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Uncatalyzed Synthesis of Arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] in Hot Water by Domino Knoevenagel/Michael Reactions

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Abstract

A simple and ecofriendly method was developed for the synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] from the reaction of 5,5-dimethylcyclohexane-1,3-dione and aromatic aldehydes in an aqueous media without any catalyst via Knoevenagel condensation followed by rapid Michael addition. No cyclization product was down to convert these enolic forms to xanthene derivatives. Diverse aromatic aldehyde including electron-withdrawing (such as nitro group) groups or electron-donating groups (methoxy group) was used to give the corresponding dienolic forms successfully. This method provided several advantages such as simple work-up procedure, high yield, short reaction time and environmentally friendly nature.

Keywords: *5, 5-Dimethylcyclohexane-1, 3-dione, Arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)], Green media, Aromatic aldehyde, Tetraketones.*

Introduction

Recently, the development of environmentally benign and clean synthetic procedures has become the goal of organic synthesis. Water plays an essential role in life processes and acts as a medium for organic reactions. The use of water as a reaction medium exhibits a remarkable benefit because of its high polarity and therefore immiscibility with the most organic compounds. Reactions in aqueous media are environmentally safe, have less carcinogenic effects with a simple work up and are particularly important in the industry. Thus, there is a need for developing multicomponent reactions (MCR's) in water without the use of any harmful organic solvents and catalysts [1,

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2]. Tetraketones are important skeletons for the synthesis of many natural products and organic compounds such as acridiediones, laser dyes, xanthenedione, and thiaxanthenes derivatives and for the synthesis of various heterocyclic compounds [3-5] (figure 1.)

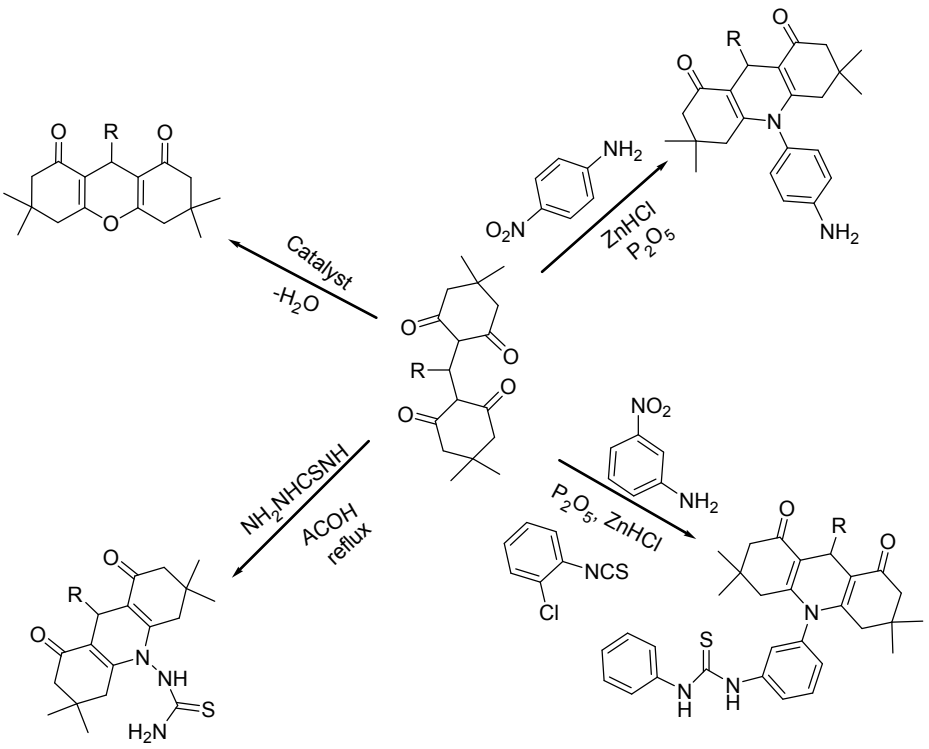


Figure 1. Tetraketone in heterocyclic synthesis.

Tetraketones show significant inhibitor activity and strong anti-oxidant potential and also act as a potential remedial source for inflammation and asthma. They exhibit a broad spectrum of therapeutic and biological properties [6-9]. These compounds are also important synthetic intermediates and can serve as versatile precursors in the synthesis of xanthenes that exhibit biological and therapeutic role such as lipoxygenase inhibitors, antioxidants, [9], antiviral and antibacterial activities [10]. In addition they are also applied in laser technology [11].

Arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) derivatives 3 are important substrates which are extensively used as valuable precursors for the synthesis of acridinediones [12]. These compounds have also shown potent activity as antioxidant lipoxygenase inhibitors and a new clinical class of tyrosinase inhibitors against very important dermatological disorders including hyperpigmentation and skin melanoma [13].

In many works, it has been reported that the reaction of aromatic aldehyde and 5,5-dimethyl-1,3-cyclohexanedione can obtain arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) as intermediate and 1,

8-dioxo-octahydroxanthene as final product. There is usually a need for a catalyst in cyclization step to get the cyclized compound. So, there are many reports about 1, 8-dioxo-octahydroxanthene derivatives, while there are less ones on the synthesis of arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) as target product.

A number of synthetic methods for arylmethylene [bis(5,5-dimethy-3-hydroxy-2-cyclohexene-1-ones) derivatives **3** have been reported by the condensation of cyclic 1,3-dicarbonyls and aryl aldehydes in the presence of $HClO_4$-SiO_2 [14], Et_4NBr/NH_4Cl [9], $FeCl_3{\cdot}6H_2O$/TMSCl/[bmim][BF_4] [15], I_2 [16], EDDA [17], benzyltriethylammoniumchloride [18], nickel nanoparticles [19], solid state grinding [20], $SmCl_3$ [21], SDS [22], neutral alumina (MW) [23], Kf/Al_2O_3 [24], $CaCl_2$ [25] and ionic liquids ([3,4-dcbsmim][Cl]) [26].

Although various methods have been developed and reported, the necessity for developing a simple and efficient methodology for the synthesis of arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) still remains given their biological importance. To continue the previous research on tetraketones and their enolic forms [27-29], here, a green and efficient method was reported for the synthesis of these products.

Experimental

General

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer (KBr). The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively on BRUKER DRX-400 AVANCE spectrometer using TMS as internal standard. Melting points were determined using an Electrotermal 9100 and were uncorrected. The reactions were monitored by thin layer chromatography and the products were identified fully or by the comparison of melting points and spectroscopic data with the previously reported ones.

General procedure for synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] derivatives in water

A mixture of dimedone (**2**) (3.0 mmol) and aryl aldehyde (1.5 mmol) in H_2O (10 mL) was heated to reflux for appropriate time (Table 2) and the reaction was monitored by TLC. After completion, the reaction mixture was cooled down to room temperature and evaporated under reduced pressure to provide the residues. Purified by recrystalization from ethanol. Spectral data of the unreported compound are given below:

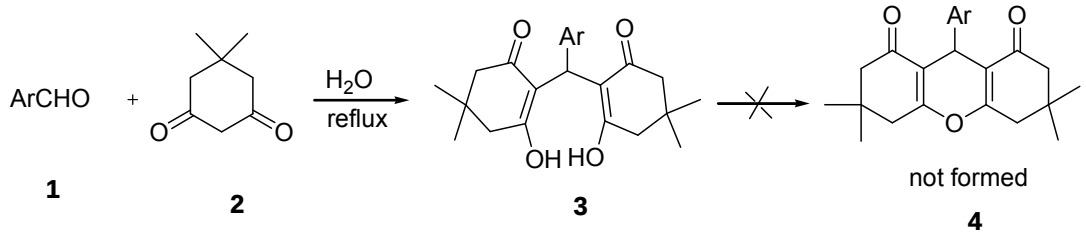
2-((5-bromo-2-hydroxyphenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-5,5-Dimethyl-cyclohexane-1,3-dione (3n).

M.p. = 246-249 C°. IR (KBr, cm^{-1}): 3441, 3106,

2960, 1622. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.97 (s, 3H, CH3), 1.05 (s, 3H, CH_3), 2.02–2.57 (m, 8H, 4CH_2), 5.03 (s, 1H, CH), 7.95 (d, J = 8.7 Hz, 1H, H-Ar), 7.03 (s, 1H, H-Ar), 7.28 (dd, J = 8.6, 2.0 Hz, 1H, H-Ar), 10.57 (br s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.1, 29.1, 31.6, 39.5, 39.7, 39.9, 40.1, 40.4, 50.3, 115.4, 117.7, 127.5, 128.2, 129.7, 130.5, 139.8, 186.5, 195.6 ppm.

Results and discussion

By paraphrasing the concept reported by Sheldon 'the best solvent is no solvent' [30] and Maggi '*the best catalyst is no catalyst*' [31] on this issue, we decided to try to synthesize arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones **3** by reacting aromatic aldehydes **1** with 5, 5-dimethylcyclohexane-1,3-dione **2** without the addition of any catalysts (Scheme 1).



Scheme 1. Synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones.

First, the reactivity of the model reaction between 3-nitrobenzaldehyde (1.5 mmol) and 5, 5-dimethylcyclohexane-1, 3-dione **2** (3 mmol) was estimated in ethanol at reflux. The reaction was complete using 1:2 molar ratio of aldehyde to dimedone in 1.5 h and 87 % of 2,2 -(3-nitrophenyl)methylene bis(3-hydroxy-5, 5-dimethyl-2-cyclohexene-1-one) **3b** was obtained as identified by m.p. and spectral data. The separation and purification processes were very simple, since they only involved a Buchner funnel filtration and washing with water and ethanol (10 ml). The reaction of 3-nitrobenzaldehyde and dimedone in equimolar ratio provided a mixture of **3b** and unreacted aldehyde.

The focus was on the systematic evaluation of different solvents for the model reaction. The attempts for studying and optimizing the reaction conditions showed that the reaction in H_2O as media had satisfactory results (table 1, entry 5). When the conversion was carried out at reflux, the dihydroxy compound 3b was formed within 13 min. No cyclization product was obtained even if the reaction time was extended to 5.0 h. However, the present conversion was possibly forming the product **3** without cyclization.

Table 1. Reactions of 3-nitrobenzaldehyde, dimedone in different solvent.

Entry	Solvent	Temperature	Time (min)	Yield (%)[a]
1	EtOH	reflux	90	87
2	EtOH:H_2O (1:1)	reflux	92	90
3	MeOH	reflux	40	67
4	MeOH:H_2O (1:1)	reflux	39	91
5	H_2O	reflux	13	92

a) Isolated yield.

In the second series of experiments, the general validity of the present methodology was explored; different arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones **3** were synthesized in 70–94% yield (Table 2). Subsequent reactions of dimedone with other aromatic aldehydes containing electron-withdrawing (such as nitro group) groups or electron-donating groups (alkoxyl group) were employed and reacted to give the corresponding tetraketones (**3a–n**). As shown in table 2, the aldehydes with electron-donating groups especially entry 8, and halide groups (entry 9-12) provided lower yields that could be resulted in stereo hindrance.

Table 2. Preparation of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones derivatives catalyzed at reflux in water.

					M.p. (°C)	
Entry	Ar	Time (min)	Product	Yield[a] (%)	Found	Reported
1	C_6H_5	20	3a	90	193-196	192-194 [14]
2	3-NO_2- C_6H_4	13	3b	92	193-196	201-203 [21]
3	4-NO_2- C_6H_4	13	3c	93	190-193	188-190 [14]
5	4-MeO-C_6H_4	130	3d	94	140-143	146-148 [14]
6	2,4-$(MeO)_2$-C_6H_3	45	3e	94	187-189	178-180 [18]
7	3,4,5-$(MeO)_3$-C_6H_2	26	3f	96	197-198	203-205 [18]
8	4-$N(Me)_2$-C_6H_4	510	3j	85	190-198	186-188 [14]
9	4-Cl-C_6H_4	25	3h	70	143-146	140-142 [14]
10	2-Cl-C_6H_4	120	3i	95	205-207	200-202 [18]
11	3-Br-C_6H_4	213	3j	79	196-198	203-204 [20]
12	2-Br-C_6H_4	240	3k	83	199-200	194-195 [19]
13	2-OH-C_6H_4	15	3l	94	200-204	205-206 [20]
14	4-OH-C_6H_4	90	3m	94	195-196	188-190 [20]
15	5-OH,2-Br-C_6H_3	6	3n	90	246-249	-----

[a]) Isolated yield.

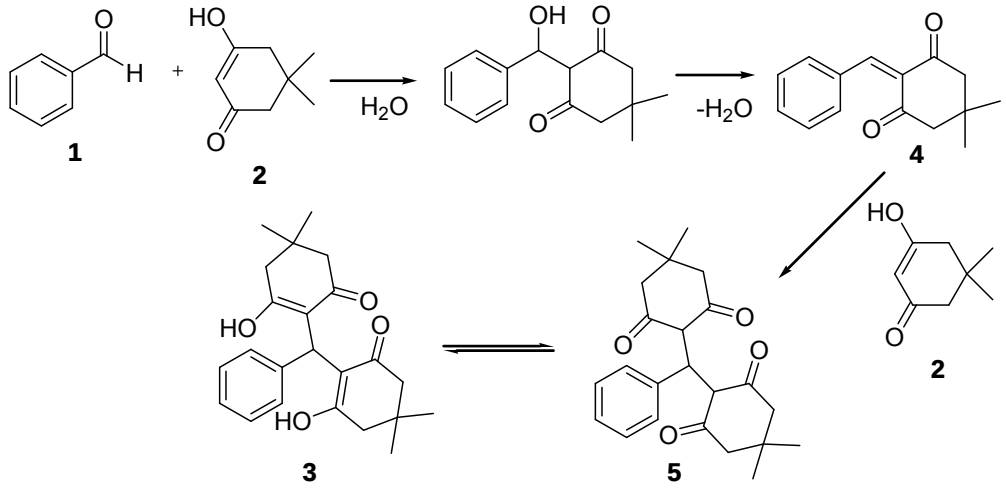
IR spectrum of compound **3n** as a new compound had an absorption band corresponding to OH bond (3441 cm^{-1}) as well as bands characteristic of carbonyl functions (1622 cm^{-1}). The ^1H NMR spectrum of **3n** exhibited five single sharp lines readily recognized as arising from four methyl groups (δ = 0.89, 0.90, 0.97, 1.05 ppm) and CH proton (δ = 5.03 ppm). It also showed multiple signals (δ = 2.02-2.57 ppm) for the methylene protons and broad singlet signal at δ = 10.57 ppm for the OH moiety. Partial assignments of these resonances are given in the experimental section.

To show the efficiency of the selected method, table 3 compares the results obtained in the present study with some of those reported in the literature.

Table 3. Comparison of our results with some of those reported in the literature for the reaction of 3-nitrobenzaldehyde and 5, 5-dimethylcyclohexane-1,3-dione.

Entry	Reaction condition	Yield (%)	Time	Ref.
1	Benzyltriethylammoniumchloride, Water, r.t.	97	25 min	[18]
2	$SmCl_3$, water, r.t	91	30 min	[21]
3	Solid-State, grinding, r.t	89	48 h	[20]
4	PVP-stabilized Ni nanoparticles, E.G., r.t.	90	10 mim	[19]
5	EDDA, THF, reflux	92	4h	[17]
6	$HClO_4$–SiO_2, water, reflux	68	1h	[14]
7	Neutral alumina, MW 150 W, 65 ^oC,	94	5-10 min	[23]
8	KF/Al_2O_3, grinding, r.t.	91	14-20 h	[24]
9	no catalyst, water, reflux	95	13 min	this work

In comparison with other works cyclized to xanthene derivatives, it seems that water as solvent prohibits the dehydration step. According to the commonly accepted xanthenes proposed mechanism, the formation of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] **3** could be rationalized by the initial condensation of arylaldehyde with dimedone followed by the Micheal addition of the second dimedone to produce tetraketone **5** that tautomer to **3** (Scheme 2).



Scheme 2. Plausible mechanism for the synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)].

Conclusion

In conclusion, a new and facile method was developed for the synthesis of arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones), which started from dimedone and aryl aldehydes in the green media. The key strategies of these reactions were one-pot domino Knoevenagel/ Michael reaction without cyclization.

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