

GREEN AND EFFICIENT SYNTHESIS OF XANTHANES IN SUPERCRITICAL DIETHYLETHER

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ABSTRACT

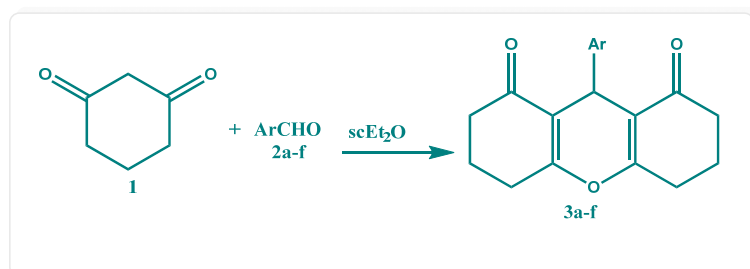
A green and efficient procedure for the preparation of 9-ary -3,4,5,6,7,9-hexahydroxanthene-1,8-diones from 1,3-cyclohexadione and aryl/alkyl aldehydes in the presence of supercritical diethylether as reaction media has been developed. The present method offers several advantages such as excellent yields, relatively short reaction time (60 min), simple work-up, and the use of a cheap solvent.

INTRODUCTION

One of the major challenges in organic synthesis is development of efficient, simple, green and general synthetic routes from readily available reagent for widely used organic compounds. As an environmentally benign medium for organic synthesis, supercritical solvents have drawn increasing attention. Supercritical solvents have many advantages over the usual organic solvents. Changing the temperature or pressure causes dramatic differences on the physicochemical properties such as viscosity, density, diffusion rate etc. Supercritical carbon dioxide and sub and supercritical water are most widely used green solvents in organic synthesis [1-4]. Carbon dioxide has a low critical temperature of 304 K and a moderate critical pressure of 73 bar while water has a critical temperature of 647 K and a critical pressure of 220 bar due to its high polarity. Supercritical diethylether (scEt₂O) is not a common solvent for organic synthesis. It has a critical temperature of 467 K and a critical pressure of 36 bar. It has relatively mild conditions, hence scEt₂O may be a suitable reaction media for organic synthesis. To our best knowledge, organic synthesis in scEt₂O didn't reported before.

Xanthenes have various biological properties such as antibacterial, antiviral and antiinflammatory activities [5]. Xanthenedione derivatives 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]. These compounds are widely used as dye [8], in laser technologies [9], and fluorescent materials for visualization of biomolecules [10]. Since these compounds are important there are several synthetic methods via the condensation of aldehyde with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in the presence of protonic acids or Lewis acids [11-14]. However, some of these methodologies suffer from low yields, prolonged reaction time, harsh reaction conditions, and the requirement of excess of catalysts [15-17].

In continuation of our work to develop new synthetic methods in supercritical fluids [1-3] we report for the first time a facile and efficient synthetic strategy for 9-ary-3,4,5,6,7,9-hexahydroxanthene-1,8-dione derivatives in excellent yield using scEt₂O (Scheme 1).



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

MATERIALS AND METHODS

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

A mixture of aldehydes (10 mmol), 1,3-cyclohexanedione (20 mmol) placed in a high temperature high pressure 25 ml SS316 batch reactor with 15 mL diethylether (Et₂O). The reactor was fitted with ¼ in. stainless steel Swagelok tube fittings, pressure gauge and thermocouple. The content of the reactor was heated at 200°C for 60 min. Reaction time was measured from the moment the reaction temperature was reached, and it does not include the time required to cool the system (15–20 min each). The pressure was depend on the reactor content. After completion of the reaction, the reactor was allowed to return to ambient temperature and pressure. The content of the reactor washed with Et₂O. The solvent was evaporated and the crude product recrystallized from ethanol to afford the pure product.

RESULTS

Our initial effort focused on the carbonylation annulation reaction between 1,3-cyclohexanedione and benzaldehyde in one-pot by using scEt₂O as solvent. We didn't use any catalyst. Reagents were combined with Et₂O in a stainless steel reactor, During the experiments it is needed to screen of various temperatures and reaction times and the results are presented in the following section.

Effect of reaction temperature and reaction time

In our initial work, we planned a model reaction conditions such as 15 mL Et₂O, 1:2 mole ratio of the reactants, 30 min reaction time and 200°C reaction temperature for the synthesis of 9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8-dione **3a** from benzaldehyde **2** and 1,3-cyclohexanedione **1**. Under these conditions, conversion of benzaldehyde and 1,3-cyclohexanedione into **3a** was 72%. After 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%). Effect of reaction temperature on the yield of **3a** was also examined at 150, 180 and 220°C. The yield of **3a** was 85% at 150°C. When the temperature increased to 220°C the

yield started to decrease (92%). Hereafter, 60 min and 200°C were chosen as optimum reaction conditions for further synthesis.

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 (psi)	Yield (%)
200	30	800	72
200	45	800	76
200	60	800	97
200	90	800	64
200	120	1000	20

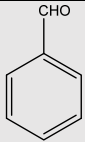
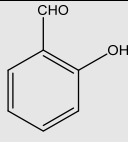
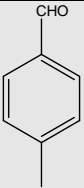
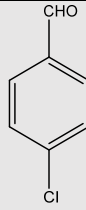
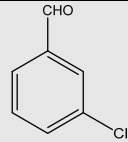
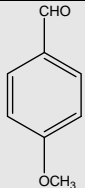
Synthesis of 9-ary-3,4,5,6,7,9-hexahydroxanthene-1,8-diones in supercritical diethylether

The reaction of various aromatic aldehydes **2a-f** and 1,3-cyclohexadione **1** in the presence of scEt₂O at the optimum condition (15 mL Et₂O, 200°C and 60 min) resulted in the formation of the 9-ary-3,4,5,6,7,9-hexahydroxanthene-1,8-diones **3a-f** (Scheme 1). Several functionalities present in the aryl aldehydes such as halogen, methoxy and methyl group were tolerated. In all the cases the corresponding xanthenediones were obtained in good/excellent yield except with **2d** (Table 2). During the formation of compounds **3a** to **3f**, irrespective of whether it has electron donating or withdrawing substituents on the aromatic ring all the starting materials underwent reaction within 60 min. However, a significant decrease in the rate of the reaction could be observed when electron donating groups are present. Generally substituent on aromatic ring decreased the yield of xanthenediones when compared with benzaldehyde **2a**.

Among the different chloro benzaldehydes studied, 3-chloro-benzaldehyde **2d** underwent reaction faster (94%) compared to 4-chloro-benzaldehyde **2c** (30%). This may be explained mesomerically electron donating character of chloro substituent at *para* position. This cause a decrease of electrophilic character of benzaldehyde hence the reaction took place slowly compared to substrate with substituent at *meta* position.

In case of aliphatic aldehydes (acetaldehyde, n-butylaldehyde and n-pentylaldehyde) only acetaldehyde gave 9-methyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione with a good yield along with a mixture of side product (aldol product). Reaction of n-butylaldehyde and n-pentylaldehyde with 1,3-cyclohexadione **1** in scEt₂O gave side products (aldol condensation products) with minor xanthenediones. These results show that arylaldehydes are more suitable due to their more electrophilic character for xanthenedione synthesis in scEt₂O.

Table 2: Synthesis of 9-ary-3,4,5,6,7,9-hexahydroxanthene-1,8-dione

Aromatic aldehydes					
					
2a	2b	2c	2d	2e	2f
97%	75%	81%	30%	94%	51%
Aliphatic aldehydes					
CH₃CHO	n-C₄H₉CHO	n-C₅H₁₁CHO			
89%	Aldol products	Aldol products			

CONCLUSION

In this study, we demonstrated that condensation between 1 eq Benzaldehyde and 2 eq 1,3-cyclohexadione in scEt₂O without using any acid or base catalyst. In all the reactions, no by-products anone were detected by GC–MS in the reaction products, indicating that neither Cannizzaro reaction of aldehyde nor condensation of ketone took place under the reaction conditions. scEt₂O was found as a good solvent for synthesis of 9-ary -3,4,5,6,7,9 hexahydroxanthene-1,8-diones from 1,3-cyclohexadione and benzaldehydes. It can concluded that arylaldehydes are more suitable for xanthenedione synthesis in scEt₂O.

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