Ruthenium-catalysed synthesis of indoles from anilines and trialkanolamines in the presence of tin(II) chloride dihydrate

Chan Sik Cho, Hyo Kyun Lim, Sang Chul Shim,*† Tae Jeong Kim and Heung-Jin Choi

Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea

Anilines react with trialkanolamines in dioxane in the presence of a catalytic amount of a ruthenium catalyst together with tin(II) chloride dihydrate to give the corresponding indoles in moderate to good yields.

Transition metal-catalysed cyclisation reactions have been a useful and convenient method for the formation of a wide variety of heterocycles. Thus, the formation of the structural core of indoles has also been attempted using transition metal catalysts[1] since several naturally occurring indoles exert a broad spectrum of physiological activities.[2] As part of our continuing studies on transition metal-catalysed synthesis of *N*-heterocyclic compounds,[3] we have recently developed and reported a novel ruthenium-catalysed synthesis of *N*-alkylindoles from *N*-alkylated anilines and triethanolamine as the C_2-fragment.[4] However, aniline did not act as a cyclisation counterpart in the formation of indole itself under the ruthenium-catalysed system. After numerous attempts were made to achieve the formation of indoles from the primary aromatic amines under the reaction system used, eventually, it was found that the addition of tin(II) chloride dihydrate allows the formation of indoles. We now report a facile synthesis of indoles from readily available primary aromatic amines and triethanolamine in the presence of a ruthenium catalyst together with $SnCl_2·2H_2O$.

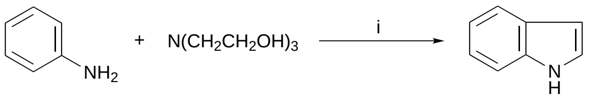
We examined the cyclisation between aniline (**1**) and triethanolamine (**2**) in the presence of $SnCl_2·2H_2O$ to optimise the reaction conditions using similar catalytic systems which we employed for the synthesis of *N*-alkylindoles. The yield of indole (**3**) was considerably affected by the molar ratio of **1** to **2** as has been observed in our recent report (Scheme 1).[4] Table 1 shows that the highest yield of **3** was obtained at the molar ratio of 10. The reaction was also affected by the amount of $SnCl_2·2H_2O$. The use of equimolar amounts of **2** and $SnCl_2·2H_2O$ resulted in the best yield of **3**. A decrease in the amount of $SnCl_2·2H_2O$ afforded **3** in a lower yield, but the yield of **3** did not change with an increase in the amount of $SnCl_2·2H_2O$ employed. However, the reaction did not proceed at all without $SnCl_2·2H_2O$. The effect of several metallic halides other than $SnCl_2·2H_2O$ upon this cyclisation was examined. As shown in Table 1, all the salts except for iron(III) chloride examined were moderately effective in the formation of **3**, but $FeCl_3$ exhibited nearly the same activity as $SnCl_2·H_2O$ under the reaction conditions employed.

Table 1 Ruthenium-catalysed synthesis of indole (**3**) under various conditions[a]

Molar ratio (**1** : **2**)	Metallic halides (mmol)	GLC yield (%)[b]
4	$SnCl·2H_2O$ (1)	30
6	$SnCl·2H_2O$ (1)	29
8	$SnCl·2H_2O$ (1)	30
10	$SnCl·2H_2O$ (1)	52
10	$SnCl·2H_2O$ (0.5)	25
10	$SnCl·2H_2O$ (2.0)	51
10	—	Trace
10	$AlCl_3$ (1)	20
10	$SbCl_3$ (1)	16
10	$BiCl_3$ (1)	7
10	$LaCl_3$ (1)	7
10	$FeCl_3$ (1)	52
10	$ZnCl_2$ (1)	15

[a] All reactions were carried out with **2** (1 mmol), $RuCl_3·nH_2O$ (7 mol% based on **2**), and PPh_3 (2 mol% based on **2**) in dioxane (10 ml) at 180 °C for 20 h. [b] Based on **2**.

The present cyclisation could also be applied to many primary aromatic amines, several representative results being summarised in Table 2.‡ The product yield was dependent on the electronic nature of the substituent on anilines. With anilines such as toluidine and anisidine, having electron-donating character, the product yield was generally higher than that when chloroanilines having electron-withdrawing Cl substituent were used (runs 2–8). In the cases of *meta*-substituted anilines such as *m*-toluidine and *m*-anisidine, the corresponding indoles were obtained as a regioisomeric mixture in good yields (runs 3 and 5). The enhancement of reactivity of the two-methyl substituted anilines is interesting when compared to the reactivity of the mono-substituted anilines (runs 10–12). However, in the case of 2,5-dimethoxyaniline, the corresponding indole was obtained only in 15% yield (run 13).



1 **2** **3**

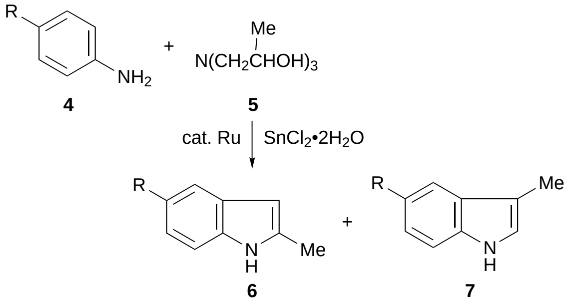
Scheme 1 *Reagents and conditions*: i, $RuCl_3·nH_2O$, PPh_3, $SnCl_2·2H_2O$, dioxane, 180 °C, 20 h

Similar treatment of anilines **4** with tri(propan-2-ol)amine (**5**) under the above reaction system afforded two regioisomeric

Table 2 Ruthenium-catalysed synthesis of various indoles[a]

Run	Anilines	Indoles	Isolated yield (%)[b]
1	Aniline	Indole	46
2	*o*-Toluidine	7-Methylindole	66
3	*m*-Toluidine	4- and 6-Methylindole	65[c]
4	*p*-Toluidine	5-Methylindole	38
5	*m*-Anisidine	4- and 6-Methoxyindole	47[c]
6	*p*-Anisidine	5-Methoxyindole	33
7	*o*-Chloroaniline	7-Chloroindole	9
8	*p*-Chloroaniline	5-Chloroindole	21
9	*p*-Isopropylaniline	5-Isopropylindole	56
10	2,3-Dimethylaniline	6,7-Dimethylindole	99
11	2,5-Dimethylaniline	4,7-Dimethylindole	86
12	3,5-Dimethylaniline	4,6-Dimethylindole	90
13	2,5-Dimethoxyaniline	4,7-Dimethoxyindole	15

[a] All reactions were carried out with anilines (10 mmol), **2** (1 mmol), $RuCl_3·nH_2O$ (7 mol% based on **2**), PPh_3 (2 mol% based on **2**), and $SnCl_2·2H_2O$ (1 mmol) in dioxane (10 ml) at 180 °C for 20 h. [b] Based on **2**. [c] Isomeric molar distributions were determined by ^1H NMR spectroscopy (300 MHz): 4-methylindole : 6-methylindole = 1 : 1; 4-methoxyindole : 6-methoxyindole = 1 : 2.8.



	6 + **7**	**6**:**7**
R = Me	99%	4:1
R = OMe	96%	5:1
R = Cl	66%	5:1
R = Bu^i	99%	5:1

Scheme 2

indoles, **6** and **7**, in quantitative isolated yields, favoring the formation of 2-methylindoles **6** (Scheme 2). In a separate experiment, we observed that a similar reaction of *p*-toluidine with **5** gave two isomeric indoles in 118% GLC yield based on **5**. This result indicates that at least two propan-2-ol groups out of three in **5** are available for the C_2-fragment counterpart.

Although the exact role of $SnCl_2•2H_2O$ in the present reaction is still obscure, the reaction pathway seems to be the initial formation of 2-anilinoethanols§ by amine exchange reactions[4b,5] between anilines and trialkanolamines followed by a similar catalytic cycle to that which has already been proposed in ruthenium-catalysed synthesis of indoles from anilines and ethylene glycols.[6]

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Notes and References

† E-mail: scshim@kyungpook.ac.kr

‡ General experimental procedure: a mixture of aniline (10 mmol), alkanolamine (1 mmol), $RuCl_3•nH_2O$ (0.07 mmol), $SnCl_2•2H_2O$ (1 mmol) and PPh_3 (0.21 mmol) in dioxane (10 ml) was placed in a stainless steel autoclave. After the system was flushed with nitrogen gas, the mixture was stirred at 180 °C for 20 h. The reaction mixture was filtered through a short column (silica gel, CH_2Cl_2) and evaporated under reduced pressure. To the residual oily material was added 30 ml of CH_2Cl_2 and the mixture was washed twice with 50 ml of aq. 5% HCl solution to remove excess aniline. The organic layer was dried over anhydrous NA_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (ethyl acetate–hexane) to give indoles.

§ In a separate experiment, we observed that a similar ruthenium-catalysed reaction between *N*-benzyl-*p*-toluidine and triethanolamine resulted in the formation of a small amount of 2-(*N*-benzyl-*p*-tolylamino)ethanol by GC–MS analysis.

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