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## Microwave-accelerated cross-dehydrogenativecoupling (CDC) of *N*-(quinolin-8-yl)amides with acetone/acetonitrile under metal-free conditions<sup>†</sup>

Chao Zhou, Yunwei Liu, Qi Luo, Yicheng Zhang,\* Jingwen Zhou, Haoyu Zhang and Jie Liu<sup>®</sup>\*

A highly selective remote  $C(sp^3)$ -H acetonation of *N*-(quinolin-8-yl)amide scaffolds at the C5-position under microwave irradiation has been developed. In the absence of a transition-metal-catalyst, benzoyl peroxide (BPO)-promoted cross-dehydrogenation coupling (CDC) of *N*-(quinolin-8-yl)amides with acetone/acetonitrile occurred smoothly to generate the corresponding 5-acetonated/acetonitriled *N*-(quinolin-8-yl)amides in good yields. The transformation is operationally simple, rapid, easily scaled-up to the gram scale, and shows a broad substrate scope.

Quinolines play an important role as nitrogen-containing heterocyclic compounds in natural products, pharmaceuticals and pesticides (Fig. 1).<sup>1</sup> As a particular member of the quinoline compounds, *N*-(quinolin-8-yl)benzamide has an irreplaceable role in the C–H bond activation reaction system as a classical bidentate directing group or as a ligand auxiliary.<sup>2</sup> In recent years, brilliant achievements have been made in C–H bond functionalization reactions accomplished at the C-2,<sup>3</sup> C-3,<sup>4</sup> C-4,<sup>5</sup> C-5 and C-8 (ref. 6) positions of quinoline and its derivatives. It is worth mentioning that the C-5 position functionalization reactions of *N*-(quinolin-8-yl)benzamide have a certain medicinal value with high activity and involve more types of reactions, such as amidation,<sup>7</sup> sulfonylation,<sup>8</sup> cyanoalkoxylation,<sup>9</sup> allylation,<sup>10</sup> alkylation,<sup>11</sup> halogenation<sup>12</sup> and so on.<sup>13</sup>

In the past decades, with the boom in the area of inert C-H bond activation, cross-dehydrogenation coupling (CDC)



Fig. 1 Representative drug candidates and natural products with quinoline skeleton.

Key Laboratory of Green and Precise Synthetic Chemistry, Ministry of Education, Huaibei Normal University, Huaibei, Anhui 235000, P. R. China. E-mail: jieliu\_1024@163.com; lbqzhych@163.com

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ra03651k reactions involving inert C–H bond activation have been developed,<sup>14</sup> which was pioneered by Li in 2014.<sup>15</sup> Currently, their group has not only constructed intermolecular C–C bond reactions by CDC of inert C(sp<sup>3</sup>)–H bonds,<sup>16</sup> but also achieved CDC reactions of C(sp<sup>3</sup>)–H heteroarylation between alkanes and heteroarenes by visible light irradiation.<sup>17</sup> Subsequently, CDC-type reactions have been widely used and rapidly developed (Scheme 1). Among the CDC reactions, there are even rarer dehydro-coupling reactions in which acetonitrile/acetone was used as a reaction substrate, for example, oxidant-promoted CDC reactions reported by Kianmehr,<sup>18</sup> and Tan *et al.*<sup>19</sup>



Scheme 1 The C-5 position functionalization reactions of N-(quino-lin-8-yl)amide.

Table 1 Optimization of the reaction conditions<sup>a</sup>



<sup>*a*</sup> Reaction conditions: *N*-(quinolin-8-yl)benzamide (**1a**, 0.10 mmol), BPO, acetone (**2a**, 3.0 mL) under microwave irradiation. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> In an oil bath at 100 °C for 12 h [DTBP = di-*tert*-butyl peroxide; TBHP = *tert*-butyl hydroperoxide; LPO = dilauroyl peroxide; n.r. = no reaction].

Since microwave contain many advantages such as short reaction time and environmental friendliness which have been used in organic reactions, it has already attracted the attention of chemists and achieved remarkable results in the field of C–H bond activation.<sup>20</sup> In the past few years, microwave-facilitated organic synthesis has developed into one of the most powerful tools in organic chemistry. Herein we wish to report a microwave-accelerated cross-dehydrogenative-coupling (CDC) of *N*-(quinolin-8-yl)amides with acetone/acetonitrile in the presence of benzoyl peroxide (BPO) as oxidant under metal-free conditions, delivering good yields of C-5-acetonated *N*-(quinolin-8-yl)amides as products.

We initiated our study with microwave irradiation of *N*-(quinolin-8-yl)benzamide (**1a**) and acetone (**2a**) in the presence of benzoyl peroxide (BPO). After 20 min at 100 °C, the desired acetonation product **3a** was obtained in 62% yield (Table 1, entry 1). The reaction did not proceed with other oxidants such as  $H_2O_2$ , DTBP, TBHP and LPO (entries 2–5). Screening of oxidant loading indicated that 2.0 equiv. is the most effective choice for the reaction, afforded the product **3a** in 71% yield (entries 6–9). Investigation of the reaction time and temperature gave no obvious improvement in the product yield of **3a** (entries 10–16). Interestingly, when the model reaction was carried out in an oil bath at 100 °C for 12 h, only 18% yield of **3a** was obtained (entry 17). For detailed optimization of reaction conditions, please see the (Tables S1–S4 in ESI).†

Under optimal reaction conditions, we next investigated the substrate scope of acetonation reaction (Scheme 2). A variety of



Scheme 2 The substrates scope of N-(quinolin-8-yl)arylamides [reaction conditions: **1** (0.10 mmol), BPO (2.0 equiv.) and acetone (**2a**, 3.0 mL) under microwave irradiation at 100 °C for 20 min; isolated yield of the product].

N-(quinolin-8-yl)arylamides with para-substituents, such as Me, MeO, <sup>t</sup>Bu, CO<sub>2</sub>Me, F, Cl and Br groups, in differed electronic properties are well tolerated (3a-3h), affording the desired C-5acetonated N-(quinolin-8-yl)arylamides in good yields. Some meta-substituted groups including Me, F and CF<sub>3</sub> on the benzene ring in N-(quinolin-8-yl)arylamides were examined, and exhibited good reactivity in the reaction, providing the corresponding products (3i-3k) in 46-53% yields. When disubstituted N-(quinolin-8-yl)arylamide 1l was employed in this transformation, the corresponding product 31 was afforded in 40% yield. In addition, the reactions with an electrondonating group (Me or OMe) or an electron-withdrawing group (F or Cl) at the C2-position of the aryl rings generated the products 3m-3p with 49-71% yields. Notably, N-(quinolin-8yl)-1-naphthamide reacted with acetone, affording the desired product 3q in 43% yield.

It is gratifying that the aliphatic-derived *N*-(quinolin-8-yl) amides reacted acetone under optimal conditions, indicating that it is not affected by the length of the aliphatic carbon chain, and the corresponding products **3r**-**3w** were isolated in 69–81% yields (Scheme 3). It is also worth mentioning that the presence of a methyl substituent at the C-6 or C-3 position of the quinoline ring could also formed the desired products (**3x** and **3y**) in 54% and 69%, respectively. Additionally, cyclopropanamide and cyclohexanamide also participated in the reaction and the acetonation products **3z** and **3aa** could be obtained in good yields (71% and 83%, respectively). It should be noted that *N*-



Scheme 3 The substrates scope of N-(quinolin-8-yl)aliphatic amides and N-(quinolin-8-yl)heteroarylamides [reaction conditions: 1 (0.10 mmol), BPO (2.0 equiv.) and acetone (2a, 3.0 mL) under microwave irradiation at 100 °C for 20 min; isolated yield of the product].

(quinolin-8-yl)nicotinamide 1ab underwent the reaction smoothly with 2a to give the corresponding product 3ab in 60% yield. Encouragingly, when the quinoline moiety was replaced with naphthalene one, the obtained compounds were also compatible with this reaction, giving the anticipated products



Scheme 4 Gram-scale reaction



Scheme 5 The substrates scope of N-(quinolin-8-yl)arylamides and N-(quinolin-8-yl)aliphaticamides [reaction conditions: 1 (0.10 mmol), BPO (2.0 equiv.) and acetonitrile (3.0 mL) under microwave irradiation at 100 °C for 20 min; isolated yield of the product].



3ac-3ae in 59-65% yields. Moreover, the optimized conditions were also suitable for the reaction of N-(5-bromonaphthalen-1yl)picolinamide with acetone (2a), and the expected product (3af) was formed in 43% yield. Furthermore, when 1.0 g of 1a

tained in 78% yield (Scheme 4). Remarkably, the reaction system was also capable of cyanomethylation reaction under optimal conditions, the results of which were summarized in Scheme 5. We were delighted to observe the acetonitrile was good coupling partner, enabling the production of 4a in 71% yield. Additionally, this reaction can tolerate functional groups such as N-(quinolin-8-yl) arylamides with para-Me (1b) and aliphatic-derived N-(quinolin-8-yl)amides can afford the corresponding products in 66%, 75%, and 67% yield, respectively.

was subjected to the reaction, the targeted product 3a was ob-

To gain insight into the reaction mechanism, the radical trapped experiments were conducted (Scheme 6). When radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) was added, no desired product was detected under the standard conditions, suggesting that a free radical was involved in this transformation. The TEMPO adduct 5 and BHT adduct 6 were detected by HRMS analysis (ESI<sup>†</sup>).

Based on the control experiment, a plausible mechanism is proposed as in Scheme 7. First, the benzoate radical A is generated as a result of microwave irradiation from BPO, and it then captures a hydrogen atom from the substrate acetone 2a to form the carbon radical B, which is trapped by TEMPO or BHT to its adducts 5 or 6. The obtained acetone radical B reacts with substrate *N*-(quinolin-8-yl)benzamide **1a** to afford an



Scheme 7 The proposed mechanism.

BY-NC

(cc)

intermediate C, which further reacts with benzoate radical A to generate the final product 3a.

### Conclusions

In summary, we have developed a microwave-accelerated crossdehydrogenative-coupling (CDC) of N-(quinolin-8-yl)amides with acetone/acetonitrile under metal-free conditions. In the presence of benzoyl peroxide (BPO) as promoter, a crossdehydrogenation coupling (CDC) of N-(quinolin-8-yl)amides with acetone underwent smoothly to generate the corresponding 5-acetonated/acetonitriled N-(quinolin-8-yl)amides in good yields. Compared with the traditional strategy for C-5 position coupling reactions, this reaction provides an environmentally friendly, efficient, and convenient access to C-5 position functionalization of N-(quinolin-8-yl)amides. Moreover, a plausible reaction mechanism is proposed based on a radical trapped experiment and HRMS studies. Further attempts to apply microwave acceleration coupling reactions are currently underway in our laboratory.

### Conflicts of interest

There are no conflicts to declare.

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