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Copper Catalysed Direct Amidation of Methyl Groups with N-H Bonds

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An efficient copper catalyzed direct aerobic oxidative amidation of methyl groups of azaarylmethanes with N-H bonds producing amides is successfully developed, which can produce primary, secondary and tertiary amides, including those with functional groups. This reaction represents a straightforward method for the preparation of amides from the readily available hydrocarbon starting materials.

Introduction

New green synthetic reactions via direct transformations of inert chemical bonds play an important role in sustainable chemistry.1-3 In this regard, the cleavage and functionalization of C-H bonds have attracted extensive interests.2 The direct functionalization of C-H bonds can short-cut the synthetic procedures and is the most straightforward way for the generation of valuable chemicals.2 Aromatic amides are one of the basic starting materials for industry. They are also important building blocks for the synthesis of fine chemicals such as pharmaceuticals, natural products and functional materials. Current methods4-9 for their preparation are based on the transformations of carboxylic acids derivatives,5 organohalides,6 amides,7 alcohols8 and aldehydes9 etc. These reactions are based on the functional group transformations and require preactivation, prefunctionalization or a strong oxidant, suffering from low atom-economic efficiency. No need to say, the direct aerobic oxidative amidation of methyl groups with N-H bonds is the most economic and clean way for the preparation of such compounds (eqn 1). However, to date, this strategy has only met with limited success.10

\[
\text{R}_1\text{N} - \text{H} + \text{NH}_4\text{OAc} + \text{Cu} + \text{air} \rightarrow \text{R}_1\text{N} - \text{O} - \text{N} - \text{R}_2
\]

Herein, we report an efficient copper catalysed synthesis of amides 2 via the direct aerobic oxidative amidation of the methyl groups of azaarylmethane 1 with N-H bonds (Scheme 1). All kinds of amides (primary, secondary and tertiary) 2, including those with functional groups, can be prepared from the readily available 1.

Scheme 1 Copper-catalysed aerobic oxidative amidation of azaarylmethanes 1 forming amides 2.

Results and Discussion

We initiate this study by examining the reactivity of 2-methylquinoline 1a with ammonium salts in the presence of a metal catalyst under oxygen atmosphere and the obtained results are compiled in Table 1. After an extensive screening on the conditions and catalysts, we found that copper salts and the metallic copper served as the catalysts for the direct aerobic oxidative amidation reaction to produce the corresponding amide 2a in high yields. Thus, under an atmospheric oxygen, a mixture of 1a (0.2 mmol) and NH4OAc (0.8 mmol) in dioxane (1.0 mL) was heated at 130 °C overnight to produce quinoline-2-carboxamide 2a in 88% yield (entry 1). Other copper compounds such as CuBr2, Cu(OAc)2, CuBr, CuI and Cu2O also similarly catalysed this aerobic oxidative dehydrogenative amidation to give 2a in good yields (entries 2-6). Interestingly, metallic copper also efficiently catalysed this reaction to produce 2a in 88% yield (entry 7). Noteworthy, copper is essential for this reaction. In the absence of copper, 2a could not be obtained at all (entry 8). FeCl3 and PdCl2 were also not effective for this transformation under similar reaction conditions (entries 9 and 10). In addition to dioxane, the reaction also took place readily in PhOMe, toluene and DMF, but hardly proceeded in Cl2CH2CH2Cl2 and DMSO (entries 11-15). As to the ammonium source, urea and ammonia only gave traces amount of the product and NH4Br did not produce...
2a at all (entries 16-18). These results indicate that a suitable pH condition would be essential.

Table 1 Metal-catalysed aerobic oxidative amidation of 2-methylquinoline with ammonium.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>[N]</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl2</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>CuBr2</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)2</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>CuBr</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>76%</td>
</tr>
<tr>
<td>6</td>
<td>Cu2O</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>71%</td>
</tr>
<tr>
<td>7</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>88%(none)</td>
</tr>
<tr>
<td>8</td>
<td>FeCl3</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>PdCl2</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>PhOMe</td>
<td>74%</td>
</tr>
<tr>
<td>12</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Toluene</td>
<td>62%</td>
</tr>
<tr>
<td>13</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>DMF</td>
<td>48%</td>
</tr>
<tr>
<td>14</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>DMSO</td>
<td>10%</td>
</tr>
<tr>
<td>15</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Cl3CHCHCl2</td>
<td>11%</td>
</tr>
<tr>
<td>16</td>
<td>Cu</td>
<td>urea</td>
<td>Dioxane</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>17</td>
<td>Cu</td>
<td>NH4Br</td>
<td>Dioxane</td>
<td>9%</td>
</tr>
<tr>
<td>18</td>
<td>Cu</td>
<td>NH4OAc</td>
<td>Dioxane</td>
<td>none</td>
</tr>
</tbody>
</table>

* Conditions: 2-methylquinoline (0.2 mmol), ammonium source (0.8 mmol based on nitrogen), 10 mol% catalyst, solvent (1 mL), 1 atm O2, 24 h, in a 25 mL sealed tube. * GC yields using dodecane as an internal standard. * Yield in the bracket under N2 atmosphere.

This copper catalysed direct aerobic oxidative amidation of methyl groups with N-H bonds could be readily applied to other substrates to produce the corresponding amides. As shown in Table 2, a variety of 2-methylquinoline analogues with either an electron-donating or electron-withdrawing group, all were converted readily to the corresponding amides efficiently (entries 1-12). Thus, in addition to 2-methylquinoline, the direct oxidative amidation of 4-methylquinoline was achieved (entry 2). High yields of the amides were also obtained from 2-methylquinoline analogues bearing methyl and methoxy groups (entries 3-5). Very interestingly, substrates with an amino NH2 group (entry 6) and an amido group (entry 7) could also be used in this reaction to produce the corresponding amides.

 Gratifyingly, 2-methylquinolines with fluoro (entry 8), chloro (entry 9) and bromo (entry 10) all served as good substrates to produce the corresponding amides 2h, 2i and 2j in excellent yields. These compounds are versatile starting materials for the synthesis of functional materials via the transformations of the carbon-halogen bonds. Copper catalysed aerobic oxidative amidation of 2-methylquinoline analogues with electron-withdrawing substituents (CO2Me and NO2) were also successfully achieved, giving the desired products 2k and 2l in 61% and 46% yields, respectively (entries 11 and 12). As exemplified by neocuproine, two amido groups could be generated in one pot to produce the corresponding bisamides in good yields (entry 13).

Table 2 Cu-catalysed aerobic oxidative amidation of methyl groups with N-H bonds producing amides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylmethane</th>
<th>N source</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2a</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>2-Me, R = H</td>
<td>NH4OAc</td>
<td>2b</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>4-Me, R = H</td>
<td>NH4OAc</td>
<td>2c</td>
<td>91%</td>
</tr>
<tr>
<td>4</td>
<td>2-Me, R = 6-Me</td>
<td>NH4OAc</td>
<td>2d</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>2-Me, R = 8-OMe</td>
<td>NH4OAc</td>
<td>2e</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>2-Me, R = 4-NH2</td>
<td>NH4OAc</td>
<td>2f</td>
<td>49%</td>
</tr>
<tr>
<td>7</td>
<td>2-Me, R = 4-NH(CO)Bu</td>
<td>NH4OAc</td>
<td>2g</td>
<td>67%</td>
</tr>
<tr>
<td>8</td>
<td>2-Me, R = 6-F</td>
<td>NH4OAc</td>
<td>2h</td>
<td>90%</td>
</tr>
<tr>
<td>9</td>
<td>2-Me, R = 6-Cl</td>
<td>NH4OAc</td>
<td>2i</td>
<td>96%</td>
</tr>
<tr>
<td>10</td>
<td>2-Me, R = 6-Br</td>
<td>NH4OAc</td>
<td>2j</td>
<td>94%</td>
</tr>
<tr>
<td>11</td>
<td>2-Me, R = 6-OMe</td>
<td>NH4OAc</td>
<td>2k</td>
<td>61%</td>
</tr>
<tr>
<td>12</td>
<td>2-Me, R = 6-NO2</td>
<td>NH4OAc</td>
<td>2l</td>
<td>46%</td>
</tr>
<tr>
<td>13</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2m</td>
<td>56%</td>
</tr>
<tr>
<td>14</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2n</td>
<td>93%</td>
</tr>
<tr>
<td>15</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2o</td>
<td>91%</td>
</tr>
<tr>
<td>16</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2p</td>
<td>20%</td>
</tr>
<tr>
<td>17</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2q</td>
<td>48%</td>
</tr>
<tr>
<td>18</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2r</td>
<td>51%</td>
</tr>
<tr>
<td>19</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2s</td>
<td>69%</td>
</tr>
<tr>
<td>20</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2t</td>
<td>60%</td>
</tr>
<tr>
<td>21</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2u</td>
<td>54%</td>
</tr>
<tr>
<td>22</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2v</td>
<td>72%</td>
</tr>
<tr>
<td>23</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2w</td>
<td>66%</td>
</tr>
<tr>
<td>24</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2x</td>
<td>39%</td>
</tr>
<tr>
<td>25</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2y</td>
<td>29%</td>
</tr>
<tr>
<td>26</td>
<td>R1</td>
<td>NH4OAc</td>
<td>2z</td>
<td>41%</td>
</tr>
</tbody>
</table>

* Conditions: 0.2 mmol arylmethane, 0.8 mmol NH4OAc (for an amine: 0.4 mmol amine and 0.2 mmol Ph2PO2H), 10 mol% copper (for an amine: 10 mol% CuI was used), 1 mL dioxane (for an amine: PhOMe was used), 1 atm O2, 130 °C, 24 h. * Isolated yield. * 10 mol% 1,10-phenanthroline and 0.5 mL H2O were used. * 1.6 mmol NH4OAc was added. * 36 h. * 20 mol% copper was loaded. * 10 mol% CuBr was used. * 150 °C. * 74% phenyl(pyridin-2-yl)methanone was produced.
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Other azaarylmethanes with two heteroatoms (entries 14-15) also produced the corresponding amides in high yields under similar reaction conditions. 2-Methylpyridine served well in the current amidative system (entry 17). Interestingly, 2-ethylpyridine also reacted with NH4OAc under similar reaction conditions to produce 2q in 27% yield through the oxidative amidation of carbon-carbon bond (entry 18); however, when 2-benzylpyridine was employed, no 2q was detectable, 74% yield of phenyl(pyridin-2-yl)methanone was produced instead (entry 19). In addition, 2-methylthiazole was employed as the substrate, no products were detected under similar reaction conditions.

In addition to the synthesis of primary amides as described above, it was particularly noteworthy that this strategy of direct aerobic oxidative amidation of methyl groups with N-H bonds is applicable for the preparation of secondary and tertiary amides. As presented by entries 21-26, the reactions of 2-methylquinoline with a variety of anilines took place smoothly to yield the corresponding secondary amides in moderate to good yields. Similar oxidative amidation with isopropylamine took place to generate 2y in 29% yield (entry 27). A tertiary amide 2z was also produced in 41% yield via the reaction of 2-methylquinoline with piperidine under similar reaction conditions (entry 28). To the best of our knowledge, this is the first successful direct aerobic oxidative amidation of aromatic methyl groups with primary and secondary amides.10

In order to clarify the mechanism, control experiments were conducted. It was found that under the reaction conditions, quinoline-2-carbaldehyde 3a was converted to 2a in 61% yield. Interestingly, in the absence of copper, 2a was also afforded in 54% yield, indicating that an aldehyde 3 could be the possible intermediate in the copper catalysed oxidative amidation and the copper catalyst perhaps only worked in the aerobic oxidation of methyl groups (eqn 2).11

In the presence of water, quinoline-2-carbonitrile 6a was hydrolyzed smoothly to give 2a in 92% yield under the standard reaction conditions (eqn 3). It is assumed that copper catalyses the aerobic oxidation of methyl groups to generate aldehydes 3 first.12-15 Quick addition of amine to 3 can afford a carbinolamine 4 which then produces nitrile 6 via dehydration and oxidation. Hydrolysis of the nitrile 6 produces the amide 2 (Scheme 3, path b).10 However, although this reaction path can well explain the formation of primary amides, it cannot explain the formation of secondary and tertiary amides. Therefore, another reaction path (Scheme 3, path a) via the direct oxygenation of carbinolamine 4 to 2 should also operate.12 This direct oxygenation (Scheme 3, path a) perhaps also works, at least partly, for the generation of the primary amide 2a.

13O experiments showed that the oxygen atom in 2a can come from both dioxygen and NH4OAc. The aerobic oxidative amidation of 2-methylquinoline 1a with NH4OAc in the presence of a large excess of H218O produced 85% yield of 2a with a 1:1 ratio of 2a-O18:2a-O16 (eqn 4). Under 18O2 atmosphere, 2a was produced in 43% yield with a 1:1.5 ratio of 2a-O18:2a-O16. The O16 clearly came from NH4OAc (eqn 5).16 It was noted that in the presence of a large excess of H218O, 2a-O16 could not be isomerized to 2a-O18 under similar reaction conditions (eqn 6).

Conclusions

In summary, we have successfully developed an efficient copper catalysed direct aerobic oxidative amidation of aromatic methyl groups with N-H bonds. Mechanistic studies indicate two reactions paths operate in this reaction. Extension of the current direct oxidative amidation to other substrates is underway.

Acknowledgements

We are grateful for the financial support from NSFC 21403062, HNNSF 2015JZ039 and Fundamental Research Funds for the Central Universities (Hunan University).

Notes and references

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A typical procedure: Under an oxygen atmosphere (1 atm), 1a (0.2 mmol), \( \text{NH}_2\text{OAc} \) (0.8 mmol), metallic Cu (0.02 mol) and dioxane (1.0 mL) were placed into a glass tube (25 mL) and sealed. The mixture was heated at 130 °C for 24 h. After removal of the volatiles in vacuum, the residues were purified by chromatography on silica gel (particle size 37-54 μm) using ethyl acetate/petroleum ether as eluent to obtain 85% yield of 2a.


3. In 2012, Mizuno and et al reported that good yields of primary aromatic amines were obtained from methylenes (as solvent) and urea in the presence of MnO₂ (4 equivs) and primary aromatic amides were obtained from methylarenes (as solvent) and urea in the presence of MnO₂ (4 equivs) and water and copper catalyst would promote the amidation via path a.

4. Considering that the reaction did not take place with toluene, rate determining. When the reaction of 2-methylquinoline was treated under the standard reaction conditions, giving 2a without CuI, 39% 10 mol% CuI, 81% 10 mol% CuI, 65% could be confirmed by GC-MS when 2-methylquinoline was treated under the standard reaction conditions.

5. The aerobic oxidation of methyl groups was thought to be rate determining. When the reaction of 2-methylquinoline with \( \text{NH}_2\text{OAc} \) was conducted at 100 °C, no product could be detected, whereas quinoline-2-carboxaldehyde 3a gave 2a in 23% yield under similar reaction conditions.

6. Considering that the reaction did not take place with toluene, 3-methylquinoline and 2-methylthiophene, the nitrogen atom in 1 would be crucial and the methyl group should be located at 2- or 4-position. Besides, suitable pH condition was required. Thus on the basis of these results and reported literatures, a plausible mechanism for the copper catalysed aerobic oxidation of azarurnethanes was proposed below.

16 The O exchange exists between the acetate and water under the reaction conditions. R. L. Redington, *J. Phys. Chem.*, 1976, 80, 229.