

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

Chan Sik Cho,\* Tae Kyung Kim, Sung Won Yoon, Tae-Jeong Kim, and Sang Chul Shim\*

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

Received February 6, 2001

**Keywords :** Ruthenium, Nitroarene, Trialkanolamine, Indole, Heteroannulation.

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'=Me) (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>

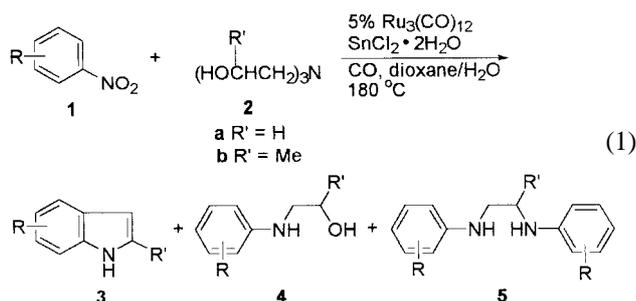
Run	<b>1a/2a</b>	Dioxane/H <sub>2</sub> O (mL/mL)	P <sub>CO</sub> (atm)	Time (h)	Conv. (%) of <b>1a</b>	Yield (%) <sup>b</sup>		
						<b>3a</b>	<b>4</b>	<b>5</b>
1	6	9/1	20	40	100	36	21	17
2	6	9/1	5	20	100	12	36	28
3	6	9/1	2	40	100	6	0	5
4	6	9/1	0	20	79	1	0	1
5 <sup>c</sup>	6	9/1	50	40	100	0	0	0
6	6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

**Acknowledgment.** This work was supported by Korea Research Foundation Grant (KRF-2000-015-DP0248) and grant of Post-Doc. (C.S.C.) Program from Kyungpook National University (2000).

## References

- For reviews, see: (a) Remers, W. A.; Spande, T. F. In *Indoles*; Houlihan, W. J., Ed.; John Wiley & Sons: New York, 1979; Vol. 25, Part III. (b) Hegedus, L. S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113-1126. (c) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225-2249. (d) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119-

- (e) Sundberg, R. J. *Indoles*; Academic Press: London, 1996.
- Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun.* **1998**, 995-996.
- Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811-1814; Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321-3329.
- Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499-1500; Cho, C. S.; Oh, B. H.; Shim, S. C.; Oh, D. H. *J. Heterocyclic Chem.* **2000**, *37*, 1315-1320.
- Cho, C. S.; Oh, B. H.; Shim, S. C. *J. Heterocyclic Chem.* **1999**, *36*, 1175-1178.
- Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747-7750.
- Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885-1886.
- Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 958-960.
- For transition metal-catalyzed amine exchange reactions, see: (a) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1973**, *95*, 3038-3039. (b) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348-350. (c) Shvo, Y.; Laine, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 753-754. (d) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249-251. (e) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759-1760. (f) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *231*, C31-C34. (g) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229-232. (h) Laine, R. M.; Thomas, D. W.; Cary, L. W. *J. Am. Chem. Soc.* **1982**, *104*, 1763-1765. (i) Jung, C. W.; Fellmann, J. D.; Garrou, P. E. *Organometallics* **1983**, *2*, 1042-1044. (j) Murahashi, S.-I. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443-2465.
- Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002-5011.
- Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839-842 and references cited therein.
- For catalytic activity of transition metal-tin complexes, see: Holts, M. S.; Wilson, W. L.; Nelson, J. H. *Chem. Rev.* **1989**, *89*, 11-49.
- It is well documented that transition metal-catalyzed *N*-alkylation of amines by primary alcohols proceeds *via* a sequence involving oxidation of the alcohol to form aldehyde, condensation of the aldehyde with amine to form imine, and reduction of imine. This methodology has been successfully applied for the synthesis of *N*-heterocycles. Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599-2660.
- In contrast to our recent reports on the ruthenium-catalyzed synthesis of indoles (refs 2 and 3), the present reaction clearly revealed the formation of intermediates **4** and **5**.