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Synthesis of dihydrofurans using biosynthesized CuO nanoparticles

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ABSTRACT

The preparation of *trans*-dihydrofurans has been achieved by a one-pot condensation reaction of 4-bromophenacyl bromide, aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione using biosynthesized CuO nanoparticles under reflux conditions in ethanol. CuO nanoparticles (CuO NPs) were prepared using extract of leaves of *Ajuga chamaecistus Subsp*. *Scoparia*. The key advantages of this process are the diastereoselective synthesis, reusability of the catalyst, low catalyst loading, excellent yields, short reaction times, simple workup and environmentally benign. Fully optimized structures of *trans* and *cis* dihydrofurans were obtained by B3LYP/6-31G(d,p) method. The structures of the prepared *trans*-2,3-dihydrofurans were fully characterized by ^{1}H and ^{13}C NMR spectra, IR spectra, and elemental analysis.

Keywords: *Dihydrofurans, Reusable catalyst, Biosynthesized CuO nanoparticles, Green synthesis, One-pot.*

1. Introduction

Dihydrofurans show biological activities including anticandidal [1], anti-influenza [2], antiherpes [3], analgesic [4], anticancer [5] anticonvulsant [6] and anti-Alzheimer's disease [7]. Therefore, seeking efficient and brief techniques for the preparation of dihydrofurans compounds through multicomponent reactions (MCRs) is an attractive area of research in organic and medicine chemistry [8-10]. A series of dihydrofurans have been synthesized in the presence of diverse catalysts including K_2CO_3 [11], piperidine [12] manganese (III) acetate [13,14] cerium(IV) ammonium nitrate (CAN) [15], CuOTf [16], ionic liquid [BMIm]OH [17] *N*-methyl imidazole [18] NaOH [19] and Et_3N [20]. However, some of the reported ways endure drawbacks such as long reaction times, and undesirable reaction conditions. Therefore, to avoid these disadvantages, the finding of an efficient, easily available catalyst with high catalytic activity for the preparation of dihydrofurans is still favored. Recently, environmental friendly and green synthesis of metallic nanoparticles (NPs) has attracted great attention. The biosynthetic methods for the preparation of metal NPs have several benefit including simplicity, low cost, low toxicity as well as suitability for biomedical and pharmaceutical applications. Among biosynthetic methods for the preparation of metal nanoparticles, plant extracts have received considerable attention owing to easy and simple sampling, and environmental friendly [21-23]. We wish to report herein a highly efficient procedure for the preparation of dihydrofurans using CuO nanoparticles as an efficient and reusable heterogeneous catalyst under reflux conditions in ethanol (Scheme 1). We reported the green synthesis of CuO nanoparticles (CuO NPs) using extract of leaves of *Ajuga chamaecistus Subsp*. *Scoparia* (Fig. 1). More than one hundred species and fifty varieties and subspecies of *Ajuga* plants are distributed over the temperate parts of Asia and Europe [24]. Compounds isolated from plant of *Ajuga* have been demonstrated the biological activities including antibacterial [25], hypoglycemic [26], cytotoxicity [27], and antioxidant [28]. In the present research, we used of the extracts of *Ajuga chamaecistus* Subsp. *Scoparia* for the green synthesis of CuO nanoparticles. Recently, CuO nanoparticles were used in many reactions including C-S Cross-Coupling [29], C-Se Cross-Coupling [30], C-N Cross-Coupling [31,32], N-arylation of indoles [33], synthesis of polyhydroquinoline [34] and synthesis of xanthenes [35].

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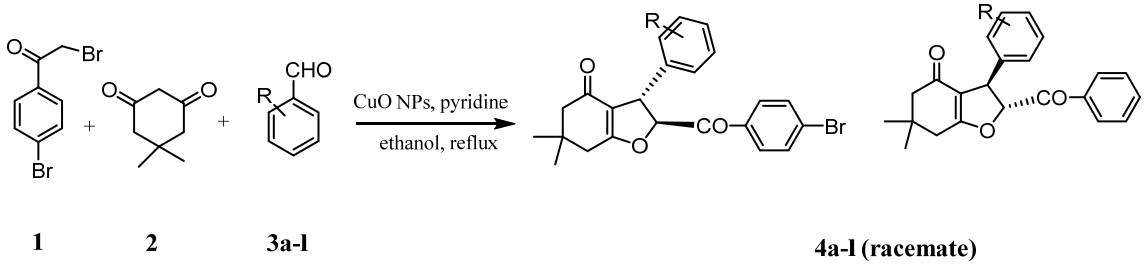


1 **2** **3a-l** **4a-l (racemate)**

Scheme 1. Synthesis of dihydrofurans using biosynthesized CuO nanoparticles

Fig. 1. Photograph of *Ajuga chamaecistus Subsp*. *Scoparia*

2. Experimental

2.1. Chemicals and apparatus

Samples of *Ajuga chamaecistus Subsp*. *Scoparia* were collected from Kashan area (Vadeqane, Iran) at an altitude of ca. 2100 m. All organic materials were purchased commercially from Sigma–Aldrich and Merck. NMR spectra were recorded on a Bruker 400 MHz spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ= 1.5406 Å). Microscopic morphology of products was visualized by SEM (QBSD).

2.2. Preparation of Ajuga chamaecistus Subsp. Scoparia leaf extract

50 grams of dried leaves powdered of *Ajuga chamaecistus Subsp*. *Scoparia* were Soxhlet extracted with 300 ml of methanol for 6 h. Solvent removal by rotary evaporation (Buchi, Flawil, Switzerland) and the extract was kept at refrigerator to use further.

2.3. Biosynthesis of CuO nanoparticles using the aqueous extract of leaves of Ajuga chamaecistus Subsp. Scoparia

50 mL of *Ajuga chamaecistus Subsp*. *Scoparia* leaf aqueous extract was added drop wise to 50 mL of well-mixed 0.005 M aqueous solution of $CuCl_2$ with constant stirring at 60 °C. After 2 min the color of the solution was changed from yellow to dark brown. The obtained precipitation was washed four times with absolute ethanol to remove impurities and then dried for 24 h at room temperature.

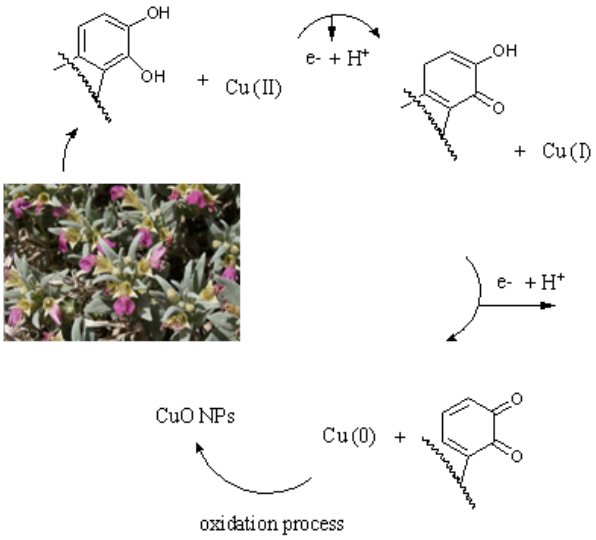
2.4. General procedure for the preparation of trans-2,3-dihydrofuran (4a-i):

A mixture of pyridine (1 mmol) and 4-bromophenacyl bromide (1 mmol) was stirred for 2 min. Subsequently, an aromatic aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) and CuO NPs (3 mol%) in 5 mL ethanol was added and the mixture was refluxed for about 60-80 min. After completion of the reaction (TLC), $CHCl_3$ was added. The catalyst was insoluble in $CHCl_3$ and it could therefore be recycled by a simple filtration. The solvent was evaporated and the solid obtained recrystallized from ethanol to afford the *trans*-2,3-dihydrofuran.

3. Results and Discussion

In the present study, CuO NPs was synthesized using *Ajuga chamaecistus Subsp*. *Scoparia* leaf extract. In our investigation, there is a focus on the preparation of nanoparticles in aqueous media using reducing activities of antioxidant phytochemicals inside the plant especially polyphenolics as a main reducing and polyhydroxyl highly polar agents in *Ajuga chamaecistus Subsp*. *Scoparia* extract according the below possible mechanism (Scheme 2). There are many antioxidant compounds inside the plant extract therefore based on the mechanism Cu(II) is reduced to Cu(0) then due to the highly oxidation potential of Cu(0) to combination with oxygen and reach the higher oxidation states it converts to the CuO NPs, Scheme 2.

The powder X-ray diffraction (XRD) pattern of the synthesized CuO nanoparticles was depicted in Fig. 2. The pattern agrees well with the reported pattern for CuO nanoparticles (JCPDS No. 80-1916). Meanwhile, we compared X-ray pattern diffraction of pure CuO [36], and CuO nanoparticles.



Scheme 2. Reducing ability of antioxidant phenolics of *Ajuga chamaecistus Subsp*. *Scoparia* extract to produce nanoparticles.

The XRD of CuO was analyzed with XRD software, shows the presence of CuO only. In some researches it has been found that transition metal gives multiple oxides [36]. The sharp peak for the CuO represents its crystalline nature.

Fig. 3 reveals the SEM images of CuO nanoparticles. The SEM image shows that the nanoparticles have a uniform size with diameters in the range of nanometers.

The elemental compositions of the nanocatalyst were studied by Energy Dispersive Spectroscopy (EDS). Presence of copper and oxygen was confirmed by EDS spectroscopy (Fig. 4).

We started our study by examining the reaction of 4-bromophenacyl bromide 1 (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione **2** (1 mmol) benzaldehyde **3a** (R= H) (1 mmol) in presence of pyridine (1 mmol) for the synthesis of dihydrofuran derivative **4a**.

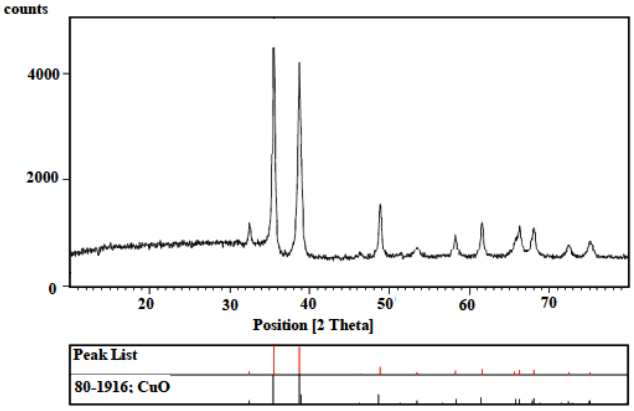


Fig. 2. The XRD pattern of CuO NPs.

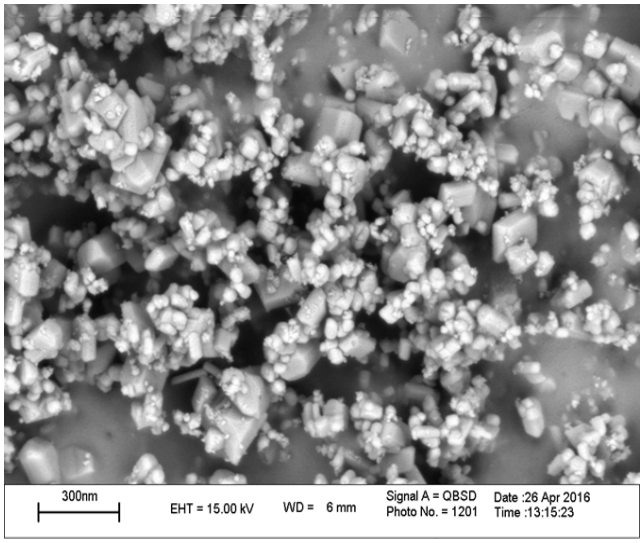


Fig. 3. SEM images of CuO NPs.

To obtain the ideal reaction conditions for the synthesis of compound **4a**, we studied some other catalysts, and solvents which are shown in Table 1. Screening of different catalysts such as Et_3N, ZrO_2, *p*-TSA, $InCl_3$, nano-CuI, nano-ZnO and nano-CuO revealed CuO nanoparticles as the most effective catalyst to perform this reaction (Table 1).

We explored the feasibility of the reaction by selecting some representative substrates (Table 2). The benzaldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups. It has been considered that better yields are achieved with substrates having electron-withdrawing groups. In addition, we examined aliphatic aldehydes such as *n*-pentanal instead of arylaldehydes in the reaction, but we could not find considerable amount of the title product from aliphatic aldehydes.

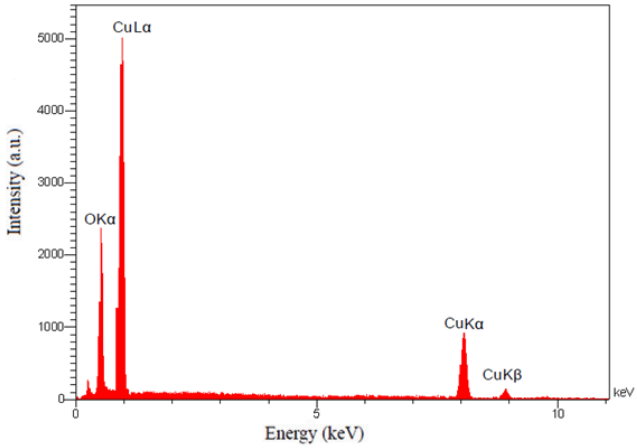


Fig. 4. EDS spectrum of CuO NPs.

Table1. Optimization of reaction condition using different catalysts.[a]

Entry	Solvent (reflux)	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	EtOH	—	250	10
2	EtOH	Et_3N (15)	350	48
3	EtOH	ZrO_2 (3)	200	25
4	EtOH	*p*-TSA (10)	300	19
5	EtOH	$InCl_3$ (5)	250	30
6	EtOH	pure CuO (5)	250	52
7	EtOH	nano-CuI (10)	250	45
8	EtOH	nano-ZnO (8)	150	38
9	EtOH	nano-CuO (1.5)	70	85
10	EtOH	nano-CuO (3)	70	90
11	EtOH	nano-CuO (4.5)	70	90
12	CH_3CN	nano-CuO (4.5)	70	75
13	DMF	nano-CuO (4.5)	90	65
14	H_2O	nano-CuO (4.5)	110	53
15	CH_2Cl_2	nano-CuO (4.5)	150	36

[a]Reaction conditions: 4-bromophenacyl bromide (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), benzaldehyde (1 mmol), pyridine (1 mmol).
[b]Isolated yield.

We also considered reusability of the CuO NPs as catalyst under reflux conditions in ethanol for the synthesis of product **4a** and it was found that product yields reduced to a small extent on each reuse (run 1, 90%; run 2, 90%; run 3, 89%; run 4, 89%; run 5, 88%). After completion of the reaction, $CHCl_3$ was added. The catalyst was insoluble in $CHCl_3$ and it could therefore be recycled by a simple filtration. The nanoparticles were then washed three to five times with ethanol and dried at 50 °C for 5 h.

Table 2. Synthesis of dihydrofurans using biosynthesized CuO nanoparticles.[a]

Entry	R	Product	Time (min)	Yield (%)[b]	m.p. (°C)
1	H	**4a**	70	90	152-154
2	*p*-Cl	**4b**	60	96	194-196
3	*o*-Cl	**4c**	65	92	174-176
4	*m*-Cl	**4d**	70	91	155-157
5	*p*-CH_3	**4e**	80	85	182-185
6	*p*-OCH_3	**4f**	90	80	175-177
7	*m*-NO_2	**4g**	70	90	204-206
8	*p*-NO_2	**4h**	60	96	215-217
9	*p*-Br	**4i**	60	95	135-137
10	*m*-F	**4j**	60	90	190-192
11	*o-Br*	**4k**	60	91	143-145
12	*o*-F	**4l**	60	88	187-189

[a]Reaction conditions: 4-bromophenacyl bromide (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), aldehyde 3 a-l (1 mmol), pyridine (1 mmol), CuO nanoparticles (3 mol%) and EtOH (5 ml) under reflux conditions.
[b]Isolated yield.

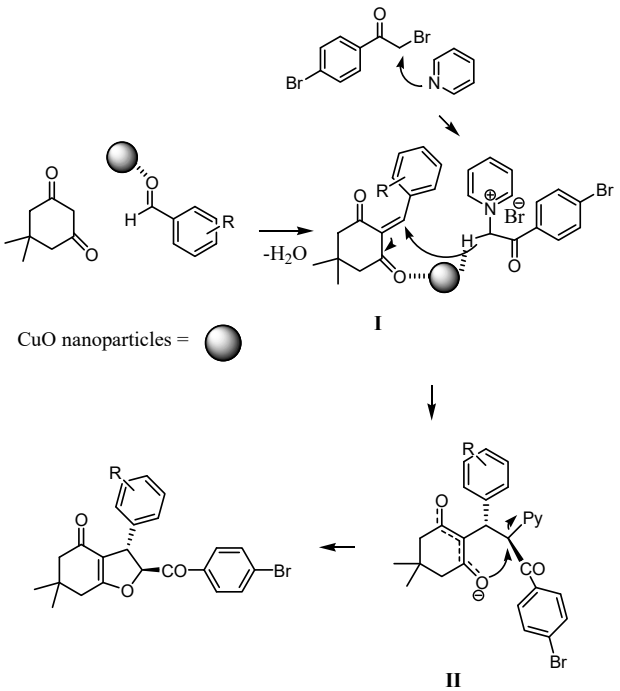
To compare the efficiency of nano-CuO with the reported catalysts for the synthesis of dihydrofurans, we have tabulated the results in Table 3. As Table 3 indicates, nano-CuO is superior with respect to the reported catalysts in terms of reaction time, yield and conditions. In addition, our catalyst was recyclable for five times. High catalytic activity and ease of recovery from the reaction mixture through filtration or centrifugation methods, and several reuse times without significant losses in performance are additional eco-friendly attributes of this catalytic system.

Table 3. Comparison of catalytic activity of nano-CuO with other reported catalysts for the synthesis of dihydrofurans.

Entry	Catalyst (condition)	Time (min)	Yield (%) [a]	Ref.
1	CAN (cerium(IV) ammonium nitrate), 2.5 mol%	900	80	[15]
2	NaOH, 10 mol%	480	75	[19]
3	Et_3N, 10 mol%	480	66	[20]
4	DABCO (1,4-diazabicyclo[2.2.2]octane), 20 mol%	180	87	[37]
5	nano-CuO, 3 mol%	70	90	This work

[a]Isolated yield.

A mechanism for the synthesis of dihydrofurans **4a-l** using CuO nanoparticles is proposed in Scheme 3. At first, we assumed that the reaction occurs *via* a Knoevenagel condensation between benzaldehydes **3a-l** and 5,5-dimethyl-1,3-cyclohexanedione **2**, forming the intermediate **I** at the active sites of CuO nanoparticles. Then, the Michael addition of pyridinium ylide with enone **I** affords the zwitterionic intermediate that undergoes cyclization to the title product. This proposed mechanism is also supported by literature examples [17, 18, 20]. The final step is a classic intramolecular S_N2 substitution reaction. The stereochemistry of the S_N2 reaction necessitates a nucleophilic attack by enolate from the back side of the electrophilic carbon atom bearing the leaving pyridinium group. The 2-benzoyl and 3-aryl groups in therefore assume *anti*-relationship due to steric hindrance in the transition states. Thus, only the *trans*-substituted isomer of 2,3-dihydrofuran is obtained [18,20]. Pyridine plays very significant role in this proposed reaction mechanism. It acts by stabilizing the ylide during the attack on intermediate **I** and functions as a good leaving group in the zwitterionic salt **II**, to finish the intramolecular substitution reaction. The formation of *trans*-2,3-dihydrofurans is in agreement with the lower heat of formation for the *trans*-isomer, which is more stable than the *cis*-isomer, as estimated using PM3 calculations [17]. The structures of the prepared *trans*-2,3-dihydrofurans were fully characterized by ^{1}H and ^{13}C NMR spectra, IR spectra, and elemental analysis. For example, in ^{1}H NMR spectrum of **4a,** the two protons at 2,3-positions of dihydrofuran ring display two doublets at 4.330 and 5.795 ppm with the vicinal coupling constant J = 4.8 Hz. The similar splitting pattern and a coupling constant of less than 6.0 Hz were also seen in other ^{1}HNMR spectra of the obtained *trans*-2,3-dihydrofurans. It has been established that in *cis*-2,3-dihydrofuran derivatives the vicinal coupling constant of the two methine protons J = 7–10 Hz, while in *trans*-2,3-dihydrofuran derivatives the vicinal coupling constant J = 4–7 Hz [20].



Scheme 3. Possible mechanism for the synthesis of *trans*-2,3-dihydrofuran using CuO NPs.

Thus, the *trans*-isomer of 2,3-dihydrofuran was obtained as the only product. Fully optimized structures of *trans* and *cis* dihydrofurans were obtained by B3LYP/6-31G(d,p) method (See supporting information).

4. Conclusion

We have developed a straightforward method to synthesis of *trans*-2,3-dihydrofuran in good to excellent yields in the presence of CuO nanoparticle as a reusable, green and efficient catalyst. Fully optimized structures of *trans* and *cis* dihydrofurans were obtained by B3LYP/6-31G(d,p) method. The advantages of this method are the use of an efficient catalyst, reusability of the catalyst, the use of low amount of the catalyst, diastereoselective synthesis, environmentally benign and easy separation of products.

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References

[1] C.P.V. Freire, S.B. Ferreira, N.S.M. de Oliveira, A.B.J. Matsuura, I.L. Gama, F.C. da Silva, M.C.B.V. de Souza, E.S. Lima, V.F. Ferreira, Med. Chem. Commun. 1 (2010) 229–232.
[2] Y. Matsuya, N. Suzuki, S. Kobayashi, T. Miyahara, H. Ochiai, H. Nemoto, Bioorg. Med. Chem. 18 (2010) 1477–1481.
[3] A. Scala, M. Cordaro, F. Risitano, I. Colao, A. Venuti, M.T. Sciortino, P. Primerano, G. Grassi, Mol. Divers. 16 (2012) 325-333.
[4] K. Salat, A. Moniczewski, R. Salat, M. Janaszek, B. Filipek, B. Malawska, K. Wieckowski, Pharmacol. Biochem. Behav. 101 (2012) 138-147.
[5] Y. Zhang, H. Zhong, T. Wang, D. Geng, M. Zhang, K. Li, Eur. J. Med. Chem. 48 (2012) 69-80.
[6] K. Wieckowski, K. Sałat, J. Bytnar, M. Bajda, B. Filipek, J.P. Stables, B. Malawska, Bioorg. Med. Chem. 20 (2012) 6533–6544.
[7] K. Sugimoto, K. Tamura, N. Ohta, C. Tohda, N. Toyooka, H. Nemoto, Y. Matsuya, Bioorg. Med. Chem. Lett. 22 (2012) 449–452.
[8] B.B.F. Mirjalili, L. Zamani, K. Zomorodian, S. Khabnadideh, Z. Haghighijoo, Z. Malakotikhah, S.A. Ayatollahi Mousavi, S. Khojasteh, J. Mol. Struct. 1116 (2016) 102-108.
[9] J. Safaei-Ghomi, S.H. Nazemzadeh, H. Shahbazi-Alavi, Appl. Organometal. Chem. 30 (2016) 911-916.
[10] L. Suresh, P.S.V. Kumar, G.V.P. Chandramouli, J. Mol. Struct. 1134 (2017) 51-58.
[11] W. Cao, W. Ding, J. Chen, Y. Chen, Q. Zang, G. Chen, Synth. Commun. 34 (2004) 1599-1608.
[12] C. Xing, S. Zhu, J. Org. Chem. 69 (2004) 6486-6488.
[13] M. Yilmaz, N. Uzunalioglu, M. Yakut, T. Pekel, Turk. J. Chem. 32 (2008) 411-422.
[14] M. Yilmaz, E. Bicer, A. T. Pekel, Turk. J. Chem. 29 (2005) 579-587.
[15] S. Maiti, P.T. Perumal, J.C. Menendez, Tetrahedron 66 (2010) 9512-9518.
[16] S. Son, G.C. Fu, J. Am. Chem. Soc. 129 (2007) 1046-1047.
[17] S.M. Rajesh, S. Perumal, J.C. Menendez, S. Pandian, R. Murugesan, Tetrahedron 68 (2012) 5631-5636.
[18] A. Kumar, S. Srivastava, G. Gupta, Green Chem. 14 (2012) 3269-3272.
[19] A.T. Khan, M. Lal, R.S. Basha, Synthesis 45 (2013) 406-412.
[20] Q.F. Wang, H. Hou, L. Hui, C.G. Yan, J. Org. Chem. 74 (2009) 7403-7406.
[21] A.K. Mittal, Y. Chisti, U.C. Banerjee, Biotechnol. Adv. 31 (2013) 346–356.
[22] A. Ehsani, R. Asgari, A. Rostami-Vartooni, H. Mohammad Shiri, A. Yeganeh-Faal, Iran. J. Catal. 6 (2016) 269-274.
[23] J. Safaei-Ghomi, M. Asgari-Kheirabadi, H. Shahbazi-Alavi, A. Ziarati, Iran. J. Catal. 6 (2016) 319-324.
[24] F. Camps, J. Coll, Phytochem. 32 (1993) 1361-1370.
[25] H. Chen, R. X. Tan, Z.L. Liu, Y. Zhang, J. Nat. Prod. 59 (1996) 668-670.
[26] T.A. Kutepova, V.N. Syrov, Z.A. Khushbaktova, Z. Saatov, Pharm. Chem. J. 35 (2001) 608-609.
[27] P. Akbay, J. Gertsch, I. Calis, J. Heilmann, O. Zerbe, O. Sticher, Helv. Chem. Acta 85 (2002) 1930-1942.
[28] S. Bouderbala, J. Prost, M.A. Lacaille-Dubois, M. Bouchenak, Nutr. Res. 30 (2010) 358–365.
[29] L. Rout, T.K. Sen, T. Punniyamurthy, Angew. Chem. Int. Ed. 46 (2007) 5583–5586.
[30] D. Alves, C.G. Santos, M.W. Paixao, L.C. Soares, D. de Souza, O.E.D. Rodrigues, A.L. Braga, Tetrahedron Lett. 50 (2009) 6635–6638.
[31] S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha, T. Punniyamurthy, J. Org. Chem. 74 (2009) 1971–1976.
[32] L. Rout, S. Jammi, T. Punniyamurthy, Org. Lett. 9 (2007) 3397–3399.
[33] N.V. Suramwar, S.R. Thakare, N.N. Karade, N.T. Khaty, J. Mol. Catal. A: Chem. 359 (2012) 28-34.
[34] J. Safaei-Ghomi, M. A. Ghasemzadeh, J. Nano Struct. 1 (2012) 243-248.
[35] G.R. Chaudhary, P. Bansal, N. Kaur, S.K. Mehta, RSC Adv. 14 (2014) 49462-49470.
[36] P.K. Chaudhari, S. Chand, I.M. Mishra, Chem. Eng. Commun. 199 (2012) 874–888.
[37] S. Golchin, M.H. Mosslemin, A. Yazdani-Elah-Abadi, N. Shams, Res. Chem. Intermed. 43 (2017) 1735-1749.