Ruthenium Complex-Catalyzed Synthesis of Indoles from N-Substituted Anilines and Alkanolamines

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Received August 12, 1996

N-Substituted anilines react with triethanolamine at 180 °C in the presence of a catalytic amount of tris(triphenylyphosphine)ruthenium(II) chloride to give the corresponding 1-substituted indoles in good to high yields. Similar treatment of the anilines with N-benzylthietanolamine or trisopropanolamine in place of triethanolamine also affords the indoles in good yields. An intermolecular alkyl group transfer between anilines and alkanolamines is assumed to be the key step of these reactions.

Introduction

Indole derivatives have been continued to be of interest because of their physiological activity.1 For the construction of the indole skeletons, the Fischer indole synthesis is the most widely used and has been extensively reviewed.2 Bischler synthesis3 and Madelung synthesis4 are also popular routes to the indoles. However, these precedents are restricted to the particular substrates, which are not easily accessible. The simplest method to build up an indole skeleton might be an intermolecular reaction between N-substituted anilines and C1-fragments such as acetaldehyde,5 ethylene glycol6 and ethylene oxide.7 However, all these reactions were carried out over heterogeneous catalyst under very severe reaction conditions and in some cases yields were not so satisfactory. From the viewpoint of organic synthesis, several recent reports on the synthesis of indoles employing homogeneous transition metals as catalysts are interesting.8 Among them, it is worth while to note Watanabe's report on the facile synthesis of indoles from N-substituted anilines and ethylene glycol by introducing a homogeneous ruthenium catalyst.9 We now disclose that alkanolamines work as a new C2-fragment for the synthesis of indoles from N-substituted anilines by a ruthenium catalyst.10 We report here the detailed results of these reactions from both synthetic and mechanistic viewpoints.

Results and Discussion

Several attempts to optimize the reaction conditions as a model reaction were carried out between N-methylaniline (1b) and triethanolamine (2). Thus, treatment of 1b (50 mmol) with 2 (5 mmol) in 1,4-dioxane in the presence of a catalytic amount of tris(triphenylyphosphine)ruthenium(II) chloride [RuCl₂(PPh₃)₃], 2 mol % based on the amine] at 180 °C for 5 h afforded 1-methylindole (3b) in 78% yield (eq 1). The reaction proceeded even by the use of catalyst precursor RuCl₂·nH₂O/3PPh₃ in place of RuCl₂(PPh₃)₃, exhibiting nearly the same catalytic activity as RuCl₂(PPh₃)₃. On the other hand, other catalyst precursor such as RuCl₂·nH₂O/3PBU₃ was moderately effective, but RuCl₂·nH₂O/3P(OEt)₃ was ineffective.

The yield of 1-methylindole (3b) was considerably affected by the molar ratio of 1b to 2. Table 1 shows that only a 25% yield of 3b was obtained for 10 h at the molar ratio of 1. The yield of 3b was gradually increased with the increase of the molar ratio. The highest yield was obtained at the molar ratio of 10. Although the reaction time was prolonged at the same molar ratio, the yield was not noticeably varied. The yield of 3b was also affected by the reaction temperature. Both lower and higher reaction temperatures resulted in lower yields of 3b. Several representative results are summarized in Table 1.

The reaction was proceeded using other alkanolamines such as N-benzylthietanolamine and N-phenylthietanolamine, but the yield of 3b was generally lower than that by the use of triethanolamine (2). Other alkanolamines such as diethanolamine, N,N-dibenzylethanolamine, and ethanolamine were moderately effective, but di(ethylene glycol) and 2,2'-thiodiethanol as other type of C₂-fragment were ineffective under the reaction conditions. Typical results are summarized in Table 2.

When the reaction using 2 or N-benzylthietanolamine could also be applied to many N-substitued anilines such as N-ethyl-, N-n-propyl-, N-n-butyl-, N-phenyl-, and N-benzylanilines under the optimized reaction conditions, the yields of the corresponding N-substituted indoles were always good. However, treatment of aniline (1a) with 2 or N-benzylthietanolamine under the conditions described so far resulted in the formation of only a trace amount of indole (3a) along...
Ruthenium-Catalyzed Synthesis of Indoles

Table 1. Ruthenium-Catalyzed Synthesis of 1-Methylindole (3b) from 1b and 2 under Various Reaction Conditions

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Molar ratio (1b/2)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl₂(PPh₃)₃</td>
<td>10</td>
<td>180</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>RuCl₂·nH₂O+3PPh₃</td>
<td>10</td>
<td>180</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>RuCl₂·nH₂O+3PPh₃</td>
<td>10</td>
<td>180</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>RuCl₂·nH₂O+3PPh₃</td>
<td>10</td>
<td>180</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>RuCl₂·nH₂O+3P(OEt)₂</td>
<td>10</td>
<td>180</td>
<td>5</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>RuCl₂(PPh₃)₃</td>
<td>1</td>
<td>180</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>RuCl₂(PPh₃)₃</td>
<td>2</td>
<td>180</td>
<td>28</td>
<td>(34)</td>
</tr>
<tr>
<td>8</td>
<td>RuCl₂(PPh₃)₃</td>
<td>2</td>
<td>180</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>RuCl₂(PPh₃)₃</td>
<td>3</td>
<td>180</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>RuCl₂(PPh₃)₃</td>
<td>3</td>
<td>180</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>11</td>
<td>RuCl₂(PPh₃)₃</td>
<td>3</td>
<td>150</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>RuCl₂(PPh₃)₃</td>
<td>3</td>
<td>210</td>
<td>5</td>
<td>30</td>
</tr>
</tbody>
</table>

*All reactions were carried out with 1b (50 mmol), 2 (5 mmol), and ruthenium catalyst (0.1 mmol) in 1,4-dioxane (10 mL). *Determined by GLC. Isolated yield is shown in parentheses.

Table 2. Ruthenium-Catalyzed Synthesis of 1-Methylindoles (3b) from 1b and Various C₃-Fragments

<table>
<thead>
<tr>
<th>Run</th>
<th>C₃-Fragments</th>
<th>GLC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₃N(CH₂CH₂OH)₂</td>
<td>70*</td>
</tr>
<tr>
<td>2</td>
<td>(PhCH₃)₂NCH₂CH₂OH</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>PhN(CH₂CH₂OH)₂</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>HN(CH₂CH₂OH)₂</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>H₂NCH₂CH₂OH</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>OCH₂CH₂OH</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Si(CH₂CH₂OH)₂</td>
<td>0</td>
</tr>
</tbody>
</table>

*All reactions were carried out with 1b (50 mmol), C₃-fragment (5 mmol), and RuCl₂(PPh₃)₃ (0.1 mmol) in 1,4-dioxane (10 mL) at 180 °C for 5 h. *Isolated yield.

with many unidentified compounds. N-Phenyl-1-naphthylamine (1b) with N-benzylidethanolamine was scarcely proceed to afford 1-naphthylindole (3b). Typical results are summarized in Table 3.

Although the details of the reaction pathway are not certain, we postulate and describe them according to precedents.⁷ ¹³ There are three possible pathways from 1 and 2 to the corresponding N-substituted indoles 3 (Scheme 1). i) The ethanol moiety of 2 is transferred to 1 to give 2-anilinoethanol 4, which reacts with another 1 under the ruthenium catalyst to form an ethylenediamine compound 6. Watanabe et al. reported that the indole 3 is not formed directly from 4 by intramolecular cyclization and suggested that the compound 6 is a key intermediate for the cyclization to the indole 3. ii) Condensation between 1 and 2 occurs to give an intermediate 5 where alkyl group exchange with 1 occurs to lead to 6. iii) The intermediate 5 thus formed is subjected to a direct intramolecular cyclization leading to 3.

It is known that the intermolecular alkyl group transfer between amines proceeds through iminium ion complex under the ruthenium catalyst.⁷ Thus, the transfer of ethanol moiety from 2 to 1 can be rationalized by Scheme 2. The initial coordination of the amine 2 to the ruthenium followed by oxidative addition to the adjacent C-H bond forms an alkylruthenium complex 7, which becomes rapid equilibrium.
with an iminium ion complex 8. Nucleophilic attack of the aniline 1 to 8 gives the 2-anilinoethanol 4. The alkyl group exchange between 5 and 1 proceeds similarly to 6. It is also well known that the N-alkylation of amine using alcohols proceeds Schiff base intermediate under the ruthenium catalyst.12-17 The formation of the intermediate 5 is explicable in terms of the N-alkylation of 1 by 2.

Next, to obtain 2- and 3-substituted indoles, triisopropanolamide (9) was employed in the reaction (eq 2). Similar treatment of N-methylaniline (1b) with 9 gave two isomeric indoles, 1,2-dimethylindole (10b) and 1,3-dimethylindole (11b) (85% yield, 10b/11b = 36/64). Other N-substituted anilines 1 could also be applied to the reaction system to give the corresponding 1,2- and 1,3-substituted indoles. However, the product distribution was very dependent on the nature of the N-substituted anilines 1. With 1c, 1d, and 1e the reaction proceeds competitively and favors the formation of 1,2-isomers. In the cases of 1f and 1g the 1,3-isomer was scarcely formed. Although the result of the selectivity remains unexplained, it indicates that the size of substituent on 1 determines the selectivity between two isomers. Typical results are summarized in Table 4.

### Experimental

**General.** $^1$H (300 MHz) and $^{13}$C (75.5 MHz) NMR spectra were recorded on a Varian Unity Plus 300 spectrometer using Me$_2$Si as an internal standard in CDCl$_3$. Chemical shifts are reported in $\delta$ units downfield from Me$_2$Si. Mass spectra were obtained on a Shimadzu GC-Ms QP 1000A spectrometer. GLC analyses were carried out with a Shimadzu IB equipped with a OV-17 (20% on Chromosorb W, 3 m). The thin-layer chromatography plate was prepared with silica gel 60 GF$_254$, Merck. Commercially available organic and inorganic compounds were used without further purification except for dioxane, which was dried by known method. RuCl$_3$(PPh$_3$)$_2$ was prepared by the known method.18

**Typical Procedure for Ruthenium-Catalyzed Synthesis of Indoles from N-Substituted Anilines (1) and Alkanolamines.** A mixture of N-methylaniline (1b) (5.358 g, 50 mmol), triethanolamine (2) (0.746 g, 5 mmol), and RuCl$_3$(PPh$_3$)$_2$ (0.056 g, 0.1 mmol) in a stainless steel autoclave was stirred magnetically in dioxane (10 mL) at 180 °C for 5 h under argon atmosphere. The reaction mixture was filtered through the short column (silica gel, 5 cm, ethyl ether) and evaporated under reduced pressure. To the residual oily material was added 100 mL of diethyl ether and washed three times with 50 mL of aqueous 5% HCl solution to remove excess N-methylaniline. The organic phase was separated and dried over anhydrous MgSO$_4$. Removal of the solvent under reduced pressure left an oil. TLC separation using ethyl acetate/hexane (1/30) mixture as an eluent gave 1-methylindole (3b) (0.512 g, 78%). The products prepared by the above procedure were characterized spectroscopically as shown below. The molar ratio of isomeric indoles was determined from the peak areas of the clearly separated protons such as vinylic and methyl in the $^1$H NMR spectrum.

**1-Methylindole (3b).** colorless oil; $^1$H NMR δ 3.79 (s, 3H), 6.50-7.60 (m, 6H), $^{13}$C NMR δ 32.7, 100.6, 109.3, 118.1, 120.7, 121.4, 128.4, 128.6, 136.6; MS m/z (relative intensity) 131 (M$^+$, 93), 130 (100), 129 (76), 128 (4), 103 (14), 102 (14).

**1-Ethylindole (3c).** colorless oil; $^1$H NMR δ 1.41 (t, $J$ = 7.0 Hz, 3H), 4.12 (q, $J$ = 7.0 Hz, 2H), 6.43-7.72 (m, 6H); $^{13}$C NMR δ 15.3, 40.7, 100.9, 109.2, 119.1, 120.9, 121.2, 126.8, 128.6, 135.6.

**1-n-Propylindole (3d).** colorless oil; $^1$H NMR δ 0.83 (t, $J$ = 7.0 Hz, 3H), 1.52-1.93 (m, 2H), 3.91 (t, $J$ = 7.0 Hz, 2H), 6.42-7.73 (m, 6H); $^{13}$C NMR δ 11.3, 23.3, 47.7, 100.7, 109.3, 119.0, 120.8, 121.1, 127.6, 128.5, 135.9.

**1-n-Butylindole (3e).** colorless oil; $^1$H NMR δ 0.91 (t, $J$ = 7.0 Hz, 3H), 1.04-1.43 (m, 2H), 1.63-1.92 (m, 2H), 4.01 (t, $J$ = 7.0 Hz, 2H), 6.41-7.12 (m, 11H); $^{13}$C NMR δ 13.6, 20.1, 32.2, 45.9, 100.8, 109.3, 119.0, 120.8, 121.2, 127.6, 128.5, 135.9.

**1-Phenylindole (3f).** colorless oil; $^1$H NMR δ 6.51-7.53 (m, 11H); $^{13}$C NMR δ 103.5, 110.5, 120.3, 121.1, 122.3, 124.3, 125.4, 127.9, 129.3, 129.5, 135.8, 139.8; MS m/z (relative intensity) 193 (M$^+$, 100), 165 (30), 91 (66), 77 (16).

**1-Benzylindole (3g).** colorless oil; $^1$H NMR δ 4.72 (s, 2H), 6.01-7.12 (m, 11H); $^{13}$C NMR δ 50.0, 101.6, 106.9, 119.5, 120.9, 121.6, 126.7, 127.5, 128.2, 128.3, 128.7, 136.3, 137.5; MS m/z (relative intensity) 207 (M$^+$, 42), 92 (100), 91 (72).

**1,2-Dimethylindole (10b).** colorless oil; $^1$H NMR δ 2.40 (s, 3H), 3.63 (s, 3H), 6.23 (s, 1H), 7.06-7.52 (m, 4H); $^{13}$C NMR δ 12.3, 28.9, 99.8, 108.8, 119.0, 119.4, 120.2, 125.5, 136.8, 137.2; MS m/z (relative intensity) 145 (M$^+$, 57), 144 (100), 143 (72), 142 (6), 128 (11), 103 (10), 77 (15).

**1,3-Dimethylindole (11b).** white solid; $^1$H NMR δ 2.12 (s, 3H), 3.26 (s, 3H), 6.41 (s, 1H), 6.89-7.39 (m, 4H); $^{13}$C NMR δ 9.4, 31.9, 108.6, 109.6, 118.3, 118.7, 121.2, 126.4, 127.9, 136.4; MS m/z (relative intensity) 145 (M$^+$, 74), 144 (100), 143 (52), 142 (6), 130 (11), 129 (8), 128 (12), 115 (12), 103 (11).

**1-Phenyl-2-methylindole (10f).** $^1$H NMR δ 3.15 (s, 3H), 6.92-7.34 (m, 10H); $^{13}$C NMR δ 40.3, 120.5, 121.3, 128.4, 128.5, 128.7, 129.2, 131.9, 132.0, 132.2, 133.6, 133.9, 140.9.
1-Benzyl-2-methylindole (10g). \(^1^H\) NMR \& 2.31 (s, 3 H), 5.19 (s, 2H), 6.71-7.61 (m, 10H); \(^1^C\) NMR \& 49.7, 54.2, 100.4, 109.1, 119.5, 119.7, 120.7, 125.9, 128.7, 127.2, 128.1, 128.7, 136.7, 137.9; MS m/z (relative intensity) 221 (M\(^+\)), 41, 92 (100), 91 (73).

Acknowledgment. The authors are grateful to KOSEF-OCRC and Ministry of Education (BSRI-96-3408) for financial support.

References


Chiral \(\beta\)-Amino Thiol Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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Received August 12, 1996

Reaction of diethylzinc with \(\alpha\)-branched aldehydes in the presence of a catalytic amount (5 mol \%) of various \(\beta\)-amino thiolates in toluene or ether provided the corresponding secondary alcohols in outstanding ee. Detailed preparative procedure for the \(\beta\)-amino thiolates are presented.

Introduction

The discovery of catalytic asymmetric addition of alkyl groups of dialkylzinc reagents to carbonyl carbon of aldehyde in the presence of \(\beta\)-amino alcohols\(^1\) has given an explosive impetus to the highly successful development of synthetic methodologies of optically active secondary alcohols.\(^2\) The \(\beta\)-amino alcohols behave as a ligand, forming an oxazazincidine species I which is an active catalyst upon the interaction of dialkylzinc.\(^3\) In search of a catalyst which would give non-substrate-specified the absolute optical purity, we have found that chiral amino thiolates containing cyclic amines could be employed as the ligand to form such a catalyst. And those chiral amino thiolates were supposed to have the following features: 1) enhanced polarizability of sulfur (thiol) as compared to oxygen (alcohol), 2) the heterocyclic nature of the ligand ring as a face blocker, 3) high affinity of thiol and thiolate toward metals, especially for zinc, and 4) less tendency of