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Selective Synthesis of (Z)-2-Enynyl-2-Hydroxy-Imidazolidine-4,5-diones via Cu(I)-Mediated Multicomponent Coupling of Terminal Alkynes, Carbodiimides and Oxalyl Chloride†

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(Z)-2-Enynyl-2-hydroxy-imidazolidine-4,5-diones 2 are synthesized for the first time via Cu(I)-mediated (Z)-selective geminal coupling among two molecules of terminal alkynes, carbodiimides, and oxalyl chloride. Further transformation of 2a is performed to yield highly functionalized spiro heterocyclic compound 5.

Considerable efforts have been devoted to the dimerization of terminal alkynes because it provides a straightforward method to construct conjugated enynes, which are versatile building blocks in organic synthesis and significant components in bioactive molecules.1,2 However, highly selective formation of conjugated enynes by a dimerization remains to be limited due to the competitive formation of three possible (E)-(Z) and gem-enyne isomers.1,2 As far as we are aware, the multicomponent coupling3 via incorporating organic components into the well-established dimerization of terminal alkynes is not reported. It is a major challenge because the deprotonation step of the final acetylide intermediate is a fast step or the reductive elimination of the final acetylide intermediate is more favorable in two reported mechanisms (Scheme 1). Another challenge is how to control the regio- and stereoselectivity of the corresponding enynes.

Scheme 1 Unexpected (Z)-selective geminal coupling of two terminal alkynes, carbodiimides and oxalyl chloride.

(Z)-2-En-4-yn-1-ols ((Z)-enynols for short), as a class of multifunctional organic skeletons, are of considerable interest in modern organic synthesis because of their important application in synthesis of O-containing heterocycles.4,5 Although the synthesis of (Z)-enynols has received much interest,6,10 (Z)-enynols bearing a heteroatomic substituent at C1 position is not reported because of the difficulty in introducing a heteroatom into the starting materials. Thus, a simple and efficient method to synthesize heteroatom-incorporated (Z)-enynols at C1 position remains to be of great importance to academia and to the pharmaceutical industry. Herein we report our new discovery of Cu(I)-mediated multicomponent coupling of two terminal alkynes, carbodiimides, and oxalyl chloride to construct the novel (Z)-enynols bearing a heterocyclic linker at C1 position. In this process, the (Z)-selective geminal coupling of two molecules of terminal alkynes is found. Further transformation of (Z)-enynol was performed to yield highly functionalized spiro heterocyclic compounds.

Scheme 2 Screening of reaction conditions.

We have focused on carbodiimide-based multicomponent reactions to construct some N-containing organic molecules.11,12 Recently we have reported one-pot sequential reaction of amines, carbodiimides, and oxalyl chloride to prepare cyclic di-oxoguanidines. The 2,2-dichlorimidazoline-4,5-dione intermediate 1a was isolated and characterized from the reaction of N,N'-disopropylcarbodiimide (DIC) and oxalyl chloride (See SI for its X-ray structure).12c,13 The connection of four electronnegatives atoms in 1a made the C2 atom be highly electrophilic. So we envisioned whether two C–Cl bonds in 1a could undergo the cross-coupling reactions with terminal alkynes
to generate 1,4-diynes. However, it was found that, in the presence of CuI and Et3N, a (Z)-2-enynyl-2-hydroxyimidazolidine-4,5-dione 2a\textsuperscript{1a} was observed via the coupling of 1a with two molecules of phenylethynes followed by a byproduct 3a. The expected 1,4-diyne product was not observed (Scheme 2). After various reaction conditions including reaction temperature, reaction time, bases,\textsuperscript{3} and the metal salts, such as CuCl, CuBr, CuI and PdCl\textsubscript{2}, were screened (See SI for details), an optimal condition was found and the expected 2a was isolated in 70% yield (Scheme 2).

With the optimized condition in hand, we began to explore the reaction scope. The representative results for the formation of (Z)-enynols 2 were summarized in Table 1. 2,2-Dichloroimidazoline-4,5-diones 1 were generated in situ from carbodiimides and oxalyl chloride. Carbodiimides (RN=C=NR, R = ‘Pr, Cy, ‘Bu) were tested to be suitable nitrogen sources for the reaction. Because of the steric hindrance of tert-butyl group, 2BuN=C=NBu gave 2c in a significantly lower yield than other N,N-dialkylcarbodiimides. As far as terminal alkynes were concerned, the reaction was not affected by the positions of the substituents at the phenyl ring of an aromatic alkyne (2d–I). Electron-donating groups such as alkyl (2d–f), alkoxy group (2k) and weak electron-withdrawing groups such as halogens (2h–j) would give good yields. It was noted that strong electron-withdrawing groups at the phenyl ring of an aromatic alkyne would result in no product. Heterocyclic terminal alkyne such as 3-ethynylthiophene gave the desired product 2l in 65% isolated yield. The single crystal structure of 2d clearly revealed the Z-configuration of the alkene moiety (See SI for its X-ray structure).\textsuperscript{1,6}

<table>
<thead>
<tr>
<th>Table 1 Formation of (Z)-enynols.\textsuperscript{a}</th>
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<tbody>
<tr>
<td>1a: R\textsuperscript{1} = ‘Pr (70%)</td>
</tr>
<tr>
<td>2a: R\textsuperscript{1} = ‘Pr (70%)</td>
</tr>
<tr>
<td>2b: R\textsuperscript{1} = Cy (70%)</td>
</tr>
<tr>
<td>2d: R\textsuperscript{1} = Ph (68%)</td>
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</table>

\textsuperscript{a} Byproducts 3 were formed in 5–10% yields.

These interesting and novel results intrigued us to explore the reaction mechanism. A series of experiments were performed. First, the necessity of iodide was investigated. Iodide is usually considered to be a good nucleophile as well as a good leaving group. To obtain the evidence of iodo-substituted intermediate, the 1:1 mixture of 1a and NaI in THF-d\textsubscript{6} was monitored by NMR spectroscopy. Both \textsuperscript{1}H and \textsuperscript{13}C NMR spectra showed the formation of a new compound. The in situ NMR spectra also showed that the ratio of 1a and 4a was 1.0:1.8 and remained unchanged after a long period (ca. 7 days), indicating there was an equilibrium between them (See SI for details). 4a is proposed to be monoiodo-substituted intermediate. Therefore, 2,2-Dichloroimidazoline-4,5-dione was proposed to undergo a Cl–I exchange giving an important intermediate (eq 1).

Next, the sources of the alkenyl hydrogen and hydroxyl group in the product 2 were explored. A series of isotopic labeling experiments were carried out. The final reaction mixture of 1a with phenylethynyl was quenched with H\textsubscript{2}18O to produce the 18O-labeling product 2a-18O. This result clearly showed that the hydroxyl group in 2 should come from water (eq 2). Deuterium labeling experiments were performed with phenylacetylene-d\textsubscript{1} and/or D\textsubscript{2}O. A single deuterium source gave the deuterated product 2a-D with low proportion of deuterium (eq 3–4). Only a combination of the two deuterium sources could lead to a fully deuterated product (eq 5). The results showed that the alkynyl proton should be from both terminal alkynes and water.

Based on the experimental results above, a plausible mechanism for the formation of 2 is proposed in Scheme 3. In the presence of Et3N, the copper acetylidyne (A) is generated from terminal alkynes and CuI/CuCl, releasing the chloride and iodide anions simultaneously. The nucleophilic substitution of 1 by iodide generates the intermediate 4. A Sonogashira type cross-coupling reaction of 4 with A would give rise to the intermediate B and regenerate CuI. The regenerated CuI would participate the next catalytic cycle. B then undergoes an isomerization to form...
chloroallenone C, or further protonation by Et$_3$NH$^+$ to form C'. A Stephens-Castro coupling of C or C' with A would form D or D'. D is quenched with water to give the final product 2.

Further transformation of (Z)-enynol 2a was tested under various conditions. A new spiro heterocyclic compound 5 was synthesized by electrophilic cyclization of 2a with I$_2$ in THF solution with K$_3$PO$_4$ as base, which showed the potential of this synthetic strategy (eq 6).  

In conclusion, Cu(I)-mediated (Z)-selective geminal MCR coupling among two molecules of terminal alkynes, carbodimides, and oxalyl chloride is achieved for the first time to afford (Z)-enynols bearing a heterocyclic linker at C1 position. (Z)-Enynol shows the potential application for the synthesis of highly functionalized spiro heterocyclic compounds. It is noted that the multicomponent coupling via incorporating organic components into the well-established dimerization of terminal alkynes is affected for the first time. Further investigations on their application are ongoing.

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**Notes and references**


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