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# Remote Radical Halogenation of Aminoquinolines with Aqueous Hydrogen Halide (HX) and Oxone

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## Abstract

Simple and halide-atom economical HX reagents (X= Cl, Br and I) were applied to the remote C-H bond halogenation reaction of 8-aminoquinoline amides. This strategy features a broad substrate scope and good functional group tolerance. A series of C5-halogenated 8-aminoquinolines were obtained in moderate to good yields under mild conditions.

**Keywords**: 8-Aminoquinolines, Catalyzed-free, C-H functionalization, Halogenation, Hydrogen Halide (HX)

## Introduction

Recently, 8-aminoquinoline derivatives have drawn significant attention due to their unique characteristics in applications towards pharmaceuticals,[1] organic sythesis[2] and functional materials.[3] Inspired by the transition-metal-catalyzed remote C–H bond chlorination of 8-aminoquinolines by Stahl and co-workers in 2013,[4] strategies for the synthesis of substituted 8-aminoqunolines have attracted increased attention. Various valuable functional groups including sulfonyl,[5] nitryl,[6] halide,[7] and benzyl,[8] have been introduced to the phenyl counterparts of quinoline rings.

As important precursors for coupling reactions[9] or the preparation of organometallic reagents,[10] carbon−halogen bonds have been widely used in organic chemistry.[11] Therefore, it is meaningful to develop more efficient, eco-friendly and atom economical methods to synthesize these halogenated quinoline scaffolds.

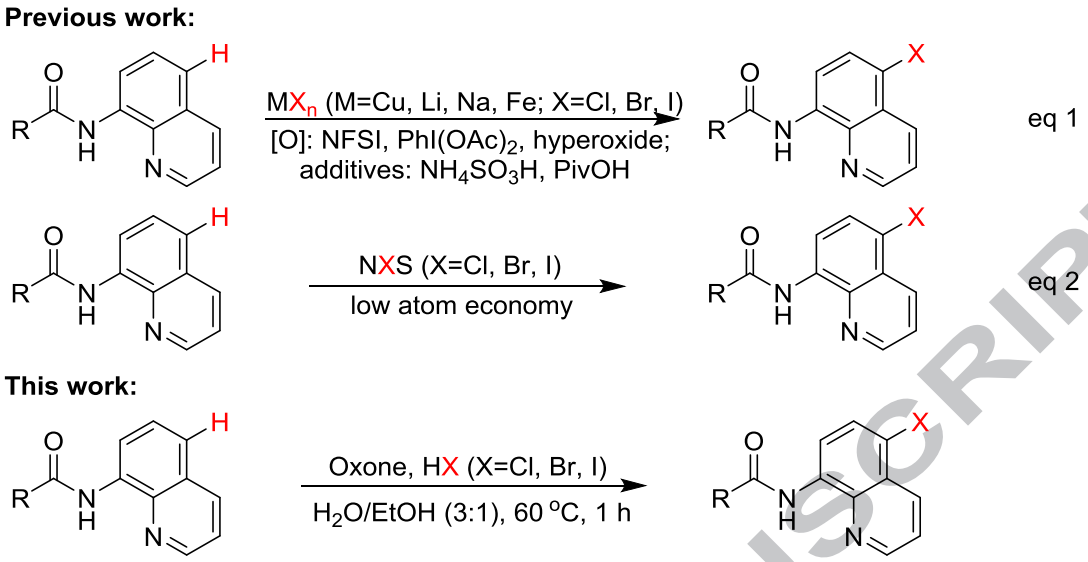



**Figure. 1** Construction of C5 halogenated quinolines

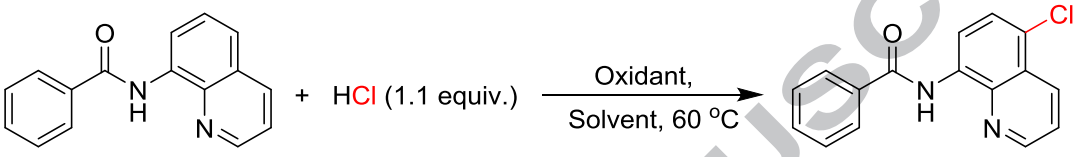
Compared with the traditional halogenation of aromatic compounds which suffers from poor site-selectivity,[12] high toxicity[13] and low atom economy,[14] recent attention has been focused on concise and low-cost oxidative C-H activation reactions. In our previous work, we reported a highly regioselective C-H halogenation of 8-acylaminoquinolines catalyzed by copper(II).[7b] However, the requirement for the usage of hypervalent iodine reagents made the reaction system unsuitable. To the best of our knowledge, most papers for the synthesis of halogenated aminoquinolines featured metal halides ($MX_n$) as the catalyst or the halogen source, such as $CuX_n$, LiX, NaX and $FeX_n$ (X=Cl, Br, I) (Fig. 1, eq. 1),[7a-c] in which organometallic waste could often not be avoided. Although Xu and co-workers demonstrated halogenation based on *N*-halosuccinimide (NXS, X=Cl, Br, I) without additional additives or oxidants,[7d] the halogen source was relatively expensive (Fig. 1, eq. 2). Herein, we report a new strategy for the halogenation of 8-acylaminoquinolines using HX (X= Cl, Br, I) as the halogen source[15] and propose a radical mechanism, which differs from the oxidative halogenation mechanism reported by Li and co-workers.[7e]

## Results and Discussion

Initially, we chose *N*-(quinolin-8-yl)benzamide **1a** and HCl as model substrates to investigate the aromatic C-H functionalization reaction (Table 1). The reactivity of various oxidants was first tested in the presence of HCl (1.1 equiv.), at 60 °C in water under an air atmosphere (Entries 1-6). The target material *N*-(5-(chloro)quinolin-8-yl)benzamide **2a** was isolated in 55% yield in the presence of Oxone (Entry 4). The structure of product **2a** was confirmed by single X-ray

crystallography (Fig. 2). Simple organic initiators such as hydrogen peroxide ($H_2O_2$) and *tert*-butyl peroxide (TBHP) showed poor chlorination activity in the transformation with low yields (Entries 5-6). Organic solvents including DCE, EtOH, THF, MeCN, and DMF were then added to the reaction system (Entries 7-12), and the results suggested that $H_2O$/EtOH (3:1, v/v) was the most suitable (89%). Further screening under oxygen or nitrogen atmospheres did not enhance the product yield (Entries 13-14).

**Table 1.** Optimization of the chlorination reaction conditions [a]




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

| Entry | Oxidant (equiv.) | Solvent | Yield 2a (%)[b] |
|---|---|---|---|
| 1 | $Na_2S_2O_8$ (2.0 ) | $H_2O$ | 19 |
| 2 | $K_2S_2O_8$ (2.0 ) | $H_2O$ | 23 |
| 3 | $NH_4HS_2O_8$ (2.0 ) | $H_2O$ | 0 |
| 4 | Oxone (1.0 ) | $H_2O$ | 55 |
| 5 | $H_2O_2$ (4.0 ) | $H_2O$ | 5 |
| 6 | TBHP (4.0 ) | $H_2O$ | 0 |
| 7 | Oxone (1.0 ) | 3:1 $H_2O$/DCE | NR |
| 8 | Oxone (1.0 ) | 3:1 $H_2O$/EtOH | 89 |
| 9 | Oxone (1.0 ) | 3:1 $H_2O$/THF | 60 |
| 10 | Oxone (1.0 ) | 3:1 $H_2O$/MeCN | NR |
| 11 | Oxone (1.0 ) | 3:1 $H_2O$/Dioxane | 12 |
| 12 | Oxone (1.0 ) | 3:1 $H_2O$/DMF | 63 |
| 13[c] | Oxone (1.0 ) | 3:1 $H_2O$/EtOH | 89 |
| 14[d] | Oxone (1.0 ) | 3:1 $H_2O$/ EtOH | 88 |

[a] Reagents and conditions: **1a** (0.2 mmol), HCl (1.1 equiv.), oxidant, solvent (2.0 mL), 1 h. [b] Isolated yield. [c] Under $O_2$. [d] Under $N_2$.

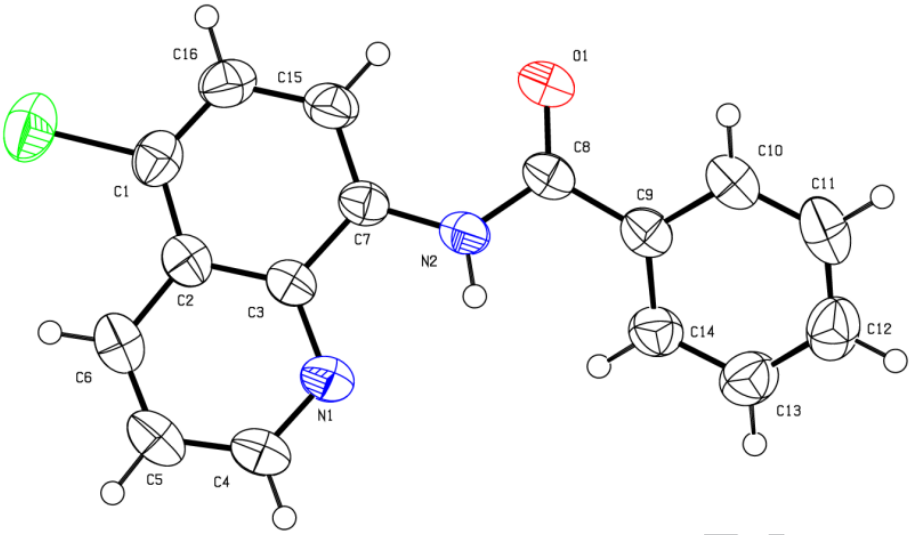
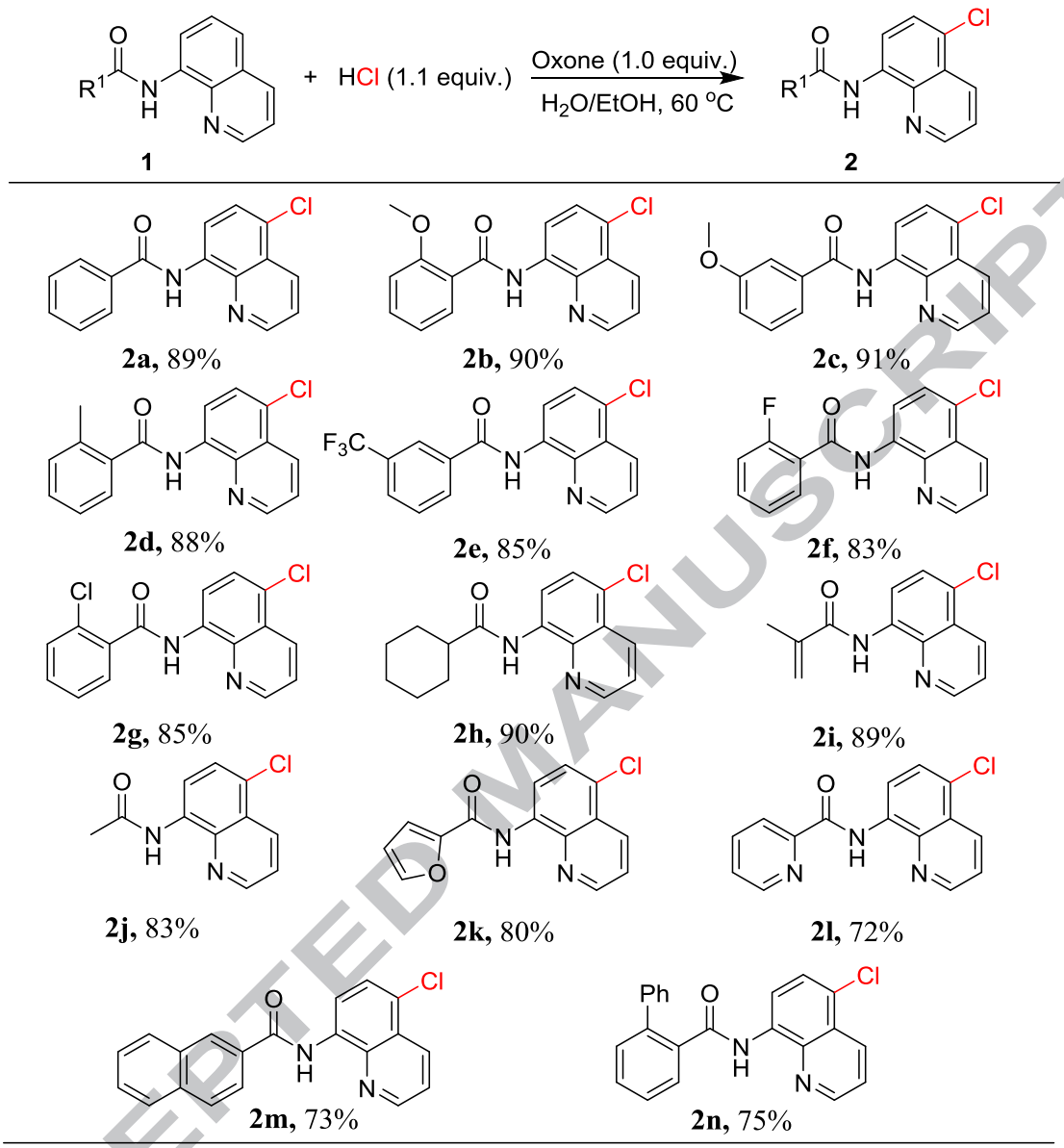


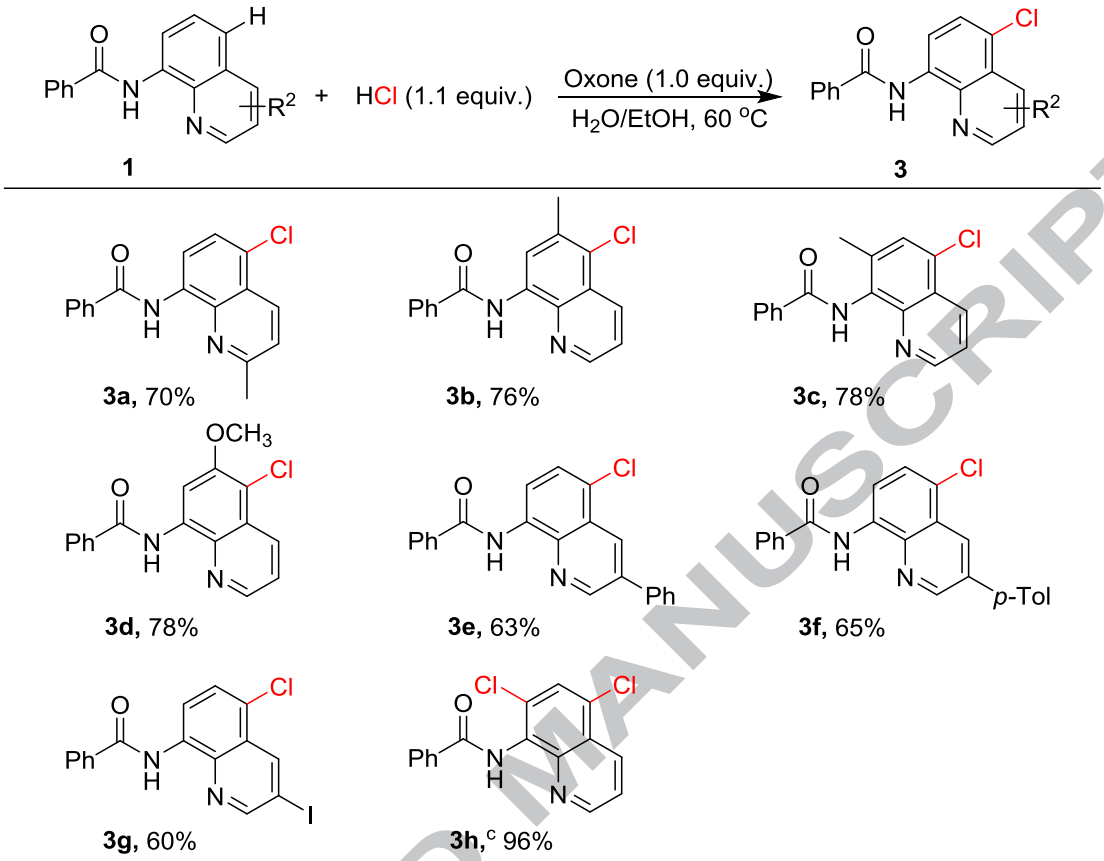

**Figure. 2** X-ray crystal structure of **2a**

With the optimum reaction conditions in hand (Table 1, entry 8), the substrate scope was examined with diversely substituted *N*-(8-quinolinyl)amides (Scheme 1). Pleasingly, almost all of the chlorination reactions using aryl, alkyl and heterocyclic substrates proceeded smoothly under the standard conditions to afford the corresponding products in moderate to good yields (72-91%). Several functionalized benzamides containing simple groups, such as methoxy (**2b-c**), methyl (**2d**), trifluoromethyl (**2e**), fluoro (**2f**) and chloro (**2g**) on the phenyl ring were well tolerated (83-91% yield). Chlorinated aliphatic amides with cyclohexyl, allyl, or ethyl substituents were also obtained in high yields (**2h-j**). It is worth noting that heterocycle amides with furyl (**2k**) or pyridyl (**2l**) substituents and bulky 8-acylaminoquinolines with naphthyl (**2m**) or biphenyl (**2n**) substituents all performed well in chlorination reaction and provided the desired products in high yields.



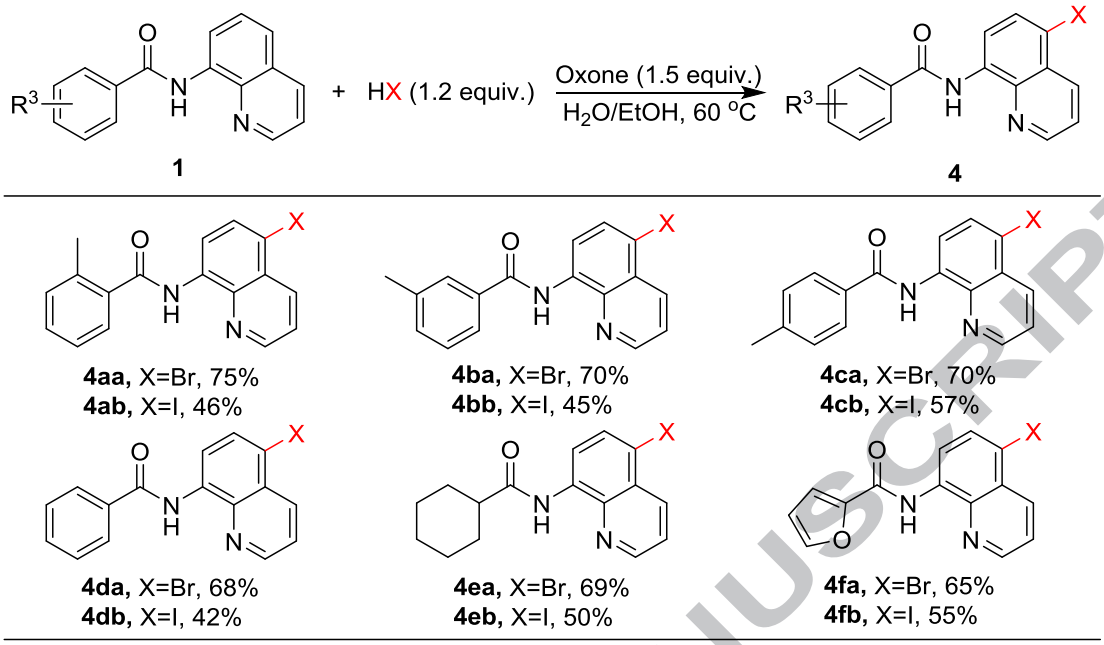

**Scheme 1.** Substrate scope of the quinoline amides. [a] Reagents and conditions: **1** (0.2 mmol), HCl (1.1 equiv.), Oxone (1.0 equiv.), $H_2O$/EtOH (3:1), 60 °C, 1 h. [b] Isolated yield.

We subsequently explored the scope of the reaction with diverse 8-aminoquinoline scaffolds (Scheme 2). This protocol was examined for methyl groups at the C2, C6 and C7 positions of the quinoline substrates, which gave the target products **3a-c** in 72-80% yield. Similarly, the substrate bearing a methoxyl group at C6 gave the corresponding product in 72% yield. (**3d**). However, substrates containing phenyl, *p*-methylphenyl and iodine groups at the C3 position of the pyridine moiety were not tolerated with lower yields (**3e-g**). The dichlorination of 8-aminoquinoline amide at the C5 and C7 positions could be achieved in 96% yield when using double HCl and Oxone (**3h**).



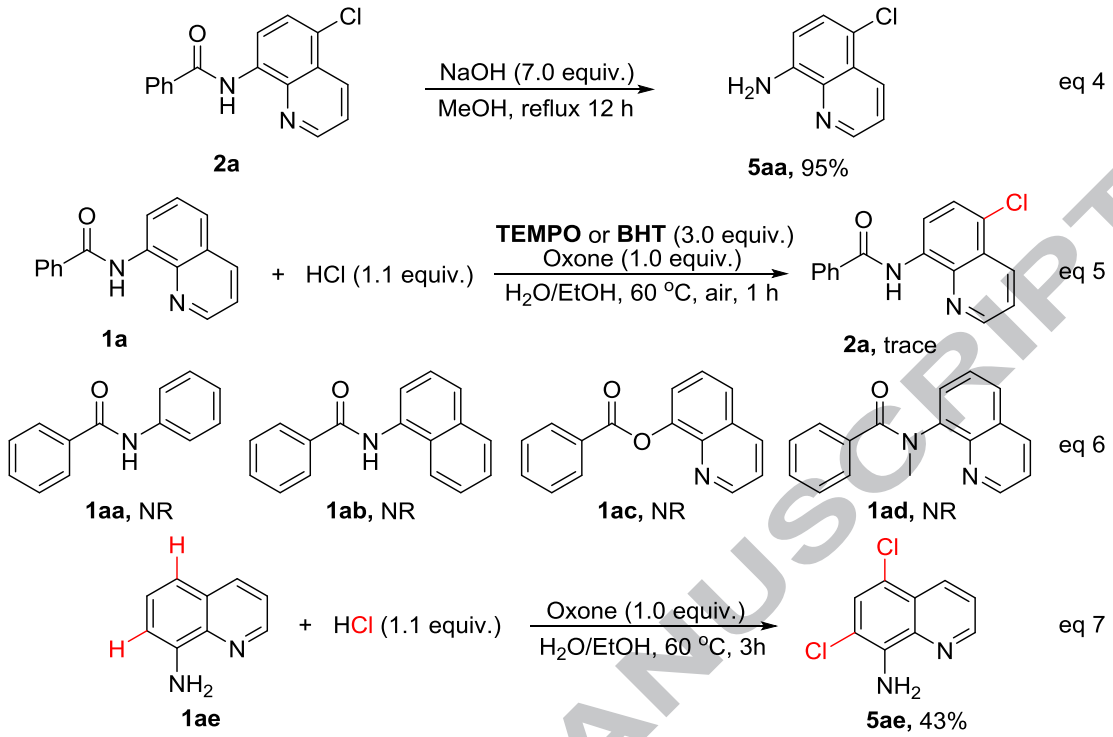

**Scheme 2.** Substrate scope of the quinoline amide. [a] Reagents and conditions: **1** (0.2 mmol), HCl (1.1 equiv.), Oxone (1.0 equiv.), $H_2O$/EtOH (3:1), 60 °C, 1 h. [b] Isolated yield. [c] HCl (2.2 equiv.), Oxone ( 2.0 equiv.).

We found that HBr and HI could also serve as the reactant. Adjusting the loading of the halide source and oxidant, both brominated and iodinated quinolines at the C5 position could be obtained in moderate yields (Scheme 3). Clearly, the reactivity for chlorination of 8-acylaminoquinolines was highest under these reaction conditions, followed by bromination, then iodination.



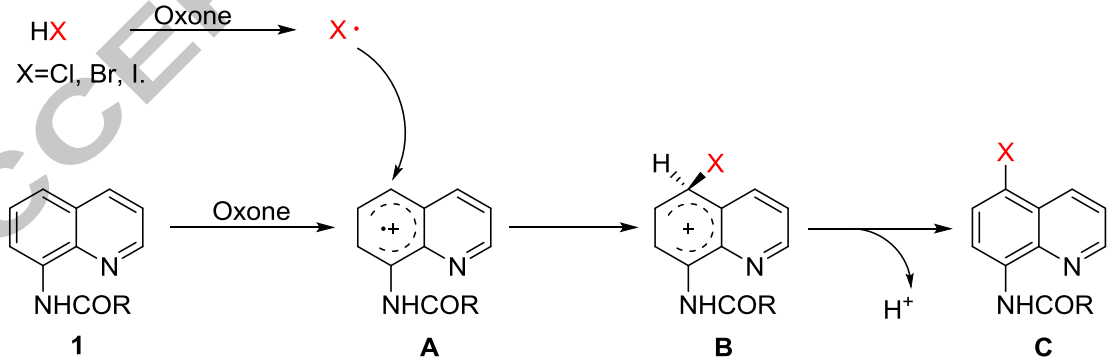

**Scheme 3**. Substrate scope for the brominated and iodinated quinoline amide. [a]Reagents and conditions: **1** (0.2 mmol), HX (1.2 equiv.), Oxone (1.5 equiv.), $H_2O$/EtOH (3:1), 60 °C, 1 h. [b] Isolated yield.

To provide insight into the mechanism of the C-H bond halogenation with HX (X= Cl, Br, I), a series of control experiments were performed. First, the structure of **2a** was confirmed through hydrolysing **2a** under strong alkaline conditions to give 5-chloroquinolin-8-amine[15] in 95% yield (Scheme 4, eq 4). Second, the reaction was supressed when 3.0 equivalents of the radical scavengers TEMPO (2,2,6,6-tetra-methylpiperid-idine-*N*-oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) were added, implying that a radical reaction pathway might exist (Scheme 4, eq 5). Furthermore, structurally similar substrates including *N*-phenylbenzamide **1aa**, *N*-(naphthalen-1-yl)benzamide **1ab**, quinolin-8-yl benzoate **1ac** and *N*-methyl-*N*-(quinolin-8-yl)benzamide **1ad** failed to afford the corresponding product under the standard conditions; these results demonstrate that the quinoline structure and amide group with a free NH unit were required (Scheme 4, eq 6).[17] To evaluate the function of the amido linkage, 8-aminoquinoline was examined and surprisingly only the 5,7-dichlorinated product was detected (Scheme 4, eq 7). The poor site-selective C-H activation and reduced reactivity account for the vital role of the acyl protecting groups during the reaction.




**Scheme 4.** Investigation of the mechanism

A radical mechanism was then proposed to explain the C5 halogenation of 8-aminoquinoline amides (Scheme 5). Initially, the halogen radical X· and radical cation intermediate **A** were formed using Oxone. These combined with each other to form species **B** which after deprotonation affords the desired product **C**.




**Scheme 5.** Plausible mechanism for the halogenation of 8-aminoquinoline amides

## Conclusion

In conclusion, we report a highly atom-economical and site-selective protocol for the radical C-H halogenation of 8-acylaminoquinolines in moderate to good yields.

In this reaction, HX (X= Cl, Br, I) and Oxone were utilised to afford the halogen-radicals. This new halogenated method avoids the use of metal catalysts and proceeds with highly efficiency, broad substrate scope and functional group tolerance.

## Acknowledgements

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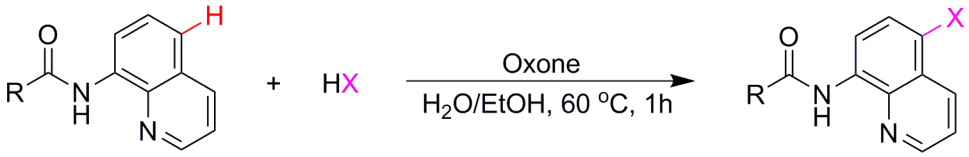


R = arene, alkane and heterocycle

X = Cl, Br, I

- High halide atom economy
- Simple reaction condition
- Clean halogenation reagents
- Broad substrate scope

1. We developed a simple method to synthesizing halogenated 8-aminoquinoline amides;
2. The most halide-atom economical HX were used to afford halogen resources;
3. A range of halogenated products were obtained in moderate to good yields;
4. The reaction system was carried out in green solvents: water and alcohol.