Ruthenium-Catalyzed Synthesis of Quinolines *via* Reductive Heteroannulation of Nitroarenes with 3-Amino-1-propanols

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Nitroarenes are reductively cyclized with 3-amino-1-propanols in dioxane/H_2O in the presence of a ruthenium catalyst and tin(II) chloride dihydrate together with isopropanol to afford the corresponding quinolines. A reaction pathway involving initial reduction of nitroarenes to anilines, propanol group transfer from 3-amino-1-propanols to anilines, *N*-alkylation of anilines by 3-anilino-1-propanols and hetero-annulation of 1,3-dianilinopropanes is proposed.

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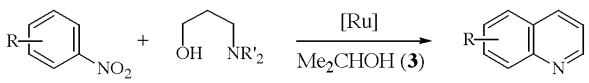
Introduction.

The Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses have been used for the formation of quinolines. Recently, many homogeneous transition metal-catalyzed reactions have been attempted as alternative synthetic methods for quinolines [1-4]. During our studies on homogeneous transition metal-catalyzed organic transformations, we have recently focused on a carbon-nitrogen bond activation of alkylamines by ruthenium catalyst. Thus, we have developed and reported an alkyl group transfer from alkylamines to anilines [5-11] as well as α-carbon atom of ketones [12]. The former leads to indoles [5-7] and quinolines [8-11] and is well known as an amine exchange reaction [13]. The synthesis of *N*-heterocycles using the amine exchange reaction methodology has previously been limited to palladium-catalyzed synthesis of pyrimidines and imidazoles [14]. Herein, we report a ruthenium-catalyzed reductive heteroannulation of nitroarenes with 3-amino-1-propanols which leads to the formation of quinolines.

Results and Discussion.

The results of ruthenium-catalyzed heteroannulation between nitrobenzene (**1a**) and 3-amino-1-propanol (**2a**) under various conditions are listed in Table 1 (Scheme 1). In order to reduce nitrobenzene (**1a**) to aniline, we employed isopropanol (**3**) as hydrogen donor and tin(II) chloride dihydrate ($SnCl_2$•$2H_2O$)/aqueous medium (H_2O/dioxane). Generally, **1a** was treated with **2a** and **3** in solvent in the presence of a ruthenium catalyst at 180° for 20 hours to afford quinoline (**4a**). As has been observed previously [5-11], the yield of **4a** was affected by the molar ratio of **1a** to alkyl group transfer agent **2a** (runs 1-3). The use of either dioxane or reverse amount of H_2O/dioxane stopped the reaction almost completely (runs 4 and 5). The presence of $SnCl_2$•$2H_2O$ was essential for the effective formation of **4a**. The reaction in the absence of $SnCl_2$•$2H_2O$ did not proceed at all. The yield of **4a** increased with increasing amounts of $SnCl_2$•$2H_2O$ up to 1 mmol (runs 6-8). Considering the conversion of the starting **1a** into aniline, $SnCl_2$•$2H_2O$ might be participated as reducing agent in present reaction. It is well known that nitroarenes can be easily converted into anilines in the presence of tin(II) chloride under both aqueous and non-aqueous media [15]. Next, the activity of various ruthenium precursors was examined. Interestingly, all ruthenium catalysts ranging from zero to trivalent exhibited the similar catalytic activity as $RuCl_3$•nH_2O/-$3PPh_3$ (runs 10-14).

Scheme 1



1 **2** **4**

a: R' = H
b: R' =Me

Given these results, several reactions of various nitroarenes **1** with **2a** as well as 3-dimethylamino-1-propanol (**2b**) were screened using $RuCl_3$•nH_2O/$3PPh_3$ catalytic system. Representative results are summarized in Table 2. As is the case for the reaction with **2a**, the use of **2b** as C_3-fragment also worked well for the formation of quinolines (runs 2, 3, 8, 11, 14, and 16). As shown in Table 2, the quinoline yield was considerably affected by the position of the substituent on nitroarene. With *ortho*-substitued nitroarene, the quinoline yield was lower than that when *meta*- and *para*-substitued nitroarenes were used (run 6). Expectedly, in the reaction with 4-methyl-2-nitroanisole

Table 1

Ruthenium-Catalyzed Synthesis of **4a** from **1a** and **2** under Various Reaction Conditions [a]

Run	Ruthenium catalysts (mmol)	Molar ratio **1a**:**2a**:**3**	$SnCl_2$•$2H_2O$ (mmol)	H_2O/Dioxane (mL/mL)	Conversion of **1a**	Yield of **4a** [b]
1	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	1	1/9	100	47
2	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	2:1:6	1	1/9	100	31
3	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	6:1:6	1	1/9	90	44
4	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	1	0/10	24	1
5	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	1	9/1	100	0
6	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	-	1/9	37	0
7	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	0.2	1/9	54	9
8	$RuCl_3$•nH_2O/$3PPh_3$ (0.1)	4:1:6	2	1/9	100	46
9	$RuCl_3$•nH_2O/$3PPh_3$ (0.05)	4:1:6	1	1/9	100	38
10	$RuCl_2(PPh_3)_3$ (0.05)	4:1:6	1	1/9	94	40
11	$RuH_2(PPh_3)_4$ (0.05)	4:1:6	1	1/9	88	41
12	$RuCl_2(=CHPh)(PCy_3)_2$ (0.05)	4:1:6	1	1/9	100	41
13	Cp*$RuCl_2(CO)$ (0.05) [c]	4:1:6	1	1/9	82	5
14	$Ru_3(CO)_{12}$ (0.05)	4:1:6	1	1/9	89	44

[a] Reaction conditions: 180°, 20 hours. [b] Determined by GLC based on **2a**. [c] Cp* = η^5-C_5Me_5.

(**1k**) which has a bulkier substituent near the nitro group, although **1k** was considerably reduced to 2-methoxy-5-methylaniline, the corresponding quinoline (**4k**) was not formed at all (run 17). In the case of 3-nitrotoluene (**1c**), the corresponding quinolines (**4c**) were obtained as a regioisomeric mixture, favoring the 7-methyl isomer which was formed *via* less sterically hindered position on **1c** (run 5). Isomeric molar ratio between 5-methylquinoline and 7-methylquinoline was determined from the signal areas of the methyl protons in ^{1}H NMR spectrum.

As concerns the reaction pathway, although the exact role of $SnCl_2$•$2H_2O$ is not yet fully understood [16] and no intermediates were detected, it seems to proceeded *via* a sequence involving initial reduction of nitroarenes to anilines, propanol group transfer from **2** to anilines to form 3-anilino-1-propanol, *N*-alkylation of anilines by 3-anilino-1-propanol to form 1,3-dianilinopropanes and heteroannulation of 1,3-dianilinopropanes to produce quinolines. Watanabe and Tsuji reported that 3-anilino-1-propanol and 1,3-dianilinopropane are key intermediates

Table 2

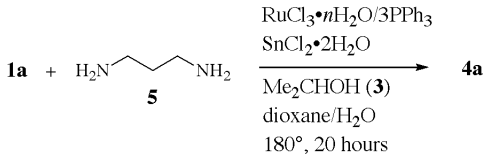
Ruthenium-Catalyzed Synthesis of **4** from **1** and **2** [a]

Run	Nitroarene **1**	3-Amino-1-propanol **2**	Quinoline **4**	Yield [b]
1	R = H (**1a**)	**2a**	R = H (**4a**)	40
2	**1a**	**2b**	**4a**	46 [c]
3	R = 4-Me (**1b**)	**2a**	R = 6-Me (**4b**)	48
4	**1b**	**2b**	**4b**	42
5	R = 3-Me (**1c**)	**2a**	R = 5- and 7-Me (**4c**)	46 [d]
6	R = 2-Me (**1d**)	**2a**	R = 8-Me (**4d**)	14
7	R = 4-OMe (**1e**)	**2a**	R = 6-OMe (**4e**)	40
8	**1e**	**2b**	**4e**	38
9	R = 4-Cl (**1f**)	**2a**	R = 6-Cl (**4f**)	28
10	R = 4-Acetyl (**1g**)	**2a**	R = 6-Acetyl (**4g**)	40
11	**1g**	**2b**	**4g**	40
12	R = 4-Benzoyl (**1h**)	**2a**	R = 6-Benzoyl (**4h**)	21
13	R = 3,5-Me (**1i**)	**2a**	R = 5,7-Me (**4i**)	51
14	**1i**	**2b**	**4i**	45
15	R = 3-Me, 4-OMe (**1j**)	**2a**	R = 6-OMe, 7-Me (**4j**)	43
16	**1j**	**2b**	**4j**	43
17	R = 2-OMe, 5-Me (**1k**)	**2a**	R = 5-Me, 8-OMe (**4k**)	0

[a] Reaction conditions: **1** (4 mmol), **2** (1 mmol), isopropanol (**3**) (6 mmol), $RuCl_3$•nH_2O (*n* = 3, 10 mol% based on **2**), PPh_3 (30 mol% based on **2**), $SnCl_2$•$2H_2O$ (1 mmol), H_2O/dioxane (= 1 mL/9 mL), at 180 °, for 20 hours. [b] Isolated yield based on **2**. [c] GLC yield. [d] Regioisomeric ratio was determined by ^{1}H NMR (400 MHz): 7-methylquinoline/5-methylquinoline=3.6/1.

in the ruthenium-catalyzed synthesis of quinolines from anilines and 1,3-diols [3f]. They confirmed that 3-anilino-1-propanol reacted with aniline in the presence of a ruthenium catalyst to give quinoline and 1,3-dianilinopropane was intramolecularly cyclized to give quinoline. In a separate experiment, we also observed that 1,3-diaminopropane (**5**) can be used as C_3-fragment under the similar conditions, resulting in 13% quinoline yield from the reaction between **1a** and **5** (Scheme 2). This result indicates that the reaction proceeds *via* a double amine exchange reaction between aniline and both amino moieties of **5**.

Scheme 2



In summary, we have demonstrated that nitroarenes were reductively cyclized with 3-amino-1-propanols in the presence of a ruthenium catalyst and $SnCl_2•2H_2O$ together with isopropanol as hydrogen donor in an aqueous medium to give quinolines.

EXPERIMENTAL

The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Mattson Galaxy 6030E FT-IR spectrophotometer. Electron impact mass spectra were obtained on a Shimadzu QP-1000 spectrometer. GLC analyses were carried out with Shimadzu GC-17A equipped with CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm x 25 m, 0.25 μm film thickness) using nitrogen as the carrier gas. GLC yields were determined using undecane as an internal standard. Melting points were determined on a Thomas Scientific Capillary Melting Points Apparatus and are uncorrected. The isolation of pure products was carried out *via* column chromatography (silica gel 60 HF_{254}, 70-230 mesh, Merck) and thin layer chromatography. Commercially available organic and inorganic compounds were used without further purification. Ruthenium catalysts such as $RuCl_2(PPh_3)_3$ [17], $RuH_2(PPh_3)_4$ [18], $Cp^*RuCl_2(CO)$ [19] and $Ru_3(CO)_{12}$ [20] were prepared by literature methods.

General Procedure for Ruthenium-Catalyzed Synthesis of Quinoline (**4a**) from Nitrobenzene (**1a**) and 3-Amino-1-propanol (**2a**) (For GLC Analysis).

A mixture of nitrobenzene (2-6 mmol), 3-amino-1-propanol (75 mg, 1 mmol), isopropanol (361 mg, 6 mmol), ruthenium catalyst (0.05-0.1 mmol), triphenylphosphine [in the case of the use of ruthenium(III) chloride hydrate, 3-fold molar amount to ruthenium(III) chloride hydrate], and tin(II) chloride dihydrate (226 mg, 1 mmol) in solvent was charged in a 50 mL stainless steel autoclave. 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) to eliminate inorganic compounds and concentrated under reduced pressure. The organic layer was poured into saturated brine and extracted with chloroform. To the extract was added appropriate amount of an internal standard and analyzed by GLC.

General Procedure for Ruthenium-Catalyzed Synthesis of Quinolines **4** from Nitroarenes **1** and 3-Amino-1-propanols **2** (For Isolation).

A mixture of nitrobenzene (4 mmol), 3-amino-1-propanol (1 mmol), isopropanol (361 mg, 6 mmol), ruthenium(III) chloride hydrate (26 mg, 0.1 mmol), triphenylphosphine (79 mg, 0.3 mmol), and tin(II) chloride dihydrate (226 mg, 1 mmol) in dioxane/H_2O (9 mL/1 mL) was placed in a 50 mL stainless steel pressure vessel. After the system was flushed with argon, the 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 organic layer was poured into saturated brine, extracted with chloroform, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residual oily material was separated by column chromatography (ethyl acetate-hexane) to give the product quinoline. The products obtained by the above procedure were characterized spectroscopically. Spectroscopic data of the products **4a**-**4f** and **4i** are noted in our recent report [9].

6-Acetylquinoline (**4g**).

This compound was obtained as pale yellow solid, mp 72-73° (ethanol) (lit [21] mp 75-76°); ^1H NMR ($CDCl_3$): δ 2.74 (s, 3H, -$COCH_3$), 7.48 (dd, J = 4.5 and 8.3 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 8.25-8.29 (m, 2H), 8.44 (d, J = 1.5 Hz, 1H), 9.01 (dd, J = 1.5 and 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 26.8, 122.0, 127.5, 127.7, 129.9, 130.1, 134.9, 137.6, 150.1, 152.6, 197.4 (C=O).

6-Benzoylquinoline (**4h**).

This compound was obtained as white solid, mp 59-61° (petroleum ether) (lit [22] mp 63°); ir (KBr): ν 1657 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39-7.46 (m, 3H), 7.55 (t, J = 7.3 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 8.06-8.17 (m, 4H), 8.94 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 121.0, 126.2, 127.4, 128.5, 128.8, 129.1, 130.3, 131.7, 134.4, 136.3, 136.4, 148.8, 151.5, 195.0 (C=O); ms: m/z (%) 233 (M^+, 99), 156 (100), 128 (69), 105 (86), 77 (90).

6-Methoxy-7-methylquinoline (**4j**).

This compound was obtained as pale yellow oil; ^1H NMR ($CDCl_3$): δ 2.77 (s, 3H, -CH_3), 3.89 (s, 3H, -OCH_3), 6.90 (d, J = 1.5 Hz, 1H), 7.22 (d, J = 1.5 Hz, 1H), 7.33 (dd, J = 4.0 and 8.0 Hz, 1H), 8.00 (dd, J = 1.5 and 8.0 Hz, 1H), 8.78 (dd, J = 1.5 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.1, 55.3, 103.1, 121.2, 122.2, 129.4, 135.0, 138.4, 143.8, 146.8, 157.3.

Ruthenium-Catalyzed Synthesis of Quinoline (**4a**) from Nitrobenzene (**1a**) and 1,3-Diaminopropane (**5**).

A mixture of nitrobenzene (492 mg, 4 mmol), 1,3-diaminopropane (74 mg, 1 mmol), isopropanol (361 mg, 6 mmol), ruthenium(III) chloride hydrate (26 mg, 0.1 mmol),

triphenylphosphine (79 mg, 0.3 mmol), and tin(II) chloride dihydrate (226 mg, 1 mmol) in dioxane/H_2O (9 mL/1 mL) was placed in a 50 mL stainless steel pressure vessel. After the system was flushed with argon, the mixture was stirred at 180° for 20 hours. The reaction mixture was filtered through a short silica gel column (ethyl acetate-chloroform mixture), poured into saturated brine, extracted with chloroform and dried over anhydrous sodium sulfate. GLC analysis revealed the presence of quinoline (13%).

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