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Ruthenium-catalyzed synthesis of indoles from anilines and trialkanolammonium chlorides in an aqueous medium

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Abstract

Anilines react with trialkanolammonium chlorides in an aqueous medium (H₂O–dioxane) at 180°C in the presence of a catalytic amount of ruthenium(III) chloride hydrate and triphenylphosphine together with tin(II) chloride dihydrate to afford the corresponding indoles in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

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It is well-known that indole skeletons play an important role as an intermediate for the design of many pharmacologically active compounds.¹ The Fischer, Madelung, Bischler, and related syntheses are the most commonly used routes for the construction of the structural core of indoles and have been extensively reviewed. Recently, in contrast to the conventional synthesis, the formation of indole skeletons has also been attempted by a remarkable catalytic action of transition metal catalysts such as palladium,^{2–6} ruthenium,^{7–12} and rhodium^{13–15} utilizing various substrates. 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^{16–18} and quinolines^{19,20} from anilines and functionalized aliphatic amines. It was suggested that all reactions proceed via amine exchange reactions^{21–24} between anilines and functionalized aliphatic amines. However, a clear-cut example for the synthesis of *N*-heterocyclic compounds using amine exchange reactions seems to be limited to the palladium-catalyzed synthesis of pyrimidines and imidazoles²⁴ and ruthenium-catalyzed synthesis of indoles^{16–18} and quinolines.^{19,20} We now report a first ruthenium-catalyzed approach for the synthesis of 1,2,3-unsubstituted indoles from primary aromatic amines and trialkanolammonium chlorides in an aqueous medium via amine exchange reaction.

The several results of the ruthenium-catalyzed heteroannulation between aniline (**1**) and triethanolammonium chloride (**2**) under various conditions are listed in Table 1. Treatment of **1** with **2** in H₂O:dioxane (1:9) under an argon atmosphere in the presence of a catalytic amount of RuCl₃·*n*H₂O/PPh₃ together with

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$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ at 180°C for 20 h afforded indole (**3**) in 63% yield (Eq. (1)). The reaction condition was eventually revealed to be the best for obtaining **3** (run 1). The yield of **3** was considerably affected by the molar ratio of **1** to **2**, the highest yield of **3** being obtained at the molar ratio of 10 (runs 2–5). The existence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ was essential for the effective formation of **3** as has been observed in our recent ruthenium-catalyzed synthesis of indoles^{18,25} and quinolines,^{19,20} the yield of **3** being only 32% in the absence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (run 6). The use of either dioxane or H_2O and reverse amount of $\text{H}_2\text{O}/\text{dioxane}$ stopped the reaction almost completely (runs 7–9).

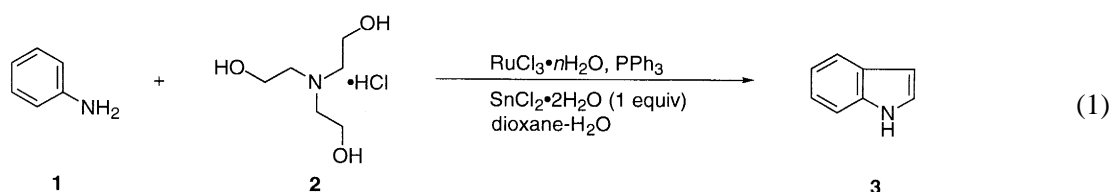


Table 1
Ruthenium-catalyzed synthesis of **3** from **1** and **2** under various conditions^a

Run	Molar ratio of 1/2	$\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (mmol)	$\text{H}_2\text{O}/\text{dioxane}$ (mL/mL)	Time (h)	Yield (%) ^b
1	10	0.1	1/9	20	63
2	10	0.05	1/9	20	37
3	6	0.05	1/9	6	11
4	6	0.05	1/9	20	26
5	6	0.1	1/9	20	39
6	10	0.1	1/9	20	32 ^c
7	6	0.1	0/10	20	1
8	6	0.1	10/0	20	0
9	6	0.1	9/1	20	1

^a All reactions were carried out with **2** (1 mmol), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1 mmol) and PPh_3 (3 times as molar amount as $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$) unless otherwise stated. ^b GLC yield based on **2**. ^c In the absence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$.

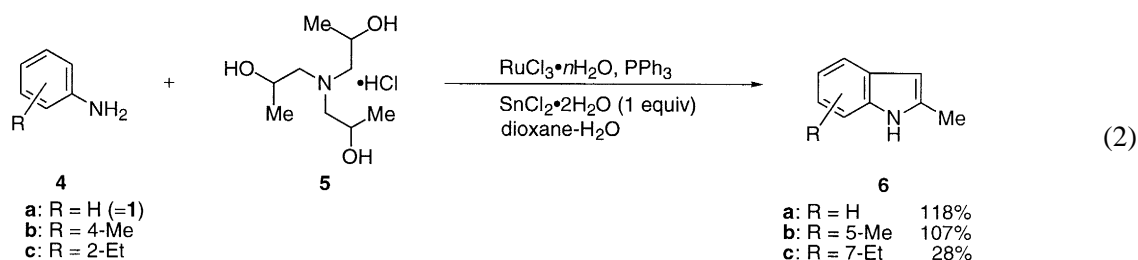
From other easily available anilines the corresponding indoles were also formed in good yields, several representative results being summarized in Table 2. The indole yield was considerably affected by the electronic nature and position of the substituent on aniline. With chloroanilines having electron-withdrawing Cl substituents, the product yields were generally lower than when anilines having electron-donating characters were used (runs 2–8). With *ortho*- and *meta*-substituted anilines, the indole yields were higher than when *para*-substituted anilines were used (runs 2–4, 7, 8). In the case of two-methyl substituted anilines, the reaction proceeded quite well even with the use of 5 mol% of ruthenium catalyst when compared to mono-substituted anilines as has been observed in our recent report (runs 9–11).¹⁸ The formation of >100% yields of indoles indicates that at least two alkanol groups out of three in **2** are available for the C_2 -fragment counterpart.

Interestingly, similar treatment of anilines **4** with triisopropanolammonium chloride (**5**) under identical reaction conditions afforded 2-methyl substituted regioisomers almost exclusively, no 3-methyl isomers being detected on both GLC and ^1H NMR (Eq. (2)). As is the case for the reaction with **2**, however, in a different manner, the product yield was also affected by the position of the substituent on aniline.

Table 2
Ruthenium-catalyzed synthesis of indoles from anilines and triethanolammonium chloride (2)^a

Run	Aniline	Indole	Yield ^b (%)	Run	Aniline	Indole	Yield ^b (%)
1			57	7			87
2			48	8			49
3			98 ^c	9			68 ^d
4			80	10			107 ^d
5			43	11			169 ^d
6			16	12			21

^a All reactions were carried out with aniline (10 mmol), **2** (1 mmol), RuCl₃•*n*H₂O (0.1 mmol), PPh₃ (3 times as molar amount as RuCl₃•*n*H₂O), SnCl₂•2H₂O (1 mmol) in dioxane/H₂O (9 mL/1 mL) at 180 °C for 20 h unless otherwise stated. ^b Isolated yield based on **2**. ^c Isomeric molar ratio was determined by ¹H NMR (300 MHz): 4-methyl indole:6-methylindole = 1:1.8 ^d RuCl₃•*n*H₂O (0.05 mmol).



The initial formation of 2-anilinoethanols by amine exchange reactions^{21–24} between anilines and trialkanolammonium chlorides seems to be a key step as has been observed in our recent ruthenium-catalyzed synthesis of indoles and quinolines from anilines and functionalized aliphatic amines.^{16–20} Subsequent steps seem to proceed via a similar catalytic cycle to that which has already been proposed in ruthenium-catalyzed synthesis of indoles from anilines and ethylene glycols.⁸

A typical experimental procedure is as follows: A mixture of aniline (**1**) (10 mmol), triethanolam-

monium chloride (**2**) (1 mmol), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ ($n=3$, 0.1 mmol), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1 mmol) and PPh_3 (0.3 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 poured into an aqueous 5% HCl solution to remove excess aniline, and extracted with chloroform. The organic layer was filtered through a short silica gel column. Removal of the solvent left an oil which was separated by column chromatography using an ethyl acetate/hexane mixture as an eluent to give indole (**3**) in 57% yield.

In summary, we have shown that indoles can be synthesized from anilines and trialkylammonium chlorides in the presence of a ruthenium catalyst in an aqueous medium. Although several reports are known for the synthesis of *N*-heterocyclic compounds using amine exchange reactions in organic media, the present aquatic process is a first synthetic approach for *N*-heterocyclic compounds using 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.

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