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Copper fluorapatite catalyzed *N*-arylation of heterocycles with bromo and iodoarenes

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Abstract—Copper exchanged fluorapatite (CuFAP) is an effective heterogeneous catalyst for *N*-arylation of heterocycles with bromo- or iodoarenes using K_2CO_3 as base. *N*-Arylated products were isolated in good to excellent yields, demonstrating the versatility of the reaction.

N-Arylheterocycles are common motifs in pharmaceutical research.[1] Arylation of heterocyclic nitrogen is a long-standing problem and traditionally *N*-arylated heterocycles have been prepared by Ullmann-type coupling of N–H containing heterocycles with readily available and cheap aryl halides. The discovery and development of the catalytic path for *N*-arylation of heterocycles with bromo- and iodoarenes by Buchwald and co-workers[2] and Lam et al.[3] and exhaustive arylation with several nucleophiles by Taillefer[4] using copper catalysts in the presence of basic ligands generated great interest in industry.

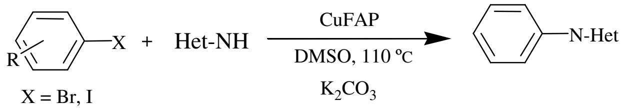
Heterogeneous catalysis is particularly attractive as it allows the production and ready separation of large quantities of products with the use of a small amount of catalyst.

Apatites are metal basic phosphates for which the chemical formula is $M_{10}(PO_4)_6(OH)_2$ [M = divalent metal]; the most typical apatite is calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$(CaHAP). CaHAP has attracted wide attention due to its versatile applications in the field of bioceramics, as a chromatographic adsorbent, and in acid–base catalysis. It has been well established that the Ca^{2+} sites of CaHAP can be replaced by divalent cations, such as Sr^{2+}, Ba^{2+}, Pb^{2+} and Cd^{2+}.[5] Fluorapatites are metal basic phosphates for which the chemical formula is $M_{10}(PO_4)_6(F)_2$(CaFAP) [M = divalent metal].

Kaneda and co-workers demonstrated the utility of CaHAP as a solid support for Ru and Pd to perform several organic transformations: oxidation of alcohols, Heck and Diels–Alder reactions.[6]

Recently we reported the preparation of recyclable heterogeneous Cu-exchanged fluoroapatite and copper exchanged *tert*-butoxyapatite catalysts, by incorporating basic species $F^-/t\text{-BuO}^-$ in apatite in situ by co-precipitation and subsequent exchange with Cu(II) for *N*-arylation of imidazoles and other heterocycles with chloroarenes and fluoroarenes (EW), with good to excellent yields for the first time.[7] In continuation of our work on apatites, we herein report *N*-arylation of heterocycles with bromo- and iodoarenes catalyzed by using the recyclable heterogeneous copper exchanged fluorapatite (Scheme 1).

Copper-exchanged fluorapatite (CuFAP) was characterized by XPS, SEM-EDAX and IR. XPS analysis of the CuFAP catalyst indicated the same binding energy values for Ca, P and O as in CaFAP. A narrow scan of Cu $2p_{3/2}$ for CuFAP showed the binding energy peak at 934.9 eV (The binding energy of Cu in Cu(II) is around 935 eV.),[8] which indicates copper in the +2 oxidation state in CuHAP. The copper content was estimated to be 1.25 mmol g^{-1} using SEM-EDAX.



Scheme 1. *N*-Arylation of *N*-heterocycles with bromo- or iodoarenes.

Keywords: CuFAP; *N*-Arylation; Heterocycles; Heterogeneous catalyst.

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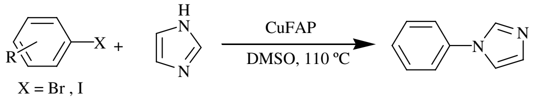
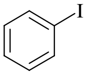
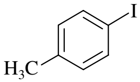
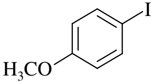
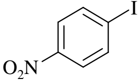
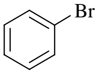
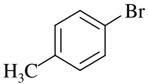
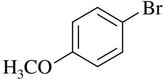
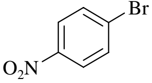
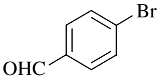
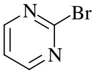
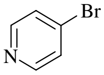
To identify the best system for *N*-arylation of imidazole with bromobenzene,[9] a variety of bases were screened and it was found that CuFAP catalyst with K_2CO_3 (2 equiv) afforded a good yield (90%) in DMSO at 110 °C. A control reaction conducted under identical conditions devoid of CuFAP gave no coupled product. CuFAP was recovered quantitatively by simple filtration and reused, which gave consistent activity even after a fourth cycle (Table 1, entry 5). Moreover, the absence of copper in the filtrate was confirmed by AAS, which reiterates that no leaching of copper occurred during the reaction and provides evidence for heterogeneity throughout the reaction.

We chose a variety of substituted bromo- and iodoarenes possessing a wide range of functional groups for our study, to demonstrate the scope and the generality of the CuFAP promoted *N*-arylation of imidazole with K_2CO_3 as base, and the results are summarized in Table 1. 2-Bromopyridine, 2-bromopyrimidine and bromobenzenes with electron-withdrawing groups, such as 4-nitro bromobenzene and 4-bromobenzaldehyde, provided excellent yields in short reaction times (Table 1, entries 8–11) compared with bromobenzene. Bromobenzenes with electron-donating groups such as 4-bromotoluene and 4-bromoanisole, took longer reaction times with moderate yields (Table 1, entries 6 and 7). Among the iodoarenes tested, iodobenzenes with electron-withdrawing groups underwent smooth reaction with excellent yields compared to iodobenzene with electron-donating groups (Table 1, entries 2–4). As expected iodobenzene provided good yields in a shorter time than bromobenzene (Table 1, entry 1).

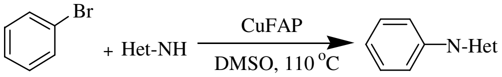
Table 1. *N*-Arylation of imidazole with bromo- or iodoarenes[a]

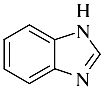
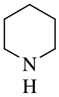
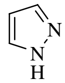
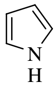


Entry	Aryl halide	Time (h)	Yield[b] (%)
1		6	92
2		14	90
3		14	91
4		3	95
5		10	90, 89[c]
6		15	88
7		15	85
8		4	95
9		8	90
10		2	98
11		6	92

[a] Reaction conditions: aryl halide (1 mmol), imidazole (1.2 mmol), CuFAP (0.1 g), DMSO (5 mL), 110 °C.
[b] Isolated yields.
[c] Yield after fourth cycle.

Table 2. *N*-Arylation of various nitrogen heterocycles[a]



Entry	*N*-Het	Time (h)	Yield[b] (%)
1		15	88
2		12	90
3		10	92
4		10	89

[a] Reaction conditions: aryl halide (1 mmol), Het-NH (1.2 mmol), CuFAP (0.1 g), DMSO (5 mL), K_2CO_3 (2 equiv), reaction, 110 °C.
[b] Isolated yields.

In order to expand the scope of the methodology, a variety of other nitrogen containing heterocycles, such as benzimidazole, pyrrole, pyrazole and piperidine, were successfully coupled with bromobenzene to give the corresponding *N*-arylated products in good yields. Among these heterocycles, piperidine and pyrrole gave the corresponding *N*-arylated products in good yields in short periods (Table 2, entries 3 and 4).

In conclusion, we have developed a simple and efficient method for *N*-arylation of heterocycles using CuFAP as a heterogeneous catalyst. Various bromo- and iodoarenes were coupled with *N*-heterocycles to yield the corresponding *N*-arylated products with good to excellent yields (85–98%). The catalyst can be readily recovered and reused. This methodology may find widespread use for the preparation of *N*-arylated products.

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9. A typical procedure for *N*-arylation of imidazole with bromobenzene: Bromobenzene (157 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), potassium carbonate (276 mg, 2 mmol) and the catalyst (CuFAP, 100 mg) were stirred in DMSO (5 mL) at 110 °C for 10 h. After 10 h, the catalyst was filtered and the filtrate was quenched with aq sodium hydrogen carbonate and the product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and concentrated in vacuo to give the crude product. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 70/30) to afford *N*-phenylimidazole (130 mg, 90%, Table 1, entry 5). The spectroscopic data for the known products compared well with the reported data and melting points.
   1-Phenyl-1*H*-imidazole (Table 1, entry 5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.50–7.30 (m, 5H), 7.25 (br s, 1H), 7.18 (br s, 1H); EI-MS: 144 (100%), 117, 77, 51 GC/MS: $t_R = 16.20$ min; m/z: 144.20; IR: (thin film/neat): cm^{-1}: 3424, 3117, 1600, 1509, 1304, 1253, 1110, 1058, 908, 760, 690, 659, 520.