HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 3: (1), 2013, 41-48**

MICROWAVE PROMOTED SUZUKI COUPLINGS OF 2,6-DIBROMO PYRIDINE WITH ARYL BORONIC ACIDS : SYNTHESIS OF MONO AND DIARYL PYRIDINES

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ABSTRACT

A simple and general method for the synthesis of symmetrical and unsymmetrical aryl pyridines developed under Microwave irradiation by adopting Suzuki-Miyaura cross couplings. A variety of boronic acids are coupled with 2, 6-dibromo pyridines **(1a – h)** using Pd[dppf]Cl_2 under conventional and Microwave irradiation. Microwave irradiation facilitated reaction course and afforded mono**(2a – h)** and double coupled**(3a – h)** products in moderate to high yields in just 15 mins.

KEYWORDS : 2,6-Dibromo pyridine, Aryl boronic acids, Pd-cross coupling, Microwave irradiation(MWI), Aryl pyridines.

INTRODUCTION

Palladium catalyzed carbon carbon bond formation is a versatile practical[1] tool in organic synthesis. Suzuki-Miyaura coupling of aryl halides with organo boronic acids has been recognized as one of the most important palladium catalyzed cross coupling reaction and represents one of the most widely used method for the synthesis of biaryls and functionalized heterocyclics which are important intermediates in organic synthesis[1,2]. Versatility of this reaction ranges from the synthesis of novel materials to industrial manufacture of pharmaceuticals[3]. Suzuki coupling tolerates multifunctions and co-solvent water[4]. Phosphine ligands are generally used to complex and accelerate the palladium species and excellent results have been reported for the palladium catalyzed cross coupling.
Pyridine derivatives exhibited various types of biological activities such as antimicrobial[5], antibacterial[6], analgesic[7], antiparkinson[8], anticonvulsantant[8] antitumorial[9], cytotoxic[10], antimalarial[11], antidiabetic[12] and receptor antagonists[13]. Son et al have synthesized diaryl substituted pyridines and reported antitumor activity[14]. Direct cross coupling of pyridyl halides and boronic acids represents one of the most convenient approaches to diaryl pyridines synthesis. Previously only a handful of reports of multiple cross couplings of halo pyridines carried out

under conventional conditions[15]. In order to examine efficiency of Suzuki-Miyaura cross coupling on symmetrically substituted 2,6-dihalo pyridines and to synthesize 2,6-diaryl pyridines, we have chosen cheaper and readily available 2,6-dibromo pyridine and carried out cross coupling with various aryl boronic acids using Pd[dppf]Cl_2 catalyst under conventional heating and microwave irradiation conditions. The study of cross coupling of halo pyridines with various palladium (II) catalysts are carried out but Pd[dppf]Cl_2 catalyst is not much explored. To the best of our knowledge there is no systematic study of Suzuki couplings on 2,6-dibromo pyridines by the conventional heating and microwave irradiation. Microwave promoted synthesis is currently an area of increasing interest[16]. The first microwave promoted Suzuki Miyuara couplings were reported in 1996, since then a large number of investigations focused on this subject[17].
The present paper describes results of cross coupling reactions of 2,6-dibromo pyridine with various aryl boronic acids under conventional heating and microwave irradiation.

RESULTS AND DISCUSSION

Initially cross couplings were performed on 2,6-dibromo pyridine (1eq, **1a-h**), with aryl boronic acids (1eq), using Pd[dppf]Cl_2 (.02eq) as catalyst and Na_2CO_3 (2eq) in dioxane-water(1:1) solvent medium by conventional heating (**Scheme – I**). Under these conditions, we obtained mixture of mono **2a-h** and double coupled **3a-h** products in variable amounts **(Table-1)** in all boronic acid couplings. This coupling has taken long reaction times and required upto 2-7 hours of refluxing. In an attempt to obtain double coupled products the Pd[dppf]Cl_2 catalysed reaction of 2,6 dibromo pyridine with an excess (2eq) of boronic acids was performed by conventional heating. However, the analysis of reaction products has shown mixture of mono and double coupled products as in the earlier process. The conversion could not be improved by enhancing the reaction times and temperature. To develop more efficient method for the synthesis, we optimized the Suzuki reaction conditions under microwave irradiation. The same reaction when carried out with MW irradiation at 120^{o}c (**Scheme – II**) gave mixture of mono and double coupled products in good yields in just 15 mins compared to long reaction times (2-7 hours) under thermal conditions (at other temperatures the results were not satisfactory). However, the yields of mono and double coupled products are variable (**Table-2**) as in thermal conditions. The relative amounts of two products 2a**-h** and **3a-h** was estimated according to the peak areas obtained from the LC/MS. In contrast to thermal conditions when reaction of 2,6 dibromopyridine with excess boronic acid (2eq) is conducted in presence of catalyst and base with MWI at 120^{o}C (**Scheme – III**). surprisingly, the double coupled products were the major products with 70-90% yields in all boronic acids couplings(**Table-3**). The reaction proceeded well with electron rich, electron deficient and even sterically crowded boric acids and gave good yields of products. The structures of all the compounds were confirmed by spectral analysis. Our study reveals that with 1 eq boronic acids under thermal or microwave irradiation neither mono nor double coupled products were obtained exclusively but with excess boronic acids (2eq) under MWI yielded double coupled compounds as major products in good yields.

Table 1 : Method 1- for cross coupling of 2, 6-dibromo pyridine with aryl boronic acids (1.0 eqt) under conventional heating

Entry	R	Time(h)	Monocoupled		Double coupled	
			Product	Yield (%)	Product	Yield (%)
1a.	4-F-C_6H_4	7	2a	33	3a	51
1b	3-F-C_6H_4	2	2b	42	3b	44
1c	4-CF_3-C_6H_4	2	2c	37	3c	50
1d	3-MeO-C_6H_4	7	2d	55	3d	32
1e	2-MeO-C_6H_4	7	2e	50	3e	20
1f	3-Me-C_6H_4	3	2f	50	3f	35
1g	2-Me-C_6H_4	2	2g	39	3g	43
1h	4-CN-C_6H_4	3	2h	49	3h	36

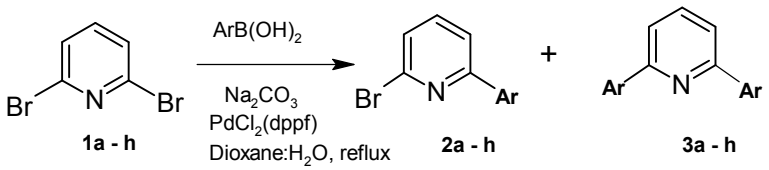
Table 2 : Method 2- for cross coupling of 2, 6-dibromo pyridine with aryl boronic acids (1.0 eqt) under microwave irradiation

Entry	R	Time(mins)	Monocoupled		Double coupled	
			Product	Yield (%)	Product	Yield (%)
1a.	4-F-C_6H_4	15	2a	43	3a	45
1b	3-F-C_6H_4	15	2b	42	3b	49
1c	4-CF_3-C_6H_4	15	2c	61	3c	33
1d	3-MeO-C_6H_4	15	2d	53	3d	36
1e	2-MeO-C_6H_4	15	2e	46	3e	38
1f	3-Me-C_6H_4	15	2f	40	3f	45
1g	2-Me-C_6H_4	15	2g	38	3g	50
1h	4-CN-C_6H_4	15	2h	45	3h	45

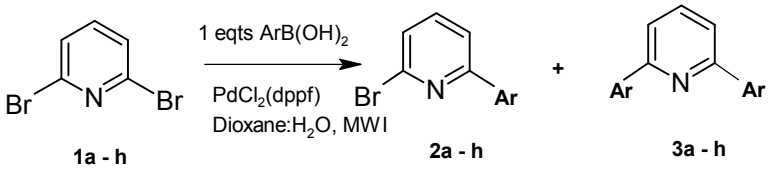
Table 3 : Method 3- for cross coupling of 2, 6-dibromo pyridine with excess aryl boronic acids (2 eqts) under microwave irradiation

Entry	R	Time(mins)	Double coupled	
			Product	Yield (%)
1a	4-F-C_6H_4	15	3a	85
1b	3-F-C_6H_4	15	3b	89
1c	4-CF_3-C_6H_4	15	3c	73
1d	3-MeO-C_6H_4	15	3d	76
1e	2-MeO-C_6H_4	15	3e	78
1f	3-Me-C_6H_4	15	3f	85
1g	2-Me-C_6H_4	15	3g	87
1h	4-CN-C_6H_4	15	3h	85

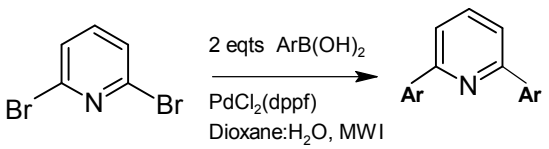
Scheme - I: cross coupling of 2,6-dibromo pyridine with aryl boronic acids (1.0 eq) under conventional heating



Scheme - II : cross couping of 2,6- dibromo pyridine with aryl boronic acids(1.0 eq) under Microwave irradiation



Scheme - III: cross coupling of 2,6-dibromo pyridine with excess aryl boronic acids (2.0 eq) under Microwave Irradiation



1a - h **2a - h**

EXPERIMENTAL SECTION

Samples were analyzed by HPLC. For hplc purification a BEH C 18(2.1 x 50mm) 1.7µ with mobile phase 0.1 % formic acid and acetonitrile and 0.1 % formic acid in water , 0.1% formic acid in acetonitrile, 0.4ml per minute, diluent-MeOH. ^{1}Hnmr spectra recorded at varian 400MHz using $CDCl_3$ solvent and TMS as internal reference. All MW experiments were carried out in the initiator biotage reactor (power setting 260 W, 15 minutes at 120^{o}C). The reactions were performed in an argon atmosphere, All the products are analyzed by ^{1}HNMR and LC/MS.

General procedure for the cross coupling

Method A: Conventional heating

2,6-dibrmopyridines**(1a-h)** (1eqt) was dissolved in a mixture of dioxane (2.5ml) and water(2.5 ml). This solution was degassed with argon for 5 mins. To the degassed solution aryl boronic acids (1eq), $PdCl_2$(dppf) (0.2eq) DCM adduct and sodium carbonate (2eq) were added sequentially. This solution was heated to the reflux temperature till the completion of the reaction and the reaction mixture was diluted with ethyl acetate and washed with water followed by saturated brine solution. The organic layer was concentrated under reduced pressure to get crude. The analysis of the crude with TLC and HPLC showed two compounds mono and double coupled products. These compounds from crude were separated by preparative TLC by eluting with 100% pet ether for three times (3a, 2a, 2b, 3a, 3b, 2f, 3f, 2g, 3g), and 5% ethyl acetate in pet ether for two times (2h, 3h) reversed phase HPLC with 0.1% TFA (2c, 3c) and chromatography over (100-200) silica gel by eluting with 1% ethyl acetate in pet ether (2d,3d; 2e, 3e; 2i, 3i)

*Method B- Microwave irradiation***:** 2,6-dibrmopyridine was dissolved in a mixture of dioxane (2.5ml) and water(2.5 ml). This solution was degassed with Argon for 5 mins. To the degassed solution aryl boronic acids (1eq), $PdCl_2$(dppf) (0.2eq) DCM adduct and sodium carbonate (2eq) were added sequentially. The reaction vial was sealed and placed in the microwave reactor (Biotage Initiator EXP^{TM} microwave reactor) and irradiated at 120^{o}c with 3 bar pressure for 15 mins, after being cooled to room temperature, the mixture was diluted with ethyl acetate, dried over sodium sulfate and filtered. The solution was concentrated in vacuum and the residue was subjected to separation as in method A.

Method C- Microwave irradiation: 2,6-dibrmopyridine was dissolved in a mixture of dioxane (2.5 ml) and water(2.5 ml). This solution was degassed with argon for 5 mins. To the degassed solution excess aryl boronic acids (2eq), $PdCl_2$(dppf) (0.2eq) DCM adduct and sodium carbonate (2eq) were added to the reaction mixture sequentially. The reaction vial was sealed and placed in the microwave reactor (Biotage Initiator EXP^{TM} microwave reactor) and irradiate at 120^{o}c with 3 bar pressure for 15 mins after being cooled to room temperature, the mixture was diluted with

ethyl acetate, dried over sodium sulfate and filtered. The solution was concentrated in vacuum and the residue was subjected to separation as in method A. The substrates synthesized were confirmed by spectral and elemental analysis as follows.

2-bromo-6-(4-flourophenyl) pyridine-2a : Solid, MP 61-63^{o}C; ^{1}Hnmr : δ7.78 (2H, m), 7.60 (2H, m), 7.48 (1H, m), 7.18 (2H, m); LCMS : 252.11(M+1), 254.10(M+2)
Anal. Calcd for $C_{11}H_7BrFN$: C, 52.41; H, 2.80; N, 5.56. Found C,52.25; H, 2.62, N, 5.43

2-bromo-6-(3-flourophenyl) pyridine-2b. Solid, MP 54-57^{o}C; ^{1}Hnmr : δ7.75 (2H, m), 7.65 (2H, m), 7.45 (2H, m), 7.10 (1H, m); LCMS : 252.11(M+1), 254.12(M+2); Anal. Calcd for $C_{11}H_7BrFN$: C, 52.41; H, 2.80; N, 5.56. Found C,52.28; H, 2.62, N, 5.39

2-bromo-6-(4-(triflouromethyl) phenyl) pyridine-2c Solid, MP 74-77^{o}C; ^{1}Hnmr : δ8.10 (2H, d), 7.75 (3H, d), 7.65 (1H, t), 7.50 (1H, d); LCMS : 302.11(M+1), 304.12(M+2); Anal. Calcd for $C_{12}H_7BrF_3N$: C, 47.71; H, 2.34; N, 4.64. Found C, 47.58; H, 2.19, N, 4.59.

2-bromo-6-(3-methoxy phenyl) pyridine-2d Oil, ^{1}Hnmr : δ7.68 (1H, d), 7.55 (3H, m), 7.40 (2H, m), 6.98 (1H, m), 3.80 (3H, s). ; LCMS : 264.27(M+1), 266.25(M+2); Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found C,54.42; H, 3.71, N, 5.22.

2-bromo-6-(2-methoxy phenyl) pyridine-2e Oil,^{1}Hnmr : δ7.85 (2H, m), 7.55 (1H, t), 7.38 (2H, m), 7.08 (1H, m), 6.98 (1H, d), 3.98 (3H, s) ; LCMS : 264.01(M+1); 266.03(M+2); Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found C, 54.43; H, 3.72, N, 5.24.

2-bromo-6-m-tolyl pyridine-2f Oil, ^{1}Hnmr : δ7.82 (1H, s), 7.78 (1H, d), 7.68 (1H, d), 7.59 (1H, t), 7.48 (1H, m), 7.42 (1H, m), 7.35 (1H, t), 7.25 (1H, s), 2.6(3H, s) ; LCMS : 248.00(M+1). 250.10(M+2); Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09; H, 4.06; N, 5.65. Found C, 57.98; H, 3.96, N, 5.59

2-bromo-6-o-tolyl pyridine-2g Oil, ^{1}Hnmr : δ7.60 (1H, t), 7.55 (2H, m), 7.38 (2H, m), 7.28 (2H, m), 2.40 (3H, s) ; LCMS : 248.04(M+1), 250.99(M+2); Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09; H, 4.06; N, 5.65. Found C, 57.96; H, 3.92, N, 5.57

4-(6-bromo pyridine-2-yl) benzo nitrile-2h . Solid, MP 129-132^{o}C; ^{1}Hnmr : δ8.10 (2H, d), 7.75 (3H, m), 7.65 (1H, t), 7.50 (1H, d) ; LCMS : 259.11(M+1), 261.13(M+2); Anal. Calcd for $C_{12}H_7BrN_2$: C, 55.63; H, 2.72; N, 10.81. Found C, 55.43; H, 2.54, N, 10.75.

2,6-bis (4-flourophenyl) pyridine-3a Solid, MP 75-78^{o}C; ^{1}Hnmr : δ8.10 (4H, m), 7.80 (1H, t), 7.64 (2H, d), 7.18 (4H, t) ; LCMS : 268.41(M+1); Anal. Calcd for $C_{17}H_{11}F_2N$: C, 76.39; H, 4.15; N, 5.24. Found C, 76.18; H, 3.96, N, 5.16.

2,6-bis (3-flourophenyl) pyridine-3b Solid, MP 73-76^{o}C;^{1}Hnmr : δ7.82 (5H, m), 7.70 (2H, d), 7.45 (2H, m), 7.15 (2H, m) ; LCMS : 268.41(M+1); Anal. Calcd for $C_{17}H_{11}F_2N$: C, 76.39; H, 4.15; N, 5.24. Found C, 76.26; H, 3.98, N, 5.13.

2,6-bis (4-(triflouromethyl) phenyl) pyridine-3c . Solid, MP 153-156^{o}C; ^{1}Hnmr : δ8.22 (4H, d), 7.90 (1H, m), 7.78 (6H, m) ; LCMS : 368.24(M+1); Anal. Calcd for $C_{19}H_{11}F_6N$: C, 62.13; H, 3.02; N, 3.81. Found C, 62.01; H, 2.96, N, 3.76.

2,6-bis (3-methoxy phenyl) pyridine-3d . Oil, ^{1}Hnmr : δ7.82 (1H, m), 7.78 (2H, m), 7.70 (4H, m), 7.40 (2H, t), 6.98 (2H, m). 3.85 (6H, s) ; LCMS : 292.38(M+1); Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found C, 78.19; H, 5.73, N, 4.74.

2,6-bis (2-methoxy phenyl) pyridine- 3e. ^{1}Hnmr : δ7.92 (2H, d), 7.75 (3H, m), 7.35 (2H, m), 7.08 (2H, m), 7.00 (2H, d) ; LCMS : 292.15(M+1); Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found C, 78.17; H, 5.71, N, 4.76.

2,6-di-m-tolyl pyridine- 3f ^{1}Hnmr : δ7.98 (2H, s), 7.40 (2H, d), 7.80 (1H, m), 7.68 (2H, d), 7.39 (2H,t), 7.25 (2H, s), 2.48 (3H, s) ; LCMS : 252.11(M+1) ; LCMS : 260.14(M+1); Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found C, 87.72; H, 6.43, N, 5.31.

2,6-di-o-tolyl pyridine- 3f ^{1}Hnmr : δ7.81 (1H, t), 7.45 (2H, m), 7.35 (2H, d), 7.28 (6H, m), 2.40 (6H, s) ; LCMS : 261.19(M+1); Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found C, 87.72; H, 6.43, N, 5.31

2,6-bis(4-cyanophenyl) pyridine-3h Solid, MP 238-241^oC;^{1}Hnmr : δ8.21 (4H, d), 7.95 (1H, m), 7.80 (6H, m) ; LCMS : 252.11(M+1) ; LCMS : 282.23(M+1); Anal. Calcd for $C_{19}H_{11}N_3$: C, 81.12; H, 3.94; N, 14.94. Found C, 81.01; H, 3.81, N, 14.89.

CONCLUSIONS

In Summary we have developed a general and simple methodology for the efficient synthesis of diaryl pyridines based on Suzuki-Miyaura coupling of 2,6-dibromo pyridines with aryl boronic acids under MWI.

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Received on October 7, 2012