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Green synthesis of CuO nanoparticles using aqueous extract of *Thymus vulgaris* L. leaves and their catalytic performance for *N*-arylation of indoles and amines

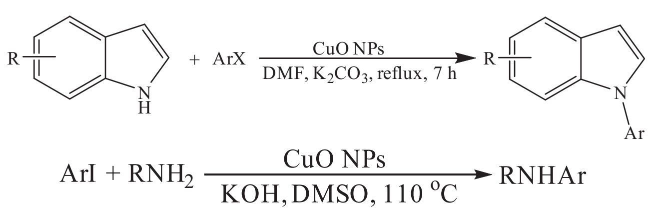
Mahmoud Nasrollahzadeh [a,*], S. Mohammad Sajadi [b], Akbar Rostami-Vartooni [a], Sarbast Mamand Hussin [c]

[a] *Department of Chemistry, Faculty of Science, University of Qom, Qom 37185-359, Iran*
[b] *Department of Petroleum Geoscience, Faculty of Science, Soran University, PO Box 624, Soran, Kurdistan Regional Government, Iraq*
[c] *Department of Chemistry, Faculty of Science, Soran University, PO Box 624, Soran, Kurdistan Regional Government, Iraq*

HIGHLIGHTS

- Green synthesis of CuO NPs using *Thymus vulgaris* L. leaf extract.
- Ligand-free *N*-arylation of indoles and amines.
- Characterization of CuO NPs by XRD, EDS, TEM, TGA/DTA, FT-IR and UV–vis.
- The catalyst can be recovered and reused for further catalytic reactions with almost no loss in activity.

GRAPHICAL ABSTRACT



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ABSTRACT

Copper oxide (CuO) nanoparticles (NPs) were synthesized by biological method using aqueous extract of *Thymus vulgaris* L. leaves as a reducing and capping agent. The progress of the reaction was monitored using UV–visible spectroscopy. The advantages of this procedure are simple operation, use of cheap, natural, nontoxic and benign precursors, absence of toxic reagents and mild and environmentally friendly conditions. The green synthesized CuO NPs was characterized by transmission electron microscopy (TEM), energy-dispersive X-ray spectroscopy (EDS), fourier-transform infrared (FT-IR) spectroscopy, X-ray diffraction analysis (XRD), thermogravimetric analysis (TGA) and differential thermal analysis (DTA). More importantly, the green synthesized CuO NPs was found to be an excellent heterogeneous catalyst for ligand-free *N*-arylation of indoles and amines. The *N*-arylated products were obtained in good to excellent yield and the catalyst can be recovered and reused for further catalytic reactions with almost no loss in activity.

1. Introduction

C—N bond formation is one of the most important reactions in organic synthesis that finds wide applications in the synthesis of many substances such as drugs, materials and natural products [1–6]. In addition, they are also utilized as key intermediates in the synthesis of some biologically active compounds [1–6].

There are several methods for the *N*-arylation of indoles by Ullmann-type coupling reactions. These reactions are generally catalyzed by soluble copper (Cu) complexes with various ligands [7–9]. These reactions were often conducted under harsh reaction conditions such as elevated temperatures as high as 200 °C, use of stoichiometric amounts of copper reagents, and moderate yields with longer reaction time [7–9]. Many of these ligands are expensive, toxic, and sensitive to air and a major challenge lies in the separation of product from expensive catalyst, much to the dismay of large-scale producers.

* Corresponding author.
E-mail address: mahmoudnasr81@gmail.com (M. Nasrollahzadeh).

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In the past years, new catalytic systems have been successfully employed for this cross-coupling reaction in the absence of organic ligands [10–22]. However, these catalytic systems often required excess substrates or high catalyst loadings and suffer from one or more limitations [10–22], such as high reaction temperature and/or prolonged reaction time. In addition, some of these catalysts are air sensitive and homogeneous. The problem with homogeneous catalysis is the difficulty to separate the catalyst and the impossibility to reuse it in consecutive reactions. From the green chemistry points of view, the development of ligand-free catalytic systems, such as heterogeneous catalysts, in place of homogeneous catalysts would be desirable.

Due to high surface-to-volume ratio and nanoparticles highly active surface, heterogeneous catalysts are more and more used in the form of nanoparticles [23–25]. Among heterogeneous catalysts, CuO nanomaterials containing high surface area and reactive morphologies have been used widely as an efficient catalyst for organic synthesis due to good chemical and thermal stability, low cost, low toxicity, ease of handling and, high catalytic activity reusability [26–28].

There are several problems arising when nanoparticles are synthesized by chemical methods which include usage of harsh reducing agents and organic solvents, toxic chemicals and it's dangerous by products [29–31]. To overcome these problems, environmental friendly and green synthesis of nanoparticles by using microorganisms, enzyme and plant or plant extract has become popular in recent years [32–39]. The biosynthetic techniques for the preparation of metal NPs has several advantages over chemical synthesis, such as simplicity, cost effectiveness as well as compatibility for biomedical and pharmaceutical applications. In the biological methods the use of plants extract has advantages such as easily available, safe to handle and possess a broad viability of metabolites. It is found that the extract of plants acts both as reducing and capping agents in the synthesizing process of the nanoparticles. In fact when a nanostructure synthesizes using a plant, the phytochemicals adsorbed on the nanosurface and beside many other benefits such as green synthesis, increasing the stability, preventing the agglomeration and deforming of nanoparticles in most cases, they as capping agents cause a better adsorption of reactants on nanosurface and therefore, enhance the yield of the reactions.

The genus *Thymus vulgaris* L. is a medicinal plant belongs to the family *Lamiaceae* is a perennials, small shrub within the Mediterranean region and a wide distribution in the other parts of the world (Fig. 1). The pharmaceutical effects of the plant such as treatment the respiratory diseases (whooping cough, bronchitis and asthma), preventing the hardening of the arteries, treatment of toothache, urinary tract infection and dyspepsia, expelling fungus from stomach, increasing appetite because of its important component thymol, which has ability to kill bacteria and parasites caused that different studies were carried out in last decades to reveal reported pharmacological activities of *T. vulgaris* both of plant extract and essential oil [40]. The leaf of the plant is usually 4–12 mm long and up to 3 mm wide, sessile or with a very short petiole. The lamina is tough, entire, lanceolate to ovate, covered on both surfaces by a grey or greenish-grey indumentums; the edges are markedly rolled up toward the abaxial surface. The midrib is depressed on the adaxial surface and is very prominent on the abaxial surface. The calyx is green, often with violet spots and is tubular; at the end are 2 lips of which the upper one is bent back and at the end has 3 lobes, the lower is longer and has 2 hairy teeth [41–43]. Studies on the extract of the leaves of *T. vulgaris* L. revealed the presence of phenolic compounds especially flavonoids to which are attributed many of the antioxidant properties, due to their hydrogen donation ability and structural requirement considered to be essential for effective radical scavenging and production of nanoparticles (Scheme 1) [44–46]. Of course it should be added that any other species containing the antioxidant phenolics can be used for biosynthesis of the nanoparticles but what is important here is the type and category of the antioxidant phytochemicals because beside those reducing effect to produce the nano particles they adsorb on nano surface and determine the size, shape and morphology of the biosynthesized nanoparticles, furthermore, they enhance the ability of catalyst and also prevent the agglomeration process and deforming the nanosurface.

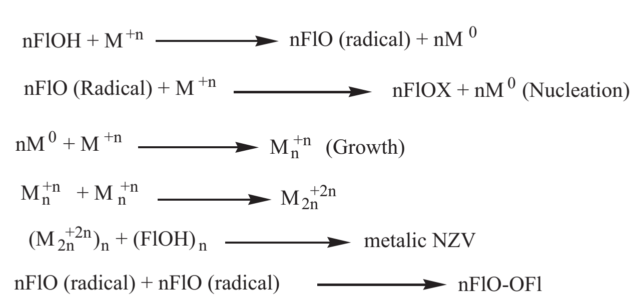
In continuation with our research program to explore different methodologies for the green synthesis of various metal NPs and their role as heterogeneous catalysts in organic reactions [47–49], we now report an environmental friendly approach to produce the CuO NPs using *T. vulgaris* L. leaf extract as a reducing and stabilizing agent. To date, there is no report on the green synthesis of CuO NPs using *T. vulgaris* L. leaf extract. In addition, we have developed and reported CuO nanoparticles as a catalyst for ligand-free *N*-arylation of indoles and amines. More significantly, only a slight loss in catalytic activity is seen after several recycles.

2. Experimental

2.1. Instruments and reagents

High-purity chemical reagents were purchased from the Merck and Aldrich chemical companies. All materials were of commercial reagent grade. Melting points were determined in open capillaries using a BUCHI 510 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer at 400 and 100 MHz, respectively. FT-IR spectra were recorded on Avatar Nicolet 370 FT/IR spectrometer (Thermo Nicolet, USA) using pressed KBr pellets, Resolution: 0.9 cm^{-1}, S/N: 15,000:1, Measurement Wavelength Range: 7800–375 cm^{-1}, Fast Scan Times, detector (DTGS) and Scan Number: 4.

Fig. 1. Image of *Thymus vulgaris* L.



Scheme 1. Reducing ability of antioxidant phenolics to produce NPs using their hydrogen donation activity, where FlOH and NZV are flavonoid and nano zero valent, respectively.