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Transition Metal Free Oxygenation of 8-Aminoquinoline Amides in Water

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Abstract: The oxygenation of 8-aminoquinoline amides by benzoyl peroxide at the C5 position in water is developed in the absence of transition metal catalyst, affording the desired products in moderate to good yields up to 88%. Mechanism studies reveal that the reaction would involve a radical process.

8-Aminoquinoline is an important scaffold in many natural products and pharmaceuticals. For example, primaquine, pamaquine and tafenoquine, which contain 8-aminoquinoline fragment, have been reported as antimalarial drugs (Figure 1).[1] Accordingly, the derivatization of 8-aminoquinolines has attracted an increasing number of attentions, and different functional groups have been introduced into the scaffold by many methods such as metal catalysis or multiple steps.[2] Recently, with considerable progress in the C–H functionalization,[3] substitutions at the C2,[4] C4[5-6] positions of quinoline has been reported. Meanwhile, some approaches for direct construction of bonds between carbons and heteroatoms at the C5 position of quinolines have also been developed. For example, as shown in Figure 2, Stahl, Zhang and co-workers reported copper-catalyzed chlorination in acetic acid.[7-8] Copper-catalyzed C5-sulfonylation in toluene, DCE or dioxane as solvent was also developed by Wei,[9] Wu,[10] Zeng,[11] Liu[12] and Chan and co-workers, respectively.[13] Kanai group reported trifluoromethylation of quinolones in DCE.[14] Xu and co-workers reported metal-free amidation reactions with DME as solvent.[15] Wu group realized phosphonation of 8-aminoquinoline amides in dioxane.[16] Although great progress has been achieved in this field, most of these transformations were performed in the presence of transition metal catalyst and in organic solvents, the method of metal free C-5 functionalization of 8-aminoquinoline in water is rare.

On the other hand, benzoyl peroxides are usually regarded as a low toxic and widely used arylation or benzoyloxylation reagent in many organic reactions.[17-21] The methodology of benzoyl peroxide as source of benzoyloxyl group for C(sp^2)-H bond activation and C-O bond construction without catalyst is less reported.

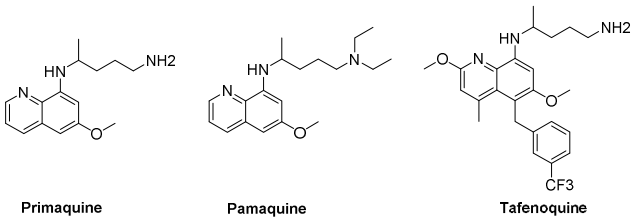
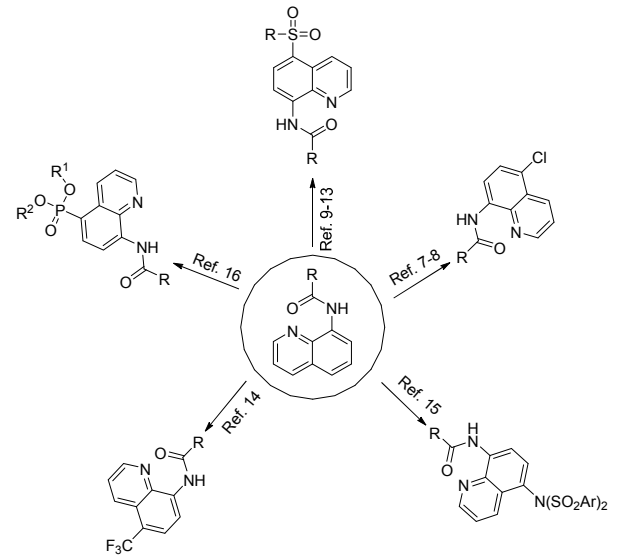


Figure 1. Representative 8-aminoquinolines as antimalarial drugs



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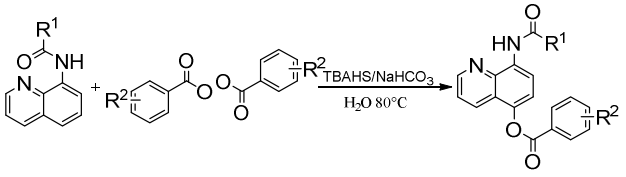

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Electronic supplementary information (ESI) available: All optimization tables and copies of crystallographic data. CCDC 1582941. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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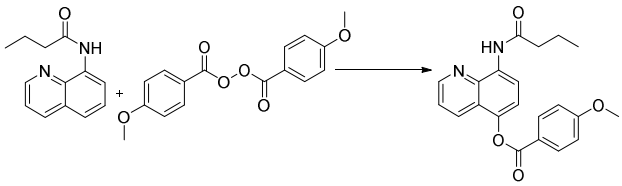
Figure 2. Some examples of C-H functionalization at C5-position of 8-aminoquinoline

Furthermore，compared with organic solvents, water is a green and friendly solvent for chemical reactions. And many successful examples of C-H bond functionalization in water have been reported.[22] In continuation of our work on aqueous catalysis,[23] herein is reported the oxygenation of 8-aminoquinoline amides in water. This work has the following advantages: water was used as solvent instead of normally used harmful organic solvents; the reactions were performed in the absence of transition metal catalyst, which would be beneficial to the workup procedure and potential applications; reaction condition is mild without inert atmosphere.

Table 1. Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Solvent	Additive	Temp. [°C]	Yield [%][b]
1	Toluene		25	5
2	DMF		25	0
3	DMSO		25	0
4	THF		25	0
5	DCE		25	Trace
6	H_2O		25	7
7	H_2O	$Pd(OAc)_2$	25	0
8	H_2O	$Cu(OAc)_2$	25	8
9	H_2O	$FeCl_3$	25	Trace
10	H_2O	$Ni(OAc)_2$	25	0
11	H_2O		40	9
12	H_2O		60	15
13	H_2O		80	20
14	H_2O		100	20
15	H_2O	K_2CO_3	80	8
16	H_2O	NH_4OAc	80	20
17	H_2O	Cs_2CO_3	80	trace
18	H_2O	CH_3COOH	80	5
19	H_2O	CF_3COOH	80	trace
20	H_2O	NaOH	80	0
21	H_2O	Sodium benzoate	80	18
22	H_2O	Na_2CO_3	80	20
23	H_2O	*t*-BuOK	80	22
24	H_2O	CH_3COONa	80	20
25	H_2O	TBAI	80	trace
26	H_2O	TBAB	80	trace
27	H_2O	TBAHS	80	47
28	H_2O	TBAHS/$NaHCO_3$	80	82
29[e]	H_2O	TBAHS/$NaHCO_3$	80	**80**

[a] All reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), additive (0.1 mmol) and solvent (1.0 mL) for 18hr. [b] Isolated yields. [d] DCE = 1,2-dichloroethane, TBAI = tetrabutylammonium iodide, TBAB = tetrabutylammonium bromide, TBAHS = tetrabutylammonium hydrogen sulfate. [e] 0.02 mmol additive for 24hr.

We commenced our investigations with 8-aminoquinoline amide **1a** and benzoyl peroxide **2a** as model substrates in toluene (1.0 mL) at room temperature without metal catalyst and additives, which gave only 5% desired product **3a** (Table 1, entry 1). After the examination of various solvents, water was found to give similar result of 7% yield, while DMF, DMSO, THF and DCE retarded the reactions (entries 2–6). Meanwhile, addition of transition metal salts such as $Pd(OAc)_2$, $Cu(OAc)_2$, $FeCl_3$ and $Ni(OAc)_2$ seemed to be unnecessary, which caused similar or less yields (entries 7-10). Further experiments indicated higher temperature would be beneficial to the reaction, and 20% yield was obtained at 80°C (entries 11-14). Acidic or basic additives seemed to have few or bad effects on the results (entries 15-24). At last, different phase transfer reagents were examined, exhibiting significant effects on the results. However, when TBAI or TBAB was used, the corresponding halogenated product was obtained as main product with only trace of desired product (entries 25-26). Therefore, TBAHS was selected for this reaction, affording 47% Yield. Furthermore, after addition of $NaHCO_3$, the yield was improved to be 82% (entries 27-28), and the amount of additive could be reduced to be 20 mmol% with similar yield 80% albeit longer reaction time 24hr. Therefore, the optimized reaction conditions were TBAHS and $NaHCO_3$ was used as additive in H_2O at 80°C.

Under the optimized reaction conditions, different amides were then tested, and the results were listed in Scheme 1. In general, both alkyl amides (**3a**-**3e**) and aryl amides (**3f**-**3k**) gave the desired products in moderate to good yields. And Aryl amides bearing electron-donating groups seemed to be more beneficial to this reaction. Methoxyl group substituted substrate gave **3g** in the highest yield 88% in Scheme 1. The molecular structure of **3j** was confirmed by single crystal X-ray diffraction study (Figure 3). Furthermore, 2-methyl or 6-chloro-8-aminoquinoline amides substrates could also give the desired products in 73% or 47% yield.

Next, a variety of benzoyl peroxides were examined in the oxygenation of *N*-(quinolin-8-yl) butyramide (**1a**). As shown in Scheme 2, benzoyl peroxides bearing electron-donating groups exhibited higher activities than those with electron-withdrawing groups. For example, *para*-methyl or ethyl substituted substrates gave 73% and 75% yields of desired products (**3s** and **3t**), while *para*-chloro or trifluoromethyl substituted ones gave 60% and 46% yields, respectively (**3p** and **3q**). Steric effect was also found in the case of *para* and *ortho*- chloro substituted substrates, which resulted in 60% and 34% yields (**3p** and **3n**). Besides, heteroarene peroxides bearing furan or thiophene ring could also be applied in this reaction, affording the desired products in 56% or 58% yield (**3w**,**3x**).

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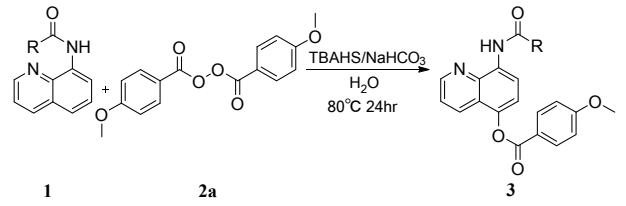
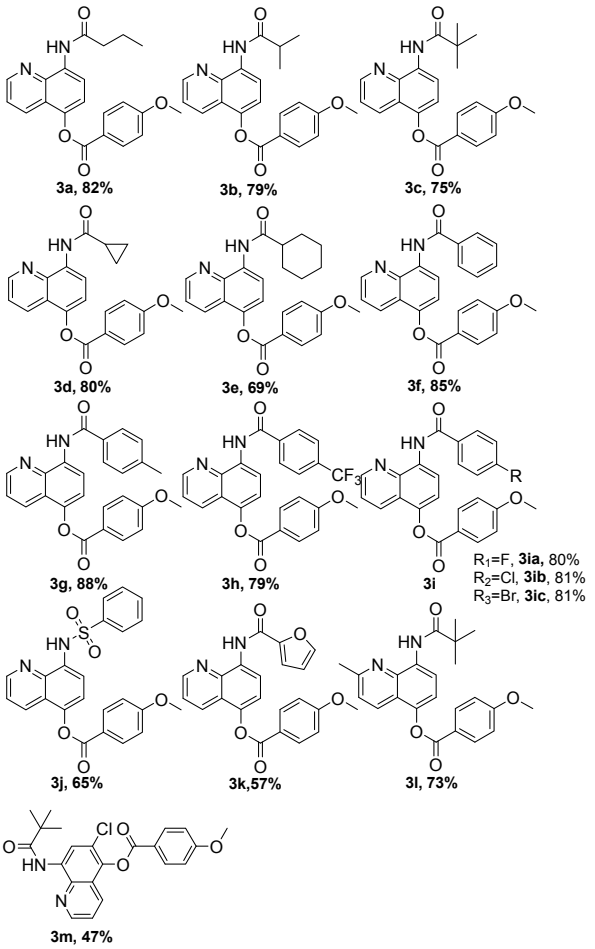
Scheme 1. Substrate scope of the 8-aminoquinoline amides



1 2a 3



Reaction conditions: **1a** (0.1 mmol), **2** (2.0 equiv), additive (0.02 mmol), H_2O (1.0 mL), 24hr. The yields shown here are isolated yields.

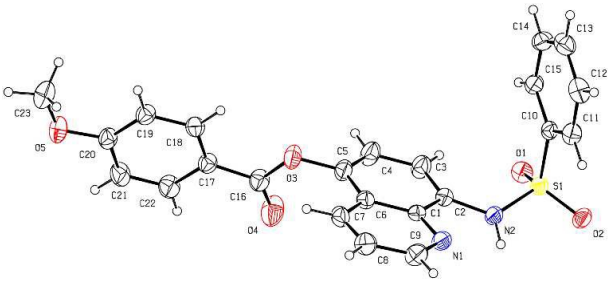
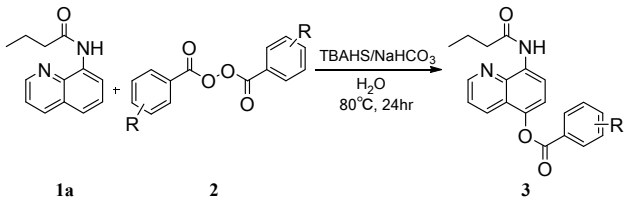
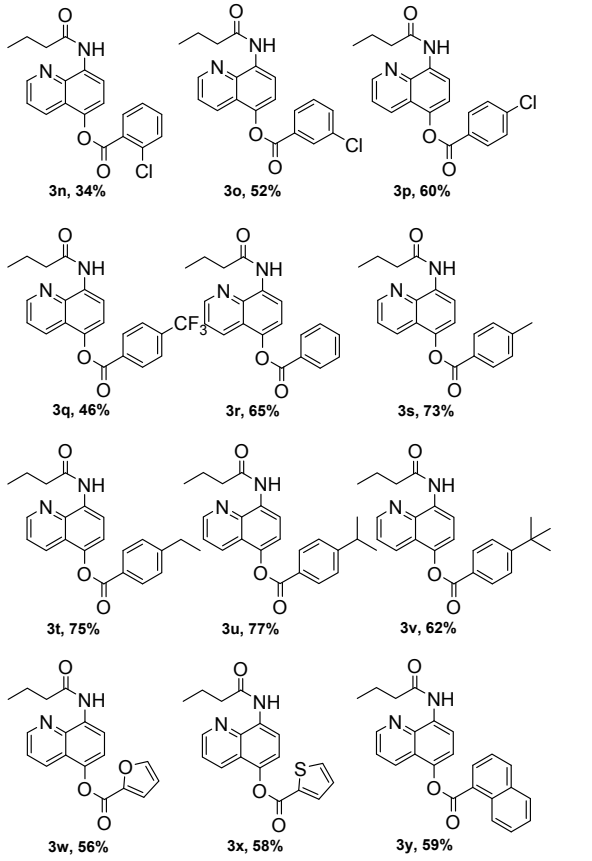


Figure 3. Crystal structure of **3j**

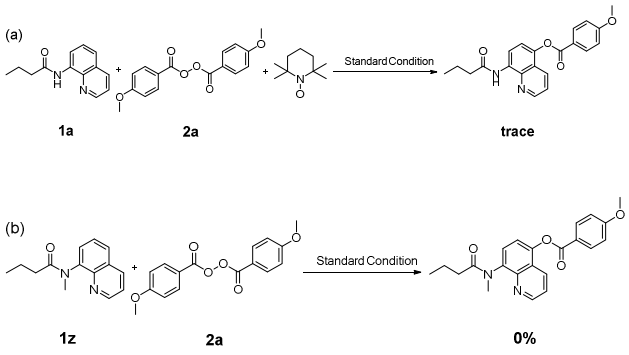
Scheme 2. Substrate scope of benzoyl peroxides.



1a 2 3



Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), additive (0.02 mmol), H_2O (1.0 mL), 24hr. The yields shown here are isolated yields.



Scheme 3. Explore the reaction pathway

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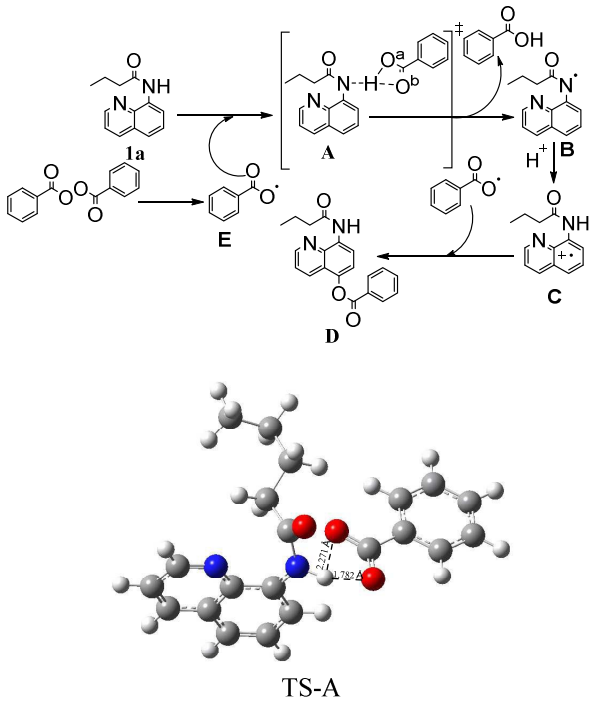
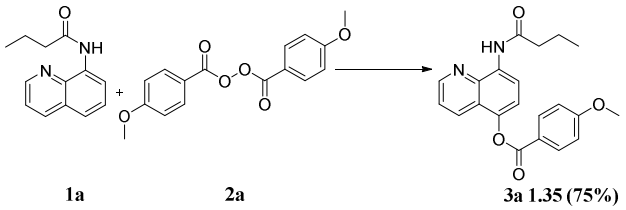
In order to explore the possible reaction pathway, free radical inhibition experiments were then performed as shown in Scheme 3a. Addition of 0.4 mmol free radical trapping reagent 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) would suppress the reaction completely, formation of only trace of product, indicating radical procedure would be involved in this reaction. Furthermore, the methyl substituted substrate **1z** was synthesized and reacted with **2a**, and no desired product was obtained, which suggested the hydrogen atom of amide group would be vital to this radical procedure (Scheme 3b).[24]



Scheme 4. Plausible reaction pathway and optimized geometry of transition state **A**

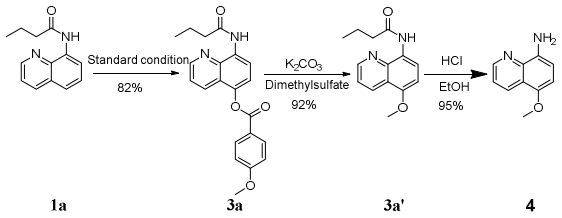
Based on these results and our preliminary computational studies using DFT methods implemented in Gaussian 09 (see supporting information), a plausible reaction pathway for the oxygenation of 8-aminoquinoline amides is outlined in Scheme 4. At first, benzoyloxyl radical **E** would be formed from BPO during reaction.[17] Then, **E** would be reacted with 8-aminoquinoline **1a** to form amidyl radical intermediate **B** through transition state **A**, which was found to be endothermic ($\Delta\Delta G_{298}$=17.8 kJmol^{-1}). The interatomic distances of H^a-O^a and H^a-O^b are 1.782Å and 2. 271Å respectively. And intermediate **C** would be formed in the presence of proton.[15] At last, the desired product **D** could be obtained from the reaction between **C** and another benzoyloxyl radical.

The scaled-up experiment was also carried out by using **1a** and **2a** as substrates, and 75% yield could be obtained, which indicated its potential applications.



Scheme 5. Reaction conditions: **1a** (1.07g, 5 mmol), **2a** (3.02g, 2.0 equiv.), additive (1 mmol), H_2O (5.0 mL), 24hr.

At last, the possibility of application of this protocol was explored. As shown in Scheme 6, compound **4**, which is a potential molecule for treating endoplasmic reticulum stress-caused disease,[25] could be synthesized by this protocol without toxic by-products and harsh conditions in a total yield of 71%.



Scheme 6. Synthesis of 5-methoxyquinolin-8-amine

Conclusions

In summary, a transition-metal free C–H bond oxygenation of 8-aminoquinolines on the C5 position with various benzoyl peroxides was developed. This synthetic approach provides a simple and direct route to a wide variety of C5-position oxygenation compounds. Further investigation is currently underway in this lab.

Acknowledgements

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