
Ruthenium-Catalyzed Synthesis of Benzimidazoles from N-Alkyl-1,2-diaminobenzenes via Alkyl Group Transfer

Chan Sik Cho* and Jun Uk Kim

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: csho@knu.ac.kr

Received April 4, 2008

Key Words : N-Alkyl-1,2-diaminobenzenes, Alkyl group transfer, Cyclization, Benzimidazoles, Ruthenium catalyst

Many synthetic methods have been developed and documented for benzimidazoles due to their intrinsic pharmacological and biological activities.1 Conventional benzimidazole synthesis can be achieved by condensation between 1,2-phenylenediamines and carboxylic acids or derivatives. Besides such a conventional route, transition metal-catalyzed reactions for benzimidazole skeletons have also been attempted as alternative synthetic methods because of the facility and efficiency of reaction and the wide availability of substrates. It was reported that primary alcohols are oxidatively cyclized with 1,2-phenylenediamines in the presence of RuCl2(PPh3)3 and MnO2 to give 2-substituted benzimidazoles.4 Benzimidazoles also can be synthesized by palladium-catalyzed carboxylation, coupling, and cyclization between 1,2-phenylenediamines and haloaromatics5 and intramolecular N-arylation of (2-bromophenyl)aldimines.6 In connection with this report, during the course of our studies directed towards ruthenium-catalyzed C-N bond activation of alkylamines, we developed an alkyl (or alkanol) group transfer from alkylamines (or alkanolamines) as well as α-carbon atom of ketones.9,10 The former transfer is known as amine exchange reaction or amine scrambling reaction and eventually leads to indoles and quinolines.11 However, except for these indoles and quinolines,7,8 a clear-cut example for the synthesis of N-heterocyclic compounds using such an amine exchange reaction seems to be limited to palladium-catalyzed synthesis of pyrimidines and imidazoles.12 Under these circumstances, herein, as another example for the synthesis of N-heterocycles via an intrinsic amine exchange reaction, this paper describes a ruthenium-catalyzed synthesis of benzimidazoles 2a-n from N-alkyl-1,2-diaminobenzenes 1a-n (Scheme 1).

The results of several attempted cyclizations of N-benzyl-1,2-diaminobenzene (1a, R=Ph) for the optimization of conditions are listed in Table 1.13 Treatment of 1a in toluene at 100 °C in the presence of RuCl2(PPh3)3 afforded 1-benzyl-2-phenyl-1H-benzo[d]imidazole (2a, R=Ph) in 56% isolated yield (entry 1). However, when acetoephene as a sacrificial hydrogen acceptor was further added, the reaction rate was considerably enhanced toward the formation of 2a with nearly complete conversion of 1a (97% conversion) (entry 2).14 We also confirmed on the formation of 1,2-phenylenediamine (21% isolated yield) and 1-phenylethanol (2% GLC yield) as identifiable products. However, no directly cyclized product 2-phenylimidazole was produced. These results indicate that the reaction proceeds via benzyl group transfer in 1a. Other hydrogen acceptors such as 1-dodecene and benzalacetone exhibited nearly the same additive effect as acetoephene under the employed conditions (entries 3 and 4). Among solvent examined under the employment of RuCl2(PPh3)3 and benzalacetone as hydrogen acceptor, toluene in terms of product 2a yield and complete conversion of 1a revealed to be the solvent of choice (entries 3 and 4). Similar catalytic activity as RuCl2(PPh3)3 was observed with RuCl3·nH2O combined with 3PPh3 and RuCl2(=CHPh)-(PCy3)2 (entries 4, 8-10).

Table 1. Optimization of conditions for the reaction of 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ru catalysts</th>
<th>Hydrogen acceptors</th>
<th>Solvents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl2(PPh3)3</td>
<td>–</td>
<td>Toluene</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>RuCl2(PPh3)3</td>
<td>Acetophene</td>
<td>Toluene</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>RuCl2(PPh3)3</td>
<td>1-Dodecene</td>
<td>Toluene</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>RuCl2(PPh3)3</td>
<td>Benzalacetone</td>
<td>Toluene</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>RuCl2(PPh3)3</td>
<td>Benzalacetone</td>
<td>Dioxane</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>RuCl2(PPh3)3</td>
<td>Benzalacetone</td>
<td>Diglyme</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>RuCl2(PPh3)3</td>
<td>Benzalacetone</td>
<td>DMF</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>RuCl2(nH2O/3PPh3)</td>
<td>Benzalacetone</td>
<td>Toluene</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>Ru5(CO)12</td>
<td>Benzalacetone</td>
<td>Toluene</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>RuCl2(=CHPh)(PCy3)2</td>
<td>Benzalacetone</td>
<td>Toluene</td>
<td>89</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.5 mmol), ruthenium catalyst (0.02 mmol), hydrogen acceptor (1 mmol), solvent (5 mL), 100 °C, for 20 h. *The formation of 0.25 mmol of 2a corresponds to 100% yield.
1,2-dialkylbenzimidazoles (the reactions with heterocycles are currently under investigation. From readily available starting methodology for the synthesis of benzimidazoles followed by cyclization. The present reaction is a straightforward methodology for the synthesis of benzimidazoles can be synthesized from a sacrificial hydrogen acceptor benzene in the presence of a ruthenium catalyst along with inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give benzimidazoles.

Having reaction conditions being established, various N-alkyl-1,2-diaminobenzenes were screened in order to investigate the reaction scope and several representative results are summarized in Table 2.15 With N-benzyl-1,2-diaminobenzenes (1a-f) 2-aryl-1-benzy limidazoles (2a-f) were formed in the range of 75-90% isolated yields with the formation of 1,2-diaminobenzene as sole identifiable side product on TLC. The product yield was not significantly affected by the position and electronic nature of the substituent on the aromatic ring of benzyl group of 1a-f. From the reactions with N-alkyl-1,2-diaminobenzenes having straight and branched alkyl chains (1g-n), the corresponding 1,2-dialkylbenzimidazoles (2g-n) were also produced and the product yield had relevance to the alkyl chain length and branching bulkiness of 1g-n. Generally, the longer straight chain length of N-alkyl-1,2-diaminobenzenes is, the lower yield of benzimidazoles is produced. With N-alkyl-1,2-diaminobenzenes having straight alkyl chain, the product yield was generally higher than that when N-alkyl-1,2-diaminobenzenes having branched alkyl chain were used.

In summary, we have shown that 1,2-disubstituted benzimidazoles can be synthesized from N-alkyl-1,2-diaminobenzenes in the presence of a ruthenium catalyst along with a sacrificial hydrogen acceptor via an alkyl group transfer followed by cyclization. The present reaction is a straightforward methodology for the synthesis of benzimidazoles from readily available starting N-alkyl-1,2-diaminobenzenes. The reaction mechanism and synthetic application for N-heterocycles are currently under investigation.

### Table 2. Ruthenium-catalyzed synthesis of benzimidazoles

<table>
<thead>
<tr>
<th>N-Alkyl-1,2-diaminobenzenes 1</th>
<th>Benzimidazoles 2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a R = Ph</td>
<td>2a</td>
<td>90</td>
</tr>
<tr>
<td>1b R = 3-MeOC$_6$H$_5$</td>
<td>2b</td>
<td>87</td>
</tr>
<tr>
<td>1c R = 4-MeC$_6$H$_5$</td>
<td>2c</td>
<td>83</td>
</tr>
<tr>
<td>1d R = 3-MeC$_6$H$_5$</td>
<td>2d</td>
<td>78</td>
</tr>
<tr>
<td>1e R = 2-MeC$_6$H$_5$</td>
<td>2e</td>
<td>75</td>
</tr>
<tr>
<td>1f R = 3-BrC$_6$H$_5$</td>
<td>2f</td>
<td>79</td>
</tr>
<tr>
<td>1g R = CH$_2$CH$_2$CH$_3$</td>
<td>2g</td>
<td>82</td>
</tr>
<tr>
<td>1h R = CH$_3$(CH$_2$)$_3$CH$_3$</td>
<td>2h</td>
<td>61</td>
</tr>
<tr>
<td>1i R = CH$_3$(CH$_2$)$_5$CH$_3$</td>
<td>2i</td>
<td>53</td>
</tr>
<tr>
<td>1j R = CH(CH$_3$)$_2$</td>
<td>2j</td>
<td>54</td>
</tr>
<tr>
<td>1k R = CH$_2$CH$_2$(CH$_3$)$_2$</td>
<td>2k</td>
<td>62</td>
</tr>
<tr>
<td>1l R = CH$_2$CH$_2$Ph</td>
<td>2l</td>
<td>48</td>
</tr>
<tr>
<td>1m R = CH(Et)CH$_2$(CH$_2$)$_2$CH$_3$</td>
<td>2m</td>
<td>29</td>
</tr>
<tr>
<td>1n R = CH(Et)CH$_2$CH$_3$</td>
<td>2n</td>
<td>28</td>
</tr>
</tbody>
</table>

*Reaction conditions: I (0.5 mmol), RuCl$_3$(PPh$_3$)$_3$ (0.02 mmol), aceto phenone (1 mmol), toluene (5 mL), 100 °C, for 20 h.

**Acknowledgements.** This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2007-359-C00021).

**References**


15. General experimental procedure: To a 50 mL organic reactor (Radleys Discovery Technologies) were added N-alkyl-1,2-diaminobenzene (0.5 mmol), aceto phenone (1 mmol), RuCl$_3$(PPh$_3$)$_3$ (0.02 mmol) and toluene (5 mL). After the system was stirred at 100 °C for 20 h, the reaction mixture was passed through a short silica gel column (ethyl acetate-hexane mixture) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give benzimidazoles.