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Cu(ii)-promoted three-component coupling sequence for the efficient synthesis of substituted quinolines†

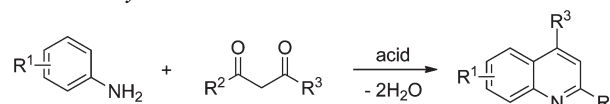Fuhong Xiao, Wen Chen, Yunfeng Liao and Guo-Jun Deng*

The copper-promoted three-component coupling sequence for substituted quinoline formation from aldehydes, anilines and acetone is described. Various 2-arylquinolines were selectively obtained in good yields under mild conditions. The reaction tolerated a wide range of functionalities.

Quinoline derivatives are one of the major classes of heterocycles and the quinoline moiety is widely found in many natural products.[1] Functionalized quinolines are widely used as agrochemicals,[2] dyes[3] and in medicinal chemistry.[4] 2-Arylquinolines also provide convenient precursors to chiral dihydro- and tetrahydroquinolines, which are important biologically active structures.[5] Therefore, the development of efficient methods for rapid construction and functionalization of substituted quinolines has gained much attention.[6] Recently, the activation of C–H bonds has received much attention for the straightforward construction of C–C and C–heteroatom bonds.[7] Various substituted quinolines, especially 2-arylquinolines, have been successfully synthesized by direct C–H activation and subsequent C–C bond formation with aryl halides, aryl boronic acids, and aryl metals.[8]
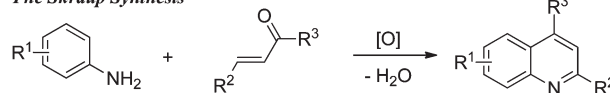
The classical methods for the construction of quinoline ring include the Combes synthesis from arylamines and 1,3-dicarbonyl compounds,[9,10] the Skraup (or Doebner–Mille) synthesis[11] from anilines and α,β-unsaturated carbonyl compounds in the presence of an oxidizing agent (Scheme 1), and the Friedländer synthesis from *ortho*-acyl-arylamines and aldehydes/ketones (must contain an α-methylene group).[12] However, these methods are sometimes limited for the preparation of quinolines with sensitive functional groups because of high reaction temperatures and the use of strong acids or bases. More recently, the metal-catalyzed cyclisation of *ortho*-substituted anilines has also been found to be efficient routes for assembling the quinoline skeleton.[13,14] However, these protocols need to use prepared starting materials, and thus require multi-step procedures.

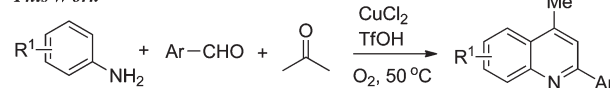The development of new quinoline syntheses in one-pot using readily available starting materials under mild reaction

Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan, 411105, China. E-mail: gjdeng@xtu.edu.cn; Fax: (+86)-731-58292251; Tel: (+86)-731-58298601
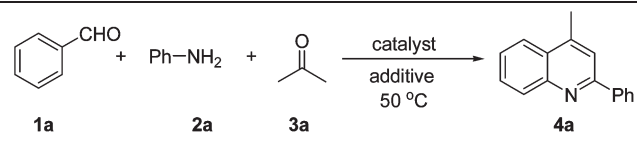†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob26484f

Scheme 1 Various routes for substituted quinoline synthesis from anilines.

conditions is highly desirable.[15,16] During our recent investigation of the direct acylation of aromatic C–H bonds with ketones and alcohols, we observed a small amount of quinoline adducts when *N*-arylimines were used as substrates.[17] This unexpected result inspired us to systematically investigate the quinoline formation using readily available starting materials. Herein, we report a copper-promoted quinoline formation from readily available and non-expensive arylamines, aromatic aldehydes and acetone, affording 2-aryl-4-methyl-quinolines in good yields under mild conditions.[18]

We began our study by examining the reaction of benzaldehyde (**1a**), aniline (**2a**), and acetone (**3a**) in ethanol at 50 °C using trifluoromethanesulfonic acid (TfOH) as an acid under an atmosphere of oxygen. Lewis acid catalysts, such as FeCl₃, NiCl₂ and LaCl₃, were efficient catalysts for this kind of transformation and the desired product 4-methyl-2-phenyl-quinoline (**4a**) was obtained in good yields, as determined by GC and ¹H NMR methods (Table 1, entries 1–3). Among the various Lewis acid catalysts examined, CuCl₂ was the most effective, and its use resulted in the formation of **4a** in 89% yield (entry 4). Other copper catalysts, such as CuBr₂ and CuF₂, were also found to be effective for this reaction (entries 5 and 9). The choice of TfOH was crucial for this reaction. The use of trifluoroacetic acid (TFA) and acetic acid completely prohibited the reaction (entries 11 and 13). The solvent also played an
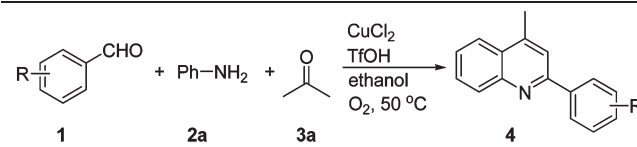
Table 1 Optimization of the reaction conditions[a]

Entry	Catalyst	Acid	Solvent	Yield[b] (%)
1	$FeCl_3$	TfOH	Ethanol	71
2	$NiCl_2$	TfOH	Ethanol	75
3	$LaCl_3$	TfOH	Ethanol	62
4	$CuCl_2$	TfOH	Ethanol	89
5	$CuBr_2$	TfOH	Ethanol	87
6	$CuSO_4$	TfOH	Ethanol	52
7	$Cu(OTf)_2$	TfOH	Ethanol	62
8	$Cu(OAc)_2$	TfOH	Ethanol	64
9	CuF_2	TfOH	Ethanol	81
10	$CuCl_2$	TsOH	Ethanol	68
11	$CuCl_2$	TFA	Ethanol	0
12	$CuCl_2$	CH_3COOH	Ethanol	0
13	$CuCl_2$	TfOH	Neat	68
14	$CuCl_2$	TfOH	Toluene	70
15	$CuCl_2$	TfOH	CH_3CN	73
16	$CuCl_2$	TfOH	H_2O	69
17	$CuCl_2$	TfOH	Methanol	82
18	$CuCl_2$	TfOH	Isopropanol	73
19[c]	$CuCl_2$	TfOH	Ethanol	80
20[d]	$CuCl_2$	TfOH	Ethanol	41

[a] Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), acid (1.0 equiv.), acetone (0.2 mL), solvent (0.3 mL), 50 °C, 24 h under oxygen unless otherwise noted. [b] GC yield. [c] Under air. [d] Under argon.

important role for the formation of substituted quinolines. Other solvents, such as toluene, acetonitrile, water and other alcohols, all resulted in lower yields (entries 13–18). Good yields could still be achieved when the reaction was carried out under an atmosphere of air (entry 19). However, the reaction yield decreased significantly when the reaction was carried out under argon (entry 20). Excess acetone is necessary to get a satisfactory yield for this transformation.

With the optimized reaction conditions established, the scope of the reaction with respect to aniline (**2a**), acetone (**3a**) and various aromatic aldehydes (**1**) was investigated (Table 2). The reactions with aromatic aldehydes bearing electron-donating groups (entries 2, 3 and 7) and electron-withdrawing substituents at the *para* position (entries 4, 5 and 9) proceeded smoothly to give the desired products in good yields. Under the optimized conditions, halogen substituents were all well tolerated (entries 4–6). Good yields were obtained when 4-chlorobenzaldehyde (**1e**) and 4-bromobenzaldehyde (**1f**) were used, and the desired products were achieved in 85 and 87% yields, respectively. The position of the substituents on the phenyl ring of benzaldehydes significantly affected the reaction yield, and the use of 2-chlorobenzaldehyde resulted in product **4j** in only 60% yield (entry 10). High yields were achieved when 3,4,5-trimethoxybenzaldehyde (**1l**) and 2-naphthaldehyde (**1m**) were used (entries 12 and 13). Notably, the reaction of hetero aromatic aldehydes, such as 2-furaldehyde (**1n**), with **2a** and **3a** afforded the desired product in moderate yield (entry 14). Unfortunately, aliphatic aldehydes are not suitable for this kind of transformation under the optimal conditions.

Table 2 Reaction of various aldehydes with aniline and acetone[a]

| Entry	Aldehyde		Product	Yield[b] (%)
1	(4-R-benzaldehyde) CHO	**1a**	**4a**	80
2	R = CH_3	**1b**	**4b**	73
3	R = OCH_3	**1c**	**4c**	71
4	R = F	**1d**	**4d**	81
5	R = Cl	**1e**	**4e**	85
6	R = Br	**1f**	**4f**	87
7	R = ^tBu	**1g**	**4g**	74
8	R = CH_3SO_2	**1h**	**4h**	85
9	R = NO_2	**1i**	**4i**	72
10	2-chlorobenzaldehyde	**1j**	**4j**	60
11	3-methylbenzaldehyde	**1k**	**4k**	78
12	3,4,5-trimethoxybenzaldehyde	**1l**	**4l**	81
13	2-naphthaldehyde	**1m**	**4m**	90
14	2-furaldehyde	**1n**	**4n**	51

[a] Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.2 mL), $CuCl_2$ (5 mol%), TfOH (0.2 mmol), C_2H_5OH (0.3 mL), 50 °C, 24 h, under oxygen. [b] Isolated yield based on **2a**.

To further explore the scope of the reaction, various arylamines were employed to react with **1a** and acetone under the optimized conditions (Table 3). A series of functional groups, including methyl, methoxy, chloro, bromo and acetyl, were well tolerated under the optimized conditions (Table 3, entries 1–6). The position of the substituents on the phenyl ring of aniline significantly affected the reaction yield (entry 7). The reaction showed good selectivity when *m*-toluidine was used, and the products **4v** and **5v** were formed in 76% total yield (entry 8). The replacement of acetone with other ketones resulted in a much lower yield.

To get more information about the reaction mechanism, several control experiments were set up under the standard conditions. The reaction of the imine generated from its corresponding amine and aldehyde with acetone afforded the desired product **4a** in 81% yield (Scheme 2, (1)). However, the reaction of aniline with benzylideneacetone, which can be easily generated from acetone and benzaldehyde, did not afford the desired product (Scheme 2, (2)). This means that the reaction did not take the Skraup pathway under the optimized reaction conditions. Based on these observations, a plausible mechanism to rationalize this transformation is illustrated in Scheme 3.

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Table 3 Reaction of various amines with **1a** and **3a**[a]

Entry	Amine		Product	Yield[b] (%)
1	(structure) NH₂ / R	**2b**	**4o**	81
2	R = OCH₃	**2c**	**4p**	56
3	R = F	**2d**	**4q**	56
4	R = Cl	**2e**	**4r**	66
5	R = Br	**2f**	**4s**	80
6	R = COCH₃	**2g**	**4t**	61
7	(structure) NH₂	**2h**	**4u**	63
8	(structure) NH₂	**2i**	**4v + 5v** (10:1)	76
9	(structure) H₃CO / NH₂ / OCH₃	**2j**	**4w**	66

[a] Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), **3a** (0.2 mL), CuCl₂ (5 mol %), TfOH (0.2 mmol), C₂H₅OH (0.3 mL), 50 °C, 24 h, under oxygen.
[b] Isolated yield based on **2**.
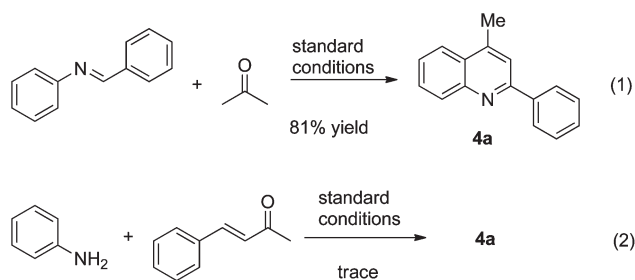
Scheme 2 Control experiments.
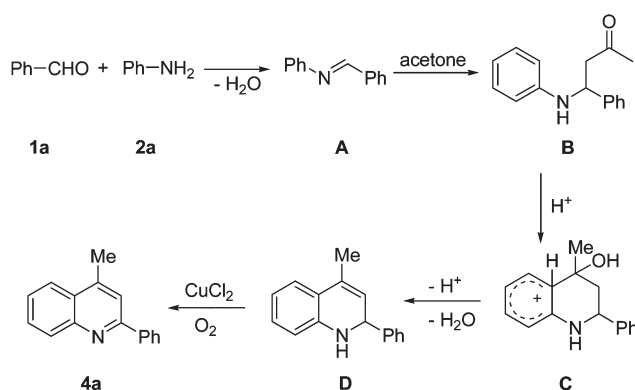
Scheme 3 A tentative mechanism.

Condensation of benzaldehyde (**1a**) with aniline (**2a**) generates an imine intermediate **A** in the presence of trifluoromethane-sulfonic acid. Addition of acetone to **A** affords an intermediate **B**, which can be cyclized to form intermediate **C** under acidic conditions. Dehydration and deprotonation of **C** provides intermediate **D**, and oxidation of **D** using CuCl₂ as a catalyst under oxidative conditions gives the final product **4a**.

In summary, we have developed copper-promoted 2-aryl-4-methyl-quinoline formation from readily available and non-expensive anilines, aromatic aldehydes and acetone. The three-component reaction completed in one-pot under relative mild reaction conditions and gave the functionalized quinolines in good yields. Functional groups, such as methyl, methoxy, acetyl, chloro and bromo, were all well tolerated under the optimized reaction conditions. This method affords a cheap and efficient alternative route for the synthesis of substituted quinolines. The scope, mechanism, and synthetic applications of this reaction are under investigation.

Acknowledgements

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