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ORIGINAL PAPER

Catalytic activity and antibacterial properties of nanopolymer-supported copper complex for C–N coupling reactions of amines and nitrogen-containing heterocycles with aryl halides

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Abstract This paper reports on the antibacterial properties and application of nanopolymer-supported copper complex for the ligand-free C–N coupling reactions of amines and nitrogen-containing heterocycles with aryl halides. This method has the advantages of high yields, simple methodology, and easy workup. The catalyst can be recovered by simple filtration from the reaction mixture and reused several times without significant loss of catalytic activity.

Keywords Nanopolymer · Copper · Complex · Amine · Nitrogen-containing heterocycles

Introduction

The synthesis of compounds bearing an arylated nitrogen moiety is an active area in organic synthesis due to their key role in medically important species, natural products, and in materials with useful interesting electronic and mechanical properties [1–4].

The convenient synthetic routes for installing the *N*-aryl functionality are based on the aromatic nucleophilic substitution reaction (S_NAr) of nitrogen nucleophiles by activating aryl halides or metal-catalyzed Ullmann-type C–N coupling reaction at higher temperature [5–8]. The classical Cu-catalyzed Ullmann coupling reaction suffers from high reaction temperatures (often 150 °C or as high as 200 °C), tedious workups, low to moderate yields, poor substrate generality, the requirement of stoichiometric amounts of homogeneous copper catalysts that make scale-up unfeasible and ecologically unfriendly, and the use of strong bases, toxic and expensive ligands, and thus limited their large scale applications in industry, the use of toxic and air-sensitive aryl coupling reagents that can be difficult to access, and excess aryl halide starting materials to achieve reasonable product yields [5–12]. Although the C–N coupling reactions catalyzed by the palladium catalysts with bulky phosphine ligands can be performed at mild conditions, the phosphine ligands are normally not easily available, air sensitive, and expensive [13–15]. The toxicity and high cost of palladium catalysts restrict their use on the industrial applications. Thus, researchers have turned their attention toward the use of less expensive, less toxic, and more efficient metals to replace Pd. Due to safety considerations, it is desirable to develop a more efficient and convenient method for the copper-catalyzed synthesis of compounds bearing an arylated nitrogen moiety under heterogeneous conditions that reduce or eliminate the use and generation of hazardous compounds is essential.

Among various catalysts for the carbon–heteroatom coupling reactions, homogeneous copper catalysts have been widely investigated [16–22], while less expensive heterogeneous copper catalysts received scanter attention. Thus, the use of ligand-free heterogeneous Cu catalysts is often desirable from the perspective of process development due to their easy handling, simple recovery, and recycling.

According to the literature, tetrazoles can play an important role in coordination chemistry for the synthesis of metal complexes. We recently published synthesis of various tetrazoles in high yields and their application in coordination chemistry [23–25].

As part of our ongoing interest in heterocyclic chemistry and application of heterogeneous catalysts [26–33], we

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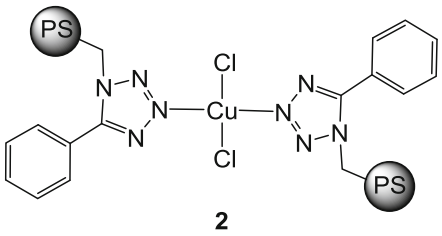
Scheme 1



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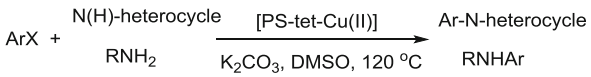
Scheme 2



now wish to report the copper-catalyzed N-arylation of amines and nitrogen-containing heterocycles with aryl halides using nanopolystyrene-anchored Cu(II) tetrazole complex (PS-tet-Cu(II), Scheme 1) as a novel and stable heterogeneous catalyst (Scheme 2).

Results and discussion

The catalyst was characterized using the SEM, TGA-DTG, and EDS spectroscopy. Scanning electron micrograph (SEM) image of PS-tet-Cu(II) is shown in Fig. 1. As expected, the pure polystyrene bead had a smooth and flat surface [34, 35], while the anchored complex showed roughening of the top layer. The presence of Cu has caused changes, demonstrated by change in the polymer particle size and roughness of the surface. Thermal stability of polymer-bound complex was investigated using TGA-DTG at a heating rate of 10 °C/min in air over a temperature range of 30–800 °C. The TGA curve of the nanopolystyrene-anchored Cu(II) tetrazole complex (PS-tet-Cu(II)) is shown in Fig. 2. The complex is stable up to 200 °C, and above this temperature it decomposes. The polymer-supported Cu(II) complex decomposed at 300 °C. We used Energy Dispersive X-ray Spectroscopy (EDS) to determine chemical composition of catalyst. The presence of the metals is confirmed by EDS. EDS results show that Cu concentration is about 3.07 wt%.

The catalytic behavior of the PS-tet-Cu(II) was studied for the N-arylation of aryl amines and nitrogen-containing heterocycles with aryl halides. Reaction conditions were optimized for the arylation of imidazole using phenyl iodide as a substrate and PS-tet-Cu(II) as catalyst in the presence of various solvents and bases (Table 1). In the

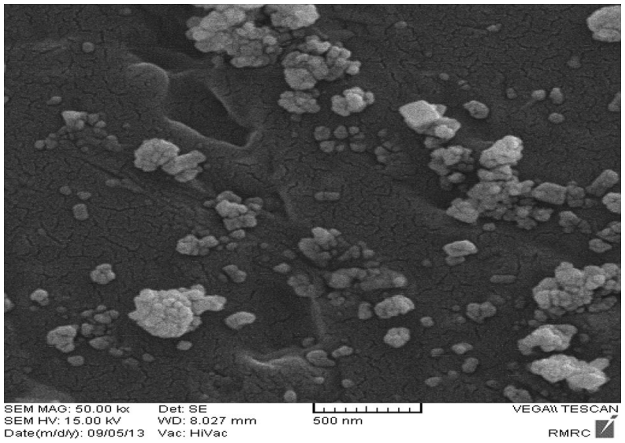


Fig. 1 SEM image of PS-tet-Cu(II)

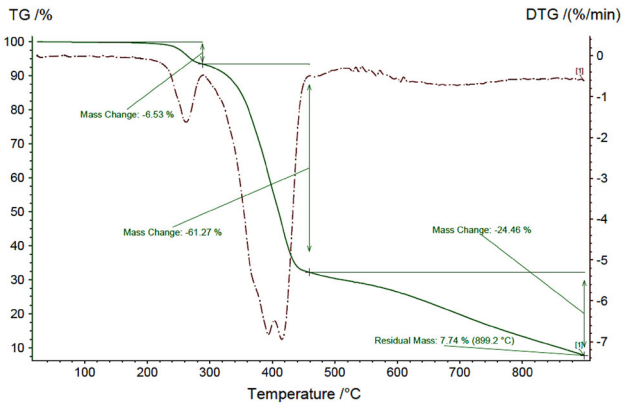


Fig. 2 Thermal studies of PS-tet-Cu(II)

absence of catalyst, the reactions did not proceed after a long reaction time (Table 1, entry 7). We believe that nanopolystyrene-anchored Cu(II) tetrazole complex (PS-tet-Cu(II)) can play an important role in the N-arylation of nitrogen-containing heterocycles. First, several solvents were screened for the reaction. According to data given in Table 1, DMSO was the most efficient solvent for this reaction (Table 1, entry 6). After choosing DMSO as the solvent, we examined several different bases. The results indicated that base had a demonstrative effect on the yield of product. Among the various bases tested, K_2CO_3 is an effective base (Table 1, entry 6). Increasing the amount of catalyst showed no substantial improvement in the yield. The best result was obtained with 1.0 mmol phenyl iodide, 1.2 mmol imidazole, 0.05 g PS-tet-Cu(II), 2.0 mmol K_2CO_3, and 9.0 cm^3 DMF at 120 °C, which resulted the product in an excellent yield (94 %).

Next, using the optimized procedure, a variety of aryl halides possessing both electron-releasing and electron-withdrawing groups were employed (Table 2). According to Table 2, the nature of the substituent on the benzene ring did affect the reaction. As shown in Table 2, aryl halides

Table 1 The model reaction in N-arylation of imidazole with iodobenzene under various reaction conditions

Entry	Base	Catalyst/g	Solvent	Temp./°C	Time/h	Yield[b]/%
1	K_2CO_3	0.05	THF	80	15	68
2	K_2CO_3	0.05	CH_3CN	80	15	75
3	K_2CO_3	0.05	DME	80	17	62
4	K_2CO_3	0.05	NMP	130	15	83
5	K_2CO_3	0.05	DMF	120	12	87
6	K_2CO_3	0.05	DMSO	120	12	94
7	K_2CO_3	0	DMSO	120	15	0
8	Et_3N	0.05	DMSO	120	12	37
9	K_3PO_4	0.05	DMSO	120	12	70
10	Cs_2CO_3	0.05	DMSO	120	12	51
11	K_2CO_3	0.08	DMSO	120	12	93

Reaction conditions: iodobenzene (1 mmol), imidazole (1.2 mmol), base (2.0 mmol), 9.0 cm^3 DMF, pressure tube, N_2 atm

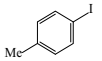
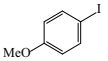
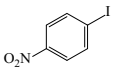
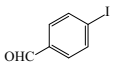
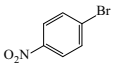
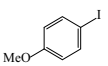
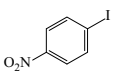
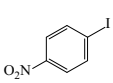
[b] Yields are after workup

having the electron-withdrawing groups (entries 4 and 5) were completed at 120 °C after 12 h, while the species bearing the electron-releasing groups (entries 2 and 3) require higher reaction times. The results are shown in Table 2 and 2-iodotoluene with a bigger steric hindrance around the reaction site gave a good yield. Thus, the reactions appeared to be insensitive to the steric hindrance around the reaction site (Table 2, entry 6).

Due to the importance of aryl amines in industry for the manufacture of pharmaceuticals, polymers, medicinal compounds and their applications in materials research, we next turned our attention to applying PS-tet-Cu(II) for the N-arylation of aryl amines with aryl halides.

For optimization of the reaction conditions, we chose the reaction of aniline with iodobenzene in DMSO in the presence of 0.05 g of PS-tet-Cu(II) as the model reaction, and the effects of the base were examined. As shown in Table 3, the reaction was influenced significantly by the base employed and the best result obtained in the case of KOH (Table 3, entry 7). The optimum conditions were found to be 1.0 mmol of aryl halide, 1.2 mmol of aromatic amine, 0.05 g of PS-tet-Cu(II), and 1.5 mmol of KOH in 9.0 cm^3 DMSO at 120 °C. Increasing the amount of catalyst showed no substantial improvement in the yield. Upon optimization of reaction conditions, the scope of the pro-

Table 2 Copper-catalyzed N-arylation of various nitrogen-containing heterocycles with aryl halides at 120°C

Entry	Substrate	Aryl halide	Time/h	Yield [b]/%
1			12	94
2			15	83
3			15	81
4			12	95
5			12	94
6			15	67
7			12	73
8			12	81
9			12	77
10			12	80
11			12	81

General reaction conditions: Het-NH (1.2 mmol), aryl halide (1.0 mmol), 0.05 g Cu source, K_2CO_3 (2.0 mmol), 9.0 cm^3 DMSO, 120 °C, pressure tube, N_2 atm

[b] Yields are after workup

Table 3 Optimization of reaction conditions in reaction of aniline with iodobenzene

Entry	Catalyst/g	Base	Yield[b]/%
1	0.05	K_3PO_4	61
2	0.05	Cs_2CO_3	58
3	0.05	K_2CO_3	65
4	0.05	KOH	85
5	0.08	KOH	85

Reaction condition: 1.0 equiv of iodobenzene, 1.2 equiv of aniline, and 1.5 equiv of base, 120 °C, 9.0 cm^3 DMSO, 12 h, pressure tube, N_2 atm

[b] Isolated yield

tocol was subsequently extended to a range of substituted aryl iodides and amines as substrates (Table 4).

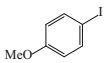
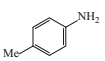
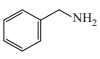
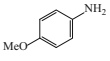
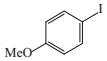
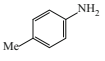
From an economic point of view, the stability and sustained activity of the catalysts is of great importance. Thus, the recovery and reusability of the PS-tet-Cu(II) was examined by applying it to the C–N coupling of imidazole with iodobenzene under the present reaction conditions. After the first run completed, the catalyst was separated by filtration, washed with ethyl acetate and dried in a hot air oven at 100 °C for 2 h and employed for the next run of the reaction. The catalytic activity did not decrease considerably after five catalytic cycles (Fig. 3). This reusability demonstrates the high stability and turnover of catalyst under operating condition.

The synthesized catalyst is found to be highly toxic against Gram-positive bacteria than Gram-negative bacteria. In vitro antibacterial activity of the PS-tet-Cu(II) was evaluated using the standard well diffusion method. One species each of a Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) were used for the antibacterial assay. The results presented in Table 5 showed the antibacterial effects of PS-tet-Cu(II) against *E. coli* (*Escherichia coli*) and *S. aureus* (*Staphylococcus aureus*). The antibacterial activity is estimated by the zone of inhibition. The diameter of the zone is measured to the nearest millimeter (mm). The standard error for each assay is presented in the parenthesis (Table 5). As shown in Table 5, PS-tet-Cu(II) has shown high antibacterial effect. The present study clearly indicates that the PS-tet-Cu(II) has good antibacterial action against Gram-positive organism than Gram-negative organisms (Table 5). It is possible that PS-tet-Cu(II) not only interact with the surface of membrane, but can also penetrate inside the bacteria.

Experimental

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification.

Table 4 Copper-catalyzed N-arylation of various amines with aryl iodides at 120 °C

Entry	Substrate	Aryl halide	Time/h	Yield [b]/%
1			12	85
2			14	77
3			14	73
4			16	70
5			14	71
6			14	72
7			16	67
8			12	79
9			12	80

General reaction conditions: amine (1.2 mmol), aryl halide (1.0 mmol), 0.05 g Cu source, KOH (1.5 mmol), 9.0 cm^3 DMSO, 120 °C, pressure tube, N_2 atm

[b] Yields are after workup

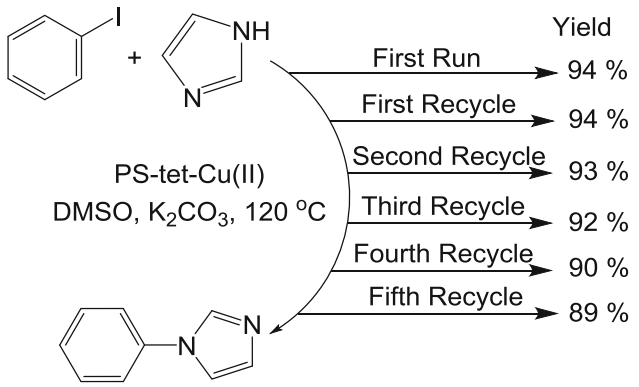


Fig. 3 Reusability of PS-tet-Cu(II) for the N-arylation of imidazole

Table 5 Zone of inhibition (mm) of PS-tet-Cu(II) against bacterial pathogens

Diameter of inhibition zone/mm				
Bacteria	50 ppm	75 ppm	100 ppm	150 ppm
E. coli (Gram −ve)	20 (±0.7)	22 (±0.9)	22 (±1.0)	25 (±1.0)
S. aureus (Gram +ve)	22 (±0.8)	24 (±1.2)	26 (±1.5)	28 (±0.8)

Chloromethylated polystyrene (4–5 % Cl and 2 % cross-linked with divinylbenzene) was purchased from Merck. Products were characterized by different spectroscopic methods (FT-IR and NMR spectra) and melting points. The NMR spectra were recorded in $CDCl_3$. ^1H NMR spectra were recorded on a Bruker Avance DRX 300 MHz instrument. The chemical shifts (δ) are reported in ppm relative to the TMS as internal standard. *J* values are given in Hz. IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BÜCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates. Morphology and particle dispersion was investigated by scanning electron microscopy (SEM) (Cam scan MV2300). The chemical composition of the prepared nanostructures was measured by EDS performed in SEM.

Preparation of nanopolystyrene-anchored Cu(II) tetrazole complex

The reaction was carried out in a round-bottomed flask of 250 cm^3 capacity. To the mixture of 2.0 g chloromethylated polystyrene (1.25 mmol/g of Cl) in 50 cm^3 of DMF, 5-phenyl-1*H*-tetrazole (5.0 mmol) and K_2CO_3 (5.0 mmol) was added. The mixture was stirred at 100 °C for 24 h. Then reaction mixture was filtrated, washed with DMF, and dried in vacuo for 12 h. Phenyltetrazole-functionalized polymer (1.0 g) was treated with 0.5 g $CuCl_2 \bullet 2H_2O$ in 50 cm^3 ethanol and the mixture stirred under reflux conditions for 24 h. The resulting bright green colored polymer, impregnated with the metal complex, was filtered, washed with ethanol and dried at 60 °C to give PS-tet-Cu(II) [35].

General procedure for the copper-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides

To a mixture of 0.05 g catalyst and aryl halide (1.0 mmol) in 9.0 cm^3 DMSO, Het-NH (1.2 mmol) and K_2CO_3 (2.0 mmol) was added and the mixture was vigorously stirred at 120 °C for the appropriate time under a dry nitrogen atmosphere. After completion (as monitored by TLC), the catalyst was filtered, and the filtrate was extracted with ethyl acetate (3 × 20 cm^3) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography. The purity of the compounds was checked by ^1H NMR and yields are based on aryl bromide. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature [36–41].

General procedure for the copper-catalyzed N-arylation of amines with aryl iodides

To a mixture of 0.05 g catalyst and aryl iodide (1.0 mmol) in 9.0 cm^3 DMSO, amine (1.2 mmol) and KOH (1.5 mmol) was added and the mixture was vigorously stirred at 120 °C for appropriate time under a dry nitrogen atmosphere. After the completion of the reaction, the catalyst was filtered off and washed with water followed by acetone and dried in oven. The filtrate was extracted with ethyl acetate (3 × 20 cm^3) and the combined organic layers were dried with anhydrous Na_2SO_4 by vacuum. The filtrate was concentrated by vacuum and the resulting residue was purified by column chromatography on silica gel to provide the desired product. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature [26].

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