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Solvent free green Synthesis of 5-arylidine Barbituric acid Derivatives Catalyzed by Copper oxide Nanoparticles

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Abstract

Copper oxide nanoparticles as an efficient catalyst was used for the synthesis of 5-arylidine barbituric acid derivatives by condensation reaction of barbituric acid and various aromatic aldehydes at room temperature with high speed stirring. The present protocol especially favoured because it offers advantages of high yields, short reaction times, simplicity and easy workup. Moreover the catalyst is inexpensive, stable, can be recycled and reused for three cycles without loss of its activity.

Keywords: Electrochemical method, CuO nanoparticles, heterogeneous catalyst, 5-arylidine barbituric acid derivatives, room temperature synthesis.

Introduction

Barbituric acid is a strong acid in aqueous medium with an active methylene group and can be involved in knoevenagel type condensation reaction[1]. The barbiturates are associated with a number of biological activities such as antibacterial, hypotensive, sedative and local anesthetic drugs[2-3] to the more recent report indicating that they have applications in anti-tumor[4], anti-cancer[5], analeptics[6], anti-AIDS agents[7] and anti-osteoporosis[8] treatments, used as oxidants for mild oxidation of thiols[9] and alcohols[10].

Owing to the wide range of biological and medicinal activities the synthesis of 5-arylidine barbituric acid compounds by the use of barbituric acid and 2-thio barbituric acid as starting compound have become an important target in recent years.

Numerous synthetic method have been reported for the synthesis of synthesis of 5-arylidine barbituric acid derivatives by solvent free grinding, using NH_2SO_3H[11], infra red promoted[12], microwave irradiation[13], ionic liquid mediated condensation[14], and uses variety of catalysts such as $ZnCl_2$[15], CdI_2[16], Ni-SiO_2[17], KF–Al_2O_3[18], natural phosphate [(NP)/KF or NP/$NaNO_3$][19] and synthetic phosphate ($Na_2CaP_2O_7$)[20], $K_2NiP_2O_7$[21], dry condensation with acidic clay catalysts[22], Ni nanoparticles[23] and $CoFe_2O_4$ nanoparticles[24] etc. However these methods are plagued by limitation of longer reaction time, effluent pollution, bis-addition and self condensation, lower yield. Owning to the importance of barbituratic acid derivatives especially 5-arylidine barbiturates there is need to develop efficient method for the Knovengel Condensation at mild conditions.

Solvent free organic reaction have drawn great interest, particularly from the viewpont of green chemistry as organic solvent are toxic and flammable. Solid state reactions are simple to handle, reduce pollution and comparatively cheaper to operate. Heterogeneous catalysts offer several intrinsic advantages over their homogeneous counterparts such as easy removal of catalyst, operational simplicity and reusability.

The use of metal nanoparticles in the field of catalysis is of great interest, since they have a large surface-to-volume ratio compared to bulk materials. Recently, there has been growing interest in using cupper nanoparticles in organic synthesis because of their potent catalytic activity, high stability and non toxic.

Material and Methods

The AR grade tetra propyl ammonium bromide (TPAB), tetrahydrofuran (THF) and acetonitrile (ACN) were purchased from Aldrich and S.D. Fine chemicals and used as such. The sacrificial anode in the form of copper sheet and platinum sheet as inert cathode having thickness 0.25 mm and purity 99.9% was purchased from Alfa Asaer. The specially designed electrolysis cell with a volume capacity of 30 ml was used. The prepared copper oxide nanoparticles were characterized by UV-Visible, XRD, SEM-EDS techniques. The UV-Visible studies were recorded [JASCO 503] spectrophotometer using a quartz cuvette with ACN / THF (4:1) as reference solvent. The X-ray powder diffraction patterns of the copper oxide nanoparticles were recorded on Bruker 8D advance X-ray diffractometer using CuKα radiation of wavelength = 1.54056 Å. To study the morphology and elemental composition in copper oxide nanoparticles were examined using energy dispersive spectrophotometer (EDS), the SEM analysis were carried out with JEOL; JSM- 6330 LA operated at 20.0kV and 1.0000nA. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AvIII HD-300 MHz FT-NMR spectrometer with $CDCl_3$ as a solvent and the chemical shift values recorded as δ (ppm units). Mass spectra were recorded on an Agilent 6520 Q-Tof mass spectrometer for ESI Scan.

Synthesis of CuO Nanoparticles: Reetz proposed an electrochemical reduction method[25] including both oxidation of bulk metal and reduction of metal ions for size selective preparation of tetra alkyl ammonium salt stabilized metal nanoparticles. In the initial experiment we have used a copper metal sheet (1x1 cm) as anode and a platinum sheet (1x1 cm) as the cathode. These two electrodes placed parallel to one another and were separated by 1.0cm in 0.01 M solution of TPAB prepared in ACN/THF (4:1) served as the supporting electrolyte. The electrolysis process was then carried out by applying current 10 mA for 2.0 hrs. The colloidal solution thus obtained was kept in air tight glass bottle to settle for a day. The agglomerated solid sample was separated from the solution by decantation and washed three to four times with THF. The washed samples were then dried under vacuum condition in desiccator and stored in air tight container for characterization.

Procedure for the Synthesis of 5-Arylidene Barbituric Acids: A mixture of aromatic aldehyde(1mmol), barbituric acid (1mmol) (solid aromatic aldehyde wetted with ethanol) and CuO nanoparticles (100mg) (scheme 1) was stirred with high speed at room temperature till the completion of reaction monitored by TLC (ethyl acetate and n-hexane 7:3). After completion of reaction solid product obtained was dissolved in 10ml ethyl acetate and concentrated on rotavapor. Finally pure product was obtained by recrystalization and authentic samples were characterized by FTIR, H^1NMR, C^{13} NMR and mass spectra.

Procedure for recovery of catalyst: The reaction mixture was stirred until complete dissolution of product in ethyl acetate. The resulting solution was centrifuged for 5 min. The ethyl acetate solution was collected by simple decantation. The catalyst was washed with ethanol for 2-3 times. Then dried catalyst reused in same reaction for over three cycles.

Spectral data: 5(4-Cl-Benzylidene)- Barbituric acid(3b): [IR (KBr) ν_{max}/cm^{-1}]: 3404, 3214, 2970, 1755, 1703, 1570 cm^{-1}; ^{1}H NMR (DMSO) δ ppm:7.53(d, 2H, Ar-H), 8.08(2d, 2H, Ar-H), 8.25(s, 1H, HC=C), 11.25(s, H, NH), 11.40(S, 1H, NH); ^{13}C NMR($CDCl_3$) δ ppm; 117.46, 127.76, 128.29, 133.25, 133.50, 148.70, 150.16, 165.10; EI-MS: m/z (%):250(M^+).

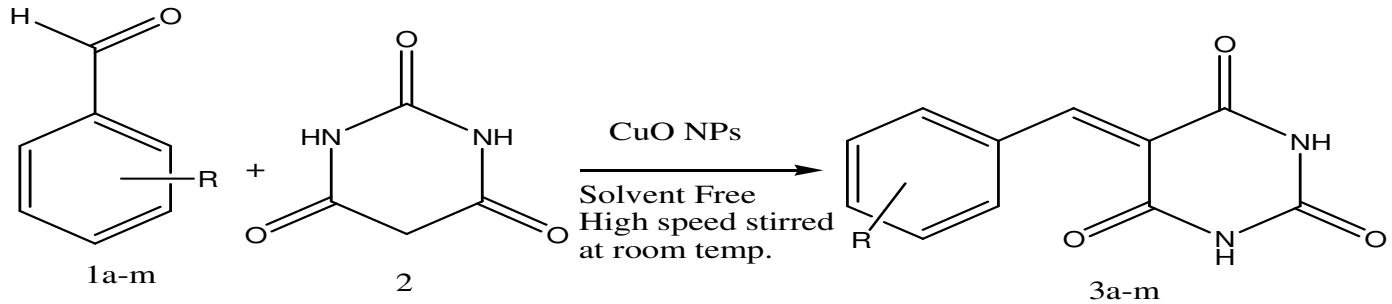
5(2-Cl-Benzylidene)- Barbituric acid(3c): [IR (KBr) ν_{max}/cm^{-1}]: 3460, 3120, 2981, 1754, 1569, 1454, 1079, 910, 782; ^{1}H NMR ($CDCl_3$) δ ppm: 7.36 (t, 1H Ar-H), 7.47 (t, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 8.29 (s, 1H, HC=C), 11.25(s,1H, NH), 11.47(s, 1H,NH); ^{13}C NMR($CDCl_3$,ppm) δ= 121.76, 126.29, 128.29, 131.88, 132.25, 133.15, 146.70, 150.16, 160.85, 162.60; EI-MS: m/z (%):250(M^+).

5(4-OH-Benzylidene)- Barbituric acid(3i): [IR (KBr) ν_{max}/cm^{-1}]: 3420, 3214, 2970, 1755, 1703, 1570 cm^{-1}; ^{1}H NMR (DMSO) δ ppm:6.86(d, 2H, Ar-H), 8.32(2d, 2H, Ar-H), 8.24(s, 1H, HC=C), 10.68(S, 1H, OH), 11.13(s, H, NH), 11.25(S, 1H, NH); ^{13}C NMR($CDCl_3$) δ ppm; 115.60, 118.76, 128.70, 148.80, 150.20, 157.65, 165.10; EI-MS: m/z (%):232(M^+).

Results and Discussion

In continuation of our previous work, we have developed cupper nanoparticles as catalyst for development of new synthetic methodologies. Herein, we would like to report a mild and high yielding solvent free method for the synthesis of5-arylidene barbiturates by a condensation reaction between aromatic aldehyde 1(a-m) and barbituric acid catalyzed efficiently by CuO nanoparticles. As electrochemical reaction proceeds, the colour of reaction mixture changes from colorless to brownish black indicating formation of CuO nanoparticles. About 4 ml of colloidal reaction mixture was withdrawn after 2 h to record UV–Visible spectrum. CuO capped with TPAB at current density of 10 mA has got broad peak at 640 nm indicating the formation of CuO nanoparticles figure-1.

XRD pattern of the CuO nanoparticles is shown in figure-2. All reflection peaks can be readily indexed to monoclinic phase of CuO nanoparticles. The particle size of solid materials can be estimated from X-ray line broadening and full width at half maximum (FWHM) values using the Debye-Scherrer's equation. Peaks corresponding to the planes (-111), (111), (012) (020) (120) (220) and (121) with lattice parameter a = 4.653, b = 3.410, c = 99.480 indicate the monoclinic phase structure of CuO nanoparticles. All peaks are in good agreement with the JCPDS card no. 74-1021. The average crystallite size of CuO has been found to be 25-30 nm.



Scheme 1
CuO nanoparticles catalyzed knoevenagel condensation of aldehydes and barbituric acid

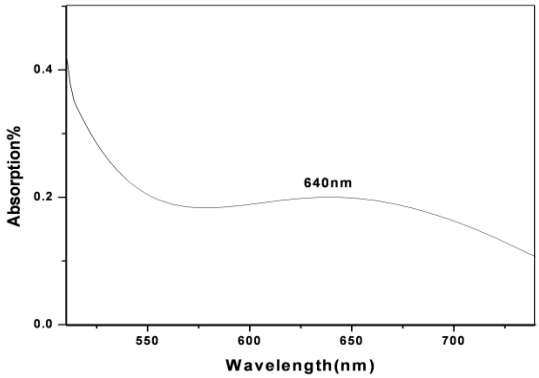


Figure-1
UV-Visible spectrum of CuO NPs

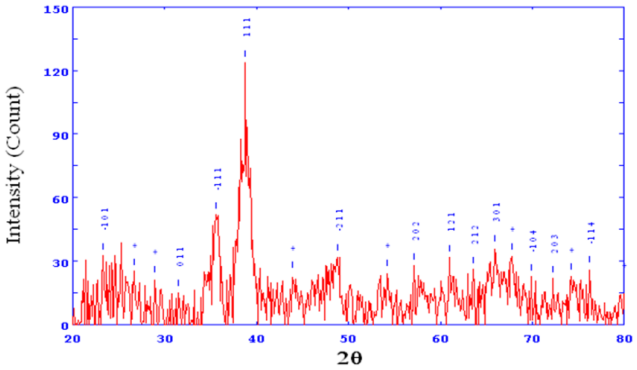
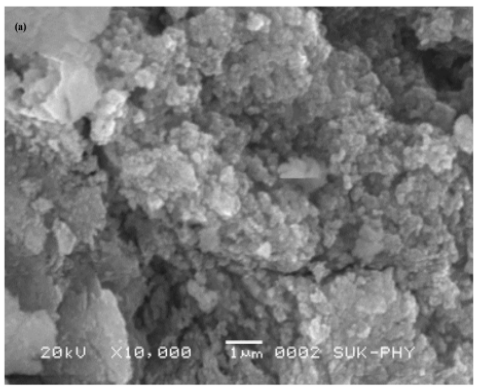


Figure-2
XRD pattern of Copper oxide Nps

The morphology of CuO nanoparticles catalysts is shown in figure-3a. The SEM micrograph of CuO nanoparticles showed agglomeration of particles and was irregular in shape. This was probably due to the partial solubility of the surfactant in the solvent under the given experimental conditions. The quantitative and qualitative analysis was done by EDS spectra and the elemental composition of CuO nanoparticles are shown in figure-3b. The elemental distribution of Cu 84.02 mass % (55.67 At %), C 7.64 mass % (26.80 At %), O 6.24mass % (16.43 At %) and Br 2.10 mass % (1.11 At %).

TEM was used to further examine the particle size, crystallinity and morphology of the sample. The sample prepare for TEM analysis was obtained by evaporation of very dilute alcoholic suspensions onto carbon-coated copper grids. A TEM image (figure-4a) of the typical product showed that CuO nanoparticles were dispersed and dense agglomeration was observed. The magnified image showed these CuO nanoparticles were spherical with size in the range of 5–30 nm. The corresponding particle size distribution of CuO nanoparticles is in agreement with the results calculated from the XRD analysis. The SAED image of shows high crystallinity of the CuO NPs. The histogram in figure-4b showed that the average mean size and standard deviation of copper oxide NPs capped with TPAB is found to be 22.39 ± 5.86 nm, which represent the aggregated copper nano-crystal size.



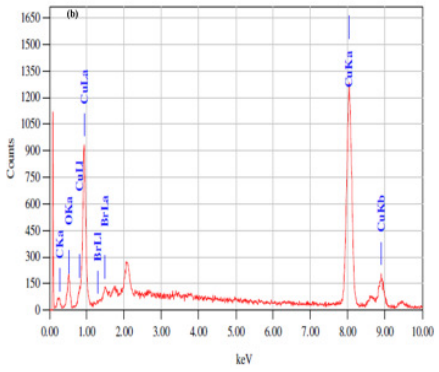


Figure-3
Copper oxide Nps a) SEM image and b) EDS spectra synthesized at10 mA current density.

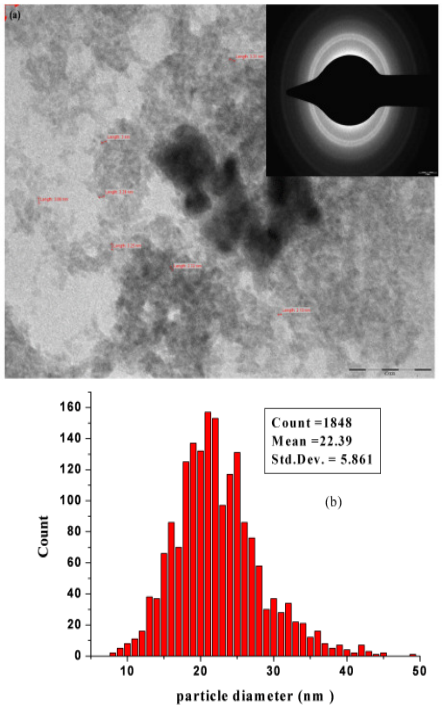


Figure-4
Copper oxide Nps at10 mA current density a) TEM image inset with SAED pattern and b) histogram

The catalytic activity of the synthesized CuO nanoparticles was investigated in the synthesis of arylidene barbituric acid derivatives at room temperature. To study the efficiency of the CuO nanocatalyst, 4-chlorobenzaldehyde (1b) and barbituric acid (2) were used as the model substrate. We also carried out the reaction without any catalyst, but the product isolated gave poor yield (25%). In optimizing the reaction conditions, the amount of catalyst was the major factor. The model reaction was studied using 25, 50, 75, 100 and 125 mg of a reaction of 4-chlorobenzaldehyde (1b). The results revealed that best yield was obtained by using 100mg catalyst. With increase in the catalyst concentration, the yield of the desired product was found to be constant. Therefore, the catalyst plays a crucial role in the success of the reaction in term of yields of the product. The results obtained are summarized in table-2. It is evident that the aromatic aldehyde carrying electron-donating or electron-withdrawing groups as well as heterocyclic system such as Furan-2-carboxyaldehyde reacted smoothly to produce high yields of products. The results with different aromatic aldehydes are summarized in table-1.

In this study, the catalyst was recovered and reused in another run. The catalyst was recovered by simple work-up using centrifugation method, washed with ethanol and reused for three successive reaction corresponding yields for each cycle were mentioned in table-3.

To compare the merits of our work to the other reported procedure; the results of the synthesis of arylidene barbituric acid derivatives in the presence of different reported catalysts with respect to time and yield of the product are listed in table-4. These results show that our catalyst CuO nanoparticles are more stable in air, nontoxic, give good yield in short time than other catalysts and there is no use of any hazardous solvent.

Table-1
Synthesis of 5-arylidine barbituric acid derivatives catalyzed by CuO Nanoparticles

Sr. No.	Reactant	Products[a]	Time (min)	Yield (%)	Melting point (°C)	
					Found	Reported
1	C_6H_5	3a	15	97	264 - 266	263-265 [24]
2	4-ClC_6H_4	3b	12	98	298 - 299	298 [24]
3	2-ClC_6H_4	3c	13	95	250-252	252-254 [24]
4	4-$NO_2C_6H_4$	3d	09	94	268-270	272-274 [11]
5	3-$NO_2C_6H_4$	3e	07	95	230-231	231-233 [11]
6	4-$CH_3C_6H_4$	3f	15	96	290-291	297-298 [11]
7	2,4-$Cl_2C_6H_3$	3g	13	94	268-270	269-271 [11]
8	4-$OMeC_6H_4$	3h	10	93	296-298	298-300 [24]
9	4-OHC_6H_4	3i	15	94	>300	>320 [24]
10	2-furfural	3j	20	95	262-263	264 [23]
11	4-FC_6H_4	3k	12	95	>300	309-10 [12]
12	4-BrC_6H_4	3l	15	92	288-290	292-293 [12]
13	C_6H_5CH=CH	3m	18	93	267-268	270 [13]

[a]Reaction condition: aldehyde (2mmol), barbituric acid (2mmol), and 100mg of CuO nanoparticles solvent free stirred at room temp.

Table-2
Screening of catalyst (CuO NPs) concentration for the synthesis of 3b

Entry	Catalyst amount(mg)	Time(min)	Yield(%)[a]
1	25	60	38
2	50	40	82
3	75	25	90
4	100	12	98
5	125	12	98

[a]isolated yield

Table-3
Studies on reusability of CuO nanoparticles in the preparation of 3b

No of Cycles	Fresh	1	2	3
Yield(%)	98	94	91	85

Table-4
Comparisation result of CuO nanoparticles with other catalysts reported in the literature.

Sr. No.	Catalyst	Reaction condition	Yield (%)	Literature
1	NH_2SO_3H	Grinding/10 min	47	11
2	KSF clay	MW, 560 W/7 min	70	12
3	PVPNi Nanoparticles	Ethyleneglycol, 50^{o}C/10–15 min	91	23
4	CuO nanoparticles	Solvent free/ R.T./7 min	95	This work

Thus, we report fast, clean and highly competent methodology for the Knoevenagel condensation of aromatic aldehydes with barbituric acids catalyzed by CuO nanoparticles to give 5-arylidene barbituric acids as the desired products in short time span and in quantitative yields by a simple high speed stirring at room temperature. The reaction time, yield and reusability of catalysts make the present protocol a useful and important addition to the present methodologies for the synthesis of 5-arylidine barbituric acid derivatives.

Conclusion

We have demonstrated mild, easy and green method for the synthesis of 5-arylidine barbituric acid derivatives using recyclable CuONps as heterogeneous catalysts at room temperature under solvent free condition. Short reaction times, appropriate yields and clean reactions make this procedure an attractive alternative to the existing methods. Furthermore, this method is of interest in the perspective of environmentally greener and safer method.

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