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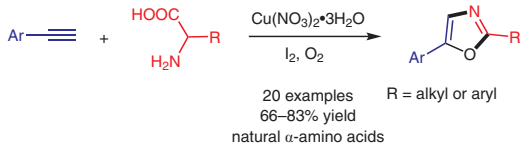
Synthesis of 2,5-Disubstituted Oxazoles from Arylacetylenes and α-Amino Acids through an $I_2/Cu(NO_3)_2 \cdot 3H_2O$-Assisted Domino Sequence

Jungang Wang[a]
Yan Cheng[b]
Jiachen Xiang[b]
Anxin Wu*[b]

[a] School of Chemical Engineering, Guizhou Minzu University, Guiyang 550025, P. R. of China
[b] Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. of China
chwuax@mail.ccnu.edu.cn



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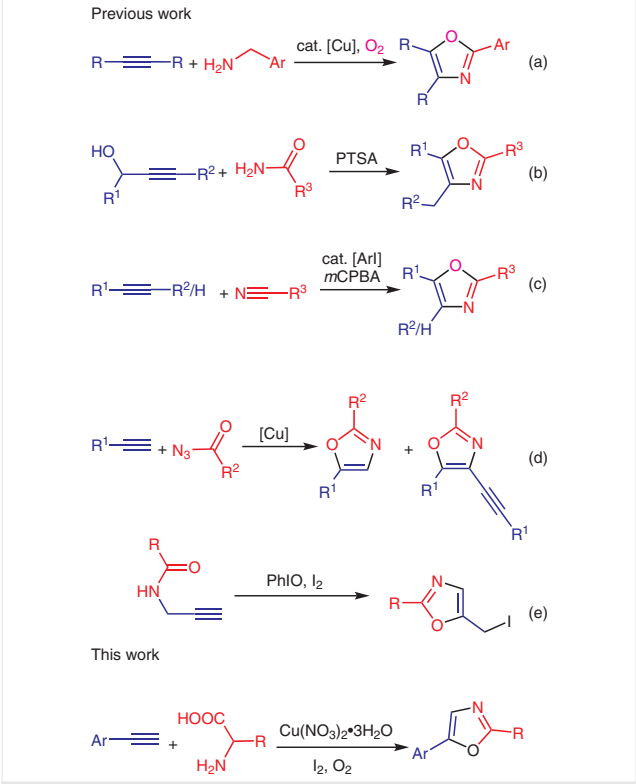
Abstract A new strategy has been developed for the synthesis of 2,5-disubstituted oxazoles from easily available arylacetylenes and α-amino acids in the presence of $Cu(NO_3)_2 \cdot 3H_2O$ and iodine. This reaction process involves the $I_2/Cu(NO_3)_2 \cdot 3H_2O$-assisted transformation of arylacetylene to α-iodo acetophenone, Kornblum oxidation to phenylglyoxal, condensation to imine, decarboxylation/annulation/oxidation reaction sequence to approach 2,5-disubstituted oxazoles.

Key words oxazoles, α-amino acids, copper catalysis, cascade reactions, alkynes

Substituted oxazoles have wide applications in many pharmacologically active synthetic molecules and natural products,[1] such as tumor-inhibitor peptide laboradorin 1-2,[2] alkaloid (–)-muscoride A,[3] antibacterial inhibitor pimprinols A–C,[4] antidiabetic agent AD-5061,[5] anti-inflammatory drugs aristoxazole,[6] oxaprozin,[7] and JTE-522.[8] They are also widely used as synthetic intermediates in organic synthesis and important ligands for transition-metal catalysis.[9] Therefore, substantial effort has been devoted to the development of methodologies for the synthesis of these privileged structural motifs. A variety of methods have been reported, including metal/halogen-promoted intramolecular[10] or intermolecular[11] cyclization of acyclic precursors, transition-metal-catalyzed bimolecular annulation,[12] oxidation of oxazolines,[13] the C–C coupling of prefunctionalized oxazoles with various organometallic reagents,[14] and other elegant protocols recently reported.[15] Among them, the cyclization of alkynes and nitrogenous compounds such as the heterocyclization of alkynes with benzyl amine,[16] amides,[17] nitrides,[18] acyl azide,[19] nitrides and intramolecular cyclization of alkynyl amides[20] attracted the chemists' attention (Scheme 1). More recently, amino acids acting as a sort of environmentally friendly starting materials aroused the interest of many chemists, because a very efficient synthetic method for heterocycles was provided.[21] To the best of our knowledge, currently not a single method has been reported for the synthesis of oxazoles from



Scheme 1 Synthesis of substituted oxazoles from alkynes and nitrogenous compounds

alkynes and amino acids. Enlightened by the reported results, we tried to synthesize 2,5-disubstituted oxazoles from arylacetylene and α-amino acids.

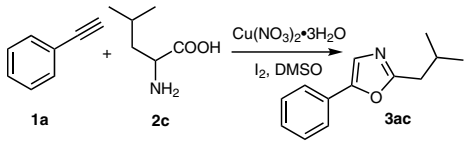
Initially, our investigation focused on the favorable conditions of the reaction to synthesize the oxazole derivatives from phenylacetylene and leucine (2-amino-4-methylpentanoic acid). To our delight, a 2,5-disubstituted oxazole product **3ac** was obtained in 58% yield when phenylacetylene (1.0 mmol) and 2-amino-4-methylpentanoic acid (1.0 mmol) were mixed with $Cu(NO_3)_2$•$3H_2O$ (1.0 mmol) and I_2 (1.0 equiv) in DMSO at 60 °C (Table 1, entry 1). Increasing or reducing the amount of iodine could not raise the yield, and the reaction could not be carried out without iodine (Table 1, entries 2–4). Different copper salts such as $CuSO_4$, CuBr, CuO and typical Lewis acids such as $ZnCl_2$, $AlCl_3$ were also used to analyze the effects of these additives (Table 1, entries 5–11). The results show that $Cu(NO_3)_2$•$3H_2O$ was best for the reaction.

After screening varying amounts of $Cu(NO_3)_2$•$3H_2O$, we found that the yield was highest when the amount was 0.5 equivalents and dropped significantly to 16% in the absence of $Cu(NO_3)_2$•$3H_2O$ (Table 1, entries 12, 13, 15, 16). Other solvents, such as DMF, NMP, DMA, were also tried, but no better results were obtained (Table 1, entries 17–19). The effect of the temperature was also considered to optimize the reaction conditions; it was difficult to perform the reaction at room temperature, whereas a lower yield (relative to Table 1, entry 13) was obtained at higher temperatures (Table 1, entries 20–22). After the above experimental optimizations, we found that **1a** (1 mmol) could react with **2c** (1 mmol) in the presence of $Cu(NO_3)_2$•$3H_2O$ (0.5 mmol) and I_2 (1.0 mmol) in DMSO at 60 °C to afford the desired product in 79% yield after 5 h.

Relying on the successful synthesis of the oxazole **3ac**, we investigated a range of other phenylacetylenes and α-amino acids as shown in Scheme 2. For example, aromatic amino acids such as phenylglycine, phenylalanine and aliphatic amino acids such as leucine, isoleucine, and valine reacted smoothly with phenylacetylene to afford the corresponding products in moderate to good yields (Scheme 2, **3aa**–**ae**, 71–79%). Meanwhile, the derivatives of ethyl phenylacetylene substituted with electron-withdrawing or electron-donating groups on the phenyl ring also exhibited good reactivity (Scheme 2, **3ba**–**fc**, 66–83%). Encouraged by the results of arylacetylenes, we further focused on heteroaryl acetylenes. Fortunately, the reactions of substrates such as 2-ethynylthiophene, 3-ethynylthiophene, 4-ethynylpyridine, and 1-ethynylnaphthalene also took place smoothly to furnish the desired products in moderate to good yields (Scheme 2, **3ka**–**lc**, 69–77%).

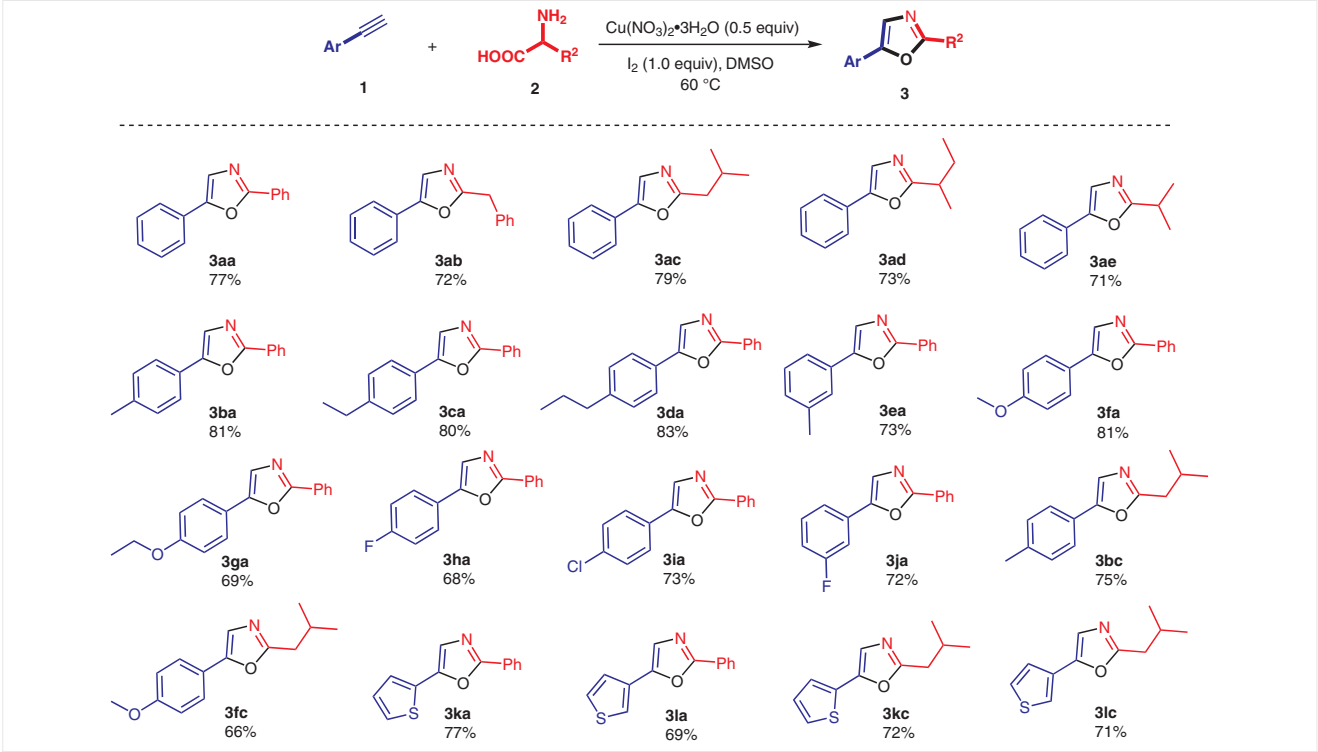
Having established the scope of the method, we performed the following experiments to gain some insight into the mechanism of the reaction (Scheme 3). First, it was found that the reaction was unable to proceed smoothly in the absence of I_2 (Table 1, entry 4), which emphasized the crucial role of I_2 in the transformation. Copper nitrate also played an important role in promoting the progress of the reaction (Table 1, entry 12). According to the control experiments, phenylacetylene was stirred under standard conditions to produce α-iodo acetophenone (**4a**) and phenylglyoxal (**5a**) in yield of 38% and 23%, respectively, in the absence of amino acid substrates (Scheme 3, a). When the phenylacetylene substrate was replaced with α-iodo acetophenone (**4a**), the desired product **3ac** was obtained in 72% in the presence of $Cu(NO_3)_2$•$3H_2O$ and in 56% without $Cu(NO_3)_2$•$3H_2O$ (Scheme 3, b and c). The reaction of phenylglyoxal (**5a**) and 2-amino-4-methylpentanoic acid (**2c**) also gave the desired product with satisfactory yields both with (76% yield) and without (74% yield) $Cu(NO_3)_2$•$3H_2O$ (Scheme

Table 1 Reaction Optimization[a]



Entry	Additive (equiv)	I_2 (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	$Cu(NO_3)_2 \cdot 3H_2O$ (1.0)	1.0	DMSO	60	58
2	$Cu(NO_3)_2 \cdot 3H_2O$ (1.0)	0.5	DMSO	60	35
3	$Cu(NO_3)_2 \cdot 3H_2O$ (1.0)	1.5	DMSO	60	51
4	$Cu(NO_3)_2 \cdot 3H_2O$ (1.0)	0	DMSO	60	<5
5	$CuSO_4$ (1.0)	1.0	DMSO	60	23
6	CuBr (1.0)	1.0	DMSO	60	26
7	CuO (1.0)	1.0	DMSO	60	8
8	$CuBr_2$ (1.0)	1.0	DMSO	60	76
9	$Cu(OAc)_2 \cdot 2H_2O$ (1.0)	1.0	DMSO	60	62
10	$ZnCl_2$ (1.0)	1.0	DMSO	60	34
11	$AlCl_3$ (1.0)	1.0	DMSO	60	<5
12	–	1.0	DMSO	60	16
13	**$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)**	**1.0**	**DMSO**	**60**	**79**
14	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	0.1	DMSO	60	25
15	$Cu(NO_3)_2 \cdot 3H_2O$ (0.2)	1.0	DMSO	60	74
16	$Cu(NO_3)_2 \cdot 3H_2O$ (2.0)	1.0	DMSO	60	42
17	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	DMF	60	20
18	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	NMP	60	<5
19	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	DMA	60	<5
20	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	DMSO	25	<5
21	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	DMSO	80	47
22	$Cu(NO_3)_2 \cdot 3H_2O$ (0.5)	1.0	DMSO	100	71

[a] Reaction conditions: **1a** (1.0 mmol), **2c** (1.0 mmol), additive, I_2, and solvent (4.0 mL) were added to a pressure vessel, and then stirred at 60 °C for 5 h.
[b] Isolated yields.

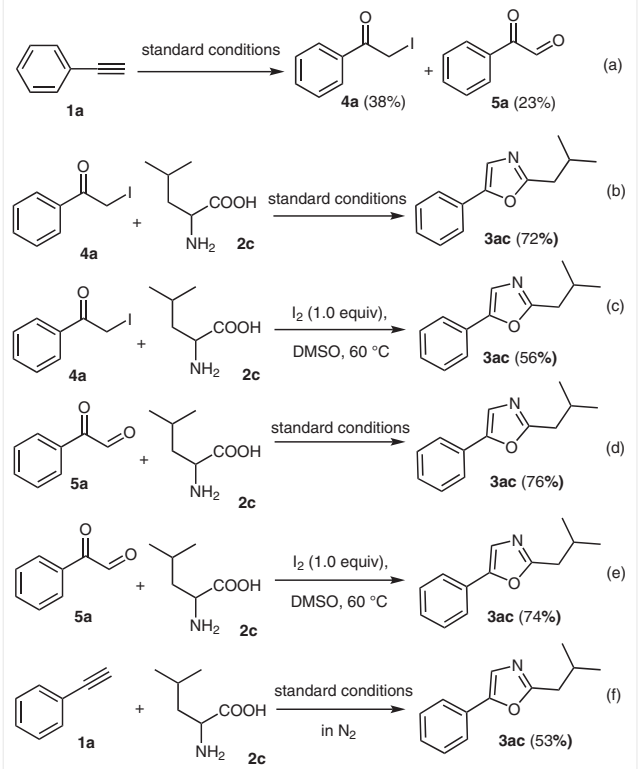


Scheme 2 Scope of aryl acetylenes and α-amino acids

3, d and e). These results show that **4a** and **5a** are the crucial intermediates in the process. Hydrated copper nitrate was irreplaceable in the formation of phenacyl iodine from phenylacetylene substrate. When the reaction was carried out under a nitrogen atmosphere, the target product could still be obtained in a yield of 53% (Scheme 3, f). This suggests that the oxygen atom in the oxazole might not be introduced from oxygen.

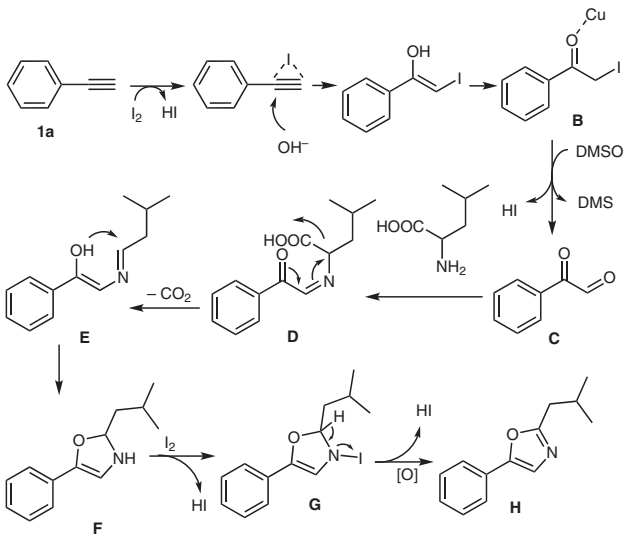
On the basis of the results described above and the literature reports[22–25], a plausible mechanism of this transformation was proposed by taking the reaction of phenylacetylene (**1a**) and 2-amino-4-methylpentanoic acid (**2c**) as an example. The substrate phenylacetylene was converted into the intermediate α-iodo acetophenone **B** in the presence of I_2 and Cu(II). Subsequently, **B** was oxidized by DMSO to phenylglyoxal **C**. Then, amino acid **2c** reacted with **C** to afford **D**, and **D** isomerized through a [1,5]-H shift, followed by decarboxylation to obtain intermediate **E**. Then, the nucleophilic hydroxyl group underwent an intramolecular cyclization, and subsequent oxidation gave the desired oxazole (Scheme 4).

In conclusion, we have developed an $I_2/Cu(NO_3)_2•3H_2O$-assisted domino reaction for the direct synthesis of 2,5-disubstituted oxazoles from easily available arylacetylenes and natural α-amino acids.[26] This reaction process involves the $I_2/Cu(NO_3)_2•3H_2O$-assisted transformation of phenylacetylene to α-iodo acetophenone, Kornblum oxidation to



Scheme 3 Control experiments

phenylglyoxal, condensation to imine, decarboxylation/annulation/oxidation reaction sequence to approach to 2,5-disubstituted oxazoles.



Scheme 4 Mechanistic proposal

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612087.

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(26) **General procedure for synthesis of 3 (3ac as an example)**
The mixture of phenylacetylene **1a** (1.0 mmol), 2-amino-4-methylpentanoic **2c** (1.0 mmol) was mixed with $Cu(NO_3)_2$•$3H_2O$ (0.5 mmol), and I_2 (1.0 mmol). The mixture was heated at 60 °C in 4 mL of DMSO in a sealed vessel for 5 h till almost completed conversion of the substrates monitored by TLC analysis. Then 50 mL water was added to the mixture, which was extracted with EtOAc three times (3 × 50 mL). The extract was washed with $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 then the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 50/1) to afford the product **3ac**" here