



Synthesis of New Bisbenzimidazole Salts and Determination Their Ligand Activities in C-C Coupling Reactions

Ülkü YILMAZ^{1*}, Hasan KÜÇÜKBAY²

¹ Department of Engineering Basic Sciences, Faculty of Engineering and Natural Sciences, Malatya Turgut Özal University, Malatya, Turkey.

² Department of Chemistry, Faculty Science and Arts, İnönü University, Malatya, Turkey.

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ABSTRACT: New bisbenzimidazole salts were synthesized with 1,4-bis(1*H*-benzo[d]imidazol-1-yl)butane and benzyl halides. These new ligands carried out in Suzuki-Miyaura and Mizoroki-Heck C-C coupling reaction in the presence of palladium(II) acetate. It was observed that remarkable ligand activities of benzimidazolium halides (**L**₁, **L**₂, **L**₃).

Keywords: Bisbenzimidazole, C-C coupling, Suzuki-Miyaura, Mizoroki-Heck, biphenyl, stilbene.

1. INTRODUCTION

Due to various bioactivities of biphenyl and stilbene cored molecules, their synthetic methods always attract attention [1-4].

The Suzuki-Miyaura (SM) cross-coupling reaction is one of the most excellent tools for the synthesis of symmetrical or unsymmetrical biphenyl derivatives derived from aryl halides and arylboronic acids [5-10]. The Mizoroki-Heck (MH) reaction is also one of the best methods for the synthesis of stilbenes from alkenes and aryl halides [11-15].

Doubtless, the center of the catalytic systems applied for the carbon-carbon bond formation reaction is palladium metal [16-18]. Moreover, because of their superior properties such as low toxicity, high electron-donating, and easy *in situ* preparation, N-Heterocyclic carbenes (NHCs) are preferred to other ligands in presence of palladium in coupling reactions [19-21]. On the other hand, because of the time of the coupling reaction is significantly shortened, microwave irradiation is preferred to conventional heating [22-26].

As mentioned above, due to the excellent properties of NHC ligands, in this study, three new benzimidazole salts were synthesized as NHC precursors and their ligand activities were investigated in the Suzuki-Miyaura and Mizoroki-Heck reactions.

*Corresponding Author: ulku.yilmaz@ozal.edu.tr

ORCID number of authors: ¹ 0000-0002-2806-4781, ² 0000-0002-7180-9486

2. MATERIAL AND METHODS

In first, the chemicals were determined required for the experiments and all of them were bought from Acros, Aldrich, Merck, and Fluka Chemical Co. All structural characterization of the new compounds were implemented via NMR, IR, microanalysis. ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded using Bruker Avanced III 400 UltraShield high-performance digital FT NMR spectrometer. Infrared spectra were recorded as KBr pellets in the range 4000-400 cm⁻¹ on a Perkin-Elmer Spectrum One FT-IR spectrometer. Elemental analysis was performed by LECO CHNS-932 elemental analyzer. Melting points were identified using an electrothermal melting point apparatus, Electrothermal 9200. All catalytic activity experiments were carried out in a microwave oven system manufactured by Milestone (Milestone Start S Microwave Labstation for Synthesis) under aerobic conditions.

2.1. Synthesis of 1,1'-(butane-1,4-diyl)bis(3-benzyl-1H-benzo[d]imidazol-3-ium) dichloride

A mixture of 1,4-bis(1H-benzo[d]imidazol-1-yl)butane (0.50 g, 1.73 mmol), benzyl chloride (0.44 g, 3.46 mmol) and DMF (5 mL) was refluxed in water bath. Then all volatiles were removed in vacuo and crude product was crystallised from ethanol. Yield: 80 %, 0.75 g, m.p.: 220-221 °C. ¹H-NMR (DMSO_d₆-400 MHz): δ 10.56 (s, 2H, NCHN), 8.19-7.36 (m, 18H, Ar-H), 5.87 (s, 4H, CH₂-C₆H₅), 4.68 (bs, 4H, N-CH₂), 2.11 (bs, 4H, -CH₂-) ppm. ¹³C-NMR (DMSO_d₆-100 MHz): δ 143.2 (NCHN), 134.6, 131.8, 131.6, 129.5, 129.4, 129.1, 127.2, 127.1, 114.5, 114.4 (Ar-C), 50.3 (CH₂-C₆H₅), 46.5 (N-CH₂), 25.8 (-CH₂-) ppm. IR: ν_(C=N): 1561 cm⁻¹. Anal. Calcd. for C₃₂H₃₂Cl₂N₄ (543.54): C, 70.71; H, 5.93; N, 10.31. Found: C, 70.42; H, 5.80; N, 10.18. **L**₂ and **L**₃ were synthesized similar method.

2.2. 1,1'-(butane-1,4-diyl)bis(3-(4-methoxybenzyl)-1H-benzo[d]imidazol-3-ium) dibromide

Yield :78 %, 0.93 g, m.p.: 225-227 °C. ¹H-NMR (DMSO_d₆-400 MHz): δ 10.48 (s, 2H, NCHN), 8.18-6.93 (m, 16H, Ar-H), 5.76 (s, 4H, CH₂-C₆H₅), 4.65 (bs, 4H, N-CH₂), 3.73 (s, 6H, OCH₃), 2.08 (bs, 4H, -CH₂-) ppm. ¹³C-NMR (DMSO_d₆-100 MHz): δ 142.9 (NCHN), 159.9, 131.8, 131.2, 130.6, 127.1, 127.0, 126.4, 114.7, 114.4 (Ar-C), 55.7 (OCH₃), 49.9 (CH₂-C₆H₅), 46.6 (N-CH₂), 25.8 (-CH₂-) ppm. IR: ν_(C=N): 1561 cm⁻¹. Anal. Calcd. for C₃₄H₃₆Br₂N₄O₂ (692.50): C, 58.97; H, 5.24; N, 8.09. Found: C, 58.52; H, 5.12; N, 8.00.

2.3. 1,1'-(butane-1,4-diyl)bis(3-(4-nitrobenzyl)-1H-benzo[d]imidazol-3-ium) dibromide

Yield :75 %, 0.94 g, m.p.: 229-231 °C. ¹H-NMR (DMSO_d₆-400 MHz): δ 10.21 (s, 2H, NCHN), 8.26-7.66 (m, 16H, Ar-H), 6.02 (s, 4H, CH₂-C₆H₅), 4.66 (bs, 4H, N-CH₂), 2.12 (bs, 4H, -CH₂-) ppm. ¹³C-NMR (DMSO_d₆-100 MHz): δ 143.4 (NCHN), 148.0, 141.8, 131.8, 131.3, 129.9, 127.4, 127.2, 124.4, 114.5, 114.2 (Ar-C), 49.5 (CH₂-C₆H₅), 46.9 (N-CH₂), 25.9 (-CH₂-) ppm. IR: ν_(C=N): 1562 cm⁻¹. Anal. Calcd. for C₃₂H₃₀Br₂N₆O₄ (722.44): C, 53.20; H, 4.19; N, 11.63. Found: C, 53.00; H, 4.12; N, 11.30.

2.4. General methode for C-C coupling reaction

A mixture of aryl halide (1 mmol), phenylboronic acid or styrene (1mmol), K₂CO₃ (2 mmol), Pd(OAc)₂ (0.01 mmol), ligand (0.01 mmol) and solvent (DMF:H₂O (1:1), 6 mL) was added in an apparatus of microwave equipment. The mixture was stirred and heated at 100 °C by microwave irradiation (300 W) for 10 min. Then, it was cooled and extracted with ethyl acetate. The purification was done by crystallization from ethyl acetate/n-hexane (1:1). The isolated yield was calculated. The product structures were determined by ¹H-NMR and a comparison of the melting point.

3. RESULTS AND DISCUSSION

All ligands were synthesized by reaction of 1,4-bis(1*H*-benzo[d]imidazol-1-yl)butane and benzyl halides (Figure 1). The structures of NHC precursor ligands were characterized by ¹H NMR, ¹³C NMR, IR and elemental analysis. The ¹H NMR and ¹³C NMR spectra of **L**₁, **L**₂ and **L**₃ ligands were viewed respectively. The decisive salt peaks for benzimidazolium salts were observed at 10.56, 10.48 and 10.21 ppm; 143.2, 142.9 and 143.4 ppm. IR spectra of ligands showed a stretching band of the C=N bonds at 1561, 1561 and 1562 cm⁻¹. These results are coherent with the literature [27, 28].

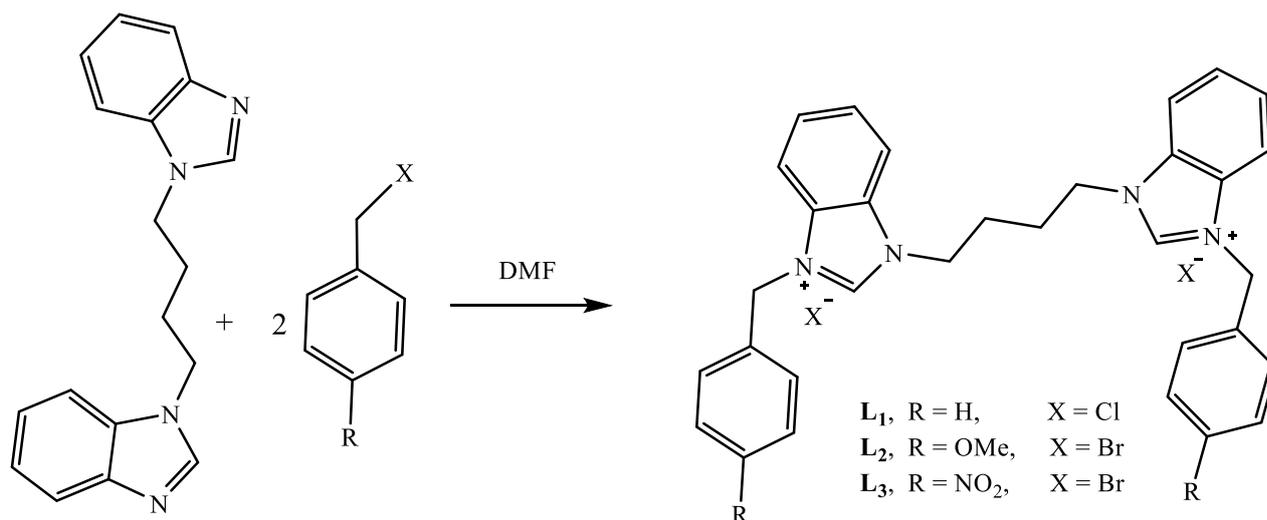


Figure 1. Synthesis procedure of bisbenzimidazolium halides

The effects of ligands derived from the new benzimidazolium halides were investigated on the Suzuki-Miyaura and Mizoroki-Heck C-C coupling reactions. Iodobenzene, bromobenzene, 4-iodoanisole, 4-bromoanisole, phenylboronic acid and styrene were used as reactants for the coupling reactions. A series of experiments were carried out to determine the optimization conditions (Table 1, entries 1-11). The results showed that the best reaction conditions were provided when using a catalytic system consist of K₂CO₃ (2 mmol), DMF:H₂O (6 mL), Pd(OAc)₂ and ligand (0,01 mmol) at 100 °C (Table 1, entry 4). When the activities of all ligands in the catalytic system were examined according to optimized conditions, it was observed that **L**₂ gave the best results. This is caused by the electron-donating methoxy group of **L**₂ compared to the other ligands.

Table 1. Effects of ligand-changing on the Suzuki-Miyaura reaction

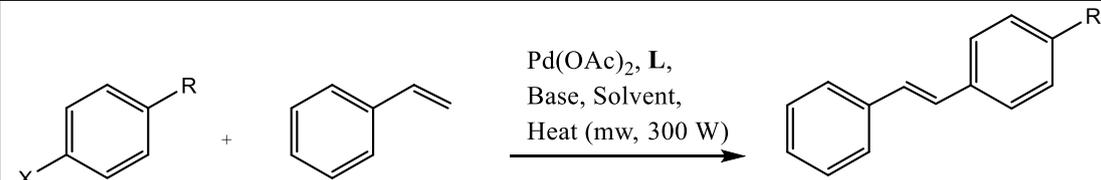
Entry	X	R	L	Base	Solvent	Time (min)	Heat (°C)	^a Yield %
1	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O (1:1)	5	60	58
2	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	5	80	71
3	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	5	100	89

4	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	99
5	I	H	L ₂	K ₂ CO ₃	EtOH	10	100	80
6	I	H	L ₂	K ₂ CO ₃	H ₂ O	10	100	38
7	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^b np
8	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^c 50
9	I	H	L ₂	KOH	DMF:H ₂ O	10	100	60
10	I	H	L ₂	NaOH	DMF:H ₂ O	10	100	57
11	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^d 75
12	I	H	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	98
13	I	H	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	95
14	I	OCH ₃	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	96
15	I	OCH ₃	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	98
16	I	OCH ₃	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	92
17	Br	H	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	90
18	Br	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	95
19	Br	H	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	86
20	Br	OCH ₃	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	87
21	Br	OCH ₃	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	90
22	Br	OCH ₃	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	80

Reaction conditions: aryl halide (1 mmol), benzenboronic acid (1 mmol), solvent (6 mL, DMF:H₂O (1:1)), base (2 mmol), Pd(OAc)₂ (0,01 mmol), L (0,01 mmol), ^aisolated yield, ^b no product, without Pd(OAc)₂, ^cwithout L, ^damount of 0.005 mmol Pd(OAc)₂/L.

The effects of ligands were also investigated for the Mizoroki Heck reaction under similar conditions. The best results were also obtained by L₂ ligand (Table 2, entries 4, 15, 18 and 21). In addition to the ligand change, the change of alkyl halides was also observed to affect yields. Iodoaryls provided more good yields because of the nature of halogen.

Table 2. Effects of ligand-changing on the Mizoroki-Heck reaction

								
Entry	X	R	L	Base	Solvent	Time (min)	Heat (°C)	^a Yield %
1	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	5	60	25
2	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	5	80	56
3	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	5	100	80
4	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	97
5	I	H	L ₂	K ₂ CO ₃	EtOH	10	100	70
6	I	H	L ₂	K ₂ CO ₃	H ₂ O	10	100	18
7	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^b np
8	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^c 48
9	I	H	L ₂	KOH	DMF:H ₂ O	10	100	51
10	I	H	L ₂	NaOH	DMF:H ₂ O	10	100	44
11	I	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	^d 65
12	I	H	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	92
13	I	H	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	80
14	I	OCH ₃	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	88
15	I	OCH ₃	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	91
16	I	OCH ₃	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	80
17	Br	H	L ₁	K ₂ CO ₃	DMF:H ₂ O	10	100	77
18	Br	H	L ₂	K ₂ CO ₃	DMF:H ₂ O	10	100	80
19	Br	H	L ₃	K ₂ CO ₃	DMF:H ₂ O	10	100	69

20	Br	OCH ₃	L₁	K ₂ CO ₃	DMF:H ₂ O	10	100	76
21	Br	OCH ₃	L₂	K ₂ CO ₃	DMF:H ₂ O	10	100	78
22	Br	OCH ₃	L₃	K ₂ CO ₃	DMF:H ₂ O	10	100	67

Reaction conditions: aryl halide (1 mmol), styrene (1 mmol), solvent (6 mL, DMF:H₂O (1:1)), base (2 mmol), Pd(OAc)₂ (0,01 mmol), L (0,01 mmol), ^aisolated yield, ^b no product, without Pd(OAc)₂, ^cwithout L, ^damount of 0.005 mmol Pd(OAc)₂/L.

4. CONCLUSIONS

A group of benzimidazole salts was synthesized including electron-withdrawing and electron-donating groups (**L₁**, **L₂**, **L₃**). The structural analysis of these ligands was via spectroscopic techniques. These benzimidazolium halides were used as NHC precursor ligands in the catalytic systems for C-C coupling (SM, MH) reactions. All ligands were showed excellent activities with isolated yields between 67-99 % in the catalytic systems including K₂CO₃ (2 mmol), DMF:H₂O (1:1) (6 mL), Pd(OAc)₂ and ligand (0,01 mmol) at 100 °C for coupling reactions. Nevertheless the best activities were obtained by **L₂** because of its electron-donating methoxy group.

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