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One-pot Synthesis of Xanthene Derivatives as Potential Antiviral and Anti-inflammatory Agents using Nano-SnO_2 as an Efficient Catalyst

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Abstract

An efficient three-component one-pot synthesis of 1,8-dioxo-octahydroxanthenes from demedone, aldehydes, in the presence of a catalytic amount of nano-SnO_2 is described. The reactions were carried out at 80 ^{o}C under EtOH-solvent media. The structures of the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectra and by elemental analysis. The advantages of the effective method were good yields, short reaction times, simple work-up, eco-friendly solvent, and inexpensive and reusable catalyst. The catalyst could be recycled and reused for five times without much loss of its activity.

Keywords:Xanthene derivatives**,** Multi–component reaction, One-pot, Nano-SnO_2.

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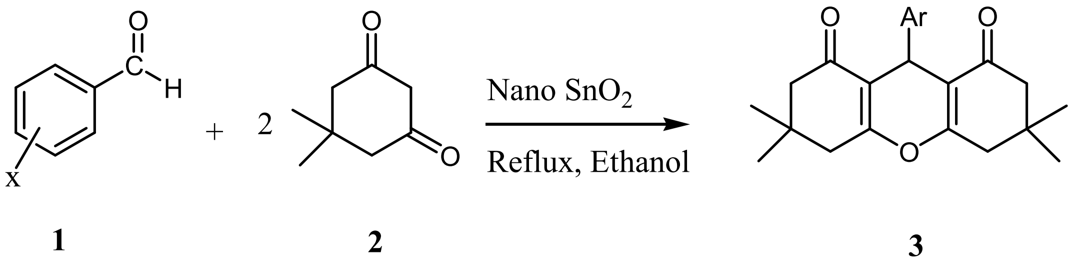
Introduction

Xanthene derivatives are very important heterocyclic compounds and have been widely used as dyes fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties [1]. They have also been reported for their agricultural bactericide activity [2], photodynamic therapy [3], anti-inflammatory effect [4] and antiviral activity [5].Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis. A wide variety of methods for the preparation of the xanthenes have been classified according to starting compounds, e.g. syntheses by cyclization of polycyclic aryltiflate esters [6], intramolecular trapping of benzynes by phenols [7] and reaction of aryloxymagnesium halides with triethylorthoformate [8].However, many of these methods are associated with several short comings such as long reaction times (16h to 5 days), expensive reagents, harsh conditions, and low product yields, use of toxic organic solvents and difficulty in recovery and reusability of the catalysts. Recently, synthesis of xanthene derivatives using *p*-dodecylbenzensulfonic acid under reflux condition [9] and ultrasound irradiation [10] and polyaniline-p-toluenesulfonate [11] salt in aqueous media and using *p*-toluenesulfonic acid [12] as catalyst in organic solvent was reported. Heterogeneous catalyzed synthesis of these compounds has also been reported [13].

In our continued interest in the development of highly expedient methods for the synthesis ofheterocyclic compounds,in this study, we wish to report a facile condensation of dimedone and aromatic aldehydes in the presence of a catalytic amount of nano-SnO_2 to produce the xanthene derivatives in excellent yields (Scheme 1).



Scheme 1. Synthesis of xanthene derivatives.

Experimental

Material and Equipments

All products are known compounds and were characterized by m.p., IR, ^{1}H-NMR and GC/MS. All melting points are uncorrected and taken with an Electrothermal melting point apparatus

(Electrothermal Eng. Ltd, Essex, UK). The ^{1}H-NMR spectrums of the synthesized compounds were measured in DMSO-d_6 solution and TMS as the internal standard using a Bruker AQS AVANCE-300 MHz instrument. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Preparation of catalyst

The $SnCl_2 \cdot 2H_2O$ (2.26 g, 10 mmol, AR grade) and NaOH (0.08 g, 20 mmol, AR grade) were ground with a mortar and pestle for 15 min. Next, sodium chloride (NaCl) was added to the mixture at a molar ratio of 1:2 and further ground for another 30 min. The mixture was then oxidized and annealed for 2 h at 400°C. The final products were washed with water and dried for 2 h at 60 ◦C. This synthesis method produced a high yield (90% mass recovery) of SnO_2 nanoparticles [14].

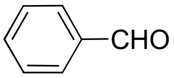
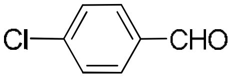
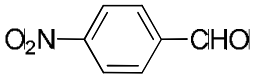
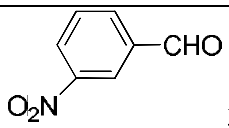
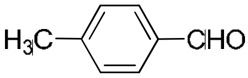
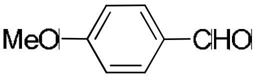
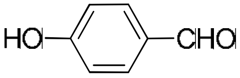
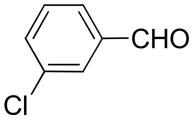
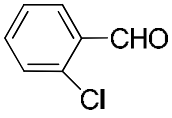
General procedure

A mixture of an aromatic aldehyde (1 mmol), dimedone (2 mmol) and nano-$SnO_2$5 mol%) in Ethanol (5 mL) was refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and filtered off. The pure product was obtained by recrystallization from ethanol.

Reusability of nano-SnO_2

In the following, the reusability of nano-$SnO_2$was investigated. At the end of the reaction, the catalyst was recovered by a simple filtration, washed with methanol, dried and subjected to a second run of the reaction process. To reassure that the catalysts were not dissolved in methanol, they were weighed after filtration and before use and reuse for the next reaction. In Table 1, the comparison of efficiency of nano-SnO_2 in synthesis of **3a** after five times is reported. As shown in Table 2 the first reaction using recovered nano-SnO_2 afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields were gradually decreased.

Table 1. synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by nano-SnO_2.

				m.p.(°C)	
Entry	**aldehyde**	**Time (h)**	**Yield(%)**[a]	**Found**	**Reported**
1		3	95	210-211	204-205[15]
2	 3a	2.5	97	246	228-230[9]
3	 3b	2.5	98	230	226-228[9]
4	 3c	2.5	97	167	168-170[9]
5	 3d	3	95	212	217-218[9]
6	 3e	3	93	248	241-243[15]
7	 3f	3	95	250	246[15]
8	 3g	2.5	96	233	230-232[9]
9	 3h	3.5	97	231	228-230[9]

a) Yields refer to isolated products.

Table 1. Reuse of nano-SnO_2 for synthesis of (**3a**).

Entry	Time(h)	Yield(%)[a]
1	1.5	95
2	2	94
3	3	92
4	4	85
5	4.5	80

Isolated yields

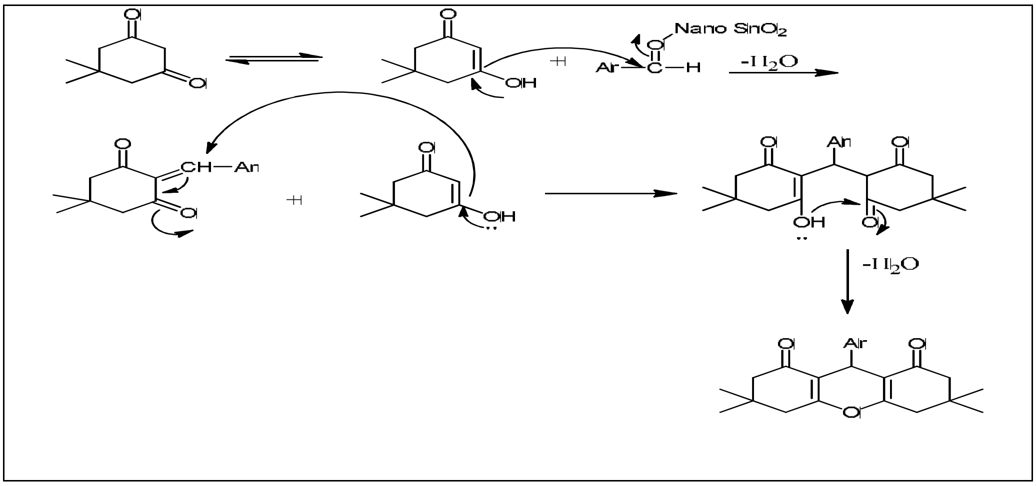
We performed on the effect of various solvents on the synthesis of 3a. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in Ethanol (Table 2).

Table 2. Synthesis of 3a in the presence of different solvents using nano-SnO_2 as a catalyst.

Entry	Solvent	Yield(%)[a]
1	THF	68
2	C_2H_5OH	95
3	CH_3CN	90
4	EtOAc	88
5	water	93

[a]Yields were analyzed by GC

A probable mechanism for this reaction has been suggested in Scheme 2. In first step the dimedone tatumerize and condenses with aldehyde that activated with the catalyst to afford intermediate. Then dimedone tatumerize attach to intermediate and the hydroxy attack after remove water. Finally, the expected products **3** were obtained.



Scheme 2. mechanism of xanthene derivatives.

Results and discussion

Firstly, we began to examine the catalytic activity of nano-SnO_2 to optimize the reaction condition of dimedone with benzaldehyde in the presence of different catalytic amounts of nano-SnO_2 at different temperatures. We found that 5 mol% of catalyst is preferred and increasing of the amount of the catalyst has not produced a better result. Meanwhile, further studies showed that raising the temperature can affect the reaction to some extent. When reaction was carried out at room temperature, the yield was not satisfactory (30% after 20h). After raising temperature, it was shown that the yield increased to 98%. Under these conditions (no anhydrous or oxygen-free conditions are required) the reaction affords 1,8-dioxo-octahydroxanthene after 3h.

In order to show the general applicability of the method, the reaction of structurally diverse aldehydes with dimedone under similar conditions was investigated. By this method, the reactions were carried out easily and very cleanly in the presence of nano-SnO_2 to produce xanthene derivatives in good to excellent yields and no undesirable by-products are observed. This protocol offers advantages in terms of its simple procedure and work-up and excellent yields.

The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methyl, methoxy, nitro, hydroxyl, halide under the reaction conditions. The results are summarized in Tables 1. It was indicated that both electron rich and electron deficient aldehydes worked well, mostly leading to high yields of products.

We found that nano-SnO_2 showed high catalytic activity and could be recovered and recycled several times without significant loss of activity.

It is known that, the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to many SnO_2-based devices, as it facilitates reaction/interaction between the devices and the interacting media.The previous research works on SnO_2 were reported by Seiyama [16] in 1962 as semiconductor materials for gas sensor materials and alternative energy. Its outstanding electrical, optical delectro-chemical properties of SnO_2 enable applications in solar cells, catalytic support materials, transparent electrodes, and solid state chemical sensors [17]. They were successfully synthesized by different methods. Various methods, including molten-salt synthesis [18] sol–gel [19], microwave technique [20,21], carbothermal reduction [22], chemical precipitation [23], laser-ablation synthesis [24], hydrothermal method [25,26], and sonochemical [27] have been developed to synthesize SnO_2 nanostructures. The investigation on nano-SnO_2 catalytic activity for the synthesis of many organic molecules is current work in our laboratory. The dimensions of applied SnO_2 nanoparticles were determined with TEM (Figures 1 and 2).

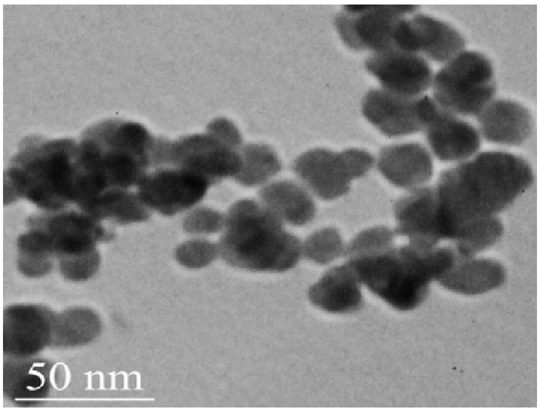


Figure 1. TEM image of nano-SnO_2.

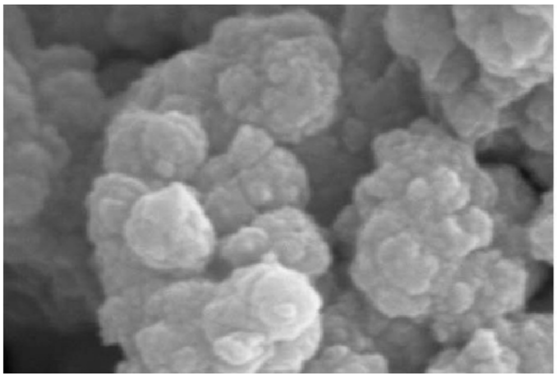


Figure 2. SEM image of nano-SnO_2.

Conclusions

In summary, we have found a simple, convenient, straightforward and practical procedure for the synthesis of xanthene derivatives. All starting materials are readily available from commercial sources. Moreover, there is no need for dry solvents or protecting gas atmospheres. Some advantages of this procedure are: 1) the experimental simplicity and the easy work-up procedure, 2) the compatibility with various functional groups, 3) use of the green, easy to handle and reusable catalyst, and 4) high yields of the products. The procedure is very simple and can be used as an alternative to the existing procedures.

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