Copper complex-catalyzed C-N coupling reaction of aryl iodides with nitrogen-containing heterocycles

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Abstract: An efficient and new method for the copper-catalyzed arylation of nitrogen-containing heterocycles is reported using 3-(diphenylphosphino)propanoic acid as an efficient ligand. The combination of CuCl and 3-(diphenylphosphino)propanoic acid is very efficient for C-N coupling reactions to afford various N-arylated products in good to excellent yields.

Keywords: Copper, Arylation, Heterocycles, 3-(Diphenylphosphino)propanoic acid

Introduction

The ability to construct N-arylated nitrogen compounds efficiently is currently an active area in organic synthesis due to their wide applications in different medicinal and natural products\textsuperscript{1-10}.

The classical approaches to synthesis of compounds bearing an arylated nitrogen moiety\textsuperscript{11-15} are based on the aromatic nucleophilic substitution reaction (S\textsubscript{N}Ar) of nitrogen nucleophiles with activating aryl halides or classical Ullmann\textsuperscript{16,17} coupling at higher temperature\textsuperscript{18-20}.

However, each of these methods suffer from different drawbacks such as high reaction temperatures (often 150 °C or as high as 200 °C), tedious work-ups, use of very expensive palladium catalysts, use of stoichiometric amount of Cu salt that make scale up unfeasible and ecologically unfriendly, the use of toxic and air-sensitive aryl coupling reagents that can be difficult to access, and excess aryl halide starting materials to achieve reasonable product
yields, low to moderate yields, sensitivity of the substituted aryl halide to the harsh reaction conditions and poor substrate generality.\textsuperscript{16-20} Thus, it is desirable to develop a convenient and simple method for the copper-catalyzed arylation of nitrogen-containing heterocycles.

Among various methods for the transition copper-catalyzed arylation of nitrogen-containing heterocycles with aryl halides, diamine, amino acid, diamines, Schiff-bases, \([1,10]-\text{phenanthroline}, \text{quinoline, aminoarenethiol, and oxime-phosphine oxide as effective ligands have been investigated.}\textsuperscript{21-24} In spite of these methods, there are no reports on the synthesis of \(N\)-arylated nitrogen compounds via arylation of nitrogen-containing heterocycles using 3-(diphenylphosphino)propanoic acid as an efficient ligand. Thus, the development of a new system for the synthesis of \(N\)-arylated nitrogen compounds still remains an active research area.

As part of our ongoing interest in nitrogen-containing compounds chemistry and synthesis of heterocyclics,\textsuperscript{25,26} we now wish to report the copper-catalyzed arylation of nitrogen-containing heterocycles with aryl iodides in the presence of 3-(diphenylphosphino)propanoic acid as a new ligand (1) under thermal conditions (Scheme 1).

\[
\text{ArI + Het-NH} \xrightarrow{\text{CuCl, Ligand 1, NaOH}} \text{DMF, 120° C, 14h} \rightarrow \text{Het-NAr}
\]

\textbf{Scheme 1}

\textbf{Results and Discussion}

Usually the ligands play an important role for a successful copper-catalyzed C-N coupling reaction. For optimization of the reaction conditions, we chose the reaction of 4-methoxyphenyl iodide with imidazole in the presence of various copper catalysts and ligand 1 as the model reaction, and the effects of the base and solvents were examined. First, several solvents were screened for the reaction. According to data given in Table 1, DMSO was the most efficient solvent for this reaction (Table 1, entry 5). After choosing DMSO as the
solvent, we examined several different Cu source and bases. As shown in Table 1, among the various Cu sources tested in the presence of 1 as ligand, CuCl led to significant conversion. Also, the reaction was influenced significantly by the base employed and the best result obtained in the case of NaOH (Table 1, entry 5). The best result was obtained with 1 (20.0 mol %), CuCl (15.0 mol %), 4-methoxyphenyl iodide (1.0 mmol), imidazole (1.4 mmol), NaOH (2.0 mmol) and DMSO (4 mL) which gave the product in a good yield (94%).

Increasing the amount of ligand 1 and copper salt showed no substantial improvement in the yield. Next, using the optimized procedure, a series of aryl iodides possessing both electron-releasing and electron-withdrawing groups were employed (Table 2). This newly developed Cu-catalyzed amination protocol was also applied to various nitrogen-containing heterocycles (Table 2). In all cases, this protocol afforded the desired products in good to excellent yields. Due to its electronic and steric nature, we also tested the N-arylation of imidazole with 2-iodotoluene. As shown in Table 2, reaction of 2-iodotoluene with imidazole afforded good yield (Table 2, entry 3). The arylations of aryl iodides with 1H-benzimidazole and 1H-1,2,4-triazole afforded the corresponding N-arylated products in reasonable yields (Table 2, entry 12,13).

Several similar mechanisms have been reported for the palladium or copper-catalyzed amination of nitrogen-containing heterocycles using various ligands. Similar to other ligands, ligand 1 can coordinate with copper via the oxygen and phosphorus atoms.

### Table 1 Copper-catalyzed amination of imidazole with 4-methoxyphenyl iodide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu source (mol %)</th>
<th>Ligand (mol %)</th>
<th>Solvent</th>
<th>Base (mol %)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl (15)</td>
<td>20</td>
<td>Toluene</td>
<td>NaOH</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuCl (15)</td>
<td>20</td>
<td>Dioxane</td>
<td>NaOH</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CuCl (15)</td>
<td>20</td>
<td>MeOH</td>
<td>NaOH</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CuCl (15)</td>
<td>20</td>
<td>DMF</td>
<td>NaOH</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>CuCl (15)</td>
<td>20</td>
<td>DMSO</td>
<td>NaOH</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>CuCl (15)</td>
<td>20</td>
<td>DMSO</td>
<td>Et3N</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>CuCl (15)</td>
<td>20</td>
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<td>K2CO3</td>
<td>20</td>
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<tr>
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<td>Na2CO3</td>
<td>18</td>
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<tr>
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<td>20</td>
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<td>K2PO4</td>
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<td>NaOH</td>
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<td>NaOH</td>
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<td>NaOH</td>
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<tr>
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<td>78</td>
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<tr>
<td>14</td>
<td>CuCl (15)</td>
<td>25</td>
<td>DMSO</td>
<td>NaOH</td>
<td>95</td>
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</tbody>
</table>

*General reaction conditions: imidazole (1.4 mmol), 4-methoxyphenyl iodide (1.0 mmol), Cu source (15 mol %), Ligand 1 (20.0 mol %), base (2.0 mmol), DMSO (4 mL), 120 °C, 14 h, pressure tube, N2 atm. b) Yields are after work-up.
In summary, a new and simple method has been developed for the copper-catalyzed arylation of nitrogen-containing heterocycles using 3-(diphenylphosphino)propanoic acid as an efficient ligand under thermal conditions. The significant advantages of this methodology are high yields and a simple work-up procedure. Further investigations on the application of this system on other catalytically synthetic reactions are in progress.

**Experimental**

**General**

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. 3-(Diphenylphosphino)propanoic acid as ligand was purchased from the Aldrich chemical company. Products were characterized by comparison of their physical and spectral data with authentic samples. The NMR spectra were recorded in DMSO. 

$^1$H NMR spectra were recorded on a Bruker Avance DRX 250 MHz instruments. The chemical shifts ($\delta$) are reported in ppm relative to the TMS as an internal standard and $J$ values are given in Hz. 

$^{13}$C NMR spectra were recorded at 62.5 Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. TLC was performed on silica gel polygram SIL G/UV 254 plates.
General procedure for the copper-catalyzed arylation of nitrogen-containing heterocycles with aryl iodides

To a mixture of CuCl (15.0 mol %) and ligand 1 (20.0 mol %) in DMF (2.0 mL), aryl iodide (1.0 mmol), NaOH (2.0 mmol), NH-containing heterocycle (1.4 mmol) and DMF (2.0 mL) was added and the mixture was vigorously stirred at 120 ºC for 14 h under a dry nitrogen atmosphere. After completion (as monitored by TLC), H2O was added and the organic layer was extracted with EtOAc, washed with brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography. The purity of the compounds was checked by 1H NMR and yields are based on aryl iodide. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature.27-31

Acknowledgements. We gratefully acknowledge from the Soran University for the support of this work.

References