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Original article

A facile access for the synthesis of some C-2 substituted imidazopyrazines by utilizing the palladium catalyzed Suzuki cross-coupling reaction under microwave irradiation

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ABSTRACT

A rapid, efficient, and facile synthesis of an assortment of C-2 substituted imidazopyrazines has been achieved by utilizing the palladium catalyzed Suzuki cross-coupling of 2-bromo-1*H*-imidazo[4,5-b]pyrazine with various boronic acids under microwave irradiation. The utilization of $(A\text{-}^{ta}phos)_2PdCl_2$ as a catalyst in combination with CsF as base and DME-H_2O (4:1) as the solvent system at 100 °C procured the diaryls in acceptable to excellent yields. Prominent features of this developed methodology include short reaction times, fewer side products, and exceptional tolerance to a wide variety of functional groups.

1. Introduction

The basis of invention of new leads for drug designing programs is the synthesis of molecules which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of biologically active and medicinally useful molecules. Hence, the synthesis and investigation of the biological activities of novel heterocyclic compounds is increasingly important in medicinal chemistry [1].

The palladium catalyzed Suzuki–Miyaura cross-coupling reaction between organoboranes and organic halides or pseudohalides has emerged as one of the foremost techniques for the creation of carbon–carbon bonds. The salient features of these reactions are the availability, stability, and non-toxicity of a variety of boronic acids, extensive functional group tolerance and easy access for product isolation. These features have evidently extended its scope in synthetic chemistry and hence this reaction has found widespread use in pharmaceutical industries [2]. Imidazopyrazines belong to an important class of heterocyclic compounds which display a broad spectrum of pharmacological activities which include antioxidant, antidiabetic, and anticancer properties [3]. The diverse applications of imidazopyrazines in the field of luminescence have been extensively reported in literature [4]. The microwave assisted organic synthesis (MAOS) has indisputably become a powerful tool in modern drug discovery laboratories for the construction of versatile chemical entities due often to superior reaction rates, selectivity, and product yields as compared to conventional thermal methodologies [5].

Prompted by these observations and as a continuation of our ongoing research program in the synthesis of biologically active molecules [6], we were interested in synthesizing some C-2 substituted imidazopyrazines which may possess significant pharmacological activities. On continuation of our research on palladium catalyzed cross-coupling reactions [7], it has been planned to apply the Suzuki cross-coupling methodology for the synthesis of a series of 2-substituted-1H-imidazo[4,5-b]pyrazines. In this paper, we report a rapid, facile, and efficient methodology for the synthesis of a series of C-2 substituted imidazopyrazines under microwave irradiation.

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2. Experimental

All solvents and reagents were obtained from commercial suppliers and used without any further purification. All the reactions were carried out under inert argon atmosphere. Analytical TLC was performed on pre-coated aluminum sheets of silica (60 F254 nm) and visualized by short-wave UV light at λ 254. Melting points were determined on an EZ-Melt automated melting point apparatus. ^{1}H NMR spectra were recorded at 400 MHz using an internal deuterium lock. Chemical shifts were measured in δ (ppm). ^{13}C NMR spectra were recorded at 100 MHz using an internal deuterium lock. LC-MS analyses were performed using ESI/APCI, with an ATLANTIS C18 (50 mm × 4.6 mm – 5 μm) column and a flow rate of 1.2 mL/min. Microwave-assisted synthesis was performed in a single mode Biotage Initiator Microwave Synthesizer and temperature was monitored using infrared. The microwave reaction was carried out in a 5 mL glass vial and high absorption level was maintained. The conditions were maintained till the completion of the reaction.

2.1. Procedure for the synthesis of intermediate **2**

To a solution of 2,3-diamino pyrazine **1**, was added CDI in THF, which was then heated at 80 °C for 4 h. The reaction completion was monitored by TLC. The mixture was diluted with water and extracted in ethyl acetate, dried in anhydrous sodium sulphate, and distilled under reduced pressure. The crude product was purified by column chromatography to procure the titled compound in 92% yield. MP: 74–76 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.84 (br, 2H, NH), 8.68 (d, 2H, J = 8.04 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 135.2, 143.7, 157.5, LC-MS: Calculated 136.1, Observed 137.1.

2.2. Procedure for the synthesis of intermediate **3**

To a solution of intermediate **2** in dichloro ethane was added $POBr_3$ at 0 °C, and the reaction mixture was gradually warmed to ambient temperature. The reaction mass was then heated at 80 °C for 6 h. The reaction mixture was poured into crushed ice, basified with $NaHCO_3$, and extracted with DCM and distilled in reduced pressure to render the titled compound in 76% yield. MP: 83–85 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (d, 2H, J = 7.76 Hz, ArH); 12.6 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.9, 138.3, 146.7; LC-MS: Calculated 198.0, Observed 199.0.

2.3. General procedure for the coupling reaction

To a solution of 2-bromo imidazopyrazine intermediate **3** (1 equiv.) in DME-H_2O (4:1), were added boronic acid (1.5 equiv.), CsF (3 equiv.), and (A-^{ta}phos)$_2PdCl_2$ (10 mol%), and the solution was purged with argon and stirred at room temperature for 10 min. The reaction solution was then placed in the microwave and heated for 20–30 min at 100 °C. When TLC and LC-MS showed full consumption of starting materials, the reaction mixture was filtered and diluted with ethyl acetate. The ethyl acetate layer was extracted, washed in water, washed in brine, dried over anhydrous sodium sulfate, and distilled in vacuum to get the crude material. The crude product was purified by column chromatography and eluted in varying polarities to obtain the substituted diaryls **4a-n**.

2-Phenyl-1*H*-Imidazo[4,5-b]pyrazine (**4a**): Mp: 85–87 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64–7.86 (m, 5H, ArH), 8.94 (s, 2H, ArH), 12.32 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.9, 129.7, 131.2, 131.7, 133.1, 146.6, 149.8; LC-MS: Calcd. 196.2, Observed 197.2; Analysis calcd. for $C_{11}H_8N_4$: C, 67.34, H, 4.11, N, 28.55, found: C, 67.38, H, 4.08, N, 28.53.

2-(4-Nitrophenyl)-1*H*-Imidazo[4,5-b]pyrazine (**4b**): Mp: 99–102 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92–7.94 (dd, 2H, J_1 = 1.96 Hz J_2 = 8.44 Hz, ArH), 8.46–8.49 (dd, 2H, J_1 = 2.08 Hz, J_2 = 8.56 Hz, ArH), 8.72 (d, 2H, J = 7.12 Hz, ArH), 12.73 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.1 (2 peaks), 129.6, 138.1, 145.8, 148.9, 149.7; LC-MS: Calcd. 241.2, Observed 242.2; Analysis calcd. for $C_{11}H_7N_5O_2$: C, 54.77, H, 2.93, N, 29.03, found: C, 54.82, H, 2.91, N, 29.03.

2-(4-Fluorophenyl)-1*H*-Imidazo[4,5-b]pyrazine (**4c**): Mp: 91–93 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35–7.39 (dd, 2H, J_1 = 2.16 Hz, J_2 = 8.04 Hz, ArH), 7.79–7.83 (dd, 2H, J_1 = 1.76 Hz, J_2 = 8.24 Hz, ArH), 8.97 (s, 2H, ArH), 12.44 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.3, 124.0, 129.9, 131.5, 131.7, 146.7, 149.9, 165.1; LC-MS: Calcd. 214.2, Observed 215.2; Analysis calcd. for $C_{11}H_7FN_4$: C, 61.68, H, 3.29, N, 26.16, found: C, 61.72, H, 3.26, N, 26.16.

Methyl 4-(1*H*-imidazo[4,5-b]pyrazin-2-yl)benzoate (**4d**): Mp: 106–108 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.96 (s, 3H, OCH_3), 7.81–7.83 (dd, 2H, J_1 = 2.44 Hz, J_2 = 8.24 Hz, ArH), 8.26–8.29 (dd, 2H, J_1 = 2.64 Hz, J_2 = 8.76 Hz, ArH), 8.75 (d, 2H, J = 6.48 Hz, ArH), 12.44 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.3, 122.9, 128.8, 132.1 (2 peaks), 136.2, 146.1, 148.8, 167.2; LC-MS: Calcd. 254.2, Observed 255.2; Analysis calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41, H, 3.96, N, 22.04, found: C, 61.45, H, 3.95, N, 22.04.

4-(1*H*-Imidazo[4,5-b]pyrazin-2-yl)benzonitrile (**4e**): Mp: 96–98 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73–7.80 (m, 4H, ArH), 8.84 (d, 2H, J = 7.28 Hz, ArH), 12.52 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.4, 117.1, 122.8, 129.7, 134.1, 136.4, 145.9, 149.2; LC-MS: Calcd. 221.2, Observed 222.2; Analysis calcd. for $C_{12}H_7N_5$: C, 65.15, H, 3.19, N, 31.66, found: C, 65.19, H, 3.16, N, 31.64.

4-(1*H*-Imidazo[4,5-b]pyrazin-2-yl)phenol (**4f**): Mp: 90–92 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.04 (s, 1H, OH), 7.01–7.04 (dd, 2H, J_1 = 2.36 Hz, J_2 = 8.16 Hz, ArH), 7.47–7.49 (dd, 2H, J_1 = 2.28 Hz, J_2 = 8.44 Hz, ArH), 8.77 (d, 2H, J = 7.44 Hz, ArH), 12.34 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.0 (2 peaks), 122.8 (2 peaks), 124.7, 130.1, 145.8, 149.1, 159.9; LC-MS: Calcd. 212.2, Observed 213.2; Analysis calcd. for $C_{11}H_8N_4O$: C, 62.26, H, 3.80, N, 26.40, found: C, 62.31, H, 3.78, N, 26.38.

2-*p*-Tolyl-1*H*-imidazo[4,5-b]pyrazine (**4 g**): Mp: 88–90 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67 (s, 3H, CH_3), 7.32–7.34 (dd, 2H, J_1 = 2.36 Hz, J_2 = 8.28 Hz, ArH), 7.65–7.68 (dd, 2H, J_1 = 1.96 Hz, J_2 = 8.36 Hz, ArH), 8.92 (d, 2H, J = 7.08 Hz, ArH), 12.12 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.7, 123.7, 129.4, 129.8, 131.8, 140.7, 146.9, 149.7; LC-MS: Calcd. 210.2, Observed 211.2; Analysis calcd. for $C_{12}H_{10}N_4$: C, 68.56, H, 4.79, N, 26.65, found: C, 68.61, H, 4.77, N, 26.62.

2-(4-Methoxyphenyl)-1*H*-imidazo[4,5-b]pyrazine (**4 h**): Mp: 98–100 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 7.09–7.13 (dd, 2H, J_1 = 2.44 Hz, J_2 = 8.36 Hz, ArH), 7.51–7.53 (dd, 2H, J_1 = 1.96 Hz, J_2 = 8.48 Hz, ArH), 8.84 (d, 2H, J = 7.56 Hz, ArH), 12.46 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.1, 116.1 (2 peaks), 123.2 (3 peaks), 129.8, 146.0, 148.9, 162.1; LC-MS: Calcd. 226.2, Observed 227.2; Analysis calcd. for $C_{12}H_{10}N_4O$: C, 63.71, H, 4.46, N, 24.76, found: C, 63.75, H, 4.44, N, 24.75.

3-(1*H*-Imidazo[4,5-b]pyrazin-2-yl)-*N*,*N*-dimethylbenzenamine (**4i**): Mp: 109–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.12 (s, 6H, CH_3), 6.85–7.04 (m, 4H, ArH), 7.45–7.48 (dd, 2H, J_1 = 2.44 Hz, J_2 = 8.36 Hz, ArH), 8.96 (s, 2H, ArH), 12.64 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.6, 114.5, 116.7, 119.1, 123.8, 132.4, 133.9, 146.6, 149.8, 152.4; LC-MS: Calcd. 239.3, Observed 240.3; Analysis calcd. for $C_{13}H_{13}N_5$: C, 65.25, H, 5.48, N, 29.27, found: C, 65.28, H, 5.47, N, 29.24.

2-(Pyridine-3-yl)-1*H*-Imidazo[4,5-b]pyrazine (**4j**): Mp: 86–88 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (dd, 1H, J_1 = 2.36 Hz, J_2 = 8.48 Hz, ArH), 8.04 (d, 1H, J = 6.36 Hz, ArH),

8.64–8.69 (m, 3H, ArH), 12.78 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.9 (2 peaks), 125.6, 134.3, 135.6, 146.1, 148.8 (2 peaks), 150.7; LC-MS: Calcd. 197.2, Observed 198.2; Analysis calcd. for $C_{10}H_7N_5$: C, 60.91, H, 3.58, N, 35.51, found: C, 60.95, H, 3.57, N, 35.48.

2-(5-Chloropyridin-3-yl)-1*H*-imidazo[4,5-b]pyrazine (**4k**): Mp: 107–109 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H, ArH), 8.75–8.81 (m, 4H, ArH), 12.83 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.0 (2 peaks), 130.1, 134.9, 138.6, 145.8, 147.9, 148.8 (2 peaks); LC-MS: Calcd. 231.6, Observed 232.6 & 234.6; Analysis calcd. for $C_{10}H_6ClN_5$: C, 51.85, H, 2.61, N, 30.23, found: C, 51.89, H, 2.59, N, 30.21.

2-(1-Methyl-1*H*-indol-5-yl)-1*H*-Imidazo[4,5-b]pyrazine (**4l**): Mp: 116–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.12 (s, 3H, NCH_3), 6.58–6.61 (dd, 1H, J_1 = 2.24 Hz, J_2 = 8.56 Hz, ArH), 6.94 (d, 1H, J = 7.28 Hz, ArH), 7.44–7.48 (m, 3H, ArH), 8.74, (d, 2H, J = 7.04 Hz, ArH) 12.47 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.4, 104.1, 112.8, 118.1, 120.3, 122.9, 130.1 (3 peaks), 137.1, 145.9, 148.8; LC-MS: Calcd. 249.3, Observed 250.3; Analysis calcd. for $C_{14}H_{11}N_5$: C, 67.46, H, 4.45, N, 28.10, found: C, 67.49, H, 4.44, N, 28.07.

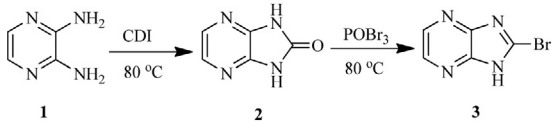
2-(Furan-2-yl)-1*H*-imidazo[4,5-b]pyrazine (**4m**): Mp: 80–82 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.74–6.78 (m, 3H, ArH), 8.78 (d, 2H, J = 7.16 Hz, ArH), 12.68 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.4, 108.6, 123.4, 137.1, 144.1, 145.8, 155.4; LC-MS: Calcd. 186.2, Observed 187.2; Analysis calcd. for $C_9H_6N_4O$: C, 58.06, H, 3.25, N, 30.09, found: C, 58.10, H, 3.25, N, 30.07.

2-(2-Methylpyridin-4-yl)-1*H*-imidazo[4,5-b]pyrazine (**4n**): Mp: 90–92 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84 (s, 3H, CH_3), 7.57–7.61 (m, 2H, ArH), 8.74–8.79 (m, 3H, ArH), 12.37 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.7, 110.9, 114.1, 123.4, 146.5 (3 peaks), 148.8, 151.1, 159.8; LC-MS: Calcd. 211.2, Observed 212.2; Analysis calcd. for $C_{11}H_9N_5$: C, 62.55, H, 4.29, N, 33.16, found: C, 62.59, H, 4.27, N, 33.14.

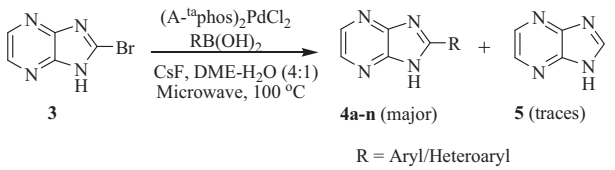
3. Results and discussion

The parent imidazopyrazine core was synthesized by treating the pyrazine 2,3 diamine **1** with CDI in THF at 80 °C (Scheme 1) which procured the 2-hydroxyimidazopyrazine intermediate **2**. The intermediate thus obtained was further brominated by treating it with $POBr_3$ in dichloroethane at 80 °C for 6 h to obtain the 2-bromoimidazopyrazine intermediate **3** (Scheme 1). The obtained bromo intermediate was then subjected to the palladium catalyzed Suzuki cross-coupling reactions with diverse boronic acids under microwave irradiation with the aim of synthesizing an array of pharmacologically relevant C-2 substituted imidazopyrazines.

We started our initial screening by coupling the intermediate **3** with phenyl boronic acid since the formation of product could be easily identified by TLC and LC-MS (Scheme 2). A sequence of palladium catalysts in combination with various bases and solvents were investigated at 120 °C, and the coupling reaction was carried out in a microwave oven for 30 min (Table 1). To our disappointment, we could not obtain the required product in acceptable yield in any of the explored conditions and the debrominated product **5** was obtained as the major product. The use of various catalysts like $Pd(dppf)Cl_2$, $Pd(dppf)CH_2Cl_2$, $PdCl_2(CH_3CN)_2$, $Pd_2(dba)_3$ *etc.* were found to be ineffective (Table 1, entries 1–4). Even though we observed the formation of product when (A-^{ta}phos)$_2PdCl_2$ was used as a catalyst and CsF as base in DME, the reaction could not reach completion even after continuing for 1 h (Table 1, entry 5).



Scheme 1. Synthesis of bromo intermediate **3.**



Scheme 2. Synthesis of various substituted imidazopyrazines.

We observed that the nature of base and the solvent system have a determining influence in facilitating the coupling reaction (Table 1, entries 6–8). We presumed that the lack of solubility of all the reagents in the reaction system was the primary reason for the incompleteness of the reaction. The hypothesis proved to be true when we observed that the formation of product was procured in acceptable yield when water was added as a co-solvent to the reaction mixture (Table 1, entry 8). Finally, we obtained the product in excellent yield when DME-H_2O (4:1) was used as a solvent system at 100 °C (Table 1, entry 9). Among the various bases screened (Table 2), CsF was found to be the best one which rendered the diaryls in exceptional yield with lesser side-products.

The plausible reason for the debromination could be the attack of metal alkoxides at the Pd(II) oxidative adduct complex followed by hydride migration and reductive elimination [8]. The attack of borate complex at the same Pd(II) oxidative adduct complex leads to the desired coupled product which could be well facilitated by the electronic effect of dimethyl amino group present in (A-^{ta}phos)$_2PdCl_2$ catalyst, thereby increasing the basicity of the phosphine ligand attached to the palladium center. Similarly, the superiority of CsF to other bases could be rationalized by the fact that CsF generated the most reactive boronate species and

Table 1
Effect of various catalysts in Suzuki coupling of **3** with phenyl boronic acid.[a]

Entry	Catalyst	Base	Solvent	Yield **4a** (%)	Yield **5** (%)
1	$Pd(dppf)Cl_2$	CsF	DME	20	68
2	$Pd(dppf)CH_2Cl_2$	CsF	DME	15	75
3	$Pd_2(dba)_3$	Cs_F	DME	Traces	90
4	$PdCl_2(CH_3CN)_2$	CsF	DME	23	60
5	(A-^{ta}phos)$_2PdCl_2$	CsF	DME	57	35
6	(A-^{ta}phos)$_2PdCl_2$	Cs_2CO_3	DME	52	40
7	(A-^{ta}phos)$_2PdCl_2$	Cs_2CO_3	DMF	38	55
8	(A-^{ta}phos)$_2PdCl_2$	CsF	DME-H_2O (4:1)	87	Traces
9	(A-^{ta}phos)$_2PdCl_2$	CsF	DME-H_2O (4:1)	95[b]	Traces

[a] Reaction conditions: Bromo intermediate (1 mmol), phenyl boronic acid (1.5 mmol), catalyst (10 mol%), base (3 mmol), solvent, microwave irradiated at 120 °C for 30 min.
[b] Reaction carried out at 100 °C.

Table 2
Effect of various bases in Suzuki cross-coupling reaction.

Entry	Base	Yield (%)[a]
1	K_2CO_3	17
2	$NaHCO_3$	20
3	Na_2CO_3	18
4	NaOH	Traces
5	Cs_2CO_3	65
6	K_3PO_4	70
7	CsF	95

Reaction conditions: Bromo intermediate (1 mmol), phenyl boronic acid (1.5 mmol), (A-^{ta}phos)$_2PdCl_2$ (10 mol%), Base (3 mmol), DME-H_2O (4:1), microwave irradiated at 100 °C for 30 min.
[a] Isolated yield.

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Table 3
Suzuki coupling of 2-bromoimidazopyrazine with various Boronic acids.[a]

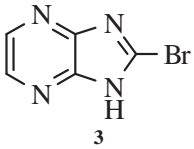
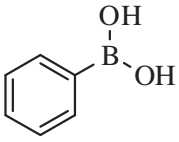
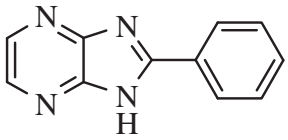
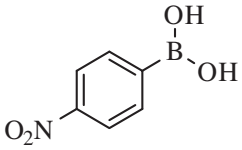
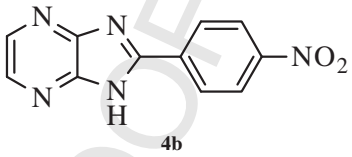
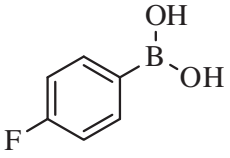
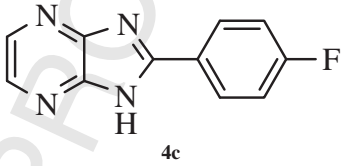
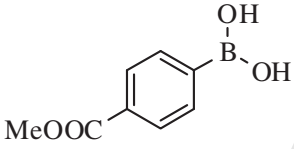
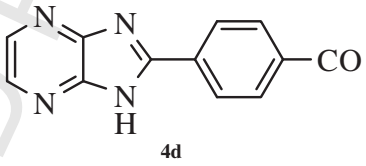
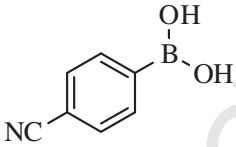
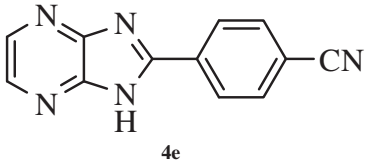
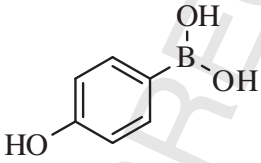
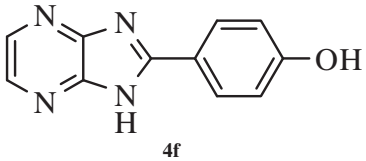
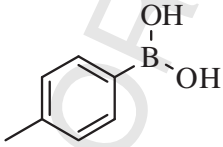
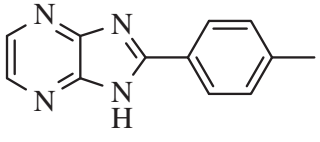
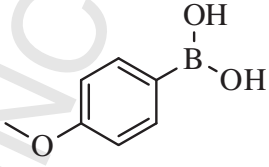
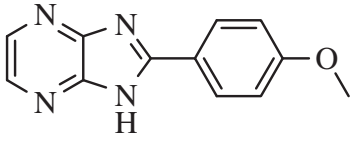
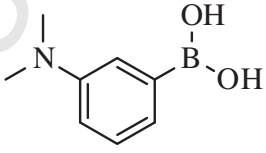
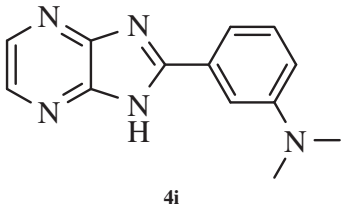
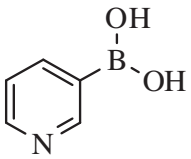
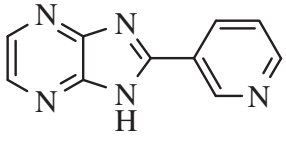
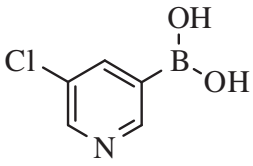
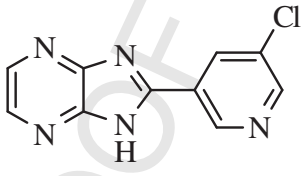
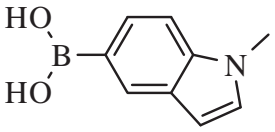
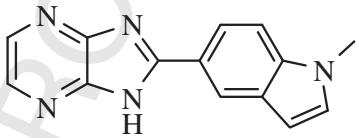
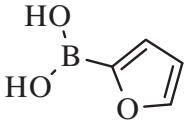
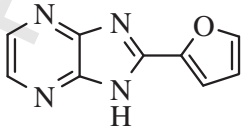
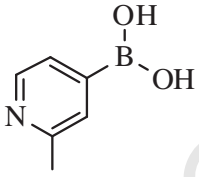
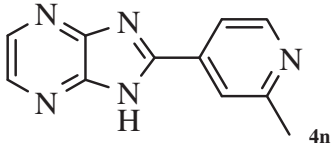
Entry	Bromo intermediate	Boronic acid	Product (**4a-n**)	Yield (%)[b]
1	 **3**		 **4a**	92
2	**3**		 **4b**	82
3	**3**		 **4c**	87
4	**3**		 **4d**	85
5	**3**		 **4e**	80
6	**3**		 **4f**	94
7	**3**		 **4g**	90
8	**3**		 **4h**	93
9	**3**		 **4i**	78

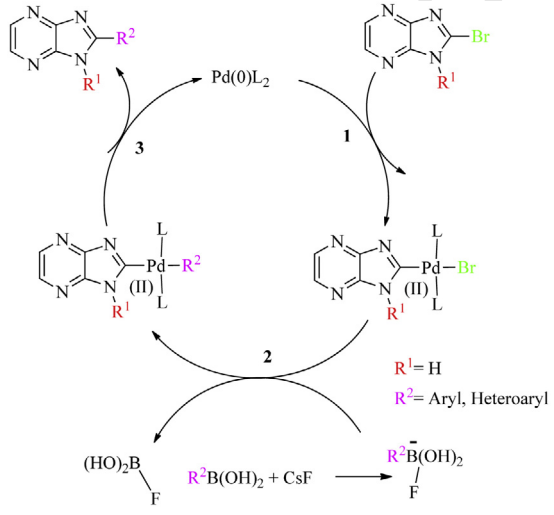
Table 3 (*Continued*)

Entry	Bromo intermediate	Boronic acid	Product (**4a-n**)	Yield (%)[b]
10	**3**		 **4j**	91
11	**3**		 **4k**	88
12	**3**		 **4l**	76
13	**3**		 **4m**	90
14	**3**		 **4n**	95

[a] Conditions: Bromo intermediate (1 mmol), boronic acid (1.5 mmol), (A-^{ta}phos)$_2$PdCl$_2$ (10 mol%), CsF (3 mmol), DME-H$_2$O (4:1), microwave irradiated at 100 °C for 30 min.
[b] Isolated yield.

facilitated transmetallation quickly which resulted in cross-coupling rather than debromination [9].

With the optimized condition in hands, our next attention was to evaluate the scope of the developed methodology. A series of sterically and electronically diverse boronic acids were coupled with the bromo intermediate **3**, and our results are summarized in Table 3. All the boronic acids coupled effectively to render the diaryls in satisfactory to excellent yields. Electron rich boronic acids gave exceptional yields of the coupled product whereas electron deficient boronic acids gave slightly lesser yields (Table 3, entries 2–8). Sterically crowded boronic acids furnished the coupled product in slightly lesser yields even after continuing the reaction for 1 h (Table 3, entries 9 and 12).



Scheme 3. Proposed mechanism of the coupling reaction.

A plausible mechanism for the Suzuki cross-coupling reaction has been proposed (Scheme 3). The first step constitutes the oxidative addition of bromo intermediate with palladium to form an organo-palladium species. The subsequent steps involve the formation of a boronate complex which facilitates transmetallation and reductive elimination of the intermediate **3** to form the coupled product and thereby completing the catalytic cycle.

4. Conclusion

In summary, we have achieved a rapid, concise and efficient protocol for the synthesis of a series of C-2 substituted imidazopyrazines under microwave irradiation. This method provided an efficient pathway for the synthesis of an assortment of pharmacologically relevant molecules and could be extended for the coupling of other densely functionalized heterocycles in future. The biological screening of the newly synthesized molecules will be conducted in due course and will be communicated shortly.

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