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Transition-metal-free Oxidative Intermolecular Cyclization Reaction: Synthesis of 2-aryl-4-quinolones

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A novel and efficient intermolecular cyclization of 2-Aminoacetophenones with aldehydes has been developed for the synthesis of 2-aryl-4-quinolones through C–C and C–N bond formation. Mild conditions, good functional group tolerance and substrates without prefunctionalization make this protocol practical, and this strategy will arouse keen interest to chemistry and biology.

Nitrogen-containing heterocycles are present in a variety of biologically active molecules which can be used in a wide range of therapeutic areas.[1] Amongst the numerous scaffolds， 4-Quinolones are ubiquitous scaffolds in many natural products[2] and are regarded as a “privileged building block” for biologically active compounds[3]. They are also featured in many commonly used antibiotics such as nalidixic acid,[4] oxolinic acid,[5]

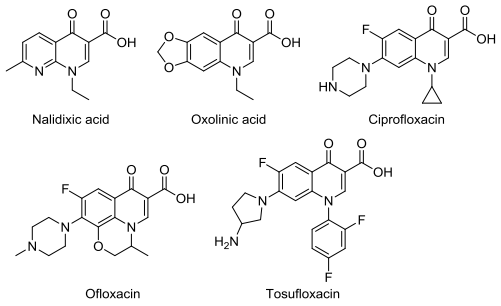
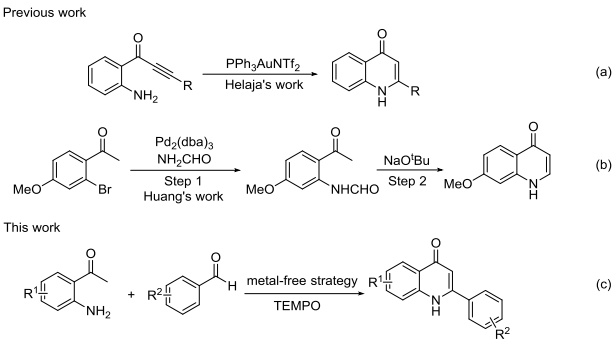


Figure 1. Structures of some commercial quinolones.

ciprofloxacin[6], ofloxacin[6] and tosufloxacin,[6] et al. And their derivatives are also versatile synthetic intermediates due to their facile derivatization of the 4-hydroxyl group[7]. In particular, 2-aryl-4-quinolones, aza analogs of flavones, have played a central role in medicinal chemistry because they possess potent antimitotic antitumor effects through inhibition of tubulin polymerization at the colchicine site.[8] More recently, certain 2-aryl-4-quinolones and their derivatives have been studied as potential treatments for a range of diseases because they exhibit antimalarial,[9] antiviral activities,[10] antiplatelet,[11] antidiabetic,[12] cathepsins inhibitory activities,[13] xanthine oxidase,[14] and have positive cardiac effects.[15]



Scheme 1. Synthetic approaches toward 2-Aryl-4-quinolones.

The “privileged” status of 2-aryl-4-quinolones and their derivatives in biological applications demands more efficient strategies for their preparation. Although various synthetic routes for the preparing of 4-quinolones have been developed such as the Conrad–Limpach16 and Niementowski.[17] They generally focus on the condensation of amines and carboxyl derivatives followed by cyclization to produce the desired quinolones. However, most of these methods suffer from harsh reaction conditions (high temperature and/or strong bases or acids) which dramatically limit the scope of these reactions. Less traditional methods are using transition metals catalyst to synthesis these compounds, including palladium-catalyzed carbonylation,[18] titanium-mediated reductive coupling,[19] and ruthenium-catalyzed reduction reactions.[20] Base-promoted cyclization of *N*-(*o*-ketoaryl) amides, known as the Camps cyclization,[21] is more attractive and has seen widespread utilization for the synthesis of quinolones. However, this

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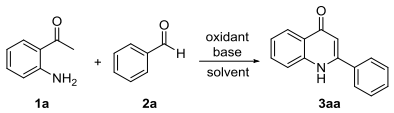
reaction is restricted by the limited access to N-(o-ketoaryl)amides. In 2014, Helaja's group developed a gold-catalyzed route for the synthesis of 2-substituted 4-quinolones from aryl- or alkyl-substituted aniline-2-propynones.[22] In 2008, Huang's group presented a Pd-catalyzed synthetic methodology for the formation of 4-quinolones.[23] However, most of these reported methods require special substrates, multiple steps and transition metal catalysts. Herein, we describe a facile approach to synthesize 2-aryl-4-quinolones *via* transition-metal-free oxidative cyclization of 1-(2-aminophenyl)ethan-1-ones with aldehydes.

Table 1. Optimization of the Reaction Conditions[a].



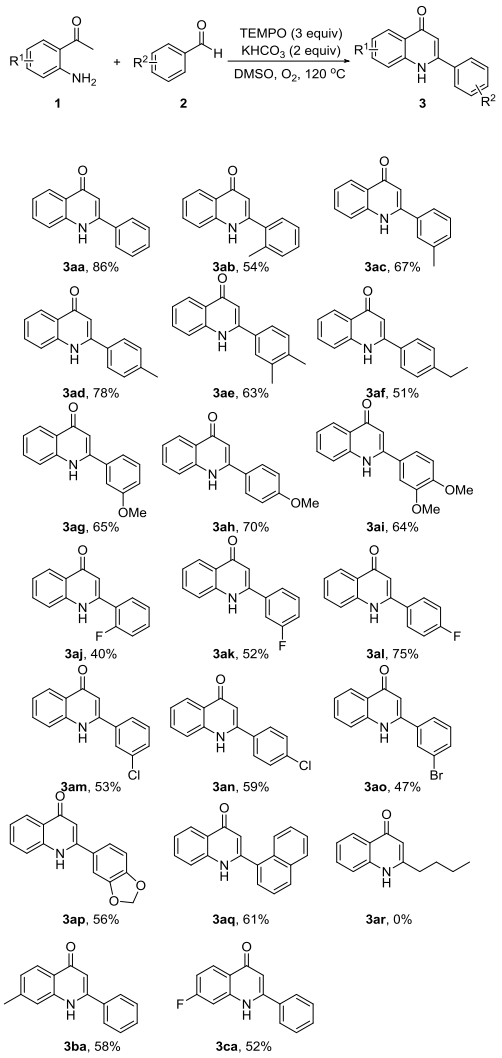
1a 2a 3aa

Enty	Oxidant	Base	Solvent	Yield[b] (%)
1	TEMPO (2)	$KHCO_3$ (2)	DMSO	68
2	TEMPO (2)	$KHCO_3$ (2)	DMA	23
3	TEMPO (2)	$KHCO_3$ (2)	DMF	18
4	TEMPO (2)	$KHCO_3$ (2)	toluene	Nd[c]
5	$PhI(OAc)_2$ (2)	$KHCO_3$ (2)	DMSO	nd
6	TBHP (2)	$KHCO_3$ (2)	DMSO	50
7	DDQ (2)	$KHCO_3$ (2)	DMSO	nd
8	$K_2S_2O_8$ (2)	$KHCO_3$ (2)	DMSO	5
9	Oxone (2)	$KHCO_3$ (2)	DMSO	nd
10	TEMPO (2)	K_2CO_3 (2)	DMSO	59
11	TEMPO (2)	Na_2CO_3 (2)	DMSO	10
12	TEMPO (2)	$NaHCO_3$ (2)	DMSO	52
13	TEMPO (2)	DBU (2)	DMSO	21
14	TEMPO (2)	Et_3N (2)	DMSO	trace
15[d]	TEMPO (2)	$KHCO_3$ (2)	DMSO	35
16[e]	TEMPO (2)	$KHCO_3$ (2)	DMSO	52
17	TEMPO (3)	$KHCO_3$(2)	DMSO	82
18	TEMPO (3)	$KHCO_3$(3)	DMSO	55
19[f]	TEMPO (3)	$KHCO_3$ (2)	DMSO	86

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (2 equiv), base (2 equiv), solvent (1 mL), 120 °C, under air atmosphere. [b]Isolated yields. [c]nd = not detected. [d]100 °C. [e]140 °C. [f]Reaction was performed under O_2 atmosphere.

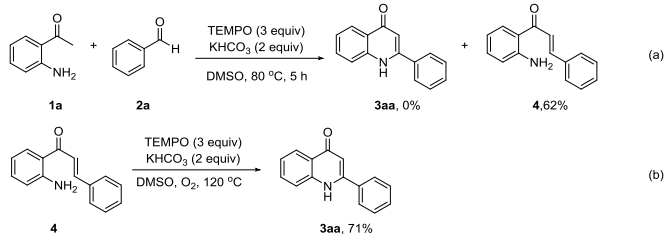
At the outset of our investigation, we selected 1-(2-aminophenyl)ethan-1-one **1a** and benzaldehyde **2a** as model substrates. In the presence of 2 equiv of TEMPO as the oxidant and 2 equiv of $KHCO_3$ as base in DMSO at 120 °C, the desired product 2-phenylquinolin-4(1H)-one **3aa** was isolated in 68% yield (Table 1, entry 1). Encouraged by this result, we continued to explore the optimal reaction conditions. The desired product **3aa** was detected when DMA and DMF were used as the solvents, respectively. The results illustrated that DMSO, DMA and DMF were better solvents in this transformation, and the highest yield was given in DMSO. **3aa** was obtained in 68% yield (Table 1, entries 1–4). Under the chosen reaction conditions, no useful conversion was observed with the presence of $PhI(OAc)_2$, DDQ and Oxone as oxidants, and TEMPO was more favorable than TBHP and $K_2S_2O_8$ (Table 1, entries 1, 5–9). In order to find the best base, we chose K_2CO_3, Na_2CO_3, $NaHCO_3$, DBU and Et_3N as candidates. The results showed that using $KHCO_3$ as base gave the best yield (Table 1, entries 1, 10–14). In addition, the screening of various reaction temperatures showed it to be a crucial factor, as the yield of **3aa** decreased when the reaction was conducted at a higher or lower temperature. The results suggest that 120 °C was favorable for the formation of the target product (Table 1, entries 1, 15–16). Gratifyingly, the yield of **3aa** was dramatically increased to 82% when the dosage of TEMPO increased to 3 equiv (Table 1, entry 17). In addition, 2 equiv of $KHCO_3$ showed a superior yield than the 3 equiv one (Table 1, entries 17–18). The investigation of reaction atmosphere showed that O_2 was better than air (Table 1, entries 17, 19). In the end, the optimized reaction conditions were obtained as follows: 1-(2-aminophenyl)ethan-1-one (0.2 mmol), benzaldehyde (0.4 mmol), TEMPO (3 equiv) and $KHCO_3$ (2 equiv) in 1 mL of DMSO at 120 °C under O_2 atmosphere.

Scheme 2. Synthesis of 2-phenylquinolin-4(1H)-one Derivatives.



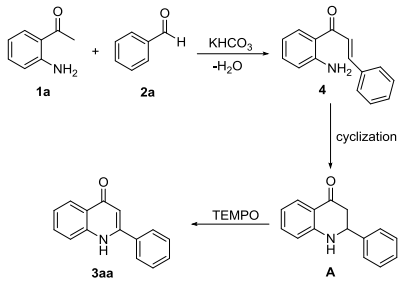
With the optimized reaction conditions in hand, we then investigated the substrate scope and generality of this oxidative coupling protocol, the results are summarized in Scheme 2. Firstly, we investigated the effect of the substituent group on the benzaldehyde (Scheme 2, **3aa**-**3aq**). A diverse array of benzaldehydes, bearing electron-withdrawing, electron-donating groups and

heterocycle-aldehyde, could react with 1-(2-aminophenyl)ethan-1-one **1a** smoothly and the desired quinolones could be obtained efficiently in good yields. Benzaldehydes with electron-donating groups such as methyl and methoxyl, achieved better results than those with electron-withdrawing groups (Scheme 2, **3ab**-**3ao**), and the functional groups at the para-position exhibited more outstanding results than those at the meta-position, followed by those at the ortho-position (Scheme 2, **3ab**-**3an**). These results demonstrated that the electronic effects and steric effect had considerable influence on the formation of the target products. Heterocycle-aldehyde **2p** and 1-naphthaldehyde **2q** were also successfully converted to the desired product respectively (Scheme 2, **3ap**-**3aq**). Unfortunately, an aliphatic aldehyde did not get desired product (Scheme 2, **3ar**). We then examined the substituent group on 1-(2-aminophenyl)ethan-1-ones. 1-(2-amino-4-methylphenyl)ethan-1-one **1b** and 1-(2-amino-4-fluorophenyl)ethan-1-one **1c** transformed smoothly to give the desired products (**3ba**, **3ca**) in 58% and 52% yields, respectively (Scheme 2, **3ba**-**3ca**).



Scheme 3. Control Experiments.

To gain mechanistic insights into this transformation, some control experiments were carried out (Scheme 3). Firstly, we carried out a reaction of **1a** and **2a** in the presence of 3 equiv of TEMPO and 2 equiv of $KHCO_3$ at 80 °C in DMSO, the desired product **3aa** was not gained, whereas the intermediate **4** was harvested as major product (Scheme 3, a). Then the intermediate **4** was performed under standard conditions and **4** could convert to **3aa** successfully (Scheme 3, b).



Scheme 4. Plausible mechanistic pathway.

Based on the above results and previous literatures,[14] a plausible mechanism is proposed for the formation of the 2-Aryl-4-quinolones as shown in Scheme **4**. Firstly, 1-(2-aminophenyl)ethan-1-one **1a** reacts with benzaldehyde **2a** to provide intermediate **4**. Then the cyclization of **4** to get the intermediate **A**, which was further oxidized to obtain the desired product **3aa**.

Conclusions

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In conclusion, we have developed a novel and efficient method to synthesize substituted 2-Aryl-4-quinolones which are useful intermediates for the preparation of biologically active compounds. Simple operation with inexpensive reagents and mild reaction conditions make this efficient protocol practical. The avoidance of preparation of substrates and fewer synthetic steps will arouse keen interest to chemistry and biology.

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