Access to Ynamides via CuO-Mediated Oxidative Amidation of Alkynes

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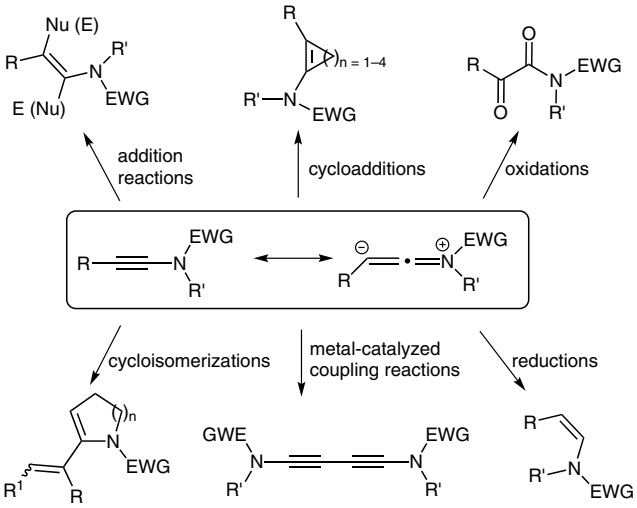
Abstract: Copper(II) oxide mediated the direct coupling of terminal alkynes and amides by way of C–H functionalization to afford ynamides as useful building blocks. Some alkali halides such as KCl were discovered to play a key role as additive in the coupling reaction, while other salts could suppress the formation of products.

Key words: alkylation, amides, copper, cross-coupling, oxidation

The nitrogen-substituted alkyne ynamines are versatile synthons for organic synthesis while being featured with instability and sensitivity. To improve the stability and expand the utility of ynamines, the electron-deficient ynamides were created by some distinguished chemists.[1,2] In 1972, Viehe and his co-workers generated the first ynamide by elimination of HCl from the corresponding α-chloroenamide which was obtained from benzylic amide.[3] Due to the excellent balance between stability and reactivity, ynamides rapidly received considerable attention from the synthetic community and became useful and versatile tools in organic synthesis in the following decades (Scheme 1).[4–11] More importantly, it is worthy to mention that some ynamides were also employed as an unparalleled building block in the total synthesis of natural products, which showed great potentialities in building some unusual skeletons.[12–15]

With regard to the development of methodologies for ynamide synthesis, the copper-catalyzed cross-coupling reaction is among the most efficient and economic methods for the formation of the ynamide C–N bond.[1,16] In 2003, Hsung and co-workers developed the pioneering copper-catalyzed C–N bond formation in ynamide synthesis. According to his study, a catalytic amount of CuCN or CuI could catalyze the oxazolidinone-based amide coupling with alkynyl bromide to form the corresponding ynamides.[17] Meanwhile, Danheiser reported a general amination strategy for the N-alkynylation of carbamates, sulfonamides, chiral oxazolidinones, and imidazolidinones via deprotonation of amides with KHMDS followed by reaction with stoichiometric CuI and an alkynyl bromide.[18] Inspired by Hsung's compelling results, Skrydstrup,[19] Urable,[20] and Kerwin[21] modified the Hsung's system to discover some new copper sources, ligands, and bases, respectively. Evano reported that the combination of CuI and DMEDA (*N*,*N*′-dimethylethyldiamine) could directly convert 1,1-dibromo-1-alkenes into the corresponding ynamides.[22] More recently, Jiao developed the copper-catalyzed aerobic oxidative amidation of propiolic acids via decarboxylation under air to synthesize various ynamides.[23] However, the direct formation of ynamides by coupling unactivated alkynes and amides was still full of challenge. In 2008, Stahl documented the first copper-catalyzed aerobic oxidative amidation of terminal alkynes and proposed a mechanism for the functionalized C–H reaction catalyzed by $CuCl_2$.[24] As part of developing methodologies for efficient natural products synthesis, herein, we report another observation of a C–H functionalization method for the synthesis of ynamides via a CuO-mediated direct coupling of terminal alkynes with nitrogen nucleophiles in the presence of alkali halide.



Scheme 1 Representative reactions of ynamides

We discovered that CuO could couple alkynes with 2-oxazolidinone to generate the corresponding ynamides without the assistance of oxygen and base. When 2.5 equivalents of CuO were added to the mixture of *p*-anisylacetylene and 2-oxazolidinone in toluene at 80 °C, we observed the formation of ynamide **3** in around 38% yield, together with trace amount of homocoupled dimer **4** (Table 1, entry 1). To improve the coupling yield, we optimized the reaction conditions by screening the solvents, temperature, as well as the ratio of substrates. But all these efforts did not considerably increase the yield, and the

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reaction did not process in some of the solvents, such as DMF, DMSO, and dioxane, etc. Excitingly, the yield of coupling product **3** was doubled when five equivalents of NaCl were added (Table 1, entry 3). We then utilized different salts as additives to explore the reaction, and noticed that some of the alkali halides, that is, KCl, NaBr ,and KBr, also could increase the formation of ynamides. Meanwhile, other salts, such as $MgCl_2$, instead were found to suppress the reaction and led to no detectable products (Table 1, entry 8). In order to figure out the ratio of alkali halide as additive, the amount of KCl was reduced, and the reaction results showed that the amount of 0.2 equivalents for the additive is still enough to accelerate the coupling reaction. Using the reduced amount of additive gave a better yield than carrying out the reaction with five equivalents (Table 1, entry 10).

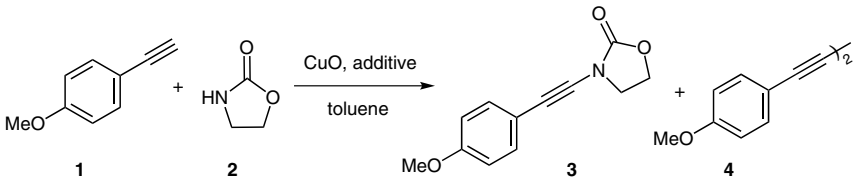
We then examined the CuO-mediated coupling reaction for the synthesis of ynamides from different oxozolidinones. The steric effects of substituents were illustrated obviously among the 4-substituted oxozolidinones (Scheme 2, compounds **7**–**9**).[25] When the substituents were bulky, the yields of the corresponding ynamides decreased.

The coupling of 2-oxazolidinone with various terminal alkynes were also investigated using the optimized reaction conditions. As depicted in Scheme 2, electron-rich alkynes including aryl- and silyl-substituted terminal alkynes led to the desired ynamides in good isolated yields (compounds **10**–**13**). However, when 4-nitrophenylacetylene and 2-ethynylpyridine were subjected to the reaction system, the corresponding *Z*/*E* enamides were obtained without observation of the expected ynamides, respectively (compounds **14** and **15**). This side reaction was also reported by Gabriele and Salerno in the synthesis of 2-ynamides by direct palladium-catalyzed oxidative aminocarbonylation of 4-nitrophenylacetylene.[26] In general, these results indicate that the electronic effect plays a crucial role in CuO-mediated coupling reaction, and electron-rich alkynes were more effective while alkynes with electron-withdrawing groups would lead to the corresponding enamides.

A mechanism for the CuO-mediated amidation of terminal alkynes is proposed, as depicted in Scheme 3. Initially, the terminal alkyne was treated with two equivalents of CuO to functionalize the terminal C–H bond. After forming the copper-intermediate **A**, it was attacked by nitrogen nucleophiles to afford copper-intermediate **B** and lose one equivalent of H_2O, which next underwent the C–N reductive elimination to give the ynamide together with Cu_2O.

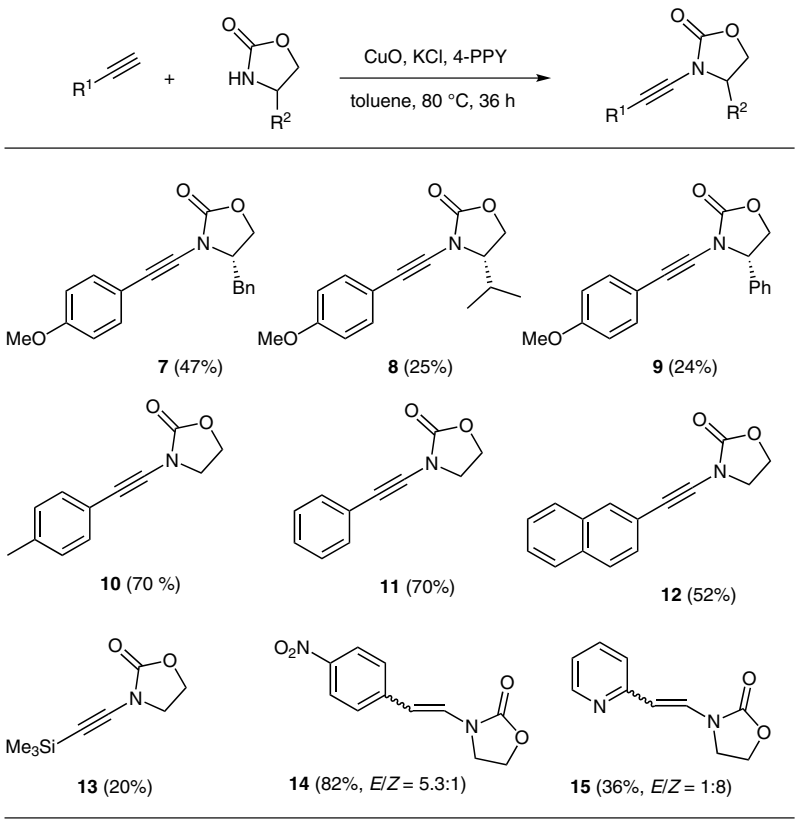
In summary, a novel CuO-mediated oxidative amidation of terminal alkynes by way of a C–H functionalization to afford versatile ynamides was described. It was discovered that alkali halides such as KCl could enhance the generation of products.

Table 1 Selected Additives for the Synthesis of Ynamides

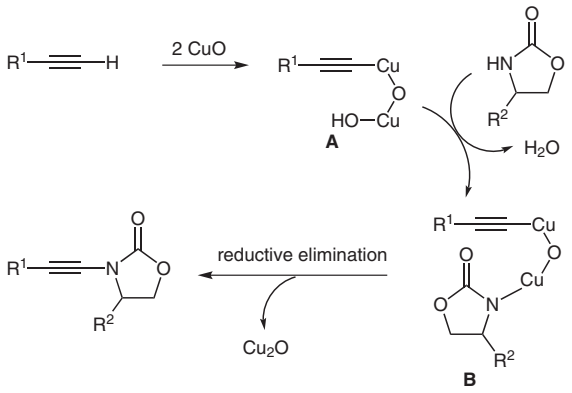


Entry[a]	Additive	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	–	38	1
2	LiCl	10	22
3	NaCl	77	5
4	KCl	81	4
5	NaBr	80	9
6	KBr	62	10
7	KI	21	25
8	$MgCl_2$	n.d.[c]	n.d.[c]
9	$CaCl_2$	18	3
10	KCl (0.2 equiv)	88	5

[a] General reaction conditions: *p*-anisylacetylene (1 equiv), 2-oxozolidinone (5 equiv), CuO (2.5 equiv), and additive (5 equiv) in toluene at 80 °C under argon for 36 h.
[b] Isolated yield.
[c] Not detected by TLC.



Scheme 2 Extended CuO-mediated coupling of alkynes and scope of nitrogen nucleophiles



Scheme 3 Proposed mechanism for the oxidative amidation of terminal alkynes mediated by CuO

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(25) **General Procedures for the Synthesis of Ynamides**
In a dry 25 mL round-bottom flask, CuO (1.93 mmol), KCl (0.154 mmol), 4-PPY (0.154 mmol), and the 2-oxazolidinone (3.85 mmol) were added to dry toluene (5 mL) under argon. The flask was placed in an oil bath, and 4-ethynylanisole (0.77 mmol) was added. Then, the reaction mixture was stirred for 36 h at 80 °C. After the crude mixture was filtered and concentrated under vacuum, the mixture was separated on a silica gel column using hexanes–EtOAc (2:1) as eluent to afford the ynamide.
Analytical Data of Selected Compounds
Ynamide 7[27a]
Colorless acicular crystal. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.1 Hz, 2 H), 7.35–7.28 (m, 3 H), 7.24–7.23 (m, 2 H), 6.85 (d, *J* = 9.1 Hz, 2 H), 4.33 (m, 2 H), 4.14 (m, 1 H), 3.80 (s, 3 H), 3.25 (dd, *J* = 14.0, 3.5 Hz, 1 H), 3.00 (m, 1 H); $[\alpha]_D^{18}$ +82.1 (*c* 3.01, $CHCl_3$); known compound.
Ynamide 8
Colorless acicular crystal. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.42 (t, *J* = 8.8 Hz, 1 H), 4.19 (d, *J* = 8.8, 6.0 Hz, 1 H), 4.03 (m, 1 H), 3.81 (s, 3 H), 2.29 (m, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 156.1, 133.4, 114.3, 113.9, 77.0, 71.9, 64.8, 62.1, 55.3, 29.2, 17.2, 15.2. ESI-HRMS: *m/z* calcd $[M + H]^+$ = 260.1286; found: 260.1281; $[\alpha]_D^{18}$ +28.2 (*c* 2.57, $CHCl_3$).
Ynamide 9[27b]
Colorless acicular crystal. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 5.05–5.01 (m, 1 H), 4.70–4.66 (m, 1 H), 4.20 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.67 (m, 3 H); $[\alpha]_D^{18}$ +154.9 (*c* 1.36, $CHCl_3$); known compound.
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