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An Efficient Synthesis of Benzimidazoles *via* Palladium-Catalyzed Amine Exchange Reaction from Trialkylamines to *o*-Phenylenediamine in an Aqueous Medium

Ngoc Thang Tran and Chan Sik Cho*

*Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: cscho@knu.ac.kr*
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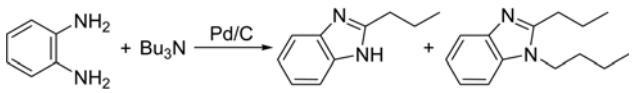
Transition metal-catalyzed alkyl group transfer between alkylamines has been known as amine exchange reaction (amine scrambling reaction) and used for the synthesis of unsymmetrical amines and *N*-heterocycles and the study of the metabolism of amines.[1] During the course of our studies directed towards transition metal-catalyzed C-N bond activation of alkylamines,[2] we developed an alkyl (or alkanol) group transfer from alkylamines (or alkanolamines) to *N*-atom of anilines[3,4] as well as α-carbon of ketones,[5] which leads to a regioselective α-alkylation of ketones. The former transfer eventually leads to indoles and quinolines under the employed reaction conditions. However, except for our findings,[3,4,6] there have been known only a few examples for the synthesis of *N*-heterocycles using such an amine exchange reaction. It is known that hydropyrimidines, imidazolidines and imidazoles could be formed by palladium-catalyzed intermolecular amine exchange reaction between diamines and alkylamines.[7] Diamines were found to be cyclized to pyrrolidine, piperidine, and azepane *via* ruthenium-catalyzed intramolecular amine exchange reaction.[8] On the other hand, in connection with this report, Murahashi *et al*. reported that *N*-methylbenzylamine reacts with *o*-phenylenediamine in the presence of Pd/C to give 2-phenylbenzimidazole and 1-benzyl-2-phenylbenzimidazole in 37% and 25% yields, respectively.[8] Under these circumstances, the present reaction was disclosed during the course of seeking for a more efficient catalytic system on an intrinsic amine exchange reaction. Herein this report describes an efficient synthesis of benzimidazoles *via* palladium-catalyzed amine exchange reaction from trialkylamines to *o*-phenylenediamine in an aqueous medium.

To investigate the effect of reaction variants such as solvent, reaction temperature and time, *o*-phenylenediamine (**1**) and tributylamine (**2a**) were chosen as a model reaction. Treatment of equimolar amounts of **1** and **2a** in toluene at 110 °C for 20 h in the presence of a catalytic amount of 5% Pd/C afforded 2-propylbenzimidazole (**3a**) in 47% isolated yield with 67% conversion of **1** (run 1). Performing the reaction for a longer reaction time under two-fold molar ratio of **2a** to **1** gave no improvement in the yield of **3a** (run 2). Higher reaction temperature in toluene was needed for the effective formation of **3a** (run 3). However, the reaction carried out under the further addition of H_2O resulted in an increased yield of **3a** (72%) along with concomitant formation of further *N*-alkylated benzimidazole **4** (2%) (run 4). In spite of further elaboration for the optimization of reaction conditions (runs 5-7), the best result in terms of the yield of **3a** and the selectivity of **3a** to **4** is best accomplished under the standard set of condition shown in run 4 of Table 1.

Based on reaction conditions of Table 1, various trialkylamines **2** were subjected to the reaction with **1** in order to investigate the reaction scope, and several representative results are summarized in Table 2. An array of trialkylamines (**2a-e**) having straight alkyl chains reacted with **1** and the corresponding benzimidazoles (**3a-e**) were obtained in a range of 57-72% yields. Generally, the product yield gradually decreased as the alkyl chain length on **2a-e** increases. Thus, in the reaction with **2d** and **2e**, a longer reaction time was needed for the allowable yield of products. Furthermore, in the case of **2e**, three-fold molar ratio of **2e** to **1** was necessary for the effective formation of **3e**. When the reaction was carried out with two-fold molar ratio of **2e** to **1** for 40 h under the employed conditions, **3e** was obtained in 31% yield. In the reaction with trialkylamines (**2f** and **2g**) having branched alkyl chains, similar reaction rate and yield were observed with triisoamylamine (**2g**), whereas higher reaction

Table 1. Optimization of conditions for the reaction of *o*-phenylenediamine (**1**) with tributylamine (**2a**)[a]

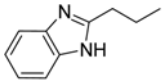
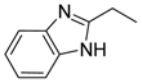
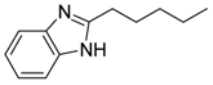
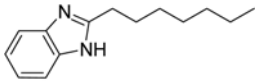
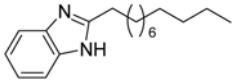
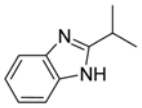
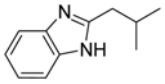
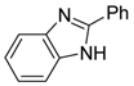


1 **2a** **3a** **4**

Run	Molar ratio of **2a** to **1**	Solvent	Temp (°C)	Time (h)	Yield (%)	
					3a	**4**
1	1	Toluene	110	20	47	0
2	2	Toluene	110	40	48	0
3[b]	2	Toluene	180	40	78	13
4	1	Toluene/H_2O[c]	110	20	72	2
5	2	Toluene/H_2O[c]	110	10	65	1
6	2	Toluene/H_2O[c]	110	20	73	10
7	2	Toluene/H_2O[c]	80	40	31	trace

[a]Reaction conditions: **1** (1 mmol), 5% Pd/C (0.05 mmol), solvent (10 mL), Ar (1 atm). [b]The reaction was performed in autoclave. [c]H_2O (0.5 mL).

Table 2. Pd/C-catalyzed synthesis of benzimidazoles from **1** and **2**

Alkylamines **2**	Conditions	Benzimidazoles **3**	Yield (%)
Bu_3N			
2a	110 °C, 20 h	**3a**	72
Pr_3N			
2b	110 °C, 20 h	**3b**	67
$[CH_3(CH_2)_5]_3N$			
2c	110 °C, 20 h	**3c**	57
OCt_3N			
2d	110 °C, 20 h	**3d**	40
	110 °C, 40 h		60
$CH_3(CH_2)_{11}N(CH_3)_2$			
2e	110 °C, 40 h	**3e**	57[a]
$^{i}Bu_3N$			
2f	150 °C, 40 h	**3f**	74
$[(CH_3)_2CHCH_2CH_2]_3N$			
2g	110 °C, 20 h	**3g**	71
$[CH_2=CHCH_2]_3N$			
2h	110 °C, 20 h	**3b**	73
$[CH_2=C(CH_3)CH_2]_3N$			
2i	110 °C, 20 h	**3f**	86
$(PhCH_2)_3N$			
2j	110 °C, 20 h	**3h**	100
$[CH_3(CH_2)_5]_2NH$			
2k	110 °C, 40 h	**3c**	31[b]
$CH_3(CH_2)_5NH_2$			
2l	110 °C, 40 h	**3c**	6[c]

[a]3 mmol of **2e** was used. [b]1.5 mmol of **2k** was used. [c]3 mmol of **2l** was used.

temperature and longer reaction time were needed for the effective formation of **3f** from the reaction with triisobutylamine (**2f**). Similar treatment of triallylamines (**2h** and **2i**) with **1** under the employed conditions afforded unexpected 2-alkyl substituted benzimidazoles instead of 2-vinyl substituted benzimidazoles. It appears that the double bonds are hydrogenated by the amine in the presence of Pd/C.[9,10] Tribenzylamine (**2j**) was also reacted with **1** to give 2-phenyl-1*H*-benzo[*d*]imidazole (**3h**) in quantitative yield. However, lower reaction rate and yield were observed with secondary and primary amines (**2k** and **2l**).

In summary, it has been shown that *o*-phenylenediamine effectively reacts with an array of trialkylamines in an aqueous medium in the presence of Pd/C to give benzimidazoles. Further study on transition metal-catalyzed amine exchange reaction in an aqueous medium along with the role of H_2O is in progress.

Experimental Section

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. The isolation of pure products was carried out via column (silica gel 60, 70-230 mesh, Merck) or thin layer (silica gel 60 GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification.

Typical Experimental Procedure. A mixture of *o*-phenylenediamine (**1**) (0.108 g, 1 mmol), tributylamine (**2a**) (0.185 g, 1 mmol), 5% Pd/C (0.106 g, 0.05 mmol) and toluene/H_2O (10 mL/0.5 mL) was placed in 25 mL round bottom flask. After the system was flushed with Ar from an Ar balloon connected to the flask *via* a reflux condenser, the reaction mixture was allowed to react at 110 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate catalyst residue. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture = 1/1) to give 2-propylbenzimidazole (**3a**) (0.115 g, 72%). All products are known and several selected spectroscopic data are shown below.

2-Propyl-1*H*-benzo[*d*]imidazole (3a). Solid; mp 156-157 °C (from diethyl ether) (lit.[11] 155-157 °C); ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3H), 1.85-1.94 (m, 2H), 2.93 (t, J = 7.6 Hz, 2H), 7.19-7.24 (m, 2H), 7.54-7.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.04, 21.98, 31.41, 114.76, 122.20, 138.79, 155.89.

2-Pentyl-1*H*-benzo[*d*]imidazole (3c). Solid; mp 162-163 °C (from ethanol) (lit.[12] 162-163 °C); ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.2, 3H), 1.21-1.37 (m, 4H), 1.83-1.91 (m, 2H), 2.97 (t, J = 7.7 Hz, 2H), 7.20-7.22 (m, 2H), 7.55-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.78, 28.58, 29.77, 31.92, 115.01, 122.44, 139.04, 156.25.

2-Isobutyl-1*H*-benzo[*d*]midazole (3g).[13,14] Solid; mp 187-188 °C (from hexane); ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 6H), 2.21-2.31 (m, 1H), 2.83 (d, J = 7.7 Hz, 2H), 7.20-7.24 (m, 2H), 7.55-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.44, 27.80, 37.78, 121.16, 154.47.

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