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Synthesis of Tetraketones from 5,5-Dimethylcyclohexane-1,3-Dione And Arylaldehydes in Aqueous Medium in Presence of Alanine

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ABSTRACT

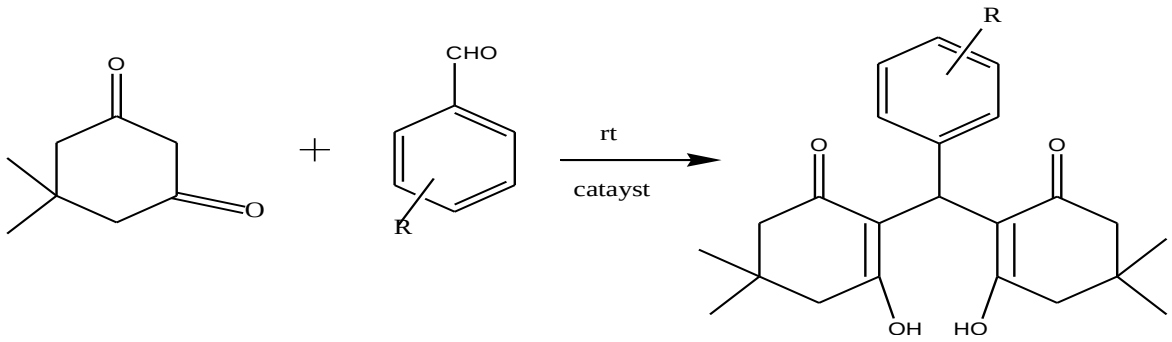
A simple and ecofriendly method has been developed for the synthesis of tetraketones from 5,5-Dimethylcyclohexane-1,3-dione and aromatic aldehydes using alanine as a catalyst in an aqueous medium at room temperature in good to excellent yields.

Keywords: 5,5-dimethylcyclohexane-1,3-dione,Arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclo hexane -1-ones)], alanine.

INTRODUCTION

There is a great demand these days on carrying out organic synthesis under environmentally benign reaction conditions and that is why great emphasis is being laid on doing away, whenever possible, with the use of volatile and toxic organic solvents[1-3]. The use of environmentally benign solvents represents a very useful and powerful green chemistry technological procedure. In fact, it would be much better, if feasible, to switch from organic solvents to water as a reaction medium in organic reactions[4-7]. The choice of aqueous medium for carrying out organic reactions assumes great significance as water is a non-flammable, inexpensive and readily available green solvent. Further, the use of aqueous medium is advantageous in organic reactions due to its high polarity and the consequent immiscibility with organic solvents. Very few Knovenagel condensations using water have been reported[8,9]. However, most of them involve harsh reaction conditions, high temperature, long reaction times tedious work ups, use of harmful organic solvents.

Tetraketones are important structural precursors for synthesis of many natural products and organic compounds such as acridiediones, xanthenedione and thiaxanthenes derivatives which are reported to show antioxidant properties, lipoxygenase inhibition activity and also act as potential remedial source for inflammation and asthma[10]. Many of the reported methods for the formation of tetraketones have employed various catalysts such as $In(OTf)_3$, $Yb(OTf)_3$-SiO_2, L-hystidine in ionic liquid[10] etc. Many of these involve traditional thermal heating or microwave irradiation andbut they suffer from many limitations. To overcome these disadvatages, we report herein a very simple, economic and green method for synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] tetraketones in an aqueous medium at room temperature using alanine as catalyst.



Scheme 1

MATERIALS AND METHODS

The melting points were measured on a perfit melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer in $CDCl_3$ as solvent and with TMS as internal standard. Chemicals were purchased from CDH and Fluka. . Confirmation of product was done by comparing with authentic samples.

General procedure for synthesis of 2, 2'-(arylmethylene)bis(3- hydroxy- 5,5- dimethyl-2-cyclohexene-1-one) : Mixture of 5,5-Dimethylcyclohexane-1,3-dione (2mmol), p-chloro benzal dehyde (1 mmol) and alanine(90 mg) in water (5 mL) was taken in a 10 mL Borosil beaker and stirred on a magnetic stirrer for 45 min. The reaction was monitored with the help of TLC. The white color product was isolated by filtration, washed with water and dried. The product was pure enough and recrystallized with pure ethanol and obtained in 92% yield.

Spectroscopic data of the products

2,2'-(4-chlorophenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3a) : M.P: 139-141 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 6H, 2 x CH_3), 1.58 (s, 6H, 2 x CH_3), 2.30–2.50 (m, 8H, 4 x CH_2), 5.48 (s, 1H, CH), 7.00 (d, *J* = 8.4 Hz, 2H, Ar), 7.20 (d, *J* = 8.4 Hz, 2H, Ar), 11.90 (s, 1H, OH).

2,2'-(2,4-dichlorophenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3b) : M.P: 169-171 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 6H, 2 x CH_3), 1.70 (s, 6H, 2 x CH_3), 2.02–2.31 (m, 8H, 4 x CH_2), 5.65 (s, 1H, CH), 4.33 (s, 1H, Ar), 6.61 (d, *J* = 8.4 Hz, 2H, Ar), 7.09 (d, *J* = 8.4 Hz, 2H, Ar), 11.80 (s, 1H, OH).

2,2'-(4-methylphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3c): M.P: 128-130 ^{0}C.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, 2 x CH_3), 1.25 (s, 6H, 2 x CH_3), 2.29 (s, 3H, CH_3), 2.32–2.47 (m, 8H, 4 x CH_2), 5.49 (s, 1H, CH), 6.98 (d, *J* = 8.0 Hz, 2H, Ar), 7.26 (d, *J* = 8.0 Hz, 2H, Ar), 11.91 (s, 1H, OH).

2,2'-(4-methoxyphenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3d): M.P: 146-148 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, 2 x CH_3), 1.22 (s, 6H, 2 x CH_3), 2.28–2.47 (m, 8H, 4 x CH_2), 3.77 (s, 3H, OCH_3), 5.48 (s, 1H, CH), 6.82 (d, *J* = 8.8 Hz, 2H, Ar), 6.79 (d, *J* = 8.0 Hz, 2H, Ar), 11.55, 11.92 (s, 1H, OH).

2,2'-(4-bromophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3e): M.P: 161-163 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, 2 x CH_3), 1.21 (s, 6H, 2 x CH_3), 2.28–2.48 (m, 8H, 4 x CH_2), 5.44 (s, 1H, CH), 6.38 (d, *J* = 10.4 Hz, 2H, Ar), 7.94 (d, *J* = 8.8 Hz, 2H, Ar), 11.88 (s, 1H, OH).

2,2'-(4-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3f): M.P: 177-179 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2 x CH_3), 1.23 (s, 6H, 2 x CH_3), 2.31–2.51 (m, 8H, 4 x CH_2), 5.54 (s, 1H, CH), 7.24-8.41 (m, 4H, Ar), 11.81 (s, 1H, OH).White solid; M.P.177-179, IR(KBr):2969,2958,1594,1513,1468,1451,1375,1345,1252,1154,1044 and 852 cm^{-1}.

2,2'-(3-nitrophenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3g): M.P: 183-185 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 6H, 2 x CH_3), 1.20 (s, 6H, 2 x CH_3), 2.24–2.45 (m, 8H, 4 x CH_2), 5.47 (s, 1H, CH), 7.32–7.98 (m, 4H, Ar), 11.79 (s, 1H, OH).

2,2'-(2-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3h): M.P: 189-191 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 6H, 2 x CH_3), 1.15 (s, 6H, 2 x CH_3), 2.17–2.47 (m, 8H, 4 x CH_2), 6.03 (s, 1H, CH), 7.23–7.55 (m, 4H, Ar), 11.58 (s, 1H, OH).

2,2'-(4-hydroxy-3-methoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3i): M.P: 193-195 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 6H, 2 x CH_3), 1.16 (s, 6H, 2 x CH_3), 2.22–2.39 (m, 8H, 4 x CH_2), 3.69 (s, 3H, OCH_3), 5.42 (s, 1H, CH), 6.49–6.74 (m, 3H, Ar), 11.90 (s, 1H, OH).

2,2'-(2-hydroxyphenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3j): M.P: 187-189 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 6H, 2 x CH_3), 2.01 (s, 6H, 2 x CH_3), 2.28–2.61 (m, 8H, 4 x CH_2), 4.67 (s, 1H, CH), 7.17 (d, *J* = 8 Hz, 2H, Ar), 6.84 (d, *J* = 8.4 Hz, 2H, Ar), 10.48 (s, 1H, OH).

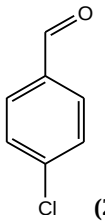
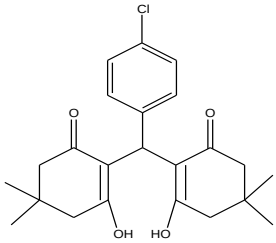
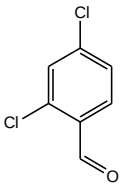
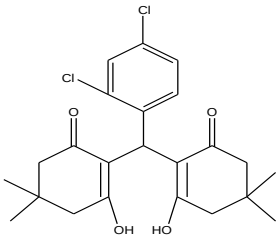
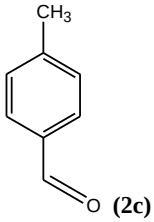
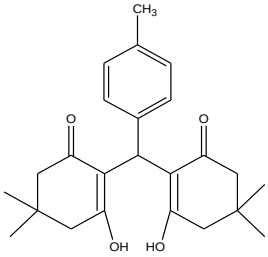
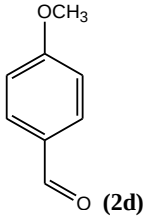
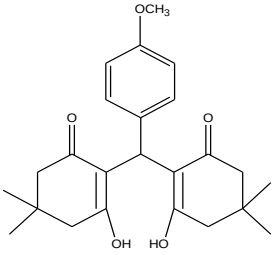
2,2'-(3,4-dimethoxyphenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (3k): M.P:178-180 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 12H, 4 x CH_3), 2.55 (s, 8H, 4 x CH_2), 3.64-3.87 (6H, 2 x OCH_3), 5.70 (s, 1H, CH), 6.69–7.51 (m, 3H, Ar), 9.81.

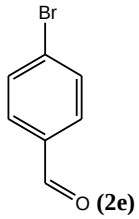
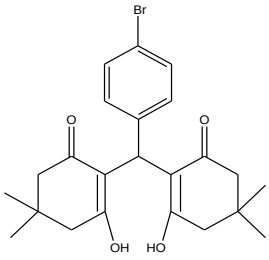
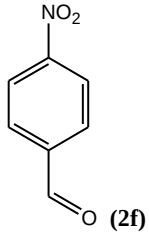
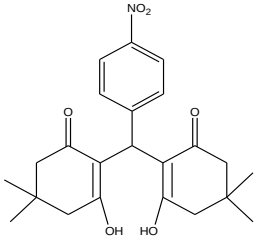
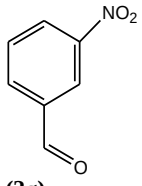
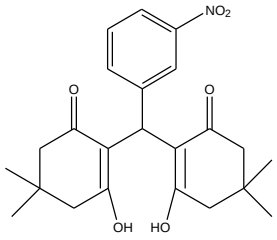
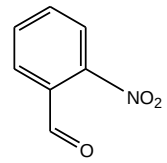
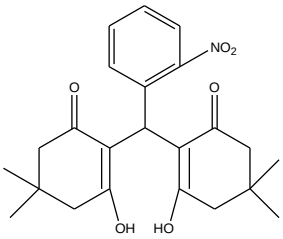
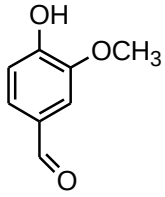
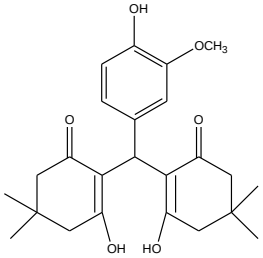
RESULTS AND DISCUSSION

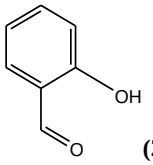
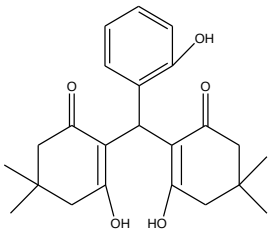
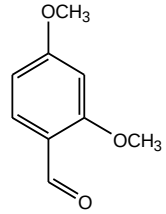
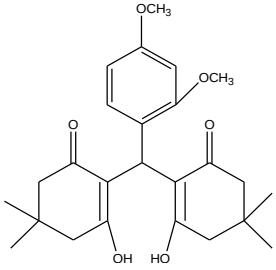
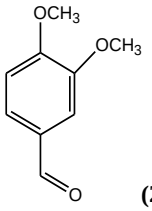
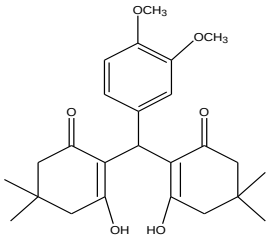
The present study started with the reaction between 5,5-dimethyl cyclohexane-1,3-dione and p-chloro-benzaldehyde (molar ratio 2:1). Mixture of the reactants with alanine as a catalyst in aqueous medium was stirred on a magnetic stirrer at room temperature, and progress of the reaction monitored with the help of TLC. The target compound (3a) was obtained in 92 % yield after 25 min.

Replacing p-chloro-benzaldehyde (2a) with a variety of other aromatic aldehydes containing electron-donating and electron attracting groups, viz., 2,4-dichlorobenzaldehyde (2b), 4-methylbenzaldehyde (2c), 4-methoxybenzaldehyde (2d), 4-bromobenzaldehyde (2e), 3-nitrobenzaldehyde (2f), 4-nitrobenzaldehyde (2g), 2-nitrobenzaldehyde (2h), vanillin (2i), salicyaldehyde (2j), 2,4-dimethoxybenzaldehyde (2k), 3,4-dimethoxybenzaldehyde (2l), gave corresponding products as shown in Table 1. As can be noticed from (Table-1) the products (**3a-l**) were obtained in good yield regardless of various electron donating and releasing groups present in the aromatic aldehyde.

Table 1: Synthesis of arylmethylene[bis(3-hydroxy-2-cyclohexene-1-ones)] via condensation of 5,5-Dimethylcyclohexane-1,3-dione and arylaldehydes in presence of alanine.

Entry	RCHO (2)	Product (3)	Time (min)	Yield (%)
1	 **(2a)**	 **(3a)**	45	86
2	 **(2b)**	 **(3b)**	40	91
3	 **(2c)**	 **(3c)**	80	80
4	 **(2d)**	 **(3d)**	65	81

5	 **(2e)**	 **(3e)**	30	82
6	 **(2f)**	 **(3f)**	30	87
7	 **(2g)**	 **(3g)**	45	84
8	 **(2h)**	 **(3h)**	50	80
9	 **(2i)**	 **(3i)**	35	96

10	 **(2j)**	 **(3j)**	90	85
11	 **(2k)**	 **(3k)**	45	92
12	 **(2l)**	 **(3l)**	50	86

APPLICATIONS

The compounds synthesized are important structural precursors for synthesis of many natural products and organic compounds such as acridiediones, xanthenedione and thiaxanthenes derivatives which are reported to show antioxidant properties, lipoxygenase inhibition activity and also act as potential remedial source for inflammation and asthma[10] .

CONCLUSIONS

A simple and ecofriendly method has been developed for the synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)], from 5,5-Dimethylcyclohexane-1,3-dione and aromatic aldehydes using alanine as a catalyst in an aqueous medium at room temperature.

ACKNOWLEDGEMENT

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