

Preparation of aryl sulfonamides using CuO nanoparticles prepared in extractive *Rosmarinus Officinalis* leaves media

Mohammad Reza Mohammad Shafiee^{1,*}, Mahboubeh Kargar¹

¹Department of Chemistry, Faculty of Sciences, Najafabad Branch, Islamic Azad University, P.O. Box: 517; Najafabad, Esfahan, Iran

*corresponding author e-mail address: mohammadreza.mohammadshafiee@gmail.com

ABSTRACT

The nano-structures of CuO were effectively prepared using an extract of *Rosmarinus Officinalis* Leaves as a green medium. Cupric sulfate was used as starting substrate. Structural and morphological properties of the synthesized nanoparticles have been characterized by using FE-SEM, BET and XRD analysis. The effect of calcination temperature on the morphology of the as synthesized powders was investigated. In order to evaluate the efficiency of the as synthesized CuO nano-structures the catalytic preparation of aryl sulfonamides were investigated in the reaction of aromatic amines and *p*-toluenesulfonyl chloride. The monoclinic single phase structure was observed in the XRD pattern of powders. The crystalline size of the samples was determined using a *Scherrer* formula from the highest peak of the XRD pattern at 76, 76, 77 nm. Different morphologies of CuO nano-structures including spherical nano-powder with the average particle sizes of about 70-130 nm, cone-shaped clusters of CuO with the average size of 0.9–0.12 μm and cubic or uniform sand like conjoined particles with the average size of 2–4 μm were observed at 400, 600 and 800 °C respectively.

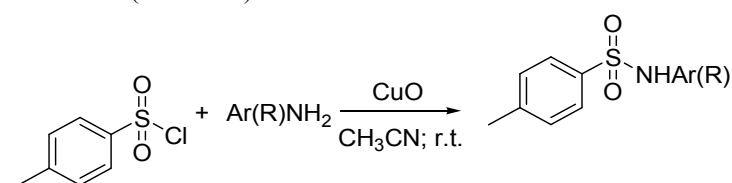
Keywords: sulfonamide; *p*-toluenesulfonyl chloride; CuO; *Rosmarinus Officinalis*.

1. INTRODUCTION

The formation of C-N and S-N bonds is of essential significance in organic synthesis, owing to the high commonness of nitrogen-containing molecules of natural and pharmaceutical pertinence [1]. The vast majority of techniques for the introduction of C-N and S-N bonds rely on functional group interconversions for their synthesis. In comparison, the formation of new S-N and C-N bonds directly from C-O or S-O bonds represents a very attractive and efficient choice [1-4].

Form the many years ago sulfonamides have been widely employed as useful compounds for drugs and crop protection agents, and are using materials for the prevention and treatment of bacterial infections, diabetes mellitus, oedema, hypertension and gout. They are used in the some have proved to be useful as herbicides and plaguicides [5-9]. Several methods have been used for the synthesis of sulfonamide derivatives. For example reaction of (a) silylamine with sulfonyl chloride [10, 11], (b) amine with a substituted sulfonyl chloride, often in the presence of an organic amine base to scavenge the acid (HCl). In this condition elevated temperature, especially for the less reactive anilines is required

[12-13], (c) Slowly add of sulfonyl chloride into an amine solution in a biphasic system of organic solvents and basic aqueous solution [14-15]. But hydrolysis of sulfonyl chlorides is the major competing reaction, which results in diminishing yields. Thus, these protocols remain a need for a simple and efficient methodology towards accessing sulfonamides under mild conditions in the absence of a strong base or competing nucleophile. In the present protocol and in continue of our works [16-23], we initiated this study to devise a simple, universal and high yielding synthetic methodology and applicable to a wide range of amines using CuO nano-particles under ambient conditions (Scheme 1).



Scheme 1. Preparation of aryl sulfonamides using CuO nano-structures.

2. EXPERIMENTAL SECTION

All reagents were purchased from Merck and Aldrich and used without further purification. Phase identification was carried out for the as-precipitated and heat treated samples by an X-ray diffraction (XRD) method with a Rigaku D-max C III, X-ray diffractometer using Ni-filtered Cu-K α radiation. Field Emission Scanning Electron Microscope (FESEM) images were obtained on HITACHI S-4160. N₂ adsorption measurements of the catalyst were carried out using micro metrics adsorption equipment (Quantachrome instrument, model Nova 2000, USA), N₂ (99.99%)

as the analysis gas and the catalyst samples were slowly heated to 140 °C for 3h under nitrogen atmosphere. The total pore volume was obtained from the maximum amount of nitrogen gas adsorbed at partial pressure P/P₀=0.999. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d₆ relative to TMS (0.00 ppm). Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

2.1. Preparation of CuO nano-structures.

At first, 20 g of Leaves of *Rosmarinus Officinalis* was grounded and inserted in a 250 balloon flask containing 100 mL of de-ionized water and 50 mL of ethanol and the mixture was refluxed for 4h. Afterwards the extract was filtered to cut off the unrequited bodies. The extract was combined with 15 mL of aqueous ammonia (37%). Next the prepared solution was pureed drop-wise to an aqueous solution of Cu(II) (prepared by dissolving of cupric sulfate (20 mmol) in 50 mL of water) under vigorous magnetic stirring. Next the resulted mixture was aged for 5h until a precipitate was formed. Finally, the mixture was filtered washed with water for three times, dried and calcinated at 400, 600 and 800 °C for 2h in an electric furnace using alumina crucibles and maintained at the stable mentioned temperature for 2h. After calcining, the obtained products of CuO were stored in airtight container for further analysis.

2.2. General procedure. To a mixture of aromatic amines (1 mmol) and *p*-toluenesulfonyl chloride (1 mmol) in acetonitrile (5

mL), CuO nano-structures (0.25 mmol) were added as the catalyst, and the mixture was stirred for an appropriate time at room temperature. After the reaction was completed (TLC is indicated), the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 × 30 ml). The combined chloroform extracts were dried with Na₂SO₄ and concentrated to afford the pure products.

Selected data: 4-methyl-N-tosylbenzenamine: ¹H NMR (400 MHz, CDCl₃): 2.23 (s, 3H), 2.35 (s, 3H), 4.81 (s, 1H, NH), 6.96 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H) ppm. **4-chloro-N-tosylbenzenamine:** ¹H NMR (400 MHz, CDCl₃): 2.34 (s, 3H), 4.83 (s, 1H, NH), 7.06 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H) ppm. **N-tosylcyclohexanamine:** ¹H NMR (400 MHz, CDCl₃): 1.31-1.84 (m, 10H), 2.33 (s, 3H), 3.90 (m, 1H), 4.64 (s, 1H, NH), 7.32 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H) ppm.

3. RESULTS SECTION

In order to obtain information about the phase characteristics of the synthesized materials, XRD analysis are done. Figure 1 shows the XRD patterns of CuO nano-catalysts calcined at 400, 600 and 800 °C for 2h. The monoclinic single phase structure (space group C2/c), with lattice parameters *a* = 4.6853Å, *b* = 3.4257Å and *c* = 5.1303Å, β = 99.5490° (JCPDS 045-0937), was observed in the XRD pattern of powders. With increasing in the calcining temperature an increase in the intensity of the diffraction peaks was acquired. The crystalline size of the samples was determined using a *Scherrer* formula from the

highest peak of the XRD pattern at 76, 76, 77 nm with the use of the following equation:

Average Crystalline Size :

$$\frac{K \lambda}{\beta \cos \theta}$$

Where *K* is taken as 0.9, λ is the wavelength of X-ray used, β is the full width half maximum of the prominent peak and θ is the glancing angle.

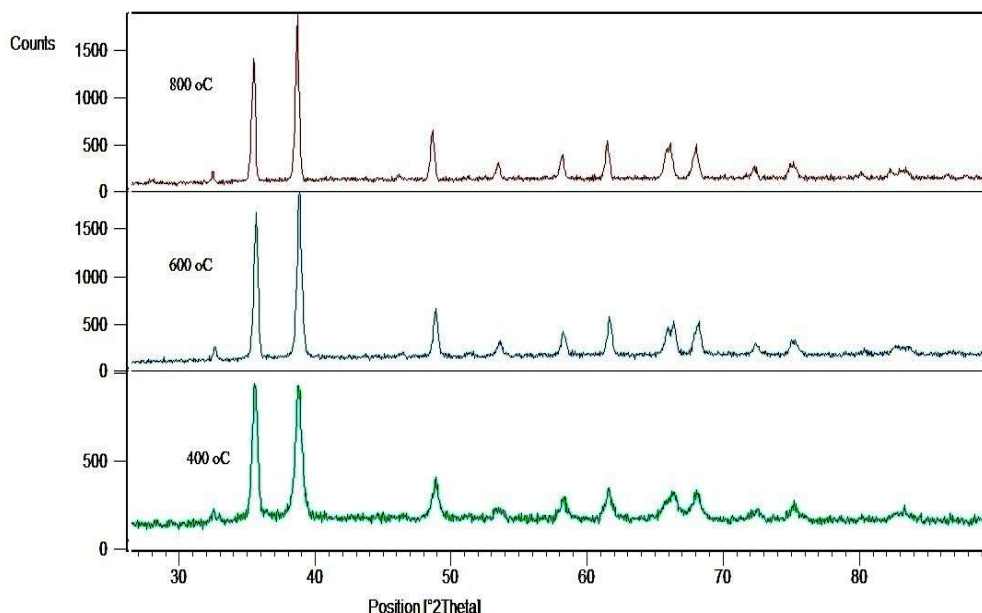


Figure 1. XRD patterns of CuO nanoparticles calcined at 400, 600, and 800 °C.

The FE-SEM images were performed to determine the shape and size of the synthesized samples and the results are shown in Figures 2-4. It was revealed that with increasing on the calcination temperature from 400 to 800 °C a change in the

morphology and size of the samples was occurring. When the sample was calcined at 400 °C the spherical nano-powder of CuO with average particle sizes of about 70-130 nm were obtained (Figure 2).

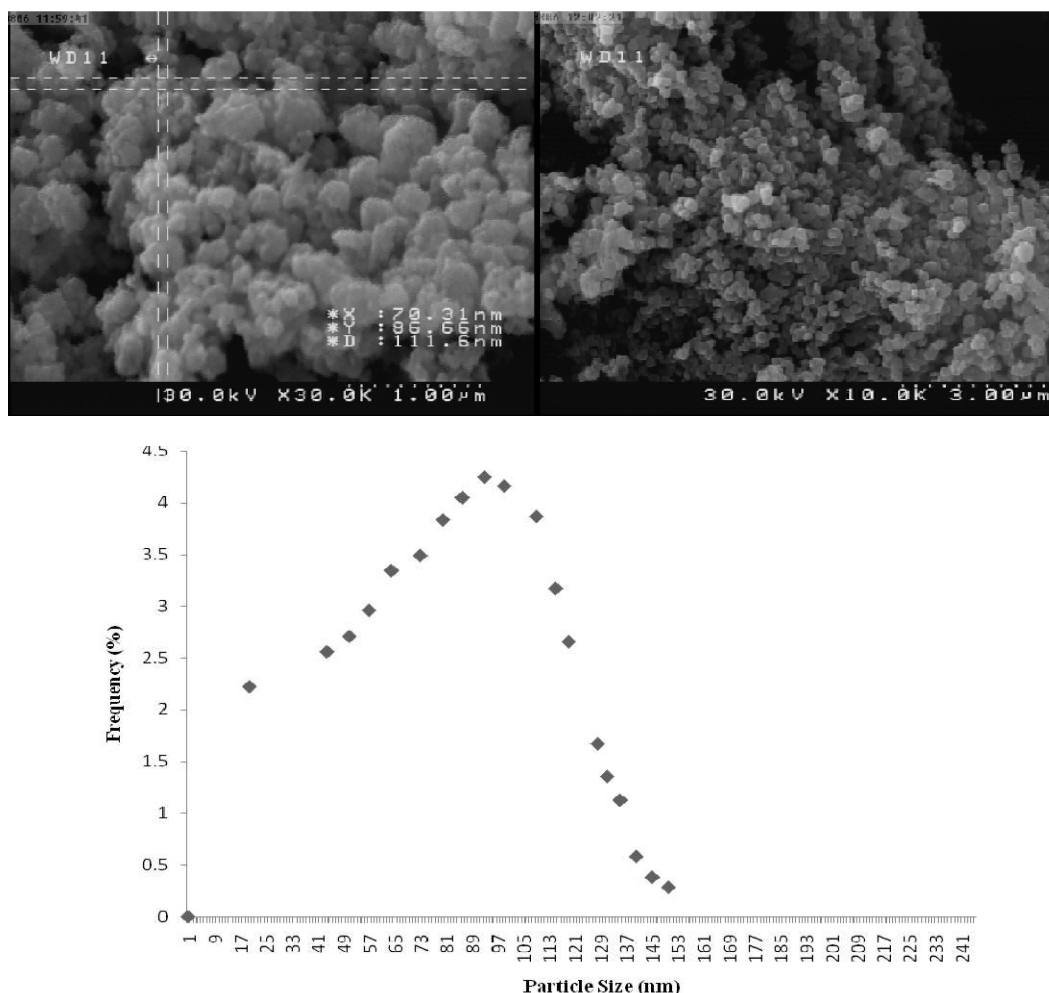


Figure 2. FE-SEM micrographs and particle size distribution of CuO nano-structure calcined at 600 °C.

The mean surface area of the sample calcined in 400 °C was determined using a BET analysis as 3.675 m²g⁻¹.

With increasing temperature to 600 °C a change in the morphology was observed. Compared to Figure 2, as shown in Figure 3, it is clear that the morphology of the as-synthesized sample is changed to the cone-shaped clusters of CuO with the

average size of 0.9–0.12 μm. These clusters are wrought from the CuO nano-spherical with the average size of about 90 nm as estimated from the particle size distribution analysis (Figure 3). The formation of different morphology is due to the fact that in higher temperatures the rate of the organic matter removal is increasing.

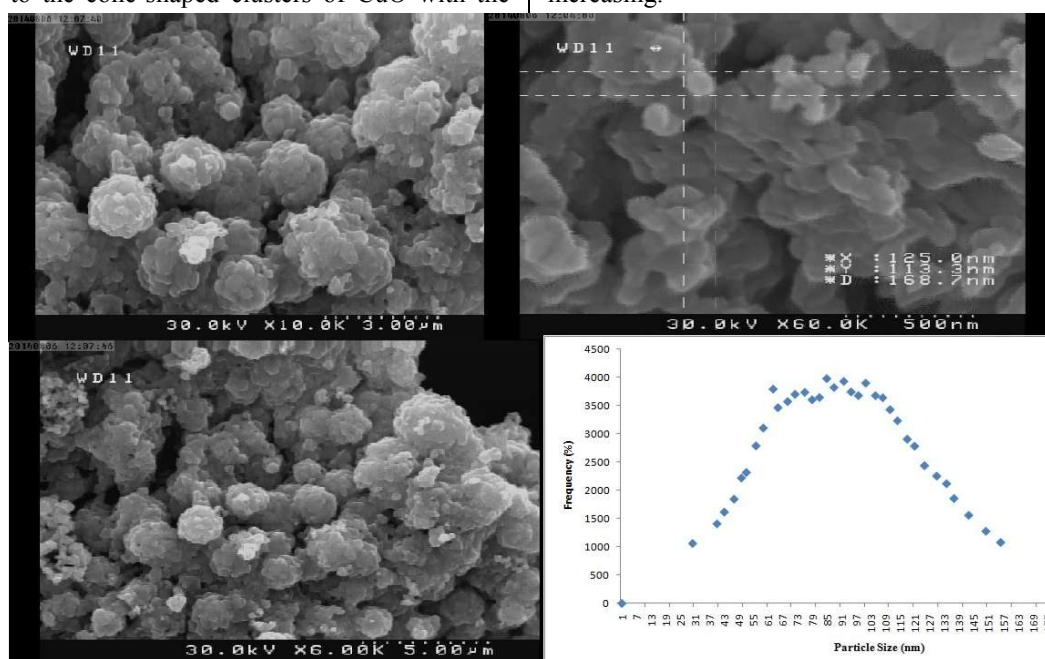


Figure 3. FE-SEM micrographs and particle size distribution of CuO nano-structure calcined at 600 °C.

After that a fresh sample was calcined in 800 °C and the obtained morphology was studied by FE-SEM (Figure 4). As it was shown in Figure 4 the agglomeration of the nano-particles were speeding and the morphology was changed from cluster like to the cubic or uniform sand like conjoined particles with the average size of 2-4 μm. This can be due to the fast nucleation of the CuO nano-crystals which causes a big aggregation of the CuO nanoparticles.

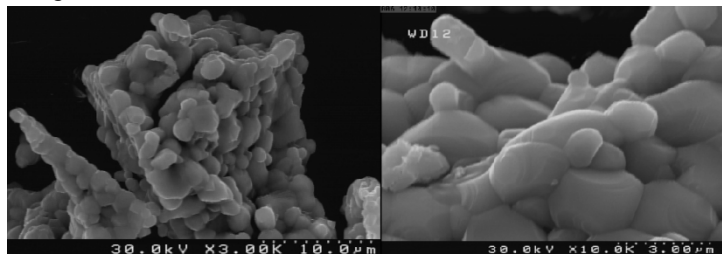
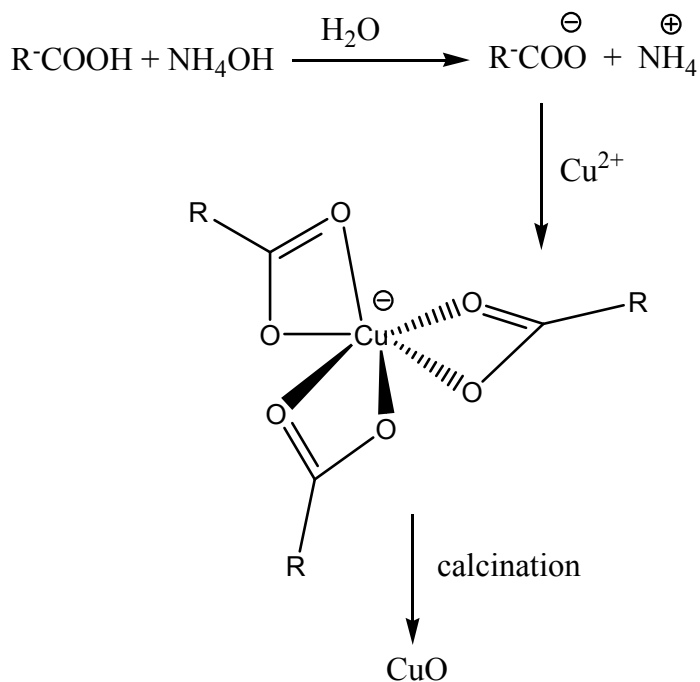


Figure 4. FE-SEM micrographs of CuO nano-structure calcined at 800 °C.

Rosmarinus Officinalis extract was known to be reached in carboxylic acids such as rosmarinic acid and carnosic acid [19]. The carboxyl group is converted to carboxylic anion following the addition of ammonia solution. The presenters of chelating agents such as carboxylic anions are the main reason for the preparation of CuO nano-structures.

The proposed mechanism for the preparation of CuO nano-structures is shown in Scheme 2.



Scheme 2. Proposed mechanism for the preparation of CuO nano-structures.

3.1. Catalytic testing.

In order to examine the catalytic activity of CuO nano-structures, the reaction of equimolar 4-methylbenzene-1-sulfonyl chloride and 4-methoxyaniline was chosen as a model of substrates. No other additive was necessary to promote the reaction.

Table 1. Preparation of *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide in different solvents and under solvent-free conditions.

Solvent (2 mL)	Catalyst (mmol)	CuO calcined at 400 °C Time (h)/ Yield (%) ^a	CuO calcined at 600 °C Time (h)/ Yield (%) ^a	CuO calcined at 800 °C Time (h)/ Yield (%) ^a
CH ₃ CN	0.25	2/89	2.2/85	2.5/80
CH ₂ Cl ₂	0.25	4/70	4/65	5/68
Et ₂ O	0.25	2/74	2/71	3/72
EtOAc	0.25	2/84	2/85	2.2/74
<i>n</i> -Hexane	0.25	5/65	5.5/70	6/65
CHCl ₃	0.25	3/75	3/70	3.3/71
CH ₃ CN	0.1	3/60	3/55	4/54
CH ₃ CN	0.5	1.5/77	2/72	2/71
CH ₃ CN	0.75	1.5/78	1.5/75	1.5/72
CH ₃ CN	1	1/75	1/75	1/70

^aIsolated Yield

First, the effect of solvent was examined using different samples of CuO nano-structures calcined at 400, 600 and 800 °C and the results are summarized in Table 1. As shown in Table 1, the mentioned reaction in some of the common organic solvents such as *n*-Hexane, Et₂O, CH₂Cl₂ and CHCl₃ gave *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide in moderate yields. As can be seen from Table 1, best results were obtained using CH₃CN as solvent under ambient conditions. The results are summarized in Table 1. The next reaction was done using various amounts of catalyst loading. The optimal catalyst amount was found to be 0.25 mmol. The use of lesser amounts of the CuO afforded inferior product yield (Table 1). On the other hand, the

use of higher quantities of the CuO did not provide any significant advantage in the increasing of the reaction yield (Table 1).

As it was expected the obtained results are similar for different samples of CuO nano-structures. However the activity of samples is decreased in order of the samples calcined at 400, 600 and 800 °C respectively. This may be due to differences in the morphology and surface area of the samples.

Following the typical optimized reaction conditions, the present methodology was elaborated to a variety of amines to prepare a wide range of sulfonamides. The results are summarized in Table 2. A series of aromatic and aliphatic amines were sulfonylated at room temperature with considerable yields (Table 2, Entries 1–13). Aromatic amines with an electron-donating

group showed higher reactivity than those with an electron-withdrawing group (Table 2).

Table 2. Preparation of aryl sulfonamides using CuO nano-structures (0.25 mmol) calcined at different temperatures.

Entry	Amine	CuO calcined at 400 °C		CuO calcined at 600 °C		CuO calcined at 800 °C	
		Time (h)/ Yield (%) ^a	Time (h)/ Yield (%) ^a	Time (h)/ Yield (%) ^a	Time (h)/ Yield (%) ^a		
1	4-Methoxyaniline	2/92	2/80	2.5/81	5/75	2.5/80	3.5/79
2	2-Methylaniline	2.5/85	4/81	6.5/69	7.5/65	5/70	6/71
3	4-Methylaniline	2/89	2.2/85	3.5/74	4/70	4/70	5/71
4	Aniline	3/85	3/80	2/68	4/70	4/68	5/70
5	4-Nitroaniline	6/71	6.5/69	4/70	5/71	4/68	5/70
6	4-Chloroaniline	5/75	5/70	4/70	5/71	4/68	5/70
7	Cyclohexylamine	3/77	3.5/74	4/70	5/71	4/68	5/70
8	<i>n</i> -Butylamine	2/70	2/68	4/70	5/71	4/68	5/70
9	Piperidine	4/71	4/70	4/70	5/71	4/68	5/70
10	Morpholine	4/75	4/68	4/68	5/70	4/68	5/70

^aIsolated Yields

4. CONCLUSIONS

In summary, CuO nanostructures with various morphologies have been successfully prepared via a coprecipitation method with copper sulfate as precursor and *Rosmarinus Officinalis* extract as a surfactant. The usage of green synthesis is a feasible and low-cost method to obtain nanometer scale particles as shown in the results. The XRD results showed that pure CuO powders were formed with the aid of this method. The use of plant extract in the synthesis of nanostructured CuO can be a cost effective and ecofriendly approach. FE-SEM

imaging of the nano-structures showed the formation of different morphology of nano-spheres, cluster like and sand like conjoined particles for the samples calcined at 400, 600 and 800 °C respectively. The catalytic properties of CuO nano-structures were investigated in the reaction of aromatic amines and *p*-toluenesulfonyl chloride to form aryl sulfonamides. This work demonstrates the use of a green biosynthesis method using cheap precursors of *Rosmarinus Officinalis* extract which provides nano-structures of CuO with well crystalline structure.

5. REFERENCES

- [1] Hili R., Yudin A.K., Making carbon-nitrogen bonds in biological and chemical synthesis, *Nat. Chem. Bio.*, 2, 284-287, **2006**.
- [2] Beccalli E.M., Brogini G., Martinelli M., Sottocornola S., C-C, C-O, C-N bond formation on sp² carbon by Pd(II)-catalyzed reactions involving oxidant agents, *Chem. Rev.*, 107, 5318-5365, **2007**.
- [3] Ming B., Masao S., *N*-Trifluoroacetyl arenesulfenamides, effective precursors for synthesis of unsymmetrical disulfides and sulfonamides, *Tetrahedron*, 59, 9655-9659, **2003**.
- [4] Taniguchi N., Copper-Catalyzed Synthesis of Sulfenamides Utilizing Diaryl Disulfides with Alkyl Amines, *Synlett*, 1917-1920, **2007**.
- [5] Supuran C.T., Casini A., Scozzafava A., Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents, *Med. Res. Rev.*, 5, 535-358, **2003**.
- [6] Scozzafava A., Owa T., Mastrolorenzo A., Supuran C.T., Anticancer and antiviral sulfonamides, *Curr. Med. Chem.*, 10, 925-953, **2003**.
- [7] Harter W.G., Albrect H., Brady K., Caprathe B., Dunbar J., Gilmore J., Hays S., Kostlan C.R., Lunney B., Walker N., The design and synthesis of sulfonamides as caspase-1 inhibitors, *Bioorg. Med. Chem. Lett.*, 14, 809-812, **2004**.
- [8] Reddy N.S., Mallireddigari M.R., Cosenza K.G., Bell S.C., Reddy E.P., Reddy M.V.R., Synthesis of new coumarin 3-(*N*-aryl) sulfonamides and their anticancer activity, *Bioorg. Med. Chem. Lett.*, 14, 4093-4097, **2004**.
- [9] Stranix B.R., Lavallee J.F., Seigny G., Yelle J., Perron V., Leberre N., Herbart D., Wu J.J., Lysine sulfonamides as novel HIV-protease inhibitors: *N*-acyl aromatic alpha-amino acids, *Bioorg. Med. Chem. Lett.*, 16, 3459-3462, **2006**.
- [10] Holmes T.J.J., Lawton R.G., Preparation of nonsymmetrical *p*-benzoquinone diimides for evaluation as protein cleavage reagents, *J. Org. Chem.*, 48, 3146-3150, **1983**.
- [11] Yasuhara A., Kameda M., Sakamoto T., Selective Monodesulfonylation of *N,N*-Disulfonylarylamines with Tetrabutylammonium Fluoride, *Chem. Pharm. Bull.*, 47, 809-812, **1999**.
- [12] Low C.M.R., Broughton H.B., Kalindjian S.B., McDonald I.M., Novel oxathiazinones as gastrin ligands: Unexpected products from the schotten-baumann reaction of arylsulphonyl chlorides with derivatives of aspartic acid, *Bioorg. Med. Chem. Lett.*, 2, 325-330, **1992**.
- [13] Surman M.D., Mulvihill M.J., Miller M.J., Novel 1,4-Benzodiazepines from Acylnitroso-Derived Hetero-Diels-Alder Cycloadducts, *Org. Lett.*, 4, 139-141, **2002**.
- [14] Chandrasekhar S., Mohapatra S., Neighbouring group assisted sulfonamide cleavage of Sharpless aminols under acetonation conditions, *Tetrahedron Lett.*, 39, 695, **1998**.
- [15] Carvalho Jr. R.N., Moura L.S., Rosa P.T.V., Meireles M.A.A., Supercritical fluid extraction from rosemary (*Rosmarinus officinalis*): Kinetic data, extract's global yield, composition, and antioxidant activity, *J. of Supercritical Fluids*, 35, 197-204, **2005**.
- [16] Ghashang M., Kargar M., Shafiee M.R.M., Mansoor S.S., Fazlinia A., Esfandiari H., CuO Nano-structures Prepared in *Rosmarinus Officinalis* Leaves Extract Medium: Efficient Catalysts for the Aqueous Media Preparation of Dihydropyrano [3, 2-*c*] chromene Derivatives, *Recent Pat. Nanotech*, 9, 204-211, **2015**.
- [17] Ghashang M., Mansoor S.S., Aswin K., Thiourea dioxide: An efficient and reusable organocatalyst for the rapid one-pot synthesis of pyrano [4, 3-*b*] pyran derivatives in water, *Chin. J. Catal*, 35, 127-133, **2014**.
- [18] Dehbashi M., Aliahmad M., Mohammad Shafiee M.R., Ghashang M., Nickel-doped SnO₂ Nanoparticles: Preparation and Evaluation of Their Catalytic Activity in the Synthesis of 1-amido Alkyl-2-naphtholes, *Synth. React. Inorg. Metal-Org. Nano-Metal Chem*, 43, 1301-1306, **2013**.
- [19] Ghashang M., Preparation and application of barium sulfate nano-particles in the synthesis of 2, 4, 5-triaryl and *N*-aryl (alkyl)-2, 4, 5-triaryl imidazoles, *Curr. Org. Synth.* 9, 727-732, **2012**.
- [20] Shafiee M.M.R., Ghashang M., Fazlinia A., Preparation of 1, 4-dihydropyridine derivatives using perchloric acid adsorbed on magnetic Fe₃O₄ nanoparticles coated with silica, *Curr. Nanosci*, 9, 197-201, **2013**.

[21] Taghrir H., Ghashang M., Biregan M.N., Preparation of 1-amidoalkyl-2-naphthol derivatives using barium phosphate nanoparticles, *Chin. Chem. Lett.*, 27, 119-126, **2016**.

[22] Zare M., Ghashang M., Saffar-Teluri A., BaO-ZnO nano-composite efficient catalyst for the photo-catalytic degradation of 4-chlorophenol, *Biointerface Res. Appl. Chem.*, 6, 1049-1052, **2016**.

[23] Shafiee, M.R.M., Fazlinia, A., Yaghooti, N., Ghashang, M., A convenient method for the preparation of 2, 4, 5-triaryl imidazoles using barium chloride dispersed on silica gel nanoparticles (BaCl₂-nano SiO₂) as heterogeneous reusable catalyst, *Lett. Org. Chem.* 9, 351-355, **2012**.

© 2016 by the authors. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/4.0/>).