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N-Arylation of Heterocycles with Activated Chloro- and Fluoroarenes using Nanocrystalline Copper(II) Oxide

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Abstract: Nanocrystalline copper oxide was found to be an effective heterogeneous catalyst for the *N*-arylation of heterocycles with activated chloro- and fluoroarenes using potassium carbonate as base. *N*-Arylated products were isolated in good to excellent yields. The catalyst can be used for five cycles with almost consistent activity.

Keywords: *N*-arylation; heterocycles; heterogeneous catalysis; nanocrystalline copper(II) oxide; reusability

Introduction

N-Arylheterocycles are important compounds as they find wide application in medicinal,[1] biological,[2] and N-heterocyclic carbene chemistry.[3] There is thus considerable interest in developing efficient synthetic protocols for the *N*-arylation of heterocyclic compounds. Different types of reagents such as aryllead, arylsilane, arylstannane or arylboronic acid derivatives are used for this coupling reaction.[4] The use of haloarenes which are less toxic and more cost effective is highly desirable.

Buchwald et al. reported palladium-catalyzed C–N coupling reactions of aryl bromides and aryl chlorides with amines, anilines and nitrogen heterocycles in the presence of sterically hindered phosphine ligands.[5] Hartwig et al. developed the arylation of azoles and imines with aryl bromides using the Pd(0)/DPPF catalyst[6] and later the palladium-catalyzed amination of aryl halides and triflates in the presence of zinc silylamide.[7] Buchwald[8] and Taillefer[9] reported a catalytic path for the *N*-arylation of heterocycles with bromo- and iodoarenes using copper in the presence of bidentate ligands. Recently, Dawei Ma and his co-workers developed CuI/amino acid-catalyzed cross-coupling reactions in mild conditions[10] and the amino acids used are significantly inexpensive and readily available. Later Bao and co-workers reported CuI/L-proline-catalyzed coupling reactions of aryl/heteroaryl bromides and imidazole in ionic liquids.[11] CuI-mediated aryl amination can also be realized without a ligand.[12] Other copper sources such as cuprous or cupric oxides are also used in the *N*-arylation of heterocycles.[9,13]

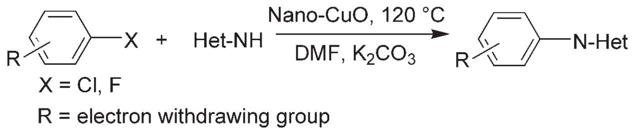
The *N*-arylation of heterocycles using chloro- and fluoroarenes is important, as it leads to a fundamental understanding of the reactivity of very stable bonds, C–Cl and C–F. C–N and C–C coupling reactions with electron-withdrawing (EW) fluoroarenes are realized using Pd(0) catalysts, but the scope is restricted to fluoroarene-tricarbonylchromium(0) or 2-nitrofluoroarene.[14] Industry favours catalytic process induced by a heterogeneous catalyst over the homogeneous one in view of ease of handling, simple work-up and regenerability. Hyeon et al. reported Cu_2O coated Cu nanoparticles for the coupling reaction using activated chloroarenes in the presence of Cs_2CO_3.[15] Later, we reported the *N*-arylation of heterocycles with chloro- and fluoroarenes using Cu(II) fluoroapatite.[16]

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals[17] and as catalysts for various organic transformations.[18] These high reactivities are due to high surface areas combined with unusually reactive morphologies. Copper oxide nanoparticles have been of considerable interest due to the role of CuO in catalysis, in metallurgy, and in high-temperature superconductors.[19] These nanoparticles were found to be effective catalysts for CO and NO oxidation as well as oxidation of volatile organic chemicals such as methanol.[20] Recently, we reported the asymmetric epoxidation, Henry and Michael addition reactions with excellent yields and enantioselectivites using nanocrystalline MgO.[21]

Results and Discussion

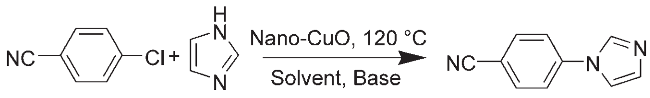
As part of our ongoing research on nanocrystalline metal oxide-catalyzed organic transformations, we herein report the *N*-arylation of heterocycles with activated chloro- and fluoroarenes in excellent yields using nanocrystalline copper oxide (nano-CuO) (Scheme 1).

Nano-CuO samples were obtained from NanoScale Materials Inc, having a surface area of 136 $m^2 g^{-1}$and crystallite size of 7–9 nm.[22] To optimize the reaction conditions, various parameters such as the effect of different solvents and bases were studied on the *N*-arylation of imidazole with 4-chlorobenzonitrile. Among the solvents screened, DMF gave the maximum yield (Table 1, entry 8). Although Cs_2CO_3 and K_3PO_4 gave excellent yields in shorter reaction times, 6 and 10 h respectively, K_2CO_3, an inexpensive inorganic base was used in this study. A lower yield of product was obtained when commercially available bulk CuO was used as catalyst (Table 1, entry 10). The increased catalytic activity of nano-CuO over the commercially available bulk CuO may be attributed to the higher surface area for nano-CuO (S.A.: 136 $m^2 g^{-1}$) than the bulk CuO (S.A: 1. 952 $m^2 g^{-1}$). This is thought to be due to morphological differences, whereas larger crystallites have only a small percentage of reactive sites on the surface, smaller crystallites will possess a much higher surface concentration of such sites.[22] The catalytic activity of nano-CuO was evident when no product was obtained in the absence of the catalyst (Table 1, entry 8).



Scheme 1. *N*-Arylation of heterocycles with activated chloro- and fluoroarenes.

Table 1. Effect of different solvents and bases for the *N*-arylation of imidazole with 4-chlorobenzonitrile.[a]



Entry	Solvent	Base	Time [h]	Yield [%][b]
1	DMF	Cs_2CO_3	6	88
2	DMSO	Cs_2CO_3	6	79
3	NMP	K_2CO_3	10	trace
4	Toluene	K_2CO_3	12	0
5	THF	K_2CO_3	12	0
6	MeCN	K_2CO_3	12	0
7	DMF	K_3PO_4	10	81
8	DMF	K_2CO_3	12	84, 79,[c] 0[d]
9	DMF:H_2O (1:1)	K_2CO_3	9	0
10	DMF	K_2CO_3	12	22[e]

[a] *Reaction conditions*: 4-chlorobenzonitrile (1 mmol), imidazole (1.2 mmol), catalyst (10 mol%), base (2 mmol), DMF (4 mL).

[b] Isolated yields.

[c] Yield after fifth cycle.

[d] Without catalyst.

[e] Using commercial CuO.

As illustrated in Table 2, the catalytic system, (10 mol% of nano-CuO, K_2CO_3, DMF at 120 °C) proved to be highly efficient with other activated chloroarenes. When *o*-, *m*- and *p*-nitrochlorobenzenes were used, the corresponding *N*-arylated products were obtained in excellent yields (Table 2, entries 1, 2 and 3). Cyano, nitro, and aldehyde groups are well tolerated (Table 2, entries 1, 4 and 6).

2-Chloropyridine, 4-chloropyridine and 2-chloropyrimidine also provided excellent yields as can be seen from Table 2 (entries 7, 8 and 10). The sterically bulky 4-chlorobenzophenone was converted to the corresponding *N*-arylated product (Table 2, entry 9) with excellent yield. In the case of deactivated chloroarenes such as chlorobenzene, this catalytic system is completely inactive (Table 2, entry 12). The activity of nano-CuO is less than that of the Cu(II) fluoroapatite catalyst previously reported by us[16] and comparable with Cu_2O coated nano Cu catalyst reported by Hyeon.[15]

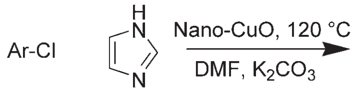
Particularly noteworthy is that fluoroarenes containing several *o*- or *p*-EW groups are also coupled with imidazole to afford the corresponding *N*-arylated products in excellent yields. Faster reactivity over the chloroarenes (Table 2 and Table 3) and selective coupling involving C−F activation only in chlorofluoroarenes (Table 3, entries 8 and 9) are other attributes of this coupling reaction. Such a type of higher reactivity of C−F over C−Cl for fluoroarenes (EW) in the Suzuki reaction is recorded.[14a]

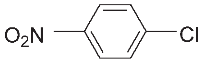
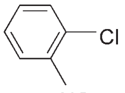
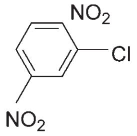
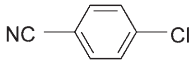
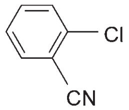
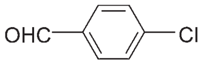
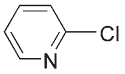
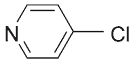
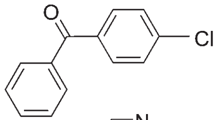
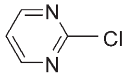
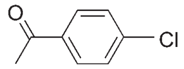
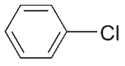
As can be seen from Table 4, other nitrogen-containing heterocycles like benzimidazole, pyrrole and pyrazole gave the corresponding *N*-arylated products with 1-chloro-4-nitrobenzene and 1-fluoro-4-nitrobenzene in excellent yields.

1-Chloro-4-nitrobenzene, 4-chlorobenzonitrile and 2-chlorobenzonitrile, as well as 2-chloropyrimidine and 2-chloropyridine are coupled with indole to give the corresponding *N*-arylated products in good to excellent yields (Table 5, entries 1–5). *N*-Arylated product was obtained in 20% yield by coupling of indole with 4-chloroacetophenone while in the case of Cu_2O coated nano Cu, a complex mixture was obtained in the arylation of indole with 4-chloroacetophenone.[15]

Catalyst recycle experiments were also carried out and the results are presented in Table 6. The nano-

Table 2. *N*-Arylation of imidazole using different chloroarenes.[a]



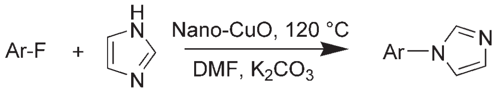
Entry	Ar-Cl	Time [h]	Yield [%][b]
1		1.5	88, 0[c]
2		4	86
3		17	81
4		12	84
5		12	91
6		18	83
7		16	87
8		18	92
9		11	87
10		1	94
11		12	89
12		24	0

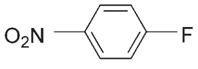
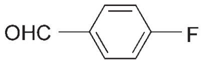
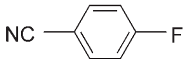
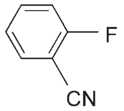
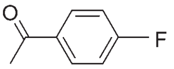
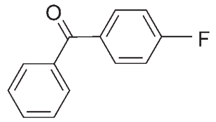
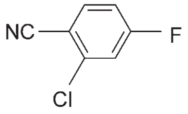
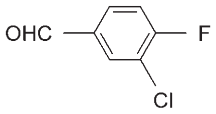
[a] *Reaction conditions*: Ar-Cl (1 mmol), imidazole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL), 120 °C.

[b] Isolated yields.

[c] Without catalyst.

Table 3. *N*-Arylation of imidazole using different fluoroarenes.[a]



Entry	Ar-F	Time [h]	Yield [%][b]
1		0.5	91, 0[c]
2		2	89
3		2	85
4		1	83
5		1.5	91
6		2	83
7		3	87
8		1.5	87
9		2	94

[a] *Reaction conditions*: Ar-F (1 mmol), imidazole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL).

[b] Isolated yields.

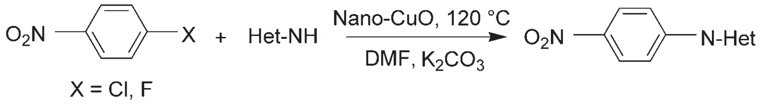
[c] Without catalyst

CuO was recovered by centrifugation and reused for several cycles without any significant loss of activity.

Transmission electron microscope (TEM) studies of both fresh and used catalysts were carried out to understand the shape and size of the particles. Figure 1a and Figure 1b show the TEM images of the fresh and the used catalyst after the fifth cycle, respectively. Interestingly, it is observed that the shape and size of the particles remain unchanged. This supports the assumption that the morphology of the catalyst remains the same even after recycling.

In conclusion, we have developed the nano-CuO-catalyzed *N*-arylation of heterocycles with activated chloro- and fluoroarenes using K_2CO_3 as base in excellent yields. The catalyst can be used for five cycles with almost consistent activity.

Table 4. *N*-Arylation of various nitrogen heterocycles.[a]



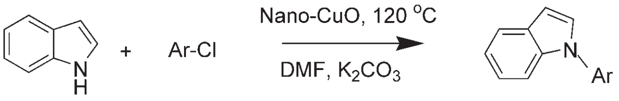
Entry	Het-NH	X = Cl		X = F	
		Time [h]	Yield [%][b]	Time [h]	Yield [%][b]
1.	Pyrrole	8	82, 0[c]	2	84, 0[c]
2.	Benzimidazole	4.5	87	3	81
3.	Pyrazole	5	84	2	94

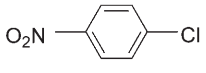
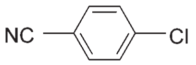
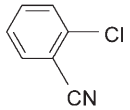
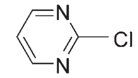
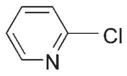
[a] *Reaction conditions*: ArX (1 mmol), Het-NH (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL).

[b] Isolated yields.

[c] Without catalyst.

Table 5. *N*-Arylation of indole with different chloroarenes.[a]



Entry	Ar-Cl	Time [h]	Yield [%][b]
1		9	89
2		18	76
3		18	83
4		1.5	94
5		23	77

[a] *Reaction conditions*: Ar-Cl (1 mmol), indole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL).

[b] Isolated yields.

Table 6. Recycle studies of nano-CuO for *N*-arylation of imidazole with 4-chlorobenzonitrile.

Run	Time	Yield [%][b]
1	12	84
2	12	81
3	12	78
4	12	81
5	12	79

[a] *Reaction conditions*: 4-chlorobenzonitrile (1 mmol), imidazole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL).

[b]. Isolated yields.

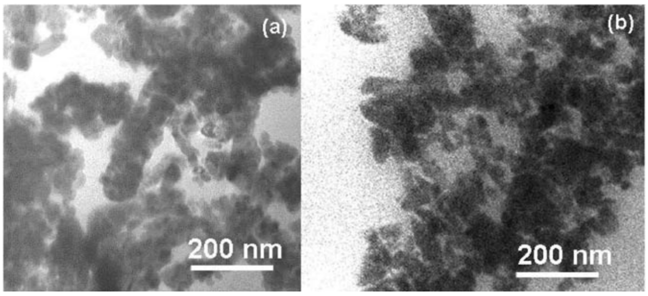


Figure 1. TEM images of (**a**) fresh nano-CuO and (**b**) used nano-CuO

Exprimental Section

Typical Experimental Procedure for the Cross Coupling Reaction

Nanocrystalline CuO (10 mol%) was added to a mixture of 1 mmol of 4-chlorobenzonitrile and 1.2 mmol of imidazole in 4 mL of anhydrous DMF and stirred at 120 °C. After completion of the reaction (as monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with ethyl acetate. The filtrate was quenched with aqueous sodium hydrogen carbonate and the product was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulphate and filtered.

The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 70/30) to afford pure 1-(4-cyanophenyl)-1*H*-imidazole; mp: 152-154 °C; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.90$ (br s, 1 H), 7.79 (d, 2 H, $J = 8.3$ Hz), 7.53 (d, 2 H, $J = 8.3$ Hz), 7.29 (br s, 1 H), 7.22 (br s, 1 H); EI-MS: $m/z = 169$ (100 %), 142, 115, 102, 75, 50; IR: (KBr): $\nu = 2924.55$, 2223.40, 1608.28, 1519.42, 1302.44, 1054.32, 834.11 cm^{-1}.

Acknowledgements

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