A novel and convenient copper-catalyzed three-component coupling of aldehydes, alkynes, and hydroxylamines leading to propargylamines

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\textbf{A R T I C L E   I N F O}

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\textbf{A B S T R A C T}

The first copper-catalyzed direct three-component coupling reaction of aldehydes, alkynes, and hydroxylamines for the synthesis of propargylamines has been developed under mild conditions, which has the advantages of ready availability of catalyst as well as operation simplicity. The present protocol provides an appealing alternative for the construction of propargylamines in a simple and one-pot procedure.

Multicomponent reactions (MCRs) are one of the most powerful and versatile tools to assemble molecular complexity and diversity from simple and readily available starting materials.\textsuperscript{1} The development of novel MCRs to construct libraries of structurally complex compounds for the evaluation of biological activities is a continuing interest at the forefront of synthetic organic chemistry.

Propargylamines are important structural elements of drug molecules and versatile synthetic intermediates, which have attracted increasingly synthetic pursuit of chemists due to their wide applications in the synthesis of a variety of nitrogenous compounds.\textsuperscript{2,3} Traditionally, propargylamines are prepared by amination of propargylic halides,\textsuperscript{4} propargylic phosphates,\textsuperscript{5} and propargylic triflates,\textsuperscript{6} or through nucleophilic attack of lithium acetylides, Grignard reagents on imines or their derivatives.\textsuperscript{7} However, these methods suffer from issues of moisture sensitivity and the requirement of strictly controlled reaction conditions. Recently, transition-metal-catalyzed coupling reactions of aldehydes, alkynes, and amines (A\textsuperscript{3} coupling reaction) to propargylamines have received much attention due to their simple operation and high efficiency, which employ amines as nitrogen sources. Li and others have reported various A\textsuperscript{3} coupling reactions under homogeneous conditions catalyzed by Cu\textsuperscript{I} salts,\textsuperscript{8} Cu/Ru\textsuperscript{II} bimetallic systems,\textsuperscript{9} Ir\textsuperscript{I} complexes,\textsuperscript{10} Au\textsuperscript{I}/Au\textsuperscript{II} salts,\textsuperscript{11} Au\textsuperscript{II} salen complexes,\textsuperscript{12} Ag\textsuperscript{I} salts,\textsuperscript{13} In\textsuperscript{III} salts,\textsuperscript{14} Ni\textsuperscript{II} salts,\textsuperscript{15} and Fe\textsuperscript{II} salts\textsuperscript{16} as well as heterogeneous conditions catalyzed by Ag\textsuperscript{I},\textsuperscript{17} and Cu\textsuperscript{II} in ionic liquids, Zn dust,\textsuperscript{18} supported Au\textsuperscript{III}\textsuperscript{19a,19b} Ag\textsuperscript{I} \textsuperscript{19b–d} and Cu\textsuperscript{II}\textsuperscript{19c–h} Herein, we report a novel and convenient copper catalyzed direct three-component coupling reactions of aldehydes, alkynes, and hydroxylamines for the construction of propargylamines under mild conditions (Eq. 1), in which hydroxylamines were used as nitrogen sources. Approach described in this communication provides a convenient and appealing alternative for the synthesis of propargylamines in a simple and one-pot procedure.

$$\text{RC}_2\text{CHO} + \text{R}_2\text{C} = \text{C} + \text{N}_2\text{H}_2\text{OH} \xrightarrow{\text{CuBr}_2 (5 \text{ mol } \%), 70^\circ \text{C}}, \text{toluene, N}_2 \rightarrow \text{R}_3\text{N} = \text{C} = \text{CR}_2 \quad (1)$$
reaction and CuBr exhibited the best catalytic activity (entries 1–8). Other metal complexes including In, Fe, Bi, Ir, Ag, Au(I), and Pd salts were not effective for this transformation (entries 9 and 10). A low yield of 4a was obtained when AuBr3 was used as catalyst (entry 11). No product was detected in the absence of catalyst (entry 12).

Next, solvents, temperatures, and the proportions of the substrates were examined using CuBr as catalyst (Table 2). Among various solvents tested, toluene was found to be the optimal reaction medium (entries 1–7). The best yield of 4a was obtained when the reaction was performed at 70 °C (entries 1, 8, 9 and 10). The appropriate proportion of the butyraldehyde 1a, phenylacetylene 2a, and N,N-diethylhydroxylamine 3a was 1:1.5:1.5 (entries 11–13).

With the optimal reaction conditions in hand, the scope and generality of this reaction were investigated with various combinations of aldehydes, alkynes, and hydroxylamines. As shown in Table 3, N,N-diethylhydroxylamine, N,N-dibenzyldihydroxylamine, and 1-hydroxypiperidine were compatible with this reaction and 1-hydroxypiperidine showed the best reactivity (4a–4c). Both aliphatic and aromatic aldehydes were suitable substrates and aliphatic aldehydes showed superior activity (4d–4k). With respect to alkynes, both electron-rich and electron-deficient aromatic alkynes in our reaction system could be transformed into the desired products (4l–4o). Heteroaryl alkyne and naphthyl alkyne were also well tolerated, affording the corresponding products in moderate to good yields (4p and 4q).

Although the detailed reaction mechanism is not clear at the present stage, the possibility that propargylamines were produced through A3 coupling reaction (coupling reaction of aldehydes, amines, and alkynes) has been excluded. It is known that propargylamines could be obtained through copper catalyzed coupling reactions of A3 coupling reaction.8,1

In our system, a trace amount of dibenzylamine was detected when the reaction of butyraldehyde 1a, phenylacetylene 2a, and N,N-dibenzyldihydroxylamine 3b22 was conducted under standard conditions.

**Table 1**

Screening of the catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>(CH3CN)4CuPF6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>CuBr</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>CuCl</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>Cu</td>
<td>5</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>In(OTf)3, FeCl3, BiCl3, IrCl3</td>
<td>12</td>
<td>0(^c)</td>
</tr>
<tr>
<td>10</td>
<td>AgOTf, AuClPPh3, Pd(OAc)2</td>
<td>12</td>
<td>Trace(^c)</td>
</tr>
<tr>
<td>11</td>
<td>AuBr3</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>None</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: Compound 1a (1.0 mmol), 2a (1.5 mmol), 3a (1.5 mmol), 70 °C, under N\(_2\).

\(^b\) Isolated yields based on 1a.

\(^c\) Isolated yields based on 3a.

**Table 2**

Optimization of the reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>1a (mmol)</th>
<th>2a (mmol)</th>
<th>3a (mmol)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>Toluene</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>THF</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>MeOH</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>Dioxane</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>CH3CN</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>DCE</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>Neat</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>rt</td>
<td>Toluene</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>Toluene</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>Toluene</td>
<td>1.5</td>
<td>1</td>
<td>1.5</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>Toluene</td>
<td>1.5</td>
<td>1</td>
<td>1.5</td>
<td>49(^d)</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>Toluene</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>42(^d)</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
<td>Toluene</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: CuBr (5 mol %), compound 1a (indicated amount), 2a (indicated amount), 3a (indicated amount), solvent (1.0 mL), under N\(_2\), 5 h.

\(^b\) Isolated yields based on 1a.

\(^c\) Isolated yields based on 2a.

\(^d\) Isolated yields based on 3a.
Table 3  
Results for the copper-catalyzed three-component coupling reactions of aldehydes, alkynes, and hydroxylamines

<table>
<thead>
<tr>
<th>Products (yields\textsuperscript{b})</th>
<th>Products (yields\textsuperscript{b})</th>
<th>Products (yields\textsuperscript{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="4a" /> (66%)</td>
<td><img src="image" alt="4b" /> (58%)</td>
<td><img src="image" alt="4c" /> (72%)</td>
</tr>
<tr>
<td><img src="image" alt="4d" /> (64%)</td>
<td><img src="image" alt="4e" /> (65%)</td>
<td><img src="image" alt="4f" /> (55%)</td>
</tr>
<tr>
<td><img src="image" alt="4g" /> (58%)</td>
<td><img src="image" alt="4h" /> (41%)</td>
<td><img src="image" alt="4i" /> (17%)</td>
</tr>
<tr>
<td><img src="image" alt="4j" /> (18%)</td>
<td><img src="image" alt="4k" /> (45%)</td>
<td><img src="image" alt="4l" /> (52%)</td>
</tr>
<tr>
<td><img src="image" alt="4m" /> (68%)</td>
<td><img src="image" alt="4n" /> (58%)</td>
<td><img src="image" alt="4o" /> (76%)</td>
</tr>
<tr>
<td><img src="image" alt="4p" /> (57%)</td>
<td><img src="image" alt="4q" /> (60%)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: CuBr (5 mol%), aldehyde (1.0 mmol), alkyne (1.5 mmol), hydroxylamine (1.5 mmol), toluene (1.0 mL), under N\textsubscript{2}, 4–10 h.

\textsuperscript{b} Isolated yields based on aldehydes.

Scheme 1. Postulated reaction pathway.
conditions (Eq. 2). To investigate whether copper catalyzed A^3 coupling reaction was involved in the present catalytic system, the following control experiments were performed. When N,N-dibenzylhydroxylamine 3b was directly stirred with CuBr in the absence of butyraldehyde 1a and phenylacetylene 2a under the standard conditions, only a trace amount of dibenzylamine was detected by HPLC even after 24 h (Eq. 3). Furthermore, the addition of butyraldehyde 1a (Eq. 4) or phenylacetylene 2a (Eq. 5) could not improve the yield of dibenzylamine. Nevertheless, a 58% yield of the desired product 4b could be obtained when the reaction of butyraldehyde 1a, phenylacetylene 2a, and N,N-dibenzylhydroxylamine 3b was conducted under the standard conditions for 6 h (Eq. 2). These results suggested that propargylamines 4 might not be produced through the coupling reactions of aldehydes, alkynes, and amines (A^3 coupling reaction) in our reaction system. In addition, previous reports indicated that the addition reaction of hydroxylamine with aldehyde might occur in our reaction system to produce α-hydroxyl-N-oxide (5, Scheme 1), which could be reduced with another molecule of hydroxylamine to generate aminal (7, Scheme 1) and nitrone (6, Scheme 1). Indeed, nitrone 6b was isolated from the reaction system of butyraldehyde 1a, phenylacetylene 2a, and N,N-dibenzylhydroxylamine 3b under standard conditions (Eq. 6).

\[
\begin{align*}
\text{CHO} + \text{Ph} \leftrightarrow \text{Ph} \quad \text{CuBr, 70°C} \\
\text{1a} + \text{Ph} \quad \text{Toulene, N}_2, 6h \\
\text{yield (48%) (detected by HPLC)} \\
\end{align*}
\]

(2)

\[
\begin{align*}
\text{Ph} \quad \text{CuBr, 70°C} \\
\text{3b} \quad \text{Toulene, N}_2, 24h \\
\text{yield (0.01%) (detected by HPLC)} \\
\end{align*}
\]

(3)

\[
\begin{align*}
\text{CHO} + \text{Ph} \leftrightarrow \text{Ph} \quad \text{CuBr, 70°C} \\
\text{1a} + \text{Ph} \quad \text{Toulene, N}_2, 24h \\
\text{yield (0.01%) (detected by HPLC)} \\
\end{align*}
\]

(4)

\[
\begin{align*}
\text{Ph} \quad \text{CuBr, 70°C} \\
\text{3b} \quad \text{Toulene, N}_2, 0.5h \\
\text{yield based on 1a (16%)} \\
\end{align*}
\]

(5)

\[
\begin{align*}
\text{CHO} + \text{Ph} \leftrightarrow \text{Ph} \quad \text{CuBr, 70°C} \\
\text{1a} + \text{Ph} \quad \text{Toulene, N}_2, 6h \\
\text{yield based on 1a (6b (33%) (detected by HPLC)} \\
\end{align*}
\]

(6)

On the basis of the above experiments and previous reports, a postulated reaction pathway was outlined in Scheme 1. The addition reaction of aldehyde 1 and hydroxylamine 3 gave amine N-oxides 5, which was reduced by another molecule of hydroxylamine to give nitrone 6 and aminal 7. Next, 7 was transformed to iminium ion 8. Then, the nucleophilic attack of copper acetylide intermediate 9 on iminium ion 8 produced the desired propargylamine 4 in a similar manner of the addition of the copper acetylide intermediate on iminium ion in A^3 coupling reaction, which was also proved by the deuterium labeling studies Eq. 7.

\[
\begin{align*}
\text{Ph} \leftrightarrow \text{Ph} \quad \text{CuBr (5 mol%), 70°C} \\
\text{Toulene (dry), N}_2 \\
\text{yield (40%) (detected by HPLC)} \\
\end{align*}
\]

(7)

In summary, we have developed the first copper catalyzed direct three-component coupling reactions of aldehydes, alkynes, and hydroxylamines leading to propargylamines. The present protocol, which utilizes simple and cheap catalyst and readily available starting materials, provides an attractive approach to propargylamines. Investigations of the detailed reaction mechanism and the synthetic application are currently underway.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.009.

References and notes

22. Dibenzylhydroxylamine was purchased from Aldrich company and no dibenzylamine was detected by HPLC and HRMS from this reagent.