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**Title:** Copper-Catalyzed Acyloxycyanation of Alkynes with Acetonitrile: Regioselective Construction of Cyclic Acrylonitriles by 6-endo or 5-exo Cyclization

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# Copper-Catalyzed Acyloxycyanation of Alkynes with Acetonitrile: Regioselective Construction of Cyclic Acrylonitriles by 6-*endo* or 5-*exo* Cyclization

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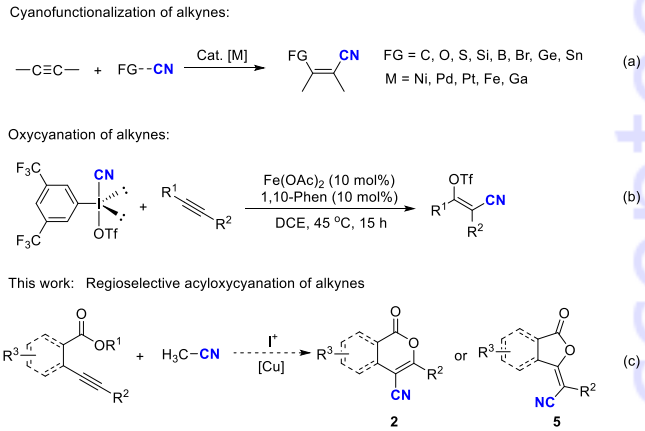
**Abstract:** An efficient difunctionalization of alkynes by tandem iodolactonization and copper-catalyzed cyanation using acetonitrile as a cyanating reagent is reported for the first time. This approach can afford cyano-containing isocoumarin or phthalide derivatives in good yields by careful choice of the carboxylate nucleophiles and electrophilic iodine sources. Thus, an acyloxycyanation strategy can be achieved in good yields and high regioselectivity of either *6-endo* or *5-exo* cyclization products.

**Keywords:** acyloxycyanation, acetonitrile, isocoumarins, phthalides, iodolactonization

Difunctionalization has emerged as an efficient method for the transformation of alkynes by introducing two functional groups in one pot.[1] Although transition metal-catalyzed cyanofunctionalization of alkynes have been reported to build vinyl C–CN bonds (i.e. X–C=C–CN where X = C, O, S, Si, B, Br, Ge, Sn) (Scheme 1a).[2,3] To date, only one example of intermolecular cyanotriflation using aryl(cyano)iodonium triflates as the cyano-source has been documented (Scheme 1b).[3k] Therefore, the available methodologies for oxycyanation of alkynes remains limited. Nitriles are versatile precursors to build other useful functional groups, but are also important motifs found in drugs, dyes, pesticides, electronic materials.[4] Due to the toxicity of many cyanating reagents, developing user-friendly protocols and green cyano-sources has been an ongoing effort.[5,6] Considering the challenge of alkyne oxycyanation, we were interested in developing an acyloxycyanation with acetonitrile as a cyano source (Scheme 1c). Acetonitrile is an attractive cyano source, featuring several advantages: 1) it is abundant, affordable, and commonly used as a solvent; 2) it is a safe and atom-economic "CN" source; 3) it can avoid the generation of high concentration of "CN" during cyanation processes.[7,8] As highlighted by Takagi,[9] the high concentration of cyanide may reduce catalytic efficiency of transition metal-catalysts due to catalyst poisoning. Herein, we describe the first Cu-catalyzed regioselective acyloxycyanation of alkynes with acetonitrile as the cyanating reagent. This reaction also offers a new way to synthesize a series of cyano-containing isocoumarin and phthalide derivatives that have not been accessed so far.

Isocoumarin and phthalide derivatives are known to have a wide occurrence in natural products and pharmaceutical compounds.[10] Due to the potential functionalities of isocoumarin and phthalide derivatives, we decided to focus our initial study on the construction of cyclic acrylonitrile structures by using methyl 2-(phenylethynyl)benzoate **1a** as a model substrate. We propose the intramolecular acyloxycyanation of alkynes may undergo two competing cyclization pathways to provide the 6-*endo* isocoumarin products **2** or *5-exo* phthalide products **5** (Scheme 1c).[11]




**Scheme 1.** Strategies for alkyne cyanofunctionalization

With this hypothesis in mind, we chose to test the acyloxycyanation with a Cu/TEMPO/$(Me_3Si)_2$ protocol, which was first reported by our group as an efficient method for acetonitrile C–CN bond cleavage (Table 1).[8d-f] However, under these conditions, no desired cyclic acyloxycyanated products **2a** or **5a** were observed. Instead, lactonization led to 3-phenyl-1*H*-isochromen-1-one **3a** in quantitative yield (Table 1, entry 1).[12]

We hypothesized that a sequential one-pot

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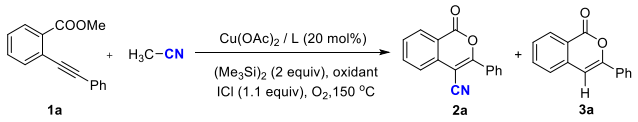
iodolactonization/cyanation protocol could avoid forming of unexpected lactonizated byproduct **3a.** Additionally, it opens a new avenue to achieve selective formation of 6-*endo* vs 5-*exo* acyloxycyanation products.[13] Gratifyingly, a 6% yield of 6-*endo* acyloxycyanation product **2a** was detected without the formation of 5-*exo* isomer **5a** when using iodine monochloride (ICl, 1.1 equiv) as an iodinating reagent. Although 6-*endo* iodolactonization intermediate **6a** was isolated in 92% yield (entry 2). Further screening of silver-salt oxidants led to substantial improvement in yields of **2a** (entries 3–5).[8b-c,8g,14] Interestingly, we noted that two equivalents of AgOAc are necessary since one equivalent of AgOAc only gave 17% yield (entry 6). By switching TMEDA to $PPh_3$, **2a** was obtained in the excellent yield of 94% within 18 h (entry 14). Other types of ligands, such as DMEDA, 1,10-phen, bpy, dppe, dppf and $PPh_3O$, furnished **2a** in moderate yields (67–83%, entries 8–13). Changing the oxygen atmosphere to air resulted in slight decrease in yield (71% yield, entry 15). Additionally, the use of nitrogen atmosphere displayed very low reactivity (15% yield, entry 16). Reducing temperature resulted in a lower yield of **2a** (63% yield, entry 17).

**Table 1.** Reaction conditions screening for 6-*endo* acyloxycyanation.[a]

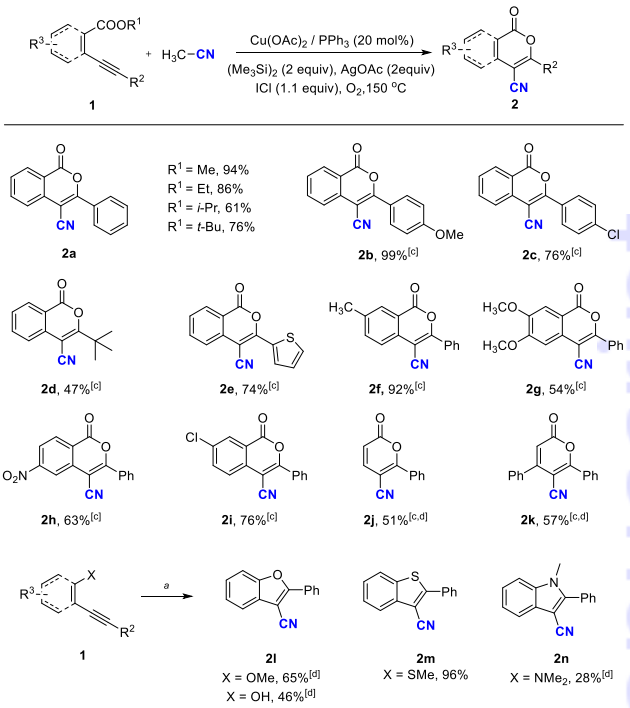



| entry | oxidant | ligand | time (h) | yield of **2a**(%)[b] |
|---|---|---|---|---|
| 1[c] | TEMPO (2 equiv) | TMEDA (20 mol%) | 9 | N.D. |
| 2 | TEMPO (2 equiv) | TMEDA (20 mol%) | 44 | 6 |
| 3 | $Ag_2CO_3$(1 equiv) | TMEDA (20 mol%) | 68 | 61 |
| 4 | $Ag_2O$ (1 equiv) | TMEDA (20 mol%) | 68 | 61 |
| 5 | AgOAc (2 equiv) | TMEDA (20 mol%) | 44 | 65[d] |
| 6 | AgOAc (1 equiv) | TMEDA (20 mol%) | 68 | 17 |
| 7 | AgOAc (2.5 equiv) | TMEDA (20 mol%) | 44 | 62[d] |
| 8 | AgOAc (2 equiv) | DMEDA (20 mol%) | 37 | 67 |
| 9 | AgOAc (2 equiv) | 1,10-phen (20 mol%) | 37 | 83 |
| 10 | AgOAc (2 equiv) | bpy (20 mol%) | 73 | 79 |
| 11 | AgOAc (2 equiv) | dppe (20 mol%) | 37 | 68 |
| 12 | AgOAc (2 equiv) | dppf (20 mol%) | 73 | 78 |
| 13 | AgOAc (2 equiv) | $PPh_3O$ (40 mol%) | 45 | 71 |
| **14** | **AgOAc (2 equiv)** | **$PPh_3$ (40 mol%)** | **18** | **94**[d] |
| 15[e] | AgOAc (2 equiv) | $PPh_3$ (40 mol%) | 18 | 71 |
| 16[f] | AgOAc (2 equiv) | $PPh_3$ (40 mol%) | 18 | 15 |
| 17[g] | AgOAc (2 equiv) | $PPh_3$ (40 mol%) | 66 | 63 |

[a] Conditions: **1a** (0.2 mmol), ICl (1.1 equiv), $CH_3CN$ (1.5 mL), $Cu(OAc)_2$ (20 mol%), ligand, $(Me_3Si)_2$ (2 equiv), oxidant, $O_2$, 150 °C. [b] Determined by $^1H$ NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] Without ICl. [d] Isolated yield. [e] Under air. [f] Under $N_2$. [g] The reaction was run at 130 °C.

With this protocol for 6-*endo* acyloxycyanation in hand, we next examined the substrate scope with a variety of 2-(alkynyl)benzoate esters, as shown in Table 2. Other ester groups ($R^1$ = Et, *i*-Pr, *t*-Bu) could also furnish the corresponding 3-phenyl-4-cyanoisocoumarin product **2a** smoothly in 61–86% yields. Alkyne moieties bearing different aryl, alkyl and heteroaryl groups were well tolerated with up to 99% yields **(2b**–**2e**). Substrates with electron-donating or electron-withdrawing groups on aromatic rings were subjected to the standard conditions. These reactions underwent 6-*endo* acyloxycyanation to provide the corresponding products in moderate to

**Table 2.** Scope of 6-*endo* acyloxycyanation.[a,b]



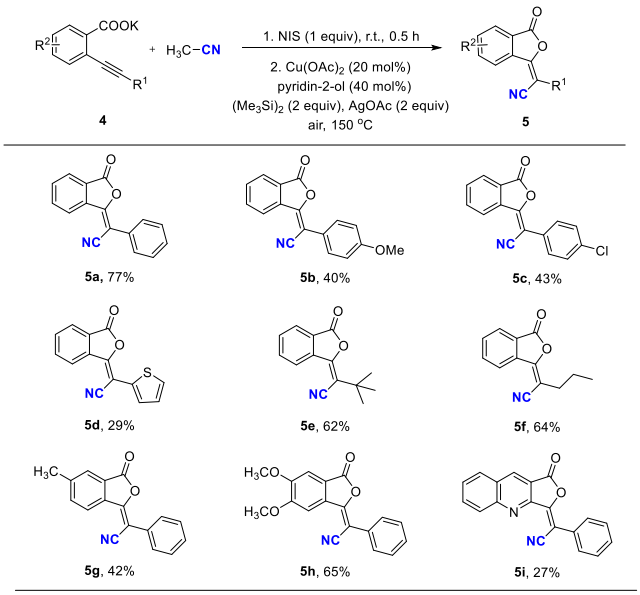

[a] Conditions: substrate **1** (0.2 mmol), $CH_3CN$ (1.5 mL), ICl (1.1 equiv), $Cu(OAc)_2$ (20 mol%), $PPh_3$ (20 mol%), $(Me_3Si)_2$ (2 equiv), AgOAc (2 equiv), $O_2$, 150 °C, 18–48 h. [b] Isolated yield. [c] $R^1$ = Me. [d] The first step: substrate **1** (0.2 mmol), $CH_3CN$ (1.5 mL), ICl (1.1 equiv), 1 h; the second step: $Cu(OAc)_2$ (20 mol%), $PPh_3$ (20 mol%), $(Me_3Si)_2$ (2 equiv), AgOAc (2 equiv), $O_2$, 150 °C, 18–48 h.

good yields of 54–92% (**2f**–**2i**). Notably, we discovered that two 4-cyano-*α*-pyrone structures could be accessed through our procedure in 51% and 57% yield, respectively (**2j** and **2k**). Additionally, heteroaromatic nitriles were formed under our procedure demonstrating the generality of our method. For example, aryl ethers (-OMe), phenols (-OH), aryl thioethers (-SMe), and anilines (-$NMe_2$) could replace the ester (-COOR) group (**2l**–**2n**) (see the supporting information, Scheme S1).

We hypothesized we could control the regioselectivity of the iodolactonization prior to Cu-catalyzed cyanation to afford 5-*exo* acyloxycyanation by careful choice of the nucleophilic carboxylate and iodinating reagent. To reach this goal, we examined potassium benzoate or carboxylic acid substrates with different $I^+$ electrophiles such as iodine monochloride (ICl), *N*-iodosuccinimide (NIS), and iodine ($I_2$). We found that the identity of the nucleophile plays a major role on the regioselectivity of iodolactonization. For example, the use of benzoate ester or benzoic acid predominantly afforded *6-endo* cyclization products. In contrast, when using potassium benzoate, *5-exo* cyclization became the major product (see the supporting information, Table S1).[12a,15] To our delight, 5-*exo* iodolactonization was achieved in good yield and selectivity (85% yield,

>20:1 selectivity) when using potassium 2-(phenylethynyl)benzoate **4a** with NIS in acetonitrile for 5 minutes at room temperature (see the supporting information, Table S1). In case of potassium benzoate, $I^+$ sources with

**Table 3.** Scope of 5-*exo* acyloxycyanation.[a,b]



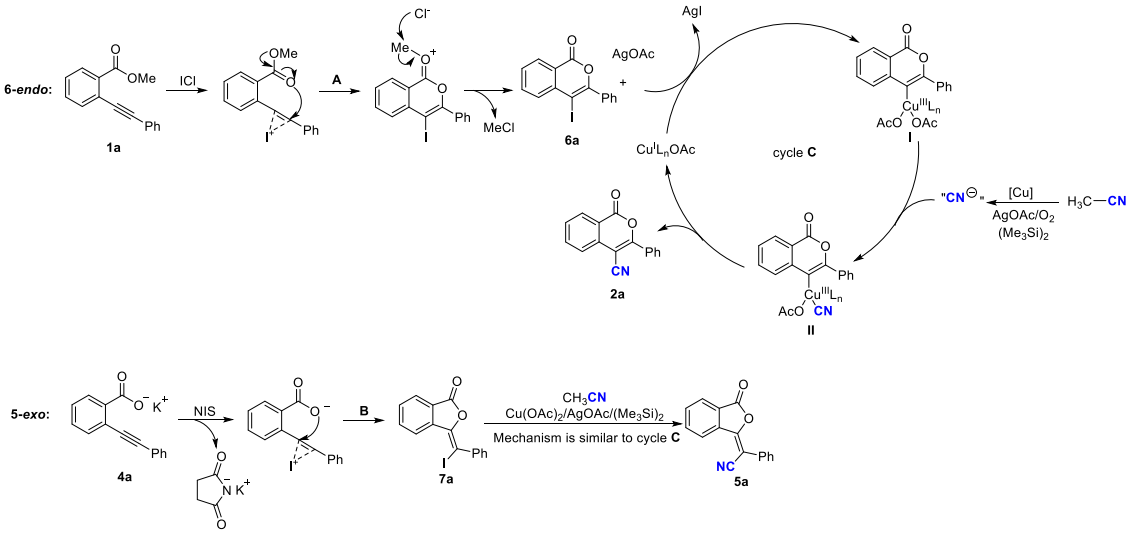

[a] Conditions: the first step: **3** (0.2 mmol), ICl (1.1 equiv), $CH_3CN$ (1.5 mL), r.t., air, 0.5 h. After extraction, the residue was washed by acetonitrile into oven-dried Schlenk tube. Then other compounds were added into it for the second step: $Cu(OAc)_2$ (20 mol%), pyridine-2-ol (40 mol%), $(Me_3Si)_2$ (2 equiv), AgOAc (2 equiv), $CH_3CN$ (1.5 mL), air, 150 °C, 18–48 h. [b] Isolated yield.

lower electrophilicity prefer 5-*exo* iodolactonization.[12] With these results in hand, we optimized the following cyanation conditions and determined that a stepwise protocol gave the desired 5-*exo* acyloxycyanation product **(**77% isolation yield, see the supporting information, Table S2).

We further explored the generalization and limitation of 5-*exo* acyloxycyanation (Table 3). Alkyne moieties attached with alkyl groups, such as *t*-Bu (**4e)** and *n*-Pr (**4f)** gave good yields (62–64%). Aromatic and heteroaromatic rings also provided the desired 5-*exo* cyclization products (**5b**–**5d**) albeit with lower yields. Different substituents on the aryl ring have been evaluated with our protocol. For example, both 5-methyl- (**4g)** and 4,5-dimethoxy- (**4h)** substituted potassium benzoates gave the desired products in 42% and 65% yields, respectively. In addition, heterocycle substrate **4i** with quinoline structure underwent cyclization, albeit in low yield (27%).

Although the detailed reaction mechanism warrants further study, a proposed mechanism for the Cu-catalyzed acyloxycyanation of alkynes with acetonitrile is depicted in Scheme 2 on the basis of literature[12a,15] and our observations. The alkyne in **1a** or **4a** is first activated by coordination to the electrophilic iodine source ($I^+$). Two competing pathways can then be involved in the following nucleophilic attack. When using methyl 2-(phenylethynyl)benzoate **1a** and iodine monochloride (ICl), 6-*endo-dig* cyclization is preferred to form product **6a** (path **A)**. Conversely, when using potassium benzoate **4a** and *N*-iodosuccinimide (NIS), 5-*exo-dig* cyclization is preferred to form product **7a** (path **B**). The cyanation of **6a** is described in cycle **C.** Intermediate **6a** may undergo oxidative addition with $L_nCu^{I}OAc$ to produce $L_nCu^{III}$ species **I** with assistance of AgOAc to precipitate AgI. Ligand exchange with cyanide, which is generated *in situ* by the cleavage of acetonitrile, gives $Cu^{III}$–cyanide species **II**. Finally, reductive elimination of the intermediate **II** provides the desired acyloxycyanation product **2a**. The Cu-catalyzed cyanation proceeds in the same fashion for the 5-*exo* acyloxycyanation product **5a**. Notably, the selective performance of 6-*endo* versus 5-*exo* acyloxycyanation depends on careful choice of the nucleophilic partner and iodinating reagent. Thus, the iodolactonization step is responsible for the regioselectivity of *6-endo* or *5-exo* acyloxycyanation. The reason for the regioselectivtiy is not fully understood at this stage.

In conclusion, we report a novel approach for



**Scheme 2.** Proposed mechanism

Cu-catalyzed acyloxycyanation of alkynes by using acetonitrile as a green and affordable cyanating reagent. This transformation displays a new avenue for selective construction of 6-*endo* or 5-*exo* cyclic acrylonitriles, which may possess synthetic applications in pharmaceutical molecules. Careful choice of the carboxylate nucleophiles and iodinating reagents allows for selective iodolactonization to furnish various 6- and 5-membered rings. By using benzoate esters or potassium benzoates bearing alkynyls, cyano-containing isocoumarin and phthalide derivatives are facilely synthesized for the first time. Further derivatization and mechanistic studies are currently ongoing in our laboratory.

# Experimental Section

### General procedure for 6-*endo* acyloxycyanation

An oven-dried Schlenk tube equipped with a magnetic stir bar was evacuated and backfilled with oxygen three times. Under oxygen, the appropriate benzoate **1** (0.2 mmol), $CH_3CN$ (1.5 mL), and ICl (1.1 equiv, 0.22 mmol) were added into the tube. Then the mixture was stirred at room temperature. Next, under oxygen, $PPh_3$ (40 mol%, 0.08 mmol), $Cu(OAc)_2$ (20 mol %, 0.04 mmol), $(Me_3Si)_2$ (2 equiv, 0.4 mmol), and AgOAc (2 equiv, 0.4 mmol) were added into the above mixture. The reaction was then heated to 150 °C for 1–2 days under an oxygen atmosphere. After completion, the mixture was filtered to remove insoluble material. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel using EtOAc/petroleum ether to give the corresponding 6-*endo* acyloxycyanated products **2**.

### General procedure for 5-*exo* acyloxycyanation

Under air, the appropriate potassium benzoate **4** (0.2 mmol), NIS (1 equiv., 0.2 mmol), and $CH_3CN$ (1.5 mL) were added into an oven-dried Schlenk tube equipped with a magnetic stir bar. Then the mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution and extracted with $CH_2Cl_2$. Extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. Next, under air, the residue was washed into another oven-dried Schlenk tube equipped with a magnetic stir bar. $Cu(OAc)_2$ (20 mol%, 0.04 mmol), pyridin-2-ol (40 %mol, 0.08 mmol), $(Me_3Si)_2$ (2 equiv., 0.4 mmol), and AgOAc (2 equiv., 0.4 mmol) were also added sequencially. The reaction was then heated to 150 °C for 16–48 hours under air. After completion, the reaction mixture was filtered to remove insoluble material. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel using EtOAc/petroleum ether to give the corresponding 5-*exo* acyloxycyanated products **5**.

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COMMUNICATION

# Copper-Catalyzed Acyloxycyanation of Alkynes with Acetonitrile: Regioselective Construction of Cyclic Acrylonitriles by 6-*endo* or 5-*exo* Cyclization

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