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To be cited as: Chem. Asian J. 10.1002/asia.201600901

Link to VoR: http://dx.doi.org/10.1002/asia.201600901

A Journal of

ACES
Asian Chemical Editorial Society

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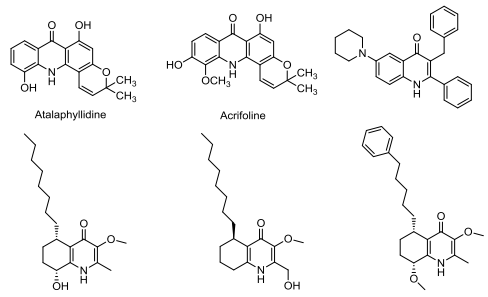
$KHCO_3$ and DBU Promoted Cascade Reaction to Synthesize 3-benzyl-2-phenylquinolin-4(1H)-ones

Haojie Ma, Xiaoqiang Zhou, DaiDong Wei, Jinhui Cao, Chong Shi, Yuxing Fan and Guosheng Huang*

A novel and convenient one-pot route for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones has been developed under transition-metal-free conditions. This new strategy is featured by high yield and good functional groups tolerance. In addition, proposed mechanistic study has been confirmed for this reaction.

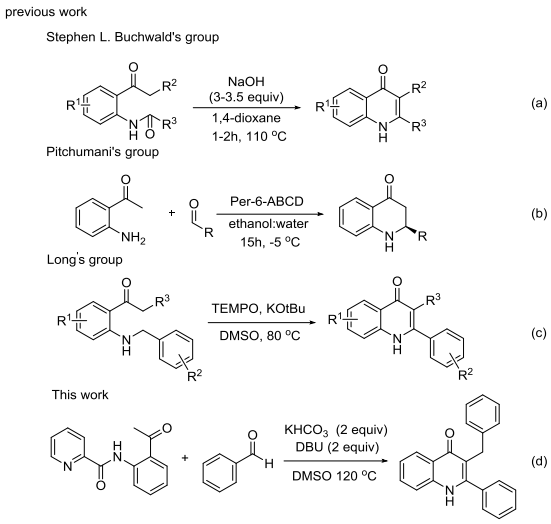
4-Quinolones, as an indispensable class of bicyclic structures, are frequently found in natural products and biologically active compounds (Scheme 1).[1, 2] They are also regarded as "privileged building blocks" for pharmaceutics in anticancer and antibiotic medicines.[3] Especially, 2-aryl-4-quinolones and their derivatives have been found as potential treatments for a range of diseases because they exhibit antiviral activities,[4] antiplatelet,[5] antimalarial,[6] xanthine oxidase,[7] cathepsins inhibitory activities[8] and have positive cardiac effects.[9] For example, current researches present kinesin spindle protein (KSP) inhibitors as promising anti-proliferative agents for cancer chemotherapy through potent antimitotic antitumor effects.[2] More recently, certain 3-benzyl-2-phenylquinolin-4(1H)-ones were evaluated and proved to have potent inhibitory activities in KSP ATPase.[2] Due to the "privileged" status, quinolones have attracted considerable attentions in the development of practical synthesis.

Scheme 1. Examples of bioactive compounds and nature products containing 4-quinolones.



Numerous synthetic strategies, especially Conrad-Limpach,[10] Niementowski reactions[11] and transition-metal catalyzed reactions including titanium-mediated reductive coupling,[12] palladium-catalyzed carbonylation,[13] and ruthenium-catalyzed reduction reactions,[14] have been developed to construct varieties of this valuable scaffolds. In 2007, Buchwald's group presented a base-promoted synthetic methodology for 4-quinolones by using N-(2-propionylphenyl)-acetamide (scheme 2, a).[15] In 2012, Pitchumani's group obtained 2-aryl-2,3-dihydro-4-quinolone from 1-(2-aminophenyl)ethan-1-one and aldehyde (scheme 2, b).[16] Subsequently in 2015, Long's group reported a novel synthesis of diverse 2-aryl-4-quinolone derivatives *via* a TEMPO-promoted intramolecular oxidative Mannich reaction (scheme 2, c),[7] in this procedure, simple narylmethyl-2-aminophenyl ketones was used as starting materials. Nevertheless there are only methyl or no functional groups at the C-3 position of 2-aryl-4-quinolone that could be synthesized by this approach.

Scheme 2. Novel routes to synthesize 4-Quinolones.



Although the synthetic routes of 4-quinolones have been well developed, in general they require multiple steps[15, 17], transition metal catalysts.[15, 18] and harsh reaction conditions, such as high temperature and strong acids.[10, 11] Moreover, various C-3 modified products are still difficult to form due to the unefficient way for the preparation of starting materials. Herein, inspired by pioneering works, we have developed a novel route for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones from N-(2-acetylphenyl)-picolinamides and aldehydes under base conditions. To our knowledge, transition-metal-free synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones has not been reported before.

Our initial efforts commenced with N-(2-acetylphenyl)-picolinamide **1a** and benzaldehyde **2a** as the model substrates in the presence of 2 equiv of K_2CO_3 at 100 °C for 10 h in DMSO, and the desired 3-benzyl-2-phenylquinolin-4(1H)-one **3aa** was able to isolated in 47% yield (Table 1, entry 1). The structure of **3aa** was further confirmed by X-ray crystallography.[19] Then the investigation of the solvent effects on the yield of the target product was carried out. As a result, toluene and xylene failed to come up with any useful conversions, and DMSO was superior to DMA and DMF (Table 1, entries 2-5). In order to find the best additives, we chose K_2CO_3, Na_2CO_3, $KHCO_3$, $NaHCO_3$, DBU, DABCO, Et_3N and KO^tBu as candidates, the results showed that $KHCO_3$ was more favorable than other bases, the yield of **3aa** was increased to 55%(Table 1, entries 1, 6-12). Gratifyingly, the yield of **3aa** was dramatically increased to 64% by using the combination of $KHCO_3$ and DBU as additive (Table 1, entry 13). Meanwhile, when the dosage of $KHCO_3$ and DBU was increased to 2 equiv, the yield was improved to 71% (Table 1, entries, 14). Further surveys of the reaction temperature indicated that 120 °C was beneficial for the formation of the desired product

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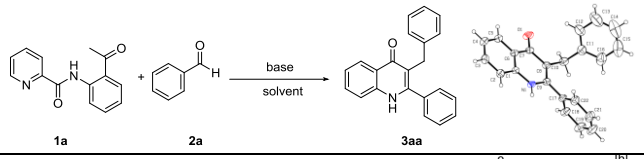
3aa and the yield was raised to 84% (Table 1, entries, 15-16). The research of reaction atmosphere presented that air was more outstanding than N_2 and O_2 (Table 1, entries 17-18). Furthermore, the choice of an adequate reactant **1** for this conversion is evaluated. We attempted to use *N*-acetyl, *N*-benzoyl, *N*-pyrazine-2-carbonyl, *N*-6-methylpicolinoyl, *N*-6-chloropicolinoyl amides and *N*-H amine as reactants under standard conditions, the results showed that all these substrates could transform this reaction successfully with moderate yields. And the highest yield was given when N-picolinoyl amide was employed (Scheme 3). These results matched well with the role of *N*-aryl groups which stabilized the iminium intermediate and increased the yield. Finally, the optimized reaction conditions are as follows: N-picolinoyl amide **1** (0.2 mmol), aldehyde **2** (3 equiv), $KHCO_3$ (2 equiv) and DBU (2 equiv) in 1mL of DMSO at 120 ^oC under air for 10 h.

Table 1. Optimization of reaction conditions[a].

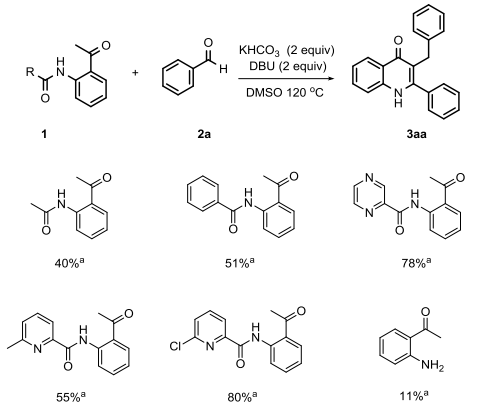


1a 2a 3aa

Entry	additive (equiv)	Solvent	Temp (^oC)	Yields[b] (%)
1	K_2CO_3 (2)	DMSO	100	47
2	K_2CO_3 (2)	DMA	100	14
3	K_2CO_3 (2)	DMF	100	5
4	K_2CO_3 (2)	Toluene	100	trace
5	K_2CO_3 (2)	Xylene	100	trace
6	Na_2CO_3 (2)	DMSO	100	20
7	$KHCO_3$ (2)	DMSO	100	55
8	$NaHCO_3$ (2)	DMSO	100	25
9	DBU (2)	DMSO	100	40
10	DABCO (2)	DMSO	100	trace
11	Et_3N (2)	DMSO	100	trace
12	KO^{t}Bu (2)	DMSO	100	43
13	$KHCO_3$ (1)+ DBU (1)	DMSO	100	64
14	$KHCO_3$ (2)+ DBU (2)	DMSO	100	71
15	$KHCO_3$ (2)+ DBU (2)	DMSO	80	41
16	$KHCO_3$ (2)+ DBU (2)	DMSO	120	84
17[c]	$KHCO_3$ (2)+ DBU (2)	DMSO	120	69
18[d]	$KHCO_3$ (2)+ DBU (2)	DMSO	120	50

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.6 mmol, 3 equiv), additive (2 equiv), solvent (1 mL), 10 h. [b]Isolated yields. [c]Reaction was performed under N_2 atmosphere. [d]Reaction was performed under O_2 atmosphere.

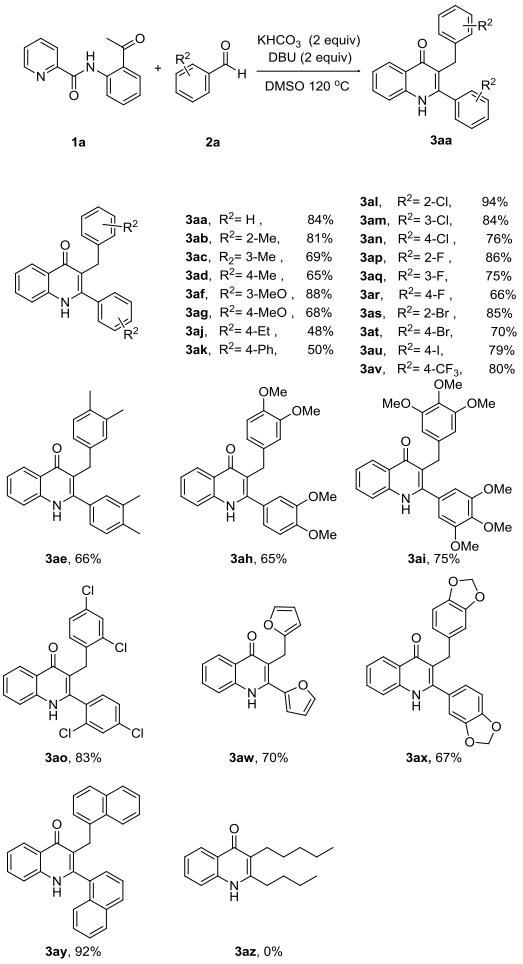
Scheme 3. Synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one **3aa** from different amide sources[a].



[a] isolated yields of **3aa**

With the optimized reaction conditions in hand, we studied the scope of aldehydes in this reaction. As shown in Scheme 4, a

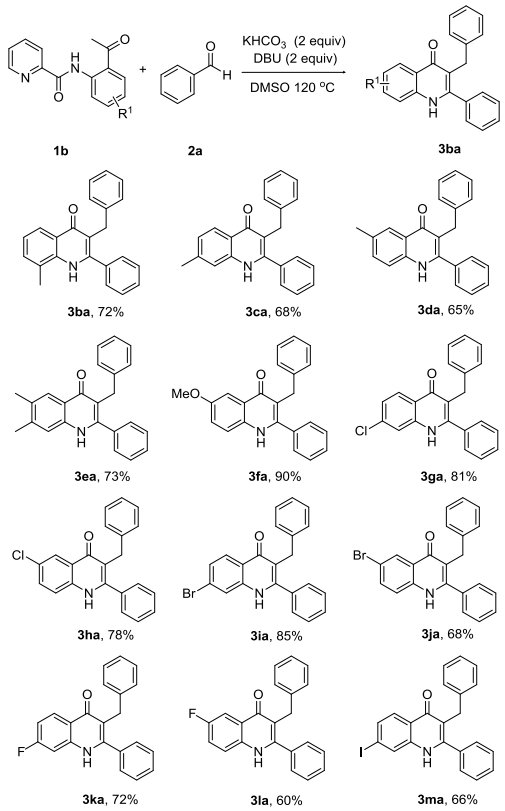
Scheme 4. Synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones from substituted aldehydes and N-(2-acetylphenyl)-picolinamide[a].



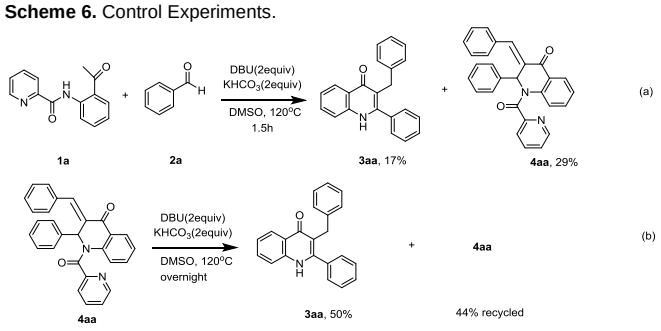
diverse array of aldehydes, bearing electron-donating, electron-withdrawing or sterically hindered group substituted aromatic rings, and heterocycle-aldehyde were examined. All of them underwent the reaction conditions smoothly and gave the corresponding products in excellent yields (Scheme 4, **3aa−3ay**), ensuring a broad range of substrate scope. It can be seen clearly that the electron-withdrawing groups exhibited more outstanding results in terms of providing the desired compounds than electron-donating groups (Scheme 4, **3ab**–**3av**), which indicated that electron-withdrawing groups on the aromatic ring were more compatible with this reaction process. Furthermore, substrates having ethyl or aryl group at the *para* position of benzaldehyde also furnished the reaction in good yields (Scheme 4, **3aj**–**3ak**). In addition, the reactions of benzaldehyde with substituents at the *ortho*, *meta*, and *para* positions were carried out, and the results showed that those with groups at the *ortho* position gave higher yields, followed by *meta* and *para* position (Scheme 4, **3ab**–**3ad**, **3af-3ag**, **3al**-**3an**, **3ap**-**3at**). Meanwhile, based on the results of benzaldehyde with mono or methyl or methoxy groups (Scheme 4, **3ab**–**3ai**), it represented distinctly that the steric effect also has significant influence on the efficiency. Additionally, heteroaromatic and condensed ring structures were also competent to produce the products efficiently (Scheme 4, **3aw**–**3ay**), and 1-naphthaldehyde reacted

excellently. However, an aliphatic aldehyde can not be introduced into desired product by this protocol (Scheme 4, **3az**).

Scheme 5. Synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones from benzaldehyde and Substituted N-(2-acetylphenyl)picolinamides[a].



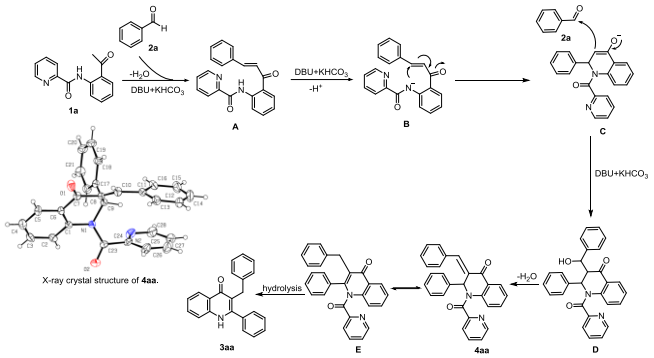
Scheme 6. Control Experiments.



To further explore the applicability and compatibility of this synthetic route, we examined the scope of N-(2-acetylphenyl)picolinamide under the same reaction conditions as shown in scheme 5. Notably, a wide range of functional groups was tolerated well under the reaction conditions, such as methyl, methoxy, halogen, etc. Concerning the electronic effects of substituents on phenyl rings, the substrates bearing either electron-withdrawing or electron-donating groups afforded the desired products in good to excellent yields (Scheme 5, **3ba**–**3ma**). The results also showed that the electron-withdrawing groups were more effective for the transformation. Moreover, N-(acetylphenyl)-picolinamide bearing halogen substituents (Scheme 5, **3ga**–**3la**) at *meta* position worked better than those at *para* position. The similar effects were also observed towards N-(acetylphenyl)-picolinamide with methyl substituents (Scheme 5, **3ba**–**3da**).

To gain insight into the reaction mechanism, we carried out several control experiments (Scheme 6). Firstly, we carried out a reaction of 1a and 2a under the optimized conditions for 1.5 h, the desired product 3aa was gained in low yield, whereas the intermediate 4aa was harvested as major product (Scheme 6, a). The structure of 4aa was confirmed by X-ray crystallography.[20] Then we performed the intermediate 4aa under standard conditions and 4aa could convert to 3aa successfully, though the efficiency was not desirable (Scheme 6, b).

Scheme 7. Proposed mechanism.



Based on the above results and previous literature, a plausible mechanism is depicted as shown in Scheme 7. The reaction is initiated by the formation of intermediate **A** through Aldol reaction of **1a** and **2a** with addition of DBU and $KHCO_3$. Then DBU and $KHCO_3$ convert **A** to **B** by a hydrogen abstraction process, which may undergo intramolecular cyclization *via* the Michael addition to generate intermediate **C**. Intermediate **C** further reacts through Aldol reaction with **2a** to gain the intermediate **D**. The elimination of hydroxyl give intermediate **4aa**, and the isomerization of **4aa** affords **E**, which can hydrolyze to the desired product **3aa**.

In summary, a novel and efficient synthesis of 3-benzyl-2-phenylquinolin-4(1H)-ones has been developed for the first time by using **1** and **2** as starting materials under transition-metal-free conditions. This protocol has provided a broad substrate scope for the synthesis of **3** with good yields under mild conditions. Step economy and ease of operation make this transformation highly useful, which will promote the development of synthesis of natural products and pharmaceutics in anticancer and antibiotic medicines.

Experimental Section

A test tube was charged with **1a** (0.2mmol), **2a** (0.6mmol), $KHCO_3$ (0.4 mmol) and DBU (0.4 mmol) in DMSO (1 mL). Then the reaction mixture was stirred at 120 °C (oil bath temperature) under air atmosphere for 10 h. After cooling to room temperature, the solvent was extracted with ethyl acetate and washed with brine, dried with Na_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluting with petroleum ether / ethyl acetate to afford pure **3aa**.

Keywords: 4-quinolones • aldol reaction • aldehydes • cycloaddition • michael addition

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[19] CCDC 1469946.

[20] CCDC 1469947.

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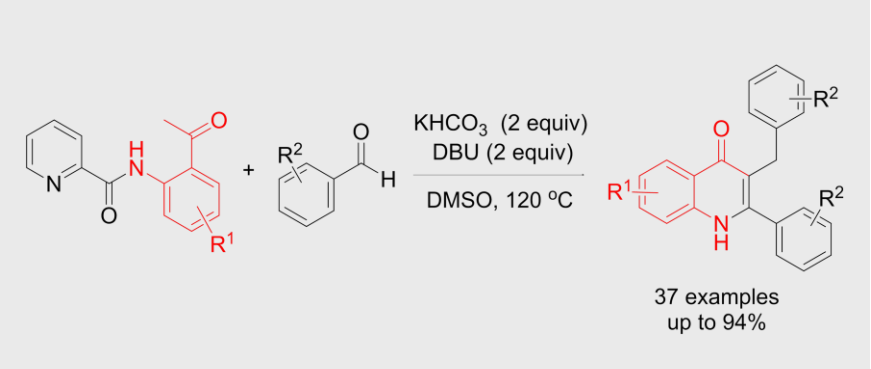

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Page No. – Page No.

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