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Three-Component Assembly of Conjugated Enyne Scaffolds via *E*-Selective Olefination of Ynals

Dong Cheng, Fei Ling, Zexiang Li, Weijun Yao, and Cheng Ma*

Department of Chemistry, Zhejiang University, 20 Yugu Road, Hangzhou 310027, People's Republic of China

mcorg@zju.edu.cn

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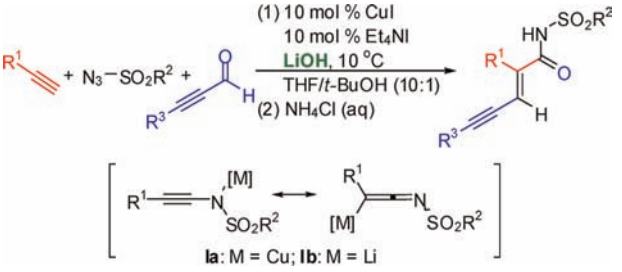
ABSTRACT



Benefited by the accessible ynamido−lithium intermediates Ib from a Cu-catalyzed azide−alkyne cycloaddition in the presence of stoichiometric amounts of LiOH, a mild and flexible three-component route to conjugated enyne scaffolds was successfully achieved via a formal *E*-selective olefination strategy.

Conjugated enynes are valuable compounds in organic synthesis since these scaffolds not only are important units in medicinal and material science but also serve as versatile synthetic building blocks.[1] Whereas significant progress has been achieved, the stereocontrolled synthesis of multisubstituted and functionalized conjugated enynes through carbonyl olefination remains a challenging task.[2] In this context, the pioneering studies of Shindo and co-workers on the torquoselective olefination of alkynyl alkyl ketones or alkynoates with pre-prepared ynolates notably provided a convergent protocol to substituted (*E*)-2-en-4-ynoic acid derivatives with high stereoselectivities, even under harsh conditions (Scheme 1a).[3]

The Cu-catalyzed azide−alkyne cycloaddition (CuAAC) reaction[4] constitutes one of the most interesting examples of the click reaction.[5] On the other hand, over the past few years, *N*-sulfonyl ketenimine species (ynamido−copper **Ia** and ketenimine **II**), arising from a CuAAC reaction, have been recognized as versatile synthons in multicomponent

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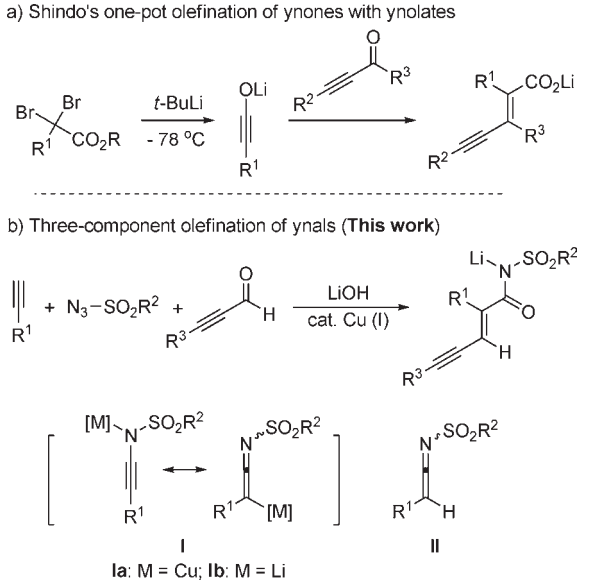
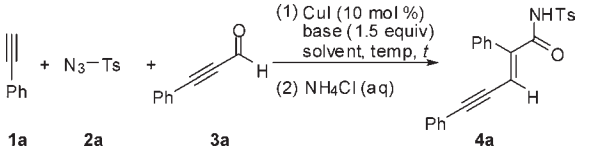
reactions.[6] However, previous studies in this area have been predominantly focused on disclosing the diverse electrophilic reactivities[7] of these intermediates toward a tethered or an extra nucleophile and subsequent tandem reactions.[8] The feasibility of generating ynamido−lithium intermediates **Ib** via a CuAAC reaction is still uncovered.[9]

Scheme 1. Formal Olefination of Carbonyl Compounds



We have previously disclosed a CuI-catalyzed cascade reaction of terminal alkynes, sulfonyl azides, and aromatic 2-oxobut-3-ynoates, giving access to two types of five-membered heterocyclic skeletons.[10] Encouraged by this result, we thus screened a variety of carbonyl compounds as substrates instead of activated ynones and found that *β*-substituted propiolaldehydes deliver good efficiency to conduct an olefination reaction, which provides a highly *E*-selective avenue to substituted conjugated enyne products, most probably, upon the nucleophilicity of ynamido−lithium (**Ib**) intermediates (Scheme 1b).[11]

Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	temp (°C)	*t* (h)	yield (%)[b]
1	Et_3N	THF	25	12	
2	2,6-lutidine	THF	25	12	
3	Cs_2CO_3	THF	25	5	49
4	NaOH	THF	25	2	31
5	Li_2CO_3	THF	25	24	11
6	*t*-BuOLi	THF	25	2	41
7	LiOH	THF	25	3	58
8	LiOH[c]	THF	25	12	51
9	LiOH[d]	THF	25	6	31
10	LiOH	CH_2Cl_2	25	7	55
11	LiOH	THF/H_2O[e]	25	6	48
12	LiOH	MeCN	25	7	<5
13	LiOH	THF/*t*-BuOH[e]	25	6	65
14	LiOH	THF/*t*-BuOH[e]	10	3	81
15	LiOH	THF/*t*-BuOH[e]	−5	12	

[a] Conditions: (1) **1a** (0.45 mmol), **2a** (0.45 mmol), **3a** (0.3 mmol), CuI (10 mol %), and Et_4NI (10 mol %) for inorganic base in solvent (5.0 mL) under N_2, then base (1.2 equiv); (2) saturated aqueous NH_4Cl (5 mL). [b] Isolated yield of **4a**. [c] In the absence of Et_4NI. [d] LiOH (0.45 equiv) was used. [e] Et_4NI = tetraethylammonium iodide; v/v = 10:1.

Preliminary investigation of the reaction of alkyne **1a**, tosyl azide **2a**, and 3-phenylpropiolaldehyde (**3a**) in the presence of CuI (10 mol %) at 25 °C revealed that the reaction outcomes strongly depend on the base used. As shown in Table 1, both triethylamine and 2,6-lutidine, two common bases employed in Cu^I-catalyzed reactions upon ketenimine intermediates, did not furnish any coupling products (Table 1, entries 1 and 2). In sharp contrast, a set of inorganic bases in combination with Et_4NI (10 mol %) provided enyne **4a** in varying yields (Table 1, entries 3−8). Lithium hydroxide turned out to perform best for this tandem reaction in terms of the product yield; the addition of Et_4NI should accelerate the formation of the product **4a** (Table 1, entry 7 versus 8). Nevertheless, when employing substoichiometric amounts of LiOH, the reaction did not reach completion even after 12 h (entry 9). Solvent screening (Table 1, entries 10−12) indicated that this reaction can be achieved in CH_2Cl_2 as well as in a mixture of THF and H_2O with comparable results; notably, reactions in acetonitrile yielded only trace amounts of **4a**. We also observed that the presence of *tert*-butyl alcohol slightly facilitated the olefination and therefore chose the mixtures of THF

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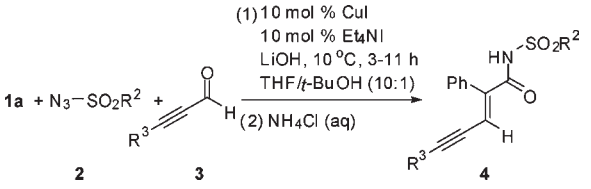
and *tert*-butyl alcohol (10:1) for further exploration.[12] It was shown that the temperature has a critical effect on this reaction (Table 1, entries 13−15): while the yield of **4a** increased to 81% by lowering the temperature to 10 °C, further decrease in temperature resulted in a very slow conversion to provide almost no detectable amount of **4a** after 12 h.

The scope of this formal olefination reaction was next investigated under the optimized conditions (Tables 2 and 3). Accordingly, a variety of substituted propiolaldehydes **3** carrying aryl or alkyl substituents achieved the tandem reaction with **1a** and **2a** smoothly, and all gave good yields with consistently high stereoselectivities (Table 2, entries 1−5). Nevertheless, an extended reaction time was required for 3-(4-fluorophenyl)propiolaldehyde to afford **4c** in a slightly lower yield (entry 3). Moreover, variation of the sulfonyl azide component (R^2 = 4-AcNHC$_6$H$_4$ and Me) was also tolerated; the corresponding products **4f** and **4g** were obtained in 72 and 65% yield, respectively (Table 2, entries 6 and 7).

Table 2. Scope of Ynals **3** and Sulfonyl Azides **2** with **1a**[a]



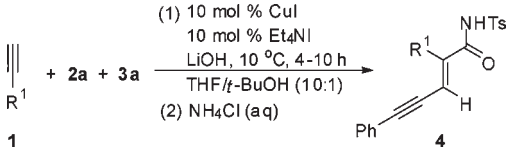
entry	R^2	R^3	time (h)	**4**, yield[b] (%)
1	4-CH$_3$C$_6$H$_4$	Ph	3	**4a**, 81
2	4-CH$_3$C$_6$H$_4$	4-CH$_3$Ph	5	**4b**, 78
3	4-CH$_3$C$_6$H$_4$	4-FC$_6$H$_4$	11	**4c**, 65
4	4-CH$_3$C$_6$H$_4$	*n*-Bu	6	**4d**, 74
5	4-CH$_3$C$_6$H$_4$	2-thienyl	4	**4e**, 86
6	4-AcNHC$_6$H$_4$	Ph	7	**4f**, 72
7	Me	Ph	3	**4g**, 65

[a] Conditions: (1) **1a** (0.45 mmol), **2** (0.45 mmol), **3** (0.3 mmol), CuI (10 mol %), and Et$_4$NI (10 mol %) in THF/*t*-BuOH (10:1, 5 mL) under N$_2$ at 10 °C, then LiOH (0.36 mmol); (2) Saturated aqueous NH$_4$Cl (5 mL). [b] Yield of isolated **4**. Almost only *E*-configuration product of **4** was formed according to the ^{1}H NMR spectra of the crude reaction product.

Subsequently, we investigated the formation of enynes **4** by using a variety of monosubstituted ethynes **1**. As depicted in Table 3, the targeted products **4h**−**n** were obtained in reasonably good yields under mild conditions. All tested ethynes with various substituted phenyl, alkyl, and alkenyl groups were cleanly converted into their corresponding derivatives with high stereoselectivity, reflecting wide scope of this reaction. In addition, the *E*-configuration of the newly formed double bond of **4l** was confirmed by single-crystal X-ray diffraction analysis.

(12) The action of *tert*-butyl alcohol is currently not clear; presumably, the solvent mixtures could facilitate the formation of lithium ynamidate intermediates.

Table 3. Scope of Monosubstituted Ethynes **1**[a]



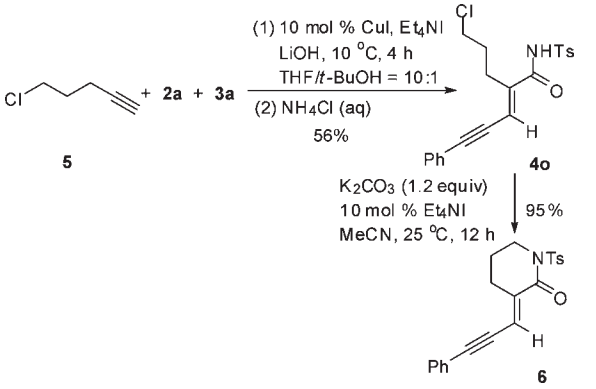
entry	R^1	time (h)	**4**, yield[b] (%)	*E*/*Z*[c]
1	2-MeC$_6$H$_4$	4	**4h**, 81	> 95:5
2	3-AcNHC$_6$H$_4$	4	**4i**, 78	> 95:5
3	3-NO$_2$C$_6$H$_4$	10	**4j**, 65	> 95:5
4	4-MeC$_6$H$_4$	6	**4k**, 74	> 95:5
5	4-BrC$_6$H$_4$	4	**4l**, 86	> 95:5
6	cyclopropyl	8	**4m**, 72	> 95:5
7		35	**4n**, 65	> 95:5

[a] Conditions: (1) **1a** (0.45 mmol), **2** (0.45 mmol), **3** (0.3 mmol), CuI (10 mol %), and Et$_4$NI (10 mol %) in THF/*t*-BuOH (10:1, 5 mL) under N$_2$ at 10 °C, then LiOH (0.36 mmol); (2) saturated aqueous NH$_4$Cl (5 mL). [b] Yield of isolated **4**. [c] Detected by the ^{1}H NMR spectra of the crude reaction product.

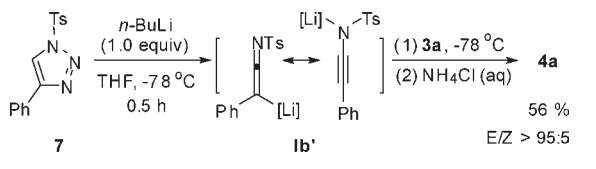
Furthermore, this reaction also tolerated 5-chloropent-1-yne (**5**), affording the targeted product **4o** in 56% yield; only trace amounts of subsequent cyclization product **6** were detected after 12 h. An intramolecular N-alkylation of **4o** by potassium carbonate in acetonitrile did give (*E*)-3-(3-phenylprop-2-ynylidene)-1-tosylpiperidin-2-one (**6**) in 95% yield with retained *E*-configuration of the double bond according to the NOESY spectrum of **6** (Scheme 2).

To gain insight into the reaction mechanism, a control test of 1-sulfonyltriazole **7** and **3a** was conducted in THF (Scheme 3). After decomposition of **7** by *n*-butyllithium

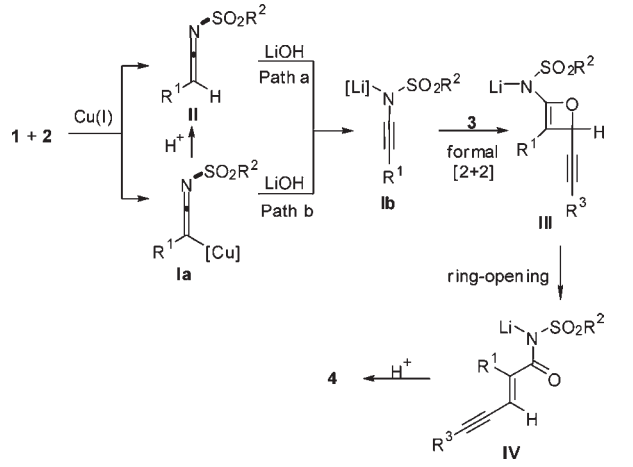
Scheme 2. Formation of Enyne Scaffolds **4o** and **6**



Scheme 3. Formation of **4a** from 1-Sulfonyltriazole **7**



Scheme 4. Plausible Mechanism for the Formation of **4**



at −78 °C, as expected, the resulting intermediate, lithium ynamidate **Ib**′,[8a] smoothly reacted with **3a** to give enyne **4a** in 56% isolated yield with high *E*-selectivity.

A plausible mechanism for this *E*-selective olefination reaction is depicted in Scheme 4. Initially, a Cu^{I}-catalyzed reaction of terminal alkyne **1** and azide **2** in the presence of stoichiometric amounts of LiOH in THF generates lithium ynamidate **Ib** presumably via a deprotonation reaction of ketenimine **II** (path a) or direct transmetalation of copper(I) alkynamide **Ia** (path b) in the absence of ligands for copper(I) complexes.[13] The intermediate **Ib** then reacts with ynal **3** to afford adduct **III**.[14] Subsequent electronic ring opening of **III** leads to the formation of lithium salt **IV**; the *E*/*Z*-selectivity of the newly formed double bond would be determined in this step. Finally, the protonation of **IV** with aqueous NH_4Cl then furnishes enyne **4**.

In summary, making use of the easily accessible lithium ynamidate intermediates from a CuAAC reaction in the presence of stoichiometric amounts of LiOH, the present protocol provided a mild and highly stereoselective access to conjugated enyne scaffolds from simple substrates via a formal *E*-selective olefination reaction of substituted ynals. Experimental results suggest that the formation of lithium ynamidate intermediates **Ib** by stoichiometric amounts of LiOH is responsible for the current reaction outcome. Additional studies on application and mechanism of the reaction are now in progress.

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Supporting Information Available. Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.