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Metal-free aerobic one-pot synthesis of substituted/annulated quinolines from alcohols via indirect Friedländer annulation

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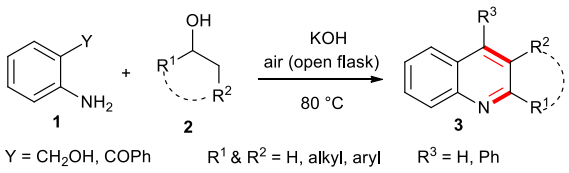
Metal-free, operationally simple, and highly efficient one-pot aerobic process for the synthesis of functionalized/annulated quinolines is devised from easily available 2-aminobenzyl alcohol/2-aminobenzophenones and alkyl/aryl alcohols for the first time. The process involves two sequential reactions, namely *in situ* aerial oxidation of alcohols to the corresponding aldehydes/ketones followed by Friedländer annulation.

Quinolines and their derivatives are privileged structural motifs, which are present in numerous natural products as well as in pharmaceutical agents. Functionalized quinolines exhibit antimalarial, antibacterial, anti-inflammatory, antiasthmatic, antifungal, analgesic and HIV-1 integrase inhibitory properties.[1,2] Owing to their broad range of biological importance, significant efforts have been made for the synthesis of quinoline derivatives.[3] The most prevalent strategies for the construction of quinoline ring involve anilines and carbonyl compounds such as Combes,[4a] Conrad–Limpach,[4b,c] Doebner–von Miller,[4d,e] Friedländer,[5] Skraup,[6a,b] Gould-Jacobs,[6c] and Povarov[7] methods. Besides these conventional methods, some other named reactions such as Pfitzinger,[8a,b] Niementowski[8c] and Knorr[8d,e] quinoline synthesis are being frequently utilized. However, most of them suffer from harsh reaction conditions, unstable and expensive starting materials, often expensive catalysts, low yields, and problems associated with the storage of carbonyl reagents. Besides above methods, several organometal-catalyzed approaches have recently been developed for the construction of quinoline scaffolds.[9]

Indirect Friedländer approaches using 2-aminobenzylic alcohols and ketones catalyzed by transition-metal complexes derived from ruthenium,[10] palladium,[11] iridium,[12] rhodium,[13] and copper[14] have also been reported. In general, the above methods are not usually employed in medicinal applications due to the contamination with traces of metals. Martínez and co-workers[15] reported potassium *tert*-butoxide catalyzed Oppenauer oxidation of 2-aminobenzyl alcohol followed by condensation with ketone to give corresponding quinolines. Common methods for the oxidation of alcohols are Dess-Martin,[16] Corey-Kim,[17] Swern[18] and Oppenauer oxidation.[19] Moreover, the usual solvents employed result in very tedious workup procedures. Furthermore, to make this century-old Friedländer reaction more practical and general, we attempted to develop a metal-free indirect Friedländer annulation that uses cheap and readily available alcohols as an electrophilic partner instead of expensive enolizable carbonyl compounds.

Cascade reactions, which allow multiple transformations in a one-pot process, were recognized as an environmentally friendly and atom-economic strategy for building molecules with structural diversity and molecular complexity.[20] It continues to be an area of intense interest to develop new protocols to construct valuable molecules from cheap and readily accessible starting materials by concise steps. Our interest in exploring the simple and efficient method for the synthesis of quinolines[21] led us to consider the use of inexpensive and easily available alkyl/aryl/benzyl alcohols towards the synthesis of functionalized quinolines. Herein, we report a metal-free, highly efficient, environmentally benign, and extremely simple strategy for the synthesis of substituted/annulated quinolines (Scheme 1). The tandem process involves *in situ* aerial oxidation of both the alcohol components followed by Friedländer annulation in the presence of KOH at 80 °C temperature in open atmosphere.



Scheme 1 Synthesis of quinolines **3** via indirect Friedlander annulation.

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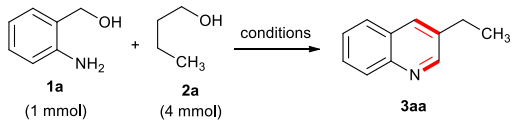
† Electronic Supplementary Information (ESI) available: [Elaborate reaction procedure, characterization data, scanned spectra of all the products]. See DOI: 10.1039/b000000x/

In our initial experiment, 2-aminobenzyl alcohol (**1a**) and 1-butanol (**2a**) were chosen as the model substrates to optimize the reaction conditions. The observations under varying conditions are summarized in Table 1. The reaction of 2-aminobenzyl alcohol (**1a**, 1 mmol) with 1-butanol (**2a**, 4 mmol) in presence of KOH (1 mmol) was carried out at 80 °C in an open flask. The workup of the reaction afforded compound **3aa** in 36% yield, which was characterized as 3-ethyl quinoline (Table 1, entry 1). Here, 1-butanol plays dual role of reactant as well as solvent. Encouraged by this observation, we performed the above test reaction at room temperature, but no trace of **3aa** was observed even after 24 h, and **1a** remained completely unreacted (Table 1, entries 2 and 3). After evaluating the role of temperature, next we performed the model reaction at 80 °C with higher loading of KOH. To our pleasure, not only the yield of the desired product **3aa** was increased to 88%, but the time required for the completion of the reaction was also reduced significantly (Table 1, entries 4 and 5). Further increment in the loading of KOH could not improve the results (Table 1, entry 6).

Table 1 Optimization of reaction conditions

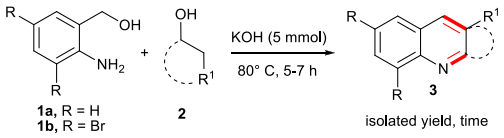


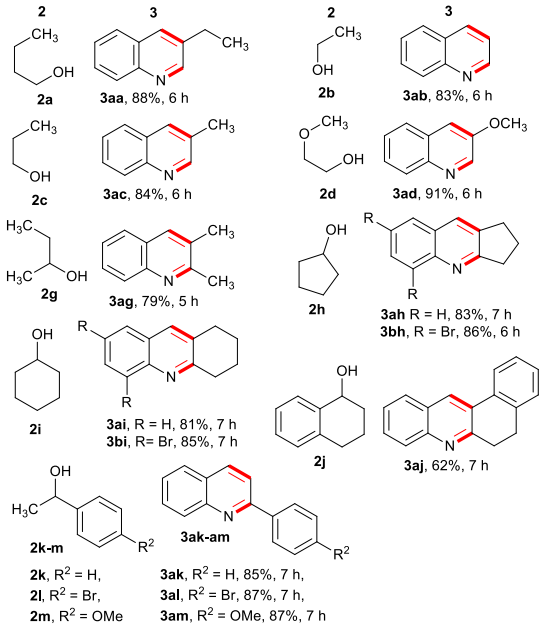
Entry	Base (mmol)	Temp (°C)	Time (h)	Yield (%)
1	KOH (1)	80	16	36
2	KOH (1)	25	24	-[a]
3	KOH (5)	25	24	-[a]
4	KOH (3)	80	10	72
5	KOH (5)	80	6	88
6	KOH (6)	80	6	88
7	KOH (5)[b]	80	24	trace
8	aq. KOH[c]	80	24	-[a]
9	NaOH (5)	80	10	76
10	K^{t}OBu (5)	80	8	64
11	Et_3N (5)	80	24	-[a]
12	DBU (5)	80	24	-[a]
13	None	80	8	-[a]
14	I_2 (5)	80	24	-[a]
15	KOH (5)[d]	80	10	49

[a] No reaction. [b] Inert atmosphere. [c] 50 mol% of aq. KOH was used. [d] 1 mmol of each **1a**, **2a** and 5 mmol of KOH in DMF was heated at 80 °C.

Next, to evaluate the role of aerial oxygen, we performed the model reaction under inert atmosphere at 80 °C. Remarkably, the rate of reaction became highly sluggish and only trace of the desired product **3aa** was observed on TLC plate after 24 h (Table 1, entry 7). The above observation suggests that air is crucial as hydride scavenger for the reaction. In an attempt to find a green solvent, we performed the model reaction in aqueous KOH, but the starting materials remained completely unconsumed even after 24 h of heating (Table 1, entry 8). Use of NaOH and K^{t}OBu separately in place of KOH could not improve the result (Table 1, entries 9 and 10). Subsequently, we screened organic bases such as Et_3N and DBU in place of KOH, which could not even trigger the reaction (Table 1, entries 11 and 12). Control experiments (without any base or in presence of oxidizing agent I_2) did not provide a trace of the desired quinoline **3aa** (Table 1, entries 13 and 14). Changing the solvent from alcohol to DMF did not offer a better result (Table 1, entry 15). Thus, the optimum reaction condition for the synthesis of quinoline **3aa** was achieved by employing **1a** (1 mmol), **2a** (4 mmol), and KOH (5 mmol) at 80 °C for 6 h in open atmosphere.

Table 2 Scope of substrates for the synthesis of quinolines **3**[a]



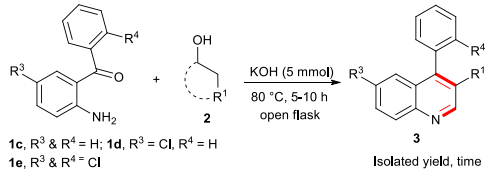


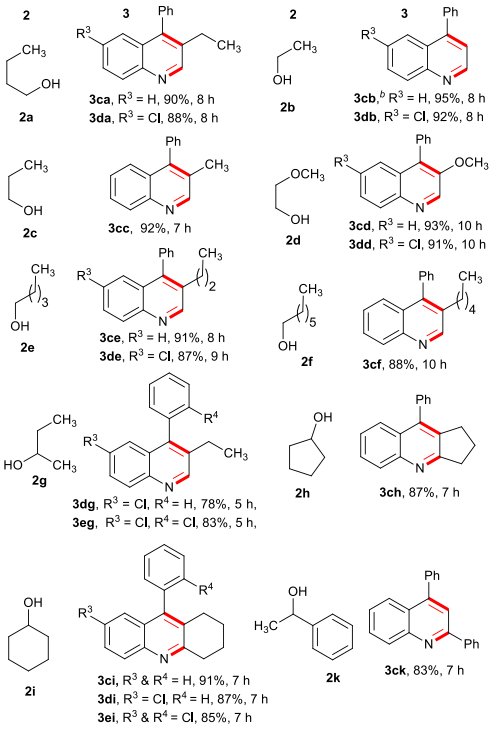
[a] Reaction conditions: 2-Aminobenzyl alcohol **1a** or **1b** (1 mmol), alcohol **2** (4 mmol), KOH (5 mmol), 80 °C, 5-7 h, open flask.

With the optimized reaction conditions in hand, the generality and scope of the substrates for the direct construction of quinolines (**3**) were examined and are shown in Tables 2 and 3. The one-pot cascade process serves as a general approach to access various substituted/annulated quinolines in high yields. The protocol tolerated well with 2-aminobenzyl alcohol (**1a**), 2-amino-2,3-dibromobenzyl alcohol (**1b**) with wide range of acyclic (**2a**-**d, 2g** and **2k-m**) and cyclic alcohols (**2h**-**j**) affording the corresponding quinolines **3** in good yields. Noteworthy, both primary and secondary alcohols undergo *in situ* aerial oxidation in presence of KOH to give the corresponding aldehydes/ketones followed by cyclocondensation to give the desired quinolines **3**. Moreover, 2-methoxy ethanol (**2d**) was also tolerated well under the optimal reaction conditions to give 3-methoxy quinoline **3ad** in 91% yield (Table 2). Accordingly, the reaction of 2-aminobenzyl alcohol (**1a**) with 2-butanol (**2g**) led to the formation of 2,3-

dimethyl quinoline (**3ag**) in 79% yield. Tetrahydronaphthalen-1-ol (**2j**) also reacted readily under the optimal conditions to furnish the corresponding fused quinoline **3aj** in 62% yield. After the successful synthesis of 3-substituted, 3,4-disubstituted, and annulated quinolines we turned our attention toward the construction of 2-substituted quinolines. Reaction of 2-aminobenzyl alcohol (**1a**) with 1-phenyl ethanols (**2k-m**) leads to the formation of corresponding quinolines **3ak-3am** in good yields (Table 2). The phenyl ring bearing both electron-withdrawing as well as electron-donating group at 2-position of the quinoline ring are well tolerated with no prominent electronic effect on the outcomes of the reaction. Interestingly, we found that the oxidation of both the alcohols **1a** and **2** could be mediated by strong base and air without the use of metal catalyst or ketone as proton scavenger.[22]

Table 3 Scope of 2-aminobenzophenones (**1c-e**) with alcohols (**2**)[a]

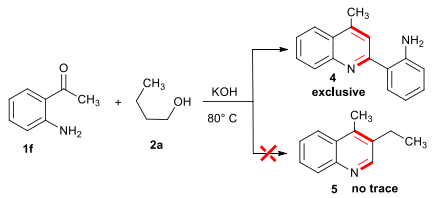




[a] Reaction conditions: 2-Aminobenzophenone **1c, 1d** or **1e** (1 mmol), alcohol **2** (4 mmol), KOH (5 mmol), 80 °C, 5-10 h. [b] gram-scale yield of **3cb** 89%.

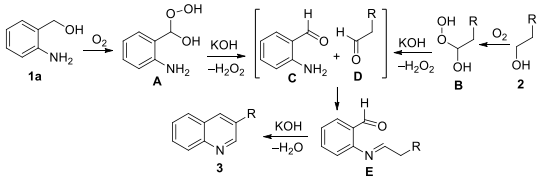
To illustrate the broad synthetic utility and generality of our one-pot cascade protocol, we further treated 2-aminobenzophenones (**1c, 1d** and **1e**) with various acyclic as well as cyclic alcohols separately under the optimal reaction conditions. Both acyclic (**2a-g** and **2k**) and cyclic alcohols (**2h** and **2i**) reacted smoothly with 2-aminobenzophenones affording the corresponding quinolines **3** in 78-95% yields (Table 3), showing the versatility of this approach.

After successful utilization of benzophenones, we next extended our study to 2-aminoacetophenone (**1f**). Treatment of **1f** with 1-butanol (**2a**) under the standard optimized reaction conditions provided unexpected 2,4-disubstituted quinoline (**4**) in 95% yield, while no trace of the expected 3-ethyl-4-methyl quinoline (**5**) was obtained (Scheme 2). The above observation limits the scope and generality of the protocol to some extent. Here, 2-aminoacetophenone under the reaction conditions undergoes self-condensation to form quinoline[23a] (**4**), and second component alcohol does not take part in the reaction and simply plays a role of solvent only. Structures of all the synthesized quinolines are confirmed by their satisfactory ^{1}H and ^{13}C NMR studies and comparison with the reported ones.[10b-f,23] The chemistry is amenable to both small and gram-scale reactions. The reaction of 2-aminobenzophenone **1c** (5 g, 25 mmol) with ethanol **2b** (6 mL) proceeded smoothly to provide 4.63 g of product **3cb** (89%), which is comparable to the small scale experiment (Table 3).



Scheme 2 Unexpected formation of 2-(2-aminophenyl)-4-methylquinoline **4**.

Based on our entire experimental outcomes and literature report,[24] a possible reaction mechanism for the formation of quinoline **3** is outlined in Scheme 3. It seems that the reaction starts with aerial oxidation of alcohols **1a** and **2** to their corresponding hydroperoxides **A** and **B**. Next, the hydroperoxides **A** and **B** react with KOH to form their respective alkoxides, and finally to aldehydes **C** and **D** with elimination of H_2O_2. Thus, *in situ* generated both the aldehydes **C** and **D** under basic conditions endure a dehydrative condensation to give intermediate **E**. Finally, the intermediate **E** undergoes intramolecular aldol-type condensation to give the desired quinoline **3**. In fact, during the reaction of 2-aminobenzyl alcohol (**1a**) and ethanol (**2b**) under optimized conditions, we isolated 2-aminobenzaldehyde (**C**), which validates the proposed pathway of the reaction.



Scheme 3 Possible mechanism for the synthesis of quinoline **3**.

To gain more insight into the reaction mechanism, we treated 2-aminobenzaldehyde with butan-1-al under the similar reaction conditions, which afforded the desired 3-ethyl quinoline **3aa** in 95% yield, suggesting the intermediacy of aldehydes during the course of the reaction.

Structurally diverse substituted/annulated quinolines have been synthesized via one-pot two-component cascade coupling of 2-aminobenzyl alcohol/2-aminobenzophenones with alkyl/aryl alcohols in open atmosphere. The reaction involved the metal-free *in situ* aerial oxidation of alcohols followed by Friedländer annulation to furnish the corresponding quinolines. This method not only provides an excellent complement to substituted/annulated quinoline synthesis, but also avoids the use of hazardous reagents and tedious purification. The merits of this procedure are its operational simplicity, user-friendly, high yields, ease of purification, economic viability, and ready availability of the starting materials. In addition to its simplicity, the protocol nicely tolerates both acyclic and cyclic alcohols.

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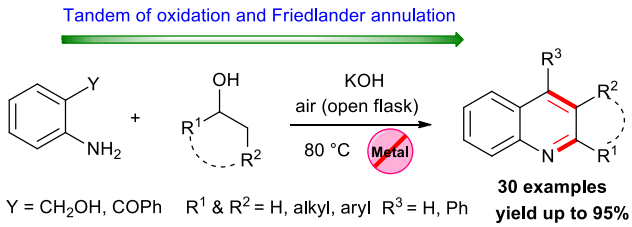
Table of Content



 # Metal & catalyst-free # Operationally simple & user-friendly

 # No protection-deprotection # 100% Carbon-economy # Gram-scale

Metal-free one-pot aerobic synthesis of functionalized/annulated quinolines is devised from viable alcohols via indirect Friedländer annulation.