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A copper (II)-thioamide combination as a robust heterogeneous catalytic system for green synthesis of 1,4-disubstituted 1,2,3-triazoles under click conditions

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Abstract: An efficient and practical synthesis of 1,4-disubstituted 1,2,3-triazoles under click conditions using a copper (II)-thioamide combination as an efficient heterogeneous catalyst is disclosed. Mild reaction conditions and high yields make this method as an attractive option for the preparation of triazole derivatives. The key to this procedure was the generation of Cu (I) required for the azide-alkyne cycloaddition, which was achieved by *in situ* reduction of Cu (II) using thiobenzanilide as reduction agent and ligand.

Keywords: Heterogeneous catalyst, 1,2,3-triazoles, click chemistry, thiobenzanilide, Huisgen cycloaddition

Introduction

The aromatic heterocyclic compounds with a five-membered ring containing two carbon atoms and three nitrogen atoms was named 1,2,3-triazoles. These compounds constitute a major class of naturally occurring compounds and privileged medicinal scaffolds that exhibit a broad range of biological and pharmaceutical properties, such as anti-HIV, antibacterial, anticancer, antifungal, and antiviral agents.[1-6] Figure 1 shows representative bioactive 1,2,3-triazole-containing drugs.[7-11]

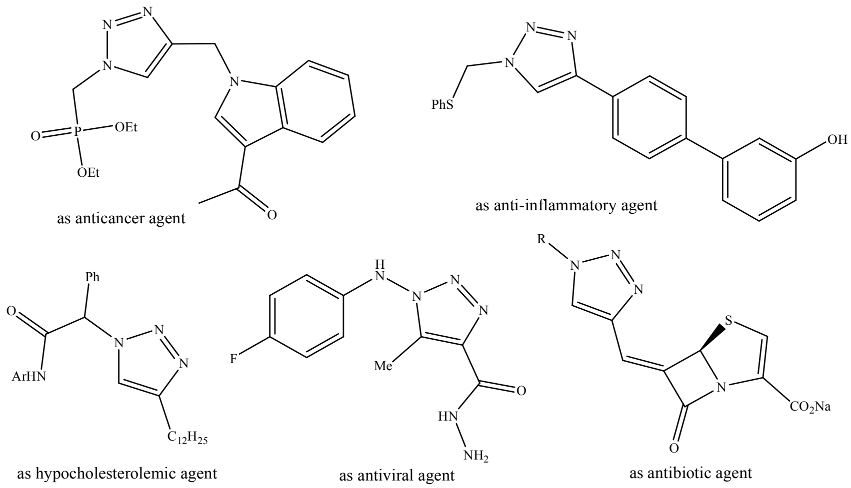
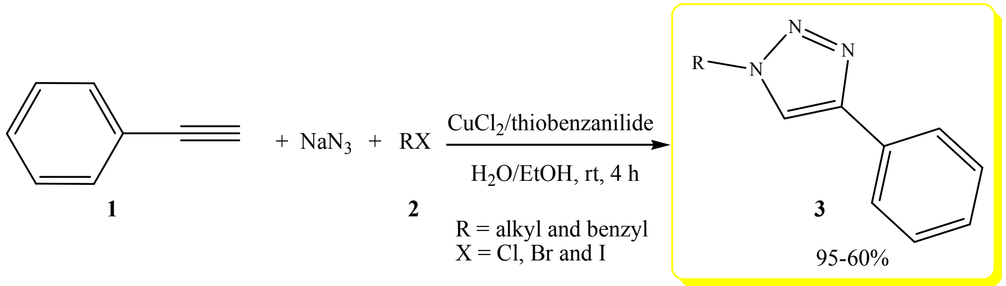


Fig. 1. Representative bioactive 1,2,3-triazoles.

Developing more efficient methods for the construction of compounds containing triazoles is a topic of immense importance. The synthesis of 1,2,3-triazoles strongly relies on copper (I)-catalyzed azide-alkyne [3 + 2] Huisgen cycloaddition reaction (CuAAC reaction) which is the best ‘click’ reaction to date, due to its wide range of applications in chemistry, biochemistry and polymer chemistry.[12, 13] A major advance in improving of this reaction was accomplished through the use of copper compounds as catalysts. 1,4-disubstituted 1,2,3-triazoles were synthesized in the presence of copper (I) with high yields under very mild conditions. Various CuAAC reactions involving different sources of copper (I) and solvents have been developed, leading to 1,4-disubstituted 1,2,3-triazoles.[14-20] Copper (I) salts are less used because of their general thermodynamic instability. One possible choice to protect the copper (I) center from oxidation or dispropotionation and to enhance its catalytic activity in the CuAAC reactions is to use Cu (I) salts supported by nitrogen, sulfur and polydentate or auxiliary ligands.[21-23] However, the preparation of such supported copper (I) catalysts are tedious, expensive and not always easy. On the other hand, recycling and reusability of them because of their generally homogeneous nature are difficult.

It should be noted that copper (II) salts did not work well in CuAAC reactions. Sharpless and co-workers established a very robust catalytic system for the CuAAC reactions, which made use of a less expensive copper (II) precatalyst, along with substoichiometric amounts of sodium ascorbate for an *in situ* reduction.[14] Designing of new specific catalytic system for the CuAAC reactions has caused profound effects in optimizing the efficiency of a wide range of 1,4-disubstituted 1,2,3-triazoles. Development of such catalysts has resulted in more economical and environmentally friendly chemistry through replacing expensive, unstable, or toxic catalysts.

In the context of our general interest in the synthesis of heterocycles and following our research on thioamide chemistry,[24-29] herein, we propose a facile synthesis of 1,4-disubstituted 1,2,3-triazoles via the CuAAC reaction in the presence of a copper (II)-thioamide combination as an efficient and inexpensive catalytic system (Scheme 1). Thioamides are a class of organosulfur compounds which recently become a very important functional group in coordination chemistry.[30-32] The presence of nitrogen atom and the larger and less electronegative sulfur atom as soft donor enables the thioamides-NH to bind to a metal in different ways, giving a variety of complexes.[32] Moreover organosulfur compounds generally can reduce copper (II) species.[31] With these two promising properties of thioamides in hands, our attention were focused on using thiobenzanilide in the CuAAC reaction as an reduction agent and ligand.



Scheme 1. One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles **3** using copper (II)-thioamide combination.

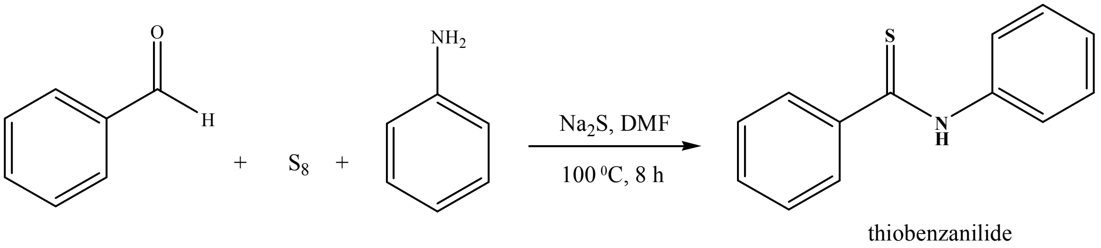
Experimental

General information

All the chemicals required for the synthesis of 1,4-disubstituted 1,2,3-triazoles **3** were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluka (Neu-Ulm, Germany) and Merck (Darmstadt, Germany) companies and were used as received. The all synthesized compounds **3** gave satisfactory spectroscopic data. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Gas chromatography-mass spectrometry (GC-MS) (Agilent HP 6890, electron ionization (EI), 70 eV, HP-5 column (30 m × 0.25 mm × 0.2 μm), HP 5793 mass selective detector) was used to record the mass spectra. IR spectra were taken films KBr pellets on a Nicolet spectrometer (Magna 550). Liquid chromatography-mass spectrometry (LC-MS) analysis was performed on an Agilent 1200 LC system (Agilent, Waldbronn, Germany) equipped with Agilent 6410 triple quadrupole tandem mass spectrometer and managed by a Mass Hunter workstation (Agilent Technologies, CA, USA). All the reactions are monitored by thin layer chromatography (TLC) carried out on silica gel with UV light and iodine, as detecting agents.

General procedure for the synthesis of thiobenzanilide

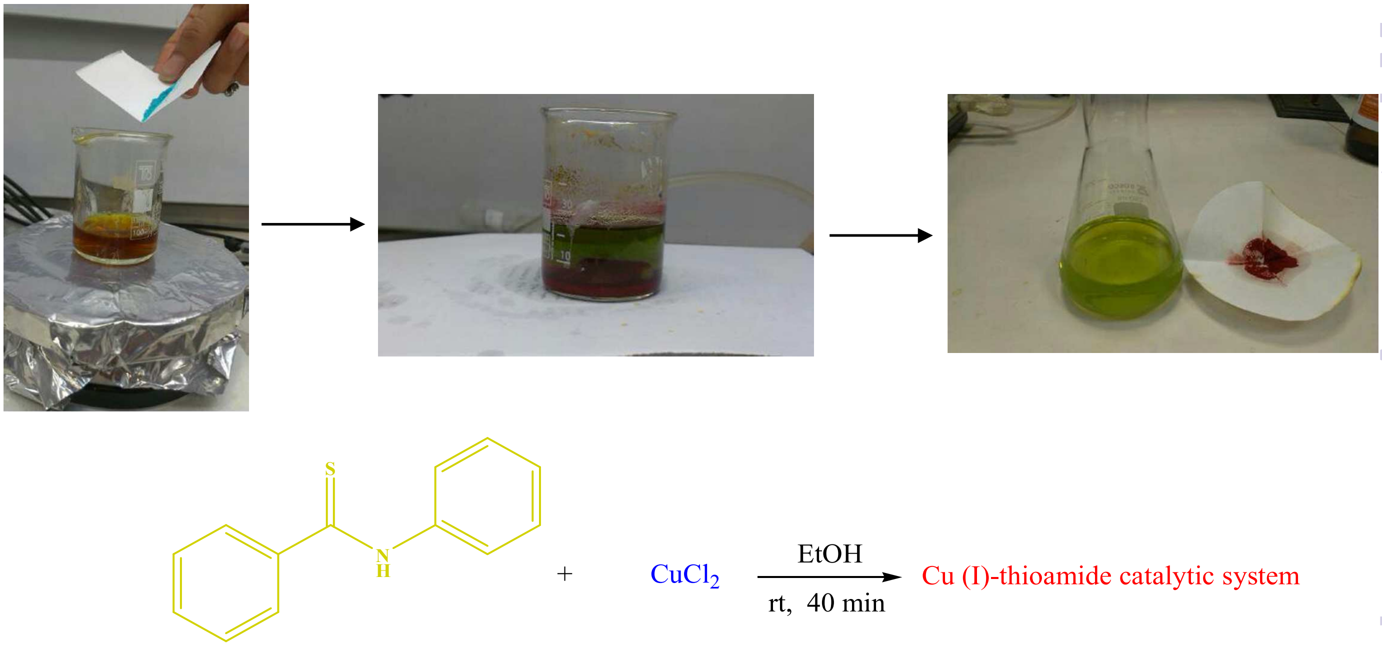
Thiobenzanilide was prepared according to previously reported procedure via Willgerodt–Kindler reaction (Scheme 2).[27] benzaldehyde (4 mmol) was added to a mixture of aniline (6 mmol), elemental sulfur (5 mmol) and Na_2S (10 mol%) in DMF (5 mL), then heated at 100°C for 8 h. After completion of the reaction, monitored by TLC (*n*-hexane/EtOAc: 5/2), the obtained solid was removed by filtration. The unreacted sulfur was removed by adding 5 mL EtOH, heating and then hot filtration. After cooling, thiobenzanilide was crystallized and separated by simple filtration.



Scheme 2. Preparation of thiobenzanilide via Willgerodt–Kindler reaction.

General procedure for the synthesis of copper (I)-thioamide catalytic system

$CuCl_2$ (2 mmol) was added into the solution of thiobenzanilide (2 mmol) in ethanol (1 mL) at room temperature. After 40 min a dark red precipitate was observed which was filtrated, washed with ethanol and dried at room temperature (Scheme 3). The obtained precipitate is stable in air and insoluble in organic solvents, except DMSO and DMF.



Scheme 3. General procedure for the synthesis of copper (I)-thioamide catalytic system.

General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles **3**

To a suspension of copper (I)-thioamide catalyst (10 mg) in H_2O/EtOH (5 mL, 1:1), was added sodium azide (0.6 mmol) and alkyl halide (0.5 mmol), and the resulting mixture was stirred at room temperature for 1 h. Phenylacetylene (0.5 mmol) was added to the reaction mixture and the mixture was stirred at an ambient temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was recovered by centrifugation and filtration. The catalyst was reused in subsequent reaction without losing any significant activity. Water (5 mL) was added to the reaction mixture and extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. The crude was concentrated under vacuum and was purified by preparative TLC (eluent: petroleum ether/ethyl acetate 4:1) to afford the desired products.

Results and discussion

In an initial attempt to synthesis of 1,4-disubstituted 1,2,3-triazoles **3** using a combination of $CuCl_2$ and thiobenzanilide as catalytic system, we focused on systematic evaluation of different conditions for the model reaction (Table 1). The reaction of phenylacetylene, benzyl bromide and sodium azide was checked without catalyst, and we get no desired product **3a** (Table 1, entry 1), while good results were obtained in the presence of copper (I)-thioamide catalytic system after 4 h. We then continued to optimize the model reaction by considering the efficiency of solvent. A mixture of H_2O/EtOH (1 : 1) was much better than H_2O and no reaction was performed in EtOH (Table 1, entry 7). The effect of temperature was also studied by carrying out the model reaction at room temperature, 50 °C, and 75 °C. It was observed that the yield was not increased as the reaction temperature was raised to 75 °C. On using the optimized amount of copper (I)-thioamide catalytic system, we found that 10 mg could effectively catalyze the reaction of phenylacetylene (0.5 mmol) and benzyl bromide (0.5 mmol) for the synthesis of the desired product **3a**. Using more than 10 mg of the catalyst had no significant effect on the yield. It is interesting to note that replacement of $CuCl_2$ with CuCl produced **3a** in moderate yield (Table 1, entry 4). Trace yield of **3a** was observed in the absence of thiobenzanilide (Table 1, entry 2).

Table 1. Optimization of the copper (I)-thioamide -catalyzed synthesis of **3a**.[a]

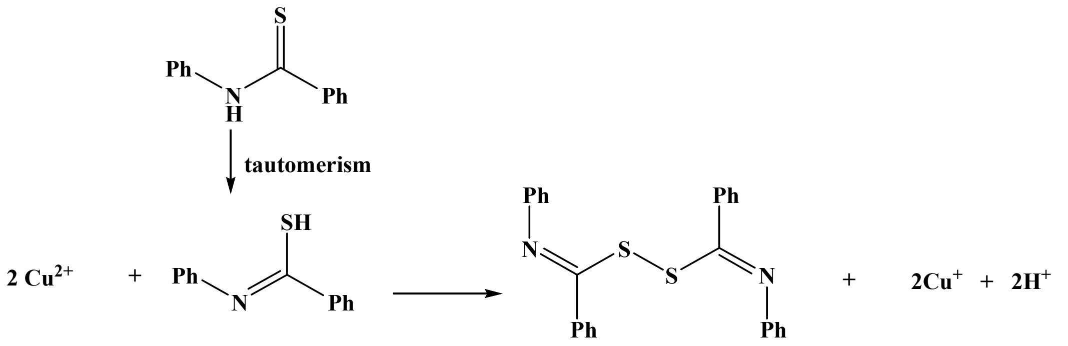
Entry	Catalyst	Solvent	T (°C)	Yield (%)
1	No catalyst	H_2O/EtOH	rt	0
2	$CuCl_2$	H_2O/EtOH	rt	trace
3	CuCl	H_2O/EtOH	rt	71
4	CuCl/PhCSNHPh	H_2O/EtOH	rt	86
5	**$CuCl_2$/PhCSNHPh**	**H_2O/EtOH**	**rt**	**95**
6	$CuCl_2$/PhCSNHPh	H_2O	rt	58
7	$CuCl_2$/PhCSNHPh	EtOH	rt	0
8	$CuCl_2$/PhCSNHPh	H_2O/EtOH	50	65
9	$CuCl_2$/PhCSNHPh	H_2O/EtOH	75	69
10	$CuCl_2$/PhCSNHPh	H_2O/EtOH	rt	70[b]
11	$CuCl_2$/PhCSNHPh	H_2O/EtOH	rt	91[c]

[a] Reaction conditions: Solvent (5 mL, 1 : 1), phenylacetylene (0.5 mmol) and benzyl bromide (0.5 mmol), catalyst (10 mg) and reaction time: 4 h; [b] catalyst (5 mg); [c] catalyst (20 mg)

As mentioned above, Organo-thiols and thiones generally can reduce copper(II) and disulfide compounds are formed according to equation (**1**):[31]

$$2RSH + 2\,Cu^{2+} \longrightarrow RSSR + 2Cu^{+} + 2H^{+} \quad (1)$$

It is conceivable that thiobenzanilide can exhibit thione-thiol tautomerism in the presence of Cu^{2+}, so formation of the corresponding disulfide is possible. Acceleration of the CuAAC reaction by using $CuCl_2$-thioamide combination supported that copper (II) is reduced to copper (I) (Table 1, entry 5 versus entry 2). During the redox reaction, thiobenzanilide acting as reduction agent is oxidized to the corresponding disulfide according to equation (**2**).



(2)

LC-Mass analysis of the alcoholic solution of catalyst system confirmed the formation of the corresponding disulfide of thiobenzanilide (Fig. 1). The disulfide formed relative low intensity $[M + H]^+$ at *m/z* 425 under positive ion electrospray ionization (ESI) conditions. The most abundant ion in its ESI-MS is observed at *m/z* 180 as iminium fragment.

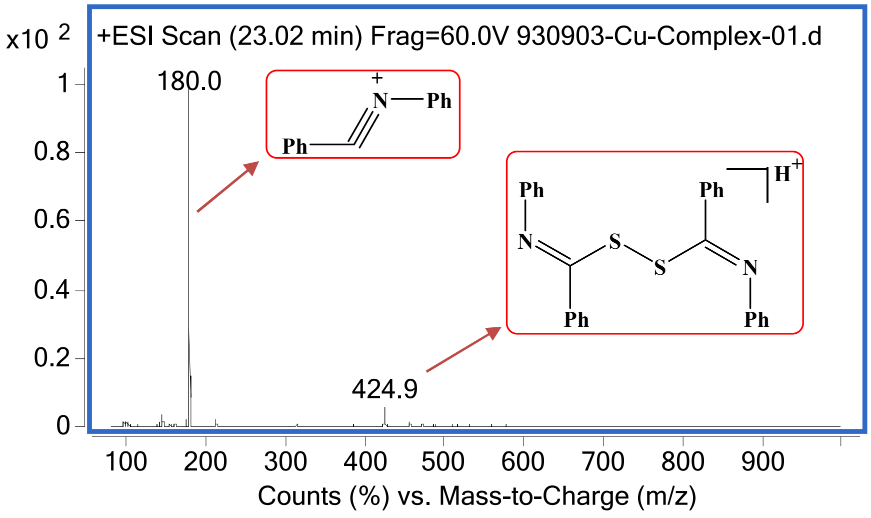
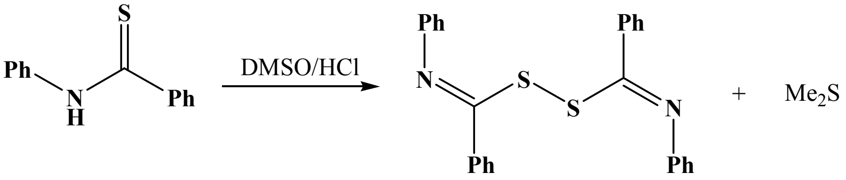


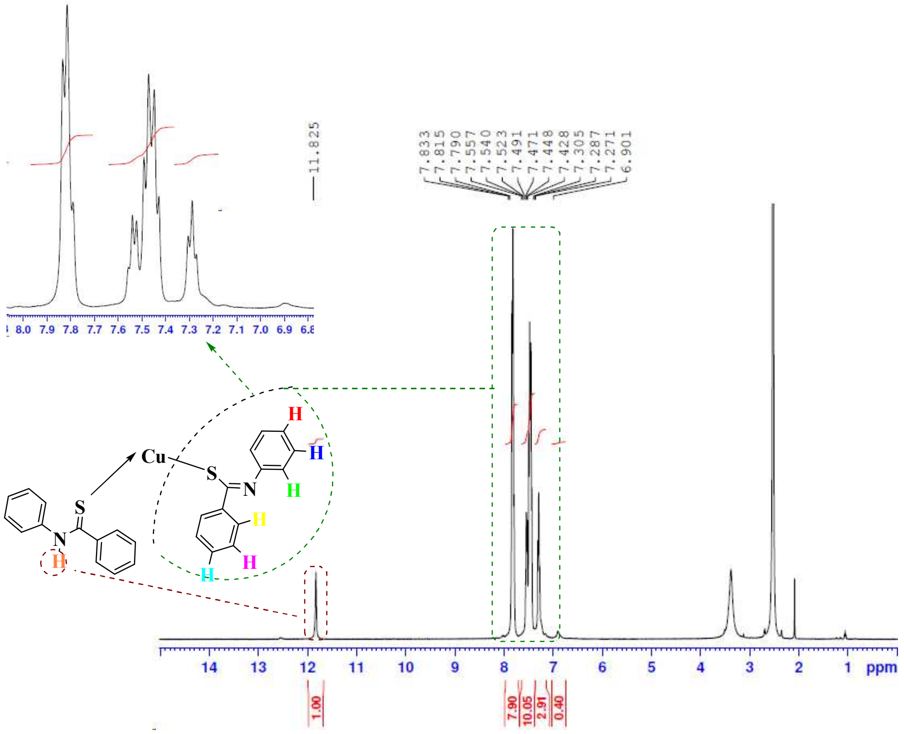
Fig. 1. LC-MS spectrum of the corresponding disulfide of thiobenzanilide.

Reduction of Cu^{2+} to Cu^{+} by thiobenzanilide is also consistent with the result obtained by ^{1}HNMR analysis of copper (I)-thioamide catalytic system in DMSO-d_6 (Fig. 2). NMR spectrum of complex bearing Cu^{2+} due to paramagnetism properties could not be obtained. The ^{1}HNMR appearance of copper-thioamide catalyst revealed that a redox reaction take place in the combination of $CuCl_2$ with thiobenzanilide in ethanol. The univalence of the copper ions in catalytic system was also confirmed by the measured diamagnetism. It can be considered that probably the generated disulfide from thiobenzanilide acts as a ligand. Therefore the disulfide was synthesized through oxidation of thiobenzanilide by using DMSO-HCl system according to Scheme 4.[33] The synthesized disulfide reacted with $CuCl_2$ and CuCl to give the corresponding complexes. The latter complex gave **3a** in moderate yield (76%), while the former afforded **3a** in very low yield.



Scheme 4. Synthesis of the corresponding disulfide of thiobenzanilide by using DMSO-HCl system.

Comparison the ^{1}HNMR spectrum of copper-thioamide catalyst with ^{1}HNMR spectrum of the disulfide (Fig. 2) shows that the thioamide acts as ligand not disulfide. The ^{1}H NMR spectrum of copper (I)-thioamide catalyst consisted of a broad line at δ = 11.82 ppm correlating with the NH and multiple lines for the aromatic protons at δ = 7.83-6.90 ppm.



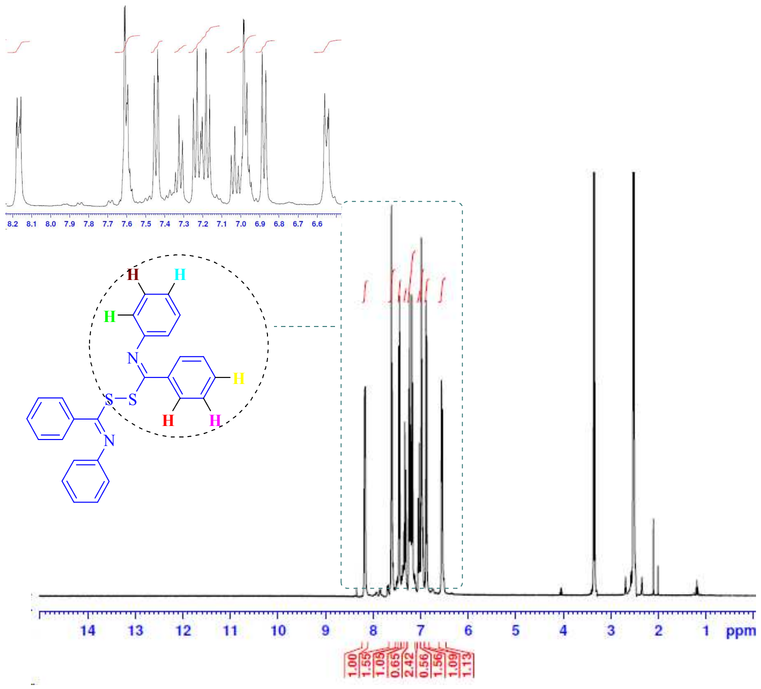


Fig. 2. ^{1}HNMR spectra of copper (I)-thioamide catalyst (**a**) and the corresponding disulfide of thiobenzanilide (**b**).

Unfortunately, all attempts to get single crystals of copper (I)-thioamide catalytic system for X-ray crystallography were failed due to its high insolubility. Assignments of selected characteristic IR bands (4000-500 cm^{-1}) for thiobenzanilide and copper (I)-thioamide catalyst are given in supporting information (Fig. 1S and 2S). The positions of bands provide significant hints regarding the bonding sites of the thiobenzanilide when complexed with copper (I). Thiobenzanilide can show thione-thiol tautomerism. The υ(S-H) band at 2550 cm^{-1} is absent in IR spectrum of thiobenzanilide but the υ(N-H) band is observed at 3418 cm^{-1}, indicating that thiobenzanilide exists in the thione rather than the thiol form in the solid state.[34] It shows that a adsorption band of the C=S bond is a region 1570-1395 cm^{-1} (1526 cm^{-1} for thiobenzanilide),[35] which is shifted to 1516 cm^{-1} after being reacted with copper (II), indicating that the sulfur of the C=S participates as a coordinating site. This coordination is confirmed by the absence of the strong band at 1361 cm^{-1} in IR spectrum of copper (I)-thioamide catalyst.[36]

Energy-dispersive X-ray spectroscopy (EDS) was used for the chemical characterization of copper (I)-thioamide catalyst. EDS analysis exhibited the existence of chlorine atoms in catalytic system (Fig. 3). CHN analysis exhibited 44.48 % C, 3.05 % H and 3.73 % N. These results indicate that copper (I)-thioamide system has a polymeric or cluster structure which explain its stability and high insolubility.[31] A possible structure of one unit in the polymeric complex of copper (I)-thioamide catalyst is shown in Fig. 4.

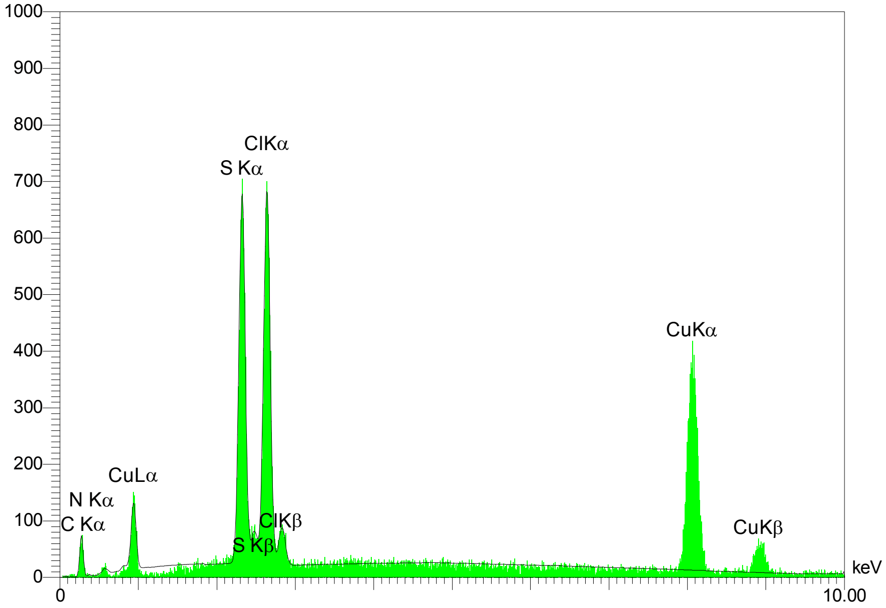


Fig. 3. EDS analysis of copper (I)-thioamide catalyst.

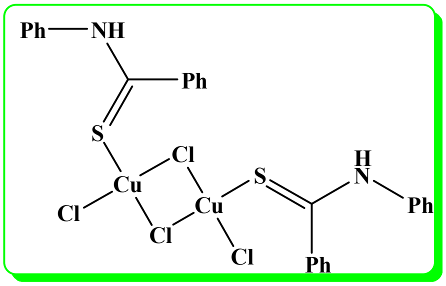
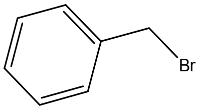
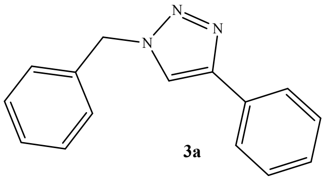
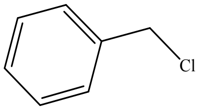
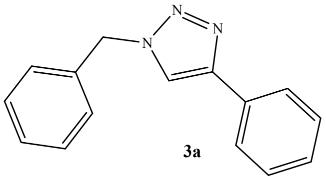
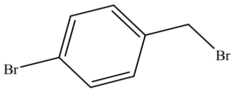
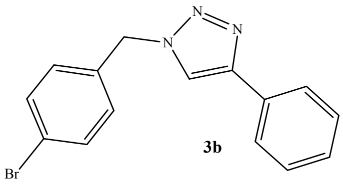
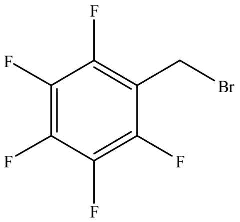
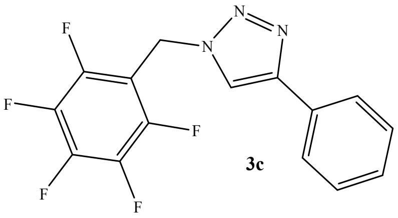
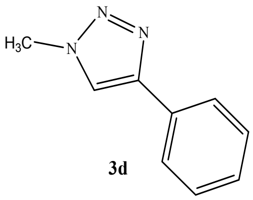
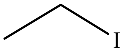
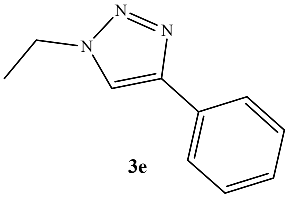
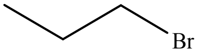
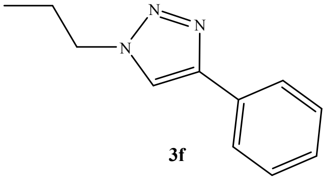
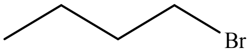
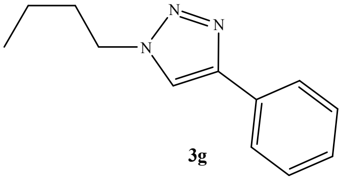
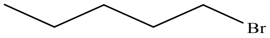
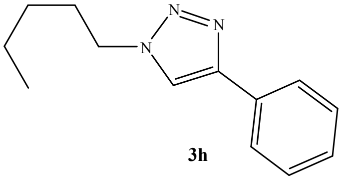


Fig. 4. A possible structure of one unit in the polymeric complex of copper (I)-thioamide catalyst.

Next we turned our attention to apply copper (I)-thioamide catalyst for the reaction of phenylacetylene with a series of alkyl/aryl halide to obtain the corresponding 1,4-disubstituted 1,2,3-triazoles **3**. All the substrates consistently furnished the desired triazoles in good to excellent yields (Table 2). Formation of azides proceeds via a S_N2 mechanism (Scheme 5). It is worth noting that direct displacement reactions take place rapidly in benzylic systems. The π systems of the benzylic group provide extended conjugation, which stabilizes the TS in the S_N2 mechanism, [37] so benzyl halides afforded the corresponding triazoles in excellent yield, as shown in Table 2. Various alkyl halides were subjected to the same reaction conditions to obtain the corresponding 1,2,3-triazoles. The yields were good in general. The structure of the products was confirmed by ^{1}H-NMR, ^{13}C-NMR, GC-MS and comparison with authentic samples prepared by reported methods (see supporting information).[20, 38]

Table 2. Copper (I)-thioamide-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazole derivatives **3**.

Entry	Halide	Product	Yield (%)
1		 **3a**	95
2		 **3a**	84
3		 **3b**	93
4		 **3c**	89
5	CH_3I	 **3d**	66

6		 3e	68
7		 3f	61
8		 3g	59
9		 3h	58

The reusability of the copper (I)-thioamide catalyst was also studied for the model reaction. The catalyst was recovered by simple filtration, washed with ethanol and reused with consistent activity even after eight catalytic cycles (Fig. 5).

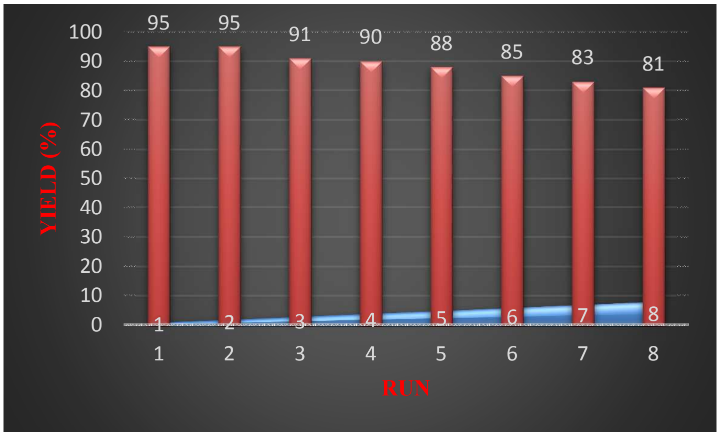
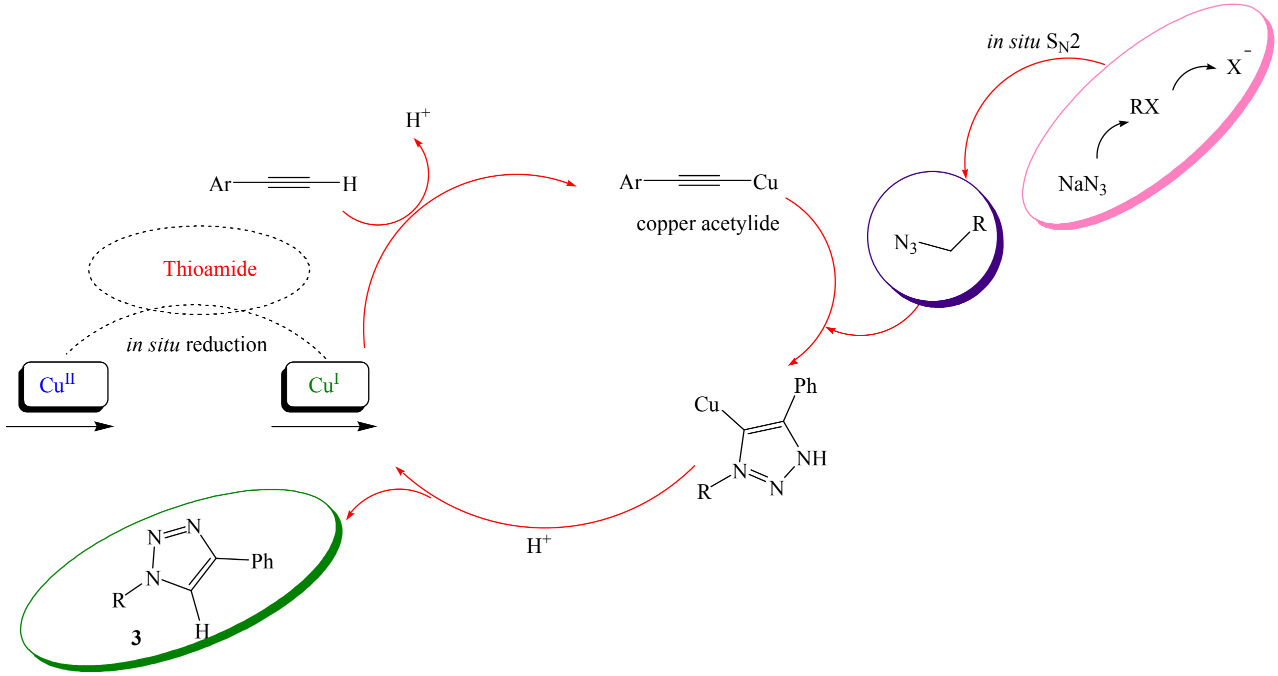


Fig. 5. Recyclability of copper (I)-thioamide catalyst in one-pot synthesis of 1,2,3-triazoles.

A possible mechanism for this copper (I)-thioamide catalyst multicomponent reaction was proposed in Scheme 5. The reaction was initiated by the metalation of phenylacetylene in the presence of Cu^+, resulting copper acetylide followed by coordination of alkyl/benzyl azides to the copper of the acetylide initiates an azide-alkyne 1,3-dipolar cycloaddition to form the desired products **3**.



Scheme 5. Proposed mechanism for copper (I)-thioamide-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazole derivatives **3**.

In summary, a very efficient protocol for the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives was reported via a multicomponent reaction in the presence of a cheap and easily recyclable heterogeneous copper (I)-thioamide catalyst. The catalyst was easily prepared with the reaction of $CuCl_2$ and thiobenzanilide. The catalyst was collected easily by filtration and the reusability of the catalyst was successfully tested for eight runs only a very slight loss of catalytic activity. Further studies of applicability of the heterogeneous copper (I)-thioamide catalyst for synthesis of useful organic compounds such as propargylamines are in progress.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at:

Acknowledgments

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A copper (II)-thioamide combination as a robust heterogeneous catalytic system for green synthesis of 1,4-disubstituted 1,2,3-triazoles under click conditions

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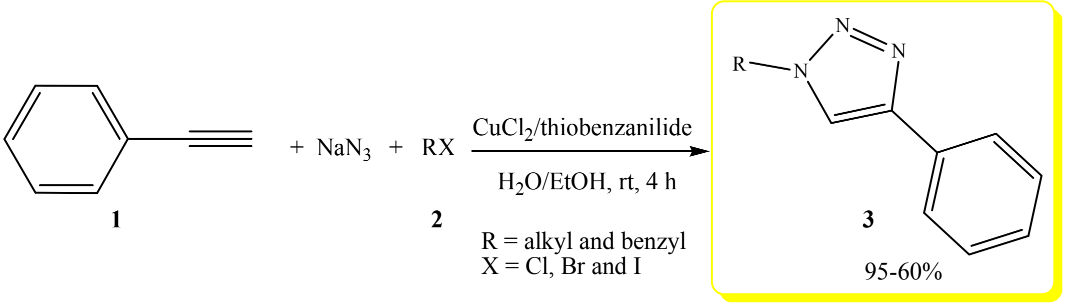

One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles **3** using copper (II)-thioamide combination was reported.