Synthesis of Quinolines *via* Pd/C-Catalyzed Cyclization of 2-Aminobenzyl Alcohol with Ketones

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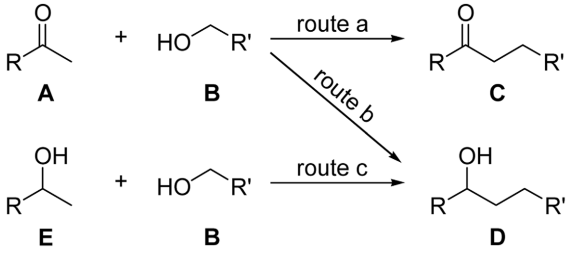
It is known that quinoline plays an important role as a basic skeleton for the design of many pharmacologically active compounds such as antiasthmatic, anti-inflammatory and antimalarial.[1] During the course of our studies directed towards C-N bond activation,[2,3] we have reported the ruthenium-catalyzed synthesis of quinolines via an alkyl or alkanol group transfer from alkylamines or alkanolamines to N-atom of anilines[4] (amine exchange reaction[5]), followed by cascade isomerization and cyclization of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols.[6] In connection with this report, several routes for the coupling of carbonyl compounds and alcohols have recently been reported as exemplified in Scheme 1.[7-9] The coupling of ketones **A** with primary alcohols **B** preferentially afforded the coupled ketones **C** (Scheme 1, route a)[7] or the coupled secondary alcohols **D** (Scheme 1, route b)[8] which depend on the molar ratio of **B** to **A**. In addition, secondary alcohols **E** was also found to be coupled with **B** to give **D** (Scheme 1, route c).[9] These reactions could be applied to modified Friedländer quinoline synthesis via ruthenium-catalyzed consecutive coupling and cyclization of 2-aminobenzyl alcohol with ketones and secondary alcohols,[10-12] which is superior to conventional Friedländer method in a sense of price and stability of 2-aminobenzyl alcohol.[13] Under these circumstances, this report describes an alternative palladium-catalyzed route for Friedländer quinoline synthesis.[14,15]

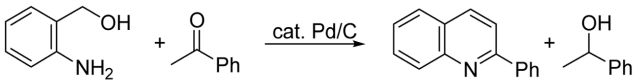
Table 1 shows several attempted results for the oxidative coupling and cyclization of 2-aminobenzyl alcohol (**1**) with acetophenone (**2a**). Generally, treatment of **1** with **2a** in dioxane in the presence of a catalytic amount of 5% Pd/C (0.5 mol%) and KOH at 100 °C afforded 2-phenylquinoline (**3a**) with concomitant formation of direct transfer hydrogenation product, 1-phenylethanol (**4**). The yield of **3a** increased with the reaction time up to 20 h (runs 1-4) and the amount of KOH employed (runs 4-6). As has been observed in our recent ruthenium-catalyzed version,[10] the molar ratio of **2a** to **1** also affected the yield of **3a**, higher molar ratio up to [**2a**]/[**1**] = 2 resulting in the effective formation of **3a** (runs 4 and 7). This could be due to the acceleration of the initial oxidation of **1** to 2-aminobenzaldehyde by transfer hydrogenation from **1** to excess **2a**.[16] However, performing the reaction in the presence of 1-decene as a hydrogen acceptor instead of excess **2a** gave no significant change on the product yield and distribution (run 8).



Scheme 1

Having established 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. From the reactions between **1** and aryl(methyl) ketones (**2a**-**2h**), the corresponding 2-aryl-quinolines (**3a**-**3h**) were produced in the range of 43-77% yields. Here again, the conventional transfer hydrogenated aryl(methyl) carbinols were produced in considerable amounts on GLC analysis. The position and electronic nature of the substituent on the aromatic ring of aryl(metnyl) ketones had no relevance to quinoline yield. The reaction proceeds likewise with heteroaryl(methyl) ketone **2i** and 2'-

Table 1. Pd/C-catalyzed optimization of conditions for the reaction of **1** with **2a**[a]



Run	[**2a**]/[**1**]	KOH (mmol)	Time (h)	Conv. (%) of **2a**	GLC yield (%)[b]	
					3a	**4**
1	2	2	5	63	54	32
2	2	2	10	76	67	44
3	2	2	15	87	76	43
4	2	2	20	88	87	53
5	2	1	20	75	70	45
6	2	3	20	90	86	52
7	1	2	20	100	60	28
8[c]	1	2	20	100	56	28

[a]Reaction conditions: **1** (1 mmol), Pd/C (0.005 mmol), dioxane (3 mL), 100 °C. [b]Based on **1**. [c]In the presence of 1-decene (2 mmol).

Table 2. Pd/C-catalyzed synthesis of quinolines **3** from **1** and **2**[a]

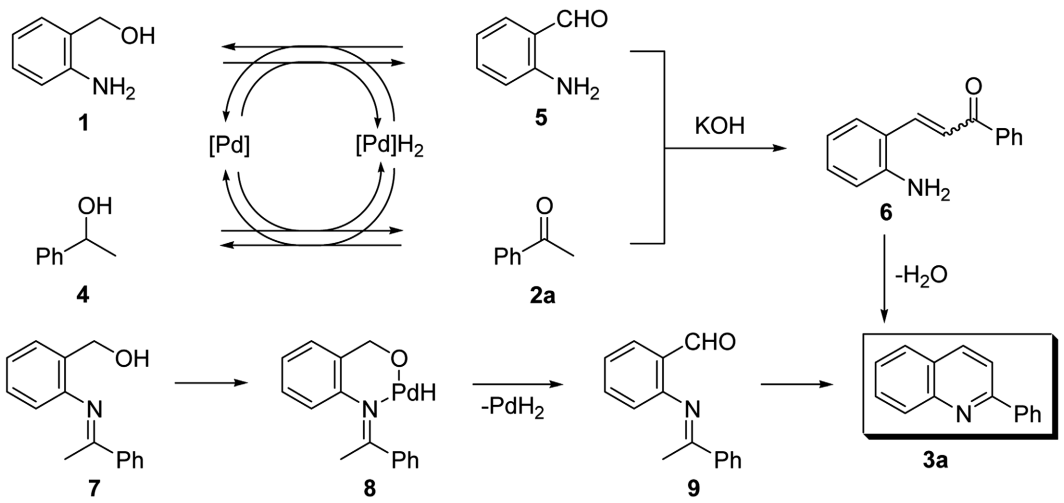
Ketones **2**	Quinolines **3**	Yield (%)[b]
R = Ph (**2a**)	R = Ph (**3a**)	77
R = 4-MeC_6H_4 (**2b**)	R = 4-MeC_6H_4 (**3b**)	73
R = 3-MeC_6H_4 (**2c**)	R = 3-MeC_6H_4 (**3c**)	69
R = 2-MeC_6H_4 (**2d**)	R = 2-MeC_6H_4 (**3d**)	59
R = 4-MeOC_6H_4 (**2e**)	R = 4-MeOC_6H_4 (**3e**)	61
R = 2-MeOC_6H_4 (**2f**)	R = 2-MeOC_6H_4 (**3f**)	72
R = 4-FC_6H_4 (**2g**)	R = 4-FC_6H_4 (**3g**)	43
R = 3-$CF_3C_6H_4$ (**2h**)	R = 3-$CF_3C_6H_4$ (**3h**)	76
R = 2-thienyl (**2i**)	R = 2-thienyl (**3i**)	50
R = 2-naphthyl (**2j**)	R = 2-naphthyl (**3j**)	55
R = Ph (**2k**)	R = Ph (**3k**)	85
R = 4-MeC_6H_4 (**2l**)	R = 4-MeC_6H_4 (**3l**)	75
R = 2-naphthyl (**2m**)	R = 2-naphthyl (**3m**)	88
R = phenethyl (**2n**)	R = phenethyl (**3n**)	41[c]
R = pentyl (**2o**)	R = pentyl (**3o**)	40[d]
2p	**3p**	44
2q	**3q**	80
2r	**3r**	58

[a]Reaction conditions: **1** (1 mmol), **2** (2 mmol), Pd/C (0.005 mmol), KOH (2 mmol), dioxane (3 mL), 100 °C, 20 h. [b]Isolated yield. [c]3-Benzyl-2-methylquinoline was also formed in 20% yield. [d]3-Butyl-2-methylquinoline was also formed in 13% yield.

acetonaphthone (**2j**) to give the corresponding quinolines **3i** and **3j**. Higher reaction rate and yield were observed with alkyl(aryl) ketones (**2k**-**2m**). In the reaction of alkyl(methyl) ketones (**2n** and **2o**) the corresponding quinolines were obtained as a regioisomeric mixture, favoring cyclization at less-hindered position over α-methylene.[2a,7-10,17] With dialkyl ketone **2p**, 3-butyl-2-pentylquinoline (**3p**) was also formed in 44% yield. Cyclic ketones such as 4-phenylcyclohexanone (**2q**) and 1-tetralone (**2r**) were also reacted with **1** to give 3-phenyl-1,2,3,4-tetrahydroacridine (**3q**) and 5,6-dihydrobenzo[*c*]acridine (**3r**) in 80% and 58% yields, respectively.

The catalytic pathway seems to proceed *via* initial oxidation of **1** to 2-aminobenzaldehyde (**5**), which in turn triggers cross aldol condensation with **2a** under KOH to give an α,β-unsaturated ketone **6**. This is followed by cyclodehydration to form **3a** (Scheme 2).[10] An alternative route for **3a** involves a sequence such as ketimine **7** formation from **1** and **2a**, oxidative addition of palladium to O-H bond of **7** to give palladium hydride complex **8**, β-hydride elimination from **8** to form ketimine aldehyde **9** and intramolecular aldol-type condensation of **9**.[12]

In summary, it has been shown that 2-aminobenzyl alcohol undergoes an oxidative coupling and cyclization with ketones in the presence of a catalytic amount of Pd/C along with KOH to give quinolines in moderate to good yields. To best of our knowledge, the present reaction is the



Scheme 2

first example for palladium-catalyzed Friedländer quinoline synthesis.

Experimental Section

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). Commercially available organic and inorganic compounds were used without further purification.

General experimental procedure. A mixture of 2-aminobenzyl alcohol (0.123 g, 1 mmol), ketone (2 mmol), palladium, 5 wt.% on activated carbon (0.011 g, 0.005 mmol) and KOH (0.112 g, 2 mmol) in dioxane (3 mL) was placed in a 5 mL screw-capped vial and allowed to react at 100 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate inorganic salts. To the extract was added appropriate amount of undecane as an internal standard and analyzed by GLC for the determination of the conversion of **2a** and the yield of **3a** and **4**. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give quinolines **3**. All products prepared by the above procedure were identified by comparison with samples noted in our recent report except for **3k**-**3m**.

3-Butyl-2-phenylquinoline (3k). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 1.19-1.28 (m, 2H), 1.45-1.53 (m, 2H), 2.74 (t, J = 8.0 Hz, 2H), 7.38-7.49 (m, 4H), 7.54 (d, J = 7.0 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.0, 33.1, 33.4, 127.0, 127.6, 128.3, 128.7, 128.9, 129.4 (× 2), 129.9, 134.7, 136.3, 141.6, 147.0, 161.4. Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.29; H, 7.69; N, 5.42.

3-Butyl-2-(4-methylphenyl)quinoline (3l). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 3H), 1.22-1.31 (m, 2H), 1.48-1.56 (m, 2H), 2.41 (s, 3H), 2.77 (t, J = 8.0 Hz, 2H), 7.27 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.8 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.76 d, J = 7.5 Hz, 1H), 8.00 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.8, 22.8, 33.0, 33.2, 126.6, 127.3, 128.0, 129.1 (× 2), 129.4, 129.7, 134.6, 136.0, 138.2, 138.5, 146.8, 161.2. Anal. Calcd for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.25; H, 8.04; N, 5.13.

3-Butyl-2-(2-naphthyl)quinoline (3m).[18] Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.3 Hz, 3H), 1.16-1.25 (m, 2H), 1.47-1.55 (m, 2H), 2.78 (t, J = 7.8 Hz, 2H), 7.45-7.49 (m, 3H), 7.62-7.69 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.85-7.89 (m, 2H), 7.92 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 33.0, 33.3, 126.7, 126.8, 126.9, 127.2, 127.5, 128.1, 128.2, 128.4, 128.6, 128.9, 129.4, 129.8, 133.5, 133.7, 134.7, 136.3, 138.9, 146.9, 161.1.

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