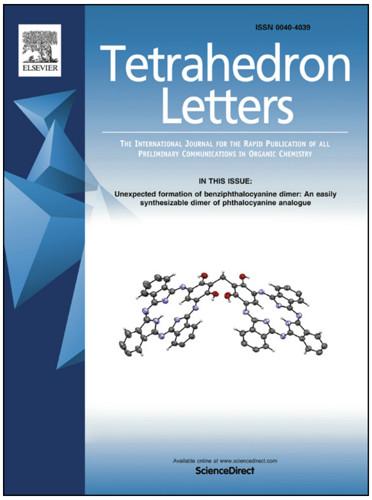

N-arylation of indole and aniline by a green synthesized CuO nanoparticles mediated by Thymbra spicata leaves extract as a recyclable and heterogeneous nanocatalyst

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Graphical Abstract

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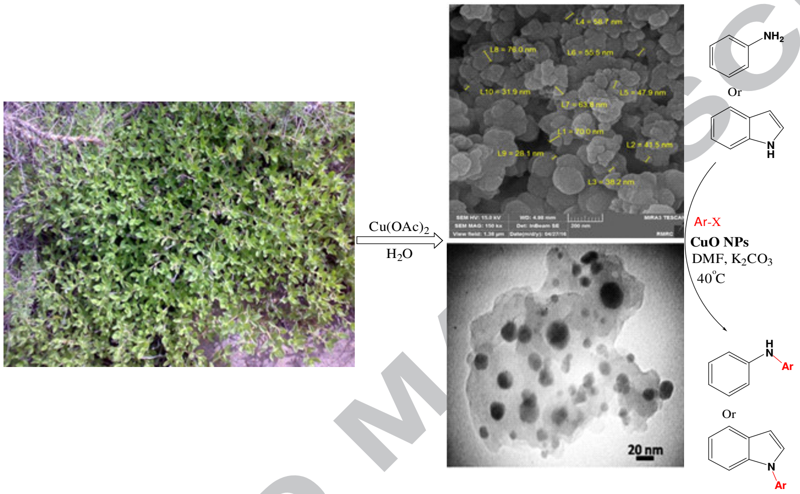

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N-arylation of indole and aniline by a green synthesized CuO nanoparticles mediated by Thymbra spicata leaves extract as a recyclable and heterogeneous nanocatalyst

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ABSTRACT

In a biological procedure where the aqueous leaves extract of Thymbra spicata was utilized as a reducing and capping agent, copper oxide (CuO) nanoparticles (NPs) were synthesized. These CuO NPs were characterized via Fourier transformed infrared spectroscopy (FT-IR), X-ray diffraction (XRD), field emission scanning electron microscopy (FE-SEM), transmission electron microscopy (TEM), energy dispersive X-ray spectroscopy (EDS), wavelength-dispersive X-ray spectroscopy (WDX), and UV-visible spectroscopy. The as prepared nanoparticles have been employed as an appropriate nanocatalyst for ligand-free *N*-arylation of indole and aniline via Ullmann-type C-N coupling reactions. Adequate to outstanding quantities of the N-arylated products were synthesized and the nanocatalyst was retrievable and reusable seven times without noticeable decrease in catalytic performance.

Introduction

For the construction of C-N bonds, the Ullmann-type coupling reaction has been demonstrated as a procedure that is highly effective and adaptable.[1] Because of this, these coupling reactions have drawn significant focus on the innovation of more resourceful methods that can be applied to form aryl substituted amines using amines and aryl halides.[2]

There are a multitude of approaches for the *N*--arylation of indoles through Ullmann-type coupling reactions. These reactions are typically catalyzed via soluble copper (Cu) complexes alongside numerous different ligands.[3-5] These reactions had usually been undertaken in severe reaction conditions like increased temperatures as great as 200 °C, application of stoichiometric quantities of copper reagents, and moderate yields with lengthier reaction durations.[3-5] A large portion of these ligands are costly, toxic, sensitive to air, and homogeneous. Once again the complexity in the removal of the product from the expensive catalyst and this poses a momentous hurdle for producers who wish to industrialize the manufacturing process.

The challenge of separation of the catalyst and its subsequent reusability in further runs is a great hindrance in homogenous catalysis. From an ecological perspective, it is essential that ligand-free catalytic systems are developed in which heterogeneous catalysts are substituted for homogeneous ones. Heterogeneous catalysts are being employed to a greater degree because of their high surface-to-volume ratio and the fact that nanoparticles are exceedingly active upon their surfaces.[4-6] Within the category of homogeneous catalysts, copper(II) oxide nanomaterials that have high surface areas and reactive morphologies have been extensively applied as efficient catalysts for organic procurement because of their decent chemical and thermal stabilities, inexpensiveness, minimal toxicity, convenient handling, and their reusability.[7-9]

A large audience has been focused on the nanomaterials as they display a unique set of physical and chemical characteristics. The nanoparticles are generally procured through chemical and physical procedures that have historically been harmful to the environment.[10-15] As of late, there has been an insurgence of a new type of nanotechnology (green nanotechnology) that is eco-friendly for the synthesis of nanomaterials.[16] This green nanotechnology provides a gateway for the development of novel ecological processes that may improve the application of nanomaterials for environmental remediation without the danger of secondary pollution.[17] For gold, silver and platinum nanoparticles a variety of ecological procedures have been reported, however these metals are uneconomically expensive.[18, 19] Copper and its oxides are substantially less costly, but the environmentally friendly procedures are scarce.[20] Within this analysis, there has been an effort to formulate a new approach for the preparation of cupric oxide nanoparticles (CuO NPs) as it is highly stable in typical environmental settings. Thymbra spicata (Fig. 1) was favored for the synthesis of CuO NPs due to its rich source of natural polyphenolic compounds and flavonoidic groups[21-23] that behave as reducing and stabilizing agents without using any harmful reducing or capping agents, and furthermore, the procured CuO NPs were effectively applied as a nanocatalyst for ligand-free Narylation of indoles via Ullmann-type C-N coupling reactions.

Fig. 1. Image of the *Thymbra spicata*.

Experimental

Preparation of Thymbra spicata leaves extract

10 g of dried leaves of Thymbra spicata was powdered and heated at 80 oC with 100 mL of sterile distilled water for 45 minute and the mixture was allowed to cool to room temperature. Then, the aqueous extract of Thymbra spicata leaves was centrifuged at 6500 rpm and supernatant separated by filtration and stored in refrigerator as reducing as well as stabilizing agent at 4 oC for further study.

Green synthesis of CuO NPs using Thymbra spicata leaves extract

For preparation of CuO NPs, 10 mL of the prepared plant extract was added dropwise to 100 mL of 1 mM aqueous Cu(OAc)2 solution and refluxed at 80 °C for 1 h. The color of the reaction mixtures gradually turned to dark brown during the heating process due to excitation of surface plasmon resonance which indicates the formation of CuO NPs and hydrogen donation activity of antioxidant phenolics inside the plant. The isolated solid product was washed twice with deionized water and dried at 100 °C for 24 h. Final dried powder was stored in properly labeled containers and used for further analysis.

Large-scale green synthesis of CuO NPs using Thymbra spicata leaves extract

For preparation of CuO NPs, 100 mL of the prepared plant extract was added dropwise to 500 mL of 30M aqueous Cu(OAc)2 solution and refluxed at 80 °C for 1 h. The color of the reaction mixtures gradually turned to dark brown during the heating process due to excitation of surface plasmon resonance which indicates the formation of CuO NPs. The isolated solid product was washed twice with deionized water and dried at 100 °C for 24 h. Final dried powder was 1.12 g.

General procedure for N-arylation of indole and aniline

In a typical N-arylation procedure, CuO NPs (0.005 g) was added to a mixture of aryl halide (1.0 mmol), indole/aniline (1.0 mmol), and K2CO3 (1.0 mmol) in DMF (5 mL) and stirred at 40 ºC for desired time (Table 2). After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with 10 mL of water and extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine and dried over anhydrous MgSO4. Solvent was evaporated under reduced pressure and the product was purified by column chromatography to obtain the desired purity. All the products are known compounds and the spectral data were identical to those reported in the literatures.[24-26] The aqueous layer was centrifuged and the catalyst was separated and recovered for the next catalytic run.

Results and discussion

In the present study, CuO NPs was synthesized using Thymbra spicata leaves extracted solution as a solvent instead of organic solvents without using any harmful reducing or capping agents. In synthesis of nanoparticles, plants extract may act both as reducing and capping agents. The formation of CuO NPs was controlled by UV-vis spectroscopy. Fig. 1s shows the UV-vis spectrum of CuO NPs formation. The reaction was completed after 60 min. Our results showed that the maximum absorbance of green synthesized CuO NPs was at 250 nm due to the surface plasmon absorption of nanosized cupric oxide particles. Changing the color of the reaction and appearance the maxima at 250 nm indicates the reduction process and formation of nanoparticles.

FT-IR analysis was performed to characterize the surface nature of the resulting CuO nanoparticles, as depicted in Fig. 2s. The appeared bands are lattice vibrational modes indicating the functional groups of biomolecules adsorbed on nanoparticles. An absorption band at 614 cm-1 related to the vibrations of the Cu-O functional group. This confirmed the presence of nano-sized CuO particles present in the nanocomposite. An intense and broad band appeared in the region 3200-3500 cm-1 corresponding to the stretching mode of the hydroxyl functional groups.[27] The band around 1429 cm-1 is generally attributed to the bending vibration of sp2-Carbon groups for aromatic and 1670 cm-1 for carbonyl functional group.

The morphology of the synthesized CuO nanostructures was studied by recording the FESEM images of synthesized CuO NPs, which enumerated the formation of homogeneous and relatively spherical of CuO NPs by reducing and capping agents (Fig. 2).

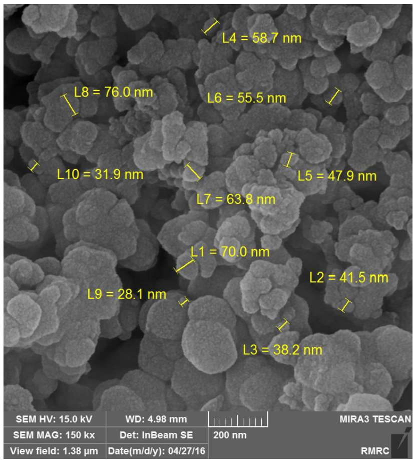


Fig. 2. FESEM image of biosynthesized CuO NPs.

The energy-dispersive X-ray spectrum (EDX) of the biosynthesized CuO NPs by Thymbra spicata leaves extract is shown in Fig. 3; and signals relating to carbon, nitrogen, oxygen and copper were observed. The strong signals in the copper region, confirmed the formation of CuO NPs. Metallic Cu nanocrystals generally show typical optical absorption peaks approximately at 1.0 and 8.0 keV due to surface Plasmon resonance. However, we have observed higher amounts of C, which must be due to phytochemicals present in plant extract.

Thus, we have attributed these elements as the evidence for the organic substances attached to the CuO NPs.

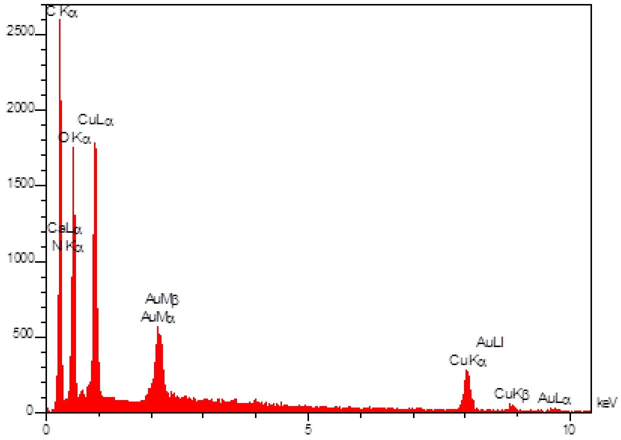


Fig. 3. EDX spectrum of biosynthesized CuO NPs.

Transmission electron microscopy has provided further insight into the morphology, shape and size of these nanoparticles. The TEM image of the synthesized CuO NPs revealed that the CuO nanoparticles with nearly spherical morphology were formed and relatively good monodispersity without agglomeration in the range of 10-20 nm (Fig. 4).

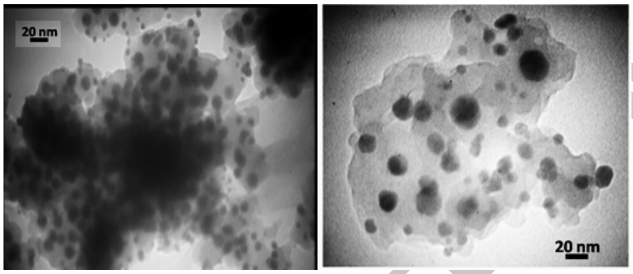
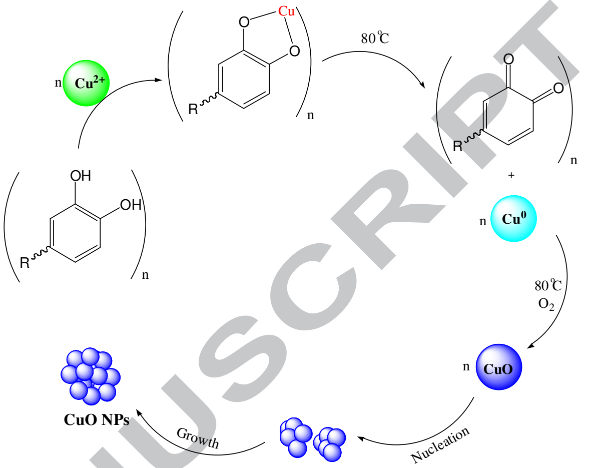


Fig. 4. TEM images of biosynthesized CuO NPs.

In combination with scanning electron microscopy (SEM), wavelength-dispersive X-ray spectroscopy (WDX) can provide qualitative information about the distribution of different chemical elements in the catalyst matrix. Fig. 3s shows representative SEM and corresponding elemental map (WDX) images for the biosynthesized CuO NPs. It can be seen that Cu metal particles are well dispersed in the composite, which agrees well with the XRD and TEM analysis. The selected area elemental analysis figure revealed the presence of C, O, and Cu throughout the sample in a homogeneous manner, which confirms the regular uniformity of the prepared sample.

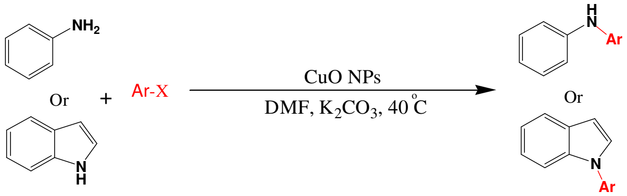
The green synthesized CuO NPs examined by XRD displays high crystallinity. Fig. 4s shows the powder XRD pattern of CuO NPs. The diffraction peaks at (110), (111), (200), (202), (020), (202), (113), (311), (220) and (400) Bragg's reflection correspond to CuO NPs.[11]

The polyphenolic compounds have been demonstrated as reducing agent during the biological extract mediated preparation of nanomaterials.28 The Thymbra spicata leaves extract is also a rich source of the polyphenolic compounds and flavonoidic groups.[21-23] These entire polyphenolic compounds may act as reducing agent for the reduction of Cu^{2+} ion. Scheme 1 shows the schematic representation of probable mechanism. In the first step, when extract mixed with the metal salt solution, the hydroxyl groups of the polyphenolic compounds formed the complex with the Cu^{2+} and reduced it into the Cu. Thus formed metallic copper atoms react with the available atmospheric oxygen to form most stable oxide i.e. CuO. In the next, formed CuO molecules come together to nucleate followed by further growth which results the formation of nanoparticles.



Scheme 1. Probable mechanism for formation of CuO NPs using *Thymbra spicata* leaves extract.

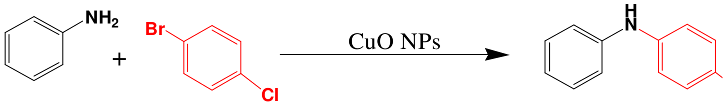
After structural characterization of the prepared CuO NPs, following through with our investigation to produce selective, efficient and ecological methods and nanocatalysts in organic synthesis,[29] its catalytic activity was investigated as a nanocatalyst in the Ullmann coupling of amine and indole with aryl halides under aerobic condition (Scheme 2).



Scheme 2. CuO NPs catalyzed *N*-arylation of amine and indole.

To find best conditions, the reaction between 4-chlorobromobenzene and aniline was selected as model substrates (Table 1). Influences of various parameters were examined to get the best possible combination; the parameters included solvent, base, temperature and catalyst loading.

Table 1. Optimization condition for reaction of aniline with 4-chlorobromobenzene.[a]



Entry	CuO NPs (g)	Base	Solvent	T (ºC)	t (h)	Yield (%)[b]
1	0.005	K_2CO_3	EtOH	40	5	65
2	0.005	K_2CO_3	DMF	40	3	80
3	0.005	K_2CO_3	Toluene	40	4	75
4	0.005	K_2CO_3	H_2O	40	12	30
5	0.005	K_2CO_3	CH_2Cl_2	40	6	35
6	0.005	K_2CO_3	CH_3CN	40	4	70
7	0.01	K_2CO_3	DMF	40	1	96

8	0.02	K_2CO_3	DMF	40	1	96
9	0.01	-	DMF	40	24	Trace
10	-	K_2CO_3	DMF	40	24	0
11	0.01	Et_3N	DMF	40	3	85
12	0.01	Na_2CO_3	DMF	40	3	60
13	0.01	KOH	DMF	40	3	80
14	0.01	$NaHCO_3$	DMF	40	3	65
15	0.01	NaOH	DMF	40	3	55
16	0.01	K_2CO_3	DMF	25	6	85
17	0.01	K_2CO_3	DMF	60	1	96

[a]Reaction conditions: aniline (1.0 mmol), 4-chlorobromobenzene (1.0 mmol), catalyst, base (1.0 mmol), solvent (3.0 mL).

[b]Isolated yield.

Initially, solvents including toluene, CH_3CN, H_2O, DMF, CH2Cl2, and EtOH were surveyed at the presence of 0.005g CuO NPs, and 1 equiv, of K_2CO_3 at 40 ºC (Table 1). The reaction was significantly affected by the nature of the solvent (entries 1-6, Table 1). The highest yield was observed using DMF (entry 2, 80%). Next, the bases, including NaOH, Et_3N, KOH, Na_2CO_3, $NaHCO_3$ and K_2CO_3 were explored, and K_2CO_3 gave the best yields (entries 7, 11-15, Table 1). However, a low yield was obtained without any base (entry 9, Table 1). It was also found that the reaction temperature has a great efficacy on this transformation (entries 7, 16, 17, Table 1). Reducing the reaction temperature to 25 °C had a negative effect on the product yield (entry 16, Table 1). In addition, when the amount of catalyst was increased from 0.005g to 0.01g, the excellent yield was also afforded (entry 7, 96%). However, when 0.02g of catalyst was employed, the reaction yield and time are same as 0.01g (entries 7, 8, Table 1). It is important to mention that *N*-arylation of aniline did not take place in absence of CuO NPs catalyst (entry 10, Table 1). Therefore, it was decided to use DMF as the solvent, K_2CO_3 as the base, and 0.01g of the CuO NPs catalyst at 40 ºC under aerobic conditions as the optimal conditions in further studies (entry 7, Table 1).

Under the optimized conditions, the catalyst was then applied to other reactions using a broader range of aryl halides and aniline/indole. In general, the coupling reaction among aryl iodides/bromides and amines was clean and high yielding (entries 1, 2, 4, 5, 7, 8, 10-13, 15, 16 Table 2). However, lower yield were obtained when the leaving group was changed to chlorides (entries 3, 6, 9, 14, Table 2). These results ascertained the arrangement of reactivity: R-I>R-Br>R-Cl.

Table 2. CuO NPs catalyzed coupling of aryl halides and amines.[a]

Entry	Aryl halides	amines	Time (h)	Yield (%)[b]	Ref.
1	Ph-I	Indole	1	98	[24]
2	Ph-Br	Indole	1.5	96	[24]
3	Ph-Cl	Indole	12	70	[24]
4	4-Me-Ph-I	Indole	1	96	[24]
5	4-Me-Ph-Br	Indole	2	90	[24]
6	4-Me-Ph-Cl	Indole	12	65	[24]
7	Ph-I	Aniline	0.5	98	[25]
8	Ph-Br	Aniline	1	90	[25]
9	Ph-Cl	Aniline	12	60	[25]
10	4-Cl-Ph-I	Aniline	0.5	98	[26]
11	4-Cl-Ph-Br	Aniline	1	96	[26]
12	4-Me-Ph-I	Aniline	1	95	[26]
13	4-Me-Ph-Br	Aniline	2	90	[25]
14	4-Me-Ph-Cl	Aniline	12	70	[25]
15	4-NO_2-Ph-I	Aniline	2	90	[25]
16	4-NO_2-Ph-Br	Aniline	3	80	[25]

[a]Reactions were carried out under aerobic conditions in 3 mL of DMF, 1.0 mmol aryl halides, 1.0 mmol amines and 1.0 mmol K_2CO_3 in the presence of CuO NPs (10 mg) and 40 ºC.

[b]Isolated yield.

The reusability of heterogeneous catalysts is very important, especially for commercial applications. Therefore, the recycling performance of CuO NPs was investigated in the reaction of aniline with 4-chlorobromobenzene under the optimized reaction conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature, EtOAc was added and the catalyst separated from the reaction mixture by centrifuge, washed with water and ethanol, and reused in a next reaction. The data listed in Fig. 5 shows that catalyst could be reused 7th times with only marginal loss of its catalytic activity.

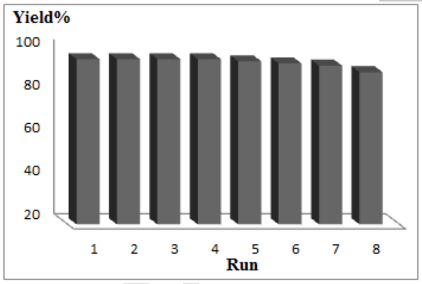


Fig. 5. The recycling of the CuO NPs.

Using a common procedure,[30] CuO NPs without the presence of Thymbra Spicata extract is prepared and used for N-arylation of aniline with 4-chlorobromobenzene under optimized conditions (Table 1). The obtained product was in 90% yield and lower than our method. It was interesting to note that the CuO NPs were surrounded by a thin bio molecular layer of extract, which increased the dispersity of the catalyst in reaction medium and also the reactions yield.

Conclusion

In conclusion, we have developed an efficient, facile and economical method for the green synthesis of CuO NPs using *Thymbra spicata* leaves extract as a reducing and stabilizing agent. CuO NPs was found to be a cheap, air stable and efficient catalyst for ligand-free *N*-arylation of aniline and indole with a variety of aryl halides. The products were obtained in good to excellent yields and the catalyst can be recycled up to seven cycles with almost consistent activity. The notable features of our method are: (i) elimination of toxic ligands and homogeneous catalysts; (ii) high yield of the products; (iii) the use of plant extract as a fast and clean synthetic route for the large scale synthesis of CuO NPs; (iv) no surfactant, capping agent, and/or template were used in the procedure; and (v) the CuO NPs can be easily recovered and reused.

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Highlights

Green synthesis of CuO NPs using *Thymbra spicata* leaves extract as a reducing and stabilizing agent.

Elimination of toxic ligands and homogeneous catalysts

High yield of the products

No surfactant, capping agent, and/or template were used in the procedure

The CuO NPs can be easily recovered and reused.