Copper-Catalyzed Amination of Vinyl Azides to α-Ketoamides

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Abstract  
An efficient approach for the amination of vinyl azides with N,N-dialkylacylamides has been developed. By using this protocol, structurally important α-ketoamides can be easily synthesized. The key to success is not only the introduction of a Cu(I)/oxygen catalytic system but also the utilization of t-BuOCl and benzoic acid as additives. The reaction is operationally simple, scalable, and displays broad scope and functional group tolerance. A possible mechanism involving copper-catalyzed oxidative generation of peroxide radicals is proposed.

Key words  
amination, α-ketoamide, vinyl azide, copper-catalysis, N,N-dialkylacylamides

Vinyl azides are a class of unique functionalized alkenes with high intrinsic reactivity.1 The numerous transformations of vinyl azides provide reliable synthetic approaches to diverse, structurally distinct molecular frameworks, including heterocarbocycles,2 amides,3 ketones,4 and 2H-azirines.5 Recently, Wu and Liu6 described an efficient and mild method for the synthesis of various α-fluoroketones from the corresponding vinyl azides by using Selectfluor® as the fluorine source (Scheme 1a). Additionally Chiba7 and Liu8a respectively, disclosed radical trifluoromethylation of vinyl azides with Me3SiCF3, to allow construction of α-trifluoromethyl azines, which could be further converted into α-trifluoromethyl ketones (Scheme 1b). Bi and co-workers presented a radical-induced examination of vinyl azides that proceeded with electron-withdrawing substrates, and a variety of β-functionalized primary enamines, including β-nitro, acyl, and sulfonyle derivatives, could be prepared, which were successfully transformed into a series of α-functionalized ketones (Scheme 1c).8 However, with respect to the construction of α-functionalized ketones, these methods usually suffer from disadvantages such as tedious multistep operations or harsh conditions. In a continuation of our efforts on the construction of C–N bond reactions,9 we herein report a novel radical amination of vinyl azides using a copper catalyst, to afford a series of α-ketoamides (Scheme 1). To our knowledge, this is the first example of the conversion of vinyl azides into α-ketoamides, which are important units in biologically active molecules, synthetic drugs, and drug candidates.10
reaction, to screen different catalysts, solvents and additives (Table 1). Firstly, when Cul was used as the catalyst in DMF as the solvent at 100 °C for 5 h under an oxygen atmosphere, the corresponding α-ketoamide 3a was obtained in 67% yield (entry 1). Using CuBr as the catalyst also gave a comparable yield under similar conditions (entry 2). Other metal catalysts, such as CuCl₂, NiCl₂, or Ag₂CO₃, gave either low yields or trace amounts of the desired product 3a (entries 3–5). Subsequent solvent screening demonstrated that DMF (Scheme 2) was examined by using a series of vinyl azides to react with DMF (Scheme 2). α-Aryl-substituted vinyl azides were readily transformed into the corresponding α-ketoamides 3a–n in moderate to excellent yields. Electron-donating groups in the para-position of the aromatic ring were well tolerated, leading to the corresponding products 3a–e in good to excellent yields. Likewise, vinyl azides possessing aryl substituents bearing electron-withdrawing groups, such as -F, -Cl, -Br, -CHO, and -CO₂Me, afforded the desired α-ketoamides 3f–j in 79–90% yield. Note that vinyl azides bearing heteroaromatic substituents such as thienyl could be smoothly incorporated onto α-ketoamide 3k in 88% yield. Moreover, vinyl azide derivatives bearing a variety of substitutions in the meta-position of the aryl ring, including both electron-donating and electron-withdrawing groups, were well tolerated; thereby affording the functionalized α-ketoamides 3l–n in 69–87% yields.

### Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cul</td>
<td>DMF</td>
<td>t-BuOCl</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>DMF</td>
<td>t-BuOCl</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>CuCl₂</td>
<td>DMF</td>
<td>t-BuOCl</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂</td>
<td>DMF</td>
<td>t-BuOCl</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>Ag₂CO₃</td>
<td>DMF</td>
<td>t-BuOCl</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Cul</td>
<td>toluene</td>
<td>t-BuOCl</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cul</td>
<td>EG</td>
<td>t-BuOCl</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cul</td>
<td>MeNO₂</td>
<td>t-BuOCl</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cul</td>
<td>DMF</td>
<td>m-CPBA</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>Cul</td>
<td>DMF</td>
<td>TBHP</td>
<td>53</td>
</tr>
<tr>
<td>11</td>
<td>Cul</td>
<td>DMF</td>
<td>BPO</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>Cul</td>
<td>DMF</td>
<td>t-BuOCl + HBF₄⁻</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>Cul</td>
<td>DMF</td>
<td>t-BuOCl + PhCO₂H</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>DMF</td>
<td>t-BuOCl + PhCO₂H</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Cul</td>
<td>DMF</td>
<td>–</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.5 mmol), 2a (0.75 mmol), catalyst (0.15 mmol), solvent (1.0 ml), additive (1.0 mmol), O₂ atmosphere, 100 °C, 5 h.  
Isolated yield.  
Acid (1.0 mmol).

With the optimized reaction conditions in hand (Table 1, entry 13), the generality of this α-ketoamide synthesis was examined by using a series of vinyl azides to react with DMF (Scheme 2). α-Aryl-substituted vinyl azides were readily transformed into the corresponding α-ketoamides 3a–n in moderate to excellent yields. Electron-donating groups in the para-position of the aromatic ring were well tolerated, leading to the corresponding products 3a–e in good to excellent yields. Likewise, vinyl azides possessing aryl substituents bearing electron-withdrawing groups, such as -F, -Cl, -Br, -CHO, and -CO₂Me, afforded the desired α-ketoamides 3f–j in 79–90% yield. Note that vinyl azides bearing heteroaromatic substituents such as thienyl could be smoothly incorporated onto α-ketoamide 3k in 88% yield. Moreover, vinyl azide derivatives bearing a variety of substitutions in the meta-position of the aryl ring, including both electron-donating and electron-withdrawing groups, were well tolerated; thereby affording the functionalized α-ketoamides 3l–n in 69–87% yields.

To investigate the applicability of this protocol further, N,N-diethyl-α-ketoamide products 4a–f were prepared using vinyl azides 1 and N,N-diethylformamide (2b) as the substrates under the optimized conditions (Scheme 3). Vinyl azides 1a–f with aromatic substituents, including aryl and heteroaryl groups, underwent the reaction smoothly to give the desired products 4a–f in 77–93% yield.

Encouraged by these results, we next turned our attention to other representative nitrogen sources (Table 2). Indeed, not only DMF (2a) and N,N-diethylformamide (2b) but also N,N-dimethylacetamide (DMA) and N,N-dimethylpropylamide (DMP) were tolerated under the standard conditions, with the resultant α-ketoamide products being obtained in slightly lower yields (entries 1–4). In addition, the long chain N,N-dimethylbutylamide (DBM) was also examined, although no desired product was detected (entry 5).
To elucidate a plausible reaction mechanism for this transformation, some potential intermediates were prepared and tested under the standard conditions (Table 1, entry 13). Vinyl azide 1a’ did not afford benzamide 3a under the standard conditions (Scheme 4a), although 3-phenyl-2H-azirine (1b’), N-(1-phenylvinyl)acetamide (1c’), and 2-chloro-1-phenylethan-1-one (1d’) all afforded 3a in good yields (Scheme 4b–d). 2-(Diethylamino)-1-phenylethan-1-one (1e’) did not react under the standard conditions (Scheme 4e),11 nor did dimethylamine (2a’; Scheme 4f). Interestingly, the addition of the radical scavengers 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-tert-butyl-p-cresol (BHT) suppressed the reaction, which indicates that free radical intermediates could be involved in this transformation (Scheme 4g). Notably, only 20% yield of 3a was observed under an argon atmosphere, suggesting that oxygen is required to oxidize the catalyst in preparation for another cycle (Scheme 4g). These control experiments indicate that the vinyl azide substrate possibly reacts with the t-BuOCl as the electrophile and then undergoes oxidation catalyzed by the Cu/O2 system.

**Table 2** Substrate Scope for the Reaction of Vinyl Azides with N,N-Di-methyl Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3a 51</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3b 44</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3g 55</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3a 20</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
<td>3a 0</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (0.5 mmol), 2 (1.0 mL), CuI (0.15 mmol), PhCO2H (1.0 mmol), t-BuOCl (1.0 mmol), O2 atmosphere, 100 °C, 5 h.

*Isolated yield.

**Scheme 4** Control experiments
According to previous reports and considering the above results, a possible mechanism for this amination reaction is proposed in Scheme 5. Initially, the vinyl azide 1a undergoes thermal decomposition into a highly strained three-membered cyclic imine (2H-azirine) A that reacts with the Cu(I) catalyst and t-BuOCl to form Cu(II) imine B, which is then converted into Cu(II) imine C. Subsequent reductive elimination of radical intermediate E generates the active Cu(I) species. Finally, α-ketoamide 3a is obtained through acid hydrolysis of intermediate F.

The potential synthetic applicability of this method was investigated on a gram scale by using the model reaction. As shown in Scheme 6, 1.54 g of α-ketoamide 3a was isolated in 87% yield without any significant loss of efficiency, demonstrating the potential of this methodology for large-scale synthesis of α-ketoamide derivatives.

In conclusion, we have developed a general and efficient method for the synthesis of α-ketoamides from vinyl azides with N,N-dialkylamidylactamide as the nitrogen source. The key to success is not only the introduction of a CuO₂ catalytic system but also the use of t-BuOCl and benzoic acid as additives. This method features readily accessible substrates, commercially available and inexpensive reagents, and mild conditions. This mild catalytic reaction demonstrates a broad substrate scope and high functional group tolerance. A possible mechanism involving copper-catalyzed oxidative generation of peroxide radicals is proposed. The reaction can be effectively scaled up and the product conveniently obtained in a one-pot process. Efforts to further clarify the mechanism and to expand the application of vinyl azides are under way in our laboratory.

**Funding Information**

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**References and Notes**


(14) Synthesis of 4a; Typical Procedure: To a solution of α-azido styrene (1a; 72.5 mg, 0.5 mmol), tert-butyl hypochlorite (113.1 µL, 1.0 mmol), and benzoic acid (122.1 mg, 1.0 mmol) in N,N-diethylformamide (2b; 1 mL) at room temperature, Cul (28.6 mg, 0.15 mmol) was added. The reaction mixture was heated at 100 °C and stirred for 5 h under an oxygen atmosphere, when TLC analysis confirmed that substrate 1a had been consumed. The resulting reaction mixture was cooled to room temperature and K2CO3 was added. The mixture was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were washed with brine (3 × 40 mL), dried over MgSO4, filtered and concentrated. Purification of the crude product by flash column chromatography (silica gel; petroleum ether) afforded 4a (77% yield) as a yellow oil.

N,N-Diethyl-2-oxo-2-phenylacetamide (4a): 1H NMR (400 MHz, CDCl3): δ = 7.93 (d, J = 7.1 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 3.61–3.53 (m, 2 H), 3.29–3.20 (m, 2 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.16 (t, J = 7.1 Hz, 3 H). 13C NMR (100 MHz, CDCl3): δ = 191.5, 166.7, 134.5, 133.2, 129.6, 128.9, 42.0, 38.7, 14.0, 12.8. HRMS (ESI): m/z [M + H]+ calcld for C12H15NO2: 206.1181; found: 206.1142.