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Supercritical diethylether: A novel solvent for the synthesis of aryl-3,4,5,6,7,9-hexahydroxanthene-1,8-diones

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ABSTRACT

An efficient and simple method for the preparation of -aryl-3,4,5,6,7,9-hexahydroxanthene-1,8-diones from 1,3-cyclohexadione and several aldehydes in the presence of supercritical diethylether has been developed. The present method has several advantages such as excellent yields, relatively short reaction time (60 min), simple work-up procedure, and the use of a cheap solvent. Experiments were also performed in subcritical water. However, subcritical water is not found a proper reaction media for the synthesis of xanthenediones.

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1. Introduction

Development of green chemistry techniques continues to grow in importance. For organic synthesis, alternative processes can reduce costs and help to conserve resources. The replacement of conventional solvents with supercritical solvents, is an interesting basic approach along these lines. Most widely used green solvents for organic synthesis are supercritical carbon dioxide, subcritical and supercritical water [1–4]. Critical temperature of carbon dioxide 31 °C and pressure is 73 bar while due to its high polarity, water has a critical temperature of 374 °C and a critical pressure of 220 bar. However, supercritical diethylether is not a common solvent for organic synthesis. It has a critical temperature of 194 °C and a critical pressure of 36 bar which are relatively mild conditions, hence it can be candidate as suitable reaction media for organic synthesis. To our best knowledge, organic synthesis in supercritical diethylether did not reported before.

1,8-Dioxo-octahydroxanthenes are a phenyl substituted pyran ring is fused on either side with two cyclohexenone rings. These compounds show several biological activities such as antibacterial, antiviral and anti-inflammatory activity [5]. These compounds constitute a structural unit in several natural products, and they are valuable synthons because of the inherent reactivity of the inbuilt pyran ring [6,7]. Presence of conjugated bis-dienone functionality makes 1,8-dioxo-octahydroxanthenes sensitive to attack by nucleophiles and light energy which are widely used as dye [8], in laser technologies [9], and fluorescent materials for visualization of biomolecules [10]. In the synthesis xanthenediones, the intermediate can take place even without a catalyst. However, cyclization of this intermediate always needs a catalyst, mainly acids such as H_2SO_4, HCl, $AlCl_3$, and BF_3 are commonly used for to accomplish this transformation [11–14]. However, these catalysts have several disadvantages because they are corrosive, toxic or volatile, and generate large amount of waste. On the other side conventional methods for the synthesis of xanthenediones have its own disadvantages such as long reaction times, unsatisfactory yield, harsh reaction conditions and an excess of reagents and catalysts [15–23].

Our research group works to develop new synthetic methods in supercritical fluids [1–3] hence, we planned to develop more useful and greener method for the synthesis of xanthenediones. This is the first report for a facile and efficient synthetic strategy for the synthesis of xanthenediones derivatives in excellent yield using supercritical diethylether (Fig. 1). To compare the effect of subcritical water (subcritical water) on the synthesis of xanthenediones, experiments were also performed at 275 °C with 5 mL water.

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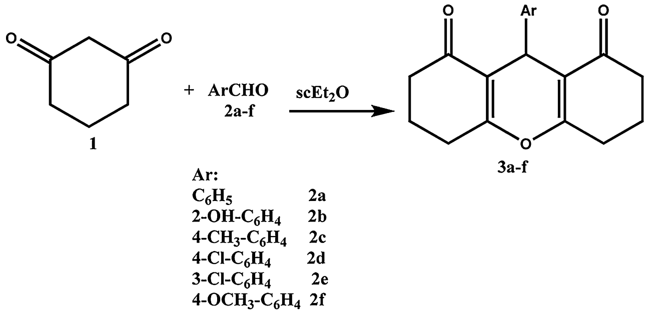

Fig. 1. Reaction of aldehydes with 1,3-cyclohexanedione in the presence of supercritical diethylether.

2. Materials and methods

2.1. General procedure for the preparation of 9-aryl-3,4,5,6,7,9-hexahydroxanthene-1,8-diones

All reactions were carried out in a high temperature high pressure 25 mL SS316 batch reactor. A mixture of aldehydes (10 mmol), 1,3-cyclohexanedione (20 mmol) was mixed in the reactor with 15 mL diethylether or 5 mL water. The reactor was fitted with ¼ in. stainless steel Swagelok tube fittings, pressure gauche and thermocouple. The reaction conditions were 200 °C and 60 min for supercritical diethylether works and 275 °C and 60 min for subcritical water works. Reaction time was measured from the moment the reaction temperature was reached (20 min), and it does not include the time required to cool the system (20 min) because we wanted to be sure that the reaction was carried out at supercritical condition. The pressure was depend on the reactor content. After completion of the reaction, the reactor was allowed to return to ambient temperature and pressure in a cooling pot. When the reactor and contents were reached to room conditions, the reactor washed with Et_2O. The solvent was evaporated and the crude product recrystallized from ethanol to afford the pure product. Yield was calculated by considering the amount of product recrystallized from ethanol as pure products and considering the initial amount of 1,3-cyclohexadione.

2.2. GC–MS analysis

GC–MS analysis were carried out by using a Finnigan-Trace GC–MS with manual injection. One microliter of sample volume was injected using split method with 50 split ratio. Chromatographic separations were accomplished with a Zebron ZB-5 capillary column (5% phenyl–95% dimethylpolysiloxane, 0.25 mm i.d. × 60 m, film thickness 0.25 μm) with injections in the split mode with 50 split ratio. Analysis was carried out using helium as the carrier gas, flow rate 1.0 mL/min. The column temperature was programmed from 50 to 240 °C at 3 °C/min. The sample size was 2 mL. The injection port temperature was 250 °C. The ionization voltage applied was 70 eV, mass range m/z 41–400 a.m.u.

3. Results and discussion

Initially, we carried out the carbonylation annulation reaction between 1,3-cyclohexadione (**1**) and benzaldehyde (**2a**) in supercritical diethyl ether at 200 °C for 60 min. We did not use any catalyst in this experiment. GC–MS analysis showed that synthesis of 9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8-dione **3a** was completed successfully without any by product. After this promising result, it is needed to study the effect of various temperatures and reaction times on the yield, and the results are presented in the following section.

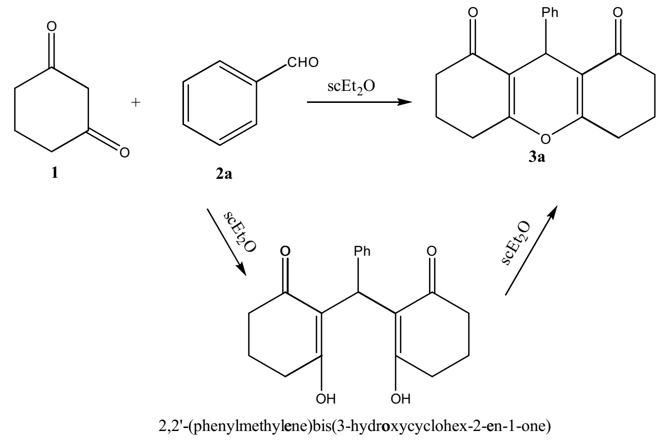

Fig. 2. Condensation and cyclisation reaction of 1,3-cyclohexadione (**1**) and benzaldehyde (**2a**) in $scEt_2O$.

Table 1
Effect of reaction time on the yield of 9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8-dione **3a**.

Temperature (°C)	Time (min)	Pressure (bar)	Yield (%)
200	30	56	72
200	45	56	76
200	60	56	97
200	90	56	64
200	120	69	20

3.1. Effect of reaction temperature and reaction time

Reaction between benzaldehyde (**2a**, 10 mmol) and 1,3-cyclohexadione (1, 20 mmol) in presence of 15 mL at 200 C for 60 min was identified as the test reaction and different reaction parameters were studied for the formation of corresponding 9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8-dione **3a**. At 200 °C and 60 min, conversion of benzaldehyde **2a** and 1,3-cyclohexadione **1** into **3a** was 72%. During this experiment we did not observed the open chain intermediate 2,2′-(phenylmethylene)bis(3-hydroxycyclohex-2-en-1-one) by GC–MS analysis (Fig. 2). This result confirmed that super critical diethylether media was suitable for carbonylation and cyclisation reactions.

Based on this result, the effect of the reaction time on the yield of **3a** at 200 °C was examined between 45–120 min. The yield of **3a** increased with increasing reaction time from 30 to 60 min (Table 1). When the reaction time prolonged to 90 and 120 min the yield of **3a** gradually decreased. Maximum yield was observed at 60 min at 200 °C (97%). Since, this reaction is an equilibrium reaction, at prolonged reaction time the reaction changed the direction because of increased concentration of product of **3a**. Hence 60 min was decided as optimum reaction time.

Effect of reaction temperature on the yield of **3a** was also examined at 150, 180 and 220 °C. The yield of **3a** was determined as 85% at 150 °C. As could seen from Fig. 3, when the temperature increased to 220 °C the yield of **3a** started to decrease (92%). Hereafter, 60 min and 200 °C were chosen as optimum reaction conditions for further xanthene synthesis in supercritical diethylether.

A plausible mechanism is given in Fig. 4. With increasing temperature, dipol–dipol interaction between ether molecules decreases. Hence, two lone pairs of electron on the oxygen atom make hydrogen bonding with α-hydrogen of 1,3-diketone compound. After removing proton, Knoevenagel reaction takes place between enolate and benzaldehyde. Product of this first reaction

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