J IRAN CHEM SOC
DOI 10.1007/s13738-013-0307-4

ORIGINAL PAPER

Copper-doped silica cuprous sulfate (CDSCS) as a highly efficient heterogeneous nano catalyst for synthesis of 3,5-disubstituted isoxazoles

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Received: 14 December 2012 / Accepted: 25 June 2013

Abstract A facile and highly efficient protocol for 1,3-dipolar cycloaddition of in situ generated nitrile oxides with terminal alkynes catalyzed by copper-doped silica cuprous sulfate (CDSCS) as a new and convenient heterogeneous nano catalyst is described. In this protocol, 'click' cycloaddition of various structurally diverse alkynes and imidoyl chlorides in the presence of CDSCS and $NaHCO_3$ in a solution of *i*-PrOH/H_2O (1:1, V/V) furnishes the corresponding 3,5-disubstituted isoxazoles in good to excellent yields at room temperature. CDSCS was approved as a chemically and thermally stable nano catalyst that can be recovered and reused for many consecutive trials without considerable decline in its reactivity.

Keywords Alkyne · CDSCS · 3,5-Disubstituted isoxazole · Heterogeneous nano catalyst · Nitrile oxide

Introduction

Isoxazoles are versatile substrates in medicinal and organic chemistry [1–4]. Isoxazole derivatives are known to exhibit a wide spectrum of biological activities such as hypoglycemic [5], analgesic [6], anti-inflammatory [7, 8], antibacterial [9], antiviral [10, 11], antitumor [12], anti-HIV [13], anticancer [14], herbicide [15], insecticide [16], and fungicide [17]. Many famous drugs such as cotrimoxazole, cloxacillin, glisoxepide, isocarboxazid, oxacillin, valdecoxib and … having different chemotherapeutic activities contain isoxazole cores in their structures [1]. In addition, isoxazoles can be converted into several important synthetic units such as β-hydroxy-ketones [18–21], γ-amino-alcohols [22, 23], α,β-unsaturated oximes [24, 25], and β-hydroxy-nitriles [26, 27].

Numerous general methods have been developed so far to access 3,5-disubstituted isoxazoles including approaches based on condensation of hydroxylamine with 1,3-dicarbonyl compounds [28–32] or α,β-unsaturated carbonyl compounds [33–37], cyclization of alkynyl oxime ethers [38–41], and oxidation of 2-isoxazolines [42, 43]. The traditional 1,3-dipolar cycloaddition reaction between alkynes and in situ generated nitrile oxides from imidoyl chlorides is a well-known and extensively used strategy for the construction of 3,5-disubstituted isoxazoles [44–48]. However, the non-catalyzed thermal cycloaddition reactions of nitrile oxides with alkynes are neither chemo- nor regioselective, resulted in the formation of multiple side products in low yields. Recently, copper(I) catalyzed 1,3-dipolar cycloaddition reaction between alkynes and nitrile oxides reported by Sharpless [49] and Fokin [50] has made considerable progress in the synthesis of isoxazoles. This methodology enables the preparation of unsymmetrical 3,5-disubstituted isoxazoles with specific regioselectivity at satisfactory rates and yields. Active copper(I) as the catalytic species normally is CuI [51] or it can be in situ generated by reduction of copper(II) salt [49] and copper(II)/copper(0) comproportionation [50]. In recent years, there has been a growing demand for application of heterogeneous catalysts in

Electronic supplementary material The online version of this article (doi:10.1007/s13738-013-0307-4) contains supplementary material, which is available to authorized users.

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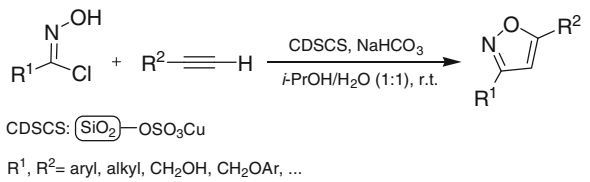
Published online: 04 July 2013



Scheme 1 1,3-Dipolar cycloaddition of alkynes and in situ generated nitrile oxides using CDSCS at room temperature

organic reactions. However, to the best of our knowledge, there have been no reports yet on the application of heterogeneous copper catalyst for cycloaddition reaction between alkynes and nitrile oxides. Hence, a practical method for the preparation of 3,5-disubstituted isoxazoles is still of great interest in organic synthesis. Recently, we have reported the synthesis, characterization, and application of copper-doped silica cuprous sulfate (CDSCS) as a novel and efficient heterogeneous nano catalyst for the Cu(I)-catalyzed 'click' cycloaddition of organic azides with terminal alkynes [52]. In continuation of our interest in discovering the new applications for CDSCS in organic synthesis hereby, we report that 1,3-dipolar cycloaddition of structurally diverse alkynes and in situ generated nitrile oxides can be efficiently achieved using CDSCS in *i*-PrOH/H_2O (1:1, V/V) at room temperature to afford 3,5-disubstituted isoxazoles in good to excellent yields (Scheme 1).

Experimental

General information

All chemicals were prepared from Fluka or Merck chemical companies. Solvents were purified and dried by standard procedures, and stored over molecular sieves 0.3 nm. The progress of reaction was followed with TLC using silica gel SILG/UV 254 plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM) was used for column chromatography. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Brüker Advanced DPX-250, FT-NMR spectrometer; Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin–Elmer 240-B microanalyzer. Melting points (m.p.) were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected.

General procedure for synthesis of 3,5-disubstituted isoxazoles using CDSCS

To a round bottom flask (50 mL), was added a mixture of alkyne (0.012 mol), CDSCS (0.3 g, 0.05 mol %), the appropriate imidoyl chloride [53] (0.01 mol), and $NaHCO_3$ (0.012 mol) in a mixture of *i*-PrOH/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 (Table 4). The catalyst was filtered off, washed with *i*-PrOH/H_2O (1:1 V/V, 3 × 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 short column chromatography on silica gel eluting with *n*-hexane:EtOAc (10:1). All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, CHN and MS analysis. Selected spectral data for entries 10, 11, 16 and 17 are given below:

5-Pentyl-3-phenylisoxazole (Table 4, entry 10)

Column chromatography on silica gel (EtOAc:*n*-hexane, 1:10) afforded the product as a colorless foam; yield: 1.87 g (87 %); R_f (EtOAc:*n*-hexane, 1:10) = 0.48; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.2 Hz, 3H, CH_3), 1.24–1.27 (m, 2H, CH_2CH_3), 1.35–1.39 (m, 2H, $CH_2CH_2CH_3$), 1.71–1.75 (m, 2H, $CH_2(CH_2)_2CH_3$), 2.63 (t, J = 7.4 Hz, 2H, $CH_2(CH_2)_3CH_3$), 6.38 (s, 1H, C(4)-H, isoxazole), 7.54–7.61 (m, 5H, aryl); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.23, 24.67, 32.85, 34.79, 37.15, 101.63, 126.50, 129.46, 130.17, 134.76, 159.28, 170.81; IR (liquid film): 3087, 2961, 1695, 1542, 1431 cm^{-1}; MS (EI) m/z (%): 215 (7.3) [M^+]; Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51; Found: C, 78.25; H, 7.89; N, 6.63.

3-(4-Methoxyphenyl)-5-pentylisoxazole (Table 4, entry 11)

Column chromatography on silica gel (EtOAc:*n*-hexane, 1:10) afforded the product as a colorless foam; yield: 2.08 g (85 %); R_f (EtOAc:*n*-hexane, 1:10) = 0.35; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.0 Hz, 3H, CH_3), 1.28–1.31 (m, 2H, CH_2CH_3), 1.37–1.40 (m, 2H, $CH_2CH_2CH_3$), 1.73–1.78 (m, 2H, $CH_2(CH_2)_2CH_3$), 2.71 (t, J = 7.5 Hz, 2H, $CH_2(CH_2)_3CH_3$), 3.79 (s, 3H, OCH_3), 6.34 (s, 1H, C(4)-H, isoxazole), 6.92 (d, J = 8.6 Hz, 2H, aryl), 7.38 (d, J = 8.6 Hz, 2H, aryl); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.45, 25.13, 33.80, 34.92, 38.31, 56.37, 101.27, 127.64, 130.76, 134.31, 158.49, 162.09, 170.24; IR (liquid film): 3050, 2975, 1698, 1552, 1446 cm^{-1}; MS (EI)

m/z (%): 245 (9.5) [M^+]; Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; Found: C, 73.52; H, 7.95; N, 5.78.

7-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (Table 4, entry 16)

Column chromatography on silica gel (EtOAc:*n*-hexane, 4:1) afforded the product as a white solide; yield: 2.93 g (80 %); m.p.: 215 °C; R_f (EtOAc:*n*-hexane, 4:1) = 0.35; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.28 (s, 3H, N3-CH_3), 3.50 (s, 3H, N1-CH_3), 3.88 (s, 3H, OCH_3), 5.82 (s, 2H, NCH_2), 6.95 (s, 1H, C(4)-H, isoxazole), 7.08 (d, J = 8.5 Hz, 2H, aryl), 7.83 (d, J = 8.5 Hz, 2H, aryl), 8.36 (s, 1H, C(8)-H, theophylline); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.97, 29.93, 41.95, 55.71, 101.26, 106.37, 114.87, 120.87, 128.57, 143.35, 148.81, 151.47, 154.72, 161.22, 162.11, 168.22; IR (KBr): 3100, 2946, 1720, 1706, 1693, 1558, 1470 cm^{-1}; MS (EI) m/z (%): 367 (5.2) [M^+]; Anal. Calcd for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06; Found: C, 58.94; H, 4.71; N, 19.02.

1,3-Dimethyl-7-((3-phenylisoxazol-5-yl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (Table 4, entry 17)

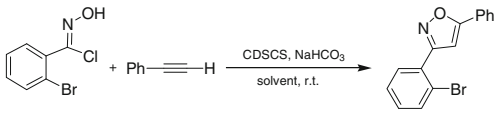
Column chromatography on silica gel (EtOAc:*n*-hexane, 4:1) afforded the product as a white solide; yield: 2.83 g (84 %); m.p.: 123 °C; R_f (EtOAc:*n*-hexane, 4:1) = 0.39; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.41 (s, 3H, N3-CH_3), 3.59 (s, 3H, N1-CH_3), 5.69 (s, 2H, NCH_2), 6.75 (s, 1H, C(4)-H, isoxazole), 7.44–7.46 (m, 3H, aryl), 7.75–7.79 (m, 3H, aryl, C(8)-H, theophylline); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.01, 31.22, 41.16, 102.45, 106.24, 126.81, 128.22, 128.96, 130.36, 141.27, 148.83, 151.54, 155.20, 162.88, 165.70; IR (KBr): 3075, 2938, 1725, 1708, 1697, 1556, 1462 cm^{-1}; MS (EI) m/z (%): 337 (7.4) [M^+]; Anal. Calcd for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76; Found: C, 60.41; H, 4.45; N, 20.69.

Results and discussion

In order to optimize the reaction conditions, we initially chose the cycloaddition reaction of phenyl acetylene with 2-bromo-*N*-hydroxybenzimidoyl chloride in the presence of CDSCS (0.3 g, 0.05 mol %) and $NaHCO_3$ to afford 3-(2-bromophenyl)-5-phenylisoxazole as a model reaction. We screened a variety of 1:1 (V/V) H_2O-organic solvents and examined their influence on reaction times and yields. The results are summarized in Table 1.

From Table 1, it is well demonstrated that solvent's type has a significant role in progress of reaction. Among the examined solvents, a solution of *i*-PrOH/H_2O (1:1, V/V) (Table 1, entry 8) afforded the best result. Therefore, it was used for all subsequent reactions. Moreover, equal ratio solutions of other solvents in water such as the solution of THF, dioxane, and acetone (Table 1, entries 5–7) also yielded the product in reasonable times and yields. Employing the other mixtures afforded the moderate yields of product for different periods of time (5–8 h). In addition, when water and *i*-PrOH were used alone, the yields of 35 and 60 % for the model reaction were obtained after 7 h, respectively (Table 1, entries 9 and 10). The low yield

Table 1 Effect of various solvents on the model reaction

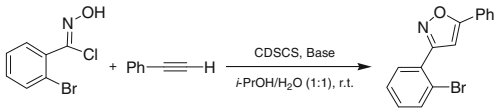


Entry	Solvent[a]	Time (h)	Yield[b] (%)
1	H_2O/DMSO	5	75
2	H_2O/DMF	5	68
3	H_2O/MeCN	6	62
4	H_2O/HMPA	8	61
5	H_2O/THF	3.5	84
6	H_2O/Dioxane	3.5	82
7	H_2O/Acetone	3.75	81
8	H_2O/*i*-PrOH	3	91
9	H_2O	7	35
10	*i*-PrOH	7	60

[a] For entries 1–8, a mixture of 1:1 (V/V) solvents was used

[b] Isolated yield

Table 2 Effect of various bases on the model reaction



Entry	Base	Time (h)	Yield[b] (%)
1	None	48	NR[c]
2	$NaHCO_3$	3	91
3	Al_2O_3[a]	5	60
4	NaH	4	51
5	MgO	8	38
6	Et_3N	3.5	84
7	DBN	3.5	82
8	DBU	3.5	85
9	DABCO	5	75
10	DMAP	7	72

[a] Basic alumina

[b] Isolated yield

[c] No reaction

obtained for the corresponding isoxazole using pure water as a solvent is attributed to lack of organic material solubility in H_2O.

The choice of the base for the in situ generation of nitrile oxides from imidoyl chlorides is of great significance. In this case, we investigated the effect of various organic and inorganic bases on the model reaction (Table 2).

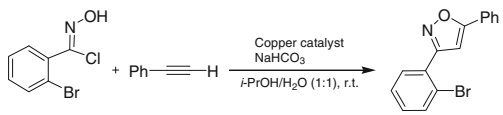
In the absence of base, no reaction was achieved even when the reaction time was prolonged (Table 2, entry 1). Among the examined bases, $NaHCO_3$ (Table 2, entry 2) was found to be the most efficient base for the progress of the reaction. The use of Et_3N, DBN, and DBU (Table 2, entries 6–8) also afforded good results. However, $NaHCO_3$ was preferred to use in this protocol because of higher yield, reasonable reaction rate and also for its cheapness, ease of handling and availability. Other bases tested in this experiment did not afford any satisfactory results.

To investigate the catalytic potency of CDSCS in 1,3-dipolar cycloaddition, in the same circumstance, we tested the model reaction using other reported copper catalysts under the optimized condition. The comparative results are depicted in Table 3. According to the results in Table 3, a higher yield of 3-(2-bromophenyl)-5-phenylisoxazole and shorter reaction time were obtained when CDSCS was used (Table 3, entry 4) in comparison with other examined copper catalysts. Using the other catalysts, the satisfactory yields of the corresponding product were afforded; however, the reactions required longer reaction time for completion.

The optimized stoichiometric ratio of imidoyl chloride/alkyne to access 3-(2-bromophenyl)-5-phenylisoxazole using CDSCS (0.05 mol %) was found to be 1:1.2. It is important to use an equimolar ratio of imidoyl chloride/alkyne. The increment in the molar ratio of alkyne can lead to the appearance of by-products as the result of Cu(I)-catalyzed alkyne–alkyne coupling.

The scope of this protocol was examined by its application to various imidoyl chlorides and alkynes (Table 4). As shown in Table 4, CDSCS proved to be admissible

Table 3 Effect of various catalysts on the model reaction



Entry [Ref.]	Copper catalyst	Time (h)	Yield[b] (%)
1 [49]	$CuSO_4{\cdot}5H_2O$[a]	4	88
2 [50]	$Cu^0/CuSO_4$	6	82
3 [51]	CuI	6	84
4	CDSCS	3	91

[a] The reaction was carried out in the presence of sodium ascorbate

[b] Isolated yield

nano catalyst for Cu(I)-catalyzed 1,3-dipolar cycloaddition between alkynes and in situ generated nitrile oxides affording 3,5-disubstituted isoxazoles. The chemistry works well with various structurally diverse aliphatic and aromatic imidoyl chlorides and alkynes, and also tolerates a wide spectrum of electron-donating and electron-withdrawing functional groups in both alkynes and imidoyl chlorides. As expected, disubstituted alkynes such as diphenyl acetylene were inactive in this protocol. This behavior is completely consistent with the mechanism of Cu(I)-catalyzed nitrile oxides-alkyne cycloaddition in which the formation of a Cu(I)-acetylide species is inevitable [49].

All synthesized compounds were fully characterized, and their structures were confirmed by ^{1}H- and ^{13}C-NMR, elemental analysis, mass and IR spectroscopy methods. Structural assignments of synthesized isoxazoles were made by comparison of their ^{1}H-NMR and ^{13}C-NMR spectra with those reported in the literatures [49, 50]. Thus, the reaction was achieved with excellent regioselectivity and the corresponding 3,5-disubstituted isoxazoles were mainly obtained in good to excellent yields and short reaction times at room temperature. The imidoyl chlorides used in these experiments were pre-synthesized by the reaction of corresponded aldoximes with *N*-chlorosuccinimide [53], whereas the majority of terminal alkynes were prepared via S_N2-type reaction of propargyl bromide and corresponded nucleophiles.

To investigate the applicability of this protocol in preparative scale, the 1,3-dipolar cycloaddition of model substrates was carried out at a 100-mmol scale under the optimized conditions. Indeed, the reaction proceeded efficiently comparable to smaller scale synthesis (Table 4, entry 4). 86 % yield of 3-(2-bromophenyl)-5-phenylisoxazole after 3 h was attained when reaction was conducted in larger scale.

The reusability of the CDSCS was studied during the synthesis of 3-(2-bromophenyl)-5-phenylisoxazole (Table 5). 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 *i*-PrOH/H_2O (1:1 V/V, 3 × 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.

As the results in Table 5 indicate, the catalyst can be recovered, recycled, and reused for many consecutive trials without remarkable loss of its activity. The amount of leached copper from CDSCS is negligible (0.012 % after five runs), as it is indicated by analyzing Cu(I) contents in both fresh catalyst and recycled catalyst (after five runs) using ICP analysis.

Table 4 CDSCS catalyzed synthesis of 3,5-disubstituted isoxazoles

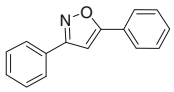
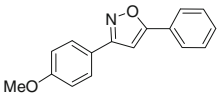
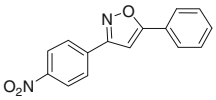
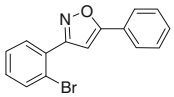
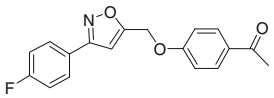
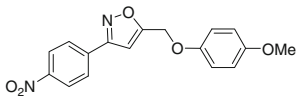
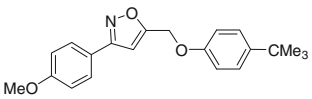
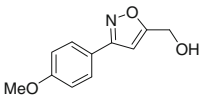
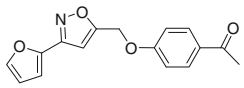
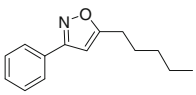
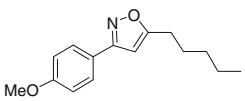
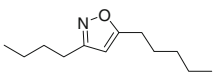
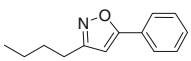
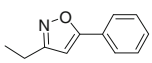
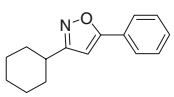
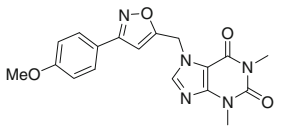
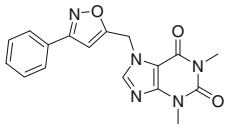
Entry	Structure[a]	Mp (Lit.)	Time (h)	Yield[b] (%)	Reference
1		140 (139–140)	3	95	[50]
2		123 (122)	3	92	[49]
3		222 (222)	3	94	[49]
4		76 (74–76)	3	91	[50]
5		113 (114–115)	3.5	92	[50]
6		139 (138–140)	3.5	89	[50]
7		121 (120–122)	3.5	88	[50]
8		90 (88–91)	4	85	[50]
9		137 (135–136)	4	80	[50]
10		Foam	4	87	–
11		Foam	4	85	–
12		Oil	4.5	80	[50]
13		29 (27–28)	4.5	86	[50]
14		27 (27–28)	5	84	[50]
15		33 (33–34)	5	86	[50]

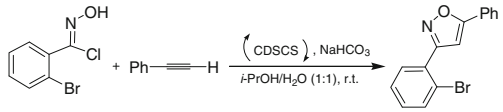
Table 4 continued

Entry	Structure[a]	Mp (Lit.)	Time (h)	Yield[b] (%)	Reference
16		215	6	80	–
17		123	6	84	–

[a] All products were characterized by ^{1}H- and ^{13}C-NMR, IR, CHN, and MS analysis

[b] Isolated yield

Table 5 The reusability of CDSCS in successive trails



Run no.[a]	Time (h)	Yield[b] (%)
1	3	91
2	3	91
3	3.5	85
4	3.5	82
5	4	80

[a] The entry number corresponds to the trial number

[b] Isolated yield

Conclusions

In summary, we have developed a simple and highly efficient protocol for regioselective synthesis of 3,5-disubstituted isoxazoles using CDSCS as a new and convenient heterogeneous nano catalyst. In this synthetic methodology, CDSCS catalyzes 1,3-dipolar cycloaddition of various structurally diverse alkynes and imidoyl chlorides in the presence of $NaHCO_3$ in a (1:1, V/V) solution of *i*-PrOH/H_2O at room temperature. Good to excellent yields of 3,5-disubstituted isoxazoles were obtained 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 trials without a significant decrease in its catalytic reactivity.

Acknowledgments We are grateful to Shiraz University of Technology Research Council for partial support of this work.

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