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ARTICLE

# Copper-catalyzed rapid C-H nitration of 8-aminoquinolines by using sodium nitrite as the nitro source under mild conditions

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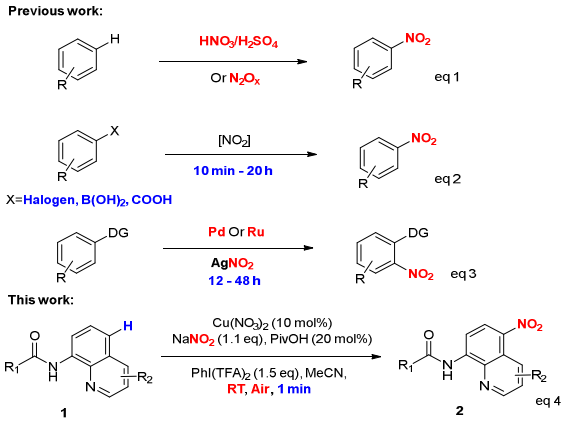
**A mild, rapid and efficient method for copper-catalyzed nitration of quinolines at C5 or C7 position was reported firstly by using sodium nitrite as the nitro source. A series of nitrated quinoline derivatives were achieved in moderate to good yields via remote C-H activation. The method overcomes some shortcomings reported in previous nitration strategies, such as employing expensive metal catalysts or using toxic and unstable nitrating agents. Furthermore, some of products can be obtained through filtration which displayed the operational simplicity of this methodology. Importantly, this protocol may provide a practical synthetic tool for the introduction of nitro group into drug molecules.**

## Introduction

Oganic nitro compounds are important raw materials in the synthesis of dyes, plastics, explosives, perfumes and pharmaceuticals.[1] The traditional routes to aromatic nitro compounds, such as the electrophilic aromatic nitration, usually require harsh conditions($HNO_3/H_2SO_4$), and suffer from regioselectivity issues as well as the unsatisfactory functional group tolerance (Scheme 1 eq 1).[2] To overcome these problems, recently several strategies of regiospecific synthesis of nitroarenes, including the ispo-nitration of aryl boronic acids,[3] aryl halides, pseudohalides,[4] and aryl carboxylic acids[5] have been developed (Scheme 1 eq 2). Alternatively, ispo-oxidation of aryl amines or azides also provided a nitration protocol to give the nitroarenes indirectly.[6] However, these promising approaches are low atom economy. Furthermore, related wastes are produced.




**Scheme 1** A series of strategies leading to nitroarenes

In view of the encouraging achievements made in recent transition-metal-catalyzed auxiliary-assisted C-H functionalization which successfully construct C-C, C-O, C-S, C-N and C-halogen bonds,[7] a similar strategy would be appealing also for the direct C-H nitration (Scheme 1 eq 3). Specially, liu et al. has shown a method for palladium-catalyzed regiospecific synthesis of nitroarenes at 130 °C.[8] Bi's copper-catalyzed *ortho* nitration of (hetero)arenes also required high temperature and used expensive $AgNO_2$ as the nitro source.[9] The latest radical C-H nitration of arenes by Jiao and co-workers performs at 80 °C, but employed expensive Pd catalyst.[10] Obviously, these protocols should abide a number of limitations, mainly using expensive metal catalysis, choosing costly silver(I) salt as the nitrating agent or requiring harsh reaction conditions.[11] Therefore, mild and efficient strategies for selective nitration is still a great need. In 2014, the carretero group have disclosed a mild and efficient copper-catalyzed nitration of aromatic derivates but using unstable nitric acid as the nitrating agent at 100 °C.[12] Just recently, the Ribas group reported a mild protocol for remote C-H nitration of 8-aminoquinoline amides using inexpensive cobalt nitrate hexahydrate as catalyst and *t*ert-butyl nitrate(TBN) as nitro source.[13] However, the lack of selectivity for the unsymmetrical

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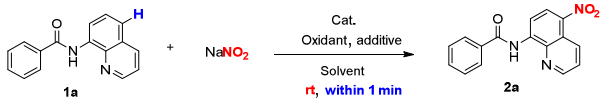
quinoline rings(Ratio C5:C7: 3:1), the excess use of unstable and toxic nitrating agent and long reaction times(18h) have limited the synthesis value of this methodology. Herein, we report a copper-catalyzed mild and efficient method for the remote C-H nitration of 8-aminoquinoline amides using cheap and stable sodium nitrite as the nitro source (Scheme 1 eq 4). It is noteworthy that the reaction was completed within one minute at room temperature.

## Results and discussion

Our original goal was to achieve the copper-catalysed 8-aminoquinoline directed *ortho* C-H nitration of benzoic acid derivates. We started our study by choosing the reaction of benzamide **1a** with sodium nitrite as the model (Table 1). To our surprise, the nitration product at the *ortho* position of benzoic acid derivates was not observed. Instead, in the presence of $Cu(NO_3)_2$ (10 mol%), PivOH (20 mol%), and $PhI(OAc)_2$ (2.0 equiv.) at 70 °C in $CH_3CN$ overnight, unexpected nitrated product **2a** was obtained in 70% yield by filtration (Table 1, entry 15). Encouraged by this result, we further investigated the reaction parameters from catalyst, oxidant, and solvent. Gratifyingly, the reaction proceeded rapidly at room temperature in higher yield when $PhI(TFA)_2$ was used as an oxidant, and the additive PivOH was indispensable (Table 1, entry 9). The transformation could not take place in the presence of other oxidants, such as TBHP and $K_2S_2O_8$ (Table 1, entries 16-17). The

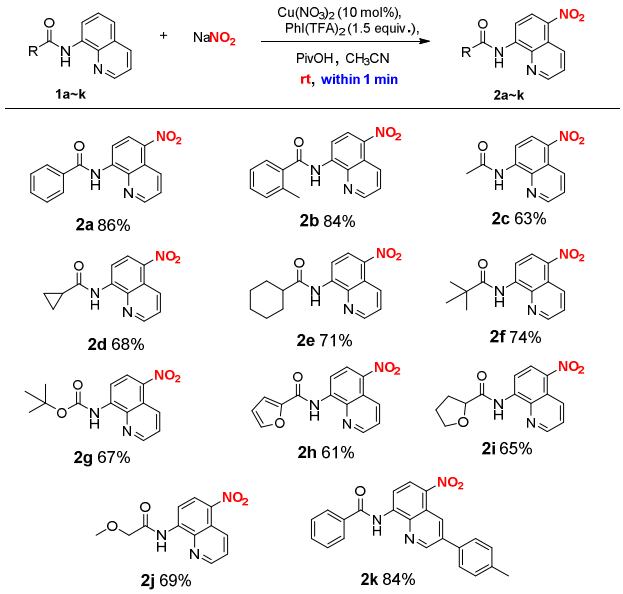
**Table 1** Screening of reaction conditions for nitration of 8-aminoquinoline amides[a,b]




| Entry | Catalyst | Oxidant | Solvent | Yield(%)[b] |
|---|---|---|---|---|
| 1 | CuI | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| 2 | $PdCl_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| 3 | $AgNO_3$ | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| 4 | $Fe(NO_3)_3$ | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| 5 | $Co(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| 6[c] | $Cu(OAc)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 76 |
| 7 | $Cu(NO_3)_2$ | none | $CH_3CN$ | 0 |
| 8 | none | $PhI(TFA)_2$ | $CH_3CN$ | 0 |
| **9** | **$Cu(NO_3)_2$** | **$PhI(TFA)_2$** | **$CH_3CN$** | **86** |
| 10[e] | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 80 |
| 11[d,e] | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 30 |
| 12[f] | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 73 |
| 13[g] | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 85 |
| 14[h] | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3CN$ | 83 |
| 15 | $Cu(NO_3)_2$ | $PhI(OAc)_2$ | $CH_3CN$ | trace(70)[e] |
| 16 | $Cu(NO_3)_2$ | TBHP | $CH_3CN$ | 0 |
| 17 | $Cu(NO_3)_2$ | $K_2S_2O_8$ | $CH_3CN$ | 0 |
| 18 | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | DMF | trace |
| 19 | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | $CH_3NO_2$ | trace |
| 20 | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | dioxane | trace |
| 21 | $Cu(NO_3)_2$ | $PhI(TFA)_2$ | DCE | trace |

[a]Reaction conditions: **1a** (0.20 mmol), sodium nitrite (1.1 equiv), catalyst (10 mol %), oxidant (1.5 equiv), PivOH (20 mol %), solvent (2.0 mL); [b] Isolated yield of **2a**. [c] The reaction was completed in 5 min; [d] No PivOH was added; [e] The reaction was carried out at 70 °C; [f] The reaction time was 30 min; [g] Under $N_2$; [h] Under $O_2$.

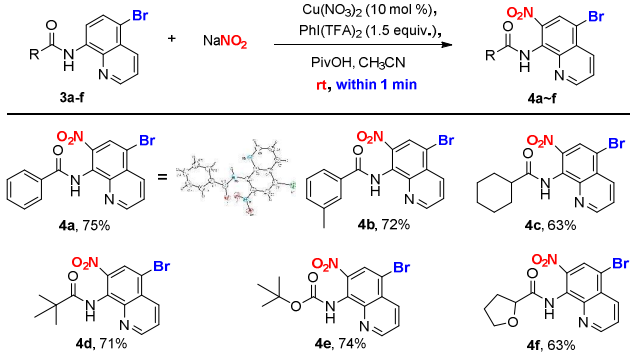
**Table 2** Substrate scope of Cu(II)-catalysed nitration of C5-H of 8-aminoquinoline amides[a,b]




[a] Reaction conditions: **1** (0.20 mmol), sodium nitrite (0.22 mmol), $Cu(NO_3)_2$ (10 mol %), $PhI(TFA)_2$ (1.5 equiv.), PivOH (20 mol %), $CH_3CN$ (2.0 mL); [b] Isolated yield.

yield of product **2a** was declined slightly with reaction temperature increasing (Table 1, entry 10). Instead of $Cu(NO_3)_2$, $Cu(OAc)_2$ resulted in lower yield and longer reaction time (Table 1, entry 6). Other metal salts such as CuI, $PdCl_2$, $AgNO_3$, $Fe(NO_3)_2$, $Co(NO_3)_2$ proved ineffective for this reaction (Table 1, entries 1-5). A screening of different solvents showed that $CH_3CN$ was still the optimum solvent and no reaction occurred in other solvents (Table 1, entries 18-21). When the reaction time was extended to 30 min, however, the nitration product just be obtained in lower yield (Table 1, entry 12). Impressively, control experiments revealed that atmosphere has no effect on the reaction outcome, which highlighted the operational simplicity of this method (Table 1, entries 13 and 14). Furthermore, the reaction did not work in

**Table 3** Substrate scope of Cu(II)-catalysed nitration of C7-H of 8-aminoquinoline amides[a,b]




[a] Reaction conditions: **3** (0.20 mmol), sodium nitrite (0.22 mmol), $Cu(NO_3)_2$ (10 mol %), $PhI(TFA)_2$ (1.5 equiv), PivOH (20 mol %), $CH_3CN$ (2.0 mL); [b] Isolated yield.

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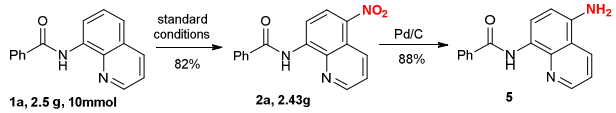
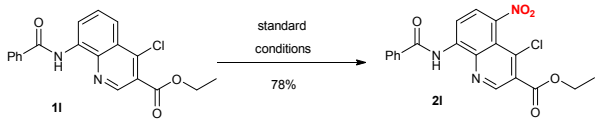
absence of either $Cu(NO_3)_2$ or $PhI(TFA)_2$ (entries 7-8).

With the optimized conditions in hand, the scope of this reaction was investigated (Table 2). The results showed that a wide range of 8-aminoquinoline amides reacted smoothly with sodium nitrite to generate the corresponding nitrated products (**2a-2k)**. 8-aminoquinolinebenzamide was successfully converted into the desired product **2a** in an excellent yield of 86% under the standard conditions. The substrate bearing Me group on the phenyl ring could afford the nitrated product **2b** in 84% yield. Moreover, aliphatic amides, including those with methyl, cyclopropyl, cyclohexyl and *tert*-butyl could also be employed to afford the target compounds **2c-2f** in moderate to good yields. Aliphatic amides with oxygen heteroatom **1g, 1i and 1j** were also found apply to this transformation. In addition, the furancarboxylic acid derived substrate 1**h** was suitable for this reaction. Especially, the substrate of Ph group on the quinoline ring was also been well tolerated, giving the desired product **2k** in 84% yield.

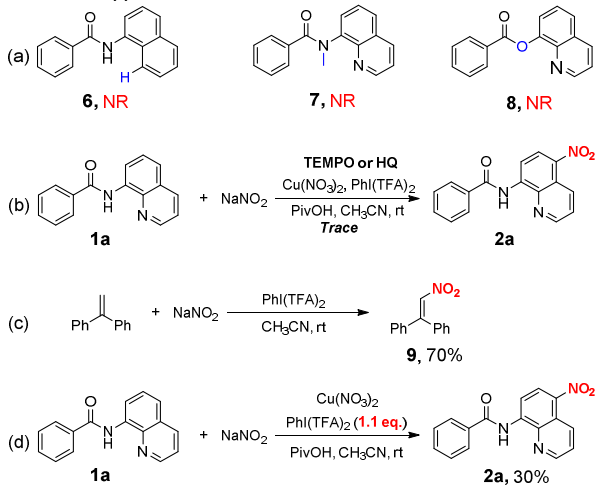
Encouraged by the wide functional group tolerance of this C5-H nitration, we wondered whether this protocol could be applied to the nitration of quinoline ring at C7 position. To our delight, the reaction exclusively occurred at the C7 position of quinoline ring under the typical reaction conditions if the C5 position was brominated (table 3).[14a] Various C5-brominated aminoquinoline amides reacted with sodium nitrite to obtain the desired product **4a-4f** in moderate to good yields. The structure of the product **4a** was confirmed by X-ray crystallography (1444178, CCDC NO.), as shown in the supporting information.




**Scheme 2** Gram scale reaction

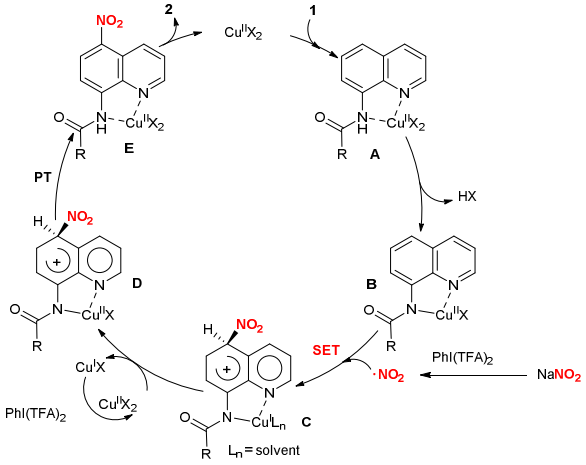



**Scheme 3** Application




**Scheme 4** control experiments

**Scheme 5** plausible mechanism




Given the easy available of the raw materials and the operational simplicity of this method, we performed on a gram scale reaction (Scheme 2), and the nitrated product **2a** was obtained in 82% yield. The obtained product could be further transformed into *N*-(5-aminoquinolin-8-yl)benzamide **5** in 88% yield by Pd/C hydrogenation.[15] These two transformations demonstrated that the nitration product is also provided with synthetic usefulness. Importantly, quinolone derivate **1l** was easily converted to C5 nitrated product **2l** under standard conditions which might be further used to synthesize some interesting compounds of biological and pharmacological activities (Scheme 3).[16]

In order to obtain the mechanistic information about this transformation, some control experiments were carried out. Substrate **6** (1-aminonaphthalene derived benzoic acid) did not give any nitrated product under standard conditions (Scheme 3, a). No desired product was obtained in the reaction when the substrate was changed into *N*-methyl aninoquinoline **7** or 8-acyloxyquinoline **8** (Scheme 4, a). These reactions showed that the formation of the bidentate structure was crucial to the remote C-H nitration.[17] To figure out whether the radical progress would be involved in the reaction, a radical inhibition experiment of **1a** with the addition of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or hydroquinone was further performed under the standard reactions (Scheme 4, b). Completely suppression of the reaction suggested that a radical pathway might be responsible for this transformation. In addition, capturing of radical test was carried out to prove the feasibility of the radical progress and the result revealed that the nitro radical($NO_2$•) was existent in the reaction process (Scheme 4, c). The influence of the quantity of $PhI(TFA)_2$ and reaction atmosphere were further investigated (Scheme 4, d; Table 1, entries 11 and 12). The results explained that reducing the oxidant loading would apparently affect the reaction efficiency. This phenomenon illustrated that the $PhI(TFA)_2$ plays a dual role in the reaction, generating nitro radical and oxidating the intermediate in the reaction process.

Based on above experimental results and our previous studies,[14] a plausible mechanism was depicted in Scheme 5. First, the coordination of substrate **1a** with Cu(II) produced chelated complex

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**A**. Afterwards, the deprotonation of the amide group leads to formation of the complex **B**. Then, nitro radical($NO_2$•) was released in the presence of $PhI(TFA)_2$ and $NaNO_2$. Subsequently, the single electron transfer (SET) occurred between the nitro radical($NO_2$•) and Cu(II) complex **B** to afford the Cu(I) intermediate **C**, followed by the formation of complex **D** through oxidation. Finally, the intermediate **E** generated through proton transfer process, and the desired product **2a** was obtained via ligand dissociation, along with the regeneration of the Cu(II) species to complete the catalytic cycle.

## Conclusions

In summary, we have developed a novel copper-catalyzed highly regioselective direct C-H nitration of quinolines with cheap sodium nitrite, which afforded good yields of C5-H or C7-H nitrated quinoline derivates. This transformation featured a mild reaction system, wide substrate scope as well as the short reaction times. Importantly, this protocol may provide a green and practical approach to construct nitrated quinoline derivatives, which were the key intermediates in the drug synthesis.

## Experimental section

### General information

Unless indicated, all reagents were obtained commercially and used without further purification. Flash chromatography was carried out with silica gel (200-300 mesh). $^1H$ and $^{13}C$ NMR spectras were recorded in $CDCl_3$ or DMSO-$d_6$ on a Bruker Advance 500 spectrometer at ambient temperature with $CDCl_3$ or DMSO-$d_6$ as solvent and tetramethylsilane (TMS) as the internal standard. $^1H$ NMR data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J* values, Hz). $^{13}C$ NMR data were reported in terms of chemical shift (δ ppm). Melting points were determined on an X-5 Data microscopic melting point apparatus. The small-angle X-ray diffraction(SAXRD) data was performed at room temperature using German Bruker D4 X-ray diffractometer. Analytical thin layer chromatography (TLC) was performed with Merk precoated TLC (silica gel 60 F254) plates. High resolution mass spectra (HRMS) were recorded using Agilent 6530 QTOF mass spectrometer. **1a**-**1k** were obtained according to literature reported[14], **3a-3f** were formed according to literature reported.[14a]

### General procedure

General method for Copper(II)-catalyzed C5-H and C7-H nitration of 8-aminoquinoline amides. (**2a**, **2b**, **2k**, **4a** and **4b**): A mixture of amide (0.2 mmol), $NaNO_2$ (15.0 mg, 0.22 mmol, 1.1 equiv), $PhI(TFA)_2$ (129.0 mg, 0.3 mmol, 1.5 equiv), $Cu(NO_3)_2$ (3.8 mg, 0.02 mmol, 10 mol %), PivOH (4.0 mg, 0.04 mmol, 20 mol %), and $CH_3CN$ (2.0 mL) were stirred at room temperature for 1 min. After completion (monitored by TLC), the mixture was filtered through a celite pad, then washed with $CH_3CN$ and dried to give the corresponding product. (**2c-2j, 4c-4f**): A mixture of amide (0.2 mmol), $NaNO_2$ (15.0 mg, 0.22 mmol, 1.1 equiv), $PhI(TFA)_2$ (129.0 mg, 0.3 mmol, 1.5 equiv), $Cu(NO_3)_2$ (3.8 mg, 0.02 mmol, 10 mol %), PivOH (4.0 mg, 0.04 mmol, 20 mol %), and $CH_3CN$ (2.0 mL) were stirred at room temperature for 1 min. After completion (monitored by TLC), the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the corresponding product.

**Pd/C hydrogenation of 2a**. Compound **2a** (60.0 mg, 0.2 mmol), and Pd/C (1.2 mg, 20%) were taken in a dried schlenk tube with a magnetic stir bar under hydrogen, then MeOH (3.0 mL) was added with a syringe and the resulting mixture was stirred for 6 h at room temperature. After completion (monitored by TLC), the mixture was filtered through a celite pad, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the reduction product.

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# Copper-catalyzed rapid C-H nitration of 8-aminoquinolines by using sodium nitrite as the nitro source under mild conditions

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We report the first example of copper(II) catalyzed remote C-H nitration of 8-aminoquinoline amides by using sodium nitrite as nitration reagent under mild conditions in 1 minute which undergoes single electron process.