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Cellulose Sulfonic Acid: An Efficient Heterogeneous Catalyst for the Synthesis of 1, 8-Dioxo-octahydroxanthenes

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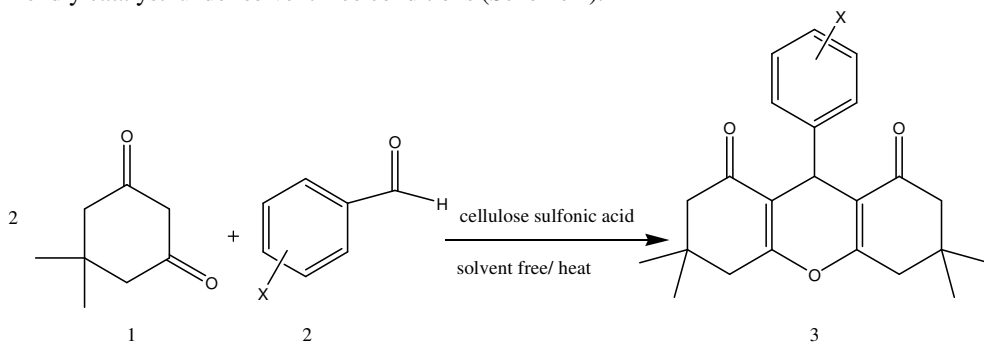
Abstract: 1,8-Dioxo-octahydroxanthenes have been synthesized good yields via a reaction of aldehydes and dimedone in the presence of cellulose sulfonic acid as a heterogeneous catalyst under solvent-free condition.

Keywords: Xanthene derivatives, Solvent-free condition, Cellulose sulfonic acid, Heterogeneous catalyst.

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 properties¹. They have been reported for their agricultural bactericide activity², photodynamic therapy³, anti-inflammatory effect⁴ and antiviral activity⁵. These compounds are also utilized as antagonists for paralyzing action of zoxazolamine⁶ and in photodynamic therapy (PDT)⁷. The other useful applications of these heterocycles are as dyes⁸, fluorescent materials for visualization of biomolecules⁹ and in laser technologies¹⁰. 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 aryltriflate esters¹¹, intramolecular trapping of benzynes by phenols¹² and reaction of aryloxymagnesium halides with triethylorthoformate¹³. However, many of these methods are associated with several shortcomings such as long reaction times (16 h to 5 days), expensive reagents, harsh conditions, low product yields, use of toxic organic solvents and difficulty in recovery and reusability of the catalysts. Heterogeneous catalysts have gained interesting attraction in recent years due to economic and environmental

considerations. These catalysts are generally inexpensive and easily available. They can conveniently be handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly. As part of our continued interest in the development of highly expedient methods for the synthesis of heterocyclic compounds of biological importance¹⁴, we would like to report a simple and efficient method to produce 1,8-Dioxo-octahydroxanthenes in very good yields catalyzed by cellulose sulfonic acid as a heterogeneous and reusable eco-friendly catalyst under solvent-free conditions (Scheme 1).



Scheme 1

Experimental

Chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. Melting points were measured with a Bamstead Electrothermal 9200 apparatus and are uncorrected. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. ¹HNMR spectra were recorded on a Bruker DRX Avance spectrometer at 300 MHz, respectively, with CDCl₃ as solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

Preparation of 1, 8-dioxo-octahydroxanthenes

General procedure

A mixture of an aromatic aldehyde (1 mmol), dimedone (2 mmol) and cellulose sulfonic acid (0.05 g) was heated at 110 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, hot ethanol or methanol was added to the mixture and the catalyst was filtered off. The pure product was obtained by recrystallization from the solvent.

Synthesis of 3,4,6-tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8 (5H,9H)-dione (4a)

M.p: 206 °C. IR (KBr) (ν_{\max} , cm⁻¹): 1670, 1674 (C=O); ¹H NMR (CDCl₃, 300 MHz) δ_{H} (ppm): 1.1 2 (12H, s), 2.01(4H, s), 2.88 (4H, s), 3.46 (1H, s), 7.21-7.30 (m, 5H, aromatic CH).

Results and Discussion

In a typical general experimental procedure, a mixture of dimedone and aldehyde was heated in the presence of a catalytic amount of cellulose sulfonic acid, the corresponding products were obtained in good yields. The results are summarized in Table 1. The catalyst plays a crucial role in the success of the reaction in terms of time and the yields.

In the absence of the catalyst, the reaction of benzaldehyde with dimedone as an example, could be carried out but the product was obtained in very low yield after prolonged time. The catalyst is very active, stable to air and moisture, nontoxic and inexpensive. In addition, it can be quantitatively recovered by filtration and reused. We were able to separate cellulose sulfuric acid from the reaction medium easily by washing with CH_2Cl_2 . After drying it was reused for subsequent reactions.

Table 1. Solvent-free synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by cellulose sulfonic acid.

Entry	X	Product	Time, h	Yield, % ^a	m.p., °C	
					Found	Reported
1	H	3a	5	94	206	204-205 ¹⁵
2	4-OH	3b	6	95	231	228-230 ¹⁶
3	4-Br	3c	5	94	225	222-224 ¹⁶
4	3-NO ₂	3d	5	95	167	168-170 ¹⁶
5	4-NO ₂	3e	5	95	227	226-228 ¹⁶
6	4-Cl	3f	5	94	229	228-230 ¹⁶
7	4-OCH ₃	3g	6	95	243	241-243 ¹⁵
8	4-CH ₃	3h	6	94	219	217-218 ¹⁵

Yields refer to isolated products.

Thus, this process could be also interesting for large-scale synthesis. In order to show the general applicability of the method, the reaction of structurally diverse aldehydes with dimedone (Scheme 1) under similar conditions was investigated. By this method, the reactions were carried out easily and very cleanly in the presence of cellulose sulfonic acid (0.05 g) at 110 °C under solvent-free conditions to produce xanthene derivatives in good 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. It was indicated that both electron rich and electron deficient aldehydes worked well, mostly leading to high yields of products. It is noteworthy to mention that similar results were obtained in H_2O , but in longer reaction times. All reactions were carried out under solvent-free condition at 110 °C and the desired products were characterized by melting points, ¹HNMR and IR spectroscopic analyses. The optimum temperature was also examined using the reaction of benzaldehyde and dimedone in the presence of cellulose sulfonic acid under solvent-free condition and the best result was obtained at 110 °C. Among the tested solvents such as methanol, ethanol, DMF, CH_3CN , chloroform, 1,2-dichloroethane and solvent-free system, the reaction was more facile and proceeded to gave highest yield, under solvent free conditions.

In summary, we have found a simple, convenient, straightforward and practical procedure for the synthesis of xanthene derivatives under solvent-free condition. 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 inexpensive, 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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