

SUPPORTING INFORMATION

Cross-Coupling Reaction of 2-halo1-methyl-1H-imidazo[4,5-b]pyridine Offers a New Synthetic Route to Mutagenic Heterocyclic Amine-PHIP and DMIP

Ayyiliath M. Sajith^{†,*}, Arayambath Muralidharan^{‡,§*}, Ranjith P. Karuvalam[§], and Karickal R. Haridas[§]

[†]Organic Chemistry Division, School of Chemical Sciences, Kasargod Govt. College, Kannur University, Kasargod, India.

*E-mail: sajithmeleveetil@gmail.com

[‡]Organic Chemistry Division, School of Chemical Sciences, Nehru Arts and Science College, Kannur University, Kannur, India

*E-mail: drmuralinasc@yahoo.com

[§]Organic Chemistry Division, School of Chemical Sciences, Kannur University Payannur Campus, India

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EXPERIMENTAL

All experiments were performed under nitrogen atmosphere. All reagents including Palladium catalysts, boronic acids and inorganic bases were purchased from commercial sources and used as received. THF was distilled over sodium prior to use. Commercially available pre packed silica gel plugs and hexane/ethyl acetate solvents were used for column chromatographic purification of organic products. Isolated yields correspond to products of greater >90% purity as determined by LCMS and NMR. All NMR (¹H, ¹³C) chemical shifts are reported in parts per million (ppm) downfield from TMS and all coupling constants are reported in Hertz (Hz).

N³-methylpyridine-2,3-diamine (4)

An oven dried flask was charged with **3** (2 g, 0.0130 mol) in acetic acid (10 mL). Iron powder (3.56 g, 0.0653 mol) was added in portion wise and the reaction contents were heated at 90 °C for 3 hr. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and the crude was taken as such for the next step.

Dark brown liquid, Yield 87%; ¹HNMR (300 MHz, CDCl₃) δ: 2.67 (s, 3H), 5.34 (bs, 2H), 6.42–6.50 (m, 2H), 7.24–7.26 (m, 1H); LCMS 124.15 (M+H); Anal. Calcd. for C₆H₉N₃: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.31; H, 7.43; N, 34.42%.

1-methyl-1H-imidazo[4,5-b]pyridine (5)

An oven dried flask was charged with diammine (5 g, 0.0375 mol), and formic acid (50 mL) and the reaction contents were heated at 120 °C for 24 hr. Reaction contents were concentrated to dryness and crude obtained was purified by column chromatography (70% EtOAc in Hexane) to get brown oil.

Brown oil, Yield 68%; ¹HNMR (400MHz, CDCl₃) δ: 3.87 (s, 1H), 7.24 (dd, 1H), 7.68–7.73 (m, 1H), 8.11 (s, 1H), 8.50–8.54 (m, 1H); LCMS 134.15 (M+H); Anal. Calcd. for C₇H₇N₃: C 63.14; H 5.30; N, 31.56%. Found: C, 63.21; H, 5.40; N, 31.62%.

2-chloro-1-methyl-1H-imidazo[4,5-b]pyridine (6)

Compounds **6a** and **6b** were synthesized according to the procedure mentioned in ref 8.

Yield: 59%; ¹HNMR (400 MHz, CD₃OD) δ: 3.93 (s, 3H), 7.42 (dd, 1H), 8.06 (dd, 1H), 8.47 (dd, 1H); LCMS 168.15 (M+H); Anal. Calcd. for C₇H₆ClN₃: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.31; H, 3.53; N, 25.22%.

1-methyl-1H-imidazo[4,5-b]pyridin-2-amine (7)

An oven dried vial was charged with **6a** or **6b** (0.5 g, 0.00193 mol) in Dioxan (5 mL). Benzophenoneimine (0.52 g, 0.00289 mol) was added in one portion followed by the addition of dry K₃PO₄ (0.66 g, 0.00482 mol). The reaction vessel was purged with N₂ for 10 min. Pd₂(dba)₃ (5 mol %) and Ru-Phos (10 mol %) were added and the vial was heated to 120 °C for 1 hr in microwave. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to get the crude material. To the crude mixture in THF was added HCl and stirred the reaction mixture at RT overnight. Concentrated the reaction mixture, added methanol and solids were filtered off and dried. Dark brown solid, Yield 67%; mp=276.5 °C. ¹HNMR (300 MHz, CD₃OD) δ: 3.54 (s, 3H), 6.93–6.97 (m, 1H), 7.43–7.46 (m, 1H), 7.97–7.99 (m, 1H); ¹³CNMR (75 MHz, CD₃OD): 27.48, 114.1, 114.6, 128.21, 140.55, 128.21, 140.55, 155.43, 157.97; IR (KBr) 1680, 1625, 1597, 1545, 1432, 1266, 1244, 1122, 930, 908, 770, 707 cm⁻¹; LCMS 149.11 (M+H); Anal. Calcd. for C₇H₈N₄: C, 56.74; H, 5.44; N, 37.81. Found: C, 56.61; H, 5.33; N, 37.72%.

1-methyl-6-phenyl-1H-imidazo[4,5-b]pyridin-2-amine (9)

An oven dried vial was charged with **8** (0.5 g, 0.00223 mol) in Dioxan:H₂O (4:1 mL). Phenylboronic acid (0.42 g, 0.00339 mol) was added in one portion followed by the addition of dry K₂CO₃ (0.62 g, 0.00442 mol). The reaction vessel was purged with N₂ for 10 min. Pd₂(dba)₃ (5 mol %), and S-Phos (10 mol %) were added and the vial was heated to 120 °C for 1 hr. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to get the crude material. The crude was column purified using DCM/MeOH (10%) to get the compound as dark brown solid. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to get the crude material. Yield 85%; mp=331.2–332.5 °C. ¹HNMR (400 MHz, DMSO) δ: 3.54 (s, 3H), 7.03 (s, br, 2H), 7.33 (dd, 1H), 7.43 (dd, 2H), 7.68 (d, J=7.3 Hz, 2H), 7.77 (d, J=2.1 Hz, 1H), 8.28 (d, J=2.1 Hz, 1H); ¹³CNMR (75 MHz, CD₃OD): 29.03, 112.1, 127, 127.11, 127.18, 127.21, 128.58, 129.5, 139.8, 140, 157, 158.6; IR (KBr) 3289, 3081, 1667, 1628, 1597, 1545, 1470, 1440, 1423, 1279, 1100, 1045, 945, 915, 880,

870, 760, 695, 595, 515 cm⁻¹; LCMS 225.11 (M+H); Anal. Calcd. for C₁₃H₁₂N₄: C, 66.70; H, 6.05; N, 22.71; C, 66.74; H, 6.34; N, 27.81. Found: C, 56.61; H, 5.33; N, 37.72%.

2-Amino-1,6-dimethylimidazo[4,5-b]pyridine (10)

An oven dried vial was charged with **8** (1 equiv) in Dioxan (4 mL). Trimethyl boroxine (1.2 equiv) was added in one portion followed by the addition of dry K₂CO₃ (3 equiv). The reaction vessel was purged with N₂ for 10 min. Pd₂(dba)₃ (5 mol %), and P (tBu)₃ (10 mol %) were added and the microwave vial was heated to 120 °C for 1 hr. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to get the crude material. The crude was column purified using DCM/MeOH (10%) to get the compound.

Yield 57%; mp=273–275 °C. ¹HNMR (400 MHz, DMSO) δ: 2.32 (dd, 3H), 3.64 (s, 3H), 7.29 (dd, 1H), 7.94 (dd, 1H); IR (KBr) 3281 cm⁻¹; LCMS 163.11 (M+H); Anal. Calcd. for C₈H₁₀N₄: C, 59.24; H, 6.21; N, 32.54; Found: C, 59.41; H, 6.29; N, 32.79%.