A Rhodium-Catalyzed Route for Oxidative Coupling and Cyclization of 2-Aminobenzyl Alcohol with Ketones Leading to Quinolines

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2-Aminobenzyl alcohol undergoes oxidative cyclization with aryl(alkyl), alkyl(alkyl) and cyclic ketones in dioxane at 80° in the presence of a catalytic amount of $RhCl(PPh_3)_3$ along with KOH to afford the corresponding quinolines in good yields. The catalytic pathway seems to be proceeded *via* a sequence involving initial oxidation of 2-aminobenzyl alcohol to 2-aminobenzaldehyde by a rhodium catalyst, cross aldol reaction between 2-aminobenzaldehyde and ketones, and cyclodehydration.

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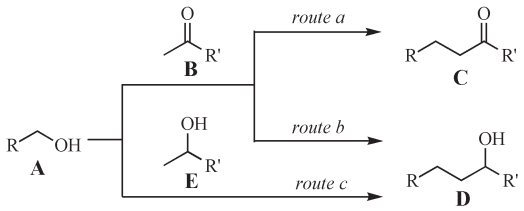
Introduction.

It is known that many quinoline containing compounds exhibit a wide spectrum of pharmacological activities such as antiasthmatic, antiinflammatory and antimalarial [1]. As part of our studies directed toward ruthenium-catalyzed synthesis of N-heterocycles, we have reported on the synthesis of quinolines *via* an alkyl and alkanol group transfer from alkylamines and alkanolamines to anilines (amine exchange reaction [2]) [3]. Furthermore, in connection with this report, we recently found an unusual ruthenium-catalyzed coupling between primary alcohols **A** and ketones **B** leading to coupled ketones **C** (Scheme 1, route a) [4,5] or coupled secondary alcohols **D** (Scheme 1, route b) [6] according to the molar ratio of **A** to **B**. It was also disclosed that primary alcohols **A** were found to couple with secondary alcohols **E** in the presence of a ruthenium catalyst along with a sacrificial hydrogen acceptor to give coupled secondary alcohols **D** (Scheme 1, route c) [7]. Thus, these reactions could be applied to modified Friedländer quinoline synthesis [8] *via* ruthenium-catalyzed consecutive coupling and cyclization of 2-aminobenzyl alcohol with ketones [9] and secondary alcohols [10]. Under these circumstances, we have directed our attention to the application of an alternative catalyst to the oxidative cyclization of 2-aminobenzyl alcohol with ketones. This report describes a rhodium-catalyzed similar oxidative coupling and cyclization between 2-aminobenzyl alcohol and ketones leading to quinolines [11].

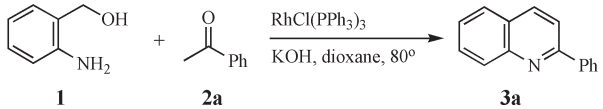
Scheme 1



Results and Discussion.

Based on our recent report on ruthenium-catalyzed oxidative cyclization of 2-aminobenzyl alcohol (**1**) with ketones [9], several reactions of **1** with acetophenone (**2a**) were performed in the presence of chlorotris(triphenylphosphine)rhodium(I) $RhCl(PPh_3)_3$ in order to obtain optimal conditions (Scheme 2). Treatment of **1** and **2a** in dioxane at 80° in the presence of a catalytic amount of $RhCl(PPh_3)_3$ (1 mol%) along with KOH afforded 2-phenylquinoline (**3a**) with the concomitant formation of 1-phenylethanol by direct transfer hydrogenation from **1** to **2a** on GLC analysis. As has been observed in our ruthenium-catalyzed version [9], equimolar amount of KOH relative to **1** and the molar ratio of **2a** to **1** ([**2a**]/[**1**] = 2.0) were required for the effective formation of **3a**. The yield of **3a** increased from 39% (0.2 equiv. KOH), 52% (0.5 equiv. KOH), to 85% (1 equiv. KOH). Lower reaction rate, determined by the disappearance of **1** on TLC, was observed with this rhodium catalytic system (for 24 hours) compared with ruthenium catalytic system (for 1 hour).

Scheme 2



1 **2a** **3a**

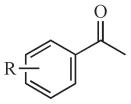
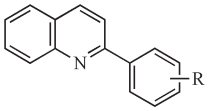
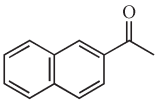
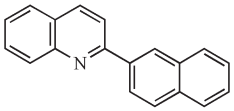
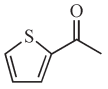
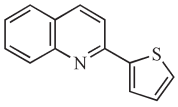
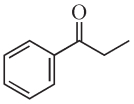
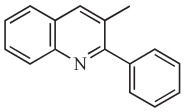
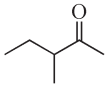
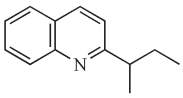
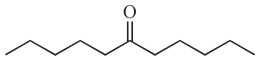
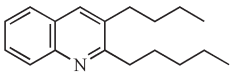
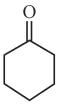
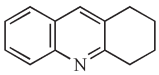
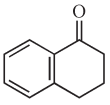
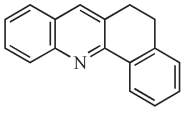
Table 1 shows the representative results for the oxidative cyclization of **1** with various ketones **2** under the controlled conditions, [**2**]/[**1**] =2.0/$RhCl(PPh_3)_3$ (1 mol%)/KOH (1 equiv.)/dioxane/80°/24 hours. From the reactions between **1** and aryl(methyl) ketones (**2b**-**2f**),

the corresponding 2-arylquinolines (**3b**-**3f**) were produced in the range of 53-82% yields. Here again, the conventional transfer hydrogenated aryl(methyl) carbinols were produced in considerable amounts on GLC analysis. The product yield was not significantly affected by the position of the substituent on the aromatic ring of aryl(methyl) ketones, whereas the electronic nature of that had some relevance to quinoline yield. 2'-Acetonaphthone (**2g**) also undergoes oxidative coupling and cyclization with **1** to afford 2-(2-naphthyl)quinoline (**3g**) in 55% yield. With heteroaryl-(methyl) ketone **2h**, 2-(2-thienyl)quinoline (**3h**) was also formed in 53% yield. The reaction proceeds likewise with alkyl(aryl) ketone **2i** which has only methylene reaction site to give the corresponding quinoline **3i** in good yield. In the reaction of alkyl(alkyl) ketones **2j** and **2k**, the corresponding quinolines **3j** and **3k** were obtained in 56% and 50% yields, respectively. Cyclic ketones such as cyclohexanone (**2l**) and 1-tetralone (**2m**) were also reacted with **1** under the employed conditions to give 1,2,3,4-tetrahydroacridine (**3l**) and 5,6-dihydrobenzo[*c*]acridine (**3m**), respectively.

Although the reaction scheme is not yet fully understood, a plausible pathway, consistent with the products formed, is depicted in Scheme 3. The pathway seems to proceed *via* initial oxidation of 2-aminobenzyl alcohol (**1**) to 2-aminobenzaldehyde (**4**), which in turn triggers cross aldol condensation with ketone **2** under KOH to give an α,β-unsaturated ketone **6**. This is followed by cyclodehydration to form quinoline **3**. Excess ketone seems to act as a sacrificial hydrogen acceptor oxidizing $[Rh]H_2$ generated in the initial oxidation stage to [Rh] [12]. The formation of a considerable amount of carbinol **5** clearly shows such a hydrogen transfer. It is also known that rhodium has been used as hydrogenation transfer catalyst [13,14]. In a separate experiment to support a carbon-carbon coupling between ketone and primary alcohol under similar conditions, it was confirmed that treatment of equimolar amounts of acetophenone (**1a**) and benzyl alcohol under $RhCl(PPh_3)_3$ (2 mol%)/KOH (1 equiv.)/dioxane/80°/20 hours afforded 1,3-diphenylpropan-1-one and 1,3-diphenylpropan-1-ol in 69% and 16% yields, respectively.

Table 1

Rhodium-Catalyzed Oxidative Cyclization of **1** with **2** Leading to **3** [a]

Ketone **2**	Quinoline **3**	Yield
		
2a R = H	**3a** R = H	85 (97)
2b R = 4-Me	**3b** R = 4-Me	82 (96)
2c R = 3-Me	**3c** R = 3-Me	76 (96)
2d R = 2-Me	**3d** R = 2-Me	76 (94)
2e R = 4-OMe	**3e** R = 4-OMe	53 (94)
2f R = 4-F	**3f** R = 4-F	62 (97)
 **2g**	 **3g**	55 (99)
 **2h**	 **3h**	53 (78)
 **2i**	 **3i**	77 (86)
 **2j**	 **3j**	56
 **2k**	 **3k**	50
 **2l**	 **3l**	57 (66)
 **2m**	 **3m**	76 (90)

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), $RhCl(PPh_3)_3$ (0.01 mmol), KOH (1 mmol), dioxane (3 mL), 80°, for 24 hours; [b] For comparision, the ruthenium-catalyzed yields are noted in parentheses [9].

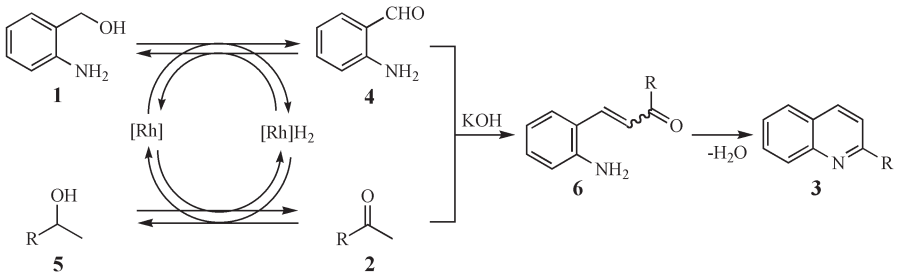
Conclusion.

In summary, we have shown a new catalytic system [$RhCl(PPh_3)_3$/KOH] for oxidative coupling and cyclization of 2-aminobenzyl alcohol with an array of ketones leading to quinolines. The present reaction will serve as an alternative transition metal-catalyzed Friedländer quinoline synthesis and further study on intramolecular oxidative cyclization using the present catalytic system is currently under investigation

EXPERIMENTAL

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting points apparatus and were uncorrected. The isolation of pure products was carried out *via* thin layer (silica gel 60

Scheme 3



GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification.

General Procedure for Rhodium-Catalyzed Oxidative Cyclization of 2-Aminobenzyl Alcohol (**1**) with Ketones (**2**) Leading to Quinolines (**3**).

A mixture of 2-aminobenzyl alcohol (123 mg, 1 mmol), ketone (2 mmol), $RhCl(PPh_3)_3$ (9 mg, 0.01 mmol), and KOH (56 mg, 1 mmol) in dioxane (3 mL) was placed in a 5 mL screw-capped vial and allowed to react at 80° for 24 hours. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by TLC (ethyl acetate-hexane mixture) to give quinolines. All products are noted in a recent report except for **3j** and **3l** [10].

2-(1-Methylpropyl)quinoline (**3j**).

This compound was obtained as a pale yellow oil, (lit [15] 105-108°/1.0 mmHg); ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.66-1.77 (m, 1H), 1.80-1.91 (m, 1H), 2.97-3.06 (m, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.44-7.48 (m, 1H), 7.64-7.68 (m, 1H), 7.74-7.77 (m, 1H), 8.06 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 11.18, 19.35, 28.92, 43.58, 118.55, 124.56, 125.93, 126.40, 127.97, 128.15, 135.22, 146.76, 165.99.

1,2,3,4-Tetrahydroacridine (**3l**).

This compound was obtained as a solid, mp 54-55° (hexane) (lit [16] mp 52-53°); ^{1}H NMR ($CDCl_3$): δ 1.85-1.91 (m, 2H), 1.96-2.02 (m, 2H), 2.96 (t, J = 6.3 Hz, 2H), 3.12 (t, J = 6.3 Hz, 2H), 7.40-7.44 (m, 1H), 7.57-7.62 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.8, 23.2, 29.2, 33.5, 125.4, 126.8, 127.1, 128.2, 128.4, 130.9, 134.9, 146.6, 159.2.

Acknowledgment.

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