RSC Advances

PAPER

Cite this: *RSC Adv.*, 2021, **11**, 30719

Metal-free site-selective C–H cyanoalkylation of 8-aminoquinoline and aniline-derived amides with azobisisobutyronitrile†

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Received 9th August 2021
Accepted 25th August 2021

DOI: 10.1039/d1ra06013a

rsc.li/rsc-advances

Using $K_2S_2O_8$, an efficient and metal-free site-selective C–H cyanoalkylation of 8-aminoquinoline and aniline-derived amides with AIBN (azobisisobutyronitrile) was developed. Without any catalyst, various substrates and functional groups were compatible to afford corresponding products in moderate to high yields. A mechanism study displayed that a radical–radical coupling process was involved *via* the N-centered radical generation and delocalization of aryl amides.

Introduction

Arylamines are important molecular skeletons widely existing in pharmaceuticals, agrochemicals and natural products (Fig. 1).[1] Thus, it is of great significance to develop synthetic methods to modify arylamine fragments with a diverse range of functional groups.[2] The direct functionalization of aromatic C–H bonds possessed various advantages such as step and atom-economy. However, in aromatic systems, it is difficult to control the regioselectivity since mixtures of regional isomers are usually formed. In recent decades, transition-metal-catalyzed direct aromatic C–H bond functionalization provided a useful tool for site-selective functionalization to synthesize various aniline and 8-aminoquinoline derivatives.[3] However, there are still limitations of the reactions involving metal catalysts due to the fact that it might result in an additional process for the isolation and purification of the products particularly in pharmaceutical manufacturing.[4] Thus, environmentally benign approaches to the metal-free, site-selective C–H functionalization of aniline and 8-aminoquinoline derivatives has been a challenging topic for a long time (Scheme 1a). In our previous study, an efficient and facile metal-free process for the remote C–H bond fluorination of 8-aminoquinoline scaffolds at the C5 position using Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) was developed.[5] Subsequently, Wang *et al.* reported the direct C5 amination[6] and sulfonylation[7] of 8-aminoquinoline amide with NFSI (*N*-fluorobenzenesulfonimide) and hypervalent iodine reagent $PhI(OAc)_2$ being employed as oxidants, respectively. Liang *et al.* demonstrated the C5 tosyloxylation of 8-aminoquinolines with PIFA (phenyliodine(III) bistrifluoroacetate) and substituted 1,2-disulfonyl hydrazides.[8] Also, a C–O cross-coupling reaction in the absence of metals was developed by Yao *et al.*[9] Besides, the metal-free C5 trifluoromethylation reactions were successively realized by Wu *et al.*,[10] Kuninobu *et al.*[11] and Tian *et al.*[12] These studies inspired us to realize the metal-free and site-selective C–H functionalization of 8-aminoquinoline and aniline-derived amides without the assistance of metal catalysts.

Taking into consideration the origin of the regioselective C–H functionalization of arylamine amides, nucleophilic agents attacking the positive charge delocalized aryl intermediate was a successful strategy.[13] In general, for the radical–radical cross coupling protocol, transition-metal-mediated SET (single electron transfer) guiding remote C–H functionalization has been regarded as a powerful tool since the early report by Stahl *et al.* in 2013.[14] The *N*-amidyl radical generation in amide bonds was also realized as an useful intermediate to induce *para*-C–H functionalization *via* a prioritized radical delocalization process, which could be reached by transition metal catalysts or special oxidative dehydrogenation reagents.[9,15] In our previous study, it was found that HAT (hydrogen atom transfer) could readily occur between the amide bond of 8-aminoquinolines and the oxidant Selectfluor (Scheme 1b).[5] However, the fluorine free radical was also generated from Selectfluor simultaneously.

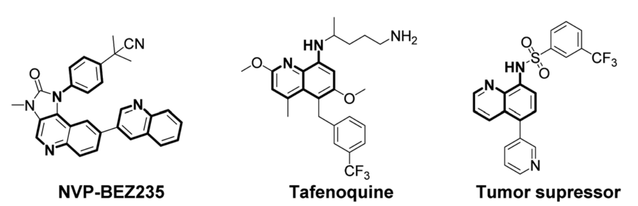

Fig. 1 Pharmaceutically active arylamine derivatives.

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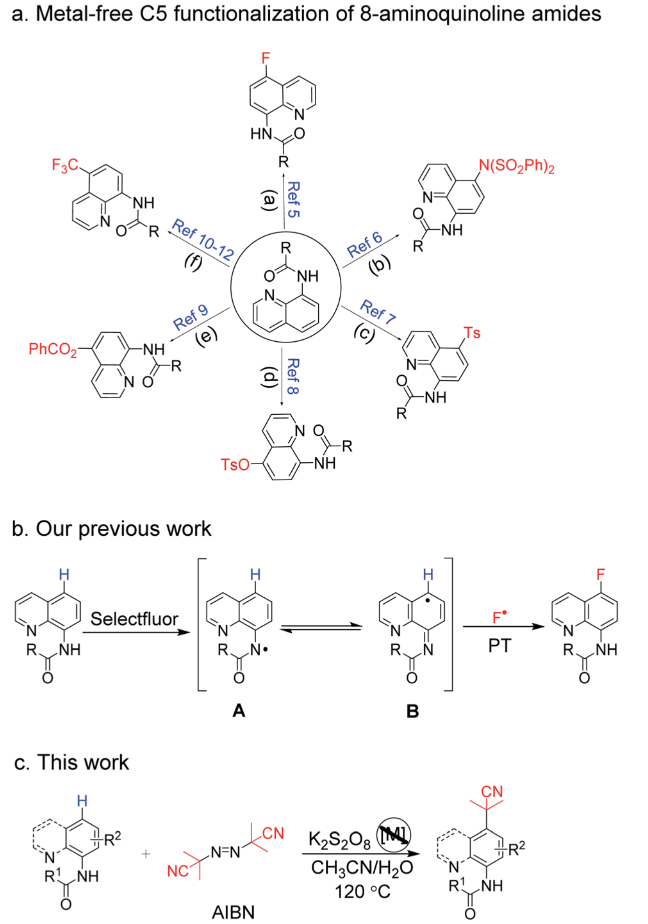
† Electronic supplementary information (ESI) available. CCDC 2091504. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra06013a



Scheme 1 Methods for the preparation of metal-free C5-selective functionalization of 8-aminoquinoline and aniline-derived amides.

This result prompts us to search for clean oxidants, which could enable the HAT process without own radical coupling with arylamine amides in the absence of a transition metal catalyst.

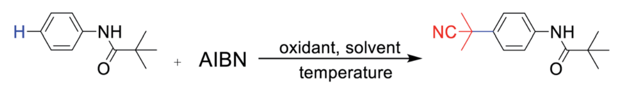
$K_2S_2O_8$ has been widely used in C–H oxidative transformations due to the excellent single electron oxidation and hydrogen abstract ability of its homolysis product ($SO_4^{-\bullet}$). Impressive progress has been made involving $K_2S_2O_8$ in recent years.[16] We speculated that the N–H bond in amides could be activated by $K_2S_2O_8$ to generate N-radicals, and the C–C bond formation in a remote position could be achieved by coupling with other suitable carbon-free radicals. Azo compound AIBN can release one molecule of N_2 to produce a steric cyanoalkyl radical upon heating.[17] As part of our studies in regioselective C–H functionalization,[3k,5,18] herein, we report a metal-free and $K_2S_2O_8$-mediated method to achieve the cyanoalkylation of 8-aminoquinoline and aniline-derived amides with AIBN, which was in concert with a C–C bond formation *via* employing an amidyl radical generation (Scheme 1c).

Results and discussion

Originally, to explore the possibility of cyanoalkylation under metal-free conditions, *N*-pivaloylaniline (**1a**) and AIBN were selected as model substrates. The results are summarized in Table 1. Using $K_2S_2O_8$ as a hydrogen abstracting agent and free radical initiator, we commenced our reaction in a mixed solvent ($MeCN/H_2O = 1/1$) for 1 h at 120 °C (entry 1). Delightedly, it was found that the desired product **2a** was obtained in 87% yield. No further yield increment was observed when the reaction time was prolonged to 4 h. Encouraged by this result, numerous oxidants such as $(NH_4)_2S_2O_8$, $PhI(OAc)_2$ and TBHP (*t*-butyl hydroperoxide) were screened subsequently. The results showed that only $(NH_4)_2S_2O_8$ was effective in 81% yield, indicating that persulfate accounted for the reaction (entries 2–4). Next, the effect of the solvents was evaluated in the presence of $K_2S_2O_8$. Single solvents such as CH_3CN, H_2O, DMF, or mixed solvent CH_3CN–DMSO (1 : 1), were found to be inferior in this reaction (entries 5–8). However, the CH_3CN–H_2O system, which can improve the solubility of inorganic salt $K_2S_2O_8$,[19] has a dramatic advantage over other solvents in this protocol. Furthermore, for the model **1a** and AIBN, no additional benefit was gained when the reaction was switched to a higher (130 °C) or a lower (110 °C) temperature (entries 9–10 *vs.* 1). Further investigation involving the loading change of the oxidant and AIBN was performed (entries 11–14). When the dosage of AIBN and $K_2S_2O_8$ was 1.3 and 1.7 equivalent, respectively, the required product **2a** was obtained with the best yield of 89% (entry 14). In addition, acidic or basic additives seemed to be unnecessary, which led to lower yields of 78% and 75% (entries 15–16).

With optimized reaction conditions in hand (Table 1, entry 14), the substrate scope of aniline-derived amides was first

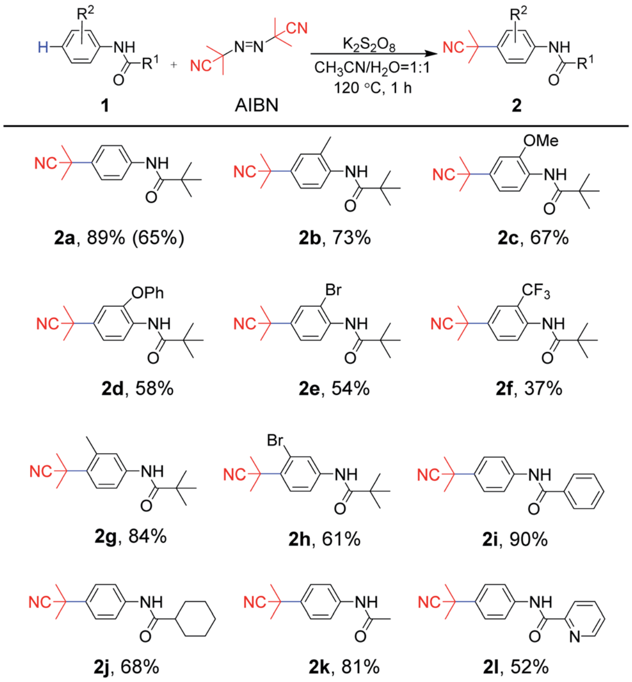
Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	Oxidant	Solvent[b]	Temp (°C)	Yield[c] (%)
1	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	87
2	$(NH_4)_2S_2O_8$(2.0)	CH_3CN/H_2O	120	81
3	$PhI(OAc)_2$(2.0)	CH_3CN/H_2O	120	26
4	TBHP(2.0)	CH_3CN/H_2O	120	Trace
5	$K_2S_2O_8$(2.0)	CH_3CN	120	Trace
6	$K_2S_2O_8$(2.0)	H_2O	120	13
7	$K_2S_2O_8$(2.0)	DMF	120	Trace
8	$K_2S_2O_8$(2.0)	CH_3CN/DMSO	120	9
9	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	130	85
10	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	110	79
11	$K_2S_2O_8$(1.7)	CH_3CN/H_2O	120	87
12	$K_2S_2O_8$(1.5)	CH_3CN/H_2O	120	84
13	$K_2S_2O_8$(2.5)	CH_3CN/H_2O	120	69
14[d]	**$K_2S_2O_8$(1.7)**	**CH_3CN/H_2O**	**120**	**89**
15[e]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	78
16[f]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	75

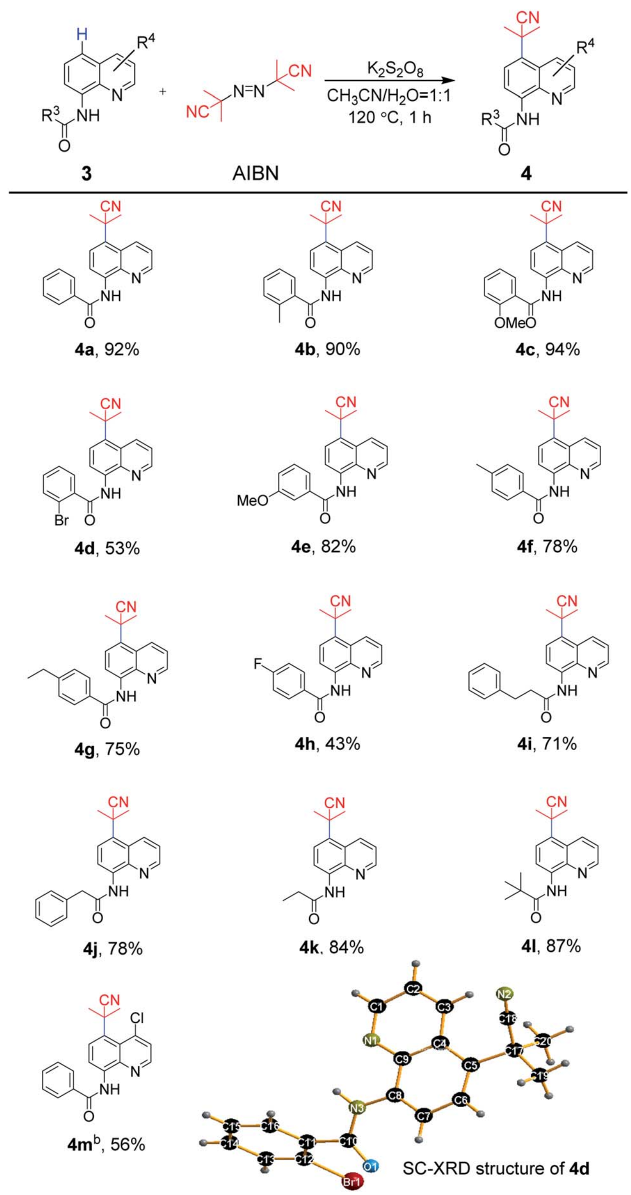
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), AIBN (0.3 mmol, 1.5 equiv.), oxidant (0.4 mmol, 2.0 equiv.), solvent (2.0 mL), in sealed tube for 1 h. [b] Solvents mentioned are mixed at a ratio of 1 : 1 unless otherwise specified. [c] Isolated yield. [d] AIBN (1.3 equiv.). [e] AcOH (3.0 equiv.). [f] Na_2CO_3 (3.0 equiv.).



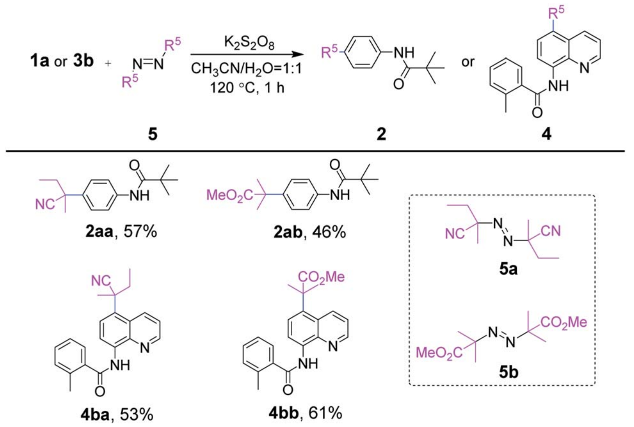
Scheme 2 Substrate scope of aniline derivatives [a]reaction conditions: 1 (0.20 mmol), AIBN (0.26 mmol), $K_2S_2O_8$ (0.34 mmol), CH_3CN (1 mL), H_2O (1 mL), 120 °C, in sealed tube for 1 h. [b]1a (4.0 mmol), AIBN (5.2 mmol), $K_2S_2O_8$ (6.8 mmol), CH_3CN (5.0 mL), H_2O (5.0 mL), 120 °C, in sealed tube for 1 h.

investigated for this radical coupling reaction (Scheme 2). Aniline moieties bearing electron-donating substituents (methyl, methoxy or phenoxy) at the C2 position of a phenyl ring afforded **2b**, **2c** and **2d** in 73%, 67% and 58% yields, respectively. However, the substrates substituted by electron-withdrawing groups (chlorine or trifluoromethyl) at the *ortho*-position of the amino group produced **2e** and **2f** in 54% and 37% yields, respectively. In addition, the reaction of substrates with *meta*-methyl or bromo groups also afforded the target products **2g** and **2h** in 84% and 61% yields. The results showed that substrates bearing electron-donating groups were more dominant in this protocol. Furthermore, substrates containing different acyl moieties were explored. For the acyl part, whether it is sterically hindered phenyl and cyclohexyl groups or ethyl group with less steric hindrance, the expected *para*-cyanoalkylated products **2i–2k** were obtained with moderate to good yields of 68–90%, which suggested that the steric hindrance nature of the acyl moiety was not crucial for the reaction transformation. It is worth noting that even 2-pyridylamide, which contains a N-heterocycle in the acyl moiety was completely compatible to afford the desired product **2l** in 52% yield. The scaled-up experiment was also carried out using **1a** and AIBN as substrates, and 65% yield could be obtained, which indicated the potential application of the protocol.

The scope of exploration of the remote C5 cyanoalkylation of 8-aminoquinoline amides was extended for the synthetic strategy (Scheme 3). As expected, the 8-aminoquinoline amide **3a** afforded the cyanoalkylation product **4a** in 92%. Similar to aniline-derived amides, the reaction of substrates bearing electron-donating groups in the benzoyl ring were beneficial under standard reaction conditions. For example, the substrates containing 2-methyl and 2-methoxy groups underwent cyanoalkylation to afford **4b** and **4c** in 90% and 94% yields, respectively, while 2-bromo one provided **4d** in 53% yield. A satisfactory result was observed for **4e**, which has the 3-methoxy group in the phenyl ring, in 82% yield. Furthermore, the transformation of the substrates bearing 4-methyl, 4-ethyl and 4-fluoro groups could be achieved in 43–78% yields (**4f–4h**). Likewise, almost unchanged yields were obtained between the linear amides and the steric hindered pivalamide (**4i–4k** *vs.* **4l**). Quinoline amide with the 4-chloro group in the quinoline moiety delivered to the target product **4m** in 56% yield



Scheme 3 Substrate scope of 8-aminoquinoline derivatives [a]reaction conditions: 3 (0.20 mmol), AIBN (0.26 mmol), $K_2S_2O_8$ (0.34 mmol), CH_3CN (1 mL), H_2O (1 mL), 120 °C, in sealed tube for 1 h. [b]$K_2S_2O_8$ (0.30 mmol), 100 °C.



Scheme 4 Substrate scope of representative azo analogues [a]reaction conditions: **1a** or **3b** (0.20 mmol), **5** (0.26 mmol), $K_2S_2O_8$ (0.34 mmol), CH_3CN (1 mL), H_2O (1 mL), 120 °C, in sealed tube for 1 h.

smoothly. Thus, for 8-aminoquinoline amides, the tolerance of the functional groups was realized. In addition, the molecular structure of **4d** was unambiguously confirmed by single-crystal X-ray diffraction.

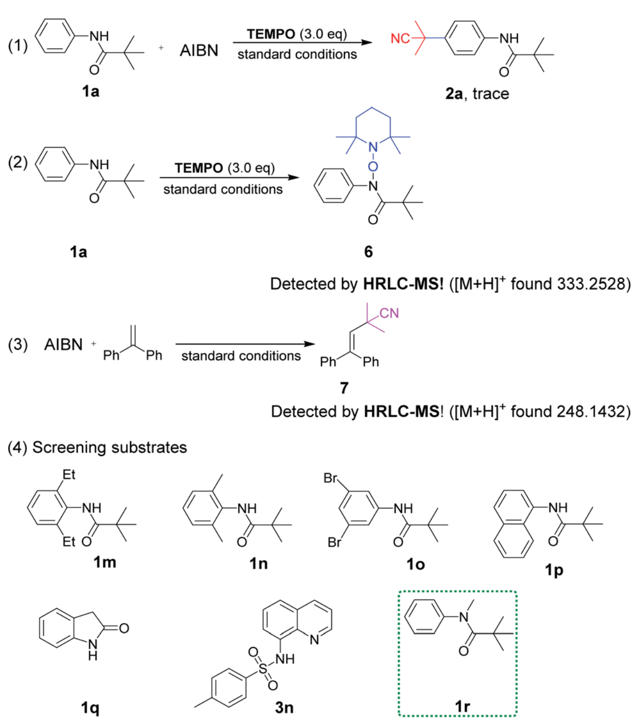
Then, analogues of AIBN including 2,2′-azodi(2-methyl butyronitrile) (**5a**) and dimethyl 2,2′-azobis(2-methyl propionate) (**5b**) were concisely examined with representatives **1a** and **3b** under optimal conditions. As shown in Scheme 4, four kinds of site-selective C–H functionalization products **2aa–4bb** were available correspondingly. However, slightly reduced yields occurred for **2aa–4bb** (46–61%), which might be due to the large steric hindrance or strong electron-withdrawing property of carbonyl carbon radical derived from **5a** and **5b**.

To gain insight into the reaction mechanism, a series of control experiments were arranged (Scheme 5). The radical scavenger experiment employing TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was carried out under standard conditions. The result of trace **2a** revealed that the reaction was suppressed completely and a radical pathway was involved (1). In addition, the adduct **6** of TEMPO and **1a** losing only one hydrogen atom could be detected by HRLC-MS, proving the nitrogen radical generation through the breaking of the N–H bond (2). Furthermore, the cyanopropyl radical derived from AIBN was easily available under heating conditions, which has been confirmed in our previous studies as depicted in (3).[3k]

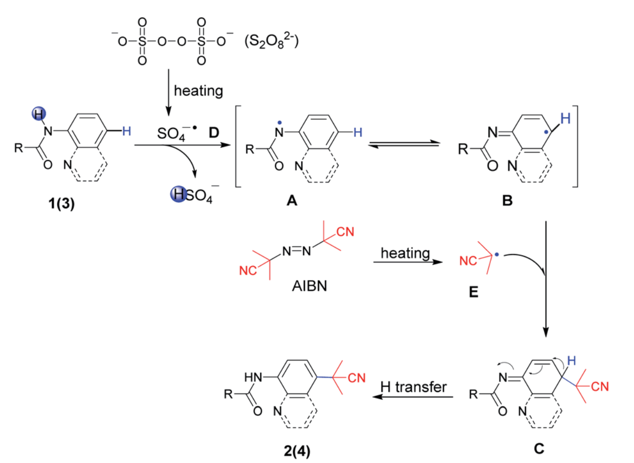
Continuously, control experiments of designed aromatic amides were investigated (Scheme 5, (4)). The aniline-derived amides **1m**, **1n** and **1o** in which C2, 6 or C3, 5 positions were double substituted failed to react, indicating that a smooth hydrogen atom transfer path from *para*-C–H to nitrogen atom was easily blocked if there was no hydrogen present on any one side of the phenyl ring. Besides, naphthylamide **1p** and indolin-2-one **1q** were not enough active to perform the reaction.

Sulfonamide derivative **3n** failed to afford the expected product, which is probably due to the intolerance property of the sulfonyl group to strong acids, but C5–H was still replaced by the cyanoalkyl group. To our surprise, *N*-methyl pivalanilide **1r** as same as the material **1a** led to the product **2a** in a moderate 45% yield, which brought to light the possibility of $N–CH_3$ bond oxidative dissociation by strong oxidant $K_2S_2O_8$.[20]

On the basis of the above control experiments and previous studies,[3k,5,9,21] a plausible mechanism was proposed, as outlined in Scheme 6. First, the decomposition of $S_2O_8^{2-}$ generated a sulfate radical anion $SO_4^{-\bullet}$ **D** by homolysis upon heating. Next, radical anion **D** as a strong one-electron oxidant abstracted the hydrogen atom in amide bonds to form the key nitrogen-centered radical **A** species. Preferentially, **A** was easily transformed to more stable aryl radical **B** *via* spin delocalization. On the other hand, AIBN provided cyanopropyl radical **E** when it was heated. Then, radical **E** coupled with intermediate



Scheme 5 Investigations of the reaction mechanism.

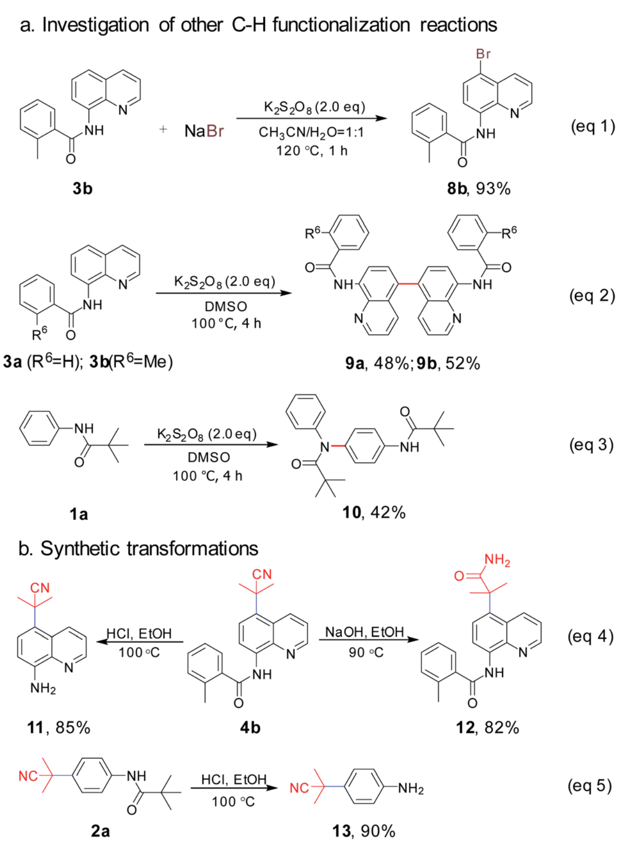


Scheme 6 Plausible mechanism.

aryl radical **B** species followed by *para*-C–H transfer to afford the regioselective cyanoalkylation products **2(4)**.

To gain insight into the utility of this direct remote C–H activation procedure using $K_2S_2O_8$, further application was implemented with **3a**, **3b** and **1a** as the model substrates. Pleasingly, as shown in Scheme 7, under the $K_2S_2O_8/CH_3CN/H_2O$ system, 8-aminoquinoline amide **3b** was treated with NaBr as the bromine source to afford C5–Br **8b** readily in a high yield of 93% (eqn (1)).[20] Moreover, the *para*-dimerization products **9a** and **9b** were found when the experiment was carried out only in $K_2S_2O_8$/DMSO system at 100 °C (eqn (2)). In comparison with the reported synthetic strategy in which transition metal catalysts $[Rh(COD)Cl]_2$ (ref. 22) and $Cu(OAc)_2$ (ref. 23) were used, our method here had obvious advantages for the synthesis of quinoline dimers. Interestingly, the anilide substrate **1a** produced a *para*-amidation product **10** in 42% yield under the same conditions (eqn (3)), which has been obtained in previous report with $Cu(OAc)_2$ as the catalyst.[24] These above results revealed that $K_2S_2O_8$ could promote the remote C–H various functionalization of aromatic amides *via* HAT and N-radical generation process.

Finally, the synthetic transformations were studied. The treatment of **4b** with HCl or NaOH in ethanol solution resulted in the dissociation of amide bond (**11**, 85%) or amide bond formation from cyano group (**12**, 82%) (eqn (4)), which provided the diversity of pharmaceutical blocks.[25] Here, it's worth mentioning that the simple acid hydrolysis of **2a** produced **13** (90%) which is a paramount drug intermediate of PI3K/mTOR inhibitor **NVP-BEZ235** (eqn (5)).[1c]



Scheme 7 Exploration of further application.

Conclusions

In summary, we have successfully developed a highly efficient metal-free method for the site-selective C–H cyanoalkylation of 8-aminoquinoline and aniline-derived amides with AIBN in the presence of $K_2S_2O_8$. This protocol is an environmental benign approach with a broad substrate scope, which affords the corresponding products in moderate to excellent yields. The radical–radical coupling pathway was demonstrated in a plausible mechanism. Moreover, for 8-aminoquinoline amides, the use of $K_2S_2O_8$ under metal-free conditions could access the C5–H bromination and dimerization products. Our study indeed valued the utility of $K_2S_2O_8$ in promoting the remote C–H functionalization of aryl amides. Further efforts to extend the application of this new protocol are underway in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was mainly supported by National Natural Science Foundation of China (NSFC No. 51573069), and Open Funds of the State Key Laboratory of Rare Earth Re-source Utilization (RERU2021002).

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