

Microwave Assisted Catalytic Activity of Some *bis*-5(6)-Nitrobenzimidazole Salts for Heck and Suzuki Cross-Coupling Reactions

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A mixture of *bis*-5(6)-nitrobenzimidazole salts (**2a-h**), Pd(OAc)₂ and K₂CO₃ in DMF-H₂O catalyzes, in good yield the Suzuki and Heck cross-coupling reactions for synthesis of biaryl and stilbene derivatives assisted by microwave irradiation in the short time.

Key Words: *Bis*-benzimidazoles, N-Heterocyclic carbenes, Palladium carbene complexes, Heck coupling, Suzuki coupling, Microwave.

INTRODUCTION

Metal-mediated cross-coupling reactions encompass an array of transformations that create a new single bond between a nucleophilic (usually an organometallic derivative, amine or alcohol) and an electrophilic (an organic halide or pseudohalide) reactants¹. The cross-coupling of organoboron derivatives (Suzuki-Miyaura reaction) is currently the most widely used cross-coupling protocol because of the commercial availability of a wide selection of solid as well as air- and moisture tolerant boronic acids^{2,3}. The Heck reaction⁴, Pd catalyzed C-C coupling between aryl or vinyl halides and triflates with alkenes, has been extensively explored and became an important tool for fine chemical synthesis and industrial applications^{5,6}. Palladium-catalyzed C-C bond-forming reactions are among the most versatile and powerful synthetic methods. For the last two decades, N-heterocyclic carbenes (NHC's) have enjoyed increasing popularity as ligands in Pd-mediated cross-coupling and related transformations because of their superior performance compared to the more traditional tertiary phosphanes². Both N-heterocyclic carbenes and electron-rich alkenes which can be used as N-heterocyclic carbenes source highly air and moisture sensitive and require handling under strictly inert conditions⁷⁻¹⁰. Contrary to cumbersome preparation and isolation of N-heterocyclic carbenes and electron-rich alkenes, *in situ* preparation of N-heterocyclic carbenes are more advantages using a strong base, diazolium salts and a common palladium source such as PdCl₂ or Pd(OAc)₂, etc. in number of catalytic synthesis, particularly C-C coupling reactions. Pd(II)-NHC complexes are more attractive as precatalysts because of their stability to air, moisture

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and heating and also have an excellent long-term storage profile². Pd(OAc)₂/benzimidazole or imidazole ligands could be very effective catalytic system particularly in Suzuki and Heck cross-coupling reactions^{11,12}. Although, there are extensive studies about Pd(OAc)₂/benzimidazole or imidazole catalytic system in Heck and Suzuki cross-coupling reactions. But, less attention has been paid to the Pd(OAc)₂/*bis*-benzimidazole catalytic system in Heck and Suzuki cross-coupling reactions^{13,14}.

On the other hand, high-speed synthesis with microwaves has attracted a considerable amount of attention in recent years. The use of metal catalysts in conjunction with microwaves may have significant advantages over traditional heating methods since the inverted temperature gradient under microwave conditions may lead to an increased lifetime of catalyst through elimination of wall effects¹⁵. The C-C cross-coupling in Suzuki and Heck reactions have also been carried out in short time in high yield, incorporating of microwave irradiation¹⁶⁻²⁰.

Herein, we report the microwave-assisted catalytic activity of Pd(OAc)₂/*bis*-5(6)-nitrobenzimidazole catalytic system in Heck and Suzuki cross-coupling reactions, after reported on synthesise and antimicrobial activities of *bis*-5(6)-nitrobenzimidazole derivatives²¹.

EXPERIMENTAL

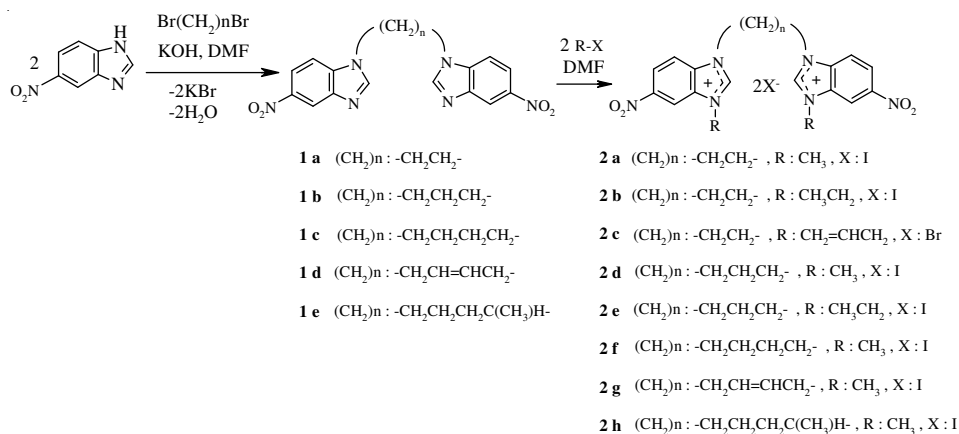
Unless otherwise stated, all reactions were performed under a dry argon atmosphere using standard Schlenk techniques. All reagents were purchased from Merck, Aldrich and Fluka Chemical Co. Solvents and substrates were dried with standard methods and freshly distilled prior to use. ¹H NMR spectra were recorded using Bruker DPX-300 high performance digital FT-NMR (Bruker WM360, Bruker Instruments, Inc., Billerica, USA) spectrometers. Melting points were recorded using an electrothermal melting point apparatus, Electrothermal 9200 (Electrothermal Engineering Ltd., Essex, UK). GC-MS spectra were recorded on an Agilent 6890 N GC and 5973 Mass Selective Dedector using with HP-INNOWAX column of 60 m length, 0.25 mm diameter and 0.25 μm film thicknesses.

Bis-5(6)-nitrobenzimidazole salts (**2a-h**) used in this work were prepared according to recently reported literature procedures summarized in **Scheme-I**²¹.

General procedure for the Suzuki reactions: Pd(OAc)₂ (1 mmol %), *bis*-5(6)-nitrobenzimidazolium halides (**2a-h**) (1 mmol %), aryl chloride (1 mmol %), phenylboronic acid (1.2 mmol %), K₂CO₃ (2 mmol), water (3 mL), DMF (3 mL) were added to microwave apparatus and the mixture was heated at 145 °C (400 W) for 5 min. It was carried out ramp time 4 min to reach to 145 °C temperature. At the end of reaction, the mixture cooled and extracted with ethyl acetate/*n*-hexane (1:5). The extract filtered on silica gel column. The purity of coupling compounds was checked by GC-MS, NMR and yields on based aryl halide.

General procedure for the Heck reactions: Pd(OAc)₂ (1 mmol %), *bis*-5(6)-nitrobenzimidazolium halides (**2a-h**) (1 mmol %), aryl chloride (1 mmol %), styrene (1.2 mmol %), K₂CO₃ (2 mmol), water (3 mL), DMF (3 mL) were added to microwave

apparatus and the mixture was heated at 145 °C (400 W) for 5 min. It was carried out ramp time 4 min to reach to 145 °C temperature. At the end of reaction, the mixture cooled and extracted with ethyl acetate/*n*-hexane (1:5). The extract filtered on silica gel column. The purity of coupling compounds was checked by GC-MS, NMR and yields on based aryl halide.



Scheme-I: Synthesis pathway of *bis*-5(6)-nitrobenzimidazole salts, **2a-h**

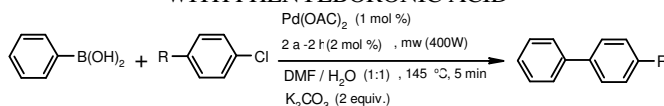
RESULTS AND DISCUSSION

Bis-5(6)-nitrobenzimidazolium halides (**2a-2h**) were obtained derived from reactions of 1,1'-alkylenedi-5(6)nitrobenzimidazoles and methyl iodide, ethyl iodide and allyl bromide in refluxing DMF in good yields according to the literature method²¹. The purities of *bis*-5(6)-nitrobenzimidazolium halides (**2a-2h**) were checked by ¹H NMR spectrometer and melting points.

The Suzuki coupling reaction: The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids is one of the most efficient methods for the preparations of biaryl derivatives. The catalytic yield of the coupling is dependent on a variety of parameters such as temperature, solvent, base and catalyst loading. In order to find the optimum reaction conditions for the Suzuki coupling reaction, a series of test experiments was performed with catalyzed by 4-chloroanisole and phenylboronic acid as model compounds. The optimum parameters (1 mol % Pd(OAc)₂ and 2 equivalents K₂CO₃ in DMF-H₂O (1:1) at 145 °C/400 W by microwave irradiation in 5 min) followed in Suzuki coupling reaction. Control experiments showed that the Suzuki coupling reaction did not occur in the absence of **2a-h** in 5 min both under microwave or conventional heating.

Of the five different aryl chlorides used in the Suzuki coupling with phenylboronic acid, the ones with electron-withdrawing substituents were found to give the highest yields (Table-1, entries 25-32). As can be seen in Table-1, high C-C coupling product was observed from reaction of 4-chlorobenzaldehyde with

TABLE-1
SUZUKI COUPLING REACTIONS OF ARYL CHLORIDES
WITH PHENYLBORONIC ACID



Entry	R	Compd.	Yield (%)	Entry	R	Compd.	Yield (%)
1	CH ₃	2a	80	21	SCH ₃	2e	52
2	CH ₃	2b	81	22	SCH ₃	2f	83
3	CH ₃	2c	82	23	SCH ₃	2g	82
4	CH ₃	2d	80	24	SCH ₃	2h	81
5	CH ₃	2e	74	25	CHO	2a	87
6	CH ₃	2f	86	26	CHO	2b	85
7	CH ₃	2g	83	27	CHO	2c	83
8	CH ₃	2h	84	28	CHO	2d	81
9	OCH ₃	2a	64	29	CHO	2e	76
10	OCH ₃	2b	66	30	CHO	2f	80
11	OCH ₃	2c	64	31	CHO	2g	90
12	OCH ₃	2d	61	32	CHO	2h	86
13	OCH ₃	2e	67	33	NH ₂	2a	63
14	OCH ₃	2f	62	34	NH ₂	2b	64
15	OCH ₃	2g	69	35	NH ₂	2c	69
16	OCH ₃	2h	72	36	NH ₂	2d	42
17	SCH ₃	2a	81	37	NH ₂	2e	56
18	SCH ₃	2b	80	38	NH ₂	2f	70
19	SCH ₃	2c	78	39	NH ₂	2g	65
20	SCH ₃	2d	50	40	NH ₂	2h	71

Yields are based on aryl chloride. All reactions were monitored by GC-MS.

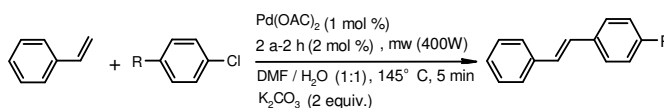
phenylboronic acid as expected. It can be also said that, increasing the bridge carbon chain between the benzimidazole moieties can effect the catalytic yield positively.

Heck coupling reaction: The Heck reaction, a palladium-catalyzed vinylic substitution, is typically conducted with alkenes and organohalides or pseudohalides as reactants. Numerous elegant synthetic transformations based on C-C bond-forming Heck reactions have been developed both in classical organic synthesis and natural product chemistry^{15,22}. The similar optimum parameters (1 mol % Pd(OAc)₂ and 2 equivalent K₂CO₃ in DMF-H₂O (1:1) at 145 °C/400 W by microwave irradiation in 5 min) followed in Suzuki coupling reaction were also used in Heck reactions to obtain the efficient catalytic conversation. Control experiments showed that the Heck coupling reaction did not occur in the absence of **2a-h** in 5 min both under microwave or conventional heating.

The results obtained from optimum conditions are given in Table-2. Under the optimized reaction conditions, five different aryl chlorides bearing electron-donating and electron-withdrawing groups reacted with styrene, affording the coupled products in almost good yield. As expected, aryl chlorides with electron-deficient substituents

were beneficial for the conversions. Increasing the bridge carbon chain between the benzimidazole moieties can also effect the catalytic yield positively in Heck reaction as seen in Table-2. At the end of the reaction, black coloured particles which probably from palladium nanoparticles were observed in the reaction mixture. As can be seen in Table-2, high C-C coupling product (Table-2, entries 25-32) was observed from reaction of 4-chlorobenzaldehyde with styrene as expected.

TABLE-2
HECK COUPLING REACTIONS OF ARYL CHLORIDES WITH STYRENE



Entry	R	Compd.	Yield (%)	Entry	R	Compd.	Yield (%)
1	CH ₃	2a	69	21	SCH ₃	2e	76
2	CH ₃	2b	65	22	SCH ₃	2f	86
3	CH ₃	2c	62	23	SCH ₃	2g	82
4	CH ₃	2d	68	24	SCH ₃	2h	85
5	CH ₃	2e	69	25	CHO	2a	74
6	CH ₃	2f	67	26	CHO	2b	76
7	CH ₃	2g	70	27	CHO	2c	78
8	CH ₃	2h	71	28	CHO	2d	75
9	OCH ₃	2a	50	29	CHO	2e	83
10	OCH ₃	2b	69	30	CHO	2f	87
11	OCH ₃	2c	60	31	CHO	2g	86
12	OCH ₃	2d	61	32	CHO	2h	88
13	OCH ₃	2e	65	33	NH ₂	2a	64
14	OCH ₃	2f	70	34	NH ₂	2b	65
15	OCH ₃	2g	81	35	NH ₂	2c	64
16	OCH ₃	2h	64	36	NH ₂	2d	62
17	SCH ₃	2a	78	37	NH ₂	2e	61
18	SCH ₃	2b	80	38	NH ₂	2f	65
19	SCH ₃	2c	68	39	NH ₂	2g	66
20	SCH ₃	2d	73	40	NH ₂	2h	67

Yields are based on aryl chloride. All reactions were monitored by GC-MS.

Conclusion

The precatalysts used in this work were prepared from the corresponding *bis*-5(6)-nitrobenzimidazolium salts (**2a-2h**) directly, thereby avoiding the handling of an isolated, highly moisture- and air-sensitive carbene.

We tested eight *bis*-5(6)-nitrobenzimidazolium salts bearing methyl, ethyl, allyl substituents (**2a-2h**) from *bis*-benzimidazole and appropriate alkyl halides. The use of palladium catalyst system including the *bis*-benzimidazolium salts in the Suzuki coupling and Heck reactions gives better yields under microwave-assisted moderate conditions and very short reaction times compared with those given in

literature. Both the Suzuki and Heck reactions were carried out by 400 W power microwave irradiation at 145 °C in only 5 min. It can be concluded that, both Suzuki and Heck coupling reactions may accelerate by microwave irradiation particularly bearing electron-withdrawing substituents in Suzuki and Heck coupling reactions.

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