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Synthesis of substituted quinoline via copper-catalyzed one-pot cascade reactions of 2-bromobenzaldehydes with aryl methyl ketones and aqueous ammonia

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ABSTRACT

In this Letter, a new version of the Friedländer synthesis of quinoline derivatives starting from 2-bromobenzaldehydes, aryl methyl ketones, and aqueous ammonia with copper-catalyzed amination as a key step is presented. Remarkable advantages of this new quinoline synthesis include commercially available and economical starting materials, simple operational process, and excellent efficiency.

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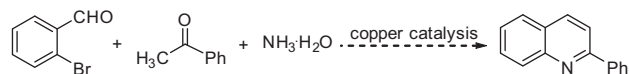
Quinoline and its derivatives have attracted tremendous attention due to their frequent occurrence in natural products and synthetic compounds possessing remarkable biological and chemical properties.^{1–5} Because of their importance, several protocols for their preparation, such as Friedländer synthesis,⁶ Combes synthesis,⁷ Skraup synthesis,⁸ and Gould–Jacobs synthesis,⁹ have been well established. More recently, a number of new methods for the synthesis of quinolines starting from various kinds of substrates have also been developed.^{10,11} Among the above mentioned strategies, Friedländer annulation, involving a condensation of 2-aminobenzaldehyde/ketone with carbonyl compound bearing an α -methylene functionality followed by an *intramolecular* cyclization of the in situ formed 2-amino chalcone intermediate, has been frequently used due to its simple and straightforward nature. Notwithstanding its success, this strategy still suffers from pitfalls such as harsh reaction conditions and limited availability of substrates. The required 2-aminobenzaldehydes are in most cases not commercially available or quite expensive. Therefore, they have to be prepared through the reduction of the corresponding *o*-nitrobenzaldehydes or ketones. Thus, the development of an alternative version of the classical Friedländer synthesis by using readily available starting materials and carried out under mild conditions is still highly desired.

In the mean time, copper-catalyzed Ullmann-type reactions are emerging as a highly useful approach for the formation of C–N bond due to their high efficiency and economical sustainability.¹² In recent years, along with the discovery of more efficient copper/ligand catalytic systems that could be operated under mild conditions, copper-catalyzed cross coupling reactions have been extensively utilized in the construction of N-fused heterocycles.¹³ In this regard, we have revealed a one-pot cascade reaction leading to pyrazolo[1,5-*c*]quinazolines¹⁴ and a one-pot three-component preparation of quinolizines,¹⁵ both with copper-catalyzed amination of aryl halides as an initiating step by using aqueous ammonia as a cheap and convenient nitrogen source. The high efficiency and easy to handle manner of this synthetic strategy encouraged us to propose a new synthetic pathway toward substituted quinolines by using 2-bromobenzaldehydes, acetophenones, and aqueous ammonia as the starting materials (Scheme 1).

To study the feasibility of our proposed synthesis of quinoline, the reaction of 2-bromobenzaldehyde (**1a**) with acetophenone (**2a**) and aqueous ammonia (**3**) was initially studied. To our delight, in the presence of 10 mol % CuI and 2 equiv of K₂CO₃ in DMF, **1a** reacted with **2a** and **3** affording 2-phenylquinoline (**4a**) in a yield of 68% (Table 1, entry 1). Further effort was then made to optimize the reaction conditions. Firstly, the effect of different solvents including DMF, DMSO, 1-methyl-2-pyrrolidinone (NMP), and isopropanol was studied (entries 1–4). Among them, DMF gave the best yield of **4a**. Furthermore, experiments with different copper catalysts showed that CuI, Cu(OAc)₂, CuCl, and CuCl₂ were inferior

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Scheme 1. Proposed synthesis of substituted quinoline by using ammonia as the nitrogen source.

to CuBr in promoting this tandem reaction (entries 1, 5–8). Studies on the effect of different bases showed that Cs_2CO_3 is superior to K_2CO_3 , Na_2CO_3 , KOAc, and K_3PO_4 (entries 5, 9–12). Without a base, the yield decreased (entry 13). Next, the reaction was tried with some ligands including dimethylethylenediamine (DMEDA), tetramethylethylenediamine (TMEDA), 1,10-phenanthroline hydrate (1,10-phen), L-proline, and 4-dimethylaminopyridine (DMAP) (entries 14–18). It turned out that the addition of 1,10-phen could improve the yield of **4a** to 87% (entry 16). Temperatures higher or lower than 80 °C had adverse effect (entries 19 and 20). It was also noted that when aqueous ammonia was replaced by ammonium acetate, the yield of **4a** decreased dramatically (entry 21). Without a copper catalyst, the formation of **4a** was not observed (entry 22). In summary, treatment of **1a**, **2a**, and **3** with 10 mol % of CuBr, 2 equiv of Cs_2CO_3 , and 20 mol % of 1,10-phen in DMF at 80 °C for 20 h could afford **4a** in a yield of 87%.

With the optimized conditions (Table 1, entry 16), the scope and generality of this new reaction was studied. Firstly, 2-bromobenzaldehyde (**1a**) was reacted with various aryl methyl ketones (**2**). The results listed in Table 2 show that the R^2 unit in **2** can be with either an electron-donating (entries 2–3) or an electron-withdrawing nature (4–8), and can be at the *ortho*, *para*, or *meta* position. A variety of functional groups, such as methyl, methoxy, chloro, fluoro, trifluoromethyl, and nitro group were well tolerated and installed. Moreover, 1-(naphthalene-1-yl)ethanone could afford 2-(naphthalene-1-yl)quinoline (**4i**) in high yield (entry 9). In addition, 1-(pyridin-2-yl)ethanone was found to be also a suitable substrate affording 2-(pyridine-2-yl)quinoline (**4j**) with

good efficiency (entry 10). Notably, when acetone (**2k**) was tried for this transformation, a complicated and unidentified mixture was obtained (Table 2, entry 11).

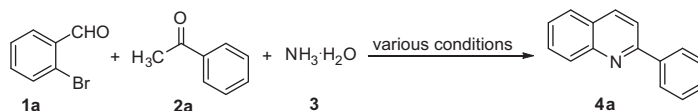
As a further aspect, the reaction of various 2-bromobenzaldehyde derivatives (**1**) with acetophenone (**2a**) was studied. The results listed in Table 3 show that 2-bromobenzaldehydes bearing diverse functional groups such as methyl, methoxy, chloro, fluoro, and trifluoromethyl could take part in this three-component reaction (Table 3). More importantly, both electron-rich and electron-deficient substrates gave the products in almost equally excellent yields.

Based on the results described above, plausible pathways for the formation of **4a** were proposed in Scheme 2. Initially, an aldol condensation between **1a** and **2a** occurs to give 3-(2-bromophenyl)-1-phenylprop-2-en-1-one (**A**). Then, **A** condenses with ammonia to give an imine intermediate (**B**). Under the reaction conditions employed, **B** should be in equilibrium with its *Z*-isomer (**B'**) albeit the formation of **B'** is less favorable. Once **B'** is formed, an intramolecular *N*-arylation under the catalysis of CuBr and promotion of Cs_2CO_3 takes place to give **4a** as a final product. Along with the consumption of **B'**, **B** is continuously transformed into **B'** to eventually complete the process. Alternatively, **A** may be firstly aminated to give intermediate **C**. Isomerization of **C** affords **C'**, which then undergoes an intramolecular condensation to give **4a**.^{6d}

The proposed mechanisms shown in Scheme 2 were partly supported by the following control experiments. Firstly, the reaction of **1a**, **2a**, and **3** under standard conditions was let to run for 1 h and workup of the resulting mixture gave **A** as a major product. Next, **A** was re-subjected to the conditions (Table 1, entry 16) and it was cleanly transformed into **4a** (Scheme 3).

In conclusion, an efficient and straightforward synthesis of substituted quinolines via copper-catalyzed one-pot cascade reactions of 2-bromobenzaldehydes with aryl methyl ketones and aqueous ammonia has been developed. This new version of

Table 1
Optimization studies on the formation of **4a**^a



Entry	Solvent	Catalyst	Base	Additive	T (°C)	Yield ^b (%)
1	DMF	CuI	K_2CO_3	—	80	68
2	DMSO	CuI	K_2CO_3	—	80	66
3	NMP	CuI	K_2CO_3	—	80	50
4	<i>i</i> -PrOH	CuI	K_2CO_3	—	80	35
5	DMF	CuBr	K_2CO_3	—	80	75
6	DMF	CuCl	K_2CO_3	—	80	48
7	DMF	$\text{Cu}(\text{OAc})_2$	K_2CO_3	—	80	56
8	DMF	CuCl_2	K_2CO_3	—	80	53
9	DMF	CuBr	Na_2CO_3	—	80	50
10	DMF	CuBr	Cs_2CO_3	—	80	80
11	DMF	CuBr	KOAc	—	80	45
12	DMF	CuBr	K_3PO_4	—	80	42
13	DMF	CuBr	—	—	80	33
14	DMF	CuBr	Cs_2CO_3	DMEDA	80	80
15	DMF	CuBr	Cs_2CO_3	TMEDA	80	72
16	DMF	CuBr	Cs_2CO_3	1,10-Phen	80	87
17	DMF	CuBr	Cs_2CO_3	L-Proline	80	80
18	DMF	CuBr	Cs_2CO_3	DMAP	80	83
19	DMF	CuBr	Cs_2CO_3	1,10-Phen	60	64
20	DMF	CuBr	Cs_2CO_3	1,10-Phen	100	80
21 ^c	DMF	CuBr	Cs_2CO_3	1,10-Phen	80	52
22	DMF	—	Cs_2CO_3	1,10-Phen	80	0

^a **1a** (0.5 mmol), **2a** (0.6 mmol), **3** (26%, 0.5 mL), copper salt (0.05 mmol), base (1 mmol), additive (0.1 mmol), solvent (3 mL), air, sealed tube, 20 h.

^b Isolated yield.

^c NH_4OAc (1.5 mmol) was used instead of $\text{NH}_3\cdot\text{H}_2\text{O}$.

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