Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c0xx00000x

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Communication

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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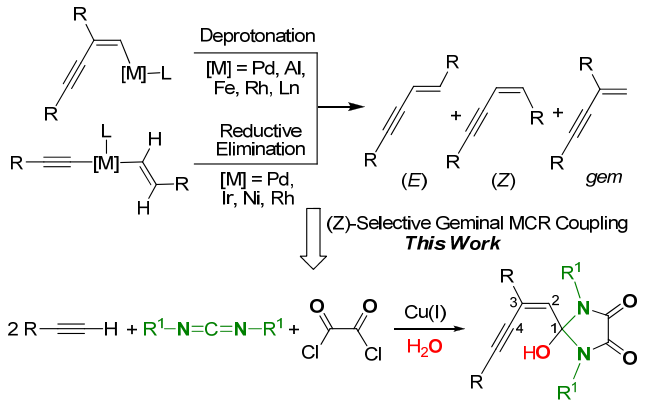
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

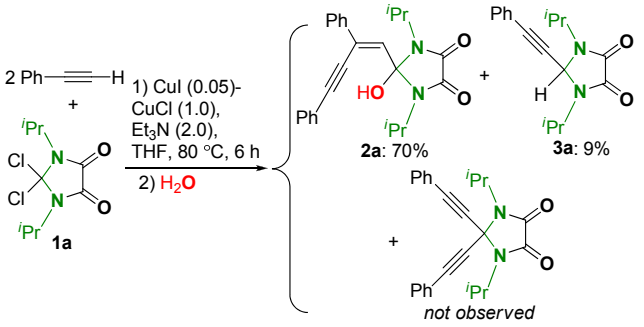
(*Z*)-2-Enynyl-2-hydroxy-imidazolidine-4,5-diones 2 are synthesized for the first time via Cu(I)-mediated (*Z*)-selective geminal coupling among two molecules of terminal alkynes, carbodiimides, and oxalyl chloride. Further transformation of 2a is performed to yield highly functionalized spiro heterocyclic 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 coupling[3] 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 enyne-containing intermediate with terminal alkyne 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.



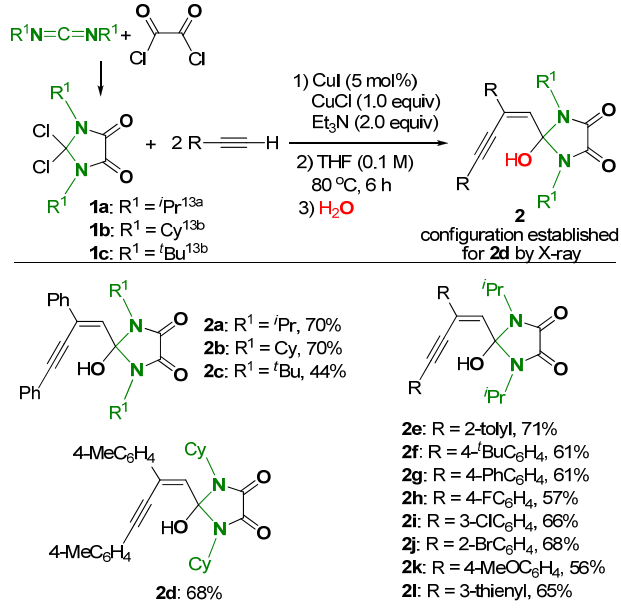
Scheme 2 Screening of reaction conditions.

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-dichloroimidazoline-4,5-dione intermediate **1a** was isolated and characterized from the reaction of *N*,*N*'-diisopropylcarbodiimide (DIC) and oxalyl chloride (See SI for its X-ray structure).[12e,13] The connection of four electronegative 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 Et_3N, a (*Z*)-2-enynyl-2-hydroxy-imidazolidine-4,5-dione **2a**[14] 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,[15] and the metal salts, such as CuCl, CuBr, CuI and $PdCl_2$, 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 = ^{i}Pr, Cy, ^{t}Bu) were tested to be suitable nitrogen sources for the reaction. Because of the steric hindrance of *tert*-butyl group, ^{t}BuN=C=N^{t}Bu 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–l**). 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).[16]

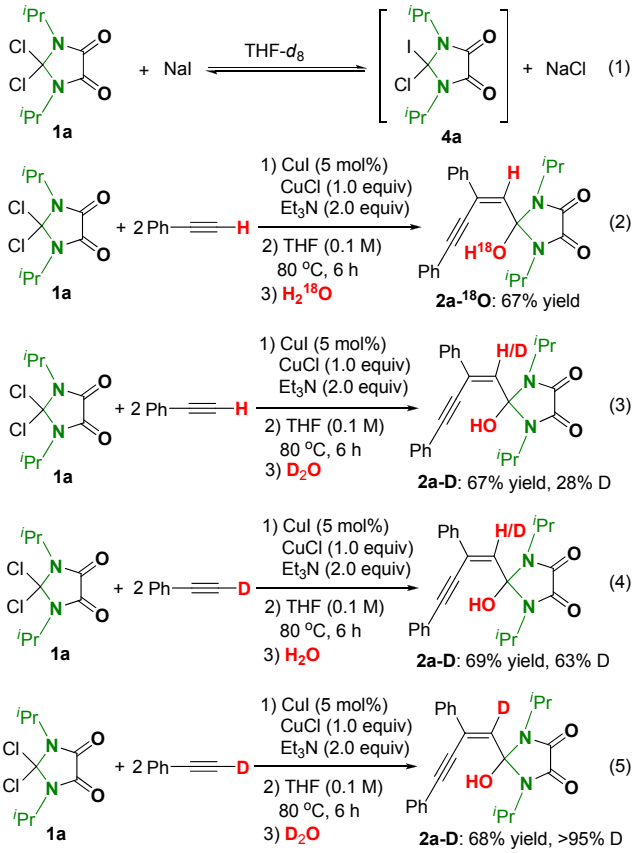
Table 1 Formation of (*Z*)-enynols.[a]



[a] Byproducts **3** were formed in 5-10% yields.

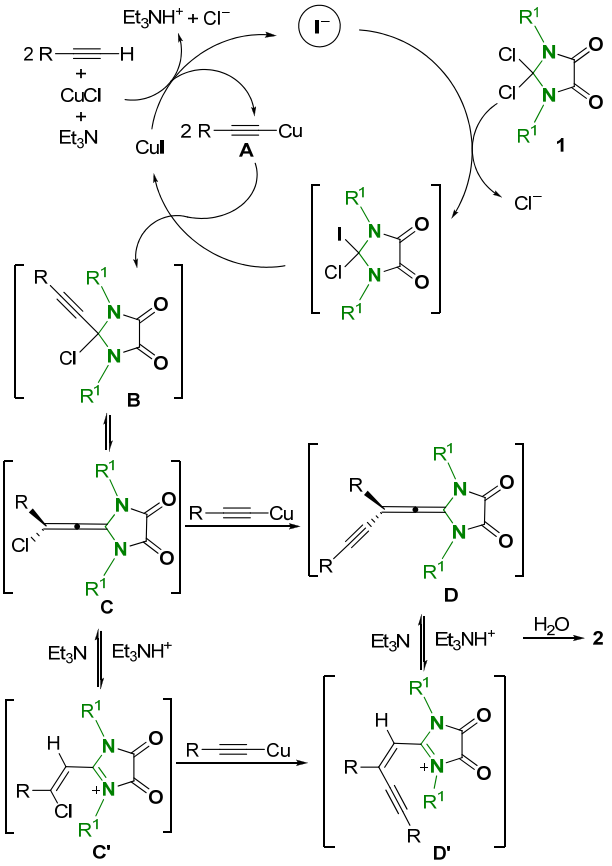
These interesting and novel results intrigued us to explore the reaction mechanism. A series of experiments were performed. First, the necessity of iodide was investigated. Iodide is usually considered to be a good nucleophile as well as a good leaving group. To obtain the evidence of iodo-substituted intermediate, the 1:1 mixture of **1a** and NaI in THF-d_8 was monitored by NMR spectroscopy. Both ^{1}H and ^{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 1:0.18 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 phenylethyne was quenched with $H_2{}^{18}O$ to produce the ^{18}O-labeling product **2a-^{18}O**. This result clearly showed that the hydroxyl group in **2** should come from water (eq 2). Deuterium labeling experiments were performed with phenylacetylene-d_1 and/or D_2O. 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 alkenyl proton should be from both terminal alkynes and water.



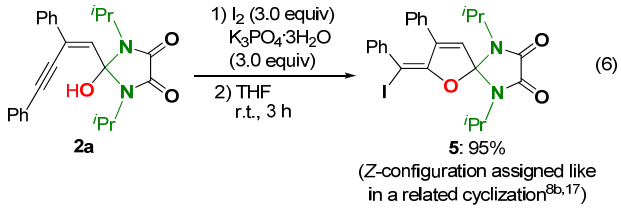
Based on the experimental results above, a plausible mechanism for the formation of **2** is proposed in Scheme 3. In the presence of Et_3N, the copper acetylide (**A**) is generated from terminal alkynes and CuI/CuCl, releasing the chloride and iodide anions simultaneously. The nucleophilic substitution 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

chloroallene **C**, or further protonation by Et_3NH^+ 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**.



Scheme 3 A proposed mechanism.

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_3PO_4 as base, which showed the potential of this synthetic strategy (eq 6). [17]



In conclusion, Cu(I)-mediated (*Z*)-selective geminal MCR coupling among two molecules of terminal alkynes, carbodiimides, 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 the multicomponent coupling via incorporating organic components into the well-established dimerization of terminal alkynes is effected for the first time. Further investigations on their application are ongoing.

Acknowledgments

This work was supported by the Natural Science Foundation of China and the "973" program from National Basic Research Program of China (2011CB808601). We also thank a reviewer of the manuscript for the valuable suggestions.

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† Electronic Supplementary Information (ESI) available: Materials including experimental procedures, NMR spectra of all new products and X-ray data for **1a**, **2d**. See DOI: 10.1039/b000000x/

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