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Copper-catalyzed cascade coupling/cyclization of terminal alkynes with diazoacetates: a straightforward route for trisubstituted furans

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ABSTRACT

A copper-catalyzed cascade coupling/cyclization of terminal alkynes with α-alkyl substituted diazoesters is developed. This new method furnished a straightforward route for 2,3,5-trisubstituted furan derivatives with good efficiency and selectivity.

Furans are important heterocycles and are present as key structural units in many biologically important natural products and pharmaceutical substances.[1] Furans are also widely used as useful building blocks for the total synthesis of complicated naturally occurring metabolites, and as versatile starting materials for the preparation of a variety of hetero-cyclic and acyclic compounds.[2] For these reasons, the development of novel and efficient approaches to furan derivatives has been an active research area over the past decades.[3] Among them, the intermolecular reaction of alkynes with metal carbene complexes, which often generated in situ from their corresponding diazo precursors, is one of the most interesting and reliable methods.[4] Pioneering work by Padwa has shown that cyclopropenation of acetylenes by rhodium carbenoids occurs to provide the cyclopropene adducts which subsequently rearrange to furan derivatives under metal catalysis.[4c–i]

Different from rhodium, copper complexes are known to catalyze the reaction between terminal alkynes with alkyl diazoacetates to give 3-alkynoates.[5] In 2004, Fu and co-worker described the CuI-catalyzed coupling of terminal alkynes with diazocarbonyl compounds to produce 3-alkynoates derivatives.[6] Although the reaction is applicable to various terminal alkynes, the diazo compounds employed in these studies are only limited to ethyl diazoacetate or *N*,*N*-dimethyl-α-diazoacetamide. Moreover, in several cases 2,3-allenoates are formed as minor products. Recently, we have developed a novel synthesis of trisubstituted allenes from Cu(I)-catalyzed cross-coupling of terminal alkynes and *N*-tosylhydrazones, which significantly extends the scope of the reaction to unstable diazo compounds.[7] More recently, Fox and co-workers have discovered an effective catalytic system for the coupling of α-aryl or α-alkyl substituted diazoesters with terminal alkynes. High yield of 2,3-allenoates are formed in the presence of base.[8] We have noticed that both 3-alkynoates[9] and 2,3-allenoates[10] are good precursors for the synthesis of ploysubstituted furans. However, a survey of literature has shown that one-pot method for accessing furans from alkynes with diazo compounds has not been described. As part of our ongoing interest in developing methods for the preparation of highly substituted furans,[11] we herein wish to report the first copper-catalyzed cascade coupling/cyclization of terminal alkynes with α-alkyl substituted diazoesters, which leads to the formation of 2,3,5-trisubstituted furans in moderate to good yields.

We began to explore this cascade coupling/cyclization process by surveying different potential catalysts and ligands with phenylacetylene (**1a**) and methyl 2-diazopropanoate (**2a**) as the substrates (Table 1). Among various copper catalysts examined, copper(II) salts, such as $CuSO_4$, $Cu(acac)_2$ and CuF_2 were not effective for the coupling of phenylacetylene with diazo compound **2a** (Table 1, entries 1–3). 1,3-Diynes, which were derived from the dimerization of phenylacetylene, was detected as the major product. However, we were delighted to find that copper(I) salts were catalytically active in this reaction (Table 1, entries 3-6) and CuI was found to afford the optimal result, leading to 27% yield of the desired trisubstituted furan **3a** and 12% yield of 3-alkynoate **4a**. Encouraged by this result, we then

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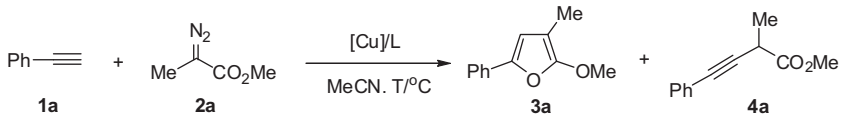
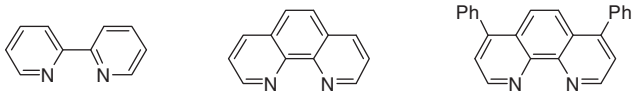
Table 1
Coupling of phenylacetylene with 2-diazopropanoate **2a** under different reaction conditions[13a]



1a **2a** **3a** **4a**

Entry	Cat (mol %)/L (mol %)	*T* (°C)	Additives	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	$CuSO_4$ (5)	rt	—	0	0
2	$Cu(acac)_2$ (5)	rt	—	0	0
3	CuF_2 (5)	rt	—	0	0
4	CuOTf (5)	rt	—	*Trace*	10
5	$Cu(MeCN)_4PF_6$	rt	—	15	15
6	CuI (5)	rt	—	27	12
7	CuI(5)/2,2'-bipyridine(5)	rt	—	52	11
8	CuI(5)/phenanthroline (5)	rt	—	57	8
9	CuI(5)/bathophenanthroline (5)	rt	—	21	16
10	CuI(5)/phenanthroline (5)	rt	HCO_2H (2.0 equiv)	*Trace*	*Trace*
11	CuI(5)/phenanthroline (5)	rt	HCO_2Na (2.0 equiv)	29	25
12	CuI(5)/phenanthroline (5)	rt	K_2CO_3 (2.0 equiv)	66	*Trace*
13	CuI(5)/phenanthroline (5)	40	—	73	<10
14	**CuI(5)/phenanthroline (5)**	**80**	**—**	**91**	**0**



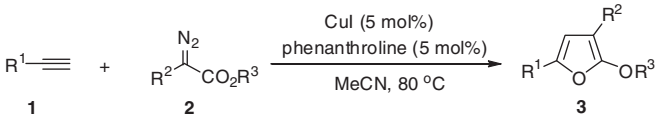
2,2'-bipyridine phenanthroline bathophenanthroline

[a] The reaction was conducted by using 0.25 mmol of diazo compound **2a** and 0.3 mmol of phenylacetylene in 2 mL MeCN for 12 h.
[b] The yield was determined by ^1H NMR spectroscopic analysis with CH_3NO_2 as the internal standard.

proceeded to test several ligands such as 2,2'-bipyridine, phenanthroline, bathophenanthroline (Table 1, entries 7–9), and the results showed that phenanthroline could efficiently promote the reaction. When phenylacetylene was reacted with **2a** in the presence of 5 mol % of CuI and 5 mol % of phenanthroline in CH_3CN at rt for 12 h, furan **3a** and 3-alkynoate **4a** were obtained in the yields of 57% and 8%, respectively. The effects of different additives such as HCO_2H, HCO_2Na and K_2CO_3 were also evaluated. It was observed that protonated reagents suppressed the formation of furan **3a**, while in the presence of base the desired furans could be obtained as the major product. Finally, we found that high temperature favored the formation of furan. When the reaction was carried out at 80 °C, the desired product **3a** could be obtained in 91% yield.

With the optimized conditions in hand, we then tested the scope of the present Cu(I)-catalyzed cascade coupling/cyclization process with a variety of terminal alkynes and α-substituted diazo compounds. As shown in Table 2, treatment of methyl 2-diazopropanoate (**2a**) and aromatic acetylene in the presence of 5 mol % of CuI and 5 mol % of phenanthroline in MeCN at 80 °C for 6 h yielded the corresponding trisubstituted furans in moderate to excellent yields (Table 2, entries 1–5). Functional group such as *t*-Bu and CF_3 were tolerated under the reaction conditions. It was noteworthy that heterocyclic alkynes (entry 7), naphthyl (entry 6) and alkyl alkynes (entries 8 and 9) were all suitable in this reaction. In several cases, 3-alkynoates were formed as minor products, however complete chemoselectivity leading to furan derivatives could be realized by adding 2 equiv of K_2CO_3. The optimized reaction conditions were also applied to a variety of diazo substrates, affording the desired trisubstituted furans **3j–m** in good to excellent yields (Table 2, entries 10–13). It is noteworthy that this reaction is operationally easy by simply mixing the diazo substrates, alkynes (1.25 equiv) and the catalyst, while in most protocols involving diazo compounds and alkynes, a larger excess of diazoester and a syringe-pump addition are usually necessary to avoid side reactions such as the formation of azines.

Table 2
Copper-catalyzed cascade coupling/cyclization with a series of terminal alkynes and diazoacetates[a]



1 **2** **3**

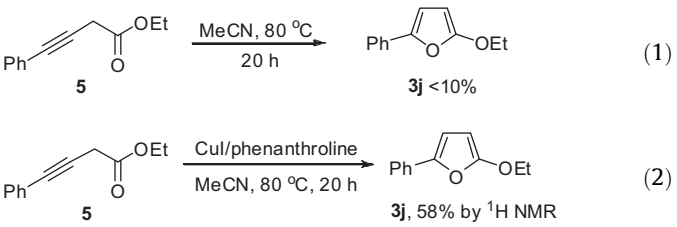
2a, R^2= Me, R^3= Me; **2b**, R^2= H, R^3= Et
2c, R^2= Me, R^3= Bn; **2d**, R^2= *n*-C_5H_{11}, R^3= Et
2e, R^2= *n*-C_5H_{11}, R^3= Et

Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	Ph	Me	Me	**3a**	92
2[c]	*p*-MeC_6H_4	Me	Me	**3b**	55
3	*p*-$^tBuC_6H_4$	Me	Me	**3c**	84
4[d]	*p*-$OMeC_6H_4$	Me	Me	**3d**	71
5	*p*-$CF_3C_6H_4$	Me	Me	**3e**	86
6	2-(6-OMe)naph	Me	Me	**3f**	79
7	3-Thienyl	Me	Me	**3g**	61
8[d]	*n*-C_4H_9	Me	Me	**3h**	82
9[d]	$PhCH_2CH_2$	Me	Me	**3i**	81
10	Ph	H	Et	**3j**	89
11	Ph	Me	Bn	**3k**	68
12	Ph	*n*-C_5H_{11}	Et	**3l**	95
13	Ph	*n*-C_5H_{11}	Bn	**3m**	86

[a] All the reactions were carried out by using 0.4 mmol of diazo compounds, 0.5 mmol of terminal alkynes in the presence of 5 mol % of CuI and 5 mol % of phenanthroline in 2 mL CH_3CN at 80 °C for 6 h.
[b] Isolated yield.
[c] 3-Alkynoate was isolated as the by-product in 31% yield.
[d] K_2CO_3 (2 equiv) was added as the base.

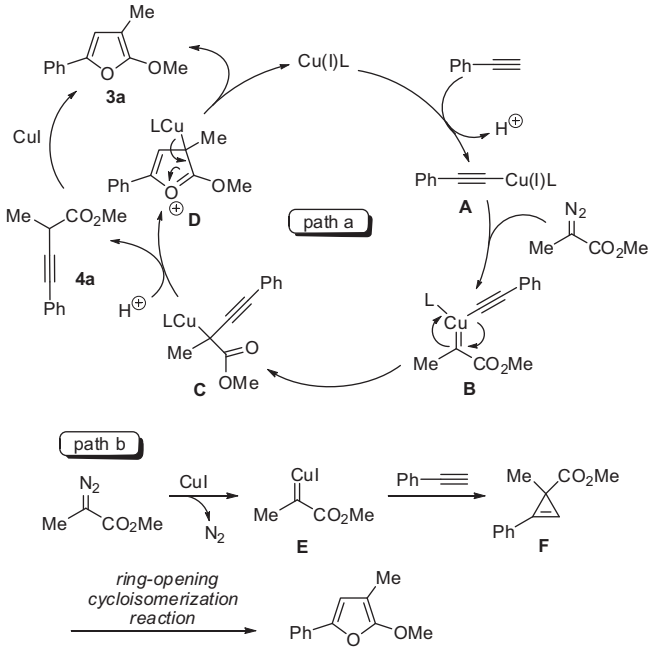
To gain insight into the reaction mechanism, we examined the reaction of 3-alkynoate **5** both in the absence and in the presence of CuI as catalyst in MeCN at 80 °C. Surprisingly, without CuI, none of the desired furan **3j** was observed even with prolonged reaction time (Eq. 1). On the contrary, with 5 mol % of CuI as the catalyst,

the furan **3j** was obtained in 58% yield after stirring in MeCN at 80 °C for 20 h (Eq. 2). These results suggest that without the promotion of CuI the triple bond cannot be attacked by carbonyl oxygen directly.



Based on our understanding on the Cu(I)-catalyzed cross coupling reaction of *N*-tosylhydrazones with terminal alkynes,[7,11c] we proposed a plausible mechanism to account for the current Cu(I)-catalyzed coupling of diazo compounds, as shown in path ***a*** of Scheme 1. Copper acetylide **A** is formed from phenylacetylene and Cu(I) salt, followed by the reaction of copper acetylide **A** with diazo substrate leading to the formation of copper carbene species **B**. Migratory insertion of alkynyl group to the carbenic carbon gives the intermediate **C**, which affords 3-alkynoate **4a** by the direct protonation. The intramolecular nucleophilic attack of the carbonyl group to triple bond produces the intermediate **D**. The latter undergoes a subsequent proton transfer to afford furan **3a** with simultaneous regeneration of the Cu(I) catalyst.

An alternative mechanism (path ***b***) is also proposed as shown in Scheme 1. The copper stabilized carbene complex **E** directly reacts with the triple bond to produce cyclopropenyl ester **F**, and then the CuI-catalyzed ring-opening cycloisomerization reaction of cyclopropenyl ester **F** affords furan and regenerates the catalyst CuI. However, Ma's reports on ring-opening cycloisomerization of cyclopropenyl carboxylates has revealed that this reaction is strictly catalyst-controlled.[12] When Cu(I) salts were employed as the catalyst, 2,3,4-trisubstituted furans were obtained in excellent yields with >99:1 selectivity. Furthermore, the observation of the formation of 3-alkynoate **4a** in our study indicates that path ***b*** is less likely in the present catalytic systems.



Scheme 1. Mechanistic rationale.

In conclusion, we have developed a copper-catalyzed cascade coupling/cyclization of terminal alkynes with α-alkyl substituted diazoesters. This new method furnished a straightforward route to 2,3,5-trisubstituted furans derivatives with good efficiency and selectivity. The scope, mechanism and synthetic application of this efficient coupling/cyclization reaction are now under investigation in our lab.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.060.

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13. *Representative experimental procedure for Cu(I)-catalyzed coupling/cyclization of diazo compounds with terminal alkynes*: CuI (3.8 mg, 5 mol %), and 1,10-phenanthroline (3.6 mg, 5 mol %) were suspended in CH_3CN (2 mL) in a 5 mL Schlenk tube under nitrogen. Then phenylacetylene (51 mg, 0.5 mmol) and methyl 2-diazopropanoate (51.2 mg, 0.4 mmol) were added. The resulting solution was stirred at 80 °C for 6 h. After cooling to room temperature, the mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 10:1) to give **3a** as a colorless oil (69 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 6.47 (q, J = 2.8 Hz, 1H), 3.74 (s, 3H), 2.00 (d, J = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 167.6, 132.5, 129.0, 127.9, 127.5, 99.3, 97.4, 52.5, 15.3; MS (70 eV), m/z (%): 188 (88) $[M]^+$, 173 (21), 145 (31), 128 (100), 105 (19), 77 (24).