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The Ruthenium Catalyzed Synthesis of Quinoline Derivatives from Nitroarenes and Aliphatic Alcohols

Yoshihisa WATANABE,* Yasushi TSUJI, and Jun SHIDA
Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606

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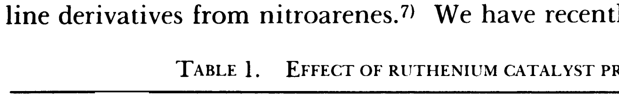
Nitroarenes are reductively converted into quinoline derivatives with aliphatic alcohols in the presence of a catalytic amount of ruthenium compound at 180 °C. Ruthenium(III) chloride is the most effective catalyst. The reaction of nitrobenzene with 1-propanol and 1-butanol gave 2-ethyl-3-methylquinoline and 3-ethyl-2-propylquinoline in 65 and 70% yields respectively. *p*-Methoxynitrobenzene gave 3-ethyl-6-methoxy-2-propylquinoline in 70% yield with 1-butanol. The reaction appears to include the redox reaction between the nitroarenes and the alcohols, that is, a catalytic hydrogen transfer reaction which generates the aminoarenes and aldehydes. Thus, the alcohol plays roles as both a reductant and an aldehyde precursor.

The Skraup synthesis is well known as the method for the preparation of quinoline derivatives.[1] This method, however, requires a large amount of strong acid and a high reaction temperature. Recently, transition metal-catalyzed synthesis of quinoline derivatives under non-acid conditions have been developed.[2,3] In the previous paper, we have reported. that several transiation metal catalysts are effective for the preparation of quinoline derivatives from aminoarenes. Aminoarenes react with aliphatic aldehydes to give quinoline derivatives in the presence of a rhodium complex such as di-μ-chlorobis(norbornadiene)dirhodium ($[RhCl(NBD)]_2$),[4] or a rutheinum complex such as dichlorotris(triphenylphosphine)ruthenium ($[RuCl_2(PPh_3)_3]$).[5,6] Employing $[RuCl_2(PPh_3)_3]$ as the catalyst, the quinoline derivatives are also obtained from aminoarenes and allylic alcohols.[6]



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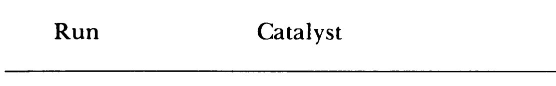


(2)

Although nitroarenes are also important as starting materials for preparations of *N*-heterocycles, few studies have been reported on the synthesis of quinoline derivatives from nitroarenes.[7] We have recently reported that nitroarenes were reductively converted into quinoline derivatives with aliphatic aldehydes in the presence of a rhodium–palladium binary catalyst system (Eq. 1).[8] In that reaction, conditions of water gas shift reaction (carbon monoxide pressure and presence of water) were effective. This reaction made a new entry in quinoline synthesis from nitroarenes.

For the preparation of the quinoline derivatives, we recently offered a new method. Aliphatic alcohols effectively reduced nitroarenes in the presence of a catalytic amount of ruthenium compound and the resulting aldehydes react with the corresponding aminoarenes to give quinoline derivatives (Eq. 2). The preliminary results have been reported with $[RuCl_2(PPh_3)_3]$ as catalyst.[9] Recently, Mares and Boyle published a similar quinoline synthesis from nitroarene and aliphatic alcohols using a binary catalyst, $[Rh(CO)_2Cl]_2$ and $MoCl_5$.[10] This method, however, required a much larger amount of each catalyst (10 mol% each).

In this work, we describe a new finding about a more effective catalyst and give full details of the results.

Results and Discussion

Nitrobenene reacted with aliphatic alcohols in the presence of ruthenium catalyst at 180 °C. Activities of various ruthenium catalysts for this reaction were

TABLE 1. EFFECT OF RUTHENIUM CATALYST PRECURSORS ON THE SYTHESIS OF QUINOLINE DERIVATIVES[a)]

Run	Catalyst	Conversion	Yields of products[b)]/%			
		%	**1a**	**2**	**3a**	**4a**
1	$RuCl_3 \cdot xH_2O$	92	42	9	8	0
2	$RuCl_3 \cdot xH_2O + P(n\text{-}Bu)_3$[c)]	73	12	12	1	0
3	$RuCl_3 \cdot xH_2O + Ph_2P(CH_2)_2PPh_2$[d)]	22	6	4	1	0
4	$RuCl_3 \cdot xH_2O + P(OPh)_3$[c)]	16	2	0	0	tr
5	$[RuCl_2(PPh_3)_3]$	96	28	6	24	6
6	$[RuHCl(CO)(PPh_3)_3]$	91	11	14	7	tr
7	$[Ru(CO)_3(PPh_3)_2]$	97	10	14	13	0
8	$[Ru_3(CO)_{12}]$	95	9	8	25	tr
9	$[RuHCl(PPh_3)_3]$	52	4	5	8	0
10	$[RuH_2(PPh_3)_4]$	60	0	9	3	0

a) Nitrobenzene (40 mmol), 1-propanol (20 ml), ruthenium compound (0.40 mmol) at 180 °C for 4 h. b) Based on nitrobenzene used (GLC analysis): **1a**, 2-ethyl-3-methylquinoline; **2**, aniline; **3a**, *N*-propylaniline; **4a**, *N,N*-dipropylaniline. c) Phosphorus ligand, 2.40 mmol. d) Phosphorus ligand, 1.20 mmol.

TABLE 2. THE SYNTHESIS OF QUINOLINE DERIVATIVES UNDER VARIOUS REACTION CONDITIONS[a)]

Run	Catalyst[b)] (mol%)	Temp	Conversion[c)]	Yields of products[c)]/%			
		°C	%	**1b**	**2**	**3b**	**4b**
11[d)]	1	180	91	(38)[e)]	5	(6)[f)]	(0)[g)]
12	1	180	58	22	0	11	tr
13	3	180	90	56	2	15	2
14	5	180	96	70	0	14	5
15	10	180	94	39	7	3	0
16	5	150	30	5	tr	2	3
17	5	200	100	61	2	9	3
18[h)]	5	180	100	(65)[i)]	tr	(5)[j)]	(8)[k)]

a) Nitrobenzene (40 mmol), 1-butanol (20 ml) for 4 h. b) $RuCl_3 \cdot xH_2O$ based on nitrobenzene used. c) Based on nitrobenzene used (GLC analysis): **1b**, 3-ethyl-2-propylquinoline; **2**, aniline; **3b**, *N*-butylaniline; **4b**, *N,N*-dibutylaniline. d) Ethanol was used as the alcohol. e) 2-Methylquinoline. f) *N*-Ethylaniline. g) *N,N*-Diethylaniline. h) 1-Propanol was used as the alcohol. i) 2-Ethyl-3-methylquinoline. j) *N*-Propylaniline. k) *N,N*-Dipropylaniline.

examined with 1-propanol as the alcohol. The results are summarized in Table 1. The yield of the product, 2-ethyl-3-methylquinoline (**1a**), strongly depends on the catalyst. Among the ruthenium catalysts examined, the highest catalytic activity is attained with ruthenium(III) chloride ($RuCl_3 \cdot xH_2O$). The addition of a phosphrous ligand on $RuCl_3 \cdot xH_2O$ suppressed the formation of the quinoline derivative (Runs 2—4). Dichlorotris(triphenylphosphine)ruthenium had some activity. With other ruthenium complexes, however, the yield of the quinoline was reduced considerably (Runs 6—10). Aniline (**2**), *N*-propylaniline (**3a**), and *N,N*-dipropylaniline (**4a**) were confirmed as the by-products.

Effects of reaction conditions were examined. The results are shown in Table 2. In Runs 12—17, 1-butanol was used as the alcohol. The yield of product, 3-ethyl-2-propylquinoline (**1b**), depends on the amounts of the catalyst. As the amount of catalyst increased from 1 mol% to 5 mol%, based on the amount of nitrobenzene used, the formation of the alkylquinoline was favored. Employing 5 mol% of $RuCl_3 \cdot xH_2O$ as the catalyst, the alkylquinoline was obtained in 70% yield (Run 14). The yield, however, decreased considerably with 10 mol% of the catalyst owing to side reactions. These results indicate that the optimum catalyst concentration is 5 mol%. 2-Ethyl-3-methylquinoline was obtained in 65% yield with 1-propanol with 5 mol% of catalyst concentration (Run 18).

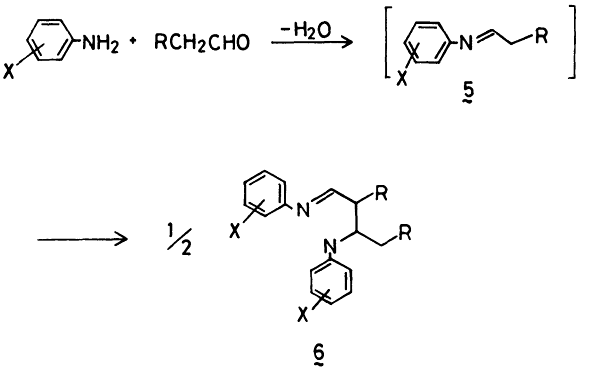
As for the reaction temperature, the best result was realized at 180 °C. By lowering the reaction temperature to 150 °C, the conversion of nitrobenzene and the yield of the quinoline derivative were drastically reduced. The yield of the product was not improved by elevating the reaction temperature to 200 °C.

This procedure is applicable to a variety of nitroarenes. The results obtained with nitrobenzenes with methyl, methoxyl, and chloro substituents at para or ortho positions are listed in Table 3. *p*-Methoxynitrobenzene and *p*-methylnitrobenzene reacted with 1-butanol to give the corresponding 2,3,6-trisubstituted quinoline derivatives in 78 and 58% yield respectively. The chloro substituent reduced the reactivity of the substrate. On the other hand, *o*-substituted nitrobenzenes gave the quinoline derivatives in much lower yields, probably owing to the steric effect (Runs 22 and 23).

TABLE 3. THE RUTHENIUM-CATALYZED REACTION BETWEEN VARIOUS NITROARENES AND 1-BUTANOL

Run	Nitroarenes	Quinolines	
	X[b)]	X (3-Et, 2-Pr)	Yield/%[c)]
19	*p*-OCH_3	6-OCH_3	78
20	*p*-CH_3	6-CH_3	58
21	*p*-Cl	6-Cl	35
22	*o*-CH_3	8-CH_3	35
23	*o*-OCH_3	8-OCH_3	5

a) Nitrobenzene (40 mmol), 1-butanol (20 ml), $RuCl_3 \cdot xH_2O$ (2.0 mmol) at 180 °C for 4 h. b) See Eq. 2. c) Based on nitroarenes used (GLC analysis).



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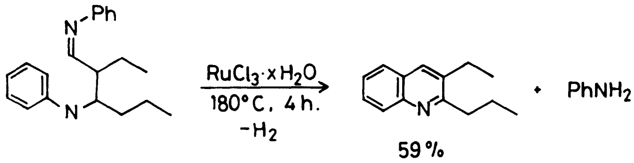
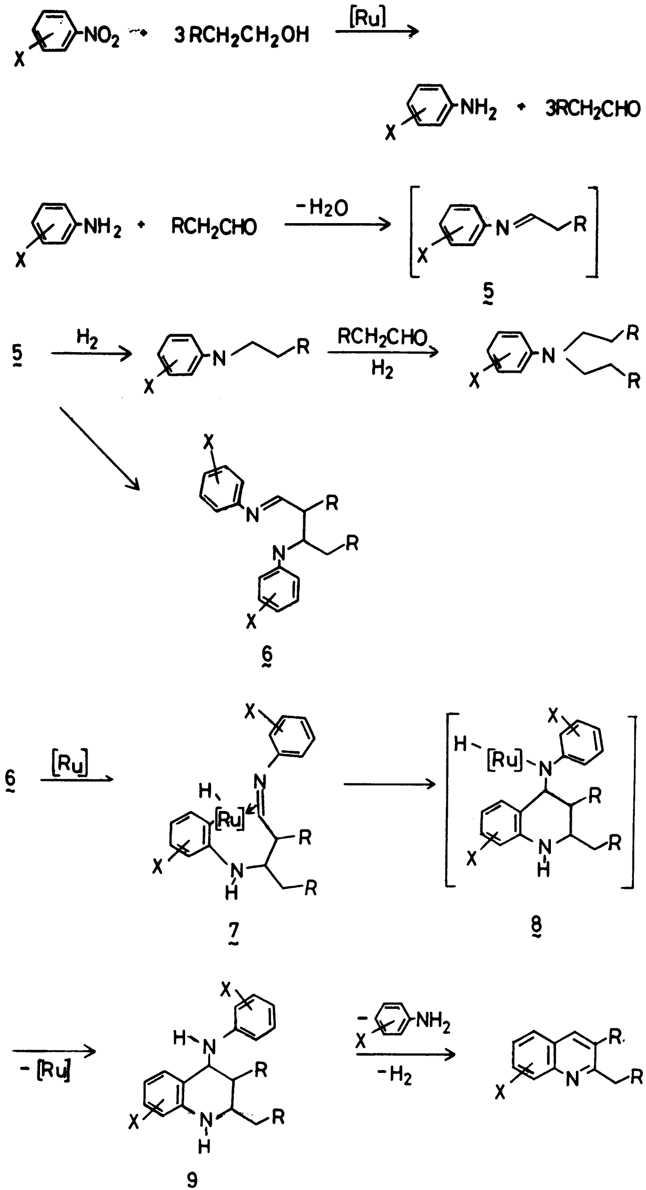


6a

(4)

The group VIII metal complexes such as palladium,[11)] rhodium,[12)] and ruthenium[13)] complexes catalyze the hydrogen transfer reaction from alcohols to various hydrogen acceptors. Several novel metal salts such as $RuCl_3 \cdot 3H_2O$, $RhCl_3 \cdot 3H_2O$, $PdBr_2$, and $PdCl_2$



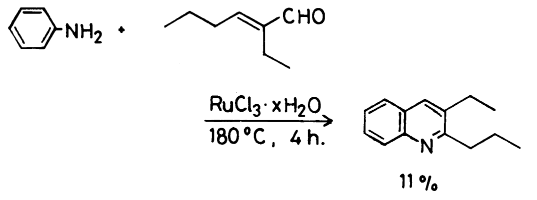
Scheme 1.

catalyze the hydrogen transfer from cyclic amines to nitrobenzenes to give corresponding aniline derivatives.14)

In this study, the reaction appears to include reduction of nitroarenes with the alcohols by the catalytic hydrogen transfer from the alcohols, generating aminoarenes and aldehydes *in situ* (see the first equation in Scheme 1). Thus the alcohols play roles as both the reductants and aldehyde precursors in these reactions. The alkylquinolines would be formed by the ruthenium catalyzed reaction of the aminoarenes with the aldehydes. Actually, aminoarenes react with aliphatic aldehydes to the corresponding quinoline derivatives in the presence of ruthenium catalysts, as previously reported.5,6)

It is well known that aminoarene reacts with aliphatic aldehyede to give a Schiff-base dimer on simply mixing at room temperature (Eq. 3).15,16) In the previous paper,6) we have suggested that the *N*-heterocyclization to the quinoline derivatives proceeds *via* these Schiff-base dimers (**6**). In a separate reaction, 3-ethyl-2-propylquinoline is obtained in 59% yield in the presence of $\mathrm{RuCl_3 \cdot \mathit{x}H_2O}$ from the corresponding Schiff-base dimer (**6a** R=Et, X=H)(Eq. 4). Therefore, we consider that the present reaction also proceeds *via* a Schiff-base dimer (**6**). (Alkylamino)- and (dialkylamino)arenes were also obtained as by-products (Tables 1 and 2). These products could be formed *via* a Schiff-base monomer (**5**).5) Such a Schiff-base monomer is liable to dimerize. The Schiff-base monomer could not be obtained and only the Schiff-base dimer (**6**) was isolated.15,16) The Schiff-base dimer (**6**) may be activated at an elevated temperature by so called orthometallation (**7**)17–23) as suggested in the previous paper,6) and transformed into the corresponding quinoline derivative. The catalyst appears to be operative in the cyclization step (**7**→**8**), since (**6**) was obtained without catalyst and even at room temperature.

3-Ethyl-2-propylquinoline was also obtained in much lower yield from aniline and 2-ethyl-2-hexenal, an aldol condensate of butanal, in the presence of $\mathrm{RuCl_3 \cdot \mathit{x}H_2O}$ (Eq. 5). Therefore the path *via* aldol condensation followed by Michael addition of aniline may be an alternative acceptable path in the present reaction (Scheme 2). Mares *et al.* suggested the path described in Scheme 2 as the most likely route, without positive evidence.10)



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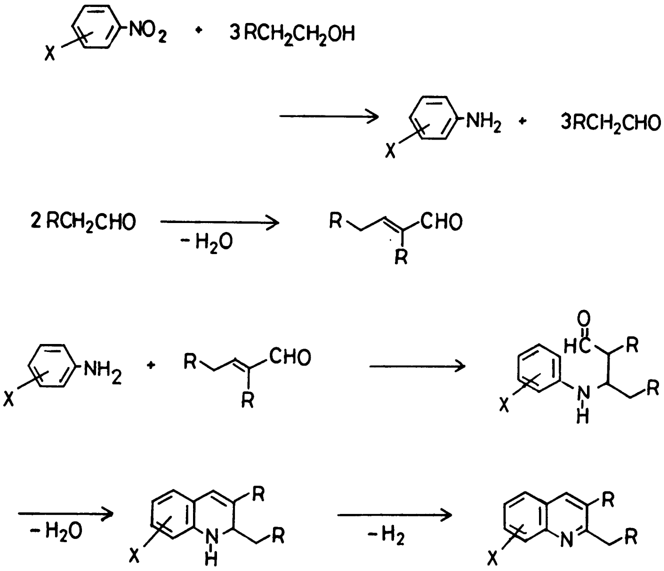

Scheme 2.

Thus, $\mathrm{RuCl_3 \cdot \mathit{x}H_2O}$ is the effective catalyst for converting nitroarenes into quinoline derivatives with alcohols. In the reaction, the alcohol plays roles as both a reductant and an aldehyde precursor.

Experimental

Materials. The alcohols, the nitroarenes, and the phosphorus ligands were commercial materials and were purified by distillation or recrystallization before use. Ruthenium(III) chloride ($RuCl_3 \cdot xH_2O$, mainly $x=3$) was purchased from Wako Chemical and used without further purification. $[RuCl_2(PPh_3)_3]$,[24] $[RuHCl(PPh_3)_3]$,[25] $[RuHCl(CO)(PPh_3)_3]$,[26] $[RuH_2(PPh_3)_4]$,[27] $[Ru(CO)_3(PPh_3)_2]$,[26] and $[Ru_3(CO)_{12}]$[28] were prepared by published methods. 2-Ethyl-2-hexenal was prepared from butanal.[29] The Schiff-base dimer (**6a**) was synthesized with aniline and butanol by the method in the literature.[16]

Analytical Procedure. The ^1H-NMR spectra were obtained at 100 MHz with a JEOL JNM FX-100 or at 220 MHz with a Varian HR-220 spectrometer. The ^{13}C-NMR spectra were recorded at 25.05 MHz with a JEOL JNM FX-100 spectrometer, with tetramethylsilane as an internal standard. IR spectra were measured on a Hitachi model 215 grating spectrometer. Elemental analysis was performed at the Microanalytical Center of Kyoto University. The mass spectra were recorded on a JMS OISG mass spectrometer. The GLC analysis was performed on a Shimadzu-GC-3BT.

Reaction Procedure. An autoclave (100 ml; SUS 316) equipped with a magnetically driven stirrer was used in the reaction. A typical reaction with 1-butanol and nitrobenzene is described here to exemplify the general procedure adopted. A mixture of nitrobenzene (4.9 g, 40 mmol), 1-butanol (20 ml), and $RuCl_3 \cdot xH_2O$ (487 mg, 2.0 mmol, 5 mol% based on nitrobenzene used) was stirred under an argon atmosphere. The autoclave was heated in 20 min to 180 °C and held at this temperature for 4 h. After cooling, the autoclave was discharged and the reaction mixture was subjected to the GLC analysis with Apiezon Grease L supported on Neopak 1A 60—80 mesh (0.3 cmϕ×3 m). The products were isolated by vacuum fractional distillations. If the products were contaminated with other products, further purification was performed by means of medium pressure column chromatography (absorbent; Silica Gel 60, 0.040—0.063 mm, 230—400 mesh, Merck No. 9385: eluent; a mixture of hexane and ethyl acetate). The products were identified by means of ^1H-NMR, ^{13}C-NMR, IR, mass spectra, and elemental analysis. The identifications are confirmed by comparing the analytical date with those published elsewhere.[4—6] The conversion of the substrate and the yield of the product were determined by the internal standard method accordng to the calibration curve obtained for each sample. Biphenyl or triphenylmethane was employed as the internal standard.

Synthesis of 3-Ethyl-2-propylquinoline from Schiff-base Dimer (6a) A solution of **6a** (3.979 g, 13.5 mmol) in benzene (20 ml) was stirred under an argon atmosphere in the presence of nitrobenzene (1.546 g, 12.6 mmol) and $RuCl_3 \cdot xH_2O$ (299 mg, 1.23 mmol, 5 mol% based on nitrogen atom) at 180 °C for 4 h. The GLC analysis of the reaction mixture showed that 8.0 mmol (59% based on **6a**) of 3-ethyl-2-propylquinoline was formed.

Reaction of Aniline with 2-Ethyl-2-hexenal. A mixture of aniline (2.150 g, 23.1 mmol), 2-ethyl-2-hexenal (2.926 g, 23.2 mmol), benzene (10 ml), $RuCl_3 \cdot xH_2O$ (1.11 mmol, 4.8 mol% based on aniline), and nitrobenzene (2.625 g, 21.3 mmol) was stirred at 180 °C for 4 h. By the GLC analysis of the reaction products, 2.6 mmol (11% based on aniline) of 3-ethyl-2-propylquinoline was detected.

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