Tetrahedron 68 (2012) 7812–7821

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-doped silica cuprous sulfate (CDSCS) as a highly efficient and new heterogeneous nano catalyst for [3+2] Huisgen cycloaddition

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ARTICLE INFO

Article history:
Received 1 May 2012
Received in revised form 16 June 2012
Accepted 10 July 2012
Available online 20 July 2012

Keywords:
Heterogeneous catalyst
Click cycloaddition
CDSCS
β-Azido alcohols
Alkyne

ABSTRACT

The synthesis and characterization of copper-doped silica cuprous sulfate (CDSCS) as a new and efficient heterogeneous nano catalyst are described. CDSCS has been fully characterized by different microscopic, spectroscopic and physical techniques, including scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic forced microscopy (AFM), X-ray diffraction (XRD), inductively coupled plasma (ICP) analysis, thermogravimetric analysis (TGA) and FT-IR. CDSCS is proved to be a useful heterogeneous nano catalyst in Cu(I)-catalyzed 'Click' cycloaddition of organic azides with terminal alkynes. CDSCS catalyzes the 1,3-dipolar cycloaddition reactions of β-azido alcohols and alkynes at room temperature, in THF/H_2O (1:1, v/v) solution. Using CDSCS, 1,4-disubstituted 1,2,3-triazole adducts are mainly obtained, in good to excellent yields and in short reaction times. These compounds have featural resemblance to β-adrenoceptor blocking agents. CDSCS was approved as a chemically and thermally stable nano catalyst that can be reused for many consecutive trials without a significant decline in its reactivity.

1. Introduction

1,2,3-Triazole derivatives are important compounds in medicinal chemistry owing to their wide applications in drug discovery. They can readily associate with biologically targets through the hydrogen bonding and dipole interactions.[1] The 1,2,3-triazole core is a key structural motif in many bioactive compounds, exhibiting a broad spectrum of biological activities, such as antiviral,[2] anticancer,[3] anti-HIV,[4] antibiotic,[5] antibacterial,[6] and antimicrobial.[7] Additionally, they have found significant industrial applications as dyes, agrochemicals, corrosion inhibitors, photo stabilizers, and photographic materials.[8]

Huisgen 1,3-dipolar azide–alkyne cycloaddition is traditionally applied for accessing 1,2,3-triazoles.[9] However, the major limitations of this non-catalyzed process are the requirement of high temperature and poor regioselectively giving a mixture of 1,4- and 1,5-disubstituted triazoles. Up to now, several efforts to control the 1,4- versus 1,5-regioselectivity have been reported.[10] As a prototype for click chemistry,[1b,11] the recent advance in Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reported by Sharpless[12] and Meldal,[13] accelerates the reaction rate up to 10^7 times. High tolerance of different functionalities under mild conditions is observed when CuAAC protocol is employed. Furthermore, remarkable regioselectivity is observed for 1,4-disubstituted 1,2,3-triazoles. Active copper(I) as the catalytic species can be in situ prepared by reduction of copper(II) salts,[14] oxidation of copper(0),[15] or copper(II)/copper(0) comproportionation.[14,16] Due to the inherent thermogravimetric instability, and the formation of undesired alkyne–alkyne homo-coupling side products, the use of cuprous salts in their simple form was limited.[17] Nevertheless, nitrogen- or phosphorus-based ligands are known to protect the metal center from oxidation and disproportionation. The use of these ligands usually causes an enhancement of cuprous-catalytic activity.[18] Moreover, immobilized copper species on various solid supports, such as charcoal,[19] amine-functionalized polymers,[20] zeolites,[21] aluminum oxyhydroxide nanofiber,[22] Wyoming's montmorillonite,[23] alumina,[24] silica-supported *N*-heterocyclic carbene,[25] amine-functionalized silica,[26] and silica gel[27] have been reported. However, the application of the immobilized catalysts on solid supports frequently suffer from many disadvantages, such as requiring additives, desorption from solid support surface and also low reactivity of the catalyst.[19a,21]

β-Adrenoreceptor antagonists are used clinically for various cardiovascular disease remedies.[28] With the exception of a few

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http://dx.doi.org/10.1016/j.tet.2012.07.032

arylethanolamines (**1**), virtually all the clinically approved β-adrenoceptor antagonists contain an aryloxypropanolamine scaffold (**2**) (Fig. 1).[29] Considering the remarkable therapeutic activities of triazole derivatives, we incorporated the triazole cores instead of amine-derived moieties in compounds **2** to obtain the new β-hydroxytriazoles **3**.

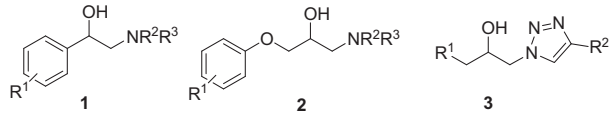
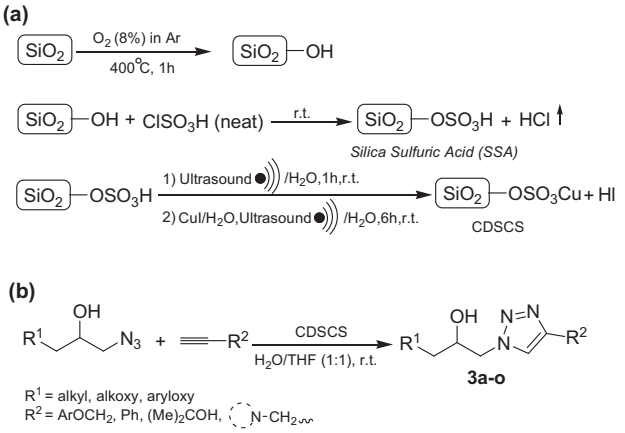


Fig. 1. The general structure of two famous classes of β-adrenergic blocking agents (**1** and **2**) and their 1,2,3-triazolyl analogues (**3**).

In continuation of our interest in the design and synthesis of new compounds having structural similarity to β-adrenoreceptor antagonist analogues,[30] we disclose the synthesis and characterization of CDSCS. This catalyst has been employed in [3+2] Huisgen cycloaddition between structurally diverse terminal alkynes and β-azido alcohols in H_2O/THF (1:1, v/v) at room temperature. Using CDSCS, the target compounds **3** were obtained in good to excellent yields (Scheme 1).



Scheme 1. (a) Routes to prepare the nano copper-doped silica cuprous sulfate (CDSCS), (b) synthesis of new β-blocking analogues **3a**–**o** using CDSCS.

2. Results and discussion

2.1. Preparation of CDSCS

The process for the preparation of CDSCS is shown in Scheme 1a. As is shown in Scheme 1a, the synthesis of CDSCS was achieved from freshly prepared silica sulfuric acid (SSA). The preparation of SSA was previously reported by mixing the normal SiO_2 and $ClSO_3H$.[31] However, in our experience, a more satisfactory result is obtained when activated SiO_2 is used to react with $ClSO_3H$. In this context, the silica was first activated by a flow of 8% O_2 in an argon atmosphere for 1 h at 400 °C in a furnace. Activation of SiO_2 using O_2 at high temperature, leads to the formation of various defects in the silica support.[32] Then, the adequate amounts of $ClSO_3H$ were mixed to active SiO_2. A slight excess of $ClSO_3H$ (2.3 g, 0.02 mol of $ClSO_3H$ for 60 g of SiO_2) was added to freshly prepared SSA to ensure the enrichment of all active sites (i.e., OH) on the parent SiO_2. No further HCl gas was evolved at this stage, which is the indication of full sulfonation. The amount of H^+ in SSA was determined by simple acid–base back-titration and the amount of H^+ in SSA was evaluated to 0.05 g (0.13 mmol) of silica sulfuric acid.[33]

For the preparation of CDSCS, the suspension of SSA in demineralized water was primarily exposed to ultrasonic irradiation at room temperature for 1 h. Then, an enriched solution of CuI with NaI (see the Experimental section) was mixed with SSA and the mixture exposed to ultrasonic irradiation for 6 h at ambient temperature. Filtration followed by washing and dehydration provided CDSCS as a dark-powdered solid.

To justify that copper is bonded as a cuprous sulfate in CDSCS rather than absorbed cuprous iodide on silica, we achieved two complementary experiments. First, it was demonstrated that releasing HI could be considered as an appropriate criterion for exchanging the Cu^+ with H^+. For this purpose, the pH of a suspension solution of SSA (0.001 g in 500 mL demineralized water) was found to be 3.52. When the solution of CuI (0.05 M, 100 mL) was added, the pH changed to 3.38. The decrease in the pH value of SSA solution after adding the CuI solution reveals the exchange of H^+ with Cu^+, and the formation of HI. In a second experiment, for further confidence about bonding of Cu^+ in CDSCS, the well-washed and well-sonicated (400 Watt, 50 min in deionized water) catalyst (0.026 g) was refluxed in a Ag(I) solution (0.01 M, 100 mL) for almost an hour in ambient temperature. This process led to the exchange of the Cu(I) with Ag(I). According to the obtained results from inductively coupled plasma (ICP) technique, more than 98% of the bonded Cu(I) was exchanged by Ag(I). This can be considered as an evidence for formation of CDSCS using the recommended procedure.

2.2. Characterization of catalysis nanostructure

Figs. 2–4 indicate the scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) images of CDSCS, respectively. Good correlation was observed for copper nanoparticles characterized by different microscopic techniques. In addition, the histogram (Fig. 5) presents the frequent distribution of CDSCS based on the AFM image (Fig. 5). Regarding this histogram, the maximum distributed diameter for the CDSCS is around 25 nm. The X-ray diffraction (XRD) pattern of CDSCS is also shown in Fig. 6. Based on the XRD pattern, the strong peaks correspond to copper nanostructure. The related data to XRD pattern are summarized in Table 1.

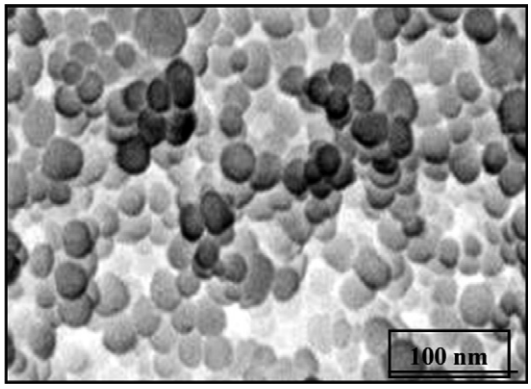


Fig. 2. Scanning electron microscopy (SEM) image of CDSCS.

Due to the results in Table 1, the peak corresponded with the plane of (111) indicates the copper(0) formation concerned with the disproportionation reaction of Cu(I) in a polar solution.

The copper nanoparticle size was also recognized from X-ray line broadening using the Debye–Scherrer formula as: $D=0.9\,\lambda/\beta_{1/2}\cos\theta$. In this formula, D, λ, $\beta_{1/2}$ and θ are the average crystalline size,

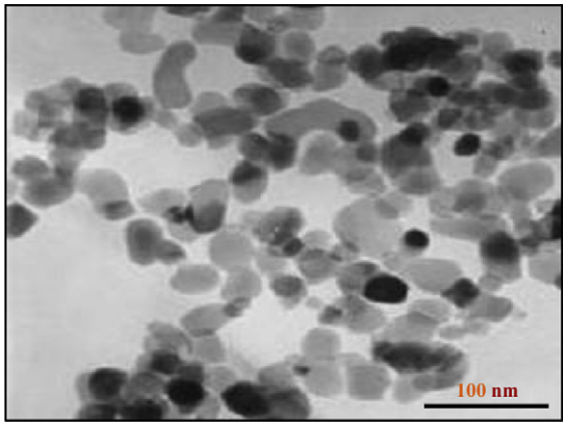


Fig. 3. Transmission electron microscopy (TEM) image of CDSCS.

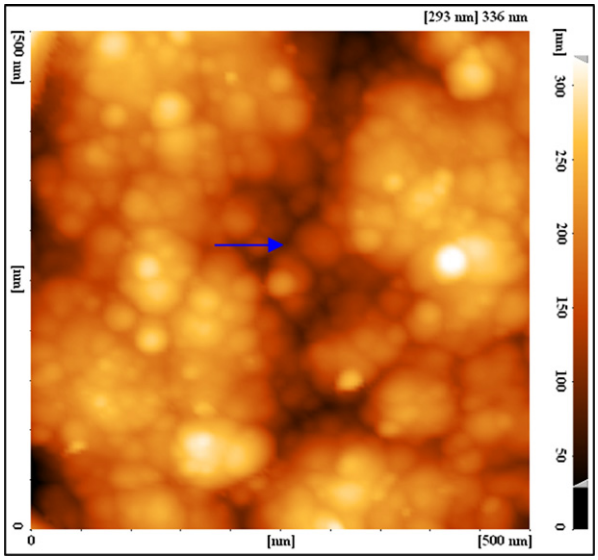


Fig. 4. Atomic force microscopy (AFM) image of CDSCS.

the applied X-ray wavelength, the angular line width at half maximum intensity and the Bragg's angle, respectively.[34]

Regarding the peak of copper nanoparticles and the corresponded plane of copper (200) for λ=1.085 Å, the average size of copper nanoparticles is estimated at around 28 nm. This value is in

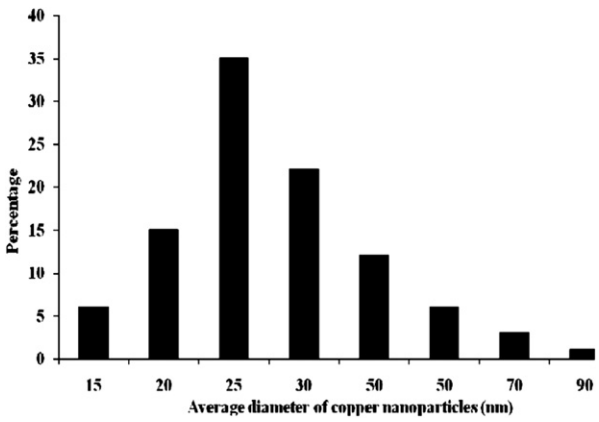


Fig. 5. Histogram representing the average diameter of CDSCS.

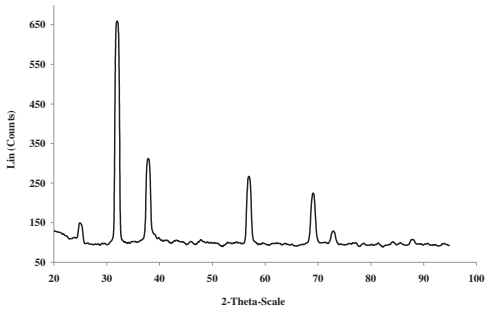


Fig. 6. Smoothed X-ray diffraction (XRD) pattern of CDSCS.

Table 1
Analysis of XRD patterns related to CDSCS after reusing for three times

2-Theta-scale (2θ)	Matrix and morphology		Reference
	Cu	Cu(I)	
25.5	—	(111)	19
30.5	—	(200)	19a
38.5	(111)	(220)	19a
57.2	—	(222)	20
68.5	—	(331)	20
72.1	—	(420)	21

a good agreement with the results attained by the microscopic techniques.

The Fig. 7 indicates the thermogravimetric analysis (TGA) of CDSCS. Based on the TG thermogram, a decrease in weight of CDSCS is observed at temperature around 95 °C and it is attributed to desorption of water and other species from CDSCS. The decrease in weight is also observed around 230 °C, which is related to desorption of sulfur from CDSCS and formation of sulfur dioxide.[35]

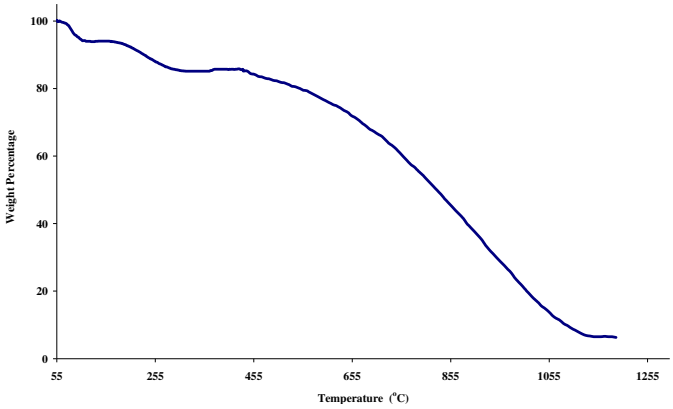


Fig. 7. Thermogravimetric (TG) analysis of CDSCS.

In addition, the increase in weight around 380 °C is attributed to the oxidation of nano copper-particles and the formation of copper oxides.[36] The sharp decrease in weight at 850 °C is assigned to the decomposition of the silica matrix. Finally, the last part of the thermogram (the obtained flexure at the low weight percentages) indicates the quantity of copper oxide as well as the amount of copper nanoparticles on silica. The estimated value of copper nanoparticles was 6.12%.

The FT-IR spectrum of the CDSCS catalyst is shown in Fig. 8. The catalyst is solid and the solid-state IR spectrum was recorded by the KBr disk technique. Metal oxides generally give absorption bands below 1000 cm^{-1}, therefore an asymmetric band at 551 cm^{-1}

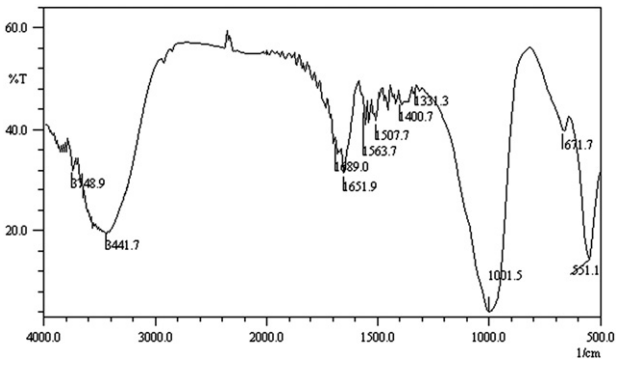


Fig. 8. FT-IR spectrum of freshly prepared CDSCS.

corresponds to the Cu–O bond. Furthermore, a band at 671 cm^{-1} is assigned to S–O stretching. A major broad-sharp peak lies at 900–1200 cm^{-1} and is overlapped by several signals, including stretching symmetric and anti-symmetric Si–O–Si, asymmetric and symmetric stretching modes of O=S=O and also symmetric band of Cu(I or II)–O bonds.[37] The bands at 1500–1700 cm^{-1} correspond to water molecules adsorbed on CDSCS and a combination of the CDSCS vibration modes. The spectrum also shows the absorption around 3441 cm^{-1}, which is assigned to stretching vibration of different types of hydroxyl groups.

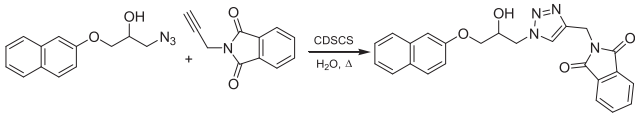
2.3. 'Click' cycloaddition of azides with terminal alkynes using CDSCS

After synthesis and characterization of CDSCS, we applied this catalyst in synthesis of new 1,2,3-triazole derivatives. The first step of this synthetic approach was started by optimizing the reaction conditions. At first, we carried out the cycloaddition reaction of 2-(prop-2-ynyl) isoindoline-1,3-dione and 1-azido-3-(naphthalen-2-yloxy)propan-2-ol as a model reaction to acquire the corresponding 1,2,3-triazole (**3a**).

The 1,3-dipolar cycloaddition of model reaction was carried out in the presence of CDSCS (0.3 g, 0.05 mol %) in H_2O at room temperature, which was afforded **3a** in 45% yield after stirring for 4 h (Table 2, entry 1). To study the influence of temperature, the model reaction was carried out at different temperatures (Table 2, entries 2–8). Due to Table 2, an increase in the temperature resulted in the promotion of cycloaddition reaction. The best result obtained when the cycloaddition reaction was conducted at 100 °C for 1 h (Table 2, entry 5). However, increasing the temperature up to 200 °C did not affect the reaction yield.

In order to optimize the reaction conditions, the influence of various 1:1 (v/v) organic solvents/H_2O was examined in the presence of CDSCS at room temperature (Table 3).

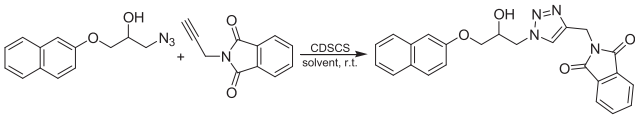
Table 2
Influence of various temperatures on conversion of 1-azido-3-(naphthalen-2-yloxy) propan-2-ol into **3a** using CDSCS in H_2O[a]



Entry	Temperature (°C)	Time (h)	Yield[b] (%)
1	25	4	45
2	50	2.5	60
3	80	1.75	69
4	90	1.25	73
5	100	1	78
6	110[c]	1	79
7	150[c]	1	79
8	200[c]	1	80

[a] Reaction condition: 1-azido-3-(naphthalen-2-yloxy)propan-2-ol (0.01 mol), 2-(prop-2-ynyl) isoindoline-1,3-dione (0.012 mol), CDSCS (0.05 mol %), H_2O (20 mL), room temperature.
[b] Isolated yield.
[c] Sealed tube was used.

Table 3
Influence of various solvents on conversion of 1-azido-3-(naphthalen-2-yloxy) propan-2-ol into **3a** using CDSCS at room temperature[a]



Entry	Solvent[b]	Time (h)	Yield[c] (%)
1	H_2O/DMSO	0.75	88
2	H_2O/DMF	0.75	84
3	H_2O/*t*-BuOH	2	70
4	H_2O/MeCN	4	50
5	H_2O/THF	0.5	93
6	H_2O/dioxane	3	63
7	H_2O/toluene	5	41
8	H_2O/acetone	5	52
9	H_2O	4	45
10	THF	4	62

[a] Reaction condition: 1-azido-3-(naphthalen-2-yloxy)propan-2-ol (0.01 mol), 2-(prop-2-ynyl) isoindoline-1,3-dione (0.012 mol), CDSCS (0.05 mol %), solvent (20 mL), room temperature.
[b] For entries 1–8, a mixture of 1:1 (v/v) solvents were used.
[c] Isolated yield.

From Table 3, it is well demonstrated the solvent has a significant role in progress of reaction. Among the examined solvents, a solution of THF/H_2O (1:1, v/v) (Table 3, entry 5) afforded the best result. Moreover, equal ratio solutions of other solvents in water, such as the solution of DMSO (Table 3, entry 1) and/or DMF (Table 3, entry 2) also yielded the product in reasonable time. Employing the other mixtures afforded a moderate yield of product over longer periods of time (2–5 h). Additionally, when water and THF were used alone, the yields of 45% and 62% for **3a** were obtained after 4 h, respectively (Table 3, entries 9 and 10). The low yield obtained for **3a** using water, is attributed to lack of organic solubility in H_2O.

The optimized stoichiometric ratio of azide/alkyne found to 1:1.2 for **3a** when 0.05 mol % of catalyst was applied. It is important to use an equimolar ratio of azide/alkyne. The use of large quantities of alkyne can lead to the appearance of by-products because of alkyne–alkyne homo-coupling in the presence of Cu(I) salts.

To illustrate the scope of this method, we extended the optimized reaction condition to other azides and alkynes cycloadditions (Table 4). As the results in Table 4 indicate, CDSCS proved to be useful nano catalyst for [3+2] Huisgen cycloaddition between the structurally diverse β-azido alcohols and alkynes. Using CDSCS, compounds **3a–o** were regioselectively synthesized as 1,4-disubstituted 1,2,3-triazoles in excellent yields and short reaction times. The internal alkyne was inactive toward β-azido alcohols (Table 4, entry 16).

Additionally, the influence of time on the progress of reaction for model substrates was investigated (Table 5). As the results in Table 5 indicate, the reaction procedes smoothly and the best result was obtained when the reaction was terminated after 0.5 h. Prolonging the reaction time had no distinguishable effect on the progress of the reaction.

To investigate the catalytic potency of CDSCS in the 1,3-dipolar cycloaddition, we tested the model reaction using other reported

Table 4
CDSCS-catalyzed 'click' cycloaddition of β-azido alcohols with alkynes[a]

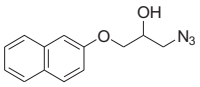
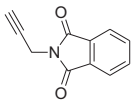
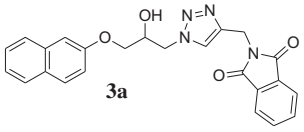
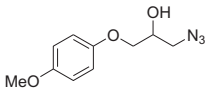
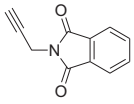
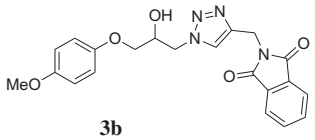
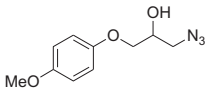
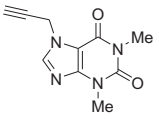
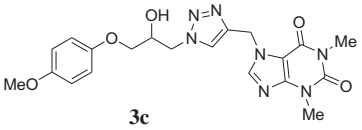
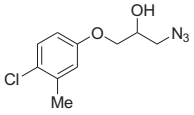
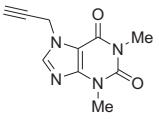
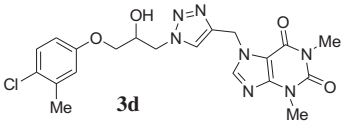
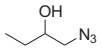
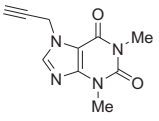
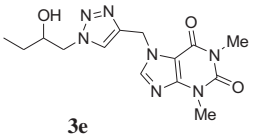
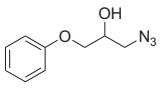
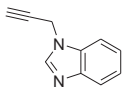
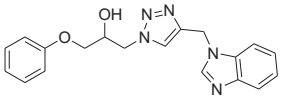
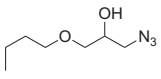
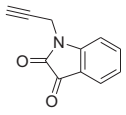
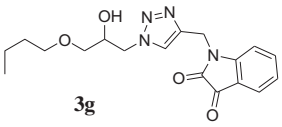
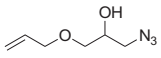
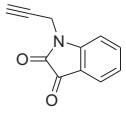
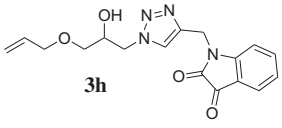
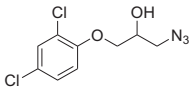
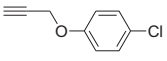
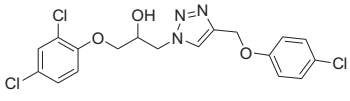
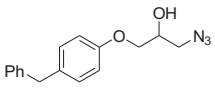
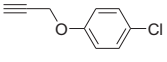
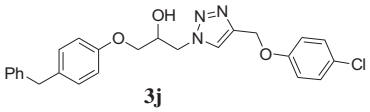
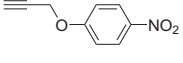
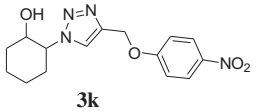
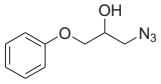
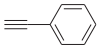
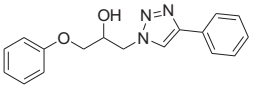
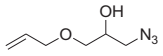
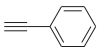
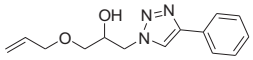
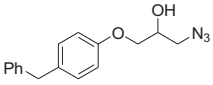
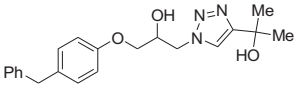
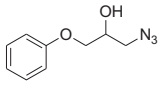
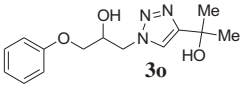
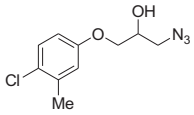
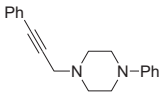
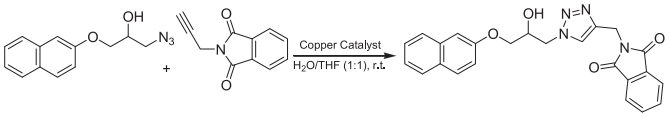
Entry	β-Azido alcohol	Alkyne	Product **3**[b]	Time (h)	Yield[c] (%)	Conversion[e] (%)
1			 **3a**	0.5	93	100
2			 **3b**	0.5	92	100
3			 **3c**	1	83	92
4			 **3d**	1	80	90
5			 **3e**	1	81	90
6			 **3f**	0.75	85	93
7			 **3g**	0.5	91	100
8			 **3h**	0.5	93	100
9			 **3i**	0.33	88	95
10			 **3j**	0.33	86	95
11			 **3k**	0.33	90	100
12			 **3l**	0.5	88	96

Table 4 (*continued*)

Entry	β-Azido alcohol	Alkyne	Product **3**[b]	Time (h)	Yield[c] (%)	Conversion[e] (%)
13			 **3m**	0.5	87	96
14			 **3n**	0.33	91	100
15			 **3o**	0.33	90	100
16			NR[d]	36	—	—

[a] Reaction condition: β-azido alcohol (0.01 mol), alkyne (0.012 mol), CDSCS (0.05 mol %), THF/H_2O (1:1, 20 mL), room temperature.
[b] All products were characterized by ^1H and ^{13}C NMR, IR, CHN, and MS analysis.
[c] Isolated yield.
[d] No reaction.
[e] GC yield.

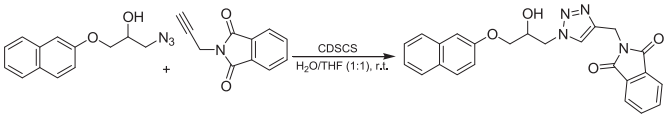
Table 5
Influence of time on conversion of 1-azido-3-(naphthalen-2-yloxy) propan-2-ol into **3a** using CDSCS at room temperature[a]



Entry	Time (h)	Yield[b] (%)	Conversion[c] (%)
1	0.1	45	53
2	0.2	60	71
3	0.3	75	85
4	0.4	82	93
5	0.5	93	100
6	0.7	93	100

[a] Reaction condition: 1-azido-3-(naphthalen-2-yloxy)propan-2-ol (0.01 mol), 2-(prop-2-ynyl) isoindoline-1,3-dione (0.012 mol), CDSCS (0.05 mol %), THF/H_2O (1:1, 20 mL), room temperature.
[b] Isolated yield.
[c] GC yield.

Table 6
Comparison of various copper catalysts with CDSCS on conversion of 1-azido-3-(naphthalen-2-yloxy) propan-2-ol into **3a**[a]



Entry[Ref.]	Copper catalyst	Time (h)	Yield[b] (%)
1	CDSCS	0.5	93
2[38]	$Cu(OAc)_2$[c]	8	73
3[13]	CuI	7	84
4[12]	$CuSO_4 \cdot 5H_2O$[c]	8	80
5[19b]	Cu/C	1	87

[a] Reaction condition: 1-azido-3-(naphthalen-2-yloxy)propan-2-ol (0.01 mol), 2-(prop-2-ynyl) isoindoline-1,3-dione (0.012 mol), copper catalyst (0.05 mol %), THF/H_2O (1:1, 20 mL), room temperature.
[b] Isolated yield.
[c] The reaction was carried out in the presence of sodium ascorbate (0.1 mol %).

copper catalysts under the optimized condition. The comparative results are summarized in Table 6. According to the results in Table 6, a higher yield of **3a** and shorter reaction time were obtained using CDSCS (Table 6, entry 1) in comparison with other examined copper catalysts. Using the other catalysts afforded the satisfactory results of **3a**, however the reactions were required longer reaction times.

All synthesized compounds **3a**–**o** were fully characterized, and their structures were confirmed by ^1H and ^{13}C NMR, elemental analysis, mass spectrometry and IR spectroscopy methods. Structural assignments of β-hydroxytriazoles **3k**–**m** were made by comparison of their ^1H NMR and ^{13}C NMR spectra with those reported in the literature.[39] In general, the ^1H NMR spectra of all compounds confirm the presence of a singlet peak relating to resonance of a proton in the 5-position of the 1,2,3-triazole rings.

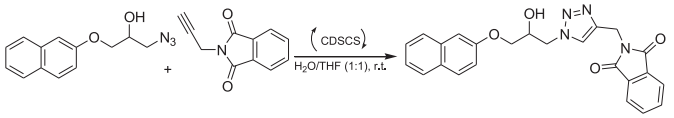
The chemistry works well with various β-azido alcohols involving aryloxy, alkoxy and alkyl residues, and also tolerates a wide spectrum of electron-donating and electron-withdrawing functional groups in both alkyne and azide molecules. Most of β-azido alcohols used in these experiments were pre-synthesized by the regioselective ring opening reaction of corresponded epoxides with sodium azide, whereas the majority of terminal alkynes were prepared via S_N2-type reaction of propargyl bromide and corresponded nucleophiles.

Biological activities of all compounds are under studying and will be reported elsewhere.

2.4. The reusability of CDSCS

The reusability of the CDSCS was studied during the synthesis of **3a** (Table 7). In this context, prior to use and also final testing of the catalyst for determination of its activity in many subsequent runs, the catalyst was recycled from the reaction mixture through a sintered glass funnel (vacuum-filtering). The catalyst was then washed successively with THF/H_2O (1:1, v/v, 5×10 mL) and dried in a vacuum oven at 100 °C for 30 min. The catalyst was tested for five consecutive runs and through each run, no fresh catalyst was added.

Table 7
The reusability of CDSCS in successive trails for synthesis of **3a**[a]



Run no.[b]	Time (h)	Yield[c] (%)
1	0.5	93
2	0.5	93
3	1	86
4	1.25	84
5	1.5	80

[a] Reaction condition: 1-azido-3-(naphthalen-2-yloxy)propan-2-ol (0.01 mol), 2-(prop-2-ynyl) isoindoline-1,3-dione (0.012 mol), recovered CDSCS, THF/H_2O (1:1, 20 mL), room temperature.
[b] The entry number corresponds to the trial number.
[c] Isolated yield.

As the results in Table 7 indicate, the catalyst can be reused for many consecutive runs without considerable decrease in its catalytic reactivity. To prove the recoverability, thermal and chemical stabilities of CDSCS, analytical techniques, such as ICP and TGA instrument were used to measure the copper amounts before and after five successive runs of CDSCS. Based on the ICP results, the amount of copper bonded on fresh CDSCS was evaluated to 6.12%. This value was also calculated to 6.14% base on TG analysis. The small difference between obtained results from ICP and TGA analyses is attributed to sample pretreatment before ICP analysis. On the basis of the ICP results, the amount of copper species was diminished to 6.11% after five sequential reuses. Additionally, the ICP analysis has endorsed the recoverability of CDSCS without significant desorption from the silica matrix. As it is well indicated, the amount of leached copper from CDSCS is negligible (0.01% after five runs) and it is reasoned that this is due to strong ionic bonds present between copper cations and sulfate group on surface of SSA. These characteristics of CDSCS demonstrate its superiority in comparison with usual catalysts, which are normally prepared by immobilization of copper species on solid supports and/or polymers.

3. Conclusions

In conclusion, we explained the synthesis and characterization of nano copper-doped silica cuprous sulfate (CDSCS). CDSCS proved to be a highly efficient heterogeneous catalyst for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles derivatives. In this synthetic methodology, CDSCS catalyzes 1,3-dipolar Huisgen cycloaddition of different functionalized β-azido alcohols and alkynes in a (1:1, v/v) solution of THF/H_2O at room temperature. Good to excellent yields of β-hydroxytriazoles were afforded using CDSCS. CDSCS was demonstrated to be an efficient, thermally and chemically stable, environmental compatible and low cost catalyst that can be easily prepared and reused for many consecutive runs without a significant decrease in its catalytic reactivity.

4. Experimental

4.1. General

All preliminary chemicals were purchased from Fluka, Merck and/or Sigma–Aldrich. Preparation of SSA was achieved due to procedure described in literature.[31] Solvents were purified and dried by standard procedures, and stored over 3 Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh, ASTM). Melting points were measured using a Büchi-510 apparatus in open capillaries and are uncorrected. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained using a Brüker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively (δ in parts per million, J in hertz). GC/MS were performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z, rel %). Elemental analyses were conducted on a Perkin–Elmer 240-B micro-analyzer.

The TG of CDSCS was analyzed using a lab-made thermogravimetric (TG) analyzer instrumentation system (Model: Q500). The Transmission electron microscopy was employed using TEM (CN-10, Philips, 100 kV). The scanning electron micrograph was attained using SEM (XL-30 FEG, Philips, 20 kV) instrument. An atomic force microscopy (AFM, DME-SPM, version 2.0.0.9) was also used for AFM image. Spectroscopic techniques, such as inductively coupled plasma (ICP) and patterned X-ray diffraction (XRD, D8 Advance, Brüker AXS) were employed for characterization of CDSCS.

4.2. Catalyst preparation

For preparation of CDSCS, 3.0 g of SSA was dispersed in 50 mL of deionized water. Then, the suspension was sonicated for 1 h in a beaker inside a sonication bath (frequency 100 MHz, 80 W) at ambient temperature. The suspension was left for about 30 min to be deposited and separated. A solution of 1.0 mM of copper(I) iodide in water was prepared by dissolving CuI in triply distilled water (100 mL) and it was enriched by addition of 10 mL of NaI (0.02 M). Then, this solution was dropwise added to the SSA, while the suspension was sonicated in a beaker inside a sonication bath (frequency 100 MHz, 80 W) at ambient temperature. The CDSCS was filtered from the suspension mixture and was subsequently washed by distillated water (3×10 mL). The CDSCS was then dried in vacuum at 80 °C and stored in a desiccator.

4.3. Catalytic test

To a round bottom flask (50 mL), was added a mixture of alkyne (0.012 mol), CDSCS (0.3 g, 0.05 mol %) and the appropriate β-azido alcohol (0.01 mol) in a mixture of THF/H_2O (1:1 v/v, 20 mL). The reaction mixture was stirred at room temperature until TLC monitoring indicated no further progress in the conversion. The catalyst was filtered off, washed with THF/H_2O (5×10 mL) and the filtrate was evaporated under vacuum to remove the solvent. The remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2×100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel and eluted with proper solvents. Characterization data of all synthesized compounds are described below.

*4.3.1. 2-((1-(2-Hydroxy-3-(naphthalen-2-yloxy)propyl)-1H-1,2,3-triazol-4-yl)methyl) isoindoline-1,3-dione (**3a**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 4:1) afforded the product as a pale-yellow solid; yield: 3.98 g (93%); mp 208.4 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.56; ^1H NMR (250 MHz, DMSO-d_6): δ=4.03–4.05 (m, 2H, NCH_2CH), 4.28 (s, 1H, OH, exchangeable with D_2O), 4.42 (dd, J=7.5, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.57 (dd, J=3.6, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.84 (s, 2H, $NCH_2C{=}C$), 5.61–5.64 (m, 1H, CHOH), 7.12–7.42 (m, 4H, aryl), 7.74–7.86 (m, 7H, aryl), 8.08 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=32.8, 52.6, 67.7, 69.5, 106.7, 118.5, 123.1, 123.6, 124.2, 126.3, 126.6, 127.4, 128.5, 129.2, 131.5, 134.1, 134.4, 142.0, 156.1, 167.3; IR (KBr): 3366, 3152, 3087, 3048, 2931, 1775, 1723, 1628, 1558,

1423 cm^{-1}; MS (EI) *m/z* (%): 428 (7.5) [M^+]; Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08; found: C, 67.36; H, 4.63; N, 13.19.

*4.3.2. 2-((1-(2-Hydroxy-3-(4-methoxyphenoxy)-propyl)-1H-1,2,3-triazol-4-yl)methyl) isoindoline-1,3-dione (**3b**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 4:1) afforded the product as a yellow solid; yield: 3.75 g (92%); mp 141.3 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.51; ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.64 (s, 3H, OCH_3), 3.81–3.83 (m, 2H, NCH_2CH), 4.17 (s, 1H, OH, exchangeable with D_2O), 4.33 (dd, *J*=7.8, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.50 (dd, *J*=3.4, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.83 (s, 2H, $NCH_2C{=}C$), 5.50–5.52 (m, 1H, CHOH), 6.81–6.85 (m, 4H, aryl), 7.80–7.82 (m, 4H, aryl), 8.03 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=32.8, 52.7, 55.2, 67.8, 70.0, 114.5, 115.4, 123.1, 124.1, 131.5, 134.4, 142.0, 152.3, 153.4, 167.3; IR (KBr): 3326, 3145, 2990, 2971, 1764, 1709, 1506, 1427 cm^{-1}; MS (EI) *m/z* (%): 408 (3.9) [M^+]; Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72; found: C, 61.70; H, 5.03; N, 13.76.

*4.3.3. 7-((1-(2-Hydroxy-3-(4-methoxyphenoxy)-propyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3c**).* Column chromatography on silica gel (EtOAc) afforded the product as a white solid; yield: 3.66 g (83%); mp 183.1 °C; R_f (EtOAc)=0.21; ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.16 (s, 3H, N(3)–CH_3), 3.35 (s, 3H, N(1)–CH_3), 3.65 (s, 3H, OCH_3), 3.80–3.83 (m, 2H, NCH_2CH), 4.15 (s, 1H, OH, exchangeable with D_2O), 4.35 (dd, *J*=7.5, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.51 (dd, *J*=3.3, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.49–5.51 (m, 1H, CHOH), 5.54 (s, 2H, $NCH_2C{=}C$), 6.75–6.83 (m, 4H, aryl), 8.07 (s, 1H, C(5)–H, triazole), 8.13 (s, 1H, C(8)–H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=27.4, 29.3, 41.0, 52.7, 55.2, 67.7, 70.0, 105.7, 114.4, 115.3, 124.8, 142.0, 142.3, 148.2, 150.9, 152.2, 153.4, 154.3; IR (KBr): 3222, 3127, 2931, 1725, 1710, 1657, 1549, 1439 cm^{-1}; MS (EI) *m/z* (%): 441 (10.3) [M^+]; Anal. Calcd for $C_{20}H_{23}N_7O_5$: C, 54.42; H, 5.25; N, 22.21; found: C, 54.31; H, 5.39; N, 22.27.

*4.3.4. 7-((1-(3-(4-Chloro-3-methylphenoxy)-2-hydroxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3d**).* Column chromatography on silica gel (EtOAc) afforded the product as a white solid; yield: 3.67 g (80%); mp 117.0 °C; R_f (EtOAc)=0.28; ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.23 (s, 3H, $ArCH_3$), 3.37 (s, 6H, N(3)–CH_3, N(1)–CH_3), 3.80–3.86 (m, 2H, NCH_2CH), 4.17 (s, 1H, OH, exchangeable with D_2O), 4.37–4.41 (m, 2H, $ArOCH_2$), 4.50–4.57 (m, 1H, CHOH), 5.55 (s, 2H, $NCH_2C{=}C$), 6.71 (s, 1H, aryl), 6.89 (d, *J*=7.5 Hz, 1H, aryl), 7.22 (d, *J*=7.5 Hz, 1H, aryl), 8.07 (s, 1H, C(5)–H, triazole), 8.13 (s, 1H, C(8)–H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=19.6, 27.4, 29.3, 41.0, 52.7, 67.6, 69.6, 105.7, 113.5, 117.0, 124.8, 129.3, 133.0, 134.5, 136.4, 148.2, 149.3, 150.8, 154.3, 156.9; IR (KBr): 3050, 2964, 2925, 1721, 1705, 1663, 1596, 1498, 1021 cm^{-1}; MS (EI) *m/z* (%): 459 (6.3) [M^+]; Anal. Calcd for $C_{20}H_{22}ClN_7O_4$: C, 52.23; H, 4.82; Cl, 7.71; N, 21.32; found: C, 52.16; H, 4.85; Cl, 7.78; N, 21.29.

*4.3.5. 7-((1-(2-Hydroxybutyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3e**).* Column chromatography on silica gel (EtOAc) afforded the product as a white solid; yield: 2.70 g (81%); mp 144.2 °C; R_f (EtOAc)=0.17; ^{1}H NMR (250 MHz, DMSO-d_6): δ=0.82 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.13–1.38 (m, 2H, CH_2CH_3), 3.16 (s, 3H, N(3)–CH_3), 3.35 (s, 3H, N(1)–CH_3), 3.68 (s, 1H, OH, exchangeable with D_2O), 4.12 (dd, *J*=7.6, 13.7 Hz, 1H, NCH_AH_B), 4.28 (dd, *J*=3.2, 13.7 Hz, 1H, NCH_AH_B), 4.94–4.97 (m, 1H, CHOH), 5.52 (s, 2H, $NCH_2C{=}C$), 8.00 (s, 1H, C(5)–H, triazole), 8.11 (s, 1H, C(8)–H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=9.6, 27.0, 27.4, 29.3, 41.0, 55.0, 70.2, 105.7, 124.5, 141.9, 142.3, 148.2, 150.9, 154.3; IR (KBr): 3252, 3107, 2961, 1719, 1708, 1665, 1542, 1431 cm^{-1}; MS (EI) *m/z* (%): 333 (11.7) [M^+]; Anal. Calcd for $C_{14}H_{19}N_7O_3$: C, 50.44; H, 5.75; N, 29.41; found: C, 50.49; H, 5.87; N, 29.54.

*4.3.6. 1-(4-((1H-Benzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenoxypropan-2-ol (**3f**).* Column chromatography on silica gel (EtOAc) afforded the product as a yellow foam; yield: 2.96 g (85%); R_f (EtOAc)=0.42; ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.88–3.94 (m, 2H, NCH_2CH), 4.16 (s, 1H, OH, exchangeable with D_2O), 4.35–4.43 (m, 1H, CHOH), 4.55–4.61 (m, 2H, $ArOCH_2$), 5.55 (s, 2H, $NCH_2C{=}C$), 6.90 (d, *J*=7.5 Hz, 2H, aryl), 7.14–7.53 (m, 5H, aryl), 7.62 (d, *J*=7.5 Hz, 2H, aryl), 8.13 (s, 1H, C(5)–H, triazole), 8.31 (s, 1H, C(2)–H, benzimidazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=50.2, 52.7, 67.7, 69.3, 110.7, 114.4, 119.4, 120.7, 128.9, 129.3, 129.4, 129.6, 133.5, 139.0, 142.2, 143.8, 158.2; IR (liquid film): 3296, 3050, 2966, 2929, 1669, 1591, 1492 cm^{-1}; MS (EI) *m/z* (%): 349 (8.5) [M^+]; Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04; found: C, 65.37; H, 5.46; N, 20.10.

*4.3.7. 1-((1-(3-Butoxy-2-hydroxypropyl)-1H-1,2,3-triazol-4-yl) methyl)indoline-2,3-dione (**3g**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a scarlet foam; yield: 3.26 g (91%); R_f (EtOAc/*n*-hexane, 4:1)=0.45, ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.53 (t, *J*=7.2 Hz, 3H, CH_3), 0.95–1.04 (m, 2H, CH_2CH_3), 1.13–1.22 (m, 2H, OCH_2CH_2), 3.08–3.14 (m, 4H, CH_2OCH_2), 3.49–3.51 (m, 1H, CHOH), 3.84 (s, 1H, OH, exchangeable with D_2O), 4.02 (dd, *J*=7.3, 14.0 Hz, 1H, NCH_AH_B), 4.20 (dd, *J*=3.4, 14.0 Hz, 1H, NCH_AH_B), 4.65 (s, 2H, $NCH_2C{=}C$), 6.72–6.91 (m, 2H, aryl), 7.18–7.26 (m, 2H, aryl), 7.58 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=13.8, 18.8, 31.5, 35.3, 53.2, 69.0, 71.3, 71.6, 111.4, 117.4, 123.9, 124.6, 125.1, 138.5, 141.3, 150.2, 157.9, 183.1; IR (liquid film): 3419, 3035, 2950, 1739, 1614, 1585, 1471 cm^{-1}; MS (EI) *m/z* (%): 358 (5.9) [M^+]; Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63; found: C, 60.47; H, 6.13; N, 15.68.

*4.3.8. 1-((1-(3-(Allyloxy)-2-hydroxypropyl)-1H-1,2,3-triazol-4-yl) methyl)indoline-2,3-dione (**3h**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a scarlet foam; yield: 3.18 g (93%); R_f (EtOAc/*n*-hexane, 4:1)=0.39; ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.18–3.22 (m, 2H, OCH_2CHOH), 3.58–3.60 (m, 1H, CHOH), 3.73–3.76 (m, 2H, $CH_2CH{=}C$), 3.96 (s, 1H, OH, exchangeable with D_2O), 4.13 (dd, *J*=7.2, 14.0 Hz, 1H, NCH_AH_B), 4.29 (dd, *J*=3.6, 14.0 Hz, 1H, NCH_AH_B), 4.75 (s, 2H, $NCH_2C{=}C$), 4.89–5.04 (m, 2H, $=CH_2$), 5.53–5.67 (m, 1H, =CH), 6.86–7.01 (m, 2H, aryl), 7.28–7.33 (m, 2H, aryl), 7.67 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=35.3, 53.2, 69.0, 71.0, 72.3, 111.4, 117.4, 117.5, 123.9, 124.6, 125.2, 134.1, 138.6, 141.3, 150.2, 158.0, 183.1; IR (liquid film): 3400, 3083, 2984, 1734, 1625, 1591, 1468 cm^{-1}; MS (EI) *m/z* (%): 342 (7.5) [M^+]; Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; found: C, 59.60; H, 5.21; N, 16.46.

*4.3.9. 1-(4-((4-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-3-(2,4-dichlorophenoxy)propan-2-ol (**3i**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a pale-yellow solid; yield: 3.77 g (88%); mp 129.5 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.62; ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.97–4.08 (m, 2H, NCH_2CH), 4.28 (s, 1H, OH, exchangeable with D_2O), 4.45 (dd, *J*=7.5, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.61 (dd, *J*=3.2, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.13 (s, 2H, $OCH_2C{=}C$), 5.66–5.68 (m, 1H, CHOH), 7.02–7.34 (m, 6H, aryl), 7.51 (s, 1H, aryl), 8.19 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=52.5, 61.3, 67.6, 70.6, 115.2, 116.4, 122.5, 124.5, 124.7, 125.6, 128.0, 128.7, 129.1, 142.1, 152.8, 156.8; IR (KBr): 3264, 3028, 2921, 1647, 1590, 1491, 1036 cm^{-1}; MS (EI) *m/z* (%): 428 (2.6) [M^+]; Anal.

Calcd for $C_{18}H_{16}Cl_3N_3O_3$: C, 50.43; H, 3.76; Cl, 24.81; N, 9.80; found: C, 50.57; H, 3.81; Cl, 24.87; N, 9.71.

*4.3.10. 1-(4-Benzylphenoxy)-3-(4-((4-chlorophenoxy)-methyl)-1H-1,2,3-triazol-1-yl)propan-2-ol (**3j**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; yield: 3.86 g (86%); mp 110.1 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.65; ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.59 (s, 2H, $PhCH_2$), 3.85–3.88 (m, 2H, NCH_2CH), 4.10 (s, 1H, OH, exchangeable with D_2O), 4.39 (dd, *J*=7.6, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.56 (dd, *J*=3.3, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.13 (s, 2H, $OCH_2C{=}C$), 5.57–5.59 (m, 1H, CHOH), 6.83 (d, *J*=8.3 Hz, 2H, aryl), 7.04–7.56 (complex, 11H, aryl), 8.18 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=40.4, 52.6, 61.3, 67.8, 69.5, 114.5, 116.4, 124.5, 125.6, 125.8, 128.3, 128.5, 129.2, 129.6, 133.5, 141.6, 142.0, 156.6, 156.9; IR (KBr): 3262, 3029, 2912, 1604, 1575, 1492 cm^{-1}; MS (EI) *m*/*z* (%): 449 (3.2) [M$^+$]; Anal. Calcd for $C_{25}H_{24}ClN_3O_3$: C, 66.74; H, 5.38; Cl, 7.88; N, 9.34; found: C, 66.86; H, 5.34; Cl, 7.81; N, 9.45.

*4.3.11. 2-(4-((4-Nitrophenoxy)methyl)-1H-1,2,3-triazol-1-yl)cyclohexanol (**3k**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a brown solid; yield: 2.59 g (90%); mp 143.6 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.58; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.31–1.45 (m, 4H, $2CH_2$), 1.80–1.98 (m, 2H, CH_2), 2.12–2.17 (m, 2H, CH_2), 3.14 (s, 1H, OH, exchangeable with D_2O), 3.97–4.10 (m, 1H, CHOH), 4.15–4.24 (m, 1H, NCH), 5.28 (s, 2H, $OCH_2C{=}C$), 7.07 (d, *J*=7.8 Hz, 2H, aryl), 7.78 (s, 1H, C(5)–H, triazole), 8.11 (d, *J*=7.8 Hz, 2H, aryl); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=23.9, 24.8, 31.7, 34.0, 62.4, 67.1, 72.6, 114.9, 123.2, 125.9, 141.9, 142.1, 163.1; IR (KBr): 3390, 3035, 2957, 1656, 1585, 1498, 1336 cm^{-1}; MS (EI) *m*/*z* (%): 318 (3.2) [M$^+$]; Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60; found: C, 56.67; H, 5.62; N, 17.55.

*4.3.12. 1-Phenoxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol (**3l**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a colorless solid; yield: 2.60 g (88%); mp 125.6 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.63; ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.84 (s, 1H, OH, exchangeable with D_2O), 4.03–4.09 (m, 2H, NCH_2CH), 4.51 (dd, *J*=3.6, 12.8 Hz, 2H, $ArOCH_2$), 4.66–4.78 (m, 1H, CHOH), 6.92–7.04 (m, 3H, aryl), 7.60–7.64 (m, 5H, aryl), 7.69–7.73 (m, 2H, aryl), 7.87 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=53.6, 68.6, 68.9, 114.5, 121.5, 121.6, 125.5, 128.2, 128.8, 129.7, 130.1, 147.2, 158.3; IR (KBr): 3420, 3071, 2927, 1661, 1595, 1490, cm^{-1}; MS (EI) *m*/*z* (%): 295 (7.1) [M$^+$]; Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23; found: C 69.05, H 5.91, N 14.15.

*4.3.13. 1-(Allyloxy)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol (**3m**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a colorless solid; yield: 2.25 g (87%); mp 71.4 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.61; ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.14 (d, *J*=5.1 Hz, $CH_2CH{=}C$, 2H), 3.72–3.77 (m, 2H, OCH_2CHOH), 3.95–4.13 (m, 2H, NCH_2CH), 4.24–4.29 (m, 1H, CHOH), 4.56 (s, 1H, OH, exchangeable with D_2O), 4.97 (dd, *J*=10.4, 17.3 Hz, 2H, $=CH_2$), 5.51–5.65 (m, 1H, =CH), 6.93–7.09 (m, 3H, aryl), 7.32–7.38 (m, 2H, aryl), 7.56 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=53.5, 69.0, 71.3, 72.3, 117.5, 121.0, 125.4, 128.1, 128.8, 129.7, 134.2, 147.1; IR (KBr): 3350, 3050, 2978,1591, 1455, 1357 cm^{-1}; MS (EI) *m*/*z* (%): 259 (10.5) [M$^+$]; Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20; found: C, 64.93; H, 6.69; N, 16.14.

*4.3.14. 1-(4-Benzylphenoxy)-3-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)propan-2-ol (**3n**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; yield: 3.34 g (91%); mp 86.5 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.36; ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.22 (s, 6H, $2CH_3$), 3.18 (s, 2H, $PhCH_2$), 3.63–3.65 (m, 2H, NCH_2CH), 3.95 (s, 1H, CHOH, exchangeable with D_2O), 4.09 (dd, *J*=7.5, 13.7 Hz, 1H, $ArOCH_AH_B$), 4.25 (dd, *J*=2.7, 13.4 Hz, 1H, $ArOCH_AH_B$), 4.88 (s, 1H, $(CH_3)_2COH$, exchangeable with D_2O), 5.29–5.31 (m, 1H, CHOH), 6.60 (d, *J*=8.2 Hz, 2H, aryl), 6.86–7.04 (m, 7H, aryl), 7.61 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=30.7, 40.4, 52.4, 67.0, 67.9, 69.5, 114.5, 121.6, 125.8, 128.3, 128.5, 129.7, 133.5, 141.6, 155.7, 156.6; IR (KBr): 3329, 3065, 2971, 1643, 1584, 1511, 1453 cm^{-1}; MS (EI) *m*/*z* (%): 367 (5.1) [M$^+$]; Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44; found: C, 68.50; H, 6.81; N, 11.53.

*4.3.15. 1-(4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-3-phenoxypropan-2-ol (**3o**).* Column chromatography on silica gel (EtOAc/*n*-hexane, 2:1) afforded the product as a white solid; yield: 2.50 g (90%); mp 92.9 °C; R_f (EtOAc/*n*-hexane, 4:1)=0.35; ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.39 (s, 6H, $2CH_3$), 3.84–3.86 (m, 2H, NCH_2CH), 4.15 (s, 1H, CHOH, exchangeable with D_2O), 4.29 (dd, *J*=7.3, 13.8 Hz, 1H, $ArOCH_AH_B$), 4.44 (dd, *J*=3.8, 13.8 Hz, 1H, $ArOCH_AH_B$), 5.03 (s, 1H, $(CH_3)_2COH$, exchangeable with D_2O), 5.48–5.50 (m, 1H, CHOH), 6.85–6.88 (m, 3H, aryl), 7.18–7.24 (m, 2H, aryl), 7.78 (s, 1H, C(5)–H, triazole); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=30.7, 52.4, 67.0, 67.9, 69.4, 114.5, 120.7, 121.4, 129.4, 155.5, 158.3; IR (KBr): 3316, 3100, 2970, 1597, 1588, 1468 cm^{-1}; MS (EI) *m*/*z* (%): 277 (1.3) [M$^+$]; Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15; found: C, 60.75; H, 6.83; N, 15.10.

Acknowledgements

We wish to thank Pars Industrial Pioneer Engineering Company for financial support of this work. We are also grateful to Shiraz University of Technology and Shiraz University Research Councils for partial support of this work.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262; (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128–1137.
2. (a) Peter, N.; Derek, H.; Levine, B. R. *Heterocycles* **1996**, *43*, 2643–2655; (b) Zhou, L.; Amer, A.; Korn, M.; Burda, R.; Balzarini, J.; De Clercq, E.; Kern, E. R.; Torrence, P. F. *Antiviral Chem. Chemother.* **2005**, *16*, 375–383.
3. (a) Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 467–470; (b) Bennett, L., Jr.; Baker, H. *J. Org. Chem.* **1957**, *22*, 707–709.
4. Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194.
5. Romero, A.; Liang, C.-H.; Chiu, Y.-H.; Yao, S.; Duffield, J.; Sucheck, S. J.; Marby, K.; Rabuka, D.; Leung, P. Y.; Shue, Y.-K.; Ichikawa, Y.; Hwang, C.-K. *Tetrahedron Lett.* **2005**, *46*, 1483–1487.
6. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.
7. (a) Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Poojari, B.; Akberali, P. M.; Kumari, N. S. *Eur. J. Med. Chem.* **2005**, *40*, 1173–1178; (b) Dabak, K.; Sezer, O.; Akar, A.; Anac, O. *Eur. J. Med. Chem.* **2003**, *38*, 215–218; (c) Willner, D.; Jelenevsky, A. M.; Cheney, L. C. *J. Med. Chem.* **1972**, *15*, 948–951.
8. (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford UK, 1996; Vol. 4, p 121; (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730–1733; (c) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025.
9. (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, 1984; pp 1–176; (b) Sha, C.-K.; Mohanakrishan, A. K. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2003; pp 623–680.

10. (a) Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J.; Sanchez, J. M. *Org. Prep. Proced. Int.* **1995**, *27*, 603–612; (b) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184–6189; (c) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302–5308; (d) Peng, W.; Zhu, S. *Synlett* **2003**, 187–190.
11. (a) Wang, K.; Bi, X.; Xing, S.; Liao, P.; Fang, Z.; Meng, X.; Zhang, Q.; Liu, Q.; Ji, Y. *Green Chem.* **2011**, *13*, 562–565; (b) Shamim, T.; Paul, S. *Catal. Lett.* **2010**, *136*, 260–265.
12. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
13. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
14. Wang, Q.; Chittaboina, S.; Barnhill, H. N. *Lett. Org. Chem.* **2005**, *2*, 293–301.
15. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.
16. Quader, S.; Boyd, S. E.; Jenkins, I. D.; Houston, T. A. *J. Org. Chem.* **2007**, *72*, 1962–1979.
17. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424; (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137–171; (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
18. (a) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951–1954; (b) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855; (c) Meng, J.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 4543–4546; (d) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A., Jr. *Tetrahedron* **2006**, *62*, 6405–6411.
19. (a) Lipshutz, B.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235–8238; (b) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009**, *351*, 207–218.
20. Girard, C.; Onen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Erscovici, J. *Org. Lett.* **2006**, *8*, 1689–1692.
21. Chassing, S.; Kumarraja, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883–886.
22. Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J. *Org. Lett.* **2008**, *10*, 497–500.
23. Jlalia, I.; Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2008**, *49*, 6756–6758.
24. Kantam, M. L.; Jaya, V. S.; Sreedhar, B.; Rao, M. M.; Choudary, B. M. *J. Mol. Catal. A: Chem.* **2006**, *256*, 273–277.
25. Li, P.; Wang, L.; Zhang, Y. *Tetrahedron* **2008**, *64*, 10825–10830.
26. Miao, T.; Wang, L. *Synthesis* **2008**, 363–368.
27. (a) Coelho, A.; Diz, P.; Caamaño, O.; Sotelo, E. *Adv. Synth. Catal.* **2010**, *352*, 1179–1192; (b) Megia-Fernandez, A.; Ortega-Muñoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Adv. Synth. Catal.* **2010**, *352*, 3306–3320.
28. Wilson, C. O.; Gisvold, O.; Block, J. H. In *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 11th ed.; Block, J. H., Beale, J. M., Jr., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2004.
29. (a) Nogrady, T.; Weaver, D. F. *Medicinal Chemistry: A Molecular and Biochemical Approach*, 3rd ed.; Oxford University: New York, NY, 2005; (b) Thomas, G. *Medicinal Chemistry: An Introduction*; John Wiley & Sons Ltd.: New York, NY, 2000.
30. Soltani Rad, M. N.; Behrouz, S.; Dianat, M. *Synthesis* **2008**, 2055–2064.
31. Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509–9511.
32. Pacchioni, G.; Skuja, L.; Griscom, D. L. In; Springer: 2000; Vol. 2.
33. Shaterian, H. R.; Ghashang, M.; Feyzi, M. *Appl. Catal., A* **2008**, *345*, 128–133.
34. Xue, B.; Chen, P.; Hong, Q.; Lin, J.; Tan, K. L. *J. Mater. Chem.* **2001**, *11*, 2378–2381.
35. (a) Li, Y.; Tong, H.; Zhuo, Y.; Wang, S.; Xu, X. *Environ. Sci. Technol.* **2006**, *40*, 7919–7924; (b) Li, Y.; Tong, H.; Zhuo, Y.; Li, Y.; Xu, X. *Environ. Sci. Technol.* **2007**, *41*, 2894–2900.
36. Feng, Z.; Marks, C. R.; Barkatt, A. *Oxid. Met.* **2003**, *60*, 393–408.
37. Topnani, N.; Kushwaha, S.; Athar, T. *Int. J. Green Nanotechnol.: Mat. Sci. & Eng.* **2009**, *1*, M67–M73.
38. Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123–3126.
39. Sharghi, H.; Beyzavi, M. H.; Safavi, A.; Doroodmand, M. M.; Khalifeh, R. *Adv. Synth. Catal.* **2009**, *351*, 2391–2410.