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ARTICLE TYPE

Nanoparticle mediated organic synthesis (NAMO-Synthesis) : CuI-NP catalyzed ligand free Amidation of Aryl halides

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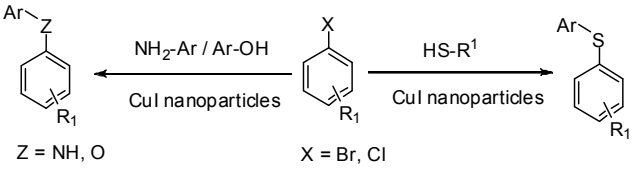
First CuI-nanoparticle catalyzed ligand free synthesis of N-aryl amides from aryl halides and arylamides / cyclic amides have been developed. This methodology is further extended for the synthesis of nitrogen heterocycles such as benimidazole, quinazolinone via intermolecular amidation reaction followed by cyclization. TEM image of CuI-NP catalyst showed that spherical, well-dispersed particles which provides large surface area for reactivity and have good recyclability.

Introduction

Transition metal-catalyzed C-N, C-C bond forming processes are extensively utilized in academics and pharmaceutical industry.[1] Metal-catalyzed amide arylation reactions of aryl halides or pseudo halides are an attractive method for synthesizing N-arylamides, which are an important pharmacophore and present in many clinically approved drugs and natural products.[2-4] In twenty first century, Nanoparticle mediated organic synthesis has been one of the most progressive research areas.[5] Therefore, we wish to introduce here Nanoparticle mediated organic synthesis (NAMO-Synthesis), a specific term for the organic synthesis involving nanoparticles.

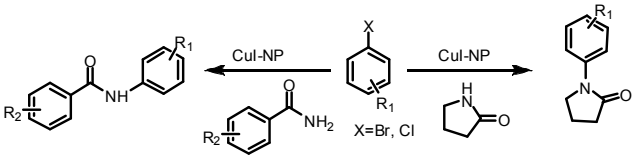
The use of nano transition-metal catalysts to perform organic reaction is becoming increasingly popular.[6] Metal nanoparticles have been enticed the synthetic chemistry due to the edge over the heterogeneous and homogeneous catalyst. Metal nano particles offer privilege of heterogeneous and homogeneous catalyst system. Recyclability and recovery offered by nanoparticles catalysis keep the main advantage of heterogeneous system. Whereas low catalyst loading and selectivity as offered by homogeneous system. Beside this nanoparticles have added advantage of large surface area and high catalytic activity.[7] Almost all the amide arylation reaction involves Palladium / ligand based catalytic systems.[8] However, the replacement of palladium with less expensive copper(I) salt as catalyst would be allowed for economic benefits and low toxicity issues.[9] Recently, Nano Cu-catalyzed N-aylation of amines, S-arylation and O-arylation reactions have been reported.[10] To the best of our knowledge, N-Aryl Amidation have not yet been exploited. Thus we developed first Nano Cu catalyzed N-aryl amidation reaction for the synthesis of diverse amides (Figure 1).

Pervious Work: N-Aryl Amination / O-arylation and S-Arylation



This Work: N-Arylation of Amides

N-Aryl amidation of simple Amides and Cyclic Amides



Application of CuI NP in synthesis of heterocycles

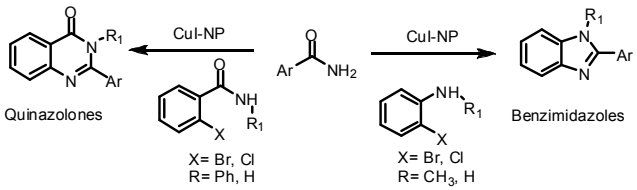


Figure 1. Nanoparticle mediated organic synthesis (NAMO- Synthesis)

Herein, we report first Nano Cu-catalyzed ligand free N-arylation of amides using CuI nanoparticles as the catalyst, ethylene glycol : 2-propanol (1:5) ratio as the solvent under mild reaction condition. This efficient methodology for arylation of amides

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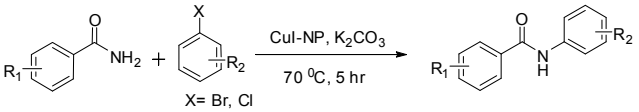
have been further utilized for the synthesis of substituted benzimidazoles and quinazolinones, which have a wide range of application in pharmaceutical industry and material sciences.[11]

Result and Discussion

We commenced our study by investigating the reaction of bromobenzene and benzamide were chosen as the model substrates to optimize reaction condition, which include the catalyst, base, and solvent. As shown in Table 1, four copper catalysts and CuI nano particle were tested at 70^{0}C temperature by using 1.5 equivalents of K_2CO_3 as the base in ethylene glycol : 2-propanol (1:5) solvent system. The copper (I) salts such as CuBr, CuCl, Cu_2O, and CuI were found to be inferior to CuI nanoparticles (Table 1, entries 11-14).

Table 1. Optimization of reaction conditions for synthesis of N-Aryl amides

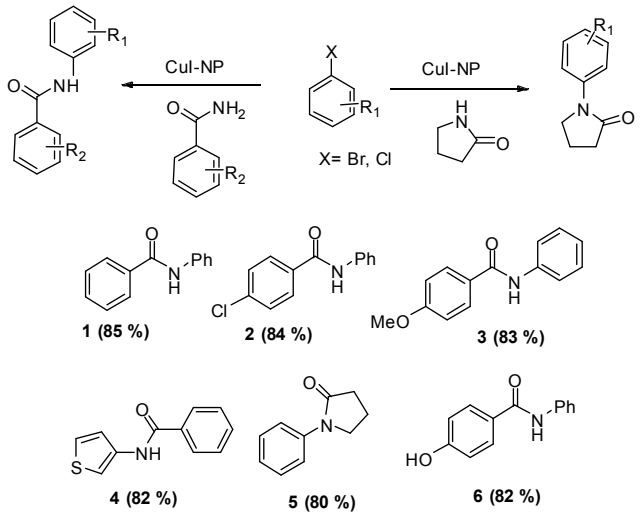


Entry	[Cu] (mol %)	Base	solvent	Yield (%)[b]
1	CuI (np (1.5))	K_2CO_3	EG/^{i}PrOH	85
2	CuI (np (1.5))	KOtBu	EG/^{i}PrOH	70
3	CuI (np (1.5))	KOH	EG/^{i}PrOH	72
4	CuI (np (1.5))	Na_2CO_3	EG/^{i}PrOH	78
5	CuI (np (1.5))	K_3PO_4	EG/^{i}PrOH	52
6	-	K_2CO_3	EG/^{i}PrOH	-
7	CuI (np (1.5))	K_2CO_3	^{i}PrOH	-
8	CuI (np (1.5))	K_2CO_3	NMP	10
9	CuI (np (1.5))	K_2CO_3	DMF	-
10	CuI (np (1.5))	K_2CO_3	H_2O	-
11	Cu_2O	K_2CO_3	EG/^{i}PrOH	35
12	$Cu(OAc)_2$	K_2CO_3	EG/^{i}PrOH	30
13	CuBr	K_2CO_3	EG/^{i}PrOH	30
14	CuCl	K_2CO_3	EG/^{i}PrOH	25
15	CuI (np (3.0))	K_2CO_3	EG/^{i}PrOH	84
16	CuI (np (5.0))	K_2CO_3	EG/^{i}PrOH	84
17	CuI (np (0.5))	K_2CO_3	EG/^{i}PrOH	65
18	CuI (10)	K_2CO_3	EG/^{i}PrOH	50

[a]Reaction conditions: bromobenzene (1.0 mmol), benzamide (1.5 mmol), CuI-NP (1.5 % mole), base (1.5 equ.), EG (ethylene glycol)/iPrOH (2-propanol) as solvent (10 mL) in 1:5 ratio for 5 hr at 70 ^{0}C. [b] Isolated yield. np = nanoparticles, DMF = dimethylformamide, NMP = N-methylpyrrolidinone.

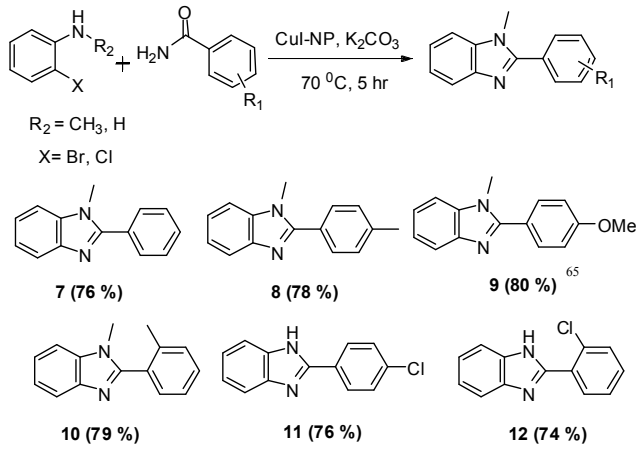
To coincidence, we used ethylene glycol : 2-propanol as the solvent and we observed that product was obtained without use of ligand in excellent yield. Control experiments revealed that no reaction was observed in the absence of ethylene glycol and CuI-NP catalyst (Table 1, entries 6,7). Solvent effects were also screened. Ethylene glycol : 2-propanol was found to be superior to the solvents tested (Table 1, entries 7–10). Presumably, ethylene glycol acts as a ligand that is more effective in stabilizing or solubilizing the nano copper complex. Beside these ethylene glycol : 2-propanol system is considered as green media.[12] Among the bases studied, KOH, Na_2CO_3, KOtBu, K_3PO_4, provided lower yields than K_2CO_3, (Table 1, entries 1–5).

Scheme 1: Arylation of Simple amides and cyclic amides



The 1.5 mol % of CuI nanoparticles showed the best activity (Table 1, entry 1). We found that 85 % yield obtained with 1.5 mol% nanocatalyst, whereas 0.5 mol% nanocatalyst gave 65% product (Table 1, entry 17).

Scheme 2: One pot synthesis of Benzimidazole derivatives



The scope of the reaction was explored with a range of substituted benzamides, cyclic amides and the bromides showed higher reactivity than the corresponding aryl chloride (Scheme 1). We were pleased to observe that the aryl bromide with electron rich, electron-poor, or sterically hindered, all of them afforded good to excellent yields with nanoparticles of CuI. We noticed that (1:5) ratio of ethylene glycol and 2-propanol as better solvent system for the reaction. Low yields were obtained when the reaction time, temperature, or amount of CuI nanoparticles were reduced. The optimal conditions of 1.5 mol % of CuI nanoparticles, 1.5 equiv of K_2CO_3 in ethylene glycol / 2-propanol at 70 ^{0}C were used for further investigations. After completion of reaction, the catalyst was recovered from the reaction mixture by centrifugation and reused for the next fresh reaction. It is noteworthy that the catalyst could be reused at least five times

without any significantly loss of efficiency. We were pleased to observe that cyclization product after the N- arylation of amides were obtained when 2-bromoaniline and 2-bromobenzamide react with benzamides in one pot (Scheme 2,3). Next we focused on 2-chloroaniline react with benzamides and surprise to obtained the cyclized product, benzimidazole only with CuI nanoparticles in low yields. Therefore, we suspected that because of large surface area, nanoparticles have very high catalytic properties as compare to other catalyst.

Scheme 3: One pot synthesis of substituted Quinazolinones

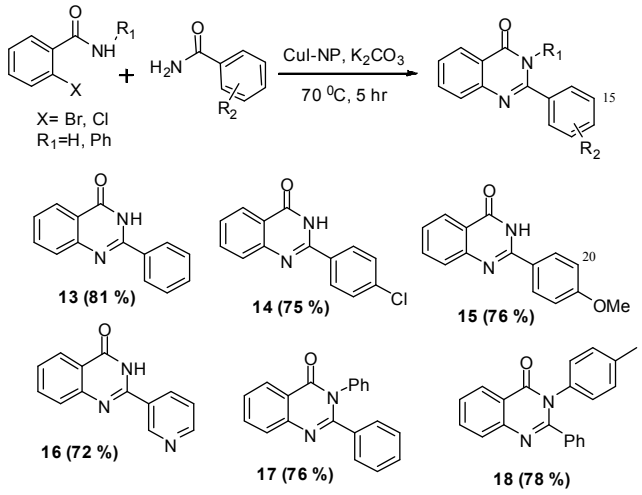
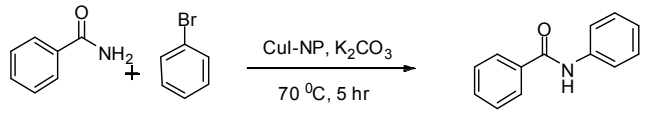


Table 2. Recyclability of CuI Nanoparticles



Run	Catalyst recovery (%)	Product Yield (%)[c]
1[a]	95	85
2[b]	90	84
3[b]	86	82
4[b]	82	80
5[b]	75	75

[a]CuI nanoparticles (1.5 mol %), bromobenzene (1.0 mmol), benzamide (1.5 mmol) base (1.5 equ.), EG (ethylene glycol)/iPrOH (2-propanol) as solvent (10 mL) in 1:5 ratio for 5 hr at 70 ^{0}C. [b]The recovered catalyst was used under identical reaction conditions to those for the first run.[C]

It was a heterogeneous process and the catalyst was recyclable with slight loss of activity (Table 2). After completion of amidation of bromobenzene, the catalyst was recovered from the reaction mixture by centrifugation and reused for the fresh reaction and only a slight decrease in catalytic activity was observed. The surface property and the composition of the catalyst were characterized from scanning electron microscope (SEM), transmission electron microscope (TEM) and energy dispersive X-ray analysis (EDX). The EDX spectrum (Figure 2) further authenticates the presence of Cu in the nanocomposite. In addition, in the SEM, TEM analysis of CuI nanoparticles, interestingly, the shape and size of the nanoparticles remained unchanged before and after the reaction.

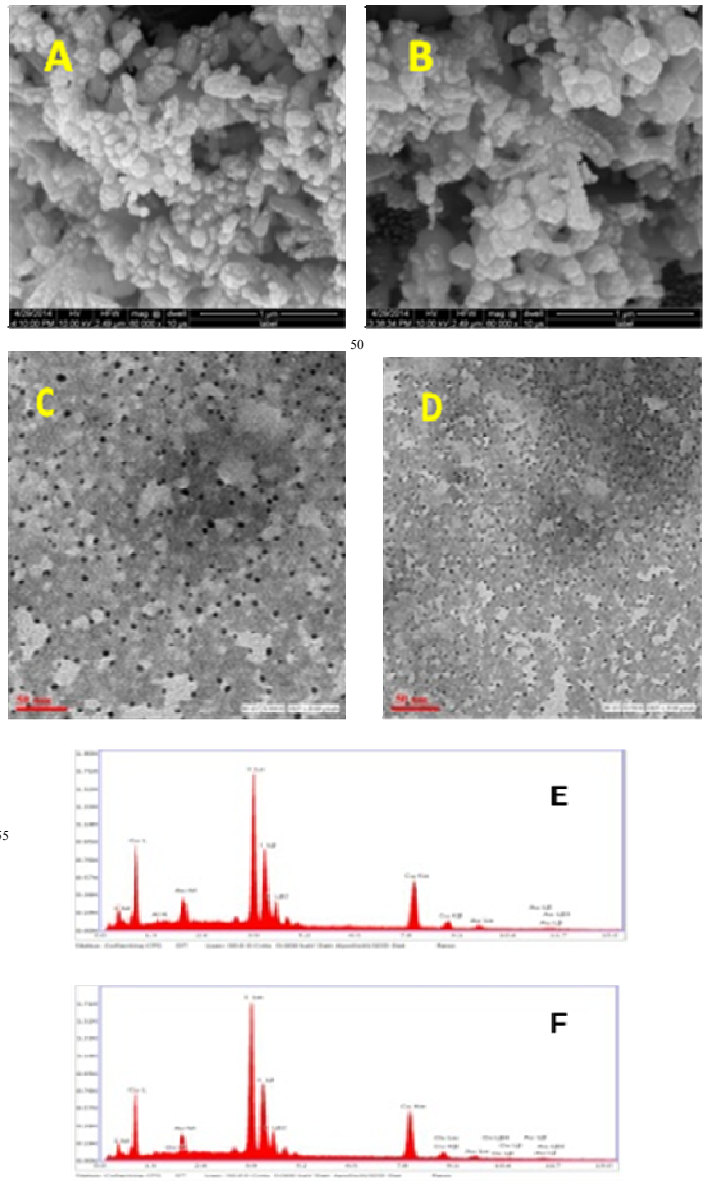


Figure 2. (a) SEM images of catalyst before the reaction (b) After the 5th run (c) TEM images before the reaction (d) After the 5th run, (e) EDX image of fresh catalyst, and (f) EDX image of catalyst after 5th run.

Conclusion

In conclusion, we have demonstrated first ligand free CuI-nanoparticle catalyzed N-arylation of amides / cyclic amindes in ethylene glycol / 2-propanol solvent system under mild condition in good yields. The methodology is also extended for one pot synthesis of benzimidazoles and quinazolones in excellent yields. The catalyst have good recyclability which provides several

advantage, including short reaction time, simple work up and high yields. The Nanoparticle mediated organic synthesis (NAMO- Synthesis) has immense future in application in the area of medicinal chemistry and material science.

Experimental Section

General procedure for preparation of CuI nanoparticles

0.464 g (4 mmol) of dimethylglyoxime (dmgH) and 0.400 g (2 mmol) of $Cu(OAc)_2.H_2O$ were added into 50 ml of absolute ethanol in sequence, which was stirred at 0 °C for 30 min to get brown precipitates Cu(dmg) 2. Then the collected precipitates dispersed in 50 ml of absolute ethanol again, 0.664 g (4 mmol) KI was added and stirred vigorously for 2 h. After that, the mixture was transferred into 60 mL Teflon-lined stainless steel autoclave. The autoclave was sealed and heated at 180 °C for 6 h, and then the reactor bomb is allowed to cool to room temperature. Black precipitates were obtained, then centrifugalized and washed with ethanol and deionized water for three times to ensure the removal of the impurities. The final product was then dried in a vacuum oven at room temperature for 12 h.

General procedure for the Arylamidation of simple amides

The Arylation of amides was carried out in a round bottomed flask. In a typical experiment, a mixture of bromobenzene (1 mmol), benzamide (1.5 mmol), CuI NPs (1.5 mol%) and K_2CO_3 (1.5 equ.) were dissolved in 10 mL of ethylene glycol / 2-propanol (1:5) and stirred for the 5 hours at 70 ^{0}C temperature. The reaction was monitored to completion using TLC. At the end of reaction, the mixture was then cooled to room temperature and poured into distilled water. The products were extracted using EtOAc and the organic layer was dried over anhydrous sodium sulphate (Na_2SO_4). The solvent was evaporated in vacuo, the crude products were purified by silica column chromatography using EtOAc / hexane solvent system.

General procedure for the benzimidazole derivatives in one-pot.

The amidation reaction was carried out in a round bottomed flask. In a typical experiment, a mixture of 2-bromo-N-methylaniline (1 mmol), benzamide (1.5 mmol), CuI NPs (1.5 mol%) and K_2CO_3 (1.5 equ.) were dissolved in 10 mL of ethylene glycol / 2-propanol (1:5) and stirred for the 5 hours at 70 ^{0}C temperature. The reaction was monitored to completion using TLC. At the end of reaction, the mixture was then cooled to room temperature and poured into distilled water. The products were extracted using EtOAc and the organic layer was dried over anhydrous sodium sulphate (Na_2SO_4). The solvent was evaporated in vacuo, the crude products were purified by silica column chromatography using EtOAc / hexane solvent system.

General procedure for the Quinazolinone derivatives in one-pot.

In a typical experiment, a mixture of 2-bromobenzamide (1 mmol), benzamide (1.5 mmol), CuI NPs (1.5 mol%) and K_2CO_3 (1.5 equ.) were dissolved in 10 mL of ethylene glycol / 2-propanol (1:5) and and stirred for the 5 hours at 70 ^{0}C temperature. The reaction was monitored to completion using TLC. At the end of reaction, the mixture was then cooled to room temperature and poured into distilled water. The products were extracted using EtOAc and the organic layer was dried over anhydrous sodium sulphate (Na_2SO_4). The solvent was evaporated in vacuo, the crude products were purified by silica column chromatography using EtOAc / hexane solvent system.

Supporting Information see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra; SEM-EDX, TEM images of catalyst.

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Graphical abstract

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