

## Ruthenium-Catalyzed Reductive Heteroannulation of Nitroarenes with Trialkanolamines Leading to Indoles

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Besides conventional named routes such as the Fischer, Madelung, Bischler, and related syntheses for the formation of indoles, homogeneous transition metal-catalyzed synthetic methods have been attempted recently because of the facility and efficiency of reaction and wide availability of substrate.<sup>1</sup> During the course of our continuing studies on homogeneous ruthenium catalysis, we recently developed an alkyl group transfer from alkylamines to anilines<sup>2-7</sup> as well as  $\alpha$ -carbon atom of ketones.<sup>8</sup> The former transformation leads to indoles<sup>2,3</sup> and quinolines<sup>4,7</sup> and is well known as amine exchange reaction (amine distribution reaction or amine scrambling reaction).<sup>9</sup> However, except for our reports, a clear-cut example for the synthesis of N-heterocycles using the amine exchange reaction seems to be limited to palladium-catalyzed synthesis of pyrimidines and imidazoles.<sup>10</sup> Herein, we describe a ruthenium-catalyzed reductive cyclization of nitroarenes with trialkanolamines using water gas shift reaction system (CO/H<sub>2</sub>O) *via* an amine exchange reaction.

We attempted the reductive cyclization between nitrobenzene (**1a**) and triethanolamine (**2a**) to obtain an optimized reaction condition for indole (**3a**), and several representative results are summarized in Table 1 (Eq. 1). The reaction was generally performed under water gas shift reaction system (CO/H<sub>2</sub>O) and the molar ratio of **1a/2a** (3-6) in the presence of a catalytic amount of a ruthenium catalyst at 180 °C. However, upon using the molar ratio of **1a/2a**=3, the product yield and distribution were not changed significantly compared to **1a/2a**=6. The absence of either H<sub>2</sub>O or CO proved to be not effective for the formation of **3a** and indole precursors **4** (R=R'=H) and **5** (R=R'=H) (runs 4 and 6). However, the starting **1a** was converted into aniline, which might be derived by SnCl<sub>2</sub>·2H<sub>2</sub>O as reducing agent.<sup>11</sup> The yield of **3a** increases with the increase in the pressure of CO up to 20 atm (runs 1-4). The presence of SnCl<sub>2</sub>·2H<sub>2</sub>O was essential for

**Table 1.** Ruthenium-catalyzed reaction of **1a** with **2a** under various conditions<sup>a</sup>

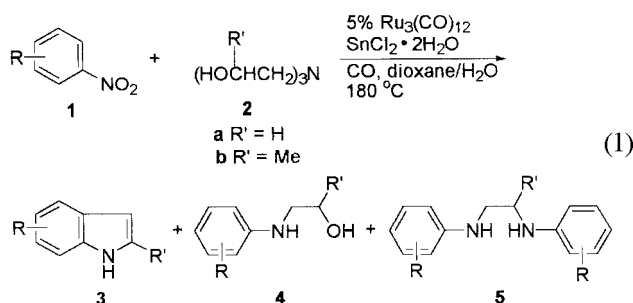
Run	<b>1a/2a</b>	Dioxane/H <sub>2</sub> O (mL/mL)	P <sub>CO</sub> (atm)	Time (h)	Conv. (%) of <b>1a</b>	Yield (%) <sup>b</sup>		
						<b>3a</b>	<b>4</b>	<b>5</b>
1	6	9/1	20	40	100	36	21	17
2	6	9/1	5	20	100	12	36	28
3	6	9/1	2	40	100	6	0	5
4	6	9/1	0	20	79	1	0	1
5 <sup>c</sup>	6	9/1	50	40	100	0	0	0
6	6	10/0	20	40	100	8	0	1
7	3	9/1	20	40	100	36	21	6
8 <sup>d</sup>	3	9/1	20	20	100	17	0	0
9 <sup>e</sup>	2	9/1	20	40	100	21	28	4
10 <sup>f</sup>	6	9/1	20	40	100	30	3	5

<sup>a</sup>Conditions: **2a** (1 mmol), Ru<sub>3</sub>(CO)<sub>12</sub> (0.05 mmol), SnCl<sub>2</sub>·2H<sub>2</sub>O (1 mmol), 180 °C. <sup>b</sup>GLC yield based on **2a**. <sup>c</sup>In the absence of SnCl<sub>2</sub>·2H<sub>2</sub>O. <sup>d</sup>RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (0.05 mmol). <sup>e</sup>Ru<sub>3</sub>(CO)<sub>12</sub> (0.1 mmol). <sup>f</sup>SnCl<sub>2</sub>·2H<sub>2</sub>O (2 mmol).

the formation of **3a** as has been observed in our recent ruthenium-catalyzed synthesis of indoles<sup>2,3</sup> and quinolines<sup>4,7</sup> (run 5). As described above, SnCl<sub>2</sub>·2H<sub>2</sub>O seems to play a decisive role as both the reduction of **1a** to aniline and the formation of **3a**.<sup>12</sup> However, the use of increased amount of SnCl<sub>2</sub>·2H<sub>2</sub>O did not give any significant change on the yield of **3a** (run 10).

Given these results, several reactions of nitroarenes **1** with **2a** were screened using the above optimized conditions. As shown in Table 2, the indole yield was not considerably affected by the position of the substituent on nitroarene (runs 2-4). In the case of 3-methylnitrobenzene (**1c**), the product (**3c**) was obtained as a regioisomeric mixture (run 3). Interestingly, treatment of **1** with triisopropanolamine (**2b**) under the employed system afforded almost exclusively 2-methyl substituted regioisomers **3g** and **3h** (runs 7, 8). We have already shown that 2-methylindoles are selectively formed in the ruthenium-catalyzed reaction of anilines with **2b** and triisopropanolammonium chloride.<sup>2,3</sup>

As concerns the reaction pathway, it seems to be proceeded *via* a ruthenium-catalyzed sequence involving ethanol group transfer from **2a** to aniline to form **4** (amine exchange reaction<sup>9</sup>). N-alkylation of aniline with **4** to form **5**,<sup>13</sup> and N-heteroannulation of **5** to give **3a**. We have already been proposed a similar catalytic cycle in the synthesis of



**Table 2.** Ruthenium-catalyzed synthesis of **3**<sup>a</sup>

Run Nitroarene <b>1</b>	<b>2</b> Indole <b>3</b>	Yield (%) <sup>b</sup>
1 R=H ( <b>1a</b> )	<b>2a</b> R=H; R'=H ( <b>3a</b> )	30
2 R=4-Me ( <b>1b</b> )	<b>2a</b> R=5-Me; R'=H ( <b>3b</b> )	30
3 R=3-Me ( <b>1c</b> )	<b>2a</b> R=4- and 6-Me; R'=H ( <b>3c</b> )	39 <sup>c</sup>
4 R=2-Me ( <b>1d</b> )	<b>2a</b> R=7-Me; R'=H ( <b>3d</b> )	33
5 R=3,5-Me ( <b>1e</b> )	<b>2a</b> R=4,6-Me; R'=H ( <b>3e</b> )	51
6 R=2-OMe, 4-Me ( <b>1f</b> )	<b>2a</b> R=4-Me, 7-OMe; R'=H ( <b>3f</b> )	30
7 <b>1a</b>	<b>2b</b> R=H; R'=Me ( <b>3g</b> )	27
8 <b>1b</b>	<b>2b</b> R=5-Me; R'=Me ( <b>3h</b> )	31

<sup>a</sup>Conditions: **1** (3 mmol), **2** (1 mmol), Ru<sub>3</sub>(CO)<sub>12</sub> (0.05 mmol), SnCl<sub>2</sub>·2H<sub>2</sub>O (1 mmol), CO (20 atm), dioxane:H<sub>2</sub>O (9 mL/1 mL), 180 °C, 40 h. <sup>b</sup>Isolated yield based on **2**. <sup>c</sup>Regioisomeric distribution was determined by <sup>1</sup>H NMR (300 MHz): 4-methylindole:6-methylindole=1:1.2.

indoles from anilines and alkanolamines (or alkanolammonium halides).<sup>2,3,14</sup>

Typical experimental procedure is as follows. A mixture of **1a** (3 mmol), **2a** (1 mmol), Ru<sub>3</sub>(CO)<sub>12</sub> (0.05 mmol), SnCl<sub>2</sub>·2H<sub>2</sub>O (1 mmol), and dioxane/H<sub>2</sub>O (9 mL/1 mL) was placed in a pressure vessel. After the system was flushed and then pressurized with carbon monoxide (20 atm), the mixture was stirred at 180 °C for 40 h. The reaction mixture was poured into aqueous 5% HCl solution and extracted with CHCl<sub>3</sub> and dried with Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent under reduced pressure left a solid which was separated by column chromatography (ethyl acetate/hexane) to give indole (0.035 g, 30%).

In summary, we have demonstrated that nitroarenes were found to be reductively cyclized with trialkanolamines in the presence of a ruthenium catalyst and SnCl<sub>2</sub>·2H<sub>2</sub>O under water gas shift reaction system to give indoles *via* an amine exchange reaction.

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