Ligand-free copper-catalysed coupling reaction of heteroaryl bromides with imidazole and benzimidazole

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The synthesis of *N*-heteroarylimidazoles by coupling heteroaryl bromides with imidazole or benzimidazole under relatively mild conditions using the stable and readily available copper(II) acetate as catalyst and cesium carbonate as base is reported to give products in moderate to good yields.

Keywords: copper, coupling reaction, imidazole, heteroaryl bromide

N-Arylimidazoles and *N*-heteroarylimidazoles are employed in the synthesis of pharmaceutical, and biological compounds.[1-5] Traditionally these compounds were synthesised via a nucleophilic aromatic substitution by an imidazole of aryl halides bearing electron-withdrawing substituents or via an Ullmann-type coupling at high temperature.[6-10] It is not surprising that newer and milder transition-metal catalysed approaches have been pursued in recent years. Indeed, mild conditions have been achieved by either using organometallic reagents[11-14] instead of aryl halides as the coupling substrates or by employing palladium complexes as the catalyst.[15-18] However, the former normally needs an additional step to convert the aryl halides into the corresponding organometallic reagents and the latter requires relatively expensive and air-sensitive catalysts. Recently, Buchwald, Taillefer and others have discovered that the *N*-arylation of nitrogen-containing heterocycles by readily available aryl halides could be carried out under milder conditions in the presence of nitrogen and/or oxygen based ligands such as 1,10-phenanthroline,[19,20] diamines,[21-23] salicylamides,[24,25] amino acids[26,27] and 8-hydroxyquinoline.[28] This has led to a resurgence of interest in Ullmann-type coupling reactions due to the economic attractiveness of copper. In addition, it is worth noting that copper precursors in various oxidation states(0,I,II) are catalytically active in some Cu-catalysed *N*-arylation reaction.[29,30] However, most of the significant results have been achieved by copper(I) complexes.

Ligand-free Ullmann-type *N*-arylation reactions are rare[31-33] and the development of a versatile and experimentally simple, ligand-free catalytic system is desirable from an economical perspective. Quite recently, Liu reported a novel microwave-assisted ligand-free protocol for the amination of aryl halides with various amines promoted by $Cu(OAc)_2$ in the presence of DBU.[34] However, this method needed stoichiometric amounts of copper reagents and a sharp decrease in yield was observed under conventional thermal condition. On the other hand, only a few reports on the *N*-arylation of imidazole or benzimidazole with nitrogen- or sulfur-containing heteroaryl halides have appeared.[35-39] We now report the successful synthesis of *N*-heteroarylimidazoles using stable and inexpensive catalytic amount copper(II) acetate in the cross-coupling reaction between heteroaryl halides and imidazole or benzimidazole without requiring any additional ligand.

Initially, the coupling reaction between 2-bromothiophene and imidazole was chosen as a model reaction. In the presence of 10 mol% of $Cu(OAc)_2{\cdot}H_2O$ and 2 equiv of K_2CO_3 in DMSO at 120 °C under a nitrogen atmosphere and without the aid of any ligand, the reaction afforded the desired cross-coupling product in 45% yield. Encouraged by this result, we continued our studies to improve the yield of product by the optimisation of reaction conditions. Among the solvents tested, DMSO was clearly the best choice, DMF and acetonitrile provided slightly lower yields, while less polar solvents like toluene and 1,4-dioxane delivered little of the desired coupling product (Table 1, entries 1–5). Then the effect of base was evaluated. Inorganic bases such as K_2CO_3, Cs_2CO_3, Na_2CO_3, NaOAc, K_3PO_4 were superior to organic bases such as triethylamine and tributylamine. Cs_2CO_3 was found to be the best base (entries 6–11). In addition, the yield was significantly improved when the amount of $Cu(OAc)_2{\cdot}H_2O$ was graually increased from 10 to 20 mol%. No obvious improvement was observed when the amount of $Cu(OAc)_2{\cdot}H_2O$ was increased further. Hence, 20 mol% $Cu(OAc)_2{\cdot}H_2O$ was the optimum loading. Furthermore using anhydrous $Cu(OAc)_2$ as the catalyst afforded *N*-thiophenylimidazole in a similar yield, i.e. the presence of water in the $Cu(OAc)_2{\cdot}H_2O$ did not influence the performance of this catalytic system (entry 14). Finally, a blank test without copper(II) acetate was carried out, and almost no product was detected under these conditions.

Table 1 *N*-arylation of 2-bromothiophene with imidazole in different conditions

Entry	Solvent	Base	Time/h	Yield/%[a]
1	DMSO	K_2CO_3	24	45
2	DMF	K_2CO_3	24	30
3	Acetonitrile	K_2CO_3	24	28
4	Toluene	K_2CO_3	24	<5
5	1,4-dioxane	K_2CO_3	24	12
6	DMSO	Cs_2CO_3	24	55
7	DMSO	Na_2CO_3	24	30
8	DMSO	NaOAc	24	25
9	DMSO	K_3PO_4	24	32
10	DMSO	Et_3N	36	<5
11	DMSO	Bu_3N	36	<5
12[b]	DMSO	Cs_2CO_3	24	62
13[c]	DMSO	Cs_2CO_3	24	72
14[d]	DMSO	Cs_2CO_3	24	71

[a]Isolated yield [b]$Cu(OAc)_2{\cdot}H_2O$ (0.15 mmol) [c]$Cu(OAc)_2{\cdot}H_2O$ (0.20 mmol) [d]$Cu(OAc)_2$ (0.20 mmol) as the catalyst.

Using the optimised reaction conditions, we explored the general applicability of $Cu(OAc)_2{\cdot}H_2O$ with different heterocyclic bromides and imidazole or benzimidazole, and the results are shown in Table 2. It was found that 2-bromopyridine worked well, affording the corresponding product in satisfactory yields (Table 2, entries 3, 4). For 3-bromopyridine and 3-bromoquinoline, the yields were slightly lower under the same conditions (entries 1, 2, 5). Thienyl halides such as 3-bromothiophene, 2-bromothiophene and 2-bromo-5-ethylthiophene gave rise to good yields (entries 6-13). The reaction seemed sensitive to the steric hindrance on the nucleophilic reagents. Indeed, compared with the coupling of heterocyclic bromides with imidazole, the yields were relatively lower when benzimidazole was used. We also employed 2-methylimidzaole as a nucleophilic reagent but it only gave a moderate yield (entries 8, 12).

In summary, we have developed an efficient and relatively mild method to synthesise *N*-heteroarylimidazoles using air-

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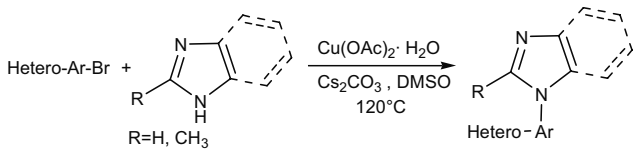
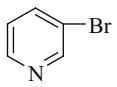
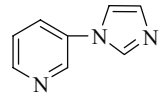
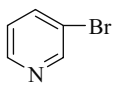
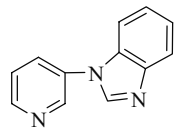
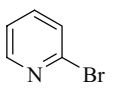
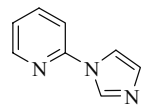
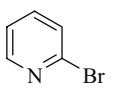
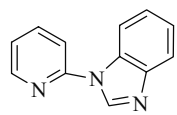
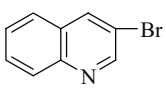
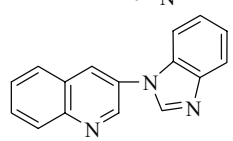
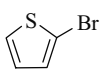
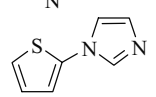
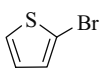
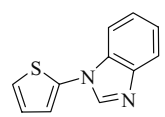
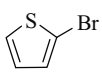
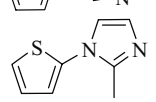
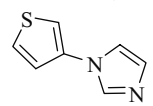
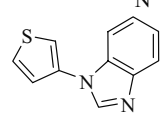
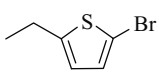
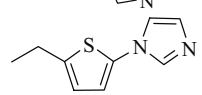
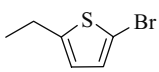
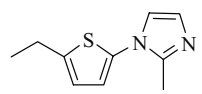
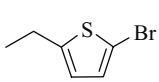
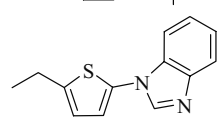
Table 2 *N*-Arylation of heteroaryl bromides with imidazole and benzimidazole



Entry	Substrates	Product	Yield/%[a]	M.p./°C[lit.]
1			68	Oil
2			65	88–90 [lit.[37] 89–91]
3			88	37–39 [lit.[40] 38–40]
4			83	59–60 °C [lit.[41] 59–60 °C]
5			65	138–141 [lit.[18] 139–141]
6			72	Oil
7			66	Oil
8			40	Oil
9			64	80–82 [lit.[41] 82–83]
10			58	89–91 [lit.[41] 90–91]
11			70	Oil
12			41	Oil
13			64	Oil

[a]Isolated yield.

stable and inexpensive copper(II) acetate as catalyst in the absence of any ligand. Further investigation of the scope and application of this reaction is currently underway.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz with Bruker Avance 300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Melting points were obtained of a XT4A melting point apparatus and were uncorrected. Elemental analyses were performed by VARIO.E13, Germany. GC analyses were conducted using a Trace GC/Thermo Finnigan equipped with an SE-54 capillary column (25 m) and an FID detector. All reagents were used as received.

General procedure for the N-arylation of imidazole and benzimidazole
Heteroaryl halide (1 mmol), imidazole or benzimidazole (1.5 mmol), Cs_2CO_3 (2.0 mmol), DMSO (1.5 mL) and $Cu(OAc)_2{\cdot}H_2O$ (0.20 mmol) were placed in a 25 mL two-neck flask. The mixture was stirred and heated at 120 °C under a nitrogen atmosphere for the required

time. After cooling to room temperature, the product was diluted with H_2O, extracted with EtOAc, washed with H_2O and brine. The extract was dried over $MgSO_4$, filtered, and the solvent evaporated. The residue was purified by chromatography on silica gel to obtain the desired products. The purity of the isolated product was determined by GC analysis. The known compounds were characterised by ^{1}H NMR and melting points (where applicable) comparisons with those of authentic samples. The spectra data of unknown compounds are as follows.

1-(5-Ethylthiophen-2-yl)-1H-imidazole (Table 2, entry 11): Viscous oil, purity: 98.5%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, 3H, J = 7.5 Hz), 2.76–2.83 (m, 2H), 6.62 (d, 1H, J = 3.6 Hz), 6.76 (d, 1H, J = 3.6 Hz), 7.12 (s, 2H), 7.69 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.74, 23.57, 118.86, 120.30, 122.12, 129.89, 135.88, 137.07, 144.29. Anal. Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72. Found: C, 60.70; H, 5.78; N, 15.68%.

2-Methyl-1-(5-ethylthiophen-2-yl)-1H-imidazole (Table 2, entry 12): Viscous oil, purity: 98.0%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.5 Hz), 2.36(s, 3H), 2.78–2.87 (m, 2H), 6.66 (d, 1H, J = 3.6 Hz), 6.75 (d, 1H, J = 3.5 Hz), 6.98 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.48, 15.68, 23.67, 121.90, 121.92, 122.16, 123.24, 127.54, 135.58, 146.29. Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57. Found: C, 62.62; H, 6.35; N, 14.50%.

1-(5-Ethylthiophen-2-yl)-1H-benz[d]imidazole (Table 2, entry 13): Viscous oil, purity: 97.6%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, 3H, J = 7.5 Hz), 2.84–2.91 (m, 2H), 6.76 (d, 1H, J = 3.6 Hz), 6.94 (d, 1H, J = 3.6 Hz), 7.31–7.35 (m, 2H), 7.53–7.56 (m, 1H), 7.82–7.85 (m, 1H), 8.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.75, 23.73, 110.61, 120.47, 121.89, 122.29, 123.02, 123.95, 133.82, 134.84, 143.28, 143.50, 145.85. Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.38; H, 5.30; N, 12.27. Found: C, 68.45; H, 5.35; N, 12.15%.

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