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A facile one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives mediated by CuCN

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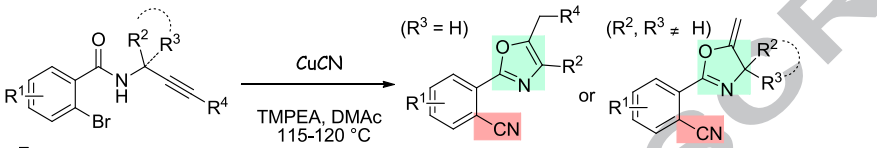

- Convenient one-pot synthesis of useful 2-*o*-cyanoaryl oxazole derivatives;
- A variety of substituents are well tolerated;
- CuCN plays dual roles as a Lewis acid and a CN^- source;
- *Ortho* effect was observed

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A facile one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives mediated by CuCN

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ABSTRACT

A convenient, inexpensive and effective approach to the synthesis of 2-*o*-cyanoaryl oxazole derivatives has been developed. Generally, the copper-mediated cyclization/coupling reactions afforded corresponding 2-cyanoaryl oxazoles and oxazolines in moderate to excellent yields. The functionalized oxazole derivatives may be useful in biological chemistry and medicinal science. Our investigation indicates that the formation of the oxazole ring might favor the C-C bond forming process on the *ortho*-position of the aryl ring. And CuCN plays dual roles as a Lewis acid catalyst and a C-nucleophile in this transformation.

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Substituted oxazoles are found in many natural products and synthetic drugs exhibiting important biological activities.[1] They are also applied as intermediates[2] in organic synthesis. And 2-aryl substituted oxazoles and oxazolines are important heterocycles because of their bioactivities and physical properties.[1b,3] Among these heterocyclic molecules, 2-cyanoaryl oxazole derivatives were reported as useful molecules in biological chemistry and medicinal science. For example, a 2-*o*-cyanoaryl oxazole derivative (Figure 1, **A**) can be utilized for treating PPAR related diabetes, dyslipidemia, obesity and inflammatory disorders;[4] an N-cyanomethylcyclohexane-carboxamide containing 2-cyanoaryl oxazole moiety (**B**) was studied as a cathepsin cysteine protease inhibitor;[5] 2-*o*-cyanophenyl oxazole (**C**) might possess antiprotozoal activity;[6] and certain oxazoles bearing cyanoaryl substituent such as (**D**) were evaluated to have potential activity against eIF4A3.[7]

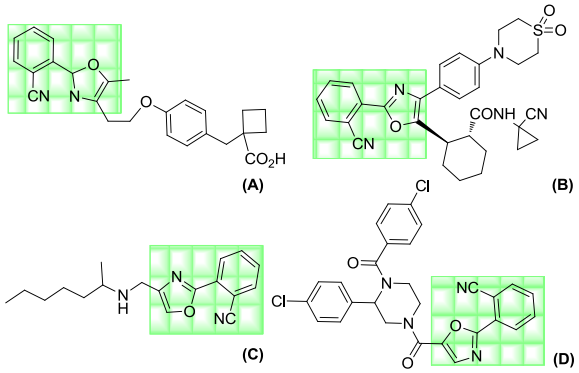

Figure 1. Some biologically active 2-*o*-cyanoaryl oxazole derivatives.

The typical methods utilized to build the 2-aryl oxazole motif include the condensation between α-hydroxynitriles and benzaldehydes (Fischer oxazole synthesis),[8] the arylation of oxazoles[9] or 2-halo oxazoles,[10] the cylization of N-propargylbenzamides,[11] etc.[1b,12] Although there are numerous synthetic routes to the assembly of 2-aryl oxazoles, there still remains a need for more convenient and efficient approaches that afford 2-*o*-cyanoaryl oxazoles in one pot.

Copper-mediated domino reactions has recently aroused increasing interest since they provide facile and efficient approaches to the one-pot construct of structurally diversified molecules.[13] Our group are interested in developing copper-mediated one-pot reactions for the convenient assembly of various heterocycles.[14] Herein, we report a facile one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives from the domino reactions of *o*-bromo N-propargylbenzamides mediated by CuCN.

At the outset of our studies, the reaction of *o*-bromo N-propargylbenzamide **1a** with CuCN was chosen as the model reaction to study the feasibility of this one-pot synthesis (Table 1, entry 1). A moderate yield of the expected *o*-cyano-modified 2-phenyl oxazole **2a** was delivered when the substrate **1a** reacted with CuCN in the presence of diisopropylethylamine (DIPEA, 2 equiv) in refluxing dioxane (entry 1). Under these conditions, a small amount (23%) of by-product **3a** generated from the simple cyclization of **1a** was isolated. Two common ligands (L-proline and 1,10-phen) were tested for this copper-mediated one-pot transformation in order to enhance the efficiency of the coupling process. However, the results were unsatisfying in both cases (entries 2 and 3). Then a variety of bases were evaluated. The

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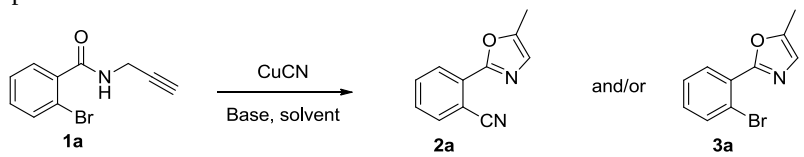
investigation indicated that the bases have significant effect on the reaction efficacy (entries 4-11). TEA and DMAP showed slightly less effective than DIPEA, and the use of TMEDA, DABCO, DBU and inorganic bases (such as K_2CO_3 and Cs_2CO_3) were ineffective for this transformation. Gratifyingly, the reaction worked better when TMPEA was employed (entry 9). Different solvents were also studied for this transformation (entries 9 and 12-17). And DMAc was proven to be the optimal solvent for the one-pot reaction (entry 14). The yield of the desired product **2a** could be improved slightly when the mixture was stirred at 115 °C (entry 18). However, the result was deteriorated when the reaction was performed at 120 °C (entry 19), probably because the rate of hydrolysis of the amide-type substrate increased at a higher temperature under the basic conditions. All of the trials afforded the cyclized product with excellent regioselectivity and 5-*exo-dig* cyclization was exclusively observed in each case.

Table 1. Optimization of the reaction conditions[a]



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

Entry	Solvent	Base	Ligand	Temp. (°C)	Yield of **2a**[b]	Yield of **3a**[b]
1	dioxane	DIPEA[c]	-	101	45%	23%
2	dioxane	DIPEA	L-proline[d]	101	32%	18%
3	dioxane	DIPEA	1,10-phen[d]	101	nd	trace
4	dioxane	TEA	-	101	38%	34%
5	dioxane	TMEDA[e]	-	101	trace	nd
6	dioxane	DABCO	-	101	trace	51%
7	dioxane	DBU	-	101	trace	45%
8	dioxane	DMAP	-	101	34%	40%
9	dioxane	TMPEA[f]	-	101	56%	16%
10	dioxane	K_2CO_3	-	101	nd	trace
11	dioxane	Cs_2CO_3	-	101	nd	nd
12	toluene	TMPEA	-	105	trace	32%
13	DMF	TMPEA	-	110	61%	18%
14	DMAc	TMPEA	-	110	70%	12%
15	DMSO	TMPEA	-	110	trace	nd
16	NMP	TMPEA	-	110	49%	21%
17	2-methoxy ethanol	TMPEA	-	110	46%	20%
18	DMAc	TMPEA	-	115	75%	7%
19	DMAc	TMPEA	-	120	62%	trace

[a] Reaction conditions: unless otherwise noted, the reaction was carried out with substrate **1a** (0.5 mmol), CuCN (0.65 mmol, 1.3 equiv.), base (2.0 mmol, 4.5 equiv.), in solvent (2 mL) at indicated temperature for 24 h.

[b] Isolated yield.

[c] DIPEA = Diisopropylethylamine.

[d] Ligand (20 mol%) was added.

[e] TMEDA = Tetramethylethylenediamine.

[f] TMPEA = Tetramethylpropylenediamine.

Having established the optimal reaction conditions for the copper-mediated cycloisomerization/coupling, the scope and generality of this method were subsequently investigated. As summarized in Table 2, the one-pot transformation showed broad substrate scope and furnished the corresponding 2-*o*-cyanoaryl oxazoles **2** in moderate to excellent yields.[15] First, several substrates with different substituents on the *o*-bromophenyl ring were employed (the synthesis of **2a**-**2d**). The reaction proceeded smoothly when the substrates have either electron-withdrawing group (*p*-Cl, *p*-CF_3) or electron-donating group (*p*-OMe) on the aromatic ring. Variation of the substituents at the α-position of the N-propargyl group was also feasible (the synthesis of **2e**-**2u**). A variety of alkyl groups such as benzyl (**2e**-**2f**), phenethyl (**2g**-**2i**), phenylpropyl (**2j**-**2k**) were well tolerated. The reactions of substrates bearing long linear or branched groups also afforded the corresponding substituted oxazoles in moderate yields (the synthesis of **2l**-**2m**). Interestingly, the substrates with α-disubstituted *N*-propargyl groups reacted more effectively and gave excellent yields of the desired 2-*o*-cyanoaryl oxazolines (the synthesis of **2n**-**2t**). Notably, several spirocyclic oxazoline derivatives were efficiently assembled when *o*-bromo *N*-(1-ethynylcyclohexyl)benzamides were utilized as the substrates (the synthesis of **2q**-**2t**). A relatively lower yield was obtained when the phenyl was introduced onto α-position of the N-propargyl group (the synthesis of **2u**). The reaction of a piperinic acid-derived substrate also proceeded successfully and the corresponding heterocyclic derivative was constructed in a moderate yield (the synthesis of **2v**). When a substrate with an α,γ-disubstituted *N*-propargyl group was applied, the desired oxazoline product could also be generated, despite the relatively lower the yield (the synthesis of **2w**).

We then attempted to apply our method to the synthesis of *m*-cyanoaryl and *p*-cyanoaryl oxazoles. To our surprise, only moderate yields of the by-products (**3h** and **3g**) generated from the simple cyclization were detected in company with trace amounts of final products **2** in both cases (Scheme 1, eq. 1 and eq

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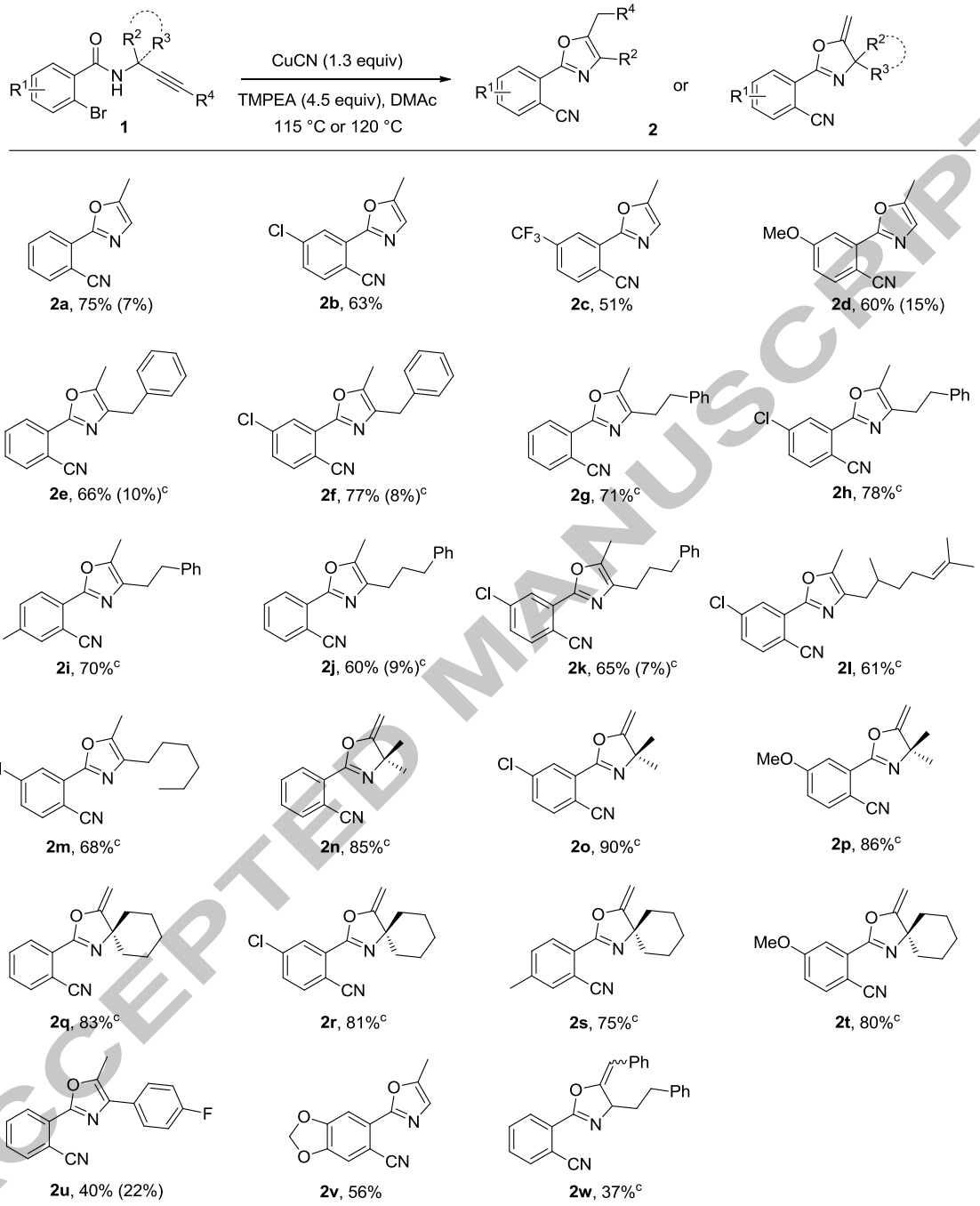
Table 2. CuCN-mediated one-pot synthesis of various 2-*o*-cyanoaryl oxazole derivatives[a,b]



[a] Reaction conditions: unless otherwise noted, the reaction was carried out with substrate **1** (0.5 mmol), CuCN (0.65 mmol, 1.3 equiv.), TMPEA (2.0 mmol, 4.5 equiv.), in DMAc (2 mL) at 115 °C for 24 h.

[b] Isolated yields of product **2** were reported. In some cases, by-product **3** generated from the simple cyclization of **1** was also isolated and the yields were given in parentheses.

[c] At 120 °C.

2). Almost no cyanated products were detected when the isolated 2-*m*- and 2-*p*-bromophenyl oxazoles **3h** and **3i** were subjected to the reactions under the CuCN-mediated conditions respectively (eq. 3 and eq. 4). However, the reaction of intermediate **3a** afforded the corresponding *o*-cyanophenyl oxazole **2a** in a good yield under the same conditions. These results indicate that the oxazole moiety at the *ortho*-position of the phenyl ring might facilitate the cyanation process.

In order to further probe the pathway of the one-pot synthesis of 2-*o*-cyanophenyl oxazoles, two additional control experiments were also performed as shown in Scheme 2. A 63% yield of product **3a** derived from the simple cycloisomerization was

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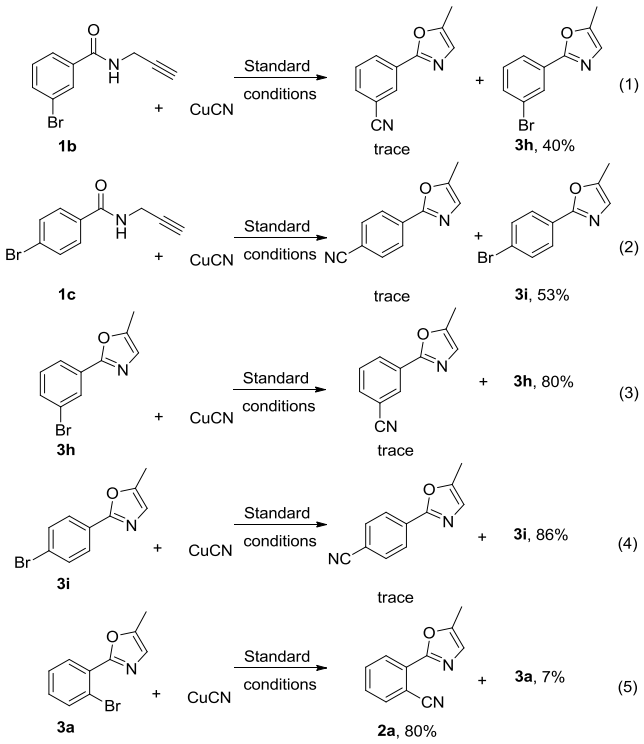
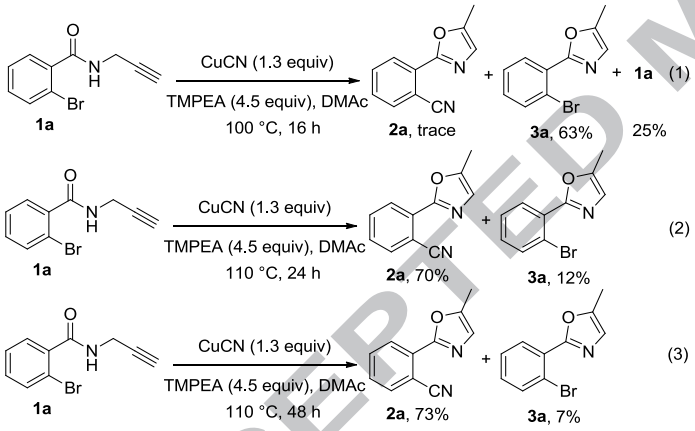


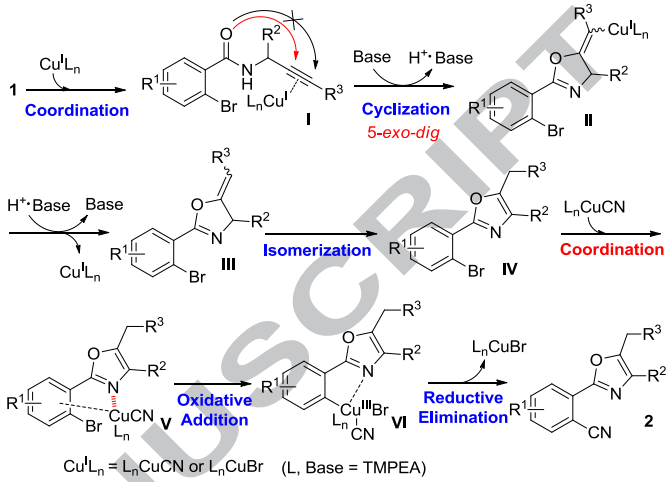
Scheme 1. The reactions of *m*-bromo and *p*-bromo substrates



Scheme 2. Two additional control experiments

isolated in company with trace amount of **2a** after the mixture was stirred at 100 °C (eq. 1). When the reaction was performed at 110 °C for 24 h, the desired product **3a** was isolated in 70% yield with small amount of **2a** (eq. 2), indicating that **3a** was an intermediate that could be converted into the final product under these conditions. However, when the reaction time was prolonged to 48 h, a slightly higher yield of **2a** was obtained in company with 7% yield of **3a** (eq. 3).[16]

On the basis of the experimental observations and the related reports,[11,17] a plausible pathway for the one-pot transformation is depicted in Scheme 3. Copper(I)-ligand species (ligand = TMPEA) coordinated with the alkynyl group of substrate **1** to afford Cu(I) complex **I** (the alkyne was electrophilically activated). Then the regioselective 5-*exo*-*dig*-type intramolecular cyclization followed by protonolysis gave the corresponding oxazoline-type intermediate **III**, which was subsequently converted into oxazole-type intermediate **IV** via an isomerization process. CuCN-ligand species coordinated with the oxazole ring and *o*-bromoaryl ring of **IV** to form Cu(I) complex **V**. **V** underwent an oxidative addition/reductive elimination process to provide the final 2-*o*-cyanophenyl oxazole **2** along with the regenerated Cu(I) species. It is worth noting that the coordination between the copper(I) species and the oxazole ring might stabilize the intermediates and facilitate the C-C bond formation on the *ortho*-position of the phenyl ring.



Scheme 3. A plausible pathway for the CuCN-mediated one-pot synthesis of 2-*o*-cyanoaryl oxazole

In conclusion, we have developed a facile and efficient one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives. Mediated by CuCN/TMPEA, a variety of substituted 2-*o*-cyanoaryl oxazole/oxazolines could be assembled in moderate to excellent yields from *o*-bromo N-propargylbenzamides and CuCN through a cyclization/coupling process. Various substituents were well tolerated under these conditions. In this transformation, CuCN plays dual roles as a Lewis acid catalyst and a cyanide anion source. Moreover, our studies found that the formation of the oxazole moiety might favor the subsequent intermolecular coupling process.[18] The convenient procedures, easily accessible starting materials and good efficiency would make the protocol useful for the synthesis of related heterocyclic molecules with interesting biological activities.

Acknowledgments

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15. *General procedure for the Cu-mediated one-pot synthesis of 2-o-cyanoaryl oxazoles*: An oven-dried Schlenk tube was charged with a magnetic stir bar, substrate **1** (0.5 mmol, 1.0 equiv), CuCN (0.65 mmol, 1.3 equiv), The tube was capped, and then evacuated and backfilled with nitrogen (3 times). TMPEA (2.25 mmol, 4.5 equiv) in DMAc (1.5 mL) was added via syringe under nitrogen at room temperature. Then the mixture was stirred at 120 ℃ for 24 h (monitored by TLC). The mixture was cooled to room temperature, diluted with water (15 mL), and extracted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel using petrol/AcOEt as eluent to give the product.
16. The yield increased rather slightly when the reaction time was extended to 48 h, probably because that small amount of the substrate was inevitably decomposed during the initial process, and the reaction rate decreased when the concentration of cyanide ion was lowered.
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18. This is the first example that systematically studies the copper-mediated intermolecular cyanation of aryl bromides assisted by an *o*-oxazolyl group, which is constructed in situ. It was observed that there was certain connection between the two different processes and the effective combination of the two protocols (cyclization and coupling) would give an alternative and convenient access to a variety of 2-*o*-cyanoaryl oxazole derivatives. Till now, although many studies on *o*-oxazoline-assisted C-X bond functionalization of aryl halides have been reported, there is only one paper described the CuCN-mediated synthesis of 2-*o*-cyanoaryl oxazole derivatives from *o*-haloaryl oxazoles: Clark, R. L.; Pessolano, A. A.; Witzel, B.; Lanza, T.; Shen, T. Y. *J. Med. Chem.* 1978; 21:1158-1162. The application scope was rather narrow (the related substrates were limited to *o*-halophenyl 2-oxazolo[4,5-*b*]pyridines), and the *ortho* effect of the oxazolyl group was not mentioned.

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Highlights

▪ It provides a convenient and efficient access to 2-*o*-cyanoaryl oxazole derivatives.

▪ Various substituents are well tolerated under these conditions.

▪ The formation of oxazole ring at the *ortho*-position favors the cyanation process.

▪ CuCN plays dual roles as a Lewis acid catalyst and a cyanide anion source.

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Graphical Abstract

A facile one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives mediated by CuCN

Senbao Fan,[a] Tao Tong,[a] Liting Fang,[a] Jingyi Wu,[a] Erfei Li,[a] Honglan Kang,[a] Xiaoxia Wang[a,b,*] and Xin Lv[a,*]

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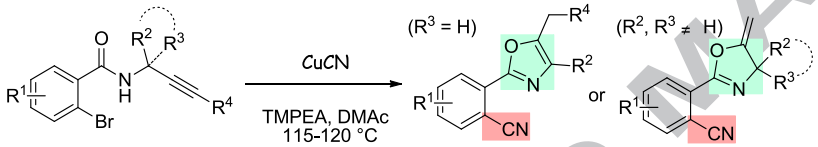
[b]*School of Environment and Civil Engineering, Dongguan University of Technology, Dongguan, 523808, People's Republic of China.*



- Convenient one-pot synthesis of useful 2-*o*-cyanoaryl oxazole derivatives;
- A variety of substituents are well tolerated;
- CuCN plays dual roles as a Lewis acid and a CN^- source;
- *Ortho* effect was observed

ACCEPTED MANUSCRIPT