Volume 7, Issue 5, 2017, 2170 - 2173 **ISSN 2069-5837**

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Original Research Article **Open Access Journal**

Received: 25.08.2017 / Revised: 30.09.2017 / Accepted: 05.10.2017 / Published on-line: 15.10.2017

Synthesis of 3,4,5-substituted furan-2(5H)-ones using ZnO nanostructure as an efficient catalyst

Mohammad Reza Mohammad Shafiee[1, *], **Mahboubeh Kargar** [1]

[1]Department 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

A family of 3,4,5-substituted furan-2(5*H*)-one derivatives are synthesized from aldehydes, aromatic amines, and acetylenic esters *via* a one-pot reaction catalyzed by nano-structured ZnO. This procedure presents advantages such as: high yields, simple methodology, and easy work up. Nanostructured ZnO was prepared*via* simple precipitation of zinc (II) ions in Prunus Cerasus juice media.

Keywords:*3,4,5-substituted furan-2(5H)-one; nanostructured ZnO; Acetylenic esters; Butenolides.*

1. INTRODUCTION

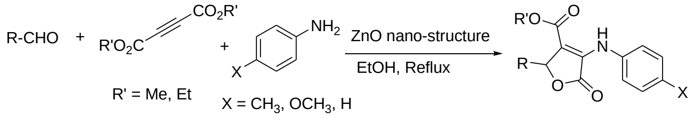
Functionalized furan-2(5H)-ones are important heterocyclic compounds, present in diverse natural, biological and medicinal compounds. They are a class of heterocyclic compounds containing furan core named as butenolides which are of synthetic interest since they show a broad area of biological activities. On the other hands, butenolides are versatile building blocks for natural product syntheses [1-7].

In recent years, butenolide derivatives have been received considerable attention, especially for organic and medicinal chemists because these compounds exhibit a broad range of biological activities, such as antimicrobial [8, 9], antifungal [10,11], anti-inflammatory [12], anticancer [13,14] and anti-viral HIV-1 [15, 16]. Therefore, the synthesis butenolide scaffolds have gained great importance in organic synthesis.

The three-component reaction of anilines, aldehydes, and acetylenic esters is one of the newly routes for the preparation of 3,4,5-substituted furan-2(5*H*)-one derivatives discovered by Murthy *et-al.*using β-cyclodextrin as an efficient catalyst [17]. Since that time various catalytic systems were reported by organic chemists involving the use of $SnCl_2$ [18], ZnO nanoparticles [19], $Al(HSO_4)_3$ [20], tetra-*n*-butylammonium bisulfate [21], PPA/SiO_2 [22], SnO nanoparticles [23] and HY zeolite [24].

The widespread interest in the chemistry and therapeutic application of furan-2(5*H*)-one derivatives is the main reason was given for developments of new strategies for the preparation of substituted furan-2(5*H*)-ones is still in demands.

As a part of our works on multi-component reactions [25-30], we wish to report a novel nano-structured ZnO synthesis of 3,4,5-substituted furan-2(5*H*)-ones *via* a multi-component reaction of aromatic amines, aldehydes and acetylenic esters. This procedure presents a new, efficient and green approach for the preparation of substituted furan-2(5*H*)-ones in good yields (Scheme 1).



Scheme 1. Preparation of 3,4,5-substituted furan-2(5*H*)-one derivatives.

2. EXPERIMENTAL SECTION

2.1. Reagents and Instrumentation. Chemicals were purchased from Merck and Aldrich and used without further purification. The catalyst characterizations were taken on a HITACHI S-4160 field emission scanning electron microscope (FE-SEM) and a D_8, Advance, Bruker, axs, X-Ray diffractometer (XRD) (Cu-Kα irradiation). The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. 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.

2.2. Preparation of nano-structured ZnO. A water solution of Prunus Cerasus juice (10 mL) was mixed with 10 ml aqueous ammonia (37%) and was drop-wise added into a solution of $ZnCl_2$ (20 mmol in 50 mL of distilled water) drop wise under magnetic stirring. The obtained mixture was stirred at room temperature for 30 min. The resultant dark green precipitate was filtered, washed with distilled water and absolute ethanol and dried at 100 °C for ~ 2h in an oven to gain homogenous mixture. The precipitate was calcined at 600 °C in an electric furnace using alumina crucibles and maintained at the stable mentioned temperature for 2h.

2.3. General procedure. Aldehyde (1 mmol), acetylenic esters (1 mmol) and aromatic amine (1 mmol), nano-structured ZnO (0.025 g), and ethanol (5 mL) was charged into a round bottom flask. The resulting mixture was allowed to be stirred at reflux condition for the appropriate time (Table 2, monitored by TLC). Upon completion, the solvent was concentrated and the reaction mixture was diluted in $CHCl_3$, the catalyst was isolated by simple filtration, and the crude product was washed with diethyl ether to afford the pure product.

Selected data:

Methyl 2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)furan-3-carboxylate (11a): ^{1}H-NMR (400 MHz, DMSO-d_6): 3.73 (s, 3H, OCH_3), 6.08 (s, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.35-7.44 (m, 5H), 7.49-7.58 (m, 4H), 8.89 (s, 1H, NH) ppm.

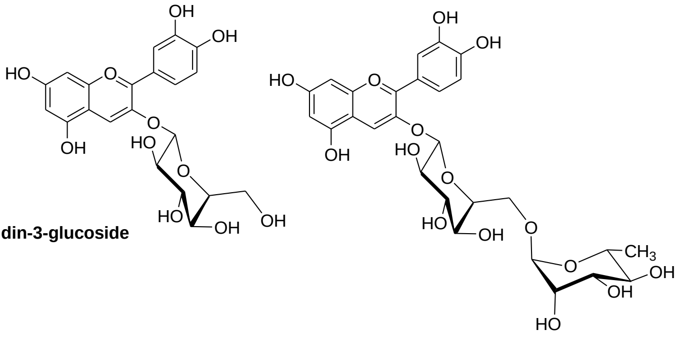
Ethyl 2,5 – dihydro – 5 – oxo – 2 – phenyl – 4-(phenylamino)furan – 3-carboxylate (12a): ^{1}H-NMR (400 MHz, DMSO-d_6): 1.24 (t, *J* = 6.8 Hz, 3H, CH_3), 4.15 (q, *J* = 6.8 Hz, 2H, OCH_2), 6.07 (s, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.35-7.44 (m, 5H), 7.49-7.58 (m, 4H), 8.91 (s, 1H, NH) ppm.

3. RESULTS SECTION

The nano-structured ZnO was synthesized *via* a simple precipitation method with the using of an extract solution of Prunus Cerasus juice.

Mechanism of the formation of nano-structured ZnO. In green chemistry processes, a medium that using of plant extracts, generally called biosynthesis method which is an environmentally friendly method, as it is reduced the use of expensive and hazardous chemicals and has been utilized widely for the synthesis of nano-structured materials. The understanding of the mechanism of green biosynthesis of nano-structured ZnO by a plant extract is still in its infancy and more investigation is required to be understandable. As it was revealed from the literatures various organic compounds like alkaloids, polyphenols and pigments are present in plant extracts which are able to chelate the metal ions through their hydroxyl and carbonyl groups [31-34].

Prunus Cerasus juice is rich from the polyphenolic compounds such as cyanidin-3-glucoside and cyanidin-3-rutinoside [34] (Scheme 2) which may be the main factor required for the biosynthesis of nano-structured ZnO. These hydroxyl groups of these compounds chelate Zn^{2+} ions. The calcination step is needed for the removing of all organic materials and finally nano-structured ZnO remain as the pure sample.



cyanidin-3-glucoside

cyanidin-3-rutinoside

Scheme 2. Chemical structure of cyanidin-3-glucoside and cyanidin-3-rutinoside present in Prunus Cerasus juice.

In order to obtain information about the phase characteristics of the synthesized materials, XRD analysis has been made. Figure 1 shows the XRD patterns of ZnO nano-catalyst calcined at 600 °C for 2h. The hexagonal single phase structure (space group P63mc), with lattice parameters a = 3.2490Å, b = 3.2490Å and$c$ = 5.2050Å, β=99.5490°, was observed in the XRD pattern of the powders which are in agreement with the reported standard values (JCPDS 00-005-0664). The characteristic peaks of hexagonal ZnO are 31.75, 34.44, 36.25, 47.54, 56.55, 62.87, 67.91, 69.05, 89.63, 95.31 2θ°. The crystalline size of the sample was determined using a *Scherrer* formula from the full width at half maximum (FWHM) of the highest peak of the XRD pattern as 86 nm.

Table 1: Optimization of the reaction condition.

Entry	Catalyst (g)	T (°C)	Solvent (5 mL)	Time (h)	Yield (%)^a
1	0.05	Reflux	*n*-Hexane	10	-
2	0.05	Reflux	CH_2Cl_2	10	-
3	0.05	Reflux	Et_2O	10	-
4	0.05	Reflux	EtOAc	10	30
5	0.05	Reflux	EtOH	8	84
6	0.05	Reflux	MeOH	8	70
7	0.05	r.t.	70	10	-
8	-	r.t.	EtOH	10	-
9	0.025	Reflux	EtOH	8	83
10	0.075	Reflux	EtOH	5	76
11	0.1	Reflux	EtOH	5	74
12	0.25	Reflux	EtOH	10	71*

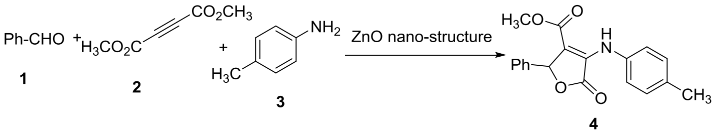
^{a} Isolated Yields; * ZnO was prepared via a same procedure without using of juice

FE-SEM analyze was used to determine the morphological structure of the nanostructured ZnO (Figure 2). The particles are regular nearly uniform spherical which some of them have dimensions less than 100 nm.

The catalytic activity of zinc oxide, in the present study, was investigated through the transformation of **1, 2,** and **3** into **4** under solvent and solvent-free condition (Scheme3, Table 1).

The results of performed experiments showed that the solvent has anomalous effect on the productivity of the reaction. Unlike polar solvents which have resulting in moderate to good yields (30-84%), using of non-polar solvents and also solvent-free condition are not effective (0%). Consequently to the obtained results, EtOH is the more suitable solvent for the reaction medium. Next, the effect of catalyst dosage (varying from 0.025-0.25g) on the product yield was investigated. An excellent yield of product was obtained when 0.025 g of catalyst was used. The further increase in the ZnO dosage did not shown any significant increase on the product yield (Table 1).

For comparison a sample of ZnO was prepared *via* a same procedure without using of juice and was used as a catalyst for the above reaction under optimized condition. The result shows that the prepared sample is less effective catalyst for the preparation of 3,4,5-substituted furan-2(5*H*)-ones (Table 1).



Scheme 3. Preparation of methyl 4-(*p*-tolylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate.

Next, using the optimized conditions, diverse anilines, aldehydes and acetylenic esters reacted together to give the corresponding 3,4,5-substituted furan-2(5*H*)-ones (Scheme 1,

Table 2). It was found that the yields and product purity for all products including electron-donating and electron-withdrawing groups substituted on the aromatic rings are good (Table 2, products **1a-17a**). Aromatic aldehydes and amines bearing electron-withdrawing groupsrequire more time to complete the reaction, whereas this time is less for the donor substitutions.

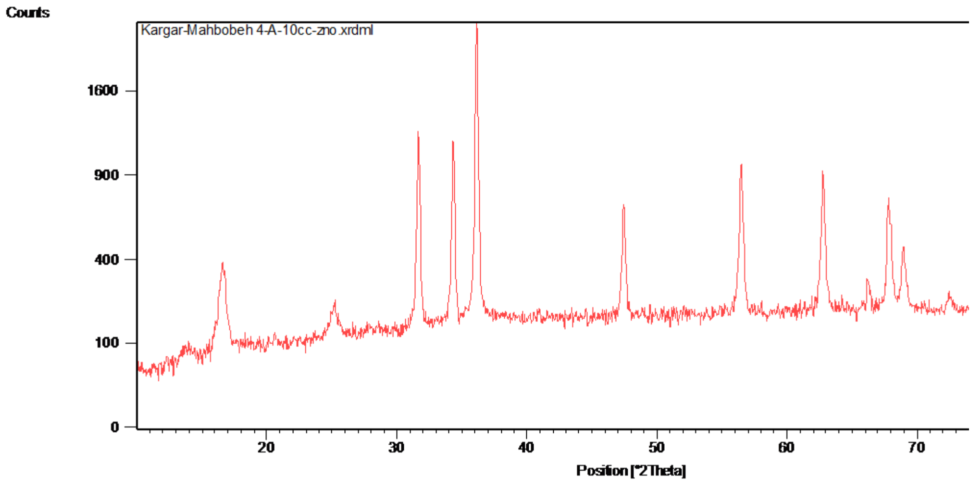


Figure 1. XRD pattern of ZnO nano-structure.

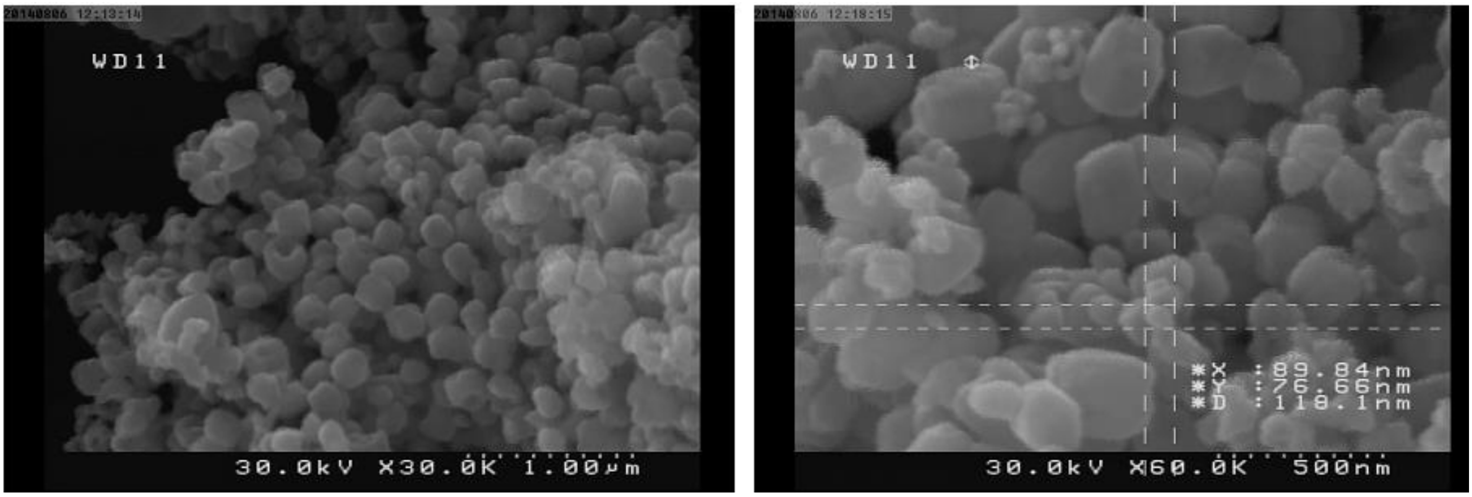


Figure 2. FE-SEM micrograph of ZnO nanostructures.

Table 2. Synthesis of 3,4,5-substituted furan-2(5*H*)-one derivatives (Scheme 1)

Product	Aldehyde	Amine	R	Time (h)	Yield (%)^a
1a	Benzaldehyde	4-Methylaniline	**Me**	8	83
2a	Benzaldehyde	4-Methylaniline	**Et**	8	81
3a	4-Methylbenzaldehyde	4-Methylaniline	**Me**	7	90
4a	4-Methylbenzaldehyde	4-Methylaniline	**Et**	7	84
5a	4-Chlorobenzaldehyde	4-Methylaniline	**Me**	8	76
6a	4-*tert*-Butylbenzaldehyde	4-Methylaniline	**Me**	7	89
7a	4-*tert*-Butylbenzaldehyde	4-Methylaniline	**Et**	7	83
8a	4-Methylbenzaldehyde	4-Chloroaniline	**Me**	9	84
9a	Benzaldehyde	4-Chloroaniline	**Me**	10	70
10a	4-Methylbenzaldehyde	4-Methoxyaniline	**Me**	6	90
11a	Benzaldehyde	Aniline	**Me**	8	82
12a	Benzaldehyde	Aniline	**Et**	10	71
13a	4-Methylbenzaldehyde	Aniline	**Me**	8	84
14a	4-Methylbenzaldehyde	Aniline	**Et**	9	80
15a	4-Chlorobenzaldehyde	Aniline	**Me**	11	74
16a	2-Chlorobenzaldehyde	Aniline	**Me**	12	68
17a	2,4-Dichlorobenzaldehyde	Aniline	**Me**	15	75

^{a}Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of NMR spectra with authentic samples [13-17].

4. CONCLUSIONS

In summary, nano-structured ZnO was prepared *via* a simple precipitation method in a solution of Prunus Cerasus juice as green media and was applied as a mild and efficient green catalyst for the syntheses of 3,4,5-substituted furan-2(5*H*)-one derivatives. Various substituted amines and aldehydes were used in reaction. All products were obtained in good and excellent yields. From the standpoint of the reaction conditions can be said that the advantages of this method are mild conditions and high yields.

5. REFERENCES

[1] Clark B., Capon R.J., Lacey E., Tennant S., Gill J.H., Bulheller B., Bringmann G., gymnoascolides A−C: aromatic butenolides from an australian isolate of the soil ascomycete gymnoascus reessii. *J. Nat. Prod.* 68, 1226-1230, **2005**.

[2] Baag M.M., Argade N.P., Synthesis of Gymnoascolide A. *Synthesis* 26-28, **2008**.

[3] Lee S.-C., Brown G.D., tribenzylbutyrolactones and dibenzyldiphenyl-4,5,6,7-tetrahydrobenzofuranones from kyrtuthrix maculans. *J. Nat. Prod.* 61, 29-33, **1998**.

[4] Seitz M., Reiser O., synthetic approaches towards structurally divers γ-butyrolactone natural product-like compound. *Curr. Opin. Chem. Biol.* 9, 285-292, **2005**.

[5] Ugurchieva T.M., Veselovsky V.V., advances in the synthesis of natural butano- and butenolides. *Russ. Chem. Rev.* 78, 337-373, **2009**.

[6] Rao Y.S., recent advances in the chemistry of unsaturated lactones. *Chem. Rev.* 76, 625-694, **1976**.

[7] Jusseau X., Chabaud L., Guillou C.,synthesis of γ-butenolides and α,β-unsaturated γ-butyrolactams by addition of vinylogous nucleophiles to Michael acceptors. *Tetrahedron* 70, 2595-2615, **2014**.

[8] Rossi R., Bellina F., Biagetti M., Mannina L., stereocontrolled synthesis of lissoclinolide by sequential transition metal-catalyzed lactonization / cross-coupling reactions. *Tetrahedron Lett.* 39, 7799-7802, **1998**.

[9] Levy L.M., Cabrera G.M., Wright J.E., Seldes A.M., 5*H*-Furan-2-ones from fungal cultures of aporpium caryae. *Phytochemistry* 62, 239-243, **2003**.

[10] Hein S.M., Gloer J.B., Koster B., Malloch D.,bombardolides: new antifungal and antibacterial γ,-lactones from the coprophilous fungus bombardioidea anartia. *J. Nat. Prod.* 64, 809-812, **2001**.

[11] Pour M., Spulak M., Balsanek V., Kunes J., Kubanova P., Butcha V., synthesis and structure-antifungal activity relationships of 3-aryl-5-alkyl-2,5-dihydrofuran-2-ones and their carbanalogues: further refinement of tentative pharmacophore group. *Bioorg. Med. Chem.* 11, 2843-2866, **2003**.

[12] Padakanti S., Pal M., Yeleswarapu K.R., an improved and practical synthesis of 5,5-dimethyl-3-(2-propoxy)-4-(4-methanesulfonylphenyl)-2-(5H)-furanone (DFP - A selective inhibitor of cyclooxygenase-2). *Tetrahedron* 59, 7915-7920, **2003**.

[13] Hoye T.R., Tan L., total synthesis of the potent antitumor, bis-tetrahydrofuranyl annonaceous acetogenins (+)-asimicin and (+)-bullatacin. *Tetrahedron Lett.* 36, 1981-1984, **1995**.

[14] Takahashi S., Kubota A., Nakata T., total synthesis of muconin. *Tetrahedron Lett.* 43, 8661-8664, **2002**.

[15] Hanessian S., Park R.Y., Yang R.Y.,zinc-mediated allylation of *N*-protected α-amino aldehydes in aqueous solution. stereoselective synthesis of Phe-Phe hydroxyethylene dipeptide isosteres. *Synlett* 351-352, **1997**.

[16] Choudhury A., Jin F., Wang D., Wang Z., Xu G., Nguyen D., Castoro J., Pierce M.E., Confalone P.N., a concise synthesis of anti-viral agent F-ddA, starting from (S)-dihydro-5-(hydroxymethyl)-2(3H)-furanone. *Tetrahedron Lett.* 44, 247-250, **2003**.

[17] Narayana Murthy S., Madhav B., Vijay Kumar A., Rama Rao K., Nageswar Y.V.D., facile and efficient synthesis of 3,4,5-substituted furan-2(5H)-ones by using β-cyclodextrin as reusable catalyst. *Tetrahedron* 65, 5251-5256, **2009**.

[18] Nagarapu L., Kumar U.N., Upendra P., Bantu R., simple, convenient method for the synthesis of substituted furan-2(5H)-one derivatives using tin(II) chloride. *Synth. Commun.* 42, 2139-2148, **2012**.

[19] Tekale S.U., Kauthale S.S., Pagore V.P., Jadhav V.B., Pawar R.P.,ZnO nanoparticle-catalyzed efficient one-pot three-component synthesis of 3,4,5-trisubstituted furan-2(5H)-ones. *J. Iran. Chem. Soc.* 10, 1271-1277, **2013**.

[20] Mohammad Shafiee M.R., Mansoor S.S., Ghashang M., Fazlinia, A. preparation of 3,4,5-substituted furan-2(5H)-ones using aluminum hydrogen sulfate as an efficient catalyst. *Compt. Rend. Chim.* 17, 131-134, **2014**.

[21] DoostmohammadiR., Maghsoodlou M.T.,Hazeri N., Habibi-Khorassani S.M.,an efficient one-pot multi-component synthesis of 3,4,5-substituted furan-2(5H)-ones catalyzed by tetra-*n*-butylammonium bisulfate. *Chin. Chem. Lett.* 24, 901-903, **2013**.

[22] Doostmohammadi R., Hazeri N., application of silica gel-supported polyphosphoric acid (PPA/SiO_2) as a reusable solid acid catalyst for one-pot multi-component synthesis of 3,4,5-substituted furan-2(5*H*)-ones. *Lett. Org. Chem.* 10, 199-203, **2013**.

[23] Safaei-Ghomi J., Heidari-Baghbahadorani E., Shahbazi-Alavi H., SnO nanoparticles: a robust and reusable heterogeneous catalyst for the synthesis of 3,4,5-substituted furan-2(5H)-ones. *Monatsh. Chem.* 146, 181-186, **2015**.

[24] Bahramian F., Fazlinia A., Mansoor S.S., Ghashang M., Azimi F., Biregan M.N., Preparation of 3, 4, 5-substituted furan-2 (5H)-ones using HY Zeolite nano-powder as an efficient catalyst. *Res. Chem. Intermed.* 42, 6501–6510, **2016**.

[25] 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**.

[26] 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**.

[27] Ghashang M., Mansoor S.S., Mohammad Shafiee M.R., Kargar M., Najafi Biregan M., Azimi F., Taghrir H., Green chemistry preparation of MgO nanopowders: efficient catalyst for the synthesis of thiochromeno [4, 3-b] pyran and thiopyrano [4, 3-b] pyran derivatives. *J. Sulfur Chem.* 37, 377-390, **2016**.

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

[29] Ghashang M., Mansoor S.S., Shams Solaree L., Sharifian-esfahani A., Multi-component, one-pot aqueous media preparation of dihydropyrano[3, 2-c]chromene derivatives over MgO nanoplates as an efficient catalyst. *Iran. J. Catal.*, 6, 237-243, **2016**.

[30] Mohammad Shafiee M.R., Sattari A., Kargar M., Ghashang M., Investigation of natural solution effect in electrical conductivity of PANI-CeO_2 nanocomposites. *Steel Compos. Struct.* 24, 15-22, **2016**.

[31] Vidhu V.K., Aswathy Aromal S., Philip D., Green synthesis of silver nanoparticles using Macrotyloma uniflorum. *Spectrochimica Acta Part A* 83, 392– 397, **2011**.

[32] Krishnaswamy K., Vali H., Orsat V.,Value-adding to grape waste: Green synthesis of gold nanoparticles. *J. Food Engin.* 142, 210–220, **2014**.

[33] Prasad K., Jha A.K., ZnO Nanoparticles: Synthesis and Adsorption Study. *Natural Sci.* 1, 129–135, **2009**.

[34] Šarić A., Sobočanec S., Balog T., Kušić B., Šverko V., Dragović-UzelacV., Levaj B., Čosić Z., Mačak Šafranko Ž., MarottiT., Improved antioxidant and anti-inflammatory potential in mice consuming sour cherry juice (Prunus Cerasus cv. Maraska). *Plant Foods Hum. Nutr.* 64, 231–237, **2009**.

6. ACKNOWLEDGEMENTS

We are thankful to the Najafabad Branch, Islamic Azad University research council for partial support of this research