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Short communication

CuI/L-histidine catalyzed *N*-arylation of heterocycles

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Abstract

CuI/L-histidine is an effective catalyst for *N*-arylation of heterocycles, using K_2CO_3 as base in DMSO solvent. *N*-Arylated products were isolated in good to excellent yields, demonstrating the versatility of the reaction.

Keywords: *N*-Arylation; Heterocycles; Histidine

1. Introduction

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 iodo-arenes by Buchwald and co-workers [2], Lam et al. [3] and exhaustive arylation with several nucleophiles by Taillefer and co-workers [4] using copper catalysts in the presence of basic ligands generated great interest in industry.

In the past years, there was a enormous progress on Ullmann type coupling reactions in homogenous catalysis, which relied on the utilization of some bidentate additives such as aliphatic diamines [2], ethylene glycol [5a], diethylsalicylamide [5b], 1,10-phenanthroline and its derivatives [6], oxime-type and Schiff base ligands [4], thiophene-2-carboxylate [7] and later Ma and co-workers explored various amino acids, which are excellent promoters for copper-catalyzed Ullmann type coupling reactions [8].

Recently, we reported the preparation of recyclable heterogeneous Cu-exchanged fluoroapatite and copper-exchanged *tert*-butoxyapatite catalysts, by incorporating basic species F^-/*t*-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 [9a]. We also explored bromo and iodoarenes for such coupling [9b].

L-Histidine is an essential amino acid in living systems and recognized as a precursor to the allergy symptom producing hormone histamine. L-Histidine is required by body to regulate and utilize essential trace minerals such as copper, zinc, iron, manganese and molybdenum. L-Histidine is essential in forming many metal bearing enzymes and compounds, examples being the antioxidant super oxide dismutase, the iron storage protein ferritin. Metals such as zinc, copper and nickel are transported by binding with L-histidine, and such binding appears essential for rapid excretion of excess metal. Thus, such an important amino acid *in vivo* that has great capability of forming complexes with Cu [10] and Zn is less explored as a ligand in organic transformations.

Thus, in continuation of our work on *N*-arylation, we here in report *N*-arylation of heterocycles catalyzed by CuI/L-histidine (Scheme 1).

2. Experimental

All chemicals used were purchased from Aldrich or Fluka and used without further purification. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F254 plates. All the other solvents were obtained from commercial sources and purified using standard methods.

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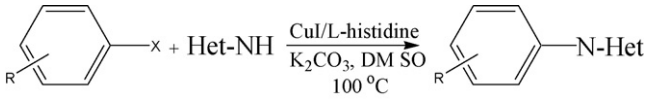


Scheme 1. *N*-Arylation of *N*-heterocycles catalyzed by CuI/L-histidine.

2.1. A typical procedure for N-arylation of imidazole with bromobenzene

CuI (0.1 mmol), L-histidine (0.2 mmol) in 5 mL DMSO was stirred in a preheated oil bath (100 °C) under nitrogen condition for 30 min, after 30 min bromobenzene (157 mg, 1 mmol), imidazole (81 mg, 1.2 mmol) and potassium carbonate (276 mg, 2 mmol) was added, and the reaction was continued for 36 h. After 36 h, the reaction mixture was washed with aqueous sodium hydrogen carbonate and the product was extracted in ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. 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 (119 mg, 82%, Table 1, entry 5). The spectroscopic data for the known products compared well with the reported data and melting points.

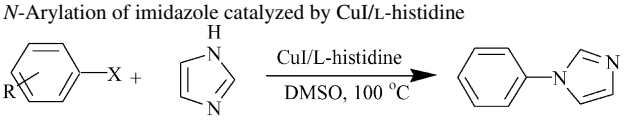
1-Phenyl-1*H*-imidazole (Table 1, entry 5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.50–7.30 (m, 5H), 7.25 (br s, 1H), 7.18 (br s, 1H); EI-MS: 144 (100%), 117, 77, 51; GC/MS: t_R = 16.20 min; *m/z*: 144.20; IR: (thin film/neat): 3424, 3117, 1600, 1509, 1304, 1253, 1110, 1058, 908, 760, 690, 659, 520 cm^{-1}.

3. Results and discussion

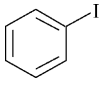
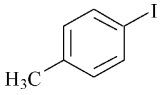
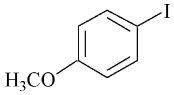
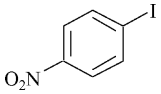
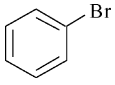
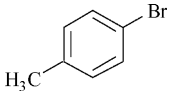
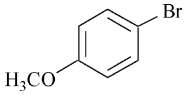
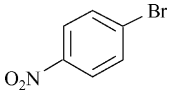
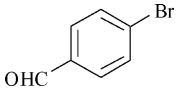
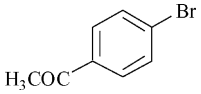
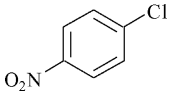
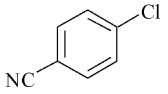
To identify the best system for *N*-arylation of imidazole with bromobenzene, a variety of bases and solvents were screened and it was found that CuI/L-histidine catalyst with K_2CO_3 (2 eq) afforded a good yield (82%) in DMSO at 100 °C where as K_3PO_4, *t*-BuOK gave moderate yields (43 and 47%, respectively) and Cs_2CO_3 showed equal activity as K_2CO_3 (83%). Among the solvents screened, DMSO has proven to be the best solvent where as DMF and NMP gave moderate yields (48 and 41%, respectively) and PEG 400 provided good yields (75%). A control reaction conducted under identical conditions devoid of Cu/L-histidine gave no coupled product despite prolong reaction time.

We chose a variety of substituted bromo- and iodo-arenes possessing a wide range of functional groups for our study to demonstrate the scope and the generality of the CuI/L-histidine promoted *N*-arylation of imidazole with K_2CO_3 as base, we also screened a couple of examples of electron withdrawing chloroarenes and the results are summarized in Table 1. Bromobenzenes with electron withdrawing groups, such as 4-nitro bromobenzene and 4-bromobenzaldehyde, provided excellent yields in short reaction times (Table 1, entries 8 and 9) 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). A couple of electron withdrawing chlorobenzenes such as 4-chloronitrobenzene and 4-chlorobenzonitrile were coupled with

Table 1
N-Arylation of imidazole catalyzed by CuI/L-histidine

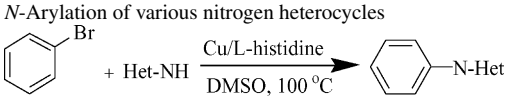


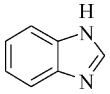
X = Br , I, Cl

Entry	Aryl halide	Time (h)	Yield (%)[a]
1		18	91
2		30	89
3		30	86
4		15	91
5		36	82
6		48	71
7		48	70
8		30	92
9		36	86
10		36	83
11		36	78
12		48	43

Reaction conditions: Aryl halide (1 mmol), imidazole (1.2 mmol), CuI (0.1 mmol), L-histidine (0.2 mmol), DMSO (5 mL), 100 °C.
[a] Isolated yields.

Table 2
N-Arylation of various nitrogen heterocycles



Entry	*N*-Het	Time (h)	Yield (%)[a]
1		48	70
2		48	66
3		48	56

Reaction conditions: Aryl halide (1 mmol), Het-NH (1.2 mmol), CuI (0.1 mmol), L-histidine (0.2 mmol), DMSO (5 mL), K_2CO_3 (2 eq), reaction, 100 °C.
[a] Isolated yields.

imidazole in moderate yields (Table 1, entries 11 and 12). Moreover, in all the cases <4% (which was monitored by GC) of side products was observed and this may be due to *N*-arylation of L-histidine. To the best of our knowledge this is the first soluble copper complex activating chloroarenes at such a low temperature (100 °C). Recently Liu et al. reported *N*-arylation of chloroarenes at 130 °C using 8-hydroxyquinoline as ligand [11].

In order to expand the scope of the methodology, a variety of other nitrogen containing heterocycles such as benzimidazole, pyrrole and pyrazole, were successfully coupled with bromobenzene to give the corresponding *N*-arylated products in moderate yields. Among these heterocycles tested, benzimidazole gave the corresponding *N*-arylated products in good yields compared with pyrazole and pyrrole (Table 2, entries 1–3).

4. Conclusions

In conclusion, we have developed a simple and efficient method for *N*-arylation of heterocycles using Cu/L-histidine as catalyst. Various bromo, iodoarenes and couple of electron withdrawing chlorobenzenes were coupled with *N*-heterocylces to yield the corresponding *N*-arylated products with moderate to good yields. Thus, this methodology may find widespread use for the preparation of *N*-arylated products.

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