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Rapid and efficient one-pot green synthesis of 12-aryl-8,9,10,12tetrahydrobenzo[*a*]xanthene-11-ones using Zr-MCM-41 catalyst

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Abstract

A new green protocol has been developed for the synthesis of 12-aryl-8,9,10,12tetrahydrobenzo[a]xanthen-11-ones via a three component, one-pot condensation reaction of dimedone, naphthols and aromatic aldehydes using Zr-MCM-41 nanoreactors as a reusable and novel catalyst at 80 °C under solvent-free conditions. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituent at ortho, meta or para-positions show equalease towards the product formation in high to excellent yields. Operational simplicity, mild reaction conditions, enhanced rates, environmentally benign, high isolated yields of the pure products and purification of products by nonchromatographic methods are significant advantages of the protocol presented here. The catalyst could be recycled and reused without a noticeably decrease in its activity.

H₂C OH HO OH Zr-MCM-41 Solvent-free CH 80 °C CH₃ CH-5 6 examples No chromatographic separation 7 examples

INTRODUCTION

Xanthenes and benzoxanthenes are important heterocycles that are known to possess multiple biological activities. Although not widely found in nature, xanthenes and compounds based on these core templates exhibit a broad spectrum of pharmaceutical activities such as anti-bacterial and anti-viral. These structural motifs have also found a niche as antagonists for paralyzing the action of zoxazolamine and demonstrate efficacy in photodynamic therapy^[1]. In addition, these compounds have been employed as dyes^[2], and pH-sensitive fluorescent materials for visualization of biomolecular assemblies^[3] and utilized in laser technologies^[4]. Thus a broad utility range has made xanthenes prime synthetic candidates thereby accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives. Previously tetrahydrobenzo[*a*]xanthenes have been synthesized under reflux for long hours in dichloromethane or 1,2dichloroethane in the presence of acid catalysts such as Sr(OTf)₂^[5], InCl₃ or P₂O₅^[6], pTSA in ionic liquid^[7], 2,4,6-Trichloro-1,3,5-triazine (TCT)^[8], BF₃·Et₂O^[9], TBAF^[10] and NaHSO₄-SiO₂^[11].

These synthetic methods afforded good yields however, have limitations of long reaction time, harsh reaction conditions and often expensive catalysts. Consequently, the development of new and simple synthetic methods such as further improvement towards lower reaction time and improved yields for the preparation of heterocyclic compounds containing xanthene fragment remains an interesting challenge. Considerable attention has been given to mesoporous materials such as MCM-41 family because of their unique properties^[12-14]. They have high specific surface areas, high pore volumes, and tunable pore sizes with a narrow distribution. However, Si-based MCM-41 exhibits only mild acidity, which is much weaker than that of the microporous zeolites. The incorporation of zirconium into the MCM-41 framework increases both the Lewis and Brönsted acidity^[15].

Due to our interest in developing solvent-free multi-component reactions^[16], we report here, a simple and facile protocol for the synthesis of a series of 12-aryl-8,9,10,12tetrahydrobenzo[a]xanthen-11-one derivatives from aldehydes, naphthols and dimedone in the presence of Zr-MCM-41^[17] as an efficient and reusable catalyst under solvent-free conditions. To the best of our knowledge in the open literature, one-pot synthesis of xanthenone derivatives catalyzed by Zr-MCM-41 has not previously been reported.

RESULTS AND DISCUSSION

Based on the green chemistry approach, we report an efficient and environmentally benign protocol for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives by multi-component condensation of naphthols, aromatic aldehydes, and dimedone catalyzed by Zr-MCM-41 under solvent-free conditions. The products were obtained in high to excellent yields by a simple work-up. Moreover, to optimize the temperature in the mentioned reaction, we have carried out a model study with salicylaldehyde (1.0 mmol), 2-naphthol (1.0 mmol) and dimedone (1.0 mmol) using 10 mol% of catalyst at various temperatures under solvent-free conditions. Our investigation demonstrated that 80 °C is an effective temperature in terms of reaction time and obtained yield. Then, we screened the catalyst concentration on model reaction at this temperature. We have varied the concentration of catalyst to 2, 5, 7, 10 and 15 mol %. The results indicated that when the reaction was carried out in the presence of 10 mol % of catalyst it gave excellent yield of product. Even after increasing the catalyst concentration at 15 mol % the yield of the product was found to be constant. So, the use of 10 mol % of catalyst appears to be optimal (Table 1).

After optimising the conditions, several syntheses of 12-aryl-

8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives from the condensation of 2naphthol (**2**) and 2,7-dihydroxynaphthalene (**3**) with a wide range of aromatic aldehydes (**1**) and dimedone utilizing Zr-MCM-41 under solvent-free conditions at 80 °C were examined (Scheme 1). All reactions were complete with in 10-20 minutes, as indicated in Table 2; in all cases the reactions afforded the desired products in high to excellent yields.

The surface acidity of the mesoporous solids is significantly influenced by the incorporation of zirconium ions into the framework. The addition of zirconium creates Brönsted acid sites and also enhances the acid strength of both the Lewis and Brönsted acid sites. The diameter of Zr^{4+} is much larger than that of Si⁴⁺ and when smaller Si⁴⁺ ions are replaced by larger Zr^{4+} ions in the framework of the solid the bond length of Zr–O–Si clearly differs from that of Si–O–Si. This must lead to the deformation of some

structures and the generation of microstrain in the lattice cell. This feature can be useful for reactions that require both types of acid sites. Therefore, a plausible mechanism for the formation of xanthenones is shown in Scheme 2.

The reaction is thought to proceed in a stepwise manner. Firstly, we assumed that the reaction may proceed via the 2-(2-hydroxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (**7a**) intermediate, which was formed by the nucleophilic addition of dimedone to aldehyde catalyzed by Zr-MCM-41. The reaction proceeds via intermediate **8a**, which is formed by the activation of carbonyl group of **7a** by Zr-MCM-41. Subsequent Michael addition of the intermediate **8a** with 2-naphthol and followed nucleophilic addition of hydroxy of naphthol to carbonyl of dimedone and dehydration is occurred in the presence of Zr-MCM-41 to give the final product. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituent at ortho, meta or para-positions show equalease towards the product formation in high to excellent yields.

Finally we investigated the reusability of the catalyst. At the end of the reaction, the catalyst was removed by centrifugation and washed with ethyl acetate and re-used in reaction. It was found that the recycled catalyst was used for four consecutive reactions without significant decrease of the yields (Table 3).

All products were well characterized by ¹H NMR, ¹³C NMR, FTIR, mass spectra, elemental analyses and melting point. For example, the ¹H NMR spectrum of synthesized compounds contained two singlet signals at about δ 0.90 and 1.06 ppm corresponding to

two chemically different methyl protons. Moreover, methylene protons appeared as two AB quartet patterns at about δ 2.10 and 2.30 ppm (J = 16.0 Hz) and at δ 2.50 and 2.70 ppm (J = 17.2 Hz) corresponding to two chemically different moieties. Methine and aromatic protons showed as a sharp singlet at about δ 5.50 and multiplet at about δ 6.50-7.70 ppm, respectively. Hydroxy protons appeared as a sharp singlet at δ 9.90 ppm. To the best of our knowledge, synthesis of compounds **5d-g** has not previously been reported in literature.

In summary, a novel and highly efficient method for the synthesis of 12-aryl-8,9,10,12tetrahydrobenzo[*a*]xanthen-11-ones by condensation reaction of naphthols with aromatic aldehydes and dimedone catalyzed by Zr-MCM-41 nanoreactors has been described. The attractive features of this protocol are simple experimental procedure, solvent-free reaction conditions, utilization of an inexpensive, non toxic, short reaction times, reusable catalyst in high yields and its adaptability for synthesis of a diverse set of xanthenone derivatives. To the best of our knowledge this is the first report on synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones with Zr-MCM-41.

EXPERIMENTAL

General Procedure For The Synthesis Of Xanthenones (4,5)

To a mixture of aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) and naphthol (1 mmol), Zr-MCM-41 (10 mol %) was added and heated at 80 °C for the appropriate amount of time as indicated in Table 2. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, ethyl acetate (10 mL)

was added and centrifugated until catalyst was separated. Then, Ethyl acetate was evaporated under vacuum to give the crude product. The crude product was recrystallized from EtOH to yield pure xanthenes-11-one derivatives.

SUPPORTING INFORMATION

Spectral data for the synthesized compounds can can be accessed on the publisher's website.

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Entry	Catalyst loading (mol %)	Yield (%)
1	2	72
2	5	80
3	7	85
4	10	92
5	15	92

Table 1. Choice of amount of Zr-MCM-41 for xanthenones formation



Table 2. Zr-MCM-41 catalyzed one-pot synthesis of xanthenones





Table 3. Recyclability of the nanocatalyst for the synthesis of xanthenones

No of Cycles	Fresh	Run 1	Run 2	Run 3
Yield (%)	92	92	90	89



Scheme 1. Zr-MCM-41 promoted one-pot synthesis of xanthenones (4, 5)

tetrahydrobenzo[a]xanthene-11-ones

