



**Subject: Submission of MS entitled “Synthesis of  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones using CuO nanoparticles as a recyclable and heterogeneous nanocatalyst under solvent-free conditions”**

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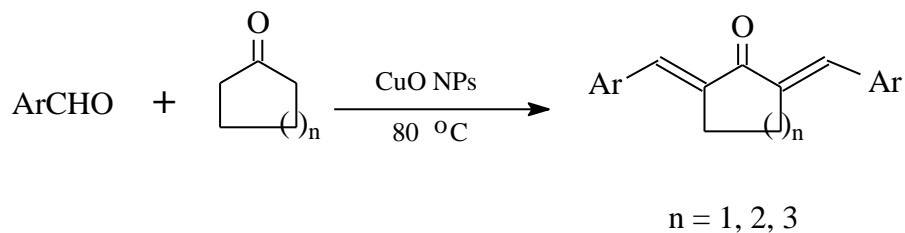
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**Important features of the present protocol**

- 1) It is the fastest method as compared to literature reported methods.
- 2) The electron donating as well as withdrawing aryl aldehydes were successfully transformed into corresponding  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones.
- 3) Simple work up procedure, inexpensive and easily available catalyst makes the protocol economically attractive and nice for industrial large scale production.
- 4) Green synthesis of CuO NPs using Rosa caninafruit extract as a reducing and stabilizing agent.
- 5) This is a truly catalytic with least loading (0.005 g) of the catalyst under solvent free conditions.
- 6) This methodology is general as variety of aldehydes and ketones furnish corresponding  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones in excellent yields.
- 7) Short reaction time, recyclability and reusability of the catalyst are the noteworthy and attractive features of the present protocol.

## Graphical Abstract

Highly efficient and green procedure is described for the synthesis of  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones with excellent yields by the reaction of cycloalkanones with aromatic aldehydes using catalytic amount of nanoparticles (NPs) of copper oxide (CuO) as catalyst where it was prepared in a biological process using *Rosa canina* fruit's aqueous extract. The nanocatalyst was reusable and retrievable several times without considerable decrease in catalytic efficiency.



**Scheme 1.** Synthesis of  $\alpha,\alpha'$ -Bis-(substituted-benzylidene) cycloalkanones using CuO nanoparticles under solvent-free conditions

## Synthesis of $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones using CuO nanoparticles as a recyclable and heterogeneous nanocatalyst under solvent-free conditions

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**Abstract :-** Highly efficient and green procedure is described for the synthesis of  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones with excellent yields by the reaction of cycloalkanones with aromatic aldehydes using catalytic amount of nanoparticles (NPs) of copper oxide (CuO) as catalyst where it was prepared in a biological process using *Rosa canina* fruit's aqueous extract. The nanocatalyst was reusable and retrievable several (5) times without considerable decrease in catalytic efficiency.

**Keywords :** Green Chemistry,  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones, Heterogeneous nanocatalyst, Copper oxide

### I. Introduction

The  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones are useful intermediates for the synthesis of bioactive pyrimidines,<sup>1</sup> agrochemicals, pharmaceuticals and perfumes<sup>2</sup> liquid crystalline polymers,<sup>3</sup> and bis-pyrrolidines.<sup>4,5</sup> Generally, benzylidenecycloalkanones are prepared by cross-aldol condensation of cycloalkanones with aldehydes in the presence of strong acids or bases. However, these protocols often suffer from reverse and side reactions and therefore give low yields of products.<sup>6</sup> Variety of catalytic procedures<sup>7</sup> using different complexes of metal (II) ions is reported to give low yields (38%) of enone products. In other cases, TMSCl/NaI,<sup>8</sup> LiOH,<sup>9</sup> I<sub>2</sub>,<sup>10</sup> KF-Al<sub>2</sub>O<sub>3</sub>,<sup>11</sup> BMPTO,<sup>12</sup> Mg(HSO<sub>4</sub>)<sub>2</sub>,<sup>13</sup> Cp<sub>2</sub>TiPh<sub>2</sub>,<sup>14</sup> polymer-supported sulphonic acid,<sup>15</sup> InCl<sub>3</sub>.4H<sub>2</sub>O,<sup>16</sup> FeCl<sub>3</sub>,<sup>17</sup> aqueous micellar media,<sup>18</sup> have also been used. However, in most cases the yields are good at high temperatures and some of the reagents require longer reaction times and complicated purification procedures. Use of Yb(OTf)<sub>3</sub>,<sup>19</sup> Cu(OTf)<sub>3</sub>,<sup>20</sup> RuCl<sub>3</sub>,<sup>21</sup> SmI<sub>3</sub>,<sup>22</sup> as catalysts has been reported with good yields. But all these procedures demand reactions to be carried out in sealed tubes at high temperatures. Therefore, there is still scope to develop a more efficient method for the preparation of these compounds.

As by convention, a great quantity of metal oxide and metal nanoparticles were regularly procured via a variety of chemical and physical procedures.<sup>23,24</sup> However, in a majority of instances, these procedures have proved to be toxic, expensive, with high pressure and energy needs, potentially unsafe and difficult removal. The biosynthetic practices applied in the metal nanoparticles preparation have revealed to be more useful over other synthetic approaches as they are cost effective and do not involve the application of toxic chemicals, high pressures, temperatures and energy.<sup>25-29</sup> Therefore, the demand for the clean nontoxic and green development methods to generate nanoparticles is extremely high. The application of plant extracts in different biosynthetic approaches has many advantages such as safe handling, simple accessibility, and a wide variety of metabolites.

The genus *Rosa* includes more than 100 species that are spread across Asia, Europe, the Middle East and North America.<sup>30</sup> The mature *Rosa canina* (dog rose) fruits (Fig. 1) includes different biologically dynamic compounds which include: organic acids, sugars, amino acids, flavonoids, tocopherol pectin, tannins, fatty acids, carotenoids ( $\beta$ -carotene and lycopene), vitamins (vitamin C in specific and a number of other vitamins: B<sub>1</sub>, B<sub>2</sub>, K, PP, D, E), macro- and microelements etc. It is found that these compounds have antimutagenic, antioxidant, and anticancer effects.<sup>31,32</sup>



(Fig. 1) *Rosa canina* (dog rose) fruits

Due to our enduring concerns for the heterogeneous catalysts<sup>33, 34</sup> and metal nanoparticles biosynthesis, we detail an eco-friendly and simplistic method for the dispersible CuO NPs biosynthesis via *Rosa canina* that does not apply any hazardous capping or reducing agents. The procedure was performed with mild reaction conditions and the suitable catalytic performance of the reactions between cycloalkanones with aromatic aldehydes was analyzed.

## II. Material And Methods

### A. General

All chemicals were purchased from Sigma-Aldrich and Merck Chemical Companies. All reactions were monitored by thin layer chromatography (TLC) using aluminum plates coated with silica gel (Merck) using 10% ethyl acetate and 90% hexane as eluent. The silica gel (230-400 mesh) for column chromatography was purchased from Spectrochem Pvt. Ltd., India. The products were characterized by comparison of their spectral and physical data with those of authentic samples. All authentic  $\alpha, \alpha'$ -bis-(substituted-benzylidene) cycloalkanones were prepared from the corresponding cyclohexanone and benzaldehyde according to the method described in Vogel.<sup>36</sup> IR spectra were recorded on Nicolet (impact 400D model) FTIR Spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300 MHz instrument using TMS as internal standard and DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub> as solvent. Mass spectra was obtained by using a GC-MS Hewlett Packard (EI, 20 eV) instrument. All yields refer to isolated ones.

### B. CuO NPs green synthesis using *Rosa canina* fruit extract<sup>37</sup>

After carefully cleaning and rinsing the fresh *Rosa canina* fruits with double-distilled water several times, to 100 mL of deionized water, 10 g of the fruits were added and in a water bath boiled for 15 minutes. This mixture was cooled off and filtered via Whatman filter paper No. 1 to achieve an aqueous extract, that was next stored at 4 °C in a refrigerator for later usage as a stabilizing and reducing agent. To provide the CuO NPs, a 10 mL extract quantity was added dropwise to 100 mL of 1 mM aqueous Cu(OAc)<sub>2</sub> solution, which was

subsequently refluxed at a temperature of 100 °C for one-hour duration. Over time the mixtures coloration slowly changed to a dark brown hue due to the heating process. This is due to the surface plasmon resonance excitation signaling the CuO NPs creation and antioxidant phenolics hydrogen donation behavior within the plant. The obtained precipitation was then washed three times with chloroform and ethanol, respectively, and air dried for 48 h at room temperature (Figure 2) .

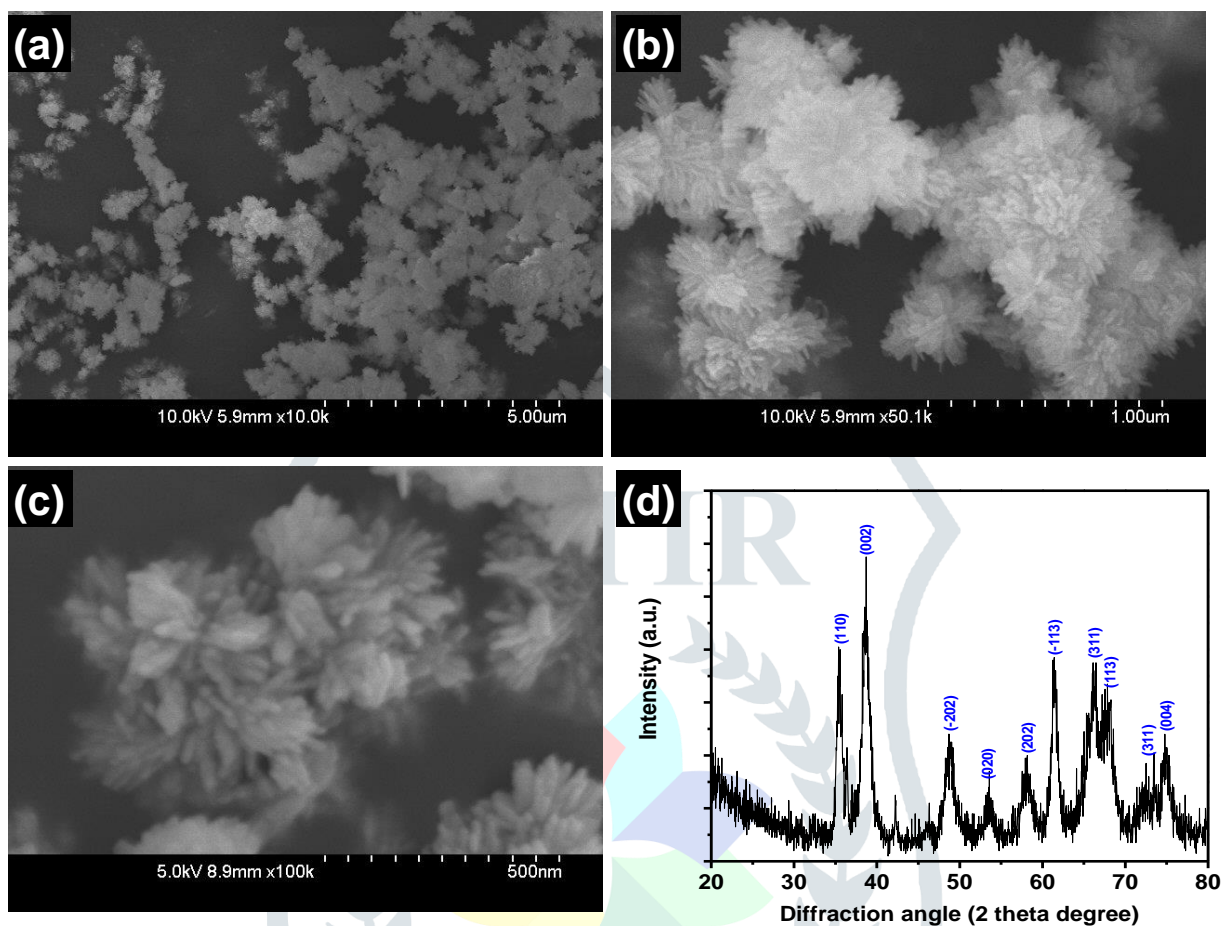


Figure 2: (a-c) FESEM images of as-synthesized CuO NPs at different magnifications; (d) corresponding XRD pattern.

### C. Typical experimental procedure

A mixture of cyclohexanone (5 mmol) and benzaldehyde (10 mmol) was stirred at 80 °C in the presence of a catalytic amount of CuO NPs (0.005 g) for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl acetate (10 mL) and the catalyst was allowed to settle down. The supernatant ethyl acetate was decanted off, washed with ethyl acetate (5 mL) and the combined ethyl acetate layer concentrated under reduced pressure to afford crude product, which was purified by recrystallization from ethanol to afford pure 2,6-dibenzylidenecyclohexanone (95%). The recovered catalyst, without activation, was reused for five more consecutive reactions of cyclohexanone (5 mmol) and benzaldehyde (10 mmol) affording 91, 89, 86, 84, 76 % yields, respectively, in 10, 15, 20, 25 and 26 min.

### D. Supporting information:

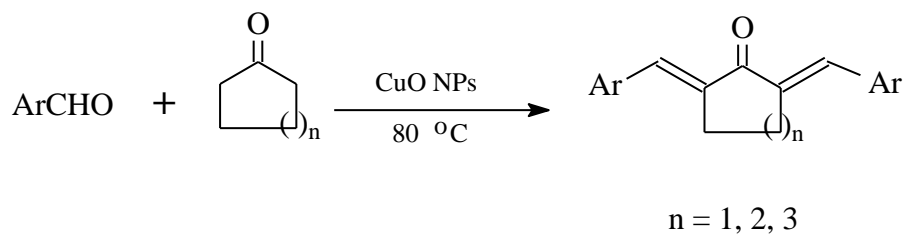
2, 6-dibenzylidenecyclohexanone (3l).

Mp 116 – 117 °C (Lit<sup>20</sup> Mp 117 – 118 °C); IR (KBr): 771, 1168, 1274, 1435, 1606, 1660, 3020, 3075 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 1.70 – 1.77 (m, 2H), 2.95 (t, *J* = 5.8 Hz 4H), 7.28 – 7.42 (m, 10H), 7.75 (s, 2H); ES-MS *E/Z* 274(M<sup>+</sup>).

## III. Results and discussion

As part of our program aiming at developing new, selective and environmental friendly methodologies for the preparation of fine chemicals employing CuO NPs as a catalyst, we wish to describe herein highly effective protocol for the synthesis of  $\alpha,\alpha$ -bis(substituted

benzylidene) cycloalkanones from the reaction of aldehydes with cycloalkanones under solvent-free conditions (**Scheme 1**).



**Scheme 1.** Synthesis of a,a'-bis-(substituted-benzylidene) cycloalkanones using CuO nanoparticles under solvent-free conditions

Initially a systematic study was carried out for catalytic evaluation of CuO NPs for the condensation of benzaldehyde (2 mmol) with cycloalkanones (1 mmol) under various conditions at 80 °C (**Table 1**). After many studies, we found that when less than 0.005 gram of CuO NPs was applied lower yields of the corresponding product (**Table 1, entries 2-5**) resulted, whereas use of more than 0.005 gram did not improve the yield (**Table 1, entries 7-8**). When attempts were made to carry out this reaction in the absence of CuO NPs, the substrate was recovered almost quantitatively (**Table 1, entry 1**).

**Table 1.** A catalytic study of CuO NPs during the reaction of benzaldehyde (2mmol) with cyclohexanone (1mmol) at 80 °C under solvent-free conditions.

Entry	CuO NPs gram	Time min/[h]	Yield (%)
1	0	[05]	
2	0.001	30	30
3	0.002	25	40
4	0.003	15	50
5	0.004	10	85
6	0.005	4	95
7	0.1	4	95
8	0.5	4	95

Next, we studied the effect of various solvents and the results of the reaction of benzaldehyde (2mmol) with cyclohexanone (1mmol) using 0.005 gram CuO NPs at 80 °C in the presence of various solvents are shown in **Table 2**.

When organic solvents such as nitromethane, tetrahydrofuran (THF), acetonitrile, dichloromethane (DCM), and chloroform was used for this reaction, the desired product was obtained in low yields (**Table 2, entries 2-6**). Whereas, an excellent yield of the desired product was obtained when the reaction was carried out at 80 °C under solvent-free conditions (**Table 2, entry 1**). These results led to the suggestion that solvent-free conditions are best suited for this reaction.

**Table 2 .** Investigation of various solvents

Entry	Solvent	Time min	Yield (%)
1	neat	4	95
2	MeNO <sub>2</sub>	120	40
3	THF	100	50
4	MeCN	90	56
5	DCM	90	45
6	CHCl <sub>3</sub>	90	41

To evaluate the scope and generality of the catalyst, the reactions of cyclopentanone, cyclohexanone and cycloheptanone with other aryl aldehydes were conducted. The results were summarized in **Table 3**.

It is important to mention that the substituted groups of aryl aldehydes such as methoxy, methyl, hydroxy, chloro, and nitro groups are well tolerated under the reaction conditions to afford the desired products in high yields (**Table 3, entries 2 - 8 and 13 - 18**).  $\alpha$ ,  $\beta$ -unsaturated aldehyde and heterocyclic aldehydes also afforded the desired product in high yields (**Table 3, entries 9-11 and 19,20**). Under the present conditions, all reactions were clean and free from any by-product, whereas, by-products are normally observed in classical conditions.<sup>35</sup>

The advantage of the use of heterogeneous catalyst for this transformation is the ease of catalyst/substrate separation. In our process, when the catalytic reaction was completed, CuO NPs could be recovered conveniently from the reaction mixture through filtration and subsequent washing with ethyl acetate. Then, efforts were made to examine the reusability of CuO NPs by using benzaldehyde and cyclohexanone as a model substrate and the results are described in typical experimental procedure.

#### IV. Conclusion

To sum up, an efficient, facile, and cost-effective method for the CuO NPs ecological synthesis was developed via the Rosa canina fruit extracts. The CuO NPs were characterized to be air-stable, inexpensive and effective in the synthesis of  $\alpha,\alpha'$ -bis-(substituted-benzylidene) cycloalkanones via condensation reaction of aryl aldehydes and cycloalkanones. Good to excellent products yields were obtained and as many as 5 runs the catalyst itself was reusable with just a negligible reduction in catalytic behavior. The most prominent properties of this process are: (i) the toxic ligands and homogeneous catalysts elimination; (ii) requirement of low amount of catalyst, non-aqueous work-up, high yields, and ease of product isolation (iii) that the plant extract employment as an efficient and economic substitute proves an eco-friendly, stimulating, and rapid synthetic route of CuO NPs commercial procurement ; (iv) that in the synthetic procedure, no capping agent, surfactant, and/or template were applied; (v) From the reaction mixture, the CuO NPs were simply retrieved and recycled.

#### V. Acknowledgment

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**Table 3.** Preparation of  $\alpha,\alpha'$ -Bis(substituted benzylidene) cycloalkanones catalyzed by CuO nanoparticles at 80°C for the time given under solvent free conditions<sup>a</sup>.

Entry	Ar.	n	Time (min)	Product	Yield(%) <sup>b</sup>
1.	C <sub>6</sub> H <sub>5</sub>	1	4	3a	95
2.	p-MeOC <sub>6</sub> H <sub>4</sub>	1	5	3b	96
3.	p-MeC <sub>6</sub> H <sub>4</sub>	1	5	3c	96
4.	p-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	1	5	3d	94
5.	p-HOC <sub>6</sub> H <sub>4</sub>	1	8	3e	92
6.	p-ClC <sub>6</sub> H <sub>4</sub>	1	5	3f	95
7.	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1	5	3g	96
8.	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1	9	3h	91
9.	C <sub>6</sub> H <sub>5</sub> CH=CH	1	5	3i	95
10.	2-furyl	1	6	3j	91
11.	3-pyridyl	1	6	3k	87
12.	C <sub>6</sub> H <sub>5</sub>	2	5	3l	94
13.	p-MeOC <sub>6</sub> H <sub>4</sub>	2	6	3m	90
14.	p-MeC <sub>6</sub> H <sub>4</sub>	2	6	3n	93
15.	p-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	2	9	3o	94
16.	p-HOC <sub>6</sub> H <sub>4</sub>	2	5	3p	92
17.	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2	5	3q	93
18.	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	2	9	3r	93
19.	C <sub>6</sub> H <sub>5</sub> CH=CH	2	5	3s	93
20.	2-thienyl	2	9	3t	92
21.	C <sub>6</sub> H <sub>5</sub>	3	6	3u	93

<sup>a</sup>Refluxed at 80°C for the time given under solvent-free conditions.<sup>b</sup> Isolated yield.

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