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Multicomponent Synthesis of 1,2,3-Triazoles in Water Catalyzed by Silica-Immobilized NHC–Cu(I)

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Abstract 1,2,3-Triazole derivatives were synthesized in one-pot procedure via three-component reaction between organic halides, aromatic alkynes and sodium azide in the presence of 0.5 mol% Silica-immobilized NHC–Cu(I) catalyst. The catalyst showed high catalytic activity and 1,4-regioselectivity for the [3 + 2] Huisgen cycloaddition in water as a green solvent. This procedure has advantages that without the need to handle organic azides because of they are generated in situ. The reaction has a broad scope and good to excellent yields were obtained. The catalyst was recycled six times without significant loss of activity.

Keywords 1,2,3-Triazole · Copper · Water · NHC ligand

1 Introduction

The application of *N*-heterocyclic carbene (NHC) ligands represents one of the most important developments in the field of metal-mediated catalysis over recent years and valuable contributions have been made to a diversity of reactions [1–3]. Due to metal–carbene complexes are often more stable than similar metal–phosphine complexes [4, 5], NHC ligands have been used as alternatives to phosphines as ligands in a broad range of transition metal catalysts owing to their special donor properties [6]. Additional advantages of NHC ligands over the classic phosphines include easy preparation, easy derivatization and low cost. As a result, a large variety of metal–NHC complexes are known, many of which have been successfully used in catalytic applications [7, 8]. In numerous instances simple substitution reaction routes involving replacement of phosphanes by NHC ligands leads to higher catalytic activity as well as improved thermal stability of the resulting organometallic complexes. The common knowledge that NHC ligands should be considered as simple σ donors is being replaced by the idea that NHC ligands are electronically much more flexible. Both filled and empty π, π^* orbitals on the NHC ring can be deeply involved in the bonding to the metal. They can contribute to stabilize electron-rich metals through a d → π^* back-donation scheme, but they are so flexible that they can also stabilize electron-deficient metals through a π → d donation scheme [9, 10].

Click chemistry is a chemical philosophy introduced by Sharpless in 2001, emphasizing reactions that generate substances quickly and reliably by joining small units together [11]. The copper(I) catalyzed Huisgen [3 + 2] dipolar cycloaddition (CuAAC) between alkynes and azides has arguably become the most popular ligation reaction that has found a wide application in polymer and drug discovery, biology and advanced material science [12–23]. Most of the reported copper(I) catalytic species were prepared in situ by reduction of Cu(II) salts [14], oxidation of Cu(0) metal [24], or Cu(II)/Cu(0) comproportionation [25]. Due to copper(I) salts are oxygen sensitive, they are less used or require the employment of amines as additives in the reaction [26]. In recent studies, the CuAAC has been proven to be accelerated by Cu(I) species supported by nitrogen [27], sulfur [28], and polydentate ligands [29], since those serve both to protect the copper(I) center from oxidation or disproportionation and to enhance its catalytic activity. However, such supported copper(I) catalysts are not always easily prepared.

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Moreover, reusability of copper catalysts for the CuAAC is scarcely studied because of the generally homogeneous nature of these catalysts, which make their recovery and recycling difficult. The catalysts only can be used for one time in the homogeneous reaction, which thus caused the waste of expensive transition metal complexes and the contamination problem in the product. Li et al. [30] reported a series of water soluble ammonium salt-tagged NHC–Cu catalysts. Although water soluble catalysts can be recycled from the reaction mixture by liquid–liquid separation, the aqueous phase was easily contaminated by organic compounds, which cause the loss of the catalysts' activity. And the products were obtained by extraction from the mixture and using a large amount of solvents, which will increase the economic expense. Furthermore, using water as reaction media is limited, because some water-sensitive substrates can not be used in this system. Moreover, high catalyst loading (5.0 mol%) was needed in the system and the catalyst was prepared through multiple steps from 2,6-diisopropylaniline. To avoid catalyst leaching and reduce the contamination of the product, activated carbon, silica-supported and other heterogeneous copper catalyst were synthesized and applied successfully to click reactions [31–35]. Recently, Wang et al. [36] reported an efficient NHC–Cu(I) heterogeneous catalyst for [3 + 2] cycloaddition of organic azides and terminal alkynes in the presence of 1 mol% Cu catalyst. Although organic azides are generally stable against most reaction conditions such as water and oxygen, isolation or purification of organic azides or polyazides can be problematic [32, 37–39]. Therefore, a procedure that avoids the isolation of organic azides is desirable.

Herein, we report an efficient silica-immobilized NHC–Cu(I) heterogeneous catalyst for the regioselective generation of 1,4-disubstituted 1,2,3-triazoles in a three-component reaction. Furthermore, the catalyst can be recovered and recycled by simple filtration from the reaction solution and reused several times without significant loss of activity.

2 Experiment

2.1 General

All reagents were commercially available and used without any further purification. The solvents were dried before use. IR spectra were recorded in KBr disks with a Bomem MB154S FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as an internal reference. Elemental analyses were performed on a Vario ELIII recorder. The ICP analysis data were obtained using a PE5300DV analyzer. Specific surface areas and pore volumes of the samples were determined in a Micromeritics ASAP-2000 automated nitrogen physisorption apparatus and calculated according to the BET method.

2.2 Preparation of 1-(2,4,6-Trimethylphenyl)-1*H*-Imidazole [40]

2,4,6-trimethylaniline (6.8 g, 0.05 mol) in MeOH (25 mL) was stirred with 30 % aqueous glyoxal (8.1 mL, 0.05 mol) for 16 h at room temperature. A yellowish mixture was formed. Then, NH_4Cl (5.4 g, 0.1 mol) was added followed by 37 % aqueous formaldehyde (8 mL, 0.1 mol). The mixture was diluted with MeOH (200 mL) and the resulting mixture was refluxed for 1 h. H_3PO_4 (7 mL, 85 %) was added over a period of 10 min. The resulting mixture was then stirred at reflux for a further 6 h. After removal of the solvent, the dark residue was poured onto ice (100 g) and neutralized with aqueous 40 % KOH solution until pH 9. The resulting mixture was extracted with EtOAc (3 × 100 mL). The organic phases were combined and washed with H_2O, brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographied on silica gel (petroleum ether/EtOAc) to afford the pure solid product (3.8 g, 41 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.91 (s, 2H), 2.36 (s, 3H), 2.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.8, 136.5, 134.4, 132.4, 128.5, 128.0, 119.1, 20.0, 16.3; Anal. (%) found (calcd): C 77.19 (77.38), H 7.56 (7.58), N 15.13 (15.04).

2.3 Preparation of 1-Mesityl-3-(3-Trimethoxysilypropyl)imidazolium Iodide [41]

3-Iodopropyltrimethoxysilane (6.4 g, 22 mmol) and dioxane (15 mL) were added under nitrogen to a Schlenk vessel containing 1-(2,4,6-trimethylphenyl)-1H-imidazole (3.7 g, 20 mmol). The mixture was refluxed for 12 h, followed by removal of the solvent under vacuum. Addition of pentane (15 mL) gave the product as an oily brown solid. Solvent was decanted and the product was dried in vacuum at 60 °C for 2 h (8.3 g, 90 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.92 (s, 1H), 7.82 (s, 1H), 7.25 (s, 1H), 7.01 (s, 2H), 4.71 (t, 2H, $J = 2.0$ Hz), 3.57 (s, 9H), 2.34 (s, 3H), 2.09–2.08 (m, 8H), 0.70 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.0, 135.6, 133.3, 129.7, 128.8, 123.7, 122.1, 66.0, 50.9, 23.8, 20.0, 17.0, 8.6.

Anal. (%) found (calcd): C 45.11 (45.28), H 6.29 (6.33), N 5.90 (5.87).

IR (KBr) ν 780, 1090, 1458, 1532, 1660, 1976, 2930, 3210.

2.4 Preparation of Iodo-1-Mesityl-3-(3-Trimethoxysilypropyl)imidazole-2-Ylidenecopper(I)

In an oven-dried Schlenk flask, CuI (0.95 g, 5 mmol), NaO-*t*-Bu (0.48 g, 5 mmol), 1-mesityl-3-(3-trimethoxysilypropyl)imidazolium iodide (2.4 g, 5 mmol) and THF (25 mL) were added. The resulting suspension was stirred at room temperature for 20 h under nitrogen atmosphere. The solvent was reduced to 5 mL and the addition of pentane (15 mL) gave the copper complex as a grey-green powder (2.5 g, 93 %), m. p. 148 °C (decomposed).

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.63 (s, 1H), 7.37 (s, 1H), 6.99 (s, 2H), 4.12 (t, 2H, J = 5.0 Hz), 3.60 (s, 9H), 2.36 (s, 3H), 1.89 (s, 6H), 1.76 (s br, 2H), 0.59 (s br, 2H).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 181.6, 138.9, 134.2, 134.1, 128.2, 120.7, 119.9, 51.9, 50.2, 25.9, 21.5, 17.6, 7.5.

Anal. (%) found (calcd): C 39.99 (40.04), H 5.37 (5.41), N 5.23 (5.19).

IR (KBr) ν 760, 1100, 1430, 1554, 1660, 1710, 1976, 3100.

2.5 Preparation of Silica-Immobilized NHC–Cu(I) Catalyst

The solution of NHC–Cu(I) complex (108 mg, 0.2 mmol) in dimethylformamide (DMF) (2 mL) was added to a well-stirred DMF suspension (40 mL) of mesoporous silica gel (2 g, average pore diameter 60 Å, 70–230 mesh, dried at 500 °C for 12 h before use). The mixture was stirred at 120 °C for 12 h. The solid was filtered off and washed with hot DMF to remove the remaining non-supported complex from the heterogenized catalyst, and then washed subsequently with water, ethanol and dried under reduced pressure at 80 °C for 6 h. The copper metal amount of the catalyst was found to be 0.096 mmol g^{-1} based on ICP analysis. The surface area and pore volume of the catalyst were found to be 419 m^2 g^{-1} and 0.65 cm^3 g^{-1} respectively.

2.6 General Procedure for Three-Component 1,3-Dipolar Cycloaddition Catalyzed by Silica-Immobilized NHC–Cu(I) Catalyst in Water

A seal tube was charged with halide (1.0 mmol), NaN_3 (1.2 mmol), substituted phenylacetylene (1.0 mmol), H_2O (2 mL) and the catalyst (0.5 mol% Cu). The mixture was stirred at 80 °C for a certain time. After the reaction was completed, the resulting mixture was extracted with EtOAc (3 × 3 mL). The collected organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum to give the corresponding triazole, the product was further purified by flash chromatography with petroleum ether/EtOAc as eluent. All the products were known compounds and were characterized by comparison of their physical and spectroscopic data with those described in the literature.

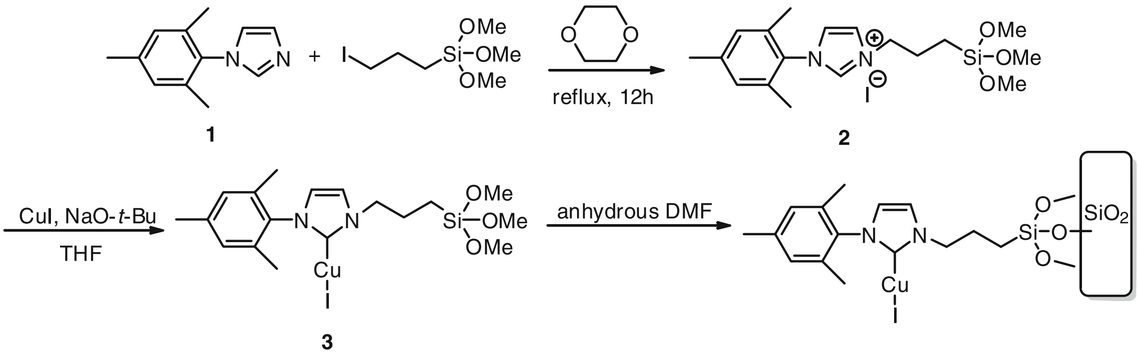
2.7 Recycling of the Silica-Immobilized Catalyst

A seal tube was charged with benzyl chloride (1.0 mmol), NaN_3 (1.2 mmol), phenylacetylene (1.0 mmol), H_2O (2 mL) and the catalyst (0.5 mol% Cu). The mixture was stirred at 80 °C for 6 h. After the reaction was completed, the catalyst was filtrated and the residue was washed with EtOAc (3 × 3 mL), water (3 × 3 mL) respectively. Then the catalyst was dried at 60 °C for 2 h for next cycle.

3 Results and Discussion

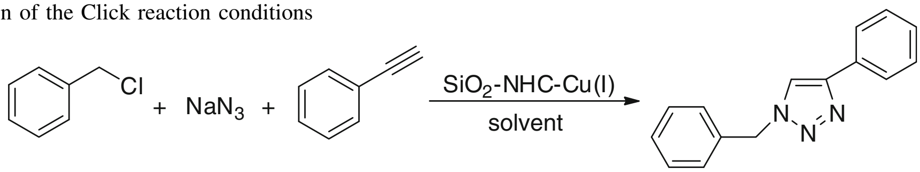
The copper catalyst immobilized on silica gel was readily prepared in a three-step procedure as shown in Scheme 1. 1-(2,4,6-trimethylphenyl)-1*H*-imidazole was synthesized according to the previous literature. In a general procedure, compound 1 was refluxed with 3-iodopropyltrimethoxysilane in 1,4-dioxane under nitrogen atmosphere for 12 h, then separated the product from the reaction mixture and washed with pentane to obtain compound 2. The ionic liquid 2 reacted with CuI in the presence of NaO-*t*-Bu in dry THF at room temperature under nitrogen atmosphere. Immobilization of complex 3 in the silica gel was carried out in DMF at 120 °C for 12 h. The copper metal amount of the immobilized catalyst was found to be 0.096 mmol g^{-1} based on ICP analysis. After immobilization of NHC–Cu(I), the surface area of silica gel decreased from 546 to 419 m^2 g^{-1} and the average pore volume decreased from 0.76 to 0.65 cm^3 g^{-1} due to the loading of the NHC–Cu(I) complex.

To investigate the catalytic activity of the silica-immobilized NHC–Cu(I), the 1,3-dipolar cycloaddition reaction between benzyl chloride, NaN_3 and phenylacetylene was chosen as the model reaction (Table 1). During our optimization studies, various solvents were examined and it was found that the solvent plays a significant role in terms of reaction rate, isolated yield, and selectivity. Among the solvents tested in Table 1, DMF, DMSO, toluene, CH_2Cl_2, CH_3CN were gave very low product yield (Table 1, entries 1–5), because of their poor solubility of NaN_3. Although the reaction in methanol gave the highest yield, water clearly stands out as the solvent of choice with its fast reaction rate, high yield, selectivity, cheapness, green solvent nature and environmental acceptability (Table 1, entries 6 and 8). However, only trace amount of the product was detected by GC–MS when the reaction was carried out under neat reaction conditions (Table 1, entry 13). Catalyst loading and reaction temperature also affected the reaction, and in our work, 0.5 mol% of the catalyst is sufficient to catalyze the



Scheme 1 Synthesis and immobilization of the copper carbene catalyst

Table 1 Optimization of the Click reaction conditions



Entry	Solvent	Temperature (°C)	Catalyst Loading (mol%)	Time (h)	Yield[a] (%)
1	DMF	70	0.5	6	21
2	DMSO	70	0.5	6	19
3	Toluene	70	0.5	6	0
4	CH_2Cl_2	70	0.5	6	0
5	CH_3CN	70	0.5	6	13
6	MeOH	70	0.5	6	94
7	EtOH	70	0.5	6	89
8	H_2O	70	0.5	6	92
9	H_2O	50	0.5	6	58
10	H_2O	80	0.5	6	96
11	H_2O	80	1.0	6	98
12	H_2O	80	0.1	6	39
13	Neat	80	0.5	6	Trace

Reaction conditions: benzyl chloride (1.0 mmol), NaN_3 (1.2 mmol), phenylacetylene (1.0 mmol), catalyst (0.5 mol% Cu) in 2 mL solvent

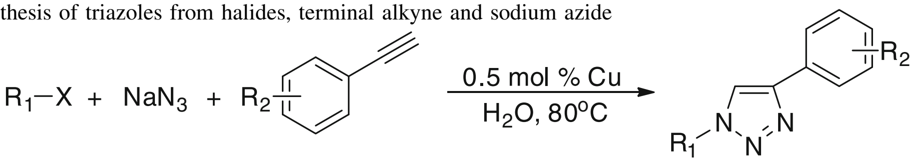
[a] Isolated yield

reaction successfully (Table 1, entries 10–12). Lowering the temperature to 50 °C caused drastic decrease of the yield (Table 1, entry 9).

To examine the generality of the reaction, we extended our studies to a variety of organic halides and aromatic alkynes to generate the corresponding 1,4-disubstituted 1,2,3-triazoles. Firstly, we screened the reactivity of benzyl chloride and its derivatives under the optimized conditions. As shown in Table 2, substituted benzyl chlorides containing both electron-donating and electron-withdrawing groups in the para position afforded the products in excellent yields. And benzyl chlorides bearing electron-donating group gave the 1,2,3-triazoles in slightly lower yield (Table 2, entries 2–6). It is noteworthy that the position of the substituted groups affects the reaction dramatically and only moderate yields were obtained (Table 2, entries 7–8). Next, we used various substituted benzyl chlorides to screen aromatic alkynes (Table 2, entries 9–14). It was found that the starting materials containing electron-donating groups gave the products in lower yield. Moreover, reaction time was prolonged to 9 h when using *p*-methoxybenzyl chloride in the Huisgen [3 + 2] cycloaddition, because of its low reactivity. As can be seen from Table 2, the reactions involving organic bromo compounds lead to the corresponding 1,4-disubstituted 1,2,3-triazoles in higher yields (Table 2, entries 15–18) and bromocyclohexane gave the product in 82 % yield (Table 2, entry 19). 3-bromo-1-propyne was investigated in this system, however, only trace of the product was obtained.

The recyclability of silica-immobilized NHC–Cu(I) catalyst was tested in the cycloaddition of benzyl chloride, NaN_3 and phenylacetylene under the optimized reaction

Table 2 One pot synthesis of triazoles from halides, terminal alkyne and sodium azide



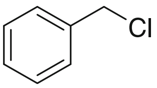
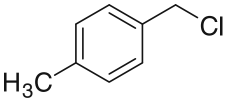
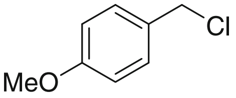
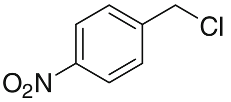
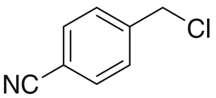
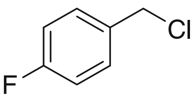
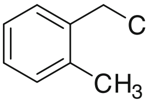
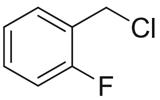
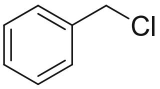
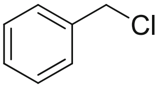
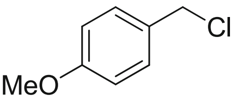
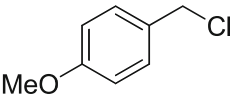
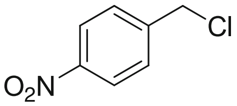
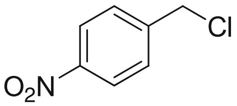
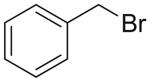
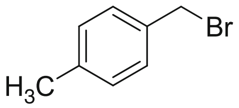
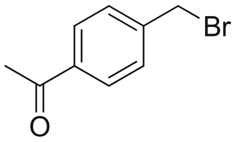
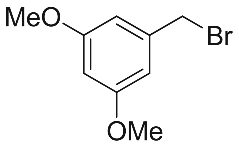
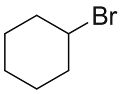
Entry	Organic Halide	R_2	Time (h)	Yield[a] (%)
1		H	6	96
2		H	6	90
3		H	6	87
4		H	6	93
5		H	6	98
6		H	6	95
7		H	6	53
8		H	6	76
9		4-CH_3	6	83
10		4-F	6	89
11		4-CH_3	9	76
12		4-F	9	85

Table 2 continued

Entry	Organic Halide	R_2	Time (h)	Yield[a] (%)
13		4-CH_3	6	88
14		4-F	6	95
15		H	6	98
16		H	6	93
17		H	6	90
18		H	6	86
19		H	6	82

Reaction conditions: halide (1.0 mmol), NaN_3 (1.2 mmol), substituted phenylacetylene (1.0 mmol), catalyst (0.5 mol% Cu) in 2 mL H_2O at 80 °C

[a] Isolated yield

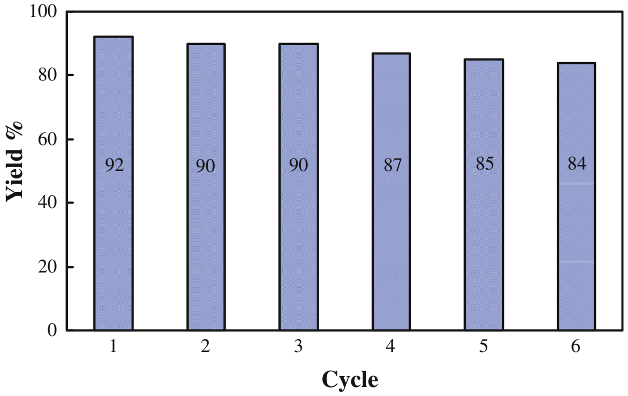


Fig. 1 Recyclability of the catalytic system

conditions. After the reaction, the catalyst was separated by simple filtration and washed with EtOAc and water. After being dried, it could be reused directly without further purification. The catalyst could be recycled in six repetitive cycles without significant loss of activity (Fig. 1). Meanwhile, copper leaching in the reaction was detected by ICP analysis. The filtrates obtained by filtration after the reaction indicated that Cu content was <0.6 ppm. However, only trace amount of the desired product was detected by GC–MS for the model reaction by adding substrates to a filtrate obtained from the filtration of the immobilized catalyst after the reaction.

4 Conclusions

In summary, an efficient and green one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from organic halides, NaN_3 and aromatic alkynes catalyzed by silica-immobilized NHC–Cu(I) has been developed. The reactions proceeded smoothly to generate the corresponding products in high yields. In addition, the catalyst could be readily recovered and reused for 6 cycles without significant loss of its activity, thus making this procedure more environmentally acceptable.

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