Tetrahedron Letters 52 (2011) 1924-1927

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper ferrite nanoparticle-mediated N-arylation of heterocycles: a ligand-free reaction

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ABSTRACT

Revised 8 February 2011 Accepted 10 February 2011 Available online 15 February 2011

Keywords: Ullmann coupling C-N cross-coupling N-Arylation N-Heterocycles CuFe₂O₄ nanoparticles

Since 1903, the copper-catalyzed Ullmann reaction¹ has been widely applied for the N-arylation of nitrogen-containing heterocycles.² The classic Ullmann reaction normally requires harsh conditions, such as high temperature (~200 °C), stoichiometric amounts of copper and selective halide substrates, which is problematic for industrial use due to high cost and waste disposal. To overcome these drawbacks, a number of efforts have been made recently to develop a new catalytic system. Successful methods include the use of catalytic amounts of copper and arylboronic acids in place of aryl halides.^{3–5} However, the relative instability of boronic acids and the tedious purification procedure limit their further application. Buchwald⁶ and Hartwig⁷ independently established the broad applicability of palladium catalysts for N-arylation of amines with aryl halides. The toxicity and high cost of Pd catalysts restrict their use on the industrial scale. Thus, researchers have turned their attention toward the use of less expensive, less toxic, and more efficient metals to replace Pd.⁸ Indeed, Buchwald⁹ and Taillefer¹⁰ independently made a significant breakthrough in the copper-catalyzed cross-coupling of N-H heterocycles with aryl bromides and iodides in the presence of chelating ligands. Other groups have also utilized various ligands, such as diamines, amino acids, β-ketoesters, 1,10-phenanthroline derivatives, poly(ethylene glycol), ninhydrin, and other nitrogen- and/or oxygen-containing ligands as chelating agents¹¹ under homogeneous conditions. Taillefer et al. used a Fe-Cu co-catalytic route for the N-arylation of numerous heterocycles with aryl bromides at relatively low

temperature (i.e., 90 °C), which was found to be economical and encouraging.^{10c} Quite recently, several CuI/Cu₂O-catalyzed 'ligand-free' catalytic systems have emerged.¹² More importantly, Punniyamurthy and co-workers¹³ exploited the high surface area and reactive morphology of the CuO nanoparticles for successful C-N, C-O, and C-S cross-coupling reactions. Park and co-workers¹⁴ also used catalytic amounts of acetylene-carbon-immobilized CuOhollow nanospheres for N-arylation reactions at high temperature (i.e., 180 °C) in a stainless steel reactor. Although these results are promising, there is still room for further development of a ligandfree, environmentally friendly, less expensive and easily separable catalytic system for the N-arylation of heterocycles with even less reactive aryl chlorides and sulfonates.

In recent years, magnetic nanoparticles have been extensively studied for various biological applications, such as magnetic resonance imaging,¹⁵ drug delivery,¹⁶ biomolecular sensors,¹⁷ bioseparation,¹⁸ and magneto-thermal therapy.¹⁹ Despite their wide use in biological systems, much less attention has been focused on the catalytic behavior of magnetic nanoparticles in organic transformations. Here, for the first time, we report the efficient catalytic activity of magnetic copper ferrite (CuFe₂O₄) nanoparticles toward the N-arylation of various N-heterocycles with aryl halides under 'ligand-free' conditions.

To develop the best magnetically separable catalyst for the Narylation reaction, Fe₃O₄ and different substituted ferrite nanoparticles, MFe_2O_4 (M = Cu²⁺, Co²⁺ and Ni²⁺), have been synthesized by thermal decomposition and were subsequently screened. Initially, we employed pyrrole and bromobenzene as model substrates for the development of optimized conditions (Scheme 1). As summa-

ARTICLE INFO Article history: Received 10 December 2010

The synergistic effects of iron and copper in copper ferrite nanoparticles for the N-arylation of heterocycles with aryl halides were demonstrated. The magnetic nature of the catalyst facilitates its removal from the reaction medium for further use. Negligible leaching of Cu and Fe in consecutive cycles makes the catalyst economical and environmentally benign for C-N cross-coupling reactions.

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Table 3

CuFe₂O₄ catalyzed N-arylation of N-heterocycles with bromobenzene



N-Arylation of pyrrole with bromobenzene in various solvents and bases in the presence of different ferrites

Entry	Catalyst	Solvent	Base	Yield ^a (%)
1	CuFe ₂ O ₄	DMF	^t BuOK	98
2	CuFe ₂ O ₄	DMF	K ₂ CO ₃	35
3	CuFe ₂ O ₄	DMF	NaOAc	≼5
4	CuFe ₂ O ₄	DMF	Cs ₂ CO ₃	35
5	CuFe ₂ O ₄	DMF	NaHCO ₃	10
6	CuFe ₂ O ₄	THF	^t BuOK	00
7	CuFe ₂ O ₄	1,4-Dioxane	^t BuOK	25
8	CuFe ₂ O ₄	DMSO	^t BuOK	38
9	CuFe ₂ O ₄	CH ₃ CN	^t BuOK	25
10	CuFe ₂ O ₄	MeOH	^t BuOK	00
11	CuFe ₂ O ₄	Ethanolamine	^t BuOK	≼5
12	CuFe ₂ O ₄	DMF	pyridine	10
13	Fe ₃ O ₄	DMF	^t BuOK	00
14	CoFe ₂ O ₄	DMF	^t BuOK	00
15	NiFe ₂ O ₄	DMF	^t BuOK	18
16	CuO	DMF	^t BuOK	68
17	CuFe ₂ O ₄	-	^t BuOK	00
18	_	DMF	^t BuOK	00
19	CuFe ₂ O ₄	Toluene	^t BuOK	≼5

 a Reaction conditions: 1.49 mmol of pyrrole, 1.52 mmol of bromobenzene, 10 mol % of catalyst, 2.0 equiv of base, 5 mL of solvent, 24 h reflux under N_2 atmosphere.

Table 2

Table 1

CuFe₂O₄ catalyzed N-arylation of pyrrole with aryl halides



 a Reaction conditions:1.49 mmol of pyrrole, 1.52 mmol of aryl halide, 10 mol % of CuFe_2O_4 nanoparticles, 2.0 equiv of 'BuOK, 5 mL of DMF, 24 h reflux under N_2 atmosphere.

rized in Table 1, it was found that Fe_3O_4 , $CoFe_2O_4$, and $NiFe_2O_4$ nanoparticles were inactive, whereas $CuFe_2O_4$ nanoparticles²⁰ catalyzed the N-arylation reaction (98% yield) in DMF at 155 °C in the presence of 2 equiv of 'BuOK. The magnetic nature of the copper ferrite nanoparticles facilitates their easy and quantitative removal from the reaction medium in the presence of an external magnetic field for further use.

When the reaction was carried out in different polar and nonpolar solvents, such as THF, toluene, DMSO, CH₃CN, 1,4-dioxane, ethanolamine, and MeOH, under reflux conditions only 0–40% of the N-arylated product and the remaining starting material was isolated. Moreover, DMF provided the best results. Direct heating of pyrrole, bromobenzene, CuFe₂O₄, and ^{*t*}BuOK at 155 °C in the ab-



 a Reaction conditions: 100 mg of azole, 1.02 equiv of bromobenzene, 10 mol % of CuFe_2O_4 nanoparticles, 2.0 equiv of 'BuOK, 5 mL of DMF, 24 h reflux under N_2 atmosphere.

sence of solvent did not yield any coupling product (Table 1, entry 17). Thus, DMF may chelate the Cu centers in $CuFe_2O_4$ and catalyze the N-arylation reaction.^{12b,11c} The reactivity of the catalyst in DMF in the presence of different bases was also investigated. Among the

Table 4			
Reusability of CuFe ₂ O ₄ nanoparticles and	l leaching of Cu and Fe	e in multi-cycle a	rvlation reactions

Cycle Recovered CuFe ₂ O ₄ (%)	Product yield ^a (%)	Cu leakage (in ppm)	Fe leakage (in ppm)
1 –	98	0.45	0.08
2 97	96	0.4	0.02
3 95	96	0.2	0.02

^a Reaction conditions: 1.49 mmol of pyrrole, 1.52 mmol of bromobenzene, 10 mol % of CuFe₂O₄ nanoparticles (for cycle 1 and the remaining recovered amount of the catalyst was used for subsequent cycles), 2.0 equiv of ¹BuOK, 5 mL of DMF, 24 h reflux under N₂ atmosphere.

tested bases (¹BuOK, Cs₂CO₃, K₂CO₃, Et₃N, pyridine, NaHCO₃, NaO-Ac), ¹BuOK was found to be superior for the highest yield of *N*-phenyl pyrrole.²¹ A decrease in the catalyst loading from 10 to 5 to 1 mol % afforded the product in lower yield, and 10 mol % of the catalyst was found to be optimum. It is worth mentioning that 10 mol % of the CuO nanoparticles catalyzed the N-arylation reaction with an appreciable yield (60–68%, Table 1, entry 16) over multiple runs, whereas our optimum conditions resulted in significantly higher yields of the product (98% over multiple runs even on a 15 mmol scale). Thus, it may be concluded that the synergistic effects of Fe and Cu in CuFe₂O₄ co-catalyze the N-arylation reaction and are in line with Taillefer's report.^{10c}

After determining the optimized conditions, we then investigated the scope of the magnetic catalyst for the C–N cross-coupling reaction of a diverse range of halides with pyrrole (Table 2). As expected, aryl iodides and bromides gave excellent yields of the coupled product. CuFe₂O₄ was found to be quite efficient in yielding the cross-coupled product with less reactive aryl chlorides (Table 2, entries 7-9), and moderate yields were obtained. It may be noteworthy that C-N cross-coupling reactions with aryl chlorides are rarely reported and, as mentioned by Taillefer, are significant challenges in Ullmann coupling reactions.^{11c} Coupling of pyrrole with different aryl halides having both electron-donating and -withdrawing groups resulted in products with moderate to good yields (Table 2). More interestingly, electron-rich bromides led to *N*-aryl pyrroles (Table 2, entries 5 and 6) in good yield; however, the transition metal-catalyzed reactions with these electron-rich arylating agents are traditionally less straightforward.

The catalytic activity of CuFe_2O_4 nanoparticles in N-arylation reactions of other nitrogen-containing heterocycles was investigated. Pyrazole, imidazole, indole, benzotriazole, carbazole, and others underwent coupling with bromobenzene under standard experimental conditions and provided products in 75–98% yield (Table 3, entries 1–5 and 8–10). However, the sterically hindered pyrazole and imidazole (Table 3, entries 6 and 7) gave the required products in lower yields (50–60%).

Next, we studied the reusability of a heterogeneous $CuFe_2O_4$ catalyst in C–N coupling reactions (Table 4). After completion of the reaction, the catalyst was recovered by the application of an external magnet, was washed with ethyl acetate and then acetone, and was dried in a hot air oven at 120 °C for 2 h. The recovered catalyst was reused under similar conditions for the next run, and the catalytic behavior of the CuFe₂O₄ nanoparticles was found to be unaltered (yield >95%), even up to three consecutive cycles.

Then, the possibility of Fe and Cu leakage from CuFe₂O₄ to the medium during the reaction was investigated. After completion of the reaction, the supernatant was collected and tested for Fe and Cu by atomic absorption spectroscopy (AAS). The leaching of Cu and Fe in three consecutive cycles was found to be ≤ 0.5 ppm (Table 4), which is well below the permissible level concerning the toxicity in humans.²²

In order to investigate the catalytic effect of leached ions in Narylation reactions, a controlled experiment was carried out under the optimum conditions. After 12 h of heating, the catalyst was removed by application of an external magnet and the remaining reaction mixture was again heated. It was observed that the concentration of *N*-aryl pyrrole was not increased further even after heating for an additional 24 h.

In conclusion, for the first time, we have demonstrated the application of copper ferrite nanoparticles for 'ligand free' N-arylation of various *N*-heterocycles from differently substituted aryl halides (X = I, Br, Cl). The magnetic nature of $CuFe_2O_4$ nanoparticles is particularly advantageous for easy, quick, and quantitative separation of the catalyst for reuse. This catalytic process is simple, efficient, economical, and environmentally safe. Further investigation of this catalytic system for C–C, C–O and C–S bond formation is underway in our laboratory.

Acknowledgment

DST (Ref. SR/FTP/CS-101/2006), Govt. of India is gratefully acknowledged for financial support.

Supplementary data

Supplementary data (synthesis and characterization of the catalyst and all other compounds with detailed experimental procedures) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.050.

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- 20. Catalyst preparation. CuFe₂O₄ nanoparticles of size 15–20 nm were prepared by thermal decomposition of Cu(NO₃)₂ and Fe(NO₃)₃ in water in the presence of

sodium hydroxide. Briefly, to a solution of Fe(NO₃)₃·9H₂O (3.34 g, 8.2 mmol) and Cu(NO₃)₂·3H₂O (1 g, 4.1 mmol) in 75 ml of distilled water, 3 g (75 mmol) of NaOH dissolved in 15 ml of water was added at room temperature over a period of 10 min. during which reddish-black precipitate was formed. Then the reaction mixture was warmed to 90 °C and stirred. After 2 h, it was cooled to room temperature and the magnetic particles so formed were separated by a magnetic separator. It was then washed with water (3 × 30 ml) and catalyst was kept in air oven for overnight at 80 °C. Then the catalyst was ground in a mortar-pestle and kept in a furnace at 700 °C for 5 h (step up temperature 20 °C/min) and then cooled to room temperature. Slowly. 820 mg of magnetic CuFe₂O₄ particles of size 10–25 mm were obtained. Copper and iron content in CuFe₂O₄ nanoparticles were estimated to be 27.5% and 47.2%, respectively, from AAS (see Supplementary data for further characterization).

- 21. General procedure for N-arylation reaction. To a solution of N-heterocycle (1 equiv), bromobenzene (1.02 equiv) and 'BuOK (2 equiv) in dry DMF, CuFe₂O₄ (10 mol %) was added and heated at reflux for 24 h under N₂ atmosphere. After cooling to room temperature, the mixture was diluted with ethyl acetate and the catalyst was separated by a magnetic separator. The catalyst was washed with ethyl acetate. The combined ethyl acetate layer was washed with water (twice), dried over anhydrous Na₂SO₄, and concentrated to yield the crude product, which was further purified by silica gel column chromatography using petroleum ether/ethyl acetate to yield N-arylated product.
- Permissible limit of Cu and Fe leaching is 2 ppm and 2 ppm respectively, see:
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