One-Pot Synthesis of 1,8-Dioxo-octahydroxanthenes Utilizing Silica-Supported Preyssler Nano Particles as Novel and Efficient Reusable Heterogeneous Acidic Catalyst

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Abstract: A highly efficient one-pot synthesis of 1,8-dioxo-octahydroxanthenes from dimedone and various aromatic aldehydes under reflux conditions in water, catalyzed by silica-supported preyssler nano particles (SPNP) is reported. The products were formed in excellent yields and the acidic catalyst was completely heterogeneous and can be recycled for many times.

Keywords: One-pot synthesis, 1,8-Dioxo-octahydroxanthene, Heteropoly acids, Nanocatalyst.

Introduction

Xanthene and their derivatives are an important family of organic compounds because they have wide range of biological and pharmaceutical properties such as antibacterial¹, antiviral², anti-inflammatory³, anti-depressants and antimalarial agents⁴. Also, they are as structural unit in a number of natural products⁵ and santalin pigments isolated from a number of plant species are major sources for xanthenes⁶. Furthermore, these compounds are utilized in industries as leuco-dye⁷, in laser technology⁸, as pH sensitive fluorescent materials for the visualization of biomolecular assemblies⁹ and used in photodynamic therapy¹⁰. Recently, xanthenes have been used as rigid carbon skeletons for the construction of new chiral bidentate phosphine ligands with potential applications in catalytic processes¹¹.

Even though, various methods have been reported for preparation of xanthenes and substituted xanthenes. The classical method for the synthesis of 1,8-dioxo-octahydro xanthenes involves the condensation of appropriate active methylene carbonyl compounds with aldehydes¹². For this purpose, react two molecules of dimedone (5,5-dimethyl-1,3-cyclohexane dione) with various aromatic aldehydes¹³, by using of different Lewis acid catalysts such as triethylbenzyl ammonium chloride¹⁴, *p*-dodecyl benzenesulfonic acid¹⁵, diammonium

hydrogen phosphate under various conditions¹⁶, sulfonic acid under ultrasonic irradiation¹⁷, ionic liquids¹⁸, Amberlyst-15¹⁹, NaHSO₄-SiO₂ or silica chloride²⁰, phosphomolybdic acid supported on silica gel²¹, nanosized MCM-41-SO₃H under ultrasonic irradiation²², sulfonic acid on silica gel²³, Dowex-50W ion exchange resin under solvent-free conditions²⁴, HClO₄-SiO₂²⁵, ZnO and ZnO-acetyl chloride²⁶ and heteropoly acid supported MCM-41²⁷.

It is worth noting that most of these techniques have problems such as long reaction times, low efficiency, expensive raw materials, toxic materials and catalysts, hazard organic solvents, tedious workup, use of excess of reagents/catalysts and side reactions of aldehydes. Therefore, to avoid these limitations, the usage of a new and efficient catalyst with high catalytic activity, short reaction time, recyclable, suitable for green chemistry and easy to work-up for preparation of 1,8-dioxo-octahydroxanthenes would be highly desirable.

In the last two decades, heteropoly acids (HPAs) have found numerous applications as useful and versatile acid catalysts for some acid-catalyzed reactions. Heteropoly acids are several times more active than inorganic and organic acids and their molar catalytic activity is 100-1000 times more active than H₂SO₄. They can also be used in low concentrations²⁸. HPAs are non-toxic, highly stable towards humidity, air stable, recyclable, compatible with the environment, ease of handling and experimental simplicity²⁹. So, in recent years, heteropoly acids were used in different reactions and synthesizes as Lewis acid catalyst³⁰. Of course, the need for character development and optimization of catalytic efficiency of heteropoly acids to be felt.

Recently, because of the unique properties of nano particles, synthetic chemists focused on nano-catalysts. Therefore, synthesis and characterization of catalysts with lower dimensions have become the most interesting topic of research. We know that as the particle size decreases, the relative number of surface atoms increases and thus the activity increases³¹. Moreover, due to quantum size effects, nanometer-sized particles may exhibit unique properties for a wide range of applications³².

We have reported in our earlier paper³³ about the synthesis and characterization of silica-supported Preyssler nano catalyst. A Preyssler acid is a highly acidic catalyst from heteropoly acid family with excellent catalytic activity in a variety of acid-catalyzed reactions³⁰. Therefore, we hope that to get better the behaviors of this catalyst with nano particle size in organic reactions and synthesizes.

Experimental

Silica-supported Preyssler nano particles catalyst was synthesized according to our previous report³³. For synthesis of this catalyst, to a solution of surfactant in cyclohexan (0.2 M), a solution of Preyssler acid in a specified amount of water was added. The molar ratio of water to surfactant selected was 3, 5 and 7. Then, tetraethoxysilan was added into the micro emulsion phase. After mixing for various times (8, 12, 18, 25 and 30 h) at room temperature, dispersed Preyssler acid/SiO₂ nano structures were centrifuged (1500 rpm) and the particles were rinsed with acetone (4 times) and dried in a vacuum oven. The optimum ratio of water to surfactant was 3:1 and the optimum time was 30 h.

Preparation of 1,8-dioxo-octahydroxanthenes

The work-up procedure of this reaction is very easy. To a solution of aromatic aldehyde (2 mmol) and dimedone (2 mmol) in water (10 mL) was added silica-supported Preyssler nanoparticles catalyst (0.05 mmol). The mixture was refluxed for 3 h. After completion of the reaction (the progress of the reaction was monitored by TLC using *n*-hexan: ethylacetate as eluent), the mixture was cooled and the solid residue was separated and dissolved in dichloromethane. The solution was filtered and solid SPNP catalyst was isolated and could

be reused. The organic phase was evaporated and the reaction mixture was recrystallized in ethanol to give pure product. All the products are known compounds and the spectral properties and melting points of them matched well with those reported earlier^{23,25}. Spectroscopic and physical data of some representative compounds are given below.

3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxooctahydroxanthene (2a)

¹H NMR(100 MHz, DMSO-d₆) δ(ppm): δ 0.86 (s, 6H, 2CH₃), 1.00 (s, 6H, 2CH₃), 2.11-2.25 (d, 4H, 2CH₂), 2.42 (s, 4H, 2CH₂), 4.53 (s, 1H, CH), 7.14 (m, 5H, Ph); IR (KBr, cm⁻¹) ν_{max}: 2959, 1662, 1624, 1360, 1197, 1166, 1139, 1001; MS(*m/z*): 350(M⁺), 273, 217, 77.

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,8-dioxooctahydroxanthene(2c)

¹H NMR(100 MHz, DMSO-d₆) δ(ppm): δ 0.86 (s, 6H, 2CH₃), 1.00 (s, 6H, 2CH₃), 2.12-2.22 (d, 4H, 2CH₂), 2.39 (s, 4H, 2CH₂), 4.48 (s, 1H, CH), 7.1-7.2 (dd, 4H, Ph); IR (KBr, cm⁻¹) ν_{max}: 2952, 1661, 1618, 1361, 1198, 1166, 1140, 1003; MS(*m/z*): 386(M+2), 384(M⁺), 273, 217, 111.

Results and Discussion

In this study and in continue of our work with heteropoly acids as catalyst in organic reactions³⁰, we synthesized 1,8-dioxo-octahydroxanthenes derivatives (**2a-g**) *via* a one-pot reaction of aromatic aldehyde (**1**) and dimedone in presence of silica-supported Preyssler nano particles (SPNP) catalyst and reflux conditions in water as solvent in excellent yields in this work (Scheme 1).

Scheme 1. One-pot reaction for the preparation of 1,8-dioxo-octahydroxanthenes derivatives (**2a-g**) in water

Scheme 2. Proposed mechanism for HPA catalyzed 1,8-dioxo-octahydroxanthenes synthesis

The mechanism of the reaction was proposed in Scheme 2. As can be seen, reaction proceeds *via* one-pot Knoevenagel condensation, Michael addition and cyclodehydration. We think that acid catalyst such as heteropoly acids might promote the reaction by accelerating the formation of enol from the 1,3-dicarbonyls such as dimedone, in the rate-determining step (Scheme 2).

To find simple and suitable conditions for synthesis of 1,8-dioxo-octahydro xanthenes derivatives, the reaction of benzaldehyde **1a** and dimedone was chosen as a model to form the 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **2a** and reaction progress was studied under different conditions by Thin Layer Chromatography (TLC).

A summary of obtained results have been shown in Table 1. As is observable, the reaction is not performed in the absence of catalyst (Table 1, entry 1). Also, the reaction was done when Preyssler heteropoly acid used as catalyst (Table 1, entry 2-5) and it should be mentioned that use of 0.5 mol% $H_{14}[NaP_5W_{30}O_{110}]$ is sufficient to push the reaction forward and larger amounts of the catalyst did not improve the results to a greater extent. Of course, silica-supported Preyssler nano particles (SPNP) acid catalyst, showed higher catalytic activity than Preyssler alone. Then, the best ratio of aromatic aldehyde, dimedone and SPNP catalyst at mole is 1:2: 0.05. It is noteworthy that the reactions were completed after about three hours and more time, did not influence on the reaction process.

Table 1. Effect of various Preyssler acid catalyst amount on xanthene synthesis

Entry	Amount of catalyst, mol % ^a	Yield, % ^b
1	0	trace
2	0.1, Preyssler	47
3	0.3, Preyssler	66
4	0.5, Preyssler	82
5	0.6, Preyssler	83
6	0.3, SPNP	79
7	0.4, SPNP	86
8	0.5, SPNP	93

a) Reaction of benzaldehyde 1a (1 mmol) and dimedone (2 mmol) in presence of different amount of Preyssler and silica-supported Preyssler nano particles (SPNP) acid catalyst under reflux conditions in water. b) Isolated yield after 3 h reflux

Also, the effect of various solvents on the rate of the reaction was studied (Table 2). As can be seen, ethanol and water were favorable solvents for this synthesis. But water was chosen, because it is acceptable solvent for green chemistry and environment.

Table 2. Effect of various solvents on xanthene synthesis

Entry	Solvent	Yield of xanthenedione, % ^a
1	Ethanol	95
2	Methanol	68
3	Acetonitrile	57
4	Ethyl acetate	71
5	Water	93

a) Reaction of benzaldehyde 1a (1 mmol) and dimedone (2 mmol) in presence of SPNP acid catalyst (0.5 mol %) after 3 h reflux

The results of optimized reaction can be seen in Table 3. As is observable, by using this nanocatalyst, the aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the products with excellent yields; although, electron-withdrawing groups were slightly better.

Table 3. One-pot synthesis of 1,8-dioxo-octahydroxanthenes using catalytic amount of SPNP as catalyst

Entry	Aldehyde	Product	Yield, % ^a	M.P, °C
1	C ₆ H ₅ CHO	2a	93	203-205
2	4-CH ₃ C ₆ H ₄ CHO	2b	89	219-221
3	4-ClC ₆ H ₄ CHO	2c	95	231-233
4	3-ClC ₆ H ₄ CHO	2d	90	192-194
5	4-CH ₃ OC ₆ H ₄ CHO	2e	82	248-250
6	4-NO ₂ C ₆ H ₄ CHO	2f	96	228-230
7	4-BrC ₆ H ₄ CHO	2g	92	231-233

^a Isolated yield after 3 h reaction

This nano catalyst also showed excellent reusability in these reactions (Table 4).

Table 4. Recyclability of supported nano catalysts

Cycles	Isolated yield of xanthenedione, % ^a
Fresh	93
1	89
2	85
3	81

^a Catalyst could be recycled by washing with diethyl ether and dried at 100 °C for 3 h

Conclusion

Silica-supported Preyssler nano particles (SPNP) is a highly efficient, reusable and green solid acid catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes *via* a one-pot condensation reaction of aromatic aldehydes and dimedone in water as green solvent and reflux conditions. Excellent yields, enhanced reaction rates and short reaction times, simplicity of operation and easy work-up are some advantages of this protocol. Also, Preyssler is a cheap, stable, reusable and agreeable with environment catalyst. Hence, we believe that this method will find wide application in organic synthesis as well as industry.

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