Chinese Chemical Letters 27 (2016) 31–36

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

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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ARTICLE INFO

Article history:
Received 25 June 2015
Received in revised form 3 August 2015
Accepted 11 August 2015
Available online 31 August 2015

Keywords:
Imidazopyrazine
Boronic acid
Suzuki coupling
Microwave

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-^{ta}phos)$_2$PdCl$_2$ 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-1*H*-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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http://dx.doi.org/10.1016/j.cclet.2015.08.015

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-bromoimidazopyrazine intermediate **3** (1 equiv.) in DME-H_2O (4:1), were added boronic acid (1.5 equiv.), CsF (3 equiv.), and (A-^{ta}phos)$_2$PdCl$_2$ (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),