



Simple and efficient synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives

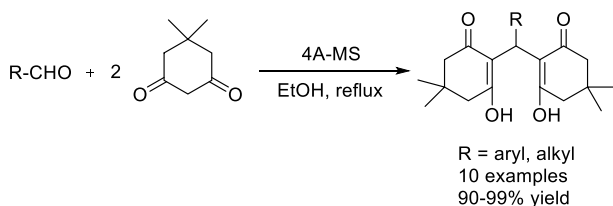
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Received: 11 September 2019 / Accepted: 3 November 2019 / Published online: 13 November 2019
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Abstract

A simple and efficient method for the synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives using 4 Å molecular sieves as catalyst is described. This approach offers several advantages such as high yields, mild reaction conditions, easily accessible, and reusable catalyst, and simple work-up procedure.

Graphic abstract



Keywords 2,2'-Arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) · Heterogeneous catalysis · Condensation reaction · Green chemistry · Three-component reaction · Molecular sieves

Introduction

2,2'-Arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives are important ring-opening precursors for the synthesis of different xanthenes [1–4] and acridinediones [5–8] (Scheme 1). They also show significant biological and therapeutic activities such as lipoxygenase inhibition [9, 10], antioxidant activity [9], and tyrosinase inhibition [11].

The simplest approach for the preparation of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives involves the condensation of aromatic

aldehydes (1 eq.) with 1,3-cyclohexanediones (2 eq.) under different conditions (Scheme 2). Several synthetic methods have been reported for the synthesis in the literature applying different types of catalysts such as L-histidine in ionic liquid [12], silica-diphenic acid [13], Pd(0) nanoparticles in water [14], Ni(0) nanoparticles anchored on acid-activated montmorillonite [15], urea under ultrasound irradiation [16], Cu(0) nanoparticles on silica [17], immobilized Ni–Zn–Fe layered double hydroxide [18], and Yb(OTf)₃–SiO₂ [19].

The abovementioned protocols are undoubtedly valuable, but suffer from one or more disadvantages; many of the catalysts are not readily available and need to be prepared through a long procedure sometimes using expensive and/or toxic reagents. Due to the biological and synthetic importance of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) compounds, the development of a mild and efficient method for their synthesis still has an importance.

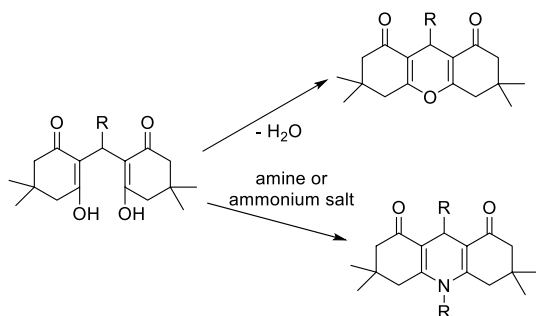
As the main research profile, our research group deals with the elaboration of new supported metal catalysts and investigates their applicability in different organic chemical

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00706-019-02515-2>) contains supplementary material, which is available to authorized users.

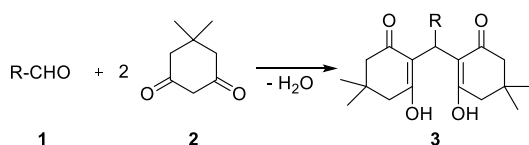
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Scheme 1



Scheme 2



reactions. Several 4 Å molecular sieves (MS-4A) supported metal catalysts have been used successfully in a wide range of organic chemical syntheses, such as iron [20], titanium [21, 22], lanthanum [23, 24], zinc [25], and copper [26]. In this communication, we present a simple and efficient method for the synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives using MS-4A as a cheap, readily available, and reusable catalyst.

Results and discussion

Recently, we have reported the efficient synthesis of 9-arylhexahydroacridine-1,8-diones via one-pot four-component reaction in the presence of a molecular sieves supported iron catalyst [20]. During our reactions, we observed the formation of the respective 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives, the well-known intermediates of the synthesis. This observation prompted us to set these compounds as target molecules during our further work.

To optimize the reaction conditions, we investigated the model reaction of dimedone (2 eq.) and 4-chlorobenzaldehyde without catalyst, as well as in the presence of different MS-4A supported metal catalysts and unmodified molecular sieves 4A and 5A. Taking into account our previous results [20], we led the reactions in refluxing ethanol. Without catalyst the reaction was incomplete after 5 h, this may confirm the catalytic effect of MS-4A. Considerable amount of starting material could also be detected by TLC and ^1H NMR, when the reaction was carried out in the presence of MS-5A. We also tested the model reaction in refluxing toluene and xylene, but at higher

temperature, some tarry byproducts have also formed. Thus, we have chosen ethanol for our further reactions, as it is a simple, easily removable, and environmentally safe solvent. In the presence of $\text{Fe}^{3+}/4\text{A}$ and $\text{La}^{3+}/4\text{A}$, the product was obtained with good yield, but the unmodified MS-4A also proved to be efficient in the synthesis. Taking into account that this way the application of expensive metals and a possible metal contamination can be avoided, we further examined the application of MS-4A. This molecular sieve is a cheap and readily available material, which is widely used in synthetic laboratories to dry gases, solvents, and liquid reagents; it can also be applied for the absorption of water in condensation reactions [27, 28], furthermore, its physicochemical properties make it possible to use it as support for catalysts. MS-4A is a basic material; its pH is 10.42. MS-5A is also used as drying agent in synthetic laboratories, but it has a lower basicity (pH 8.8). As the result obtained with MS-5A was weaker than with MS-4A, the acidity or basicity of the catalyst may not be crucial in the reaction. Since MS-4A is a microporous zeolite and the reaction may occur on the surface of the catalyst, the interactions between the surface and the reactants may be important. Moreover, the water formed in the reaction can be adsorbed readily by the pores in the vicinity.

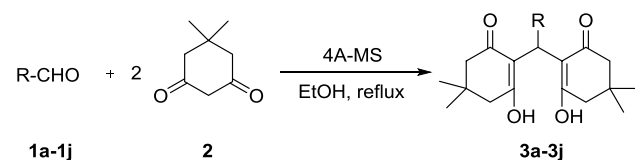
A wide range of aromatic aldehydes were reacted with dimedone in the MS-4A catalyzed synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives. The results are summarized in Table 1.

Benzaldehyde and various substituted aromatic aldehydes containing electron-withdrawing or electron-donating groups were examined in the reaction and gave the desired products with excellent yields. No significant substituent effect could be observed. As aliphatic aldehyde, we tested butyraldehyde in the reaction (Table 1, entry 10). The desired product **3j** was also formed with excellent yield. The work-up of the reaction mixture was very easy; after the filtration of the catalyst and evaporation of the solvent, the product was obtained with excellent purity.

The reusability of the catalyst was examined in the reaction of dimedone (2 eq.) and 3-bromobenzaldehyde. After the 5 h reaction time, the reaction mixture was worked up (see Experimental section for details), then the catalyst was heated at ca. 120 °C for 1 h. It was reused in two more runs without significant loss in its activity. The isolated yields for the two successive runs were both 96%, which clearly demonstrates the practical recyclability of the catalyst.

Conclusion

As a summary, 4 Å molecular sieves proved to be efficient green catalyst for the synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives

Table 1 The synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives in the presence of MS-4A

Entry	R	Product	Yield ^a /%	M.p./°C/Lit. m.p./°C
1	C ₆ H ₅	3a	90	186–188/190–192 [12]
2	3-BrC ₆ H ₄	3b	98	178–180/184–186 [12]
3	4-BrC ₆ H ₄	3c	98	166–168/172–174 [12]
4	4-ClC ₆ H ₄	3d	97	135–136/137–138 [16]
5	4-CH ₃ C ₆ H ₄	3e	99	122–124/126–128 [12]
6	4-OCH ₃ C ₆ H ₄	3f	96	138–140/142–144 [12]
7	3-NO ₂ C ₆ H ₄	3g	97	186–188/190–190 [16]
8	4-NO ₂ C ₆ H ₄	3h	99	164–166/169–171 [12]
9	4-(CH ₃) ₂ NC ₆ H ₄	3i	97	174–175/181–183 [12]
10	CH ₃ (CH ₂) ₂	3j	98	126–128/133 [29]

Reaction conditions: 2 mmol dione, 1 mmol aldehyde, 0.1 g MS-4A, 3 cm³ EtOH, reflux, 5 h

^aIsolated yield

under mild conditions. The desired products were formed with excellent yields (90–99%). The catalyst is a commercially available and cheap material, which is widely used as a drying agent in synthetic laboratories. It can be easily recovered from the reaction mixture and reused several times.

Experimental

¹H NMR spectra were obtained on BRUKER Avance-500 instrument using TMS as an internal standard in CDCl₃. Melting points were determined on Gallenkamp apparatus. All compounds and solvents were purchased from Merck Hungary, Ltd.

General procedure for the preparation of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives

A typical reaction was carried out in a 10 cm³ flask. Dione (2 mmol), aldehyde (1 mmol), 0.1 g MS-4A, and 3 cm³ ethanol were stirred at reflux temperature for 5 h. The catalyst was heated at 120 °C for 1 h before the reaction to remove the traces of water. The progression of the reaction was monitored by TLC. After completion, the solid was filtered and washed with ethanol and then the filtrate was evaporated. The product was subjected to ¹H NMR spectroscopy and its melting point was measured.

All products are known compounds and have satisfactory melting points and spectral data (¹H NMR) which are identical with those reported in the literature [12, 16, 29].

Acknowledgements Open access funding provided by Budapest University of Technology and Economics (BME). Á. M. is grateful to the József Varga Foundation for the financial support. The research reported in this paper has been supported by the National Research, Development and Innovation Fund (TUDFO/51757/2019-ITM, Thematic Excellence Program).

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