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A copper-catalyzed three component reaction of aryl acetylene, sulfonyl azide and enaminone to form iminolactone *via* 6π electrocyclization†

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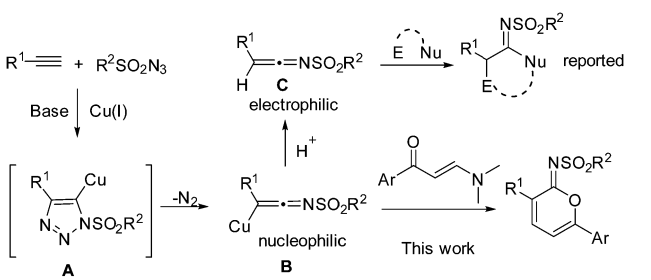
We developed a copper-catalyzed three component reaction of aryl acetylene, enaminone and sulfonyl azide to construct iminolactone *via* a cascade process involving copper-catalyzed alkyne–azide cycloaddition (CuAAC), Michael addition of metalated ketenimine followed by elimination and 6π electrocyclization.

Cascade multicomponent reactions (MCRs)[1] have grown into a powerful synthetic tool for the construction of complex molecular scaffolds through the formation of multiple carbon–carbon and carbon–heteroatom bonds in one pot. Since the pioneering work of Chang,[2] who discovered the first copper catalyzed three-component reaction involving *in situ* generated ketenimine, copper-catalyzed MCRs involving sulfonyl azides and terminal alkynes have attracted great attention from synthetic chemists. Generally, these MCRs are triggered by a copper-catalyzed azide–alkyne cycloaddition (CuAAC)[3] reaction to form 1,2,3-triazoles **A** followed by the ring opening rearrangement to release a N_2, simultaneously, to generate metalated ketenimine intermediate **B**. After protonation, ketenimine **C** is trapped by various nucleophiles to deliver diverse molecules. Due to its high reactivity and ready preparation *in situ*, the electrophilic ketenimine **C** has been widely explored[4] through nucleophilic addition,[5] cascade reactions[6] and cycloaddition reactions.[7] However, compared with considerable progress of electrophilic ketenimine **C**, there were few examples of the transformation of the nucleophilic metalated ketenimine **B**.[8] The nucleophilic ketenimine with carbonyl compounds undergoing [2+2] cyclization and the subsequent ring opening was reported by Ma's group,[9] and also they described an inverse electron-demand hetero-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadiene and *in situ* generated metalated ynamide intermediates, a tautomer of metalated ketenimine.[10] In 2014, Zhang and co-workers[11] disclosed an electrophilic addition of an immonium ion to copper ketenimine to deliver α,β-unsaturated amidine derivatives. In this context, exploring new reactions of nucleophilic ketenimine *in situ* generated from sulfonyl azides and terminal alkynes (Scheme 1) is still in demand and remains challenging.

Enaminone[12] is a type of synthetically useful synthon and has been widely applied in a huge number of reactions towards fine molecule synthesis. Herein, we document a novel copper-catalyzed three component reaction of aryl acetylene, sulfonyl azide and enaminone to form iminolactone[13] *via* a cascade process involving copper-catalyzed alkyne–azide cycloaddition (CuAAC), Michael addition/elimination and 6π electrocyclization.

Initially, we chose *p*-tolyl enaminone (**1a**), phenylacetylene (**2a**) and *p*-toluenesulfonyl azide (**3a**) as model substrates to explore the feasibility of the reaction catalyzed by copper(I) iodide (10 mol%) in the presence of triethylamine in dichloromethane at room temperature under a nitrogen atmosphere. To our delight, iminolactone **4a** could be isolated in 52% yield (Table 1, entry 1). Attempts to improve the yield by carrying out solvent screening revealed that weak polarity solvents such as dichloromethane, 1,2-dichloroethane, chloroform and toluene led to a moderate yield (Table 1, entries 1–4), while strong polar solvents (tetrahydrofuran, ethyl acetate and acetonitrile) restrained



Scheme 1 Transformation of ketenimine from terminal alkyne and sulfonyl azide.

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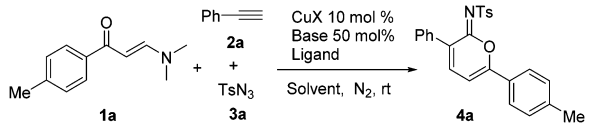
Table 1 Optimization of the three-component reaction[a]

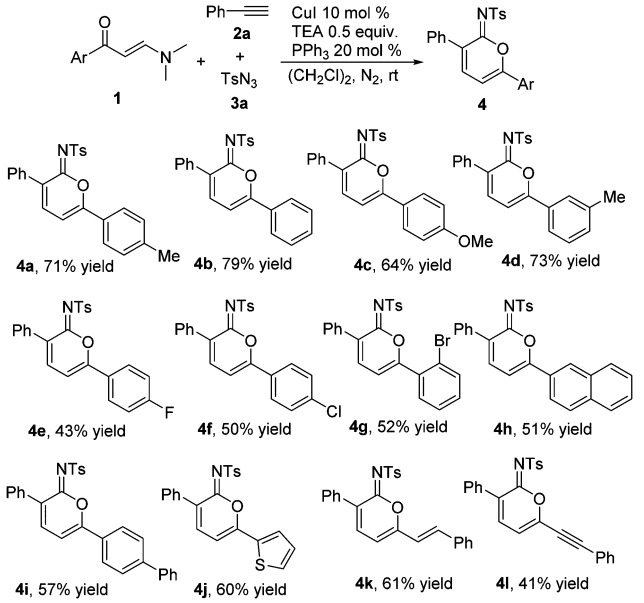


Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	CuI	—	TEA	CH_2Cl_2	52
2	CuI	—	TEA	$(CH_2Cl)_2$	57
3	CuI	—	TEA	CH_3Cl	36
4	CuI	—	TEA	Toluene	44
5	CuI	—	TEA	THF	Trace
6	CuI	—	TEA	EtOAc	Trace
7	CuI	—	TEA	CH_3CN	Trace
8	CuI	1,10-Phenanthroline	TEA	$(CH_2Cl)_2$	48
9	CuI	Proline	TEA	$(CH_2Cl)_2$	Trace
10	CuI	TEMED	TEA	$(CH_2Cl)_2$	Trace
11	CuI	Dppe	TEA	$(CH_2Cl)_2$	46
12	CuI	PPh_3	TEA	$(CH_2Cl)_2$	71
13	CuCl	PPh_3	TEA	$(CH_2Cl)_2$	38
14	CuBr	PPh_3	TEA	$(CH_2Cl)_2$	47
15	CuCN	PPh_3	TEA	$(CH_2Cl)_2$	Trace
16	Cu_2O	PPh_3	TEA	$(CH_2Cl)_2$	Trace
17	$CuBr_2$	PPh_3	TEA	$(CH_2Cl)_2$	Trace
18	$CuBr{\cdot}Me_2S$	PPh_3	TEA	$(CH_2Cl)_2$	20
19	CuI	PPh_3	DABCO	$(CH_2Cl)_2$	Trace
20	CuI	PPh_3	DBU	$(CH_2Cl)_2$	27
21	CuI	PPh_3	DIPEA	$(CH_2Cl)_2$	58
22	CuI	PPh_3	Cs_2CO_3	$(CH_2Cl)_2$	62

[a] Conditions: enaminone **1a** (0.2 mmol), phenylacetylene **2a** (0.5 mmol), *p*-toluenesulfonyl azide TsN_3 **3a** (0.5 mmol), base (0.1 mmol), solvent (2 mL), ligand (0.02 mmol, if optional) under a nitrogen atmosphere. [b] Isolated yield. dppe = 1,2-bis(diphenylphosphino)ethane; TEA = triethyl amine; DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; DIPEA = diisopropylethylamine. TEMED = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

the reaction (Table 1, entries 5–7). Common ligands (Table 1, entries 8–12) were also investigated and triphenylphosphine was the best choice to increase the yield to 71% (Table 1, entry 12). The screening of copper catalysts (Table 1, entries 12–18) shows that CuI performed the best and CuBr, CuCl and $CuBr{\cdot}Me_2S$ show poor catalysis, while CuCN, Cu_2O and $CuBr_2$ almost didn't work at all. We examined several bases simply and found that triethylamine was better than the others.

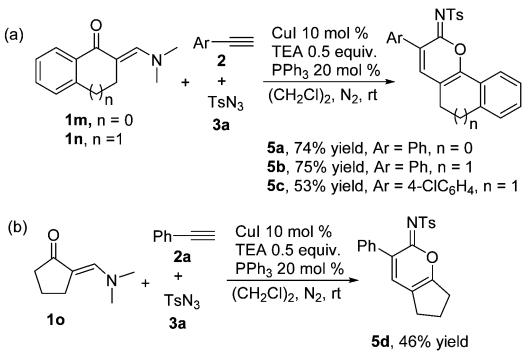
With the optimal conditions in hand, we applied this three-component cascade reaction to other enaminone substrates. As shown in Scheme 2, the substituents on the benzene ring impart some effects on the reaction. The substrate with a donating group could achieve good yield from 64% to 79% (**4a–4d**). A halogen substituted (F, Cl, and Br) substrate only gave the products in moderate yield from 43% to 52% (**4e**, **4f** and **4g**). The substrate with a nitro group only afforded a trace product which is not shown here. 2-Naphthyl substituted enaminone **1h** and 4-biphenyl substituted **1i** could also be tolerated in this process to deliver the desired products **4h** and **4i** in 51% and 57% yield, respectively. Additionally, heteroaromatic **2j** with a 2-thiophenyl group works well to give the target product **4j** in 60% yield. Moreover, the styryl enaminone **2k** proceeded smoothly to form product **4k** in 61% yield; while alkynyl substituted **2l** was suitable in this reaction despite the yield dropping to 41%. What's more, the structure of **4b** was further confirmed by X-ray crystal structure analysis.[14]



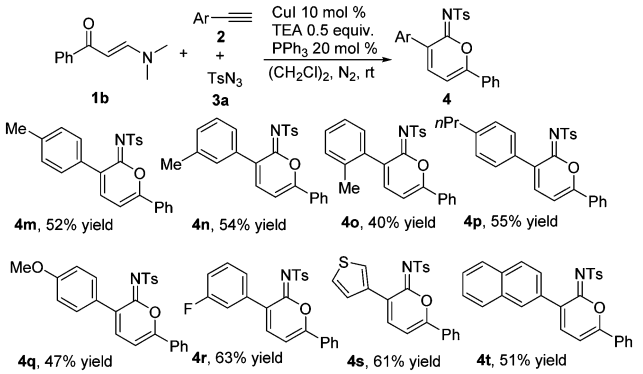
Scheme 2 Substrate scope of enaminone **1**. [a,b] [a]Conditions: enaminone **1** (0.4 mmol), **2a** (1 mmol), TsN_3 **3a** (1 mmol), TEA (0.2 mmol), PPh_3 (0.08 mmol) and CuI (0.04 mmol) in $(CH_2Cl)_2$ (2 mL). [b]Isolated yield.

Encouraged by these results, we turn our attention to exocyclic enaminones. 1-Indanone and α-tetralone derived **1m** and **1n** could also be employed in the copper catalyzed tandem reaction to provide moderate to good yields of the corresponding products (Scheme 3, eqn (a)). Meanwhile, **1o** from cyclopentanone participated well in this three component reaction despite the yield of **5d** decreasing to 46% (Scheme 3, eqn (b)).

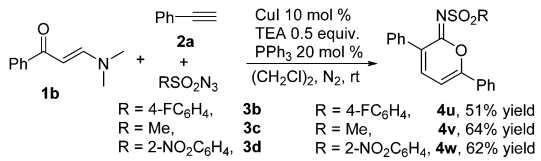
Next, a variety of aryl acetylenes was investigated to extend substrate diversity. As shown in Scheme 4, due to the steric hindrance, *o*-methyl phenylacetylene led to a lower yield of **4o**, while *m*-methyl phenylacetylene and *p*-methyl phenylacetylene afforded the corresponding products **4n** and **4m** in 54% and 52% yield, respectively. Other substituted phenylacetylenes, 2-ethynylnaphthalene and 3-ethynylthiophene, were also tolerated in this reaction to achieve the product in moderate yield. However, 1-ethynyl-1-cyclohexene only resulted in a trace product and 1-hexyne didn't work at all. Furthermore, 4-fluorobenzenesulfonyl azide **3b**, methanesulfonyl azide **3c** and 2-nitrobenzenesulfonyl azide **3d** were chosen to extend the scope of this three



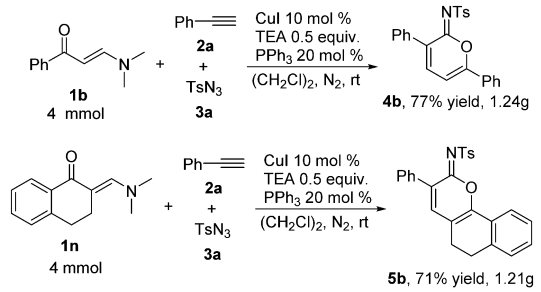
Scheme 3 Reactions of exocyclic enaminones.



Scheme 4 Substrate scope of aryl acetylene.



Scheme 5 Simple screening of sulfonyl azide.

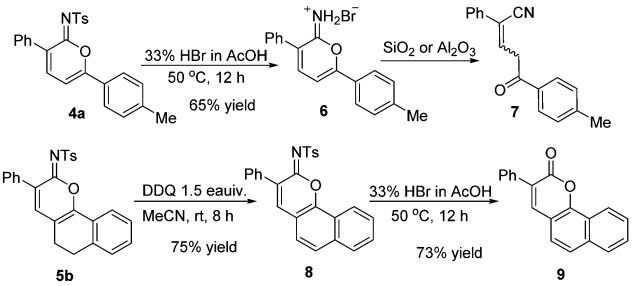


Scheme 6 Gram scale synthesis of iminolactones **4b** and **5b**.

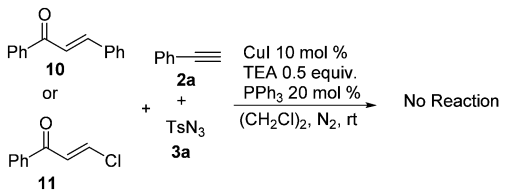
component reaction, and the target products were obtained successfully in moderate yield (Scheme 5). Notably, this copper catalyzed cascade reaction could be commenced in a gram scale for **4b** and **5b** with the yield maintained (Scheme 6).

In addition, the protection group Ts of **4a** could be removed in hydrobromic acid solution in acetic acid (33%) to get imine hydrobromide **6** in 65% yield, the analog of iminocoumarin, which is used as an antitumor agent,[15] a luminescence indicator[16] and dye.[17] The imine hydrobromide **6** was not stable on a silica gel or alumina during flash column chromatography and it was transformed to ketone **7**. Meanwhile, iminolactone **5b** could be oxidized by 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) in acetonitrile at room temperature to afford **8**, which could be hydrolysed to coumarin **9** (Scheme 7).

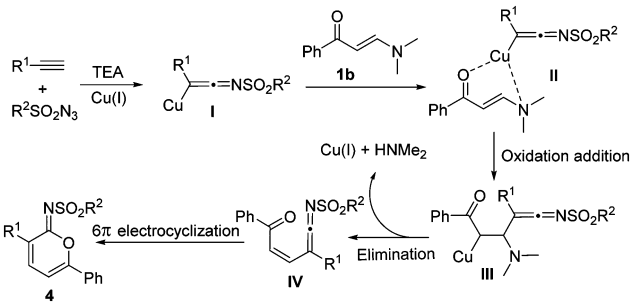
To understand this reaction better, control experiments were carried out (Scheme 8). Chalcone **10** didn't take part in this process at all, neither did 3-chloroenone **11** even if it contains a leaving group. A plausible mechanism for the present copper catalyzed three-component cascade reaction is shown in Scheme 9. Firstly, in the presence of base, copper-catalyzed alkyne–azide cycloaddition (CuAAC) took place to form metalated ketenimine **I**. The cooper in



Scheme 7 Transformation of iminolactones **4a** and **5b**.



Scheme 8 Control experiments.



Scheme 9 Proposed mechanism.

ketenimine **I** was coordinated with enaminone **1b** to give transition state **II**,[18] followed by oxidation addition and elimination to generate ketenimine **IV** that subsequently underwent 6π electrocyclization[19] to furnish iminolactone **4**.

In conclusion, we have developed a novel copper catalyzed three component cascade reaction, in which the metalated ketenimine *in situ* generated from copper-catalyzed alkyne–azide cycloaddition (CuAAC) attacked enaminone followed by 6π electrocyclization to construct iminolactone efficiently. A wide variety of aryl acetylenes and aryl enaminones could be employed to react with sulphonyl azide to deliver the desired products under mild reaction conditions. Notably, the exocyclic enaminones were also suitable in this methodology to furnish the analog of iminocoumarin. Moreover, *p*-toluenesulfonyl azide could be easily removed under mild conditions to yield imine hydrobromide.

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Conflicts of interest

There are no conflicts to declare.

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