

Green and highly efficient route for the synthesis of α,α' -bis-(substituted-benzylidene) cycloalkanones using CuO nanoparticles as a recyclable and heterogeneous nanocatalyst under solvent-free conditions

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Abstract :- In order to synthesize cycloalkanones with high yields, a green and highly efficient method is described for the reaction of cycloalkanones with aromatic aldehydes using copper oxide nanoparticles (NPs) as a catalyst, which were prepared in a biological process using *Rosa canina* fruit's water extract as the catalyst. Catalytic efficiency was not significantly reduced when the Nano catalyst was reused and recovered numerous (5) times..

Keywords : Green Chemistry, α,α' -bis-(substituted-benzylidene) cycloalkanones, Heterogeneous nano catalyst, Copper oxide

I. Introduction

The α,α' -bis-(substituted-benzylidene) cycloalkanones are useful intermediates for the synthesis of bioactive pyrimidines,¹ agrochemicals, pharmaceuticals and perfumes² liquid crystalline polymers,³ and bis-pyrrolidines.^{4,5} Generally, benzylidene cycloalkanones 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.⁶ Variety of catalytic procedures⁷ using different complexes of metal (II) ions is reported to give low yields (38%) of enone products. In other cases, TMSCl/NaI,⁸ LiOH,⁹ I₂,¹⁰ KF-Al₂O₃,¹¹ BMPTO,¹² Mg(HSO₄)₂,¹³ Cp₂TiPh₂,¹⁴ polymer-supported sulphonic acid,¹⁵ InCl₃.4H₂O,¹⁶ FeCl₃,¹⁷ aqueous micellar media,¹⁸ 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)₃,¹⁹ Cu(OTf)₃,²⁰ RuCl₃,²¹ SmI₃,²² 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.^{23,24} 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.²⁵⁻²⁹ 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.³⁰ 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 (β -carotene and lycopene), vitamins (vitamin C in specific and a number of other vitamins: B₁, B₂, K, PP, D, E), macro- and microelements etc. It is found that these compounds have antimutagenic, antioxidant, and anticancer effects.^{31,32}



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

Due to our enduring concerns for the heterogeneous catalysts^{33, 34} 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 α, α' -bis-(substituted-benzylidene) cycloalkanones were prepared from the corresponding cyclohexanone and benzaldehyde according to the method described in Vogel.³⁶ IR spectra were recorded on Nicolet (impact 400D model) FTIR Spectrometer. ¹H NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300 MHz instrument using TMS as internal standard and DMSO-*d*₆ or CDCl₃ 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 extract³⁷

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 waterbath 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 $\text{Cu}(\text{OAc})_2$ solution, which was subsequently refluxed at a temperature of 100 °C for one-hour duration. Over time the mixture 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).

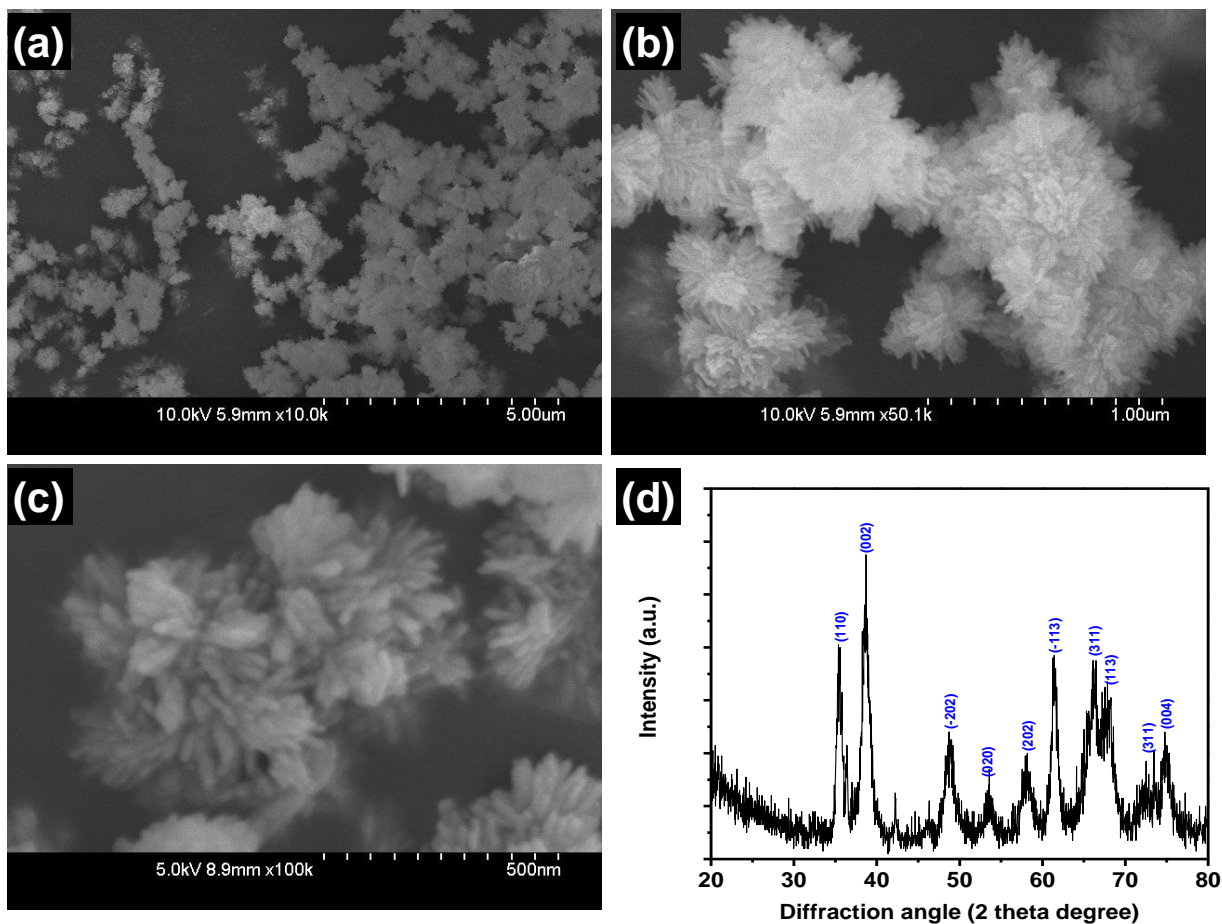


Figure2: (a-c) FESEM images of as-synthesized CuO NPs at different magnifications;
(d) corresponding XRD pattern.

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.

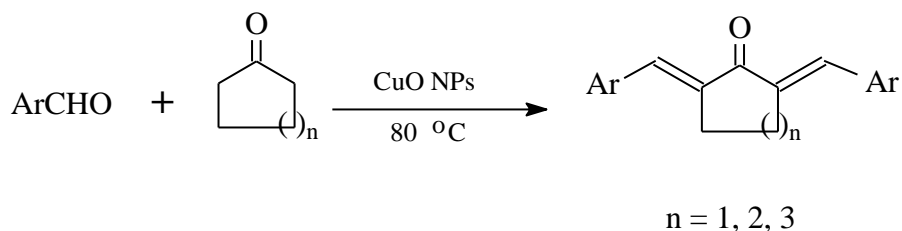
D. Supporting information:

2, 6-dibenzylidenecyclohexanone (3l).

Mp 116 – 117 °C (Lit²⁰ Mp 117 – 118 °C); IR (KBr): 771, 1168, 1274, 1435, 1606, 1660, 3020, 3075 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 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⁺).

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 α,α' -bis(substituted benzylidene) cycloalkanones from the reaction of aldehydes with cycloalkanones under solvent-free conditions (**Scheme 1**).



Scheme 1. Synthesis of α,α' -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 ₂	120	40
3	THF	100	50
4	MeCN	90	56
5	DCM	90	45
6	CHCl ₃	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**). α , β -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.³⁵

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 summarise, Rosa canina fruit extracts were used to produce an effective, simple, and inexpensive approach for synthesising CuO NPs ecologically. Condensation reaction of aryl aldehydes and cycloalkanones was carried out using the CuO NPs, which were shown to be stable, affordable, and effective. Good to exceptional product yields were achieved, and the catalyst itself was reusable for as many as five cycles with just a little loss in catalytic activity. Toxic ligands and homogeneous catalysts are eliminated, as well as the need for a low amount of catalyst, non-aqueous work ups, high yields and ease of product isolation. (iii) The plant extract employment as an efficient and economical substitute proves an eco-friendly, stimulating, and rapid synthetic route of CuO NP commercial procurement. (iv) CuO NPs were extracted and recycled from the reaction mixture without the use of a capping agent, surfactant, or template in the synthesis approach.

V. References

- [1] J. Deli, T. Lorand, D. Szabo, A. Foldesi, Potentially bioactive pyrimidine derivatives. 1. 2-Amino-4-aryl-8-arylidene-3, 4, 5, 6, 7, 8-hexahydroquinazoline, *Pharmazie*, 1984, 39, 539.
- [2] M. Ogawa, Y. Ishii, T. Nakano, S. Irifune, Production of 2-alkylidenecycloalkanone derivative, *Jpn. Kohai Tokkyo JP* 1988, 63238034-A2
- [3] G.K. Kaushal, Synthesis and characterization of photo-cross-linkable main-chain liquid-crystalline polymers containing bis(benzylidene)cycloalkanone units, *Polymer*, 1995, 36, 1903.
- [4] A.A. Raj, R. Raghunathan, Double 1,3-dipolar cycloaddition of 2,6-bis(arylmethylidene)cyclohexanones: A novel entry in to the synthesis of 2'-6'-bis-

- spiro(1-N-methyl-4-aryl- pyr- roldine)cyclohexanones, Synthetic communications, 2002, 32, 3295.
- [5] A.A. Raj, R. Raghunathan, M.R. Sridevikumari, N. Raman, Synthesis, antimicrobial and antifungal activity of a new class of spiro pyrrolidines, Bioorganic & Medicinal Chemistry, 2003, 11, 407.
- [6] B.A. Hathaway, An aldol condensation experiment using a number of aldehydes and ketones, Journal of chemical education, 1987, 64, 367.
- [7] K.Irie, K.Watanabe, Aldol condensations with metal(II) complex catalysts, Bulletin of the Chemical Society of Japan, 1980, 53, 1366.
- [8] G. Sabitha, G. S. K. K. Reddy, B. Reddy, J.S. Yadav, Iodotrimethylsilane-Mediated Cross-Aldol Condensation: A Facile Synthesis of α, α' -Bis(substituted benzylidene)cycloalkanones, Synthesis 2004, 263–266.
- [9] S. Bhagat, R. Sharma, A. K. Chakraborty, Dual-activation protocol for tandem cross-aldol condensation: An easy and highly efficient synthesis of α, α' -bis(aryl/alkylmethylidene)ketones, Journal of Molecular Catalysis. A, Chemical, 2006, 260, 235.
- [10] B.Das, P.Thirupathi, I. Mahender, K.R. Reddy, Convenient and facile cross-Aldol condensation catalyzed by molecular iodine: An efficient synthesis of α, α' -bis(substituted-benzylidene) cycloalkanones, Journal of Molecular Catalysis. A, Chemical, 2006, 247, 182–185.
- [11] J.S.Yadav, B.V.S. Reddy, A. Nagaraju, J.A. Sharma, Microwave assisted synthesis of α, α' -bis(benzylidene)ketones in dry media, Synthetic communications, 2002, 32, 893.
- [12] M. Zheng, L. Wang, J. Shao, Q. Zhong, Facile Synthesis of α, α' -bis(Substituted Benzylidene)cycloalkanones Catalyzed by bis(p-methoxyphenyl)telluroxide(bmpto) Under Microwave Irradiation, Synthetic communications, 1997, 27, 351–354.
- [13] P. Salehi, M.M. Khodaei, M.A. Zolfigol, A. Keyvan, Solvent-Free Crossed Aldol Condensation of Ketones with Aromatic Aldehydes Mediated by Magnesium Hydrogensulfate, Monatshefte für Chemie, 2002, 133, 1291.
- [14] T. Nakano, T. Migita, Convenient Synthesis of α, α' -Bis(substitutedbenzylidene)cycloalkanones, Chemistry letters, 1993, 22, 2157.
- [15] L.T. An, J.P. Zou, L.L. Zhang, Polymer-supported sulphonic acid catalyzed cross-aldol condensation: An expeditious synthesis of α, α' -bis(substituted benzylidene) cycloalkanones, Catalysis Communications, 2008, 9, 349.
- [16] L. Yang, J. Lu, Y.J. Bai, Synthesis of α, α' -bis(benzylidene)cycloketones catalyzed by $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ under solvent-free conditions and microwave irradiation, Chinese Journal of Organic Chemistry, 2003, 23, 659.
- [17] X. Y. Zhang, X.S. Fan, H. Y. Niu, J.J. Wang, An ionic liquid as a recyclable medium for the green preparation of α, α' -bis (substituted benzylidene)cycloalkanones catalyzed by $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, Green Chemistry, 2003, 5, 267.

- [18] J.J. Shrikhande, M.B. Gawande, R. V. Jayaram, Cross-aldol and Knoevenagel condensation reactions in aqueous micellar media, *Catalysis Communications*, 2008, 9, 1010.
- [19] L. Wang, J. Sheng, H. Tian, J. Han, Z. Fan, C.T. Qian, A Convenient Synthesis of α,α' -Bis(substituted benzylidene)cycloalkanones Catalyzed by $\text{Yb}(\text{OTf})_3$ Under Solvent-Free Conditions, *Synthesis*, 2004, 3060–3064.
- [20] J. Li, W. Su, N. Li, Copper Triflate–Catalyzed Cross-Aldol Condensation: A Facile Synthesis of α,α' -Bis(Substituted Benzylidene) Cycloalkanones, *Synthetic communications*, 2005, 35, 3037.
- [21] N. Iranpoor, F. Kazemi, RuCl_3 Catalyses Aldol Condensations of Aldehydes and Ketones, *Tetrahedron*, 1998, 54, 9475–9480.
- [22] W.L. Bao, Y.M. Zhang, T. Ying, A Facile Route to Synthesize α,α' -bis(Substituted-benzylidene) Cycloalkanones Promoted by SmI_2 , *Synthetic Communications*, 1996, 26, 503.
- [23] Y. Sun, B. Mayers, Y. Xia, Transformation of silver nanospheres into nanobelts and triangular nanoplates through a thermal process, *Nano Letters*. 2003, 3, 675.
- [24] D. Sadasivan, S. Khushalani, Synthesis of Calcium Phosphate Nanofilaments in Reverse Micelles, *Chemistry of materials*, 2005, 17, 2765.
- [25] E. S. Abdel-Halim, M. H. El-Rafie, S. S. Al-Deyab, Polyacrylamide/guar gum graft copolymer for preparation of silver nanoparticles, *Carbohydrate Polymers*, 2011, 85, 692.
- [26] A. R. Jassbi, Chemistry and biological activity of secondary metabolites in *Euphorbia* from Iran, *Phytochemistry*, 2006, 67, 1977.
- [27] S. P. Dubey, M. Lahtinen, M. Sillanpa, Tansy fruit mediated greener synthesis of silver and gold nanoparticles, *Process Biochemistry*, 2010, 45, 1065.
- [28] G. Zhan, J. Huang, M. Du, I. Abdul-Rauf, Y. Ma, Q. Li, Green synthesis of Au–Pd bimetallic nanoparticles: single-step bioreduction method with plant extract, *Materials Letters*, 2011, 65, 2989.
- [29] X. Huang, H. Wu, S. Pu, W. Zhang, X. Liao and B. Shi, One-step room-temperature synthesis of Au@Pd core–shell nanoparticles with tunable structure using plant tannin as reductant and stabilizer, *Green Chemistry*, 2011, 13, 950.
- [30] I. Roman, A. Stanila, S. Stanila, Bioactive compounds and antioxidant activity of *Rosa canina* L. biotypes from spontaneous flora of Transylvania, *Chemistry Central Journal*, 2013, 1.
- [31] F. Demir, M. Ozcan, Chemical and technological properties of rose (*Rosa canina* L.) fruits grown wild in Turkey, *Journal of food engineering*, 47 (2001) 333.
- [32] N. Orhan, M. Aslan, S. Hosbas, O. Deliorman, Antidiabetic Effect and Antioxidant Potential of *Rosa canina* Fruits, *Pharmacognosy Magazine*, 5 (2009) 309.
- [33] B.P. Bandgar, S.S. Gawande, S.C. Warangkar, J.V. Totre, Silica-supported fluoroboric acid ($\text{HBF}_4\text{-SiO}_2$) catalyzed highly productive synthesis of thiomorpholides as activators

- of l-asparaginase as well as the antioxidant agent, *Bioorganic & Medicinal Chemistry*, 2010, 18, 3618-3624.
- [34] B. P. Bandgar, S. S. Gawande, D. B. Muley, Silica supported perchloric acid ($\text{HClO}_4\text{-SiO}_2$): a green, reusable, and highly efficient heterogeneous catalyst for the synthesis of thioethers under solvent-free conditions at room temperature, *Green Chemistry Letters and Reviews*, 2010, 3, 49-54.
- [35] T. Nikano, S. Irifune, S. Vmano, A. Inada, Y. Ishii, M. Ogawa, Cross-condensation reactions of cycloalkanones with aldehydes and primary alcohols under the influence of zirconocene complexes, *Journal of organic chemistry*, 1987, 52, 2239.
- [36] A.I. Vogel, *A Text Book of Practical Organic Chemistry*; Longman Green: London, 1959.
- [37] S. Hemmati, L. Mehrazin, M. Hekmati, M. Izadi, & H. Veisi, Biosynthesis of CuO nanoparticles using *Rosa canina* fruit extract as a recyclable and heterogeneous nanocatalyst for C-N Ullmann coupling reactions, *Materials Chemistry and Physics*, 2018, 214, 527-532.
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