Ruthenium-Catalyzed Formation of Quinolines *via* Reductive Cyclization of Nitroarenes with Tris(3-hydroxypropyl)amine in an Aqueous Medium

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Nitroarenes react with tris(3-hydroxypropyl)amine in an aqueous medium (dioxane/H_2O) at 180° in the presence of a catalytic amount of a ruthenium catalyst and tin(II) chloride along with isopropanol as hydrogen donor to afford the corresponding quinolines in good yields. The presence of tin(II) chloride is essential for the formation of quinolines. A reaction pathway involving initial reduction of nitroarenes to anilines, propanol group transfer from tris(3-hydroxypropyl)amine to anilines to form 3-anilino-1-propanols, N-alkylation of anilines by 3-anilino-1-propanol to form 1,3-dianilinopropane and intramolecular heteroannulation of 1,3-dianilinopropane is proposed for this catalytic process.

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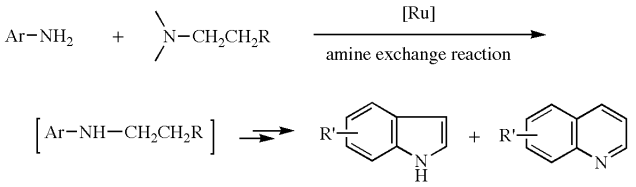
Introduction.

Compounds containing the quinoline framework have frequently been used as antimalarial compounds. Thus, along with conventional named routes such as Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses, homogeneous transition metal-catalyzed synthetic methods have been attempted as alternative methods for quinolines [1]. In connection with this report, during the course of our ongoing studies on homogeneous ruthenium-catalysis [1-9], we have directed our attention to the synthesis of quinolines [2] and indoles [3] *via* an alkyl group transfer from α-hydrogen containing amines to anilines (amine exchange reaction [10]) (Scheme 1). Under these circumstances, we also reported the direct use of nitroarenes instead of anilines for such heterocycles since nitroarenes are precursors of anilines from the viewpoint of industrial organic chemistry [11,12].

Scheme 1

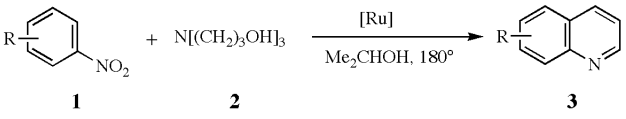


Herein, as another example for the synthesis of N-heterocycles using nitroarenes, we report a ruthenium-catalyzed consecutive reduction and cyclization of nitroarenes with tris(3-hydroxypropyl)amine [13] leading to quinolines *via* an intrinsic amine exchange reaction.

Results and Discussion.

Several attempted results of the ruthenium-catalyzed reduction and cyclization between nitrobenzene (**1a**) and tris(3-hydroxypropyl)amine (**2**) under various conditions are listed in Table 1 (Scheme 2). When **1a** was treated with **2** at 180° in the presence of a catalytic amount of a ruthenium catalyst (5 mol%) and $SnCl_2$ along with isopropyl alcohol as hydrogen donor, the reductive cyclization product quinoline (**3a**) was produced with concomitant formation of aniline. As it has been observed in our recent report on ruthenium-catalyzed reductive cyclization for quinolines and indoles [11a-c], the solvent system was critical for the effective formation of **3a** (runs 1-3). Performing the reaction in an aqueous medium (H_2O/dioxane = 1 mL/9 mL) afforded **3a** in best yield [14]. The presence of $SnCl_2$ was essential for the formation of **3a**. The reaction in the absence of $SnCl_2$ did not proceed at all with low conversion of **1a** to aniline (run 4). Comparing the results shown in runs 4 and 5 of Table 1, $SnCl_2$ seems to play a decisive role as both the reduction of **1a** to aniline and cyclization toward **3a**. It is known that nitroarenes can be easily converted into anilines in the presence of $SnCl_2$ under aqueous as well as non-aqueous media [15]. Among the activity of various ruthenium precursors examined, $RuCl_3$•nH_2O/$3PPh_3$ and $RuCl_2(PPh_3)_3$ were revealed to be the catalysts of choice (runs 5-10).

Scheme 2



Given these results, with various nitroarenes **1** the reductive cyclized products were produced in the range of 42-123% yields (Table 2). With *para*-substituted nitroarene **1b**, the quinoline yield was higher than that when *ortho*- and *meta*-substituted nitroarenes **1c** and **1d** were used. In the reaction with **1c**, the products quinolines were obtained

Table 1

Optimization of Conditions for the Reaction of **1a** with **2** Leading to **3a** [a]

Run	Ruthenium catalysts	$SnCl_2$ (mmol)	H_2O/dioxane (mL/mL)	Time (h)	Conversion of **1a**	Yield of **3a** [b]
1	$RuCl_3 \cdot nH_2O/3PPh_3$	1	0/10	5	41	16
2	$RuCl_3 \cdot nH_2O/3PPh_3$	1	1/9	5	78	52
3	$RuCl_3 \cdot nH_2O/3PPh_3$	1	5/5	20	100	0
4	$RuCl_3 \cdot nH_2O/3PPh_3$	-	1/9	20	20	0
5	$RuCl_3 \cdot nH_2O/3PPh_3$	1	1/9	20	100	91
6	$RuCl_2(PPh_3)_3$	1	1/9	20	100	92
7	$RuCl_2(=CHPh)(PCy_3)_2$	1	1/9	20	100	84
8	$Ru_3(CO)_{12}$	1	1/9	20	95	67
9	$RuH_2(PPh_3)_4$	1	1/9	20	79	61
10	$Cp^*RuCl_2(CO)$	1	1/9	20	62	40

[a] Reaction conditions: **1a** (4 mmol), **2** (1 mmol), isopropanol (6 mmol), ruthenium catalyst (0.05 mmol), 180°, under Ar; [b] GLC yield based on **2**.

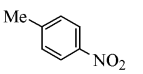
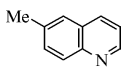
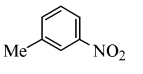
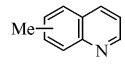
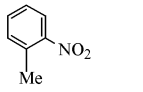
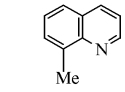
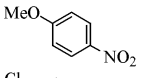
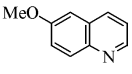
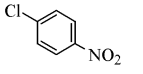
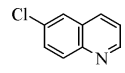
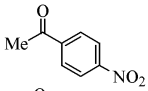
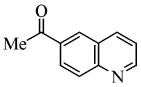
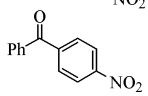
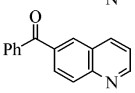
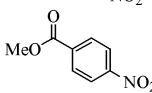
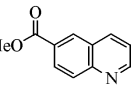
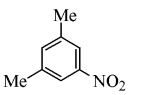
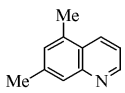
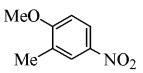
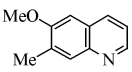
as a regioisomeric mixture, favoring 7-methyl isomer, which was formed *via* less sterically hindered position on **1c**. We found that nitroarenes substituted with either electron donating (**1e**) or electron withdrawing groups (**1f-1i**) were readily cyclized with **2** to form the corresponding quinolines in moderate to good yields. The reaction proceeds likewise with two-methyl substituted nitroarene **1j** to give 5,7-dimethylquinoline (**3j**) in high yield. The reaction of 2-methyl-4-nitroanisole (**1k**) with **2** also proceeds to give the corresponding quinoline **3k** in 123% yield with exclusive regioselectivity. The result of 123% yield indicates that at least two propanol groups out of three in **2** are available for the transfer. Similar regioselectivity was reported in our recent article on ruthenium-catalyzed cyclization of **1k** with 3-amino-1-propanol [11a].

As to the reaction pathway, although the exact role of $SnCl_2$ is not yet fully understood and no intermediates have yet been detected, this reaction seems to proceed *via* a sequence involving initial reduction of **1a** to aniline (**4**), propanol group transfer from **2** to N-atom of **4** (amine exchange reaction) to form 3-anilino-1-propanol (**5**) [10], N-alkylation of **4** with **5** to form 1,3-dianilinopropane (**6**) [16] and heteroannulation of **6** (Scheme 3). An alternative route for **6** involves a sequence such as initial N-alkylation of **4** with **2** to form 3-anilinoamine **7** and 3-aminopropyl group transfer from **7** to **4**. Watanabe and Tsuji reported that **5** reacted with **4** in the presence of a ruthenium catalyst to give **3a** and **6** was intramolecularly cyclized to give **3a** [17].

In summary, we have demonstrated that nitroarenes are reductively cyclized with tris(3-hydroxypropyl)amine in an aqueous medium in the presence of a catalytic amount of a ruthenium catalyst and $SnCl_2$ along with isopropanol to give quinolines in moderate to good yields. The present reaction is an another example for the synthesis of N-heterocycles using amine exchange reaction by the direct use of nitroarenes.

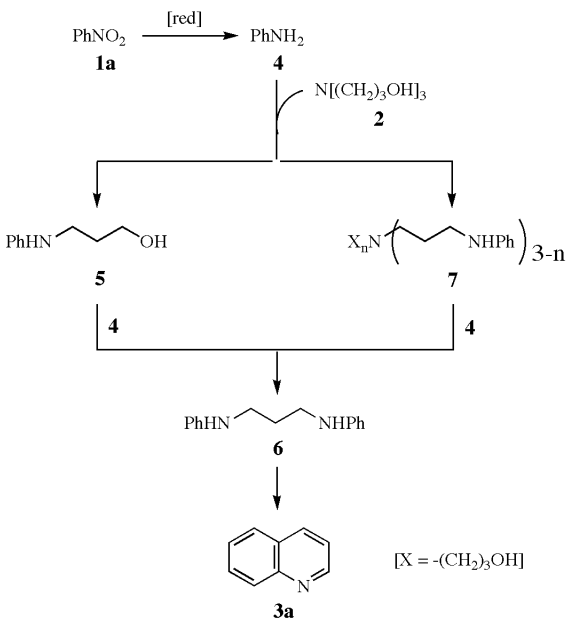
Table 2

Ruthenium-Catalyzed Reductive Cyclization of **1** with **2** Leading to **3** [a]

Nitroarene **1**		Quinoline **3**		Yield [b]
	**1b**		**3b**	93
	**1c**		**3c**	68 [c]
	**1d**		**3d**	63
	**1e**		**3e**	70
	**1f**		**3f**	85
	**1g**		**3g**	87
	**1h**		**3h**	48
	**1i**		**3i**	42
	**1j**		**3j**	95
	**1k**		**3k**	123

[a] Reaction conditions: **1** (4 mmol), **2** (1 mmol), isopropanol (6 mmol), $RuCl_3 \cdot nH_2O$ (0.05 mmol), PPh_3 (0.15 mmol), $SnCl_2$ (1 mmol), dioxane/H_2O (9 mL/1 mL), 180°, for 20 hours, under Ar; [b] Isolated yield based on **2**; [c] Regioisomeric mixture: 5-Me/7-Me = 1/4.5 (400 MHz ^1H NMR).

Scheme 3



EXPERIMENTAL

^{1}H 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. Infrared spectrum was obtained on a Mattson Galaxy 7020A spectrophotometer. GLC analyses were carried out with Shimadzu GC-17A equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm x 25 m, 0.25 μm film thickness) using N_2 as carrier gas. Commercially available organic and inorganic compounds were used without further purification. Cp*$RuCl_2$(CO) was prepared by the reported method [18].

General Procedure for Ruthenium-Catalyzed Reactions between Aniline (**1a**) and Tris(3-hydroxypropyl)amine (**2**) under Various Conditions (For GLC Analysis).

A mixture of nitrobenzene (492 mg, 4 mmol), tris(3-hydroxypropyl)amine (191 mg, 1 mmol), isopropanol (361 mg, 6 mmol), ruthenium catalyst (0.05 mmol), and $SnCl_2$ (190 mg, 1 mmol) in solvent was charged in a 50 mL pressure vessel. After the system was flushed with argon, the reaction mixture was stirred at 180° for an appropriate time. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to eliminate inorganic compounds. To the extract was added an appropriate amount of undecane as internal standard and analyzed by GLC.

General Procedure for Ruthenium-Catalyzed Synthesis of Quinolines **3** from Nitroarenes **1** and Tris(3-hydroxypropyl)-amine (**2**) (for Isolation).

A mixture of nitroarene (4 mmol), tris(3-hydroxypropyl)-amine (191 mg, 1 mmol), isopropanol (361 mg, 6 mmol), $RuCl_3$•$n$$H_2O$ (13 mg, 0.05 mmol), and $SnCl_2$ (190 mg, 1 mmol) in dioxane/H_2O (9 mL/1 mL) was charged in a 50 mL pressure vessel. After the system was flushed with argon, the reaction mixture was stirred at 180° for 20 hours. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture) to eliminate inorganic compounds and concentrated under reduced pressure. The residual mixture was separated by TLC to give the product quinoline. Except for **3i**, spectroscopic data for **3b**-**3f** [2c], **3g** [11a], **3h** [11a], **3j** [2c] and **3k** [11a] are noted in our recent report.

6-Carbomethoxyquinoline (**3i**).

This compound was obtained as a pale yellow solid, mp 85-86° (hexane) (lit [19] mp 86-88°); ir (KBr): ν 1717 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H), 7.39 (dd, J = 4.0 and 8.3 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.17-8.24 (m, 2H), 8.51 (d, J = 1.5 Hz, 1H), 8.93 (dd, J = 1.5 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 51.4, 120.8, 126.4, 127.1, 127.9, 128.8, 130.0, 136.3, 149.1, 151.5, 165.6 (C=O).

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