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A copper(II)-catalyzed protocol for modified Friedländer quinoline synthesis

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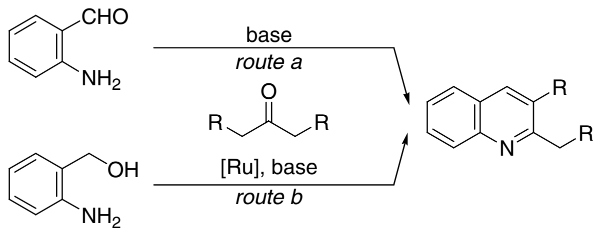
Abstract—2-Aminobenzyl alcohol reacts with an array of ketones in dioxane at 100 °C in the presence of a catalytic amount of $CuCl_2$ along with KOH under O_2 atmosphere to afford the corresponding quinolines in good yields. 2-Aminobenzyl alcohol is also oxidatively coupled and cyclized with various aldehydes by step-by-step procedure, an initial treatment of 2-aminobenzyl alcohol in the presence of $CuCl_2$ and KOH in dioxane under O_2 atmosphere and subsequent addition of aldehyde to the mixture followed by stirring under argon atmosphere, to give 3-substituted quinolines in moderate to good yields.

Many synthetic methods have been developed and documented for quinolines due to their intrinsic pharmacological and biological activities.[1] Besides conventionally named routes, transition metal-catalyzed reactions for such quinoline skeletons have also been attempted as alternative methods because of the facility and efficiency of reaction and the wide availability of substrate.[2] As part of our continuing studies toward transition metal-catalyzed cyclization reactions, we also reported on several transition metal-catalyzed routes for quinolines via ruthenium-catalyzed alkyl or alkanol group transfer from alkylamines or alkanolamines to N-atom of anilines[2b,3,4] (amine exchange reaction or amine scrambling reaction[5]) and palladium-catalyzed coupling and cyclization between 2-iodoaniline and propargylic alcohols.[6] Among them, in connection with this letter, 2-aminobenzyl alcohol was found to be oxidatively coupled and cyclized with ketones[7] (Scheme 1, route b) and secondary alcohols[8] in the presence of a ruthenium catalyst along with a base to give quinolines.[9,10] However, this protocol, even though superior to conventional Friedländer quinoline synthesis (Scheme 1, route a)[11] in a sense of price and stability of 2-aminobenzyl alcohol, led us to seek for a new elegant catalyst alternative since it also has some drawbacks requiring an expensive catalyst and a hydrogen acceptor[12] (or the use of excess starting ketone to 2-aminobenzyl alcohol). Herein, we describe a copper-catalyzed oxidative cyclization of 2-aminobenzyl alcohol with ketones as well as aldehydes leading to quinolines.[13]



Scheme 1.

The results of several attempted oxidative cyclizations of 2-aminobenzyl alcohol (**1**) with acetophenone (**2a**) are listed in Table 1. Treatment of equimolar amounts of **1** and **2a** in dioxane in the presence of a catalytic amount of $CuCl_2$ (1 mol %) along with KOH at 100 °C for 5 h afforded 2-phenylquinoline (**3a**) in 65% yield without any identifiable products (run 1). In contrast to our recent report on ruthenium-catalyzed synthesis of quinolines from **1** and ketones,[7] no direct transfer hydrogenation product 1-phenylethanol was produced. This result indicates that the present reaction proceeds irrespective of transfer hydrogenation from **1** to **2a**. In the case of ruthenium-catalyzed version, 2 equiv of **2a**

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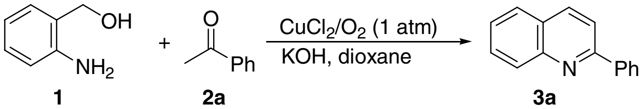
Table 1. Cu-Catalyzed optimization of conditions for the reaction of **1** with **2a**



Run	[**2a**]/[**1**]	KOH (mmol)	Cu (mmol)	Time (h)	Yield[a] (%)
1	1	1	$CuCl_2$ (0.01)	5	65
2	1	3	$CuCl_2$ (0.01)	5	70
3	1.2	3	$CuCl_2$ (0.01)	5	77
4	2	3	$CuCl_2$ (0.01)	5	77
5	1.2	3	$CuCl_2$ (0.01)	20	79
6	1.2	3	$CuCl_2$ (0.005)	5	73
7	1.2	3	$CuCl_2$ (0.05)	5	79
8	1.2	3	CuCl (0.01)	5	78
9[b]	1.2	3	$CuCl_2$ (0.01)	5	51

Reaction conditions: **1** (1 mmol), dioxane (5 mL), 100 °C, O_2 (1 atm).

[a] Isolated yield based on **1**.

[b] The reaction was carried out under air.

to **1** was necessary for the effective formation of quinolines.[7] This could be due to partial consumption of **2a** leading to 1-phenylethanol by ruthenium-catalyzed transfer hydrogenation of **2a** by **1**.[12] A slightly increased yield of **3a** was observed with an increased amount of KOH (run 2). The molar ratio of **2a** to **1** affected the yield of **3a**, higher molar ratio up to [**2a**]/[**1**] = 1.2 resulting in the effective formation of **3a** (runs 3 and 4). The reaction gave no significant change on the quinoline yield for a longer reaction time (run 5). The optimization for $CuCl_2$ amount was achieved with 1 mol % based on **1** (runs 3, 6 and 7). The reactivity toward the formation of **3a** using CuCl under the employed conditions was revealed to be as similarly effective as that using $CuCl_2$ (run 8). However, performing the reaction under air atmosphere resulted in a lower yield of **3a** compared with that under O_2 atmosphere (run 9).

Having established the reaction conditions, various ketones **2** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. Various aryl(methyl) ketones (**2a**–**i**) having electron donating and withdrawing substituents on the aromatic ring were readily coupled and cyclized with **1** to give the corresponding quinolines (**3a**–**i**) in the range of 42–82% yields. Here again, the conventional transfer hydrogenated aryl(methyl) carbinols were not detected at all on GLC analysis.[12] The position and electronic nature of the substituent on the aromatic ring of aryl(methyl) ketones had no relevance to quinoline yield except for 4′-cyanoacetophenone (**2i**). The reaction proceeds likewise with heteroaryl(methyl) ketone **2j** to give the corresponding quinoline **3j** in similar yield. 2′-Acetonaphthone (**2k**) was also readily oxidatively coupled and cyclized with **1** to afford 2-(2-naphthyl)quinoline (**3k**) in 77% yield. Similar reaction rate and yield were observed with alkyl(aryl) ketone **2l**, which has only methylene reaction site. In the cases of alkyl(methyl) ketones (**2m** and **2n**), the corresponding quinolines were produced as a regioisomeric mixture, favoring cyclization at less-hindered methyl position over α-methylene.[7,8,11c] With dialkyl ketone **2o** having only methylene reaction site, the corresponding quinoline **3o** was also formed and the yield was lower than that when previously described ketones such as aryl(methyl) ketones, alkyl(aryl) ketones and alkyl(methyl) ketones were used. Cyclic ketones such as 4-phenylcyclohexanone (**2p**) and 1-tetralone (**2q**) were also reacted with **1** to give 3-phenyl-1,2,3,4-tetrahydroacridine (**3q**) and 5,6-dihydrobenzo[*c*]acridine (**3r**) in 63% and 65% yields, respectively.

We then examined a similar oxidative cyclization between **1** with aldehydes.[13] Table 3 shows several attempted results for the reaction between **1** and octyl aldehyde (**4a**). Treatment of **1** with **4a** under similar catalytic system used in the reaction of **1** with ketones afforded 3-hexylquinoline (**3r**) in only 29% yield (run 1). However, step-by-step procedure, an initial treatment of **1** in the presence of a catalytic amount of $CuCl_2$ along with KOH in dioxane for 5 h under O_2 atmosphere and subsequent addition of **4a** to the mixture followed by stirring for 20 h resulted in an increased yield of **3r** (run 2). Performing the second reaction stage under air gave no significant change on the product yield (run 3). On the other hand, when the atmosphere of second reaction stage was changed from O_2 or air to argon, a considerably increased yield of **3r** was obtained (run 4). However, increasing the amount of $CuCl_2$ catalyst to 10 mol % rather lowered the quinoline yield (run 5).

Given suitable reaction conditions, various aldehydes **4** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 4. From the reaction between **1** and straight aldehydes (**4a**–**d**), the 3-substituted quinolines (**3r**–**u**) were formed in the range of 48–67% yields. The product yield had no relevance to the chain length of **4a**–**d**. In the case of valeraldehyde (**4b**), the second stage reaction was carried out at a lower reaction temperature to obtain an allowable yield of 3-propylquinoline (**3s**). Hydrocinnamaldehyde (**4e**) having a phenyl group at position 3 reacts similarly with **1** to give 3-benzylquinoline (**3v**) in 46% yield. The reaction proceeds likewise with isovaleraldehyde (**4f**) and 3-phenylbutyraldehyde (**4g**), which have substituents such as methyl and