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Regioselective remote C5 cyanoalkoxylation and cyanoalkylation of 8-aminoquinolines with azobisisobutyronitrile

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The efficient regioselective C-H cyanoalkoxylation and cyanoalkylation of 8-aminoquinoline derivatives at the C5 position have been achieved under O_2 and N_2 atmosphere respectively. Using 2,2'-azobisisobutyronitrile (AIBN) as radical precursor, the protocols afforded the corresponding products in moderate to good yields with broad substrate generality through $Cu(OAc)_2$ or $NiSO_4$ catalysis. Furthermore, the single electron transfer (SET) mechanism was proposed via radical coupling pathway.

The quinoline scaffolds are of great importance frequently existed in natural products, materials and bioactive molecules.[1] For example, aryloxyquinolines, as vital chemical entities, show good biological activities such as antiviral, anti-inflammatory and anticancer (Figure 1).[2] Consequently, the straightforward regioselective functionalization of quinolines has been evolved as an attractive research topic.[3] Especially, in recent years, the difficult remote C5 site selectivity was controlled successfully by SET radical mechanism. Then, many methodologies to construct C-C, C-N, C-S, C-Hal, C-P and C-Se bonds etc at the C5 position have been developed under transition metals (TM) catalysis conditions.[4-9] In our previous work, the C5 fluorination of 8-aminoquinolines was explored for the first time catalyzed by $NiSO_4$ or under metal-free conditions.[10] However, for the direct C-O bond formation of quinolines, only few examples such as C5 tosyloxylation and oxygenation to form esters were achieved.[11]

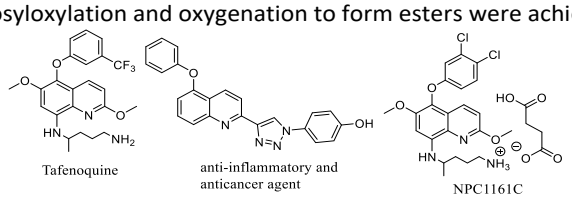

Figure 1 Selected biologically active pharmaceuticals.

AIBN was extensively used as radical initiators and radical precursors in organic synthesis. In general, AIBN could generate three different kinds of free radicals as illustrated in Scheme 1.[12] Among them, the cyanopropyl radical ($\cdot C(CH_3)_2CN$) could be easily produced along with the release of one molecule of N_2 once AIBN was heated (eq 1). Whereas, the cyanopropyloxyl radical ($\cdot OC(CH_3)_2CN$) generation required two steps including the oxygen atom capture by cyanopropyl radical in the presence of oxygen and one molecule of O_2 release spontaneously from the two peroxy radicals (eq 2 and eq 3). In addition, the cyano radical ($\cdot CN$) was available from the cyanopropyloxyl radical as well as the acetone production (eq 4). Due to the steric hindrance of isobutyronitrile group, AIBN usually serves as cyano radical source for direct aryl C-H or SP^3 C-H cyanation via radical pathway.[12b, 13] In very recent years, the cyanopropyl radical derived from AIBN was explored successfully in the copper-catalized direct cyanation of terminal alkynes.[14] Copper-catalyzed oxidative coupling of cyanopropyl radical and ketone-derived enoxysilanes to r-ketonitriles was also achieved.[15] Furthermore, the direct cyanoisopropylation of alkenes in N-arylacrylamides or benzamides for the synthesis of cyano-containing heterocycles was developed extensively via oxidative cyclization.[16] During the research of copper-catalyzed 8-amido chelation-induced remote C-H amination of quinolines, Baidya group firstly mentioned the cyanoalkylation of 8-aminoquinoline with the very low yield 24%, which proved the introduction of steric hindered quaternary carbon to C5 position of quinolines was still difficult.[5b] But, considering the cyanopropyloxyl radical, which contains one oxygen atom, to the best of our knowledge, there's no any report for the direct C-H functionalization to construct C-O ether bond.

(1) $NC(CH_3)_2C{-}N{=}N{-}C(CH_3)_2CN \xrightarrow[-N_2]{\triangle} 2\cdot C(CH_3)_2CN$

(2) $\cdot C(CH_3)_2CN + O_2 \longrightarrow \cdot OOC(CH_3)_2CN$

(3) $2\cdot OOC(CH_3)_2CN \xrightarrow{-O_2} 2\cdot OC(CH_3)_2CN$

(4) $\cdot OC(CH_3)_2CN \xrightarrow{-CO(CH_3)_2} \cdot CN$

Scheme 1 Cyanopropyl, cyanopropyloxyl and cyano radicals produced by AIBN.

On the other hand, cyano-containing compounds have been widely applied in many fields, such as materials, pharmaceuticals and organic synthesis.[17] Moreover, cyano group can be easily converted into diverse functional groups such as carboxyl,

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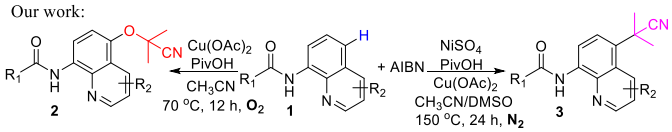
aldehyde and amide etc.[18] Given the importance of quinoline derivatives and nitriles, it is meaning for the introduction of cyano-containing group to quinoline scaffold to acquire molecules with diversity and complexity. During our continuing research work about cyanation reaction and remote selective C-H functionalization,[19] under O_2 and N_2 atmosphere respectively (Scheme 2), we envisioned that it might be feasible to achieve cyanoalkoxylation and cyanoalkylation of 8-aminoquinolines with AIBN as cyanopropyloxyl and cyanopropyl radicals source through different catalysis systems. Herein, we report our research results.

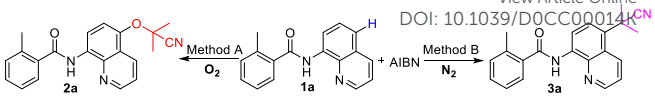


Scheme 2 Direct C-H cyanoalkoxylation and cyanoalkylation of 8-aminoquinolines at the C5 position.

Undoubtedly, considering the reaction of AIBN and quinolines, the product selectivity depends on the different radicals controlling procedures, in which, O_2, N_2, TM and temperature were important factors. In fact, at 50 °C-70 °C, the cyanopropyl radical indeed was produced from AIBN, and following the subsequent low steric cyanopropyloxyl radical under O_2.[12a] The cheap metal copper has achieved great results in the C5-H functionalizations of 8-aminoquinolines.[5d, 7b] Thus, we initiated our studies by investing the reaction of 2-methyl-N-(quinolin-8-yl)benzamide (**1a**) as model in the presence of $Cu(OAc)_2$, $PhI(OAc)_2$ and PivOH. To our delight, the desired product **2a** was obtained in 20 yield (Table 1, entry 1). $K_2S_2O_8$ was the best oxidant, providing the single product **2a** in 60% yield (entry 2). The optimal temperature was 70 °C (entry 3). Other solvents were examined (entries 4-5), and it was found that CH_3CN was still significantly superior. Without O_2, the reaction could not run (entry 6). With a set of optimized conditions for the product **2a**, next we were intrigued by the possibility of product **3a** under N_2. However, copper catalyst failed to get the desired product **3a.** Recently, nickel catalyst was reported showing good performance in C5-H functionalizations of 8-aminoquinolines.[10a, 20] Therefore, we further attempted to accomplish cyanoalkylation using $NiSO_4$ as catalyst with the same model substrate **1a**. Fortunately, compound **3a** was obtained as the exclusive product in 24% yield (entry 7). Changing several commonly used solvents, it turned out that mixed CH_3CN/DMSO (3/1) resulted in excellent yield (entries 8-9). In addition, in the presence of additives e.g. $Cu(OAc)_2$ or $Fe(acac)_3$, the product **3a** represented a significant rise at 150 °C (entries 10-11). Either nickel or copper was absent, the yield showed a negative effect (entries 12-13), (details see the ESI, Table S1 and S2). Thus, the optimal conditions were showed in entry 3 and entry 10 respectively. In addition, the molecular structure of **2a** was unambiguously confirmed by single-crystal X-ray diffraction (Figure 2).

Firstly, under the optimized conditions, the substrate scope was explored for the C5 cyanoalkoxylation in Table 2. Both arylcarboxamides and alkylcarboxamides were good reaction substrates (**2a-2n**, **2o-2s**). Arenes bearing electron-withdrawing groups (chloro, bromo, iodine) and electron-donating groups (methyl, ethyl, *tert*-butyl,

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant	Temp (°C)	Solvent	Yield[b] (%)**2a** or **3a**
1	$Cu(OAc)_2$	$PhI(OAc)_2$	90	CH_3CN	**2a**, 20
2	$Cu(OAc)_2$	$K_2S_2O_8$	90	CH_3CN	**2a**, 60
3	**$Cu(OAc)_2$**	**$K_2S_2O_8$**	**70**	**CH_3CN**	**2a, 70**
4	$Cu(OAc)_2$	$K_2S_2O_8$	70	DCE	**2a**, 10
5	$Cu(OAc)_2$	$K_2S_2O_8$	70	CH_3OH	**2a**, 20
6[c]	$Cu(OAc)_2$	$K_2S_2O_8$	70	CH_3CN	**2a**, n.r
7	$NiSO_4$	$K_2S_2O_8$	90	CH_3CN	**3a**, 24
8	$NiSO_4$	$K_2S_2O_8$	90	THF	**3a**, 28
9[d]	$NiSO_4$	$K_2S_2O_8$	90	CH_3CN/DMSO	**3a**, 35
10[d, e]	**$NiSO_4$**	**$K_2S_2O_8$**	**150**	**CH_3CN/DMSO**	**3a, 67**
11[d, f]	$NiSO_4$	$K_2S_2O_8$	150	CH_3CN/DMSO	**3a**, 50
12[d]	$NiSO_4$	$K_2S_2O_8$	150	CH_3CN/DMSO	**3a**, 42
13[d]	$Cu(OAc)_2$	$K_2S_2O_8$	150	CH_3CN/DMSO	**3a**,trace

[a] Reaction conditions for **2a** [Method A]: **1a** (0.2 mmol), AIBN (4.0 equiv), catalyst (0.1 equiv), oxidant (1.0 equiv), PivOH (0.2 equiv), solvent (2.0 mL), under O_2 for 12 h. **3a** [Method B]: **1a** (0.2 mmol), AIBN (4.0 equiv), catalyst (0.1 equiv), oxidant (2.0 equiv), solvent (2.0 mL), PivOH (2.0 equiv), under N_2 for 24 h. [b] Isolated yield. [c] Under N_2. [d] CH_3CN/DMSO (3/1). [e] Added 10 mol% $Cu(OAc)_2$. [f] Added 10 mol% $Fe(acac)_3$.

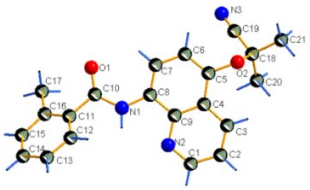
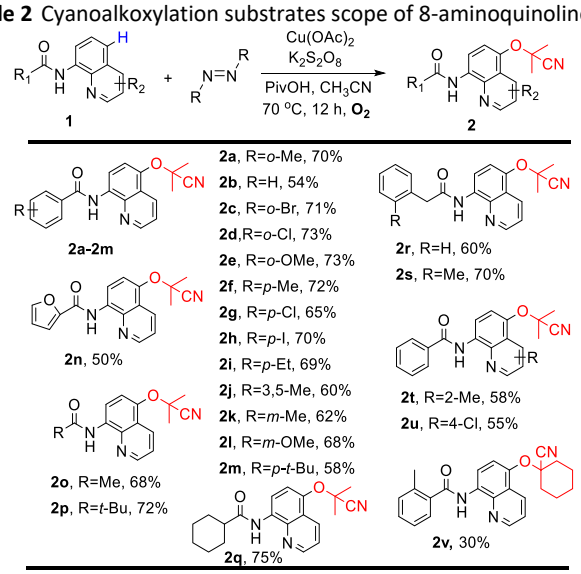


Figure 2 Single-crystal X-ray structure of **2a**.

methoxyl) had good activity without significant electronic effect. Notably, the *ortho*-substitution of benzene ring did not hardly influence the yield of the products (**2a** *vs* **2f**, **2k** and **2d** *vs* **2g**). Additionally, heterocyclic amide also gave slightly low yield (**2n**), which revealed good functional groups tolerance. Sterically bulky groups did not hinder the reaction obviously (**2o**-**2s**). Then, the substrates containing a substituent on the quinoline such as 2-Me, 4-Cl (**2t**-**2u**) were also examined with appropriate yields. Analogue of AIBN was also detected. The reaction of **1a** with 1,1'-azobis (cyclohexane-1-carbonitrile) showed relatively lower yield (**2v**).

After successfully describing the substrate scope of C5 cyanoalkoxylation, the reaction of aminoquinoline derivatives with AIBN for providing C5 cyanoalkylation products has been examined in Table 3. Pleasingly, a series of electron-donating groups such as methyl, ethyl, *tert*-butyl, methoxyl on the aromatic ring were observed to be well compatible with corresponding cyanoalkylation products (**3a**, **3c-3d**, **3f-3g**, **3j-3l**), and electron-withdrawing groups (fluoro, chloro, iodine) also had excellent products (**3e**, **3h-3i**, **3m**).

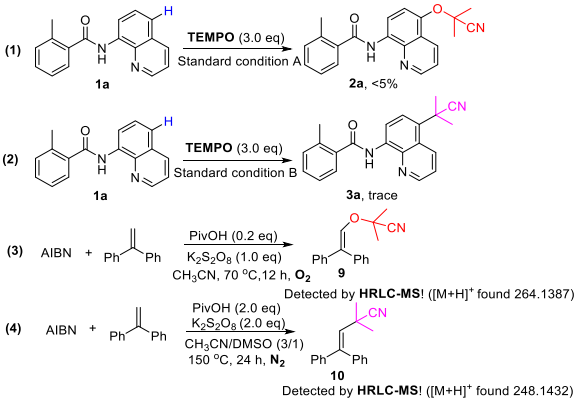
Table 2 Cyanoalkoxylation substrates scope of 8-aminoquinolines[a]



[a]Standard reaction conditions: **1** (0.2 mmol), AIBN (0.8 mmol), $Cu(OAc)_2$ (0.02 mmol), $K_2S_2O_8$ (0.2 mmol), PivOH (0.04 mmol) were mixed in CH_3CN (2.0 mL) and stirred for 12 h at 70 °C under O_2. Isolated yield.

Obviously, the reaction was little influenced by the electronic nature of the substrates. Heterocyclic amide was also detected to obtain the related product with inferior yield (**3n**). Moreover, various alkyl amides were applicable in the cyanoalkylation reaction (**3o**-**3t**). Besides, a substitution at the C4 position of quinoline was also examined with suitable yield (**3u**). Further experiments demonstrated analogues of AIBN were also suitable for this reaction to provide the desired products (**3v**, **3w, 3x, 3y, 3z, 3aa**), except the one with a carboxylic acid group (**3bb**).

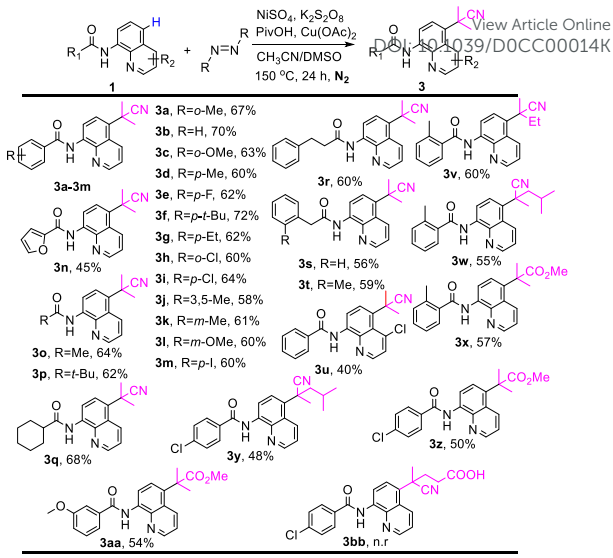
To gain insight into the reaction mechanisms, some control experiments were carried out (Scheme 3). Only a trace of the desired products **2a** and **3a** were obtained in the presence of radical scavenger TEMPO (3.0 equiv), which implied the involvement of free radical in the reaction pathway (eq 1 and eq 2). Furthermore, we tried to capture cyanopropyloxyl radical and cyanopropyl radical by using 3.0 equiv 1, 1-diphenylethylene, and radical coupling products **9** and **10** were detected by LC-MS (eq 3 and eq 4).



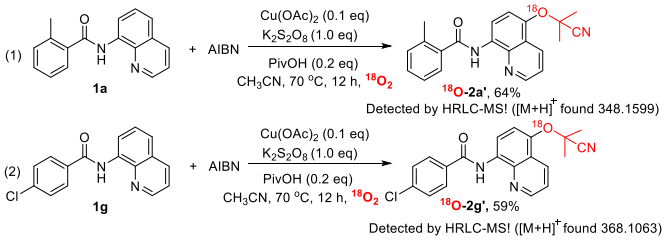
Scheme 3 Investigation of the radical pathway.

In order to verify that the oxygen atom of product **2** comes from O_2, we further performed isotopic labeling experiment under $^{18}O_2$ (97 atom% ^{18}O) (Scheme 4). The ^{18}O-labeled product **2a'** and **2g'** (yields 64% and 59%) could be detected by LC-MS, undoubtedly

Table 3 Cyanoalkylation substrates scope of 8-aminoquinolines[a]



[a]Standard reaction conditions: **1** (0.2 mmol), AIBN (0.8 mmol), $NiSO_4$ (0.02 mmol), $K_2S_2O_8$ (0.4 mmol), PivOH (0.4 mmol), $Cu(OAc)_2$ (0.02 mmol) were mixed in CH_3CN/DMSO (1.5 mL/0.5 mL) and stirred for 24 h at 150 °C under N_2. Isolated yield.

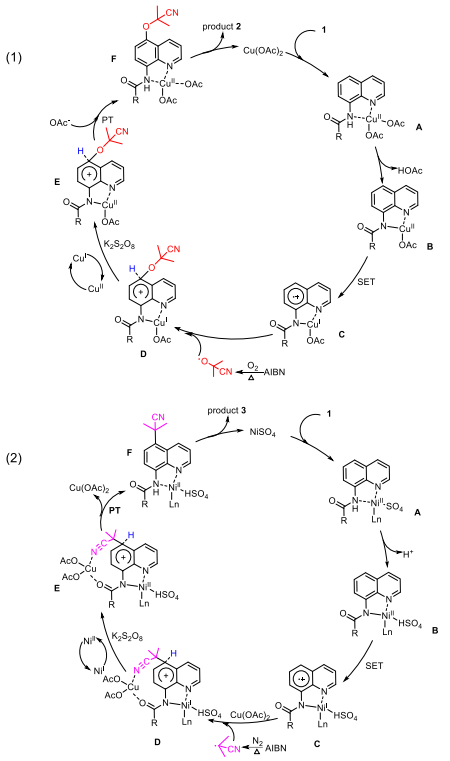


Scheme 4 Isotopic labeling experiments.

proving oxygen atom in the ether bond completely originated from O_2.

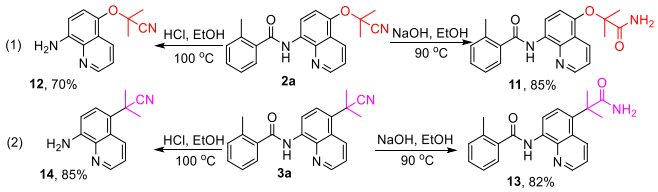
On the basis of the above experimental results and previous literature reports,[4a, d, 6c] a plausible mechanism for cyanoalkoxylation reaction was depicted (Scheme 5, (1)). The coordination of substrate **1** with $Cu(OAc)_2$ provided the complex **A**. Then, complex **A** turned into complex **B** by losing a molecule of acetic acid and intermediate **C** was formed through single electron transfer (SET) process. Addition of cyanopropyloxyl radical to intermediate **C** proceeded at the C5 position, affording the complex **D**. Next, complex **E** was generated via oxidation. Intermediate **F** was formed by a proton transfer (PT) process automatically. In the end, product **2** was achieved and $Cu(OAc)_2$ was regenerated to accomplish the catalytic cycle. Similarly, a plausible reaction pathway for cyanoalkylation reaction was proposed (Scheme 5, (2)). The catalytic cycle of cyanoalkylation underwent the processes of complexation, the loss of proton from NH, SET, cyanopropyl radical addition, oxidation by $K_2S_2O_8$ and PT transfer to form **F**. Then the nickel was dissociated to afford product **3**. Among them, the metal nickel, like copper, took place a conversion between divalent and monovalent. Here, it was noteworthy that the presence of copper acetate was conducive to promoting the addition of sterically hindered cyanopropyl radicals by coordinating with N and O atoms together, which could reduce the energy of transition state **D** (details see the ESI).

To demonstrate the potential application, the transformations of the products were also investigated (Scheme 6). The treatment of **2a**



Scheme 5 Plausible mechanisms.

and **3a** with NaOH in EtOH at 90 °C for 12 h, corresponding amide derivatives **11** and **13** were obtained in 85% yield and 82% yield respectively. In addition, the 8-aminoquinoline directing group of **2a** and **3a** could be easily removed by simple acid hydrolysis, giving the corresponding product **12** in 70% yield and **14** in 85% yield respectively.



Scheme 6 Functional groups transformation.

In summary, we have developed a novel regioselective cyanoalkoxylation and cyanoalkylation of 8-aminoquinoline derivations at the C5 position with AIBN as radical source. The protocols provide useful methodologies for the efficient construction of C-O and C-C bond on quinoline scaffold with functional group tolerance. In addition, cyanopropyloxyl radical was explored to form site selective C-O ether bond directly for the first time. The plausible radical mechanism was also demonstrated. Further efforts to extend the applications of these new protocols are underway in our lab.

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Conflicts of interest

There are no conflicts to declare.

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Graphic

Regioselective remote C5 cyanoalkoxylation and cyanoalkylation of 8-aminoquinolines with azobisisobutyronitrile

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The C5-H cyanoalkoxylation and cyanoalkylation of 8-aminoquinoline derivatives were achieved with azobisisobutyronitrile under different catalysis system.