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Synthesis of 2-(benzylidene)—5,5-dimethylcyclohexane-1,3-diones and 2-(benzylidene)-malononitriles by condensation of dimedone and malanonitrile with arylaldehydes in the presence of lithium chloride, sodium acetate, magnesium sulfate, barium chloride, zinc acetate, sodium chloride, alanine, sodium sulfate, (sodium sulfate+alanine) catalysts in high yields at room temperature in aqueous medium

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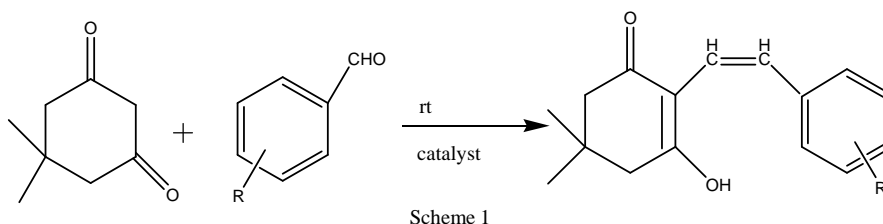
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ABSTRACT

Dimedone was condensed with arylaldehydes in 1:1 ratio to give 2-(benzylidene)—5,5-dimethylcyclohexane-1,3-diones in excellent yields in the presence of a number of catalysts in aqueous medium. The catalysts included lithium chloride, sodium acetate, magnesium sulfate, barium chloride, zinc acetate, sodium chloride, alanine, sodium sulfate, (sodium sulfate+alanine). Malononitrile was condensed with arylaldehydes in 1:1 ratio to give 2-(benzylidene)-malononitriles to give high yields in the presence of TBAB and sodium sulfate.

INTRODUCTION

Reaction of dimedone or malanonitrile and aromatic aldehydes via Knoevenagel condensation is a reaction of great significance. The product formed is a kind of Michael acceptor which has been used as a precursor or intermediate in the preparation of various heterocyclic compounds in particular, in organic synthesis, in general and has often been utilised remarkably in medicinal chemistry. Condensation of acidic methylene compound dimedone with arylaldehydes in 1:1 ratio gives 2-(benzylidene)—5,5-dimethylcyclohexane-1,3-diones (scheme 1) that act as important intermediates for the synthesis of various heterocyclic compounds like new potent antibacterials, fused isooxazole and pyrazole derivatives.¹ Similarly, the condensation of malanonitrile with arylaldehydes is also a reaction of synthetic importance. The existing methods for their synthesis of 2-(benzylidene)—5,5-dimethylcyclohexane-1,3-diones and 2-(benzylidene)-malononitriles suffer from drawbacks such as the use of toxic, expensive organic solvents. So, we became interested in developing simple, environmentally friendly methods by using various catalytic systems in aqueous medium.



MATERIALS AND METHODS

The melting points were measured on a perfit melting point apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer in CDCl₃ 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. Typical procedure for product formation is as follows.

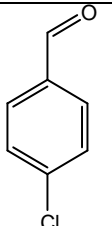
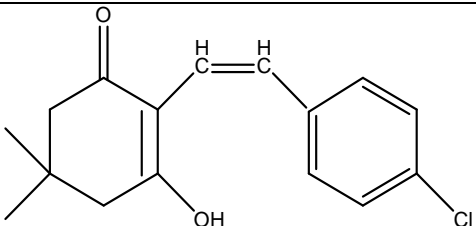
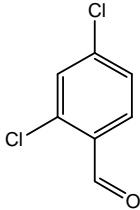
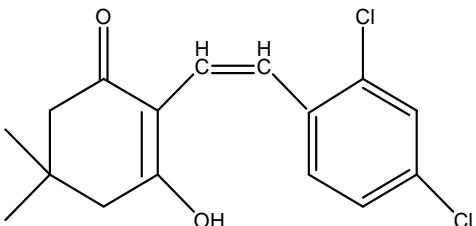
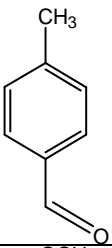
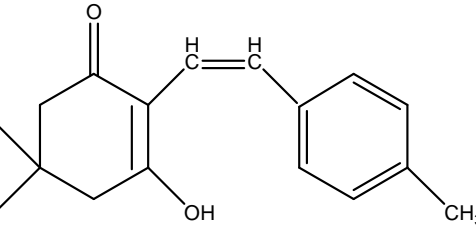
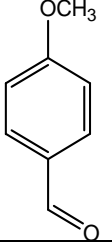
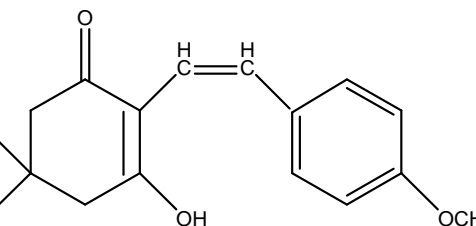
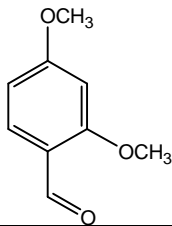
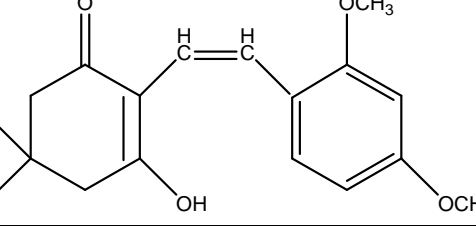
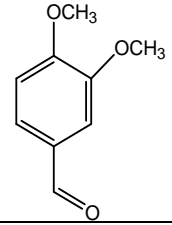
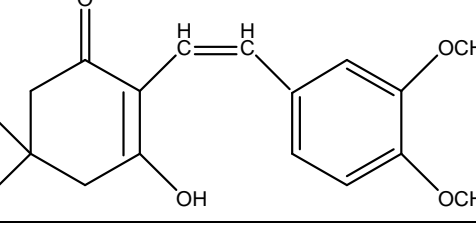
Dimedone and para chlorobenzaldehyde (1:1) were reacted in presence of an optimum amount of catalyst and aqueous conditions and then stirred on a magnetic stirrer at room temperature. Appearance of white color product occurred within a few minutes. The product, 2-(4-chlorobenzylidene)-5,5-dimethyl-cyclohexane-1,3-dione was filtered off and washed with water and recrystallized from ethanol and water.

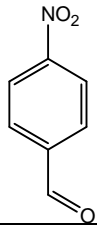
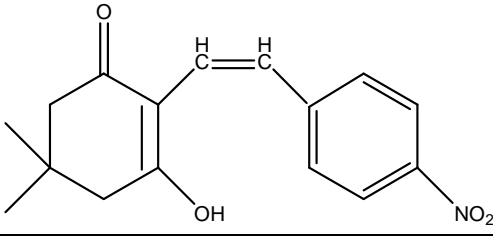
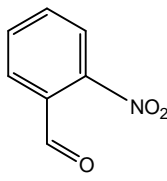
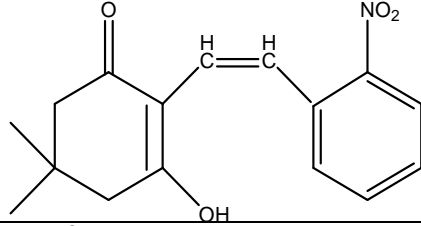
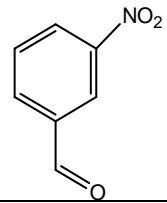
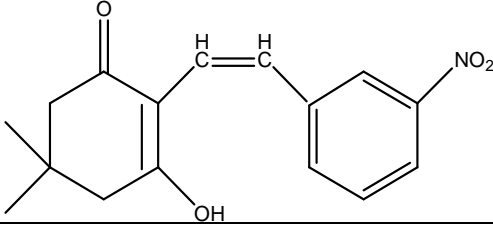
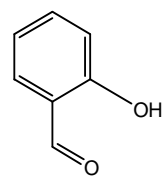
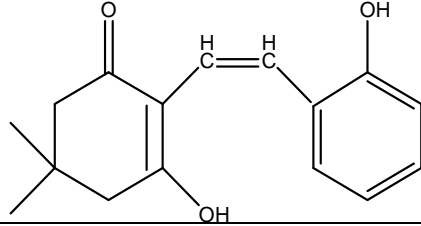
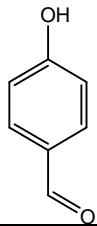
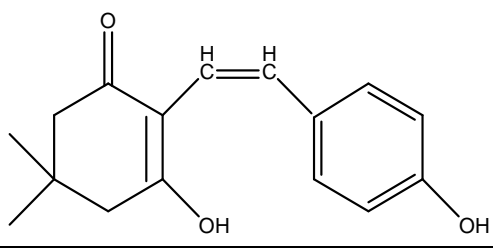
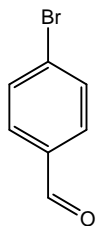
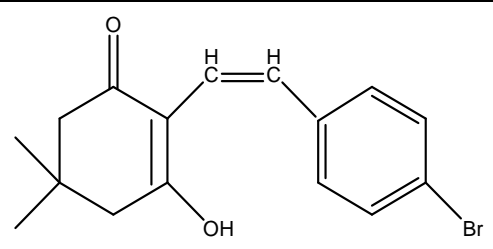
RESULTS AND DISCUSSION

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 and using 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. We have carried out the reactions in water at room temperature by simple stirring procedure in the presence of a number of catalysts.

The percentage yields obtained in the increasing order with various catalysts used were: lithium chloride (58-67), sodium acetate (62-71), magnesium sulfate (62-79), barium chloride (67-75), zinc acetate (69-81), sodium chloride (69-84), alanine (73-84), sodium sulfate (74-86) (see Table 1), (sodium sulfate +alanine) (81-94). It needs to be noted that the yields in the absence of a catalyst were much lower than those obtained with a catalyst. From these results it can be concluded that while sodium sulfate has proved to be the best among the single catalysts used, alanine gave almost identical results to sodium sulfate, of course, the mixture of sodium sulfate and alanine gave better yields with either sodium sulfate or with alanine alone. Although it is difficult to interpret all these results in the absence of additional analyses from the point of view of mechanistic aspects, some conclusions can be drawn from these results. The combination of alanine and sodium sulfate as anticipated proved to be better owing to alanine being organic and soluble in the aqueous medium thereby enhancing the homogeneity of the reaction mixture in aqueous medium and sodium sulfate providing the required anion- sulfate ions for proton abstraction. Zinc acetate and barium chloride gave slightly lower yields than the best three catalysts discovered (sodium chloride, alanine and sodium sulfate) but gave almost similar results when compared to each other. Among the three chlorides used- lithium chloride, sodium chloride and barium chloride, the highest yields were obtained as anticipated with sodium chloride followed by barium chloride followed by lithium chloride. That is possibly because sodium chloride is more ionic, giving off maximum chloride anions compared to barium chloride which is more ionic than lithium chloride in the water medium for abstraction of protons from dimedone leading to the generation of the corresponding anion for the attack on the electrophilic carbonyl carbon of the carbonyl compound. Sodium sulfate gave better yields than sodium chloride, which is possibly because sulfate anions are more nucleophilic than chloride ions for abstraction of protons in these reactions. Sodium acetate as anticipated gave lower yields compared to sodium chloride, because the acetate anion is weakly nucleophilic than the chloride ions for generation of the corresponding anion. Between zinc acetate and sodium acetate, the former as expected gave lower yields due to being less ionic than the latter. It also needs to be noted that the yields under microwave irradiation were lower in the all the catalysts than in the absence of the catalysts used.

Table: Condensation between dimedone and arylaldehydes at room temperature in water in the presence of sodium sulfate

Entry	R	Product	Time, min	Yield%
1			30	76
2			35	79
3			45	74
4			40	81
5			35	86
6			37	84

7			40	84
8			45	80
9			45	81
10			35	75
11			35	76
12			35	84

The condensation between malononitrile with arylaldehydes in 1:1 ratio in aqueous medium was also investigated at room temperature. Two catalysts were used in these reactions-tetrabutyl ammonium bromide (TBAB) and sodium sulfate. While the products were obtained in 35-40% yield in the absence of a catalyst, they were obtained in 62-78% yield with TBAB and in a slightly higher yield (70-86%) in the presence of sodium sulfate.

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