Notes

Ruthenium-Catalyzed Synthesis of 3-Substituted Quinolines from 2-Aminobenzyl Alcohol and Aldehydes

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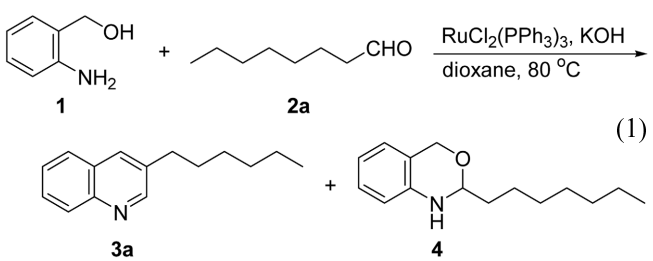
Received September 28, 2005

Key Words : Aldehydes, 2-Aminobenzyl alcohol, Oxidative cyclization, Ruthenium catalyst, 3-Substituted quinolines

It is known that many quinoline containing compounds exhibit a broad spectrum of pharmacological and biological activities.[1] During the course of our studies on transition metal-catalyzed N-heterocyclization, we have also reported on synthesis of quinolines via ruthenium-catalyzed alkyl or alkanol group transfer from alkylamines or alkanolamines to N-atom of anilines (amine exchange reaction)[2] and palladium-catalyzed coupling and cyclization between 2-iodoaniline and propargylic alcohols.[3] Furthermore, in connection with this report, it has recently been found that carbonyl compounds (or secondary alcohols) are coupled with primary alcohols in the presence of a ruthenium catalyst and KOH.[4-6] These newly developed coupling reactions could also be applied to modified Friedländer quinoline synthesis *via* ruthenium- and palladium-catalyzed coupling and cyclization of 2-aminobenzyl alcohol with ketones and secondary alcohols.[7-9] Under these circumstances, the present work was disclosed during the course of the extension of this protocol to the reaction of 2-aminobenzyl alcohol with aldehydes. Herein, we describe a ruthenium-catalyzed oxidative coupling and cyclization between 2-aminobenzyl alcohol and aldehydes leading to 3-substituted quinolines.

Initial attempts for the oxidative cyclization of 2-aminobenzyl alcohol (**1**) with octyl aldehyde (**2a**) were examined under several conditions. Treatment of 1.5 equivalent of **1** with **2a** in dioxane in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ and KOH at 80 °C for 20 h afforded 3-hexylquinoline (**3a**) in only 22% yield with concomitant formation of 2-heptyl-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazine (**4**) (2%) (Eq. 1).[10] However, step-by-step procedure, an initial treatment of **1** in the presence of $RuCl_2(PPh_3)_3$ and KOH in dioxane for 15 h and subsequent addition of **2a** to the mixture followed by stirring for 5 h at the same temperature resulted in an increased yield of **3a** (58%), whereas **4** remained constant. In contrast to our recent report on ruthenium-catalyzed synthesis of quinolines from **1** and secondary alcohols, the addition of 1-decene as a sacrificial hydrogen acceptor did not affect the yield of **3a** (58%).

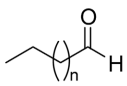
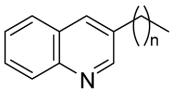
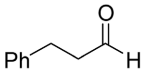
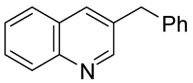
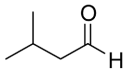
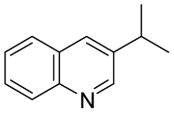
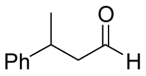
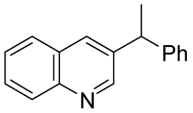
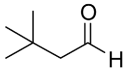
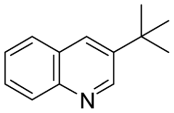
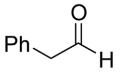
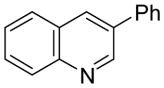


(1)

Next, various aldehydes were subjected to cyclize with **1** in order to investigate the reaction scope and several representative results are summarized in Table 1. With straight aldehydes (**2a**-**2c**) the 3-substituted quinolines (**3a**-**3c**) were formed in the range of 58-66% yields with the minimal formation of oxazines on GLC analysis. The product yield was not significantly affected by the chain length of **2a**-**2c**. The reaction proceeds likewise with hydrocinnamaldehyde (**2d**) having phenyl group at position 3 to give the corresponding quinoline **3d** in similar yield. In the reaction of isovaleraldehyde (**2e**) and 3-phenylbutyraldehyde (**2f**) which have substituents such as methyl and phenyl at position 3, the corresponding 3-isopropylquinoline (**3e**) and 3-(1-phenylethyl)quinoline (**3f**) were also obtained in 59% and 67% yields, respectively. Lower reaction rate and yield were observed with 3,3-dimethylbutyraldehyde (**2g**), which has two substituent at position 3. The reaction of phenylacetaldehyde (**2h**), which has a phenyl substituent at position 2, with **1** also proceeds to give 3-phenylquinoline (**3h**) and the quinoline yield was lower than when straight and β-substituted aldehydes were used. Finally, we attempted the oxidative cyclization of **1** with primary alcohol instead of aldehyde for the wide availability of substrates.[4] However, similar treatment of **1** with 3-methyl-2-butanol instead of **2e** under the employed conditions gave **3e** in only 5% yield without any identifiable products.

In summary, we have demonstrated that 2-aminobenzyl alcohol can be oxidatively cyclized with an array of

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

Ketones **2**	Quinolines **3**	Yield (%)
		
2a $n = 5$	**3a**	58
2b $n = 2$	**3b**	58
2c $n = 9$	**3c**	66
		
2d	**3d**	53
		
2e	**3e**	59
		
2f	**3f**	67
		
2g	**3g**	16
		
2h	**3h**	34

[a]Reaction conditions: **1** (1.5 mmol), $RuCl_2(PPh_3)_3$ (0.03 mmol), KOH (2 mmol), dioxane (5 mL), 80 °C, for 15 h; **2** (1 mmol), dioxane (3 mL), 80 °C, for 5 h.

aldehydes in the presence of a ruthenium catalyst and KOH to give 3-substituted quinolines in good yields.

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 (0.185 g, 1.5 mmol), $RuCl_2(PPh_3)_3$ (0.029 g, 0.03 mmol) and KOH (0.112 g, 2 mmol) in dioxane (5 mL) was placed in an organic reactor (Radleys Discovery Technologies) and allowed to react at 80 °C for 15 h. To the mixture was added aldehyde (1 mmol) in dioxane (3 mL). The mixture was stirred at the same temperature for 5 h and filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate inorganic salts. 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 characterized spectroscopically as shown below.

3-Hexylquinoline (3a). Oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1.29-1.34 (m, 4H), 1.35-1.40 (m, 2H), 1.68-1.75 (m, 2H), 2.79 (t, J = 7.8 Hz, 2H), 7.49-7.53 (m, 1H), 7.63-7.67 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 1.0 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.78 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.04, 22.54, 28.83, 31.07, 31.61, 33.17, 126.46, 127.25, 128.16, 128.44, 129.10, 134.05, 135.35, 146.71, 152.10.

3-Propylquinoline (3b). Oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.57-1.66 (m, 2H), 2.63 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.04, 24.59, 35.55, 126.91, 127.67, 128.54, 128.93, 129.33, 134.70, 135.46, 146.95, 152.33.

3-Decylquinoline (3c). Oil; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 6.8 Hz, 3H), 1.18-1.33 (m, 14H), 1.59-1.67 (m, 2H), 2.70 (t, J = 7.8 Hz, 2H), 7.41-7.45 (m, 1H), 7.55-7.59 (m, 1H), 7.67-7.69 (m, 1H), 7.84 (d, J = 1.5 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.70 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.49, 23.06, 29.57, 29.69, 29.81, 29.94, 29.97, 31.49, 32.26, 33.58, 127.00, 127.68, 128.61, 129.04, 129.25, 134.81, 135.83, 146.76, 152.19.

3-Benzylquinoline (3d). Viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 2H), 7.06-7.11 (m, 3H), 7.15-7.19 (m, 2H), 7.33-7.36 (m, 1H), 7.49-7.52 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.63, 127.01, 127.15, 127.89, 128.54, 129.18, 129.35, 129.37, 129.46, 134.29, 135.39, 140.06, 147.14, 152.38.

3-Isopropylquinoline (3e). Oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 7.0 Hz, 6H), 2.98-3.09 (m, 1H), 7.40-7.45 (m, 1H), 7.54-7.58 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.01, 32.23, 126.98, 127.86, 128.63, 129.06, 129.24, 132.48, 141.53, 146.97, 151.32.

3-(1-Phenylethyl)quinoline (3f). Viscous oil; ^{1}H NMR ($CDCl_3$) δ 1.70 (d, J = 7.0 Hz, 3H), 4.29 (q, J = 7.0 Hz, 1H), 7.15-7.22 (m, 3H), 7.25-7.28 (m, 2H), 7.42-7.46 (m, 1H), 7.57-7.62 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.79 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.04, 42.97, 126.97, 127.07, 128.05, 128.10, 128.49, 129.10, 129.26, 129.55, 133.43, 139.33, 145.34, 147.26, 152.24.

3-*tert*-Butylquinoline (3g). Oil; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 7.50-7.55 (m, 1H), 7.64-7.68 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 9.03 (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.33, 34.21, 126.90, 128.08, 128.26, 129.05, 129.24, 131.23, 143.71, 146.66, 150.44.

3-Phenylquinoline (3h). Viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.30 (t, J = 7.3 Hz, 3H), 7.37-7.45 (m, 3H), 7.56-7.60 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 9.06 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 127.47, 127.80, 128.42, 128.55, 129.44, 129.59 (×2), 129.90, 133.80, 134.22, 138.14, 147.49, 150.12.

Acknowledgment. The present work was supported by BK-21 in 2003 and a Research Foundation Grant (KRF-2002-070-C00055). C.S.C. gratefully acknowledges a Research Professor Grant of Kyungpook National University (2004).

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10. We separately synthesized **4** for identification by simple stirring **1** and **2a** in dioxane at 80 °C for 4 h. Oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.29-1.34 (m, 8H), 1.43-1.57 (m, 2H), 1.63-1.79 (m, 2H), 4.53 (t, J = 5.5 Hz, 1H), 4.80 (d, J = 14.6 Hz, 1H), 4.94 (d, J = 14.6 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.77-6.81 (m, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.48, 23.04, 24.91, 29.58, 29.87, 32.16, 35.60, 68.06, 84.79, 117.60, 120.02, 123.00, 125.38, 127.71, 141.98.