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We describe a novel and useful method to provide 1H-indazoles via copper-catalyzed tandem reaction which is triggered by Ullmann-type reaction and followed by N-N bond formation. Arylamines, alkylamines and sulfonamides could smoothly couple with 2-bromoaryl oxime acetates and various 1H-indazoles were formed in good to excellent yields under mild reaction conditions.

Due to a wide range of pharmaceutical activities, the 1H-indazole subunit has caused much attention of synthetic chemists and they have been widely used for anticancer, anti-inflammatory, anti-HIV, antifertility, and contraceptive drugs. Consequently, many methods have been developed for the construction of 1H-indazole frameworks, including classical diazotizations and nitrosation reactions, condensation of hydrazine with ortho-substituted benzaldehydes,[3,6] cycloaddition of arynes with diazo compounds or hydrazones[5–9] and cyclization of arylamino oximes.[9–11] With the development of transition metal catalysis, some transition metal-catalyzed routes to 1H-indazole unit also have been realized. For examples, Voskoboinikov et al. reported a palladium-catalyzed cyclization of arylelthydrozines to form the 1H-indazole derivatives.[12] Copper-catalyzed amination reactions were also used for 1H-indazole subunits.[5] Olmo and coworkers have developed an efficient synthesis for indazoles via N-arylation of hydrazines, followed by intramolecular dehydration.[5a] However, most of these methods have some limitations, such as long reaction time, poor functional group tolerance, low conversion. In addition, the biggest problem is the use of toxic organo-hydrazines. To the best of our knowledge, few examples of constructing 1H-indazoles via the formation of N-N bonds have been reported.[5b,6] Recently, Glorius et al. described an efficient synthesis of 1H-indazoles from arylimides and organo azides via RhIII/CuI-cocatalyzed C-H activation and C-N/N-N bond formations (Scheme 1a).[6] As to such fact, we thought a method which utilized the N–N bond formation to obtain the 1H-indazole unit only using the cheap metal (copper) as catalyst and without use of carcinogenic hydrazines is desired and challenging.

Copper-mediated Ullmann-type reaction was discovered a century ago.[7] However, it has not been fully utilized due to high reaction temperature, limitations of the substrates, and need of stoichiometric copper salts. In recent years, great breakthroughs have been achieved by some research groups,[8] which made Ullmann-type reactions come up with a catalytic amount of copper salts and low temperature. And these breakthroughs also made Ullmann-type reaction a good method to construct C–C, C–O and C–N bonds. In the past several years, oxime esters have been used for the nitrogen-containing heterocycles, such as pyridines,[9] pyrrold,[10] and imidazol[1,2]-pyridines[11] in the presence of copper salts. Based on our previous work on oxime esters[10a,11] and the development of Ullmann-type reactions, we envisioned that we could obtain nitrogen-containing heterocycles via tandem reaction which is triggered by Ullmann-type reactions and then undergo N-N bond formation using oxime acetates not only as substrate but also internal oxidant. Herein, we disclose a novel and efficient strategy for 1H-indazoles from 2-bromoaryl oxime acetates and amines via copper-catalyzed tandem reaction involving a sequential Ullmann-type reaction and N-N bond formation process (Scheme 1b).

Initially, we took the transformation of 1-(2-bromophenyl)ethanone oxime acetate (1a) and aniline (2a) as the model system to screen reaction parameters (Table 1). To our delight, product 3a could be obtained in 71% GC yield when we utilized CuBr (10 mol%) as catalyst and K₂CO₃ as base in DMSO at 120 °C under N₂ atmosphere after 6 h (Table 1, entry 1). Different copper salts such as CuI, CuCl, Cu(OAc)₂, and Cu(OtBu)₂ were also examined in this process (entries 2-5) and CuCl was proved to be the best catalyst, affording product 3a in 86% isolated yield. No product could be observed without copper catalyst (entry 6). The investigation of different bases, including Cs₂CO₃, Na₂CO₃, NaHCO₃, NaH₂PO₄, and Et₃N, indicated that K₂CO₃ was the best choice (entries 7-11). And the yield was decreased to 18% in the absence of base (entry 12). Decreasing the temperature to 100 °C, the yield sharply decreased to 53% and the reason was the Ullmann-type reaction could not proceed smoothly at lower temperature (entry 13). Different solvents such as toluene, DMF, DMA, NMP and MeCN were screened.
acetonitrile could obtain 85% yield, other solvents were not good for this reaction (entries 14-18). Thus, the optimal reaction conditions were 1a (0.5 mmol), 2a (0.6 mmol), CuCl (10 mol %), KO$_2$CO$_3$ (1.0 mmol), in 2 mL DMSO at 120 °C under N$_2$ atmosphere for 6 h.

**Table 1. Optimization of the reaction conditions.**

<table>
<thead>
<tr>
<th>entry</th>
<th>[Cu]</th>
<th>base</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>CuI</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>CuCl</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>92 (86)</td>
</tr>
<tr>
<td>4</td>
<td>CuOTf$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>---</td>
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<td>DMSO</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>CuCl</td>
<td>Cs$_2$CO$_3$</td>
<td>DMSO</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>CuCl</td>
<td>Na$_2$CO$_3$</td>
<td>DMSO</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>CuCl</td>
<td>NaHCO$_3$</td>
<td>DMSO</td>
<td>42</td>
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<tr>
<td>10</td>
<td>CuCl</td>
<td>NaH$_2$SO$_3$</td>
<td>DMSO</td>
<td>11</td>
</tr>
<tr>
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<td>CuCl</td>
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<td>DMSO</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
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<td>---</td>
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<td>18</td>
</tr>
<tr>
<td>13$^a$</td>
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<tr>
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<td>16</td>
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<td>K$_2$CO$_3$</td>
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<td>17</td>
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<td>K$_2$CO$_3$</td>
<td>NMP</td>
<td>37</td>
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<tr>
<td>18</td>
<td>CuCl</td>
<td>K$_2$CO$_3$</td>
<td>MeCN</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: unless otherwise noted, all reactions were performed with 1a (0.5 mmol), 2a (0.6 mmol), catalyst (10 mol %), base (1 mmol) and solvent (2 mL) at 120 °C under N$_2$ atmosphere for 6 h. $^b$ Determined by GC based on 1a. $^c$ Take the reaction at 100 °C.

With the optimum reaction conditions in hand, we started to investigate the scope of amines (Table 2). Various functional groups including methoxyl, fluor, chloro, bromo, nitro, and methylsulfonil could be tolerated at the para-position of aniline and the desired 1H-indazoles 3a-3g were formed in good to excellent yields. 4-Heterocyclic-substituted anilines, such as 4-(oxazol-5-yl)aniline, 4-(1H-pyrrol-1-yl)aniline, and 4-(1H-pyrazol-1-yl)aniline, were also suitable substrates to afford the corresponding 1H-indazoles (3h-3j). When 2-methoxyniline, 3-methoxyniline, 2,6-dimethylanilines and 2,4,6-trimethylanilines were subjected to the reaction system, 3k-3n could be isolated in 76%, 71%, 90% and 84% yields, respectively. In addition, other aromatic or heterocyclic amines even including pyridine ring, which were not usually applicable in copper-catalyzed reactions, could also be transformed to the target products in yields ranging from 78% to 96% (3o-3t). It was exciting that the alkyl amines were good starting materials and the corresponding products could be generated in moderate yields (3u). It was worth mentioning that sulfonamide derivatives could transform into products in good yields, which could bring in useful sulfone functional group (3v-3w).

**Table 2. Cu(I)-catalyzed synthesis of 1H-indazoles from 1-(2-bromophenyl)ethane oxime acetate and amine.**

\[
\begin{array}{cccc}
\text{entry} & 1a & 2 & 3 \\
1 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{DMSO} & 71 \\
2 & \text{CuI} & \text{K}_2\text{CO}_3 & \text{DMSO} & 86 \\
3 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{DMSO} & 92 (86) \\
4 & \text{CuOTf}_2 & \text{K}_2\text{CO}_3 & \text{DMSO} & 11 \\
5 & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3 & \text{DMSO} & 60 \\
6 & --- & \text{K}_2\text{CO}_3 & \text{DMSO} & 0 \\
7 & \text{CuCl} & \text{Cs}_2\text{CO}_3 & \text{DMSO} & 63 \\
8 & \text{CuCl} & \text{Na}_2\text{CO}_3 & \text{DMSO} & 33 \\
9 & \text{CuCl} & \text{NaHCO}_3 & \text{DMSO} & 42 \\
10 & \text{CuCl} & \text{NaH}_2\text{SO}_3 & \text{DMSO} & 11 \\
11 & \text{CuCl} & \text{N}_2\text{H}_4 & \text{DMSO} & 6 \\
12 & \text{CuCl} & --- & \text{DMSO} & 18 \\
13 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{DMSO} & 53 \\
14 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{toluene} & 8 \\
15 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{DMF} & 41 \\
16 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{DMA} & 69 \\
17 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{NMP} & 37 \\
18 & \text{CuCl} & \text{K}_2\text{CO}_3 & \text{MeCN} & 85 \\
\end{array}
\]

Subsequently, we examined various oxime acetates in Table 3. 2-Bromoaryl oxime acetates such as 1-(2-bromo-4-fluorophenyl)ethanone oxime acetate and 1-(2-bromo-5-fluorophenyl)ethanone oxime acetate also reacted well with aniline to afford the corresponding products (3x-3y) in 80% and 79% yields, respectively. However, when (2-bromophenyl)(phenyl)methanone oxime acetate was used as the substrate, the corresponding product 3z was obtained in lower yield and the 3-phenylbenzo[d]isoxazole was formed via (2-bromophenyl)(phenyl)methanone oxime acetate turning into (2-bromophenyl)(phenyl)methanone oxime and then intramolecular Ullmann-type reaction. $^{11a}$

**Table 3. Cu(I)-catalyzed synthesis of 1H-indazoles from oxime acetate and aniline.**
Control experiment was conducted to gain more insight into the mechanism. When we coupled acetophenone oxime acetate with aniline under the standard conditions, product 4 could not be obtained [Eq. (1)], and the analogue of 1a easily went through Ullmann-type reaction, suggesting that this reaction should be triggered by Ullmann-type reaction. Based on this experiment and previous reports,13-16 a plausible mechanism of the present reaction is described in Scheme 2. Firstly, 1a was coupled with aniline to form intermediate A via copper-catalyzed Ullmann reaction.13 Then intermediate A might go through two possible pathways for the observed product. In path a, the amino group attacked the oxime acetate to form the desired 1H-indazole product 3a with releasing of a molecule of HOAc.3f,3g,14 The other pathway might go through a organocopper(III) process (path b). Oxidative addition of CuI to the N-O bond gave intermediate B.15 Subsequently, intermediate C was formed via the coordination of nitrogen atom to copper(III), which simultaneously produced a molecule of HOAc which was neutralized by base. Finally, intermediate C could transfer to the desired product via reductive elimination (path b).16

Scheme 2. Possible reaction mechanism

In conclusion, we have developed a novel and useful method for the construction of 1H-indazoles. This transformation is supposed to be triggered by Ullmann-type reaction and then undergo N-N bond formation process. Various arylamines, alkyamines and sulfonamides could be applied to this reaction system and the desired 1H-indazole products were formed in good to excellent yields. In this process, the oxime acetates were not only used as substrate but also internal oxidant. Moreover, the use of a catalytic amount of copper salts and no need for additional ligands make this method attractive and practical. Further studies on the reaction scope and mechanism are currently on progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of 1H and 13C NMR spectra for selected compounds. See DOI: 10.1039/b000000x

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