Communications

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

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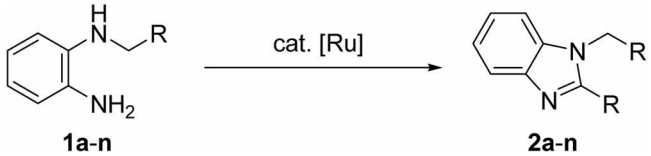
Many synthetic methods have been developed and documented for benzimidazoles due to their intrinsic pharmacological and biological activities.[1] Conventional benzimidazole synthesis can be achieved by condensation between 1,2-phenylenediamines and carboxylic acids or derivatives. Besides such a conventional 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 $RuCl_2(PPh_3)_3$[2] and MnO_2[3] to give 2-substituted benzimidazoles.[4] Benzimidazoles also can be synthesized by palladium-catalyzed carbonylation, coupling, and cyclization between 1,2-phenylenediamines and haloaromatics[5] 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) to *N*-atom of anilines[7,8] 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).



1a-n **2a-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 $RuCl_2(PPh_3)_3$ afforded 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole (**2a**, R=Ph) in 56% isolated yield (entry 1). However, when acetophenone 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 acetophenone under the employed conditions (entries 3 and 4). Among solvent examined under the employment of $RuCl_2(PPh_3)_3$ 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 4-7). Similar catalytic activity as $RuCl_2(PPh_3)_3$ was observed with $RuCl_3 \cdot nH_2O$ combined with $3PPh_3$ and $RuCl_2(=CHPh)(PCy_3)_2$ (entries 4, 8-10).

Table 1. Optimization of conditions for the reaction of **1a**[a]

Entry	Ru catalysts	Hydrogen acceptors	Solvents	Yield (%)[b]
1	$RuCl_2(PPh_3)_3$	–	Toluene	56
2	$RuCl_2(PPh_3)_3$	Acetophenone	Toluene	90
3	$RuCl_2(PPh_3)_3$	1-Dodecene	Toluene	83
4	$RuCl_2(PPh_3)_3$	Benzalacetone	Toluene	89
5	$RuCl_2(PPh_3)_3$	Benzalacetone	Dioxane	77
6	$RuCl_2(PPh_3)_3$	Benzalacetone	Diglyme	49
7	$RuCl_2(PPh_3)_3$	Benzalacetone	DMF	39
8	$RuCl_3 \cdot nH_2O/3PPh_3$	Benzalacetone	Toluene	88
9	$Ru_3(CO)_{12}$	Benzalacetone	Toluene	14
10	$RuCl_2(=CHPh)(PCy_3)_2$	Benzalacetone	Toluene	89

[a]Reaction conditions: **1a** (0.5 mmol), ruthenium catalyst (0.02 mmol), hydrogen acceptor (1 mmol), solvent (5 mL), 100 °C, for 20 h. [b]The formation of 0.25 mmol of **2a** corresponds to 100% yield.

Table 2. Ruthenium-catalyzed synthesis of benzimidazoles[a]

N-Alkyl-1,2-diaminobenzenes **1**	Benzimidazoles **2**	Yield (%)
1a R = Ph	**2a**	90
1b R = 3-$MeOC_6H_5$	**2b**	87
1c R = 4-MeC_6H_5	**2c**	83
1d R = 3-MeC_6H_5	**2d**	78
1e R = 2-MeC_6H_5	**2e**	75
1f R = 4-BrC_6H_5	**2f**	79
1g R = $CH_2CH_2CH_3$	**2g**	82
1h R = $CH_2(CH_2)_3CH_3$	**2h**	61
1i R = $CH_2(CH_2)_5CH_3$	**2i**	53
1j R = $CH(CH_3)_2$	**2j**	54
1k R = $CH_2CH(CH_3)_2$	**2k**	62
1l R = CH_2CH_2Ph	**2l**	48
1m R = $CH(Et)CH_2(CH_2)_2CH_3$	**2m**	29
1n R = $CH(Et)CH_2CH_3$	**2n**	28

[a]Reaction conditions: **1** (0.5 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), acetophenone (1 mmol), toluene (5 mL), 100 °C, for 20 h.

Having reaction conditions being established, various *N*-alkyl-1,2-diaminobenzenes **1** 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-benzylimidazoles (**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.

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15. General experimental procedure: To a 50 mL organic reactor (Radleys Discovery Technologies) were added *N*-alkyl-1,2-diaminobenzene (0.5 mmol), acetophenone (1 mmol), $RuCl_2(PPh_3)_3$ (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.