Application of Heterocyclic Compounds as Catalysts in Suzuki-Miyaura Cross-Coupling Reaction

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Received: 29.08.2019; Accepted: 19.11.2019 http://dx.doi.org/10.17776/csj.613060

Abstract. Four different benzimidazolium salts (1-4) were prepared in three steps at 80 °C and their structures were elucidated using spectroscopic methods. The compounds (1-4) obtained were tested in in situ medium as catalyst in the carbon-carbon (C-C) bond formation reactions of two different boronic acid derivatives with various aryl halides in the presence of palladium acetate (PdOAc)2 and sodium tert-butoxide (NaOBu3) as a base. With this reaction, four coupling products (5-8) were synthesized in different yields ranging from 11 to 93%. Compound 2 from the carbene precursors tested in the Suzuki-Miyaura cross-coupling reaction was found to be a more effective catalyst candidate than others.

Keywords: Suzuki-Miyaura coupling reaction, Benzimidazolium salt, Catalyst.

1. INTRODUCTION

Compounds containing benzimidazole nucleus demonstrate a wide variety of biological activity properties such as anticancer, antitubercular antimicrobial, antifungal, antioxidant, antidiabetic and etc [1-13]. On the other hand, heterocyclic benzimidazole derivatives have different application area and can be used as catalysts [14-16] and sensors [17, 18]. Therefore, benzimidazoles and their derivatives are consumed in large quantities in the chemical, medical and biological industries. So, they are among the most frequently synthesized heterocyclic compounds in the research studies, too.

Many chemicals used in pharmaceutical and agricultural chemistry have C-C (carbon-carbon) and C-N (carbon-nitrogen) bonds. Therefore, the formation reactions of these bonds are used in the synthesis of many organic materials of industrial importance [19]. Suzuki-Miyaura, Mizoroki-Heck, Sonogashira-Hagihara, Stille, Negishi, Kumada-Tamao-Corriu and Hiyama cross-coupling reactions are important C-C bond formation reactions (Scheme 1).
Suzuki-Miyaura coupling reaction, which is the most studied species among the cross-coupling reactions, is the reaction to form biaryl derivatives with organoborane derivatives of aryl halides in the presence of palladium catalyst and a base. The fact that boronic acid compounds commonly used in these reactions are non-toxic, stable against to air and moisture, and are commercially easily find adds particular importance to Suzuki-Miyaura cross-coupling reactions.

Inspired by the wide application areas of benzimidazoles, in this study, four different benzimidazolium salts were synthesized in order to find effective catalyst candidates and their structures were characterized. The catalytic activity studies were done in the Suzuki-Miyaura reaction and catalysts generated from compounds 1-4 and Pd(OAc)$_2$ as in situ gave C-C coupling products in high yields for 2 h at 80 °C.

2. MATERIALS AND METHODS

2.1. Reagents

Necessary reagents for the synthesis of the targeted heterocyclic compounds (1-4) and their catalytic activity studies were commercially purchased from Sigma-Aldrich, Merck and Scharlau. These are 3-methylbenzyl chloride, 2-(bromomethyl)benzonitrile, 2-methylbenzyl chloride, 1-(chloromethyl)naphthalene, 3-methoxybenzyl chloride, thianaphthene-2-boronic acid, phenylboronic acid, 4-chloroacetophenone, 4-chlorotoluene, 4-chloroanisole, 4-chloronitrobenzene, potassium hydroxide (KOH), sodium tertiarybutoxide (NaOBu$_t$), N,N-dimethylformamide (DMF), dichloromethane, formic acid, hexane, ethyl acetate, ethyl alcohol and diethyl ether.

NMR and IR were used for characterize the structures of the compounds obtained. In Erciyes University Central Research Laboratory, both $^1$H NMR and $^{13}$C NMR spectra were taken with Bruker Ultra Shield 400 MHz NMR Spectroscopy using CDCl$_3$ or DMSO-d$_6$ solvents. FT-IR Spectra were recorded in the range of 400-4000 cm$^{-1}$ by Pye Unicam spectroscopy.

Gas Chromatography (GC) was used to measure the catalytic activity of the generated compounds.
This was carried out by the SHIMADZU-2010 Plus (Kyoto, Japan) with a ROSTEK packed stainless steel column with a length and ID of 2.0 M, 2.0 mm respectively, was used with high purity nitrogen at a flow rate of 40 mL/min as a carrier gas and a flame ionization detector (FID) set at a temperature of 320 °C with an injection port temperature of 300 °C. Additionally, thermo Trace GC (Massachusetts, ABD) with Finnigan Polaris Q ion trap mass spectrometer in positive ion EI mode (GC-MS) was used to identify the catalytic activity results of some compounds in Suzuki-Miyaura coupling reaction. The instrument settings were used as injection port: 300 °C, injection type: split (1:20), injection volume: 1 μL (sample dissolved in 1 mL CH₂Cl₂ diluted 1:2), GC column: Zebron ZB5ms 30 m x 0.25 mm ID x 0.25 μm film thickness, carrier gas: helium (1.3 mL/min), oven program: 40 °C, hold 3 minutes, 12 °C/min ramp to 300 °C, hold 5 minutes, transfer line: 280 °C, MS temperature: 240 °C, EI electron energy: 70 eV, MS range: 46-650 m/z (3 minute solvent delay).

2.2. Synthesized benzimidazolium salts, 1-4

Four benzimidazolium salts (1-4) were prepared easily and economically according to the literature procedures [20] (Scheme 2) and their structures were characterized using different spectroscopic methods [20].

![Scheme 2. The open structures of the synthesized benzimidazolium salts 1-4.](image)

Briefly, benzimidazolium salts (2-5), Pd(OAc)₂ (0.1 mmol), aryl chlorides (1 mmol), boronic acid derivatives (1.5 mmol) and NaOBu' (2 mmol) as base in DMF/H₂O (1:1) mixture as solvents were added to a 25 mL Schlenk tube. The reaction was conducted at 80 °C for 2 h. After the specified period of time completed, the reaction temperature was dropped to room temperature. Ethyl acetate and hexane (1:5) were added on this reaction mixture and it mixed at rapidly. The two phases formed were separated and MgSO₄ was added to the organic phase for removing water. The products were purified with flash column chromatography using 5 mL of hexane and 1 mL of ethyl acetate as solvents. Final products were analyzed using GC.

3. RESULTS AND DISCUSSION

Catalytic activities of the compounds (1-4) were tested in Suzuki-Miyaura reaction. For this, benzimidazolium salt (1-4), Pd(OAc)₂, aryl chloride, phenylboronic acid/tianaphthene-2-boronic acid and NaOBu' were used. The reaction was carried out in DMF/H₂O mixture at 80 °C with heating for two hours. At the end of the this time (2 h), the waited product (5-8) was purified by column chromatography and analyzed using GC. The results obtained are presented in Table 1.

In the presence of catalysts synthesized from 1-4/Pd(OAc)₂, various Suzuki-Miyaura coupling products (5-8) were obtained from the reaction of 4-chloronitrobenzene, 4-chloroanisole or 4-chlorotoluene with phenylboronic acid and 4-chloroacetophenone with tianaften-2-boronic acid. These are 1-phenyl-4-nitrobenzene (5), 1-phenyl-4-methoxybenzene (6), 1-phenyl-4-methylbenzene (7) and 1-(4-(benzo[b]thiophen-2-yl)phenyl)ethanone (8). It is seen that from Table 1 the reaction yields of the Suzuki-Miyaura coupling products are between 11 and 93% and their conversions are among 11 and 98%.

The product 1-phenyl-4-nitrobenzene (5), formed from the coupling of phenylboronic acid with 4-chloronitrobenzene, was obtained in 27% yield using ligand 1 (Table 1, Entry 1) (Figure 1).
Table 1. Application of synthesized compounds as catalysts in the Suzuki-Miyaura cross-coupling reaction.

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\begin{array}{cccccc}
\text{Entry} & \text{Aryl chloride} & \text{Boronic acid derivative} & \text{LHX} & \text{Product} & \text{Yield (\%)} & \text{Conversion (\%)} \\
1 & \text{O}_2\text{N-} & & 1 & \text{O}_2\text{N-} & 27 & 29 \\
2 & \text{O}_2\text{N-} & & 2 & \text{O}_2\text{N-} & 61 & 93 \\
3 & \text{O}_2\text{N-} & & 3 & \text{O}_2\text{N-} & 31 & 41 \\
4 & \text{O}_2\text{N-} & & 4 & \text{O}_2\text{N-} & 31 & 56 \\
5 & \text{O}_2\text{N-} & & 1 & \text{O}_2\text{N-} & 65 & 85 \\
6 & \text{O}_2\text{N-} & & 2 & \text{O}_2\text{N-} & 91 & 96 \\
7 & \text{O}_2\text{N-} & & 3 & \text{O}_2\text{N-} & 21 & 22 \\
8 & \text{O}_2\text{N-} & & 4 & \text{O}_2\text{N-} & 19 & 52 \\
9 & \text{O}_2\text{N-} & & 1 & \text{O}_2\text{N-} & 74 & 89 \\
10 & \text{O}_2\text{N-} & & 2 & \text{O}_2\text{N-} & 48 & 85 \\
11 & \text{O}_2\text{N-} & & 3 & \text{O}_2\text{N-} & 93 & 98 \\
12 & \text{O}_2\text{N-} & & 4 & \text{O}_2\text{N-} & 13 & 68 \\
13 & \text{O}_2\text{N-} & & 1 & \text{O}_2\text{N-} & 11 & 11 \\
14 & \text{O}_2\text{N-} & & 2 & \text{O}_2\text{N-} & 82 & 94 \\
15 & \text{O}_2\text{N-} & & 3 & \text{O}_2\text{N-} & 58 & 74 \\
16 & \text{O}_2\text{N-} & & 4 & \text{O}_2\text{N-} & 44 & 61 \\
\end{array}
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*Reaction conditions: p-R-C₆H₄Cl (1 mmol), Pd(OAc)₂, boronic acid derivative (1.5 mmol), NaOBut (2 mmol), LHX (1-4), DMF-H₂O (2-2 mL), 80 °C, 2 h.

Figure 1. Carbon-Carbon coupling of 4-chloronitrobenzene with phenylboronic acid in the presence of Pd(OAc)₂ and compound 1.

Figure 2. Carbon-Carbon coupling of 4-chloroanisole with phenylboronic acid in the presence of Pd(OAc)₂ and compound 1.
The 1-phenyl-4-nitrobenzene (5) product was obtained in a higher yield in the presence of ligand 2 containing 3-methylbenzyl substituent (Table 1, entry 2). Furthermore, the highest yield was obtained when compound 2 was used in the coupling of 4-chloroanisole with phenyl boronic acid (Table 1, entry 6) (Figure 3).

Figure 3. Carbon-Carbon coupling of phenylboronic acid with 4-chloroanisole in the presence of Pd(OAc)\(_2\) and compound 2.

Using compounds 1, 2 and 4, the images of results of C-C coupling of 4-chloroacetophenone with thianaphthene-2-boronic acid in the presence of Pd(OAc)\(_2\) were given in the figures 4-6, respectively.

Figure 4. Carbon-Carbon coupling of 4-chloroacetophenone with thianaphthene-2-boronic acid in the presence of Pd(OAc)\(_2\) and compound 1.

Figure 5. Carbon-Carbon coupling of 4-chloroacetophenone with thianaphthene-2-boronic acid in the presence of Pd(OAc)\(_2\) and compound 2.

The highest yield and conversion were obtained when ligand 3 was used to obtain 1-phenyl-4-methylbenzene (7) product (Table 1, entry 11). The lowest activity in the coupling of thianaphthen-2-boronic acid with 4-chloroacetophenone was obtained when ligand 1 with 2-methylbenzyl substituent was used (Table 1, entry 13). On the other hand, the highest yield was obtained when ligand 2 was used in the same coupling reaction (Table 1, entry 14). This result attaches extreme importance to ligand 2.

4. CONCLUSION

In this study, four different organic compounds were prepared according to the methods in the literature and their structures were characterized by various spectroscopic methods. These compounds were used as catalysts for the C-C coupling of various aryl halides with two different phenylboronic acids by interacting with Pd(OAc)\(_2\) in \textit{in situ} medium. Although the activities of the tested catalysts were generally obtained very close to each other, it was seen that the catalyst formed as \textit{in situ} by using compound 2 was observed more active than the others.

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