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Synthesis of tetraketones from 5,5-dimethylcyclohexane-1,3-dione and arylaldehydes in water in presence of sodium bicarbonate, sodium sulfate, magnesium sulfate, sodium chloride, sodium lauryl sulfate, barium chloride, polyethyleneglycol and alumina in excellent yields with and without the assistance of microwaves

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ABSTRACT

Very simple and ecofriendly methods have been developed for the synthesis of the tetraketones from 5,5-Dimethylcyclohexane-1,3-dione and aromatic aldehydes using a variety of catalyst which included sodium bicarbonate, sodium sulfate, magnesium sulfate, sodium chloride, sodium lauryl sulfate, barium chloride, polyethyleneglycol and alumina in an aqueous medium at room temperature in good to excellent yields with and without the assistance of microwaves.

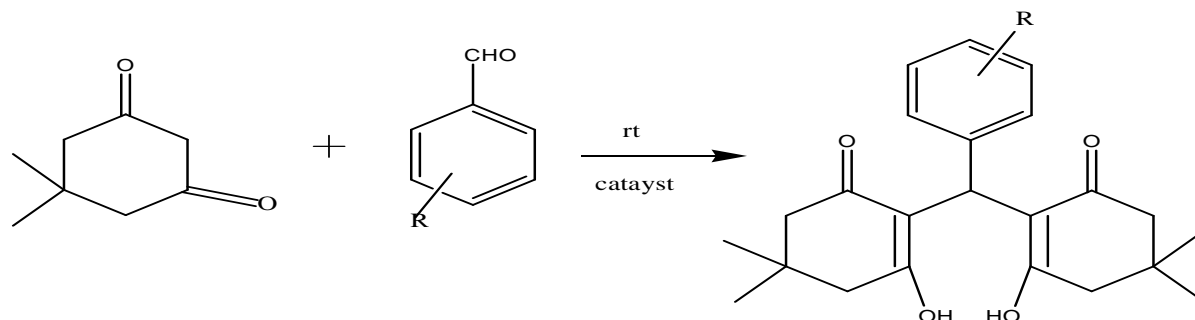
Keywords 5,5-dimethylcyclohexane-1,3-dione, Arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)], sodium bicarbonate, sodium sulfate, magnesium sulfate, sodium chloride, sodium lauryl sulfate, barium chloride, polyethyleneglycol and alumina.

INTRODUCTION

Now a days there is a great emphasis upon carrying out organic synthesis under environmentally benign reaction conditions such as doing away with the use of volatile and toxic organic solvents and instead carrying out these reactions in aqueous medium, employing catalysts if possible etc.[1-3] Albeit the use of environmentally benign solvents represents a very useful and powerful green chemistry technological procedure, 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, biocompatible 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 Knoevenagel condensations using water have been reported[8-9]. However, most of them involve harsh reaction conditions, high temperature, long reaction times, tedious work ups, and use of harmful organic solvents.

The 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 $\text{In}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3\text{-SiO}_2$, L-hystidine in ionic liquid¹⁰ etc. Many of these involve traditional thermal heating or microwave irradiation but they suffer from many limitations. To overcome these disadvantages, we report herein very simple, economic and green methods for synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexene-1-ones)] tetraketones in an aqueous medium at room temperature using sodium bicarbonate, sodium sulfate, magnesium sulfate, sodium chloride, sodium lauryl sulfate, barium chloride, polyethyleneglycol and alumina combination.



SCHEME 1

MATERIALS AND METHODS

The melting points were measured on a perfit melting point apparatus and are uncorrected. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ 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 products was done by direct comparison of the spectroscopic and physical data with those of the authentic samples.

General procedure for synthesis of 2, 2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)

5,5-Dimethylcyclohexane-1,3-dione (2mmol), p-chlorobenzaldehyde (1 mmol) and a catalyst in water was taken in a 10 mL borosil beaker and stirred on a magnetic stirrer till the reaction was complete as monitored with the help of TLC. The white colored product was isolated by filtration, washed with water and dried. The product obtained recrystallised from pure ethanol.

Spectroscopic data of the products

1. 2,2'-(4-chlorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3a) :

Mp: 139-141 °C. $^1\text{H NMR}$ (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'-(2,4-dichlorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3b) :

Mp: 169-171 °C. $^1\text{H NMR}$ (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).

3. 2,2'-(4-methylphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3c):

Mp: 128-130 °C. $^1\text{H NMR}$ (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).

4. 2,2'-(4-methoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3d)

Mp: 146-148 °C. $^1\text{H NMR}$ (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).

5. 2,2'-(4-bromophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3e):

Mp: 161-163 °C. $^1\text{H NMR}$ (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).

6. 2,2'-(4-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3f):

Mp: 177-179 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.11 (s, 6H, 2 x CH₃), 1.23 (s, 6H, 2 x CH₃), 2.31–2.51 (m, 8H, 4 x CH₂), 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.

7. 2,2'-(3-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3g): Mp: 183-185 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.05 (s, 6H, 2 x CH₃), 1.20 (s, 6H, 2 x CH₃), 2.24–2.45 (m, 8H, 4 x CH₂), 5.47 (s, 1H, CH), 7.32–7.98 (m, 4H, Ar), 11.79 (s, 1H, OH).

8. 2,2'-(2-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3h): Mp: 189-191 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.01 (s, 6H, 2 x CH₃), 1.15 (s, 6H, 2 x CH₃), 2.17–2.47 (m, 8H, 4 x CH₂), 6.03 (s, 1H, CH), 7.23–7.55 (m, 4H, Ar), 11.58 (s, 1H, OH).

9. 2,2'-(4-hydroxy-3-methoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3i):

Mp: 193-195 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.03 (s, 6H, 2 x CH₃), 1.16 (s, 6H, 2 x CH₃), 2.22–2.39 (m, 8H, 4 x CH₂), 3.69 (s, 3H, OCH₃), 5.42 (s, 1H, CH), 6.49–6.74 (m, 3H, Ar), 11.90 (s, 1H, OH).

10. 2,2'-(2-hydroxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3j)

Mp: 187-189 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.91 (s, 6H, 2 x CH₃), 2.01 (s, 6H, 2 x CH₃), 2.28–2.61 (m, 8H, 4 x CH₂), 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).

11. 2,2'-(3,4-dimethoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3k):

Mp:178-180 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.22 (s, 12H, 4 x CH₃), 2.55 (s, 8H, 4 x CH₂), 3.64-3.87 (6H, 2 x OCH₃), 5.70 (s, 1H, CH), 6.69–7.51 (m, 3H, Ar), 9.81

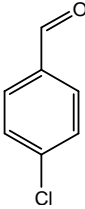
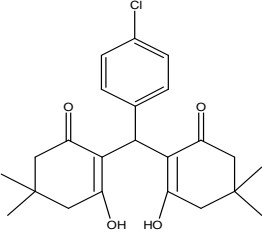
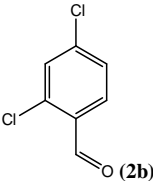
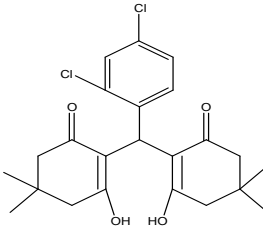
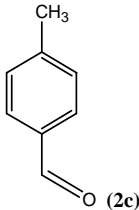
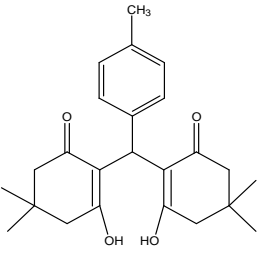
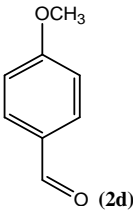
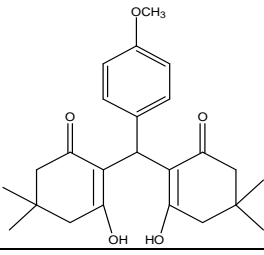
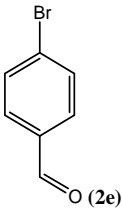
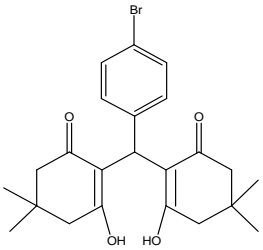
RESULTS AND DISCUSSION

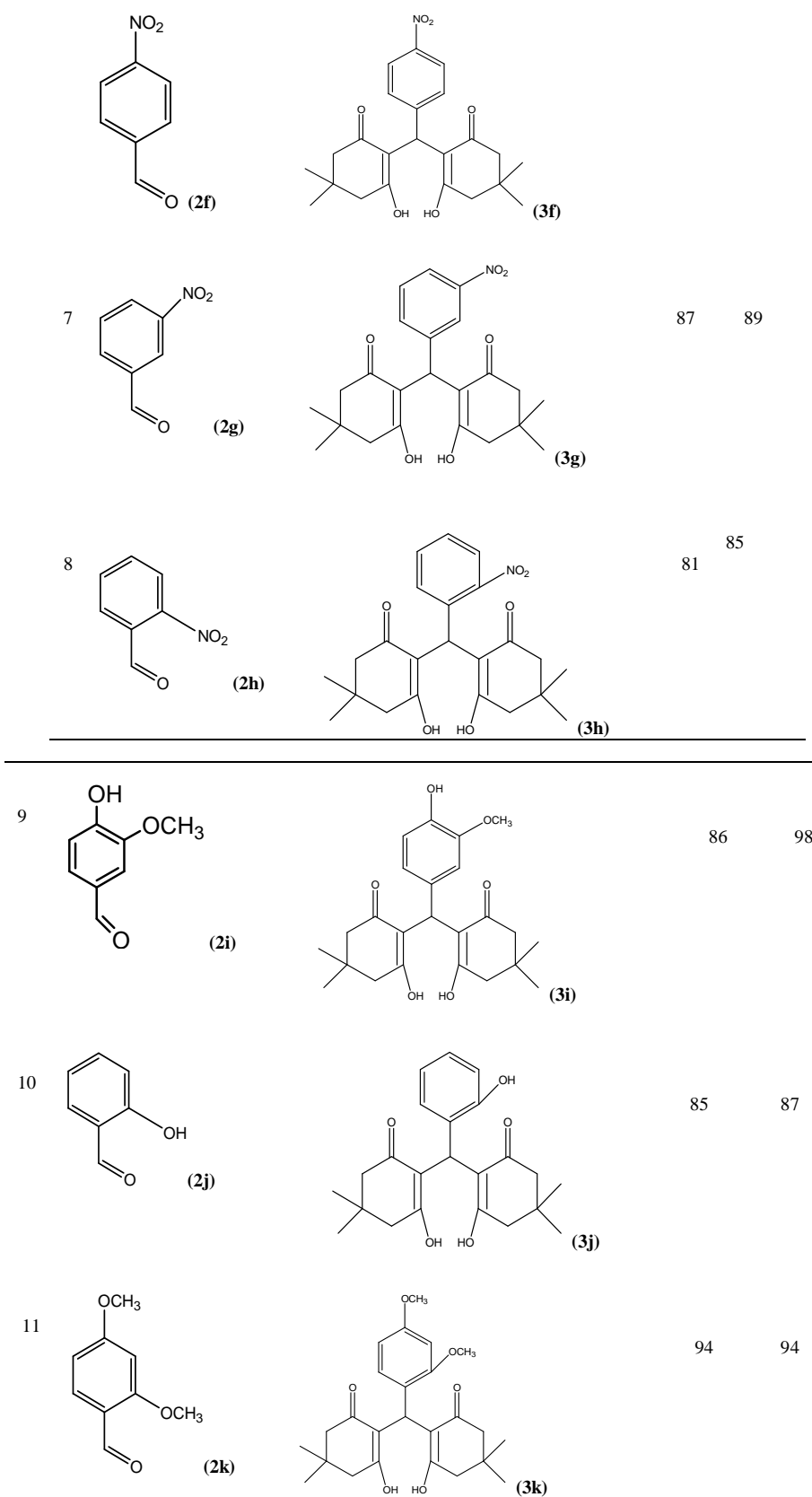
First of all, the reaction between 5,5-dimethyl cyclohexane-1,3-dione and p-chloro-benzaldehyde (molar ratio 2:1) was investigated. A mixture of the reactants with a catalyst in aqueous medium was stirred on a magnetic stirrer at room temperature or irradiated by microwaves in a microwave reactor, and progress of the reaction monitored by TLC giving the target compound (3a).

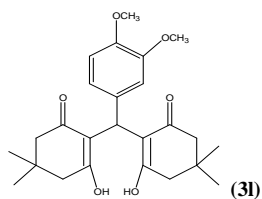
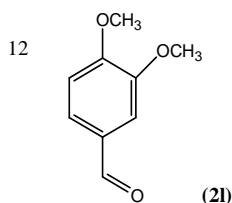
Replacing p-chloro-benzaldehyde (2a) with a variety of other aromatic aldehydes containing electron-donating and electron attracting groups, viz., 2,4-dichlorobenzaldehyde (2b), 4-methylbenzaldehyde (2c), 4-methoxybenzaldehyde (2d), 4-bromobenzaldehyde (2e), 3-nitrobenzaldehyde (2f), 4-nitrobenzaldehyde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

As can be seen from Table1, yields in the increasing order were sodium carbonate (58-75%) magnesium sulfate (61-90%), sodium chloride(64-90%), sodium lauryl sulfate (64-94%), barium chloride (68-95%) and sodium sulfate (71-96%) and (PEG+ basic alumina) (85-97%). Clearly, the latter two catalysts proved superior to the former five catalysts and (PEG+ basic alumina) proved to be the best catalyst followed by sodium sulfate although sodium sulfate catalyst appears to be the best one of all the catalysts used when we look at its price, procedural convenience and availability. We also found that the yields in the presence of TBAB (tetrabutyl ammonium bromide) were (71-95%), slightly lower than those with the (PEG+ basic alumina) combination but almost equivalent to those obtained with sodium sulfate catalyst. Further, the yields in the presence of either PEG or basic alumina alone were much lower compared to those obtained with the combination of these two catalysts. It needs to be noted that the yields under microwaves with all these catalysts were far lower than without the use of microwaves. It is also worth noting that the yields of various products were much lower without the presence of a catalyst both in the presence and absence of irradiation by microwaves.

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 sodium sulfate and (PEG+basic alumina) catalyst

Entry	RCHO (2)	Product (3)	Yield% Na ₂ SO ₄	Yield (%)
1	 (2a)	 (3a)	78	79
2	 (2b)	 (3b)	82	92
3	 (2c)	 (3c)	76	85
4	 (2d)	 (3d)	85	87
5	 (2e)	 (3e)	94	95
6			89	93





94

97

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]

CONCLUSION

In conclusion, simple and ecofriendly methods have been developed for the synthesis of arylmethylene[bis(5,5-dimethyl-3-hydroxy-2-cyclohexen-1-one)], from 5,5-dimethylcyclohexane-1,3-dione and aromatic aldehydes using sodium sulfate, magnesium sulfate, sodium lauryl sulfate and sodium chloride catalysts in an aqueous medium at room temperature in excellent yields in the absence than in the presence of microwaves.

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