synthesized and evaluated for their potential as antiviral [1], antibacterial [2], anti-inflammatory [3], anti-depressants and antimalarial agents [4]. They have been widely used as dyes fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties [5].

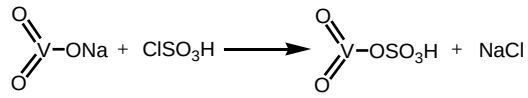
Among them, xanthenediones forms the structural unit in a number of natural products [6] and santalin pigments isolated from a number of plant species [7], and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring [8]. Also, they possess a potential antimicrobial activity similar to chlotrimazole and ampicilin, against Candida albicans and Staphlococcus aureus, respectively [9]. Furthermore, these compounds have emerged as sensitizers in photodynamics therapy [10] and are used as leuco-dyes [5] and in laser technology [11].

In recent years, several methods are reported for the preparation of 1,8-dioxooctahydroxanthenes (xanthenediones) such as cyclocondensation between 2-hydroxy aromatic aldehydes and 2-tetralone [12], trapping of benzynes by phenols [13], cyclization of polycyclic aryltriflate esters [14], and intramolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenones [15].

The conventional procedure involves acid- or base-catalyzed condensation of appropriate active methylene carbonyl compounds like dimedone with aldehydes [16], in the presence of p-dodecylbenzenesulphonic acid [17], Fe^{3+}-montmorilonite [18], $NaHSO_4$-SiO_2 or silica chloride [19], Amberlyst-15 [20], $(NH_4)_2HPO_4$ [21], Dowex-50W [22], $SbCl_3/SiO_2$ [23], and $BiCl_3$ [24], as well as with the assistance of ultrasound [25] or microwave irradiation [26]. These methods suffer from some disadvantages such as the prolonged reaction times, poor yields, side reactions of aldehydes, use of toxic solvents, use of special apparatus, and toxic catalysts. Thus, the search for the new and green catalysts is still being highly desirable.

In green chemistry point of view, heterogenation of chemical systems is an active field in laboratorial and industrial chemistry because of easy and clean reaction, simplification in handling procedures, avoidance of byproducts, reduction of corrosion, and simple work-up. Today, the use of reusable heterogeneous catalysts has received considerable importance in organic synthesis, since these can be recovered after the reaction and reused several times to achieve very high turnover numbers [27]. Furthermore, reactions with these catalysts are generally clean and selective and give high yields of products.

In continuation of above and our studies on the application of solid acid [28, 29], we found that anhydrous sodium metavanadate reacts with chlorosulfonic acid (1:1 mole ratio) to give vanadatesulfuric acid nanorod particles (VSA NRs). The reaction is performed easy, clean and without any workup (Scheme 1). It is to be noted that there is no gas production during the reaction.



Scheme 1 Synthesis of vanadatesulfuric acid nanorods

In continuation of our interesting on utility of solid acid in organic reactions, herein we made effort to examine vanadatesulfuric acid as proton source in the synthesis of 1,8-dioxooctahydroxanthenes under solvent-free condition.

II. EXPERIMENTAL

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. X-ray diffraction analysis was carried out using a D8 ADVANCE, Bruker X-ray diffractometer using Cu-Kα radiation (λ = 1.5406Å). A

Surface morphology and particle size were studied using a Philips, XL-30 SEM instrument. Transmission electron microscopy was studied using a Philips, CM-10 TEM instrument operated at 100 kV. Melting points were determined using a Barnstead Electrothermal (BI 9300) apparatus and are uncorrected. IR spectra were obtained using a FT-IR JASCO-680 spectrometer instrument. NMR spectra were taken with a Bruker 400 MHz Ultrashield spectrometer at 400MHz (^{1}H) and 125 MHz (^{13}C) using DMSO-d_6 as the solvent with TMS as the internal standard.

A. *Preparation of Vanadatesulfuric Acid Nanorods*

Anhydrous sodium metavanadate was prepared by drying of sodium metavanadate. monohydrate ($NaVO_3$. H_2O, MW = 139.94) in the oven at 250°C for 4 hours. To mixture of 0.1 mol of chlorosulfonic acid (11.6 g, 7.7 mL) and dry $CHCl_3$ in 250 mL round bottom flask in the ice-bath, 0.1 mol (12.2 g) anhydrous sodium metavanadate was added gradually with stirring. After the completion of addition of anhydrous sodium metavanadate, the reaction mixture was shaken for 1 h. Then 50 mL of cold water was added to the reaction mixture and stirred for 10 minutes. The mixture was filtered and a dark red solid of vanadatesulfuric acid, 16.3 g (91%), Mp 256 °C (dec.) was obtained. Characteristic IR bands (KBr, cm^{-1}): 3540-3300 (OH, bs), 1640 (OH, m), 1250-1140 (S=O, bs), 1050 (S-O, m), 960 (V=O, m), 840 (V=O, m), 630 (V-O, m).

B. *General Procedure for the Preparation of 1,8-Dioxooctahydro Xanthenes*

In a round-bottomed flask the aldehyde (1mmol), 1,3-cyclohexanedione derivatives (2 mmol) and VSA (10 mol%) were mixed thoroughly. The flask was heated at 80 °C with concomitant stirring. After completion of the reaction confirmed by TLC (eluent: EtOAc:*n*-hexane, 1:3), hot ethanol (10 mL) was added and filtered and separated solid catalyst. The solvent was evaporated and the crude products were recrystallized from ethanol, gave the pure products in 75-93% yields based on the starting aldehyde. The products were characterized by IR, 1H NMR, 13C NMR and via comparison of their melting points with the reported ones. Spectroscopic data of new compounds:

9-(2,6-dichlorophenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (**7**): Mp: 271-273 °C; R_f = 0.52 (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3077, 2955, 1688, 1627, 1577, 1455, 1426, 1355, 1239, 1202, 1178, 1132, 835, 779 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) : 1.85-2.31 (m, 12H), 5.28 (s, 1H), 7.13 (t, 1H, *J* = 8.0 Hz), 7.22 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) : 19.86, 26.45 , 29.79 , 36.55, 112.10, 128.15, 129.63, 136.31, 137.97, 165.70, 196.03.

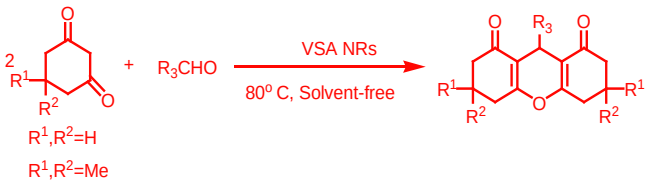
9-(5-chloro-2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (**20**): Mp: 207-208 °C; R_f = 0.56 (*n*-hexane:ethyl acetate = 3:1) ; IR (KBr): 3205, 2959, 1651, 1599, 1521, 1484, 1376, 1342, 1238, 1160, 1027, 832, 747 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm) : 0.88 (s, 6H), 1.03 (s, 6H), 2.01 (d, *J* = 15.6 Hz, 2H), 2.06 (d, *J* = 17.0 Hz, 2H), 2.23 (d, *J* = 16.0 Hz, 2H), 2.30 (d, *J* = 16.6 Hz, 2H), 4.92 (s, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) : 18.52, 25.93, 28.89, 31.66, 49.96, 55.98, 111.47, 115.91, 123.00, 123.88, 127.64, 138.78, 154.28, 163.91, 196.25.

9-(2,4-dihydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (**21**): Mp: 243-245 °C; R_f = 0.50 (*n*-hexane:ethyl acetate = 3:1); IR (KBr): 3200 (br), 2954, 1620, 1588, 1514, 1450, 1369, 1275, 1231, 1172, 1143, 844, 663 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 0.89 (s, 6H), 1.04 (s, 6H), 2.04 (d, *J* = 15.6 Hz, 2H), 2.27 (d, *J* = 16 Hz, 2H), 2.39 (d, *J* = 17.6 Hz, 2H), 2.59 (d, *J* = 17.6 Hz, 2H),4.61 (s, 1H), 5.12 (s, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 2.8 Hz, 1H), 11.04 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) : 18.52, 26.18, 29.16, 31.56, 50.40, 55.98, 101.78, 111.11, 111.73, 115.86, 128.74, 149.99, 156.04, 164.61, 195.82.

9-(2-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (**22**): Mp: 202-204 °C; R_f = 0.50 (*n*-hexane:ethyl acetate = 3:1) ; IR (KBr): 3200 (br), 2954, 1685, 1620, 1588, 1514, 1450, 1369, 1275, 1231, 1172, 1143, 844, 663 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 0.89 (s, 6H), 1.04 (s, 6H), 2.03 (d, *J* = 16.0 Hz, 2H), 2.07 (d, *J* = 15.6 Hz, 2H), 2.24 (d, *J* = 15.6 Hz, 2H), 2.32 (d, *J* = 17.6 Hz, 2H), 3.7 (s, 3H), 4.96 (s, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 10.28 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) : 24.29, 26.18, 29.16, 31.56, 40.63, 50.40, 55.98, 111.47, 115.91, 123.00, 123.88, 138.78, 154.28, 162.18, 163.91, 195.73.

III. RESULTS AND DISCUSSION

In this paper, we wish to report a novel, mild, cost-effective, and environmentally benign procedure for the one-pot synthesis of 1,8-dioxooctahydroxanthene derivatives by the condensation of aldehydes (aromatic, aliphatic, unsaturated, and heterocyclic), and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) or 1,3-cyclohexanedione in the presence of a catalytic amount of vanadatesulfuric acid (VSA) under solvent-free conditions (Scheme 2).



Scheme 2 VSA Nanorod -catalyzed 1,8-dioxooctahydroxanthene formation reaction

A. *Characterization of Vanadate Sulfuric Acid*

FT-IR spectroscopy is an effective tool which determines the changes in structure of molecular species in a system. In the IR spectra of $NaVO_3$, several absorptions appear which are apparently the result of V-O stretching modes for each of several, different oxygen atoms according

to the particular location or arrangement within the lattice [30]. At lower frequency, a broad and general absorption occurs which is apparently caused by lower frequency VO bonding. Here, the V-O stretching mode is observed as a medium band located at 950 cm^{-1}. These two spectra tend to locate the "normal" position for this stretching vibration between oxygen and vanadium. Other broad bands are presented in the spectrum of sodium metavanadate, centering at 845 and 690 cm^{-1}. The VO_3^- structure consists of VO bondings of variable bond lengths, some of which vibrate at lower frequencies than others. The 950 cm^{-1} band has been assigned to a VO bond which is considerably shorter than other bonds in the structure; the 845 cm^{-1} band very probably arises from the stretching modes of the longer VO bonds. For vanadatesulfuric acid (see corresponding FT-IR spectra in Fig. 5), the bands found at 3450 and 1640 cm^{-1} are attributed to the stretching and bending vibration of -OH group, respectively. The bands at 1050, and 1180 cm^{-1} are assigned for the sulfonic acid bonds, S–OH, S=O stretching, and S=O asymmetric stretching, respectively. The bands appearance in 960, 840 and 603 cm^{-1} related to V=O and V-O stretching.

Fig. 1 shows the XRD patterns of the $NaVO_3$ and VSA nanorod particles. A number of prominent Bragg reflections reveal that the resultant particles of vanadatesulfuric acid have a monoclinic structure (Space group: P2/m; a = 12.170 A°, b=3.602 A°, c = 7.780 A°, JCPDS card no. 16-0601). The size of the VSA particles was also determined from X-ray line broadening using the Debye-Scherrer formula ($D = k\lambda/\beta\cos\theta$, where D is the average crystalline size, k is Sherrer constant, λ is the X-ray wavelength used, β is the angular line width at half maximum intensity, and θ is the Bragg's angle). For the (001) reflection the average size of the VSA particles was estimated to be around 16 nm.

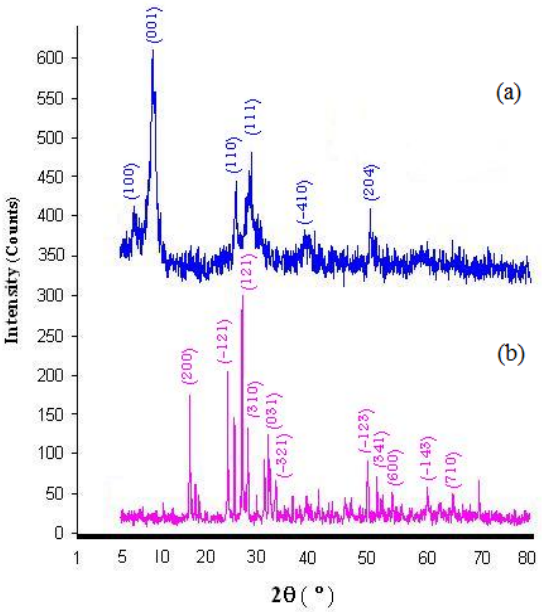


Fig. 1 Powder X-ray diffraction pattern of (a) VSA nanorod, and (b) sodium metavanadate particles

The morphology and size of the VSA were investigated by Transmission electron microscopy (TEM) (Fig. 2). They had needle-like morphology with a narrow size distribution from 15 to 20 nm and a mean size of 17 nm (nanorod particles size), confirming the results calculated from Scherrer's equation. The presence of some larger particles should be attributed to aggregating or overlapping of smaller particles.

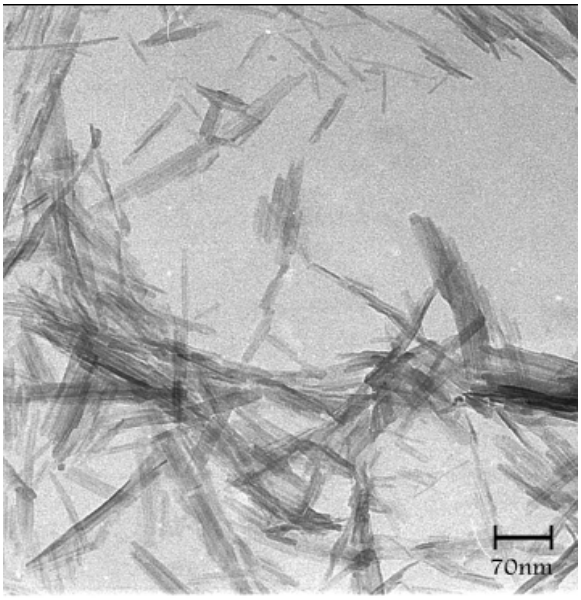


Fig. 2 The TEM image showing needle-like VSA nanorod particles of 15-20 nm in size

Scanning electron microscopy (SEM) analysis of the catalyst was taken using gold coat for high magnification showed uniform-sized particles and is shown in Fig. 3.

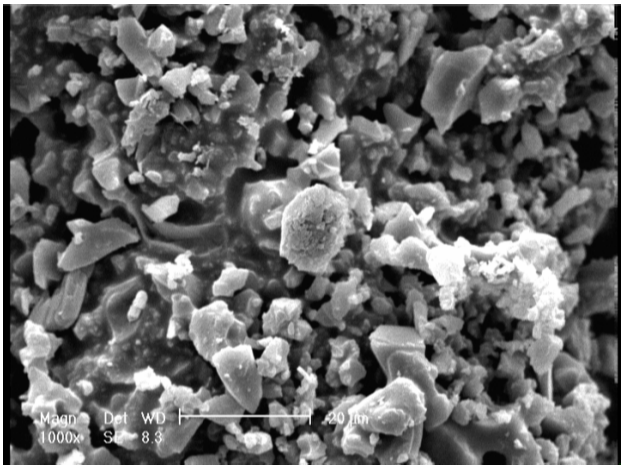


Fig. 3 SEM images of synthesized VSA

B. Effect of Solvent and Catalyst Concentration on the Synthesis of 1, 8-Dioxooctahydroxanthenes

We initially investigated the catalytic activity of VSA in the synthesis of 1, 8-dioxooctahydroxanthenes under different reaction conditions. The solvent effect in the condensation of benzaldehyde and dimedone in the presence of vanadatesulfuric acid as a model has been studied. As

shown in Table 1, among the tested solvents, such as ethanol, methanol, water, acetonitrile, chloroform and a solvent-free system, the best result was obtained after 15 min under solvent-free conditions in excellent yield (93%).

TABLE I SOLVENT EFFECT ON THE REACTION OF BENZALDEHYDE AND DIMEDONE CATALYZED BY VSA

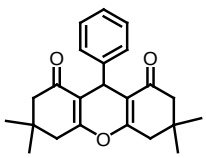
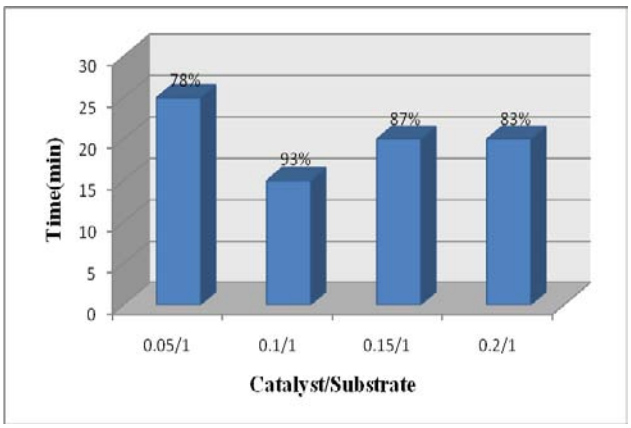
Product	Solvent	Time(h)	Yield(%)
	CH_3CH_2OH	8	73
	CH_3OH	8	65
	H_2O	8	58
	CH_3CN	8	60
	$CHCl_3$	8	55
	Solvent-free	15 min	93

Fig. 4 illustrates the effect of catalyst molar ratio on the conversion time of benzaldehyde as typical substrate under solvent-free conditions. It is important to note that no 1, 8-dioxooctahydroxanthenes were afforded when the reactions were performed in the absence of VSA in the reaction mixture. With increasing the catalyst, the reaction time is decreased up to 10% of catalyst molar ratio that was found to be an optimum amount in current conditions. The higher amount of catalyst was found that have not a notable effect on the reaction time.



[a] Based on disappearance of benzaldehyde. For 0/1 catalyst tosubstrate after 10 h the conversion was 0%.

Fig. 4 The catalyst amount effect on the synthesis of 9-phenyl-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene[a]

Therefore, this reaction was developed with other aldehydes, and the results are summarized in Table 2. The time of reaction was within 10-60 min, and high yields of 1,8-dioxooctahydroxanthenes were obtained.

TABLE II SYNTHESIS OF 1,8-DIOXOOCTAHYDROXANTHENE DERIVATIVES IN PRESENCE OF VSA AS CATALYST[A]

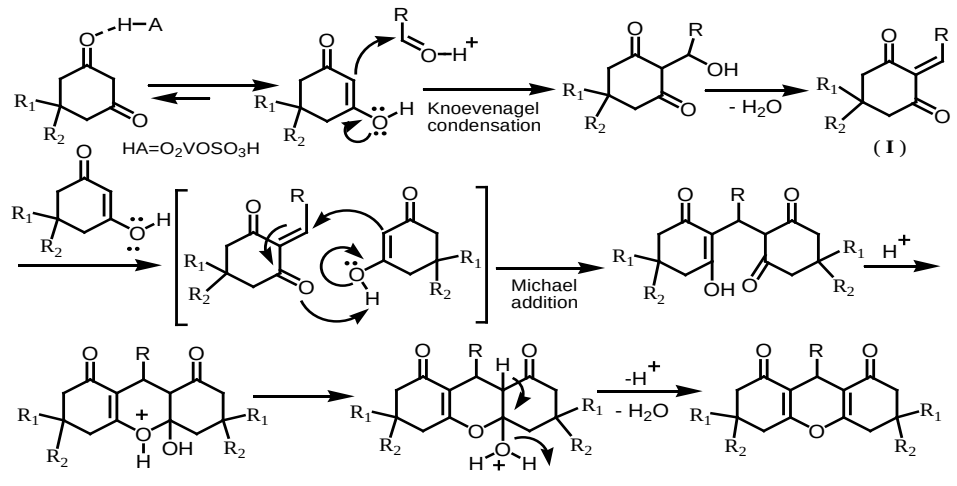
	Product	R^3	Time(min)	Yield(%)	Mp (˚C)
				Found	Reported
1	C_6H_5	20	90	269-270	267-269
2	4-$CH_3C_6H_4$	30	90	213-215	216-217
3	3-$NO_2C_6H_4$	15	92	285-287	286-288
4	4-ClC_6H_4	15	90	287-289	289-291
5	4-$OCH_3C_6H_4$	35	83	199-201	201-202
6	4-$NO_2C_6H_4$	10	92	223-225	224-226
7	2,6-$Cl_2C_6H_3$	30	88	271-273	-
8	C_6H_5	15	93	201-203	200-202
9	2-ClC_6H_4	25	87	223-225	226-228
10	4-ClC_6H_4	10	92	231-233	230-232
11	4-$OCH_3C_6H_4$	35	85	240-242	241-243
12	4-$NO_2C_6H_4$	10	90	223-225	225-227
13	4-BrC_6H_4	10	91	229-231	230-232
14	2-Cl-6-FC_6H_4	25	86	120-122	117-119
15	4-$CH_3C_6H_4$	30	80	215-217	216-218
16	3-$NO_2C_6H_4$	10	88	164-166	167-168
17	2-$OCH_3C_6H_4$	35	82	189-191	188-190
18	2,4-$Cl_2C_6H_3$	25	90	252-254	251-253
19	2-$NO_2C_6H_4$	25	87	246-248	248-249
20	2-OH-5-ClC_6H_3	30	90	207-208	-
21	2,4-$OH_2C_6H_3$	35	86	243-245	-
22	2-OH-4-$OCH_3C_6H_3$	40	90	202-204	-
23	4-OHC_6H_4	45	84	243-245	245-247
24	C_6H_5CH=CH	50	81	175-177	177-178
25	2-Thiophenyl	15	80	163-165	161-162
26	4-Pyridyl	20	82	221-223	218-220
27	$(CH_3)_2CH$-	60	75	143-145	146-147

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and comparison with these reported in the literature [31-35].
[b] Isolated yields.

By using this heterogeneous catalyst, the aromatic aldehydes, bearing electron-donating substituents such as methyl, methoxy, and hydroxy and electron-withdrawing groups such as nitro and halid, gave high yields. The procedure worked well for vinyl as well as heterocyclic aldehydes in addition to aromatic aldehydes (Table 2). Acid-sensitive substrates such as cinnamaldehyde well proceeded to give the corresponding 1,8-dioxooctahydroxanthene without any side products (Entry 24). The results indicate the generality of the procedure, because aliphatic, aromatic, heterocyclic and α, β-unsaturated aldehydes were converted into the corresponding products in good to excellent yields in short reaction time as compared with reported methods.

To use of VSA in large scale synthesis especially in chemical laboratory, a typical reaction was performed for synthesis of **8** with tenfold amounts of reactants and catalyst with respect to one mentioned in the experimental section. The results showed the yield of 90% in these conditions that is comparable with one in Table 2.

The plausible mechanism in which VSA has catalyzed this transformation is shown in Scheme 3. As can be seen, reaction proceeds via one-pot Knoevenagel condensation, Michael addition and cyclodehydration. The reaction likely proceeds via initial formation of intermediate (**I**). This intermediate reacted with another molecule of 1,3-cyclohexanediones to afford the corresponding 1,8-dioxooctahydroxanthenes.



A.

Scheme 3 The plausible VSA- catalyzed mechanism of xanthenedione synthesis

The reusability of the catalysts is an important benefit and makes them useful for commercial applications. Thus recyclability of the catalyst was also investigated. After completion of the reaction of benzaldehyde and dimedone, the catalyst was recovered from the reaction mixture. The recovered catalyst was then added to fresh substrates under the same experimental conditions for four runs without a noticeable decrease in the product yield and its catalytic activity (Table 3).

TABLE III REUSABILITY OF VANADATESULFURIC ACID IN THE SYNTHESIS OF XANTHENEDIONE OF BENZALDEHYDE AND DIMEDONE

Cycles	Isolated yield [a] (%)
Fresh	93
1	91
2	88
3	85
4	83

[a]Catalyst could be recycled by washing with ethanol and dried at 100 °C for 2h

Infrared spectra of fresh and used VSA catalyst confirmed the fact that the structure and morphology of the catalyst remained the same after recycling (Fig. 5).

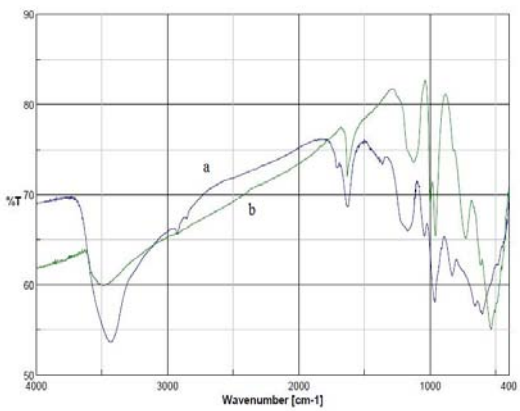


Fig. 5 FT-IR spectra of vanadatesulfuric acid: (a) before use and (b) after reuse four times

C. Comparative results

In order to show the ability of our method with respect to previous reports, some of our results in comparison to some other methods are summarized in Table 4. As shown, the yield/time ratio of the present method is better or comparable with the other reported results.

TABLE IV COMPARISON OF EFFICIENCY OF VARIOUS CATALYSTS IN SYNTHESIS OF 1,8-DIOXOOCTAHYDROXANTHENES

Entry	Catalyst	Condition	Time(h)	Yield (%)
1	VSA	Solvent-free/ 80 °C	10-60 min	80-93 (This work)
2	*p*-dodecylbenzenesulphonic acid	H_2O (reflux)	6-8	72-94 [17]
3	Fe^{3+}-montmorilonite	Solvent-free/ 100 °C	6	84-94 [18]
4	$NaHSO_4$-SiO_2or silica chloride	CH_3CN(reflux)	6-6.5	90-98 [19]
5	Amberlyst-15	CH_3CN(reflux)	5	90-96 [20]
6	Dowex-50 W	Solvent-free/ 100 °C	2-5	78-91[24]
7	Sio_2-R-SO_3H	Solvent-free/ 80 °C	3.5-5	35-93 [31]
8	Cellulose sulfonic acid	Solvent-free/ 110 °C	5-6	94-95 [32]
9	Heteropoly acid	CH_3OH(reflux)	5	81-94 [33]
10	PPA-SiO_2	CH_3CN(reflux)	10-12	54-82 [34]
11	DABCO-bromine	H_2O (reflux)	1-2.5	80-90 [35]

IV. CONCLUSION

In summary, a novel and highly efficient method for the synthesis of 1,8-dioxooctahydroxanthenes has been achieved by the condensation reaction of aldehydes (aromatic, aliphatic, unsaturated, and heterocyclic) with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) or 1,3-cyclohexanedione using catalytic amount of the reusable and environmentally benign vanadatesulfuric acid nanorods (VSA NRs) as a solid acid catalyst under solvent-free conditions. The attractive features of this protocol are

simple procedure, short reaction times, high yields, simple workup, reusability of the catalyst and simple purification of the products. Furthermore, this method is also expected to find application in organic synthesis due to the low cost of the catalyst. This approach could make a valuable contribution to the existing processes in the field of xanthenediones synthesis.

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