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Ruthenium-Catalyzed Synthesis of Quinolines from Anilines and Allylammonium Chlorides in an Aqueous Medium via Amine Exchange Reaction

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Abstract—Anilines react with allylammonium chlorides in an aqueous medium (H_2O–dioxane) in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ together with $SnCl_2{\cdot}2H_2O$ to give the corresponding quinolines in moderate to good yields. The existence of $SnCl_2{\cdot}2H_2O$ is necessary for the effective formation of quinolines, and a reaction pathway involving amine exchange reaction between anilines and allylammonium chlorides to form an imine is proposed for this catalytic process.

Introduction

It is well known that quinoline nucleus plays an important role as an intermediate for the design of many antimalarial compounds. Various named reactions such as the Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses are commonly used routes for the formation of quinolines. In contrast to the conventional syntheses which frequently require harsh and cumbersome acidic reaction conditions, the formation of quinoline skeletons also has been attempted by a remarkable catalytic action of transition metal catalysts such as palladium,[1] rhodium,[2] ruthenium,[3] and iron.[4] As part of our continuing studies on transition metal-catalyzed synthesis of *N*-heterocyclic compounds, we recently developed and reported a novel ruthenium-catalyzed synthetic approach for the formation of indoles[5–8] and quinolines[9,10] via a mechanistic amine exchange reaction between anilines and funtionalized aliphatic amines.[11] However, a clear-cut example for the synthesis of *N*-heterocyclic compounds using amine exchange reaction seems to be limited to palladium-catalyzed synthesis of pyrimidines and imidazoles[11d] and aforementioned our indoles and quinolines. We here report another ruthenium-catalyzed approach for the synthesis of quinolines from an array of anilines and allylammonium chlorides in an aqueous medium via amine exchange reaction.

Keywords: ruthenium; catalyst; cyclization; quinolines; aqueous medium.
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Results and Discussion

The several results of the ruthenium-catalyzed heteroannulation between aniline (**1a**) and *N*,*N*-diallyl-*N*,*N*-dipropylammonium chloride (**2a**) under various reaction conditions are listed in Table 1 (Scheme 1). The reaction was performed under analogous reaction conditions such as the molar ratio of **1a** to **2a** and the amount of $SnCl_2{\cdot}2H_2O$ as has been optimized in our recent ruthenium-catalyzed synthesis of indoles and quinolines.[6–10] In all cases, *N*-propylaniline (**4**) was formed as a side product by an alkyl group transfer between **1a** and **2a** and hydrogenation under the ruthenium catalyst. As shown in Table 1, the yield of 2-ethyl-3-methylquinoline (**3a**) was considerably affected by solvent system, the aqueous medium of H_2O/dioxane (1/9) being shown to be best for obtaining **3a** (runs 1–4). Dioxane could be alternatively used as solvent, whereas the yield of **4** was higher than that when an aqueous medium was used (run 5). The existence of $SnCl_2{\cdot}2H_2O$ was necessary for the effective formation of **3a** as has been observed in our ruthenium-catalyzed synthesis of indoles and quinolines, the yield of **3a** being 47% in the absence of $SnCl_2{\cdot}2H_2O$ for a longer reaction time (run 6). A variety of phosphorus chelating and phosphite ligands combined with $RuCl_3{\cdot}nH_2O$ can also be used in place of PPh_3, but the yield of **3a** was generally lower than when PPh_3 was used (runs 7–11). Among catalyst precursors examined, $RuCl_2(PPh_3)_3$ exhibited nearly the same catalytic activity as $RuCl_3{\cdot}nH_2O/3PPh_3$ under the employed reaction conditions (runs 12–14) and the formation of *N*-propylaniline was suppressed in comparison to the catalytic activity of $RuCl_3{\cdot}nH_2O/3PPh_3$.

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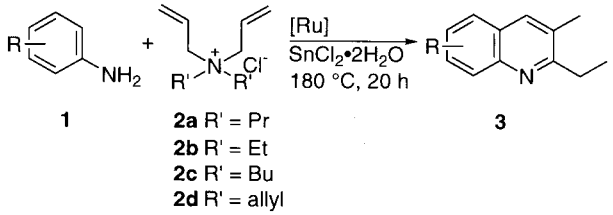
Table 1. Ruthenium-catalyzed synthesis of **3a** from **1a** and **2a** under various conditions (except as noted, all reaction were carried out with **1a** (6 mmol), **2a** (1 mmol), ruthenium catalyst (5 mol% based on **2a**), and $SnCl_2{\cdot}2H_2O$ (1 mmol) at 180°C)

Run	Ruthenium catalysts	H_2O/Dioxane (mL/mL)	*t*(h)	Products and yield (%)[a]	
				3a	**4**
1	$RuCl_3{\cdot}nH_2O/3PPh_3$	1/9	20	69	51
2	$RuCl_3{\cdot}nH_2O/3PPh_3$	5/5	24	45	2
3	$RuCl_3{\cdot}nH_2O/3PPh_3$	9/1	24	4	5
4	$RuCl_3{\cdot}nH_2O/3PPh_3$	10/0	24	5	6
5	$RuCl_3{\cdot}nH_2O/3PPh_3$	0/10	24	69	81
6[b]	$RuCl_3{\cdot}nH_2O/3PPh_3$	1/9	30	47	17
7	$RuCl_3{\cdot}nH_2O$/1.5dppm	1/9	20	57	28
8	$RuCl_3{\cdot}nH_2O$/1.5dppe	1/9	20	57	33
9	$RuCl_3{\cdot}nH_2O$/1.5dppp	1/9	20	48	18
10	$RuCl_3{\cdot}nH_2O$/1.5dppf	1/9	20	44	12
11	$RuCl_3{\cdot}nH_2O/3P(OEt)_3$	1/9	20	40	24
12	$RuH_2(PPh_3)_4$	1/9	20	48	31
13	$RuCl_2(PPh_3)_3$	1/9	20	74	11
14	$Ru_3(CO)_{12}$	1/9	20	4	55

[a] Determined by GLC based on **2a**.
[b] In the absence of $SnCl_2{\cdot}2H_2O$.

From the reaction of an array of anilines (**1b**–**1m**) with allylammonium chlorides (**2a**–**2d**) the corresponding quinolines (**3b**–**3m**) were also formed in good yields, and several representative results are summarized in Table 2. All reactions were also accompanied by the formation of *N*-propylanilines as a side product. The quinoline yield was not decisively affected by the substituent effect in the aniline derivatives. However, the product yield was generally lower in the use of *ortho*-substituted anilines than in the employment of *meta*- and *para*-substituted anilines.[12] In the cases of *meta*-substituted anilines such as *m*-toluidine (**1c**) and *m*-anisidine (**1f**), the corresponding quinolines (**3c** and **3f**) were obtained as a regioisomeric mixture, favoring 7-substituted isomers which were formed via less sterically hindered position on *meta*-substituted anilines. As shown in Table 2, the reaction of an array of anilines with tetraallylammonium chloride (**2d**) under the identical reaction conditions afforded the corresponding quinolines **3** in higher yields as compared with that in the reaction with allylammonium chlorides **2a**–**2c**.

Although the details of the present reaction pathway including the role of $SnCl_2{\cdot}2H_2O$ are not yet fully understood, a plausible pathway is presented is Scheme 2.[13] The reaction seems to proceed via an initial formation of imines by ruthenium-catalyzed amine exchange reactions between anilines and allylammonium chlorides. It is well-known that the intermolecular alkyl group transfer between alkylamines proceeds through iminium ion complex under transition metals such as palladium and ruthenium.[11] Thus, the transfer of allylic moiety from **2** to **1a** can be rationalized by *Cycle A* in



1 **2a** R' = Pr, **2b** R' = Et, **2c** R' = Bu, **2d** R' = allyl → **3**

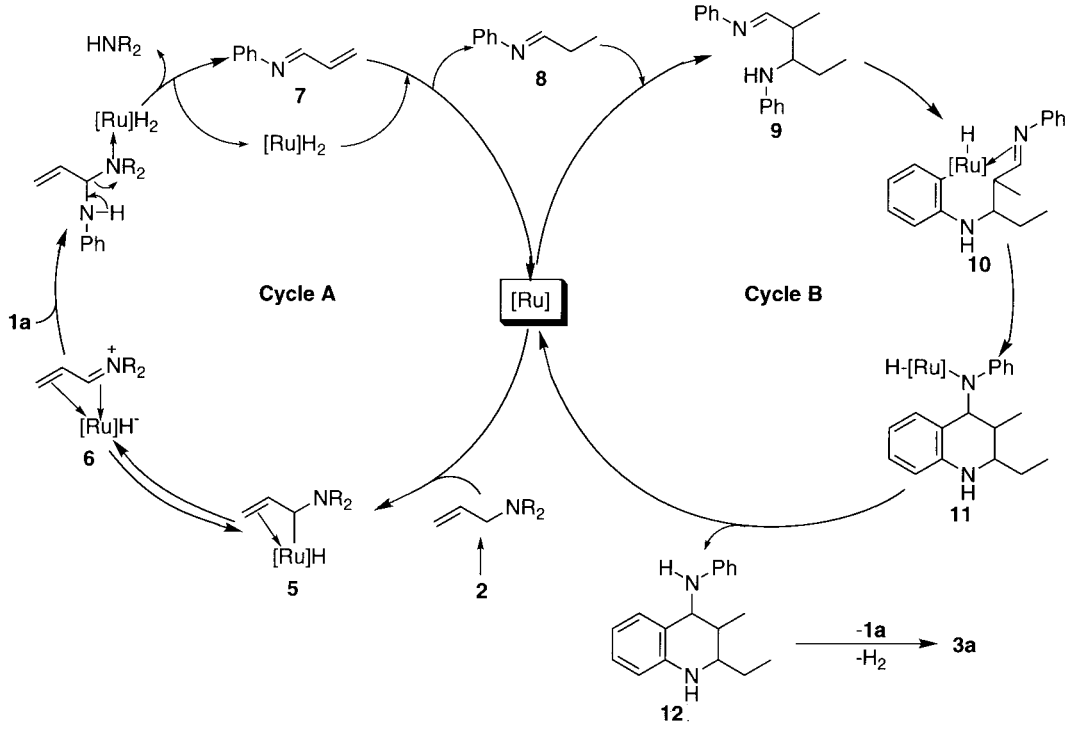
Scheme 1.

Scheme 2. Quaternary ammonium salt **2** seems to be converted into tertiary amine by cleavage of the carbon–nitrogen bond in an aqueous medium.[14] The initial coordination of tertiary amine to ruthenium followed by oxidative insertion of ruthenium in the adjacent C–H bond forms an alkylruthenium complex **5**, which rapidly equilibrates with an iminium ion complex **6**. Nucleophilic attack of **1a** to the complex **6** gives α,β-unsaturated imine **7** along with $[Ru]H_2$. This is followed by selective reduction of **7** by $[Ru]H_2$ to afford imine **8**. Subsequent steps seem to proceed via the known Schiff-base dimerization and

Table 2. Ruthenium-catalyzed synthesis of **3** from **1** and **2** (all reactions were carried out with **1** (6 mmol), **2** (1 mmol), $RuCl_2(PPh_3)_3$ (5 mol% based on **2**), and $SnCl_2{\cdot}2H_2O$ (1 mmol) in H_2O–dioxane (=1 mL/9 mL) at 180°C for 20 h)

1 (R=)	**2**	**3** (R=)	Yield (%)[a]
H (**1a**)	**2a**	H (**3a**)	57
4-Me (**1b**)	**2a**	6-Me (**3b**)	64
3-Me (**1c**)	**2a**	5- and 7-Me (**3c**)	48[b]
2-Me (**1d**)	**2a**	8-Me (**3d**)	45
4-OMe (**1e**)	**2a**	6-OMe (**3e**)	58
3-OMe (**1f**)	**2a**	7-OMe (**3f**)	50[c]
4-Cl (**1g**)	**2a**	6-Cl (**3g**)	34
4-Et (**1h**)	**2a**	6-Et (**3h**)	62
2-Et (**1i**)	**2a**	8-Et (**3i**)	23
4-Bu (**1j**)	**2a**	6-Bu (**3j**)	62
4-*sec*-Bu (**1k**)	**2a**	6-*sec*-Bu (**3k**)	66
3,5-Me (**1l**)	**2a**	5,7-Me (**3l**)	62
4-Acetyl (**1m**)	**2a**	6-Acetyl (**3m**)	63
1a	**2b**	**3a**	37
1a	**2c**	**3a**	33
1a	**2d**	**3a**	93
1b	**2d**	**3b**	82
1d	**2d**	**3d**	74
1e	**2d**	**3e**	86
1g	**2d**	**3g**	48
1k	**2d**	**3k**	91

[a] Isolated yield based on **2**. In almost all cases *N*-propylanilines (<15%) were formed.
[b] Regioisomeric ratio was determined by ^1H NMR (300 MHz): 2-ethyl-3,7-dimethylquinoline/2-ethyl-3,5-dimethylquinoline=9/1.
[c] Even if 2-ethyl-5-methoxy-3-methylquinoline is present, its amount is a trace.



Scheme 2.

ruthenium-mediated heteroannulation shown in *Cycle B* in Scheme 2. It is known that anilines react with aliphatic aldehyde to give Schiff-base dimer on simple mixing at room temperature.[15] Watanabe et al. reported that the Schiff-base dimer **9** was cyclized to give quinolines under ruthenium catalyst through oxidative addition of the ortho C–H bond of **9** to low valent ruthenium via orthometallation, insertion of C=N double bond into Ru–C bond of **10**, reductive elimination of **11**, and deamination and dehydrogenation of **12**.[3c] A similar catalytic cycle has already been proposed in ruthenium-catalyzed synthesis of indoles and quinolines by us.

On the other hand, when *N*,*N*-dibutyl-*N*,*N*-dicrotylammonium chloride was used as cyclization counterpart in the reaction with **1a** under the same reaction conditions, the reaction did not proceed satisfactory toward quinoline formation (the yield of 3-ethyl-2-propylquinoline=9%), instead, much more *N*-monoalkylated aniline was produced (the yield of *N*-butylaniline=91%). Similar treatment of **1a** with tetrabutylammonium bromide under identical reaction conditions afforded 3-ethyl-2-propylquinoline in 11% yield together with *N*-butylaniline (33%). This result indicates that the propyl moiety of **2a** also participates in the formation of quinolines.

In summary, we have demonstrated that quinolines can be synthesized by reaction of an array of anilines with allylammonium chlorides in the presence of a ruthenium catalyst in an aqueous medium. The present aquatic heteroannulation is a novel synthetic approach leading to quinolines via an amine exchange reaction. We believe that this aquatic process combined with a mechanistic amine exchange reaction will be successfully applied for the synthesis of other *N*-heterocyclic compounds.

Experimental

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Unity Plus 300 spectrometer using TMS as an internal standard. Chemical shift are reported in δ units downfield from TMS. GLC analyses were carried out with Shimadzu GC-17A equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm×25 m, 0.25 μm film thickness) using N_2 as carrier gas. The isolation of pure products was carried out with column chromatography (silica gel 60, 70–230 mesh, Merck). $RuH_2(PPh_3)_4$,[16] $RuCl_2(PPh_3)_3$,[17] and $Ru_3(CO)_{12}$[18] were prepared by the reported method.

Typical procedure for ruthenium-catalyzed synthesis of quinolines from anilines and allylammonium chlorides

A mixture of aniline (0.559 g, 6 mmol), *N*,*N*-diallyl-*N*,*N*-dipropylammonium chloride (0.218 g, 1 mmol), $RuCl_2(PPh_3)_3$ (0.048 g, 0.05 mmol) and $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in H_2O–dioxane (1 mL/9 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 20 h. The reaction mixture was passed through a short silica gel column, poured into brine, extracted with $CHCl_3$ and dried over Na_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (ethyl acetate–hexane mixture) to give 2-ethyl-3-methylquinoline (0.098 g, 57%). All compounds are known except for **3i** and **3m**.[2d,8b]

2,8-Diethyl-3-methylquinoline (3i). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J=7.5 Hz, 3H), 1.41 (t, J=7.5 Hz, 3H), 2.41 (s, 3H), 2.95 (q, J=7.5 Hz, 2H), 3.30 (q, J=7.5 Hz, 2H), 7.33 (t, J=7.8 Hz, 1H), 7.43 (br d, J=6.3 Hz, 1H), 7.51 (dd, J=7.8, 1.2 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.9, 15.0, 18.9, 24.7, 29.1, 124.5, 125.3, 126.5, 127.1, 129.0, 135.4, 142.5, 144.9, 161.1. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37, H, 8.60; N, 7.03. Found: C, 84.01; H, 8.48; N, 6.87.

6-Acetyl-2-ethyl-3-methylquinoline (3m). White solid (hexane); mp 86–88°C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J=7.5 Hz, 3H), 2.36 (s, 3H), 2.57 (s, 3H), 2.87 (q, J=7.5 Hz, 2H), 7.75 (s, 1H), 7.91 (d, J=8.7 Hz, 1H), 8.02 (dd, J=8.7, 1.8 Hz, 1H), 8.17 (d, J=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.3, 18.9, 26.5, 29.4, 126.2, 126.4, 128.7, 128.8, 130.4, 133.9, 136.6, 148.4, 165.7, 197.4; MS m/z (relative intensity) 213 (M^+, 93), 212 (100). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84, H, 7.09; N, 6.57. Found: C, 78.69; H, 7.00; N, 6.39.

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12. In contrast to the present aquatic process, similar ruthenium-catalyzed reaction between *o*-toluidine and triallylamine in an organic medium failed to form quinoline, whereas *N*-allyl-*o*-toluidine was only detectable product.[9]

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