Efficient synthesis of substituted imidazo[4,5-b]pyridines

Abstract: An efficient approach to the synthesis of 1-methylimidazo[4,5-b]pyridine derivatives 5–10 of biological interest has been developed. The key intermediate product 4 is obtained by cyclization of 2-amino-3-methylaminopyridine (3) with phenylacetic acid.

Keywords: cyclization; imidazo[4,5-b]pyridine; synthesis.

Experimental

Melting points are uncorrected. Commercial reagents were used directly without further purification. Solvents were treated according to standard methods prior to use. 1H NMR and 13C NMR spectra were recorded on a Bruker spectrometer. Mass spectra were obtained on a Shimadzu LCMS instrument. High resolution mass spectra (HRMS) were recorded on a KE465 LCT Premier/XE spectrometer. Elemental analyses were performed on an Elementar Vario EL III instrument. Prep-HPLC was performed on a Shimadzu instrument with a Fuji C18 (300 × 25) column; wavelength: 220 nm; mobile phase A, CH3CN (0.1% trifluoroacetic acid); B, water (0.1% trifluoroacetic acid).

3-Methylamino-2-nitropyridine (2)

To a stirred solution of 30% MeNH2 in EtOH (550 mL) was added 3-methoxy-2-nitropyridine (1, 50.0 g, 0.32 mol). The mixture was heated under reflux overnight, allowed to cool to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether/ethyl acetate.
(19:1) as eluent to give 29.6 g (59%) of 2 as yellow solid, mp 108–110°C [lit. mp 109–110°C] [13]; 1H NMR (400 MHz, DMSO-d6): δ 2.95 (d, J = 5 Hz, 3H), 7.53–7.81 (m, 3H), 7.90 (br, 1H).

2-Amino-3-methylaminopyridine (3)

To a stirred solution of compound 2 (28.0 g, 0.18 mol) in anhydrous methanol (450 mL) was added 10% Pd/C (5.8 g) and the mixture was hydrogenated under 1 atm at 5°C while stirring overnight. The catalyst was filtered off through celite and the filtrate was concentrated under reduced pressure to afford 22.0 g (98%) of 3 as a brown solid, mp 124–125°C [lit. mp 124–125°C] [13]; 1H NMR (400 MHz, DMSO-d6): δ 2.69 (d, J = 5 Hz, 3H), 4.88 (d, J = 4 Hz, 1H), 5.41 (s, 2H), 6.46–6.53 (m, 2H), 7.28 (dd, J = 5 Hz, 2 Hz, 1H).

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

To a suspension of phenylacetic acid (32.0 g, 0.24 mol) in tetrahydrofuran (THF) (300 mL) was added CDI (39.0 g, 0.24 mmol) at 0°C, and the mixture was stirred at 60°C for 1 h. Then compound 3 (20.0 g, 0.16 mmol) was added, and the mixture was stirred at 60°C overnight. After cooling, the mixture was concentrated and the residue dissolved in ethyl acetate (600 mL). The solution was washed successively with saturated aqueous NaHCO3 (150 mL × 5), brine (150 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with dichloromethane/methanol (50:1) as eluent to give 18.2 g (51%) of compound 4 as a brown solid, mp 124–126°C [lit. mp 123–125°C] [14]; 1H NMR (400 MHz, DMSO-d6): δ 3.73 (s, 3H), 4.36 (s, 2H), 7.20–7.35 (m, 6H), 7.93 (m, 1H), 8.35 (m, 1H).

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

To a stirred solution of compound 4 (18.0 g, 0.08 mol) in acetic acid (200 mL) was added dropwise 30% aqueous H2O2 (20 mL, 0.17 mol), and the mixture was stirred at 70°C overnight. After cooling, the mixture was treated with Na2SO3 (11.3 g, 0.09 mmol) and stirred for an additional 10 min. Solid material was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate (800 mL) and the solution was washed with 10% NaOH (200 mL × 2) and then brine (200 mL × 2). The ethyl acetate phase was dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with dichloromethane/methanol (20:1) as eluent to afford 9.2 g (48%) of compound 5 as a yellow solid, mp 143–145°C; 1H NMR (300 MHz, DMSO-d6): δ 3.77 (s, 3H), 4.35 (s, 2H), 7.16–7.37 (m, 6H), 7.58 (d, J = 8 Hz, 1H), 8.13 (d, J = 6 Hz, 1H); 13C NMR (75 MHz, DMSO-d6): δ 146.3, 144.7, 136.7, 135.2, 130.6, 129.3, 126.3, 122.8, 121.7.
2-Benzyl-7-chloro-1-methyl-1H-imidazo[4,5-b]pyridine (6)

Compound 5 (90.0 g, 376 mmol) was dissolved in POCl₃ (160 mL) and the solution stirred under reflux overnight. After cooling, the mixture was concentrated and the residue dissolved in ethyl acetate (600 mL). The solution was washed with saturated aqueous NaHCO₃ (200 mL x 2) and brine (200 mL x 2), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography with petroleum ether/ethyl acetate (12:1) as eluent to afford 5.2 g (54%) of compound 6 as a yellow solid, mp 168–170°C; ¹H NMR (300 MHz, DMSO-d₆): δ 3.96 (s, 3H), 4.37 (s, 2H), 7.24–7.36 (m, 6H), 8.27 (d, J = 5 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 154.1, 149.8, 144.7, 139.5, 133.6, 129.3, 128.8, 126.2, 124.7, 120.3, 32.2, 31.5; HRMS (ESI) m/z calcd for C₁₇H₁₅N₁ClO (M+H)⁺: 258.0798, found: 258.0793.

2-Benzyl-7-benzylamino-1-methyl-1H-imidazo[4,5-b]pyridine (7)

To a solution of 6 (1.0 g, 3.9 mmol) in 1,4-dioxane (25 mL) was added Cs₂CO₃ (1.9 g, 5.95 mmol) and xanthsoph (0.67 g, 11.6 mmol) under nitrogen atmosphere. The mixture was stirred at 90–100°C for 16 h. After cooling, the mixture was concentrated and the residue was purified by flash column chromatography with dichloromethane/methanol (10:1) as eluent to afford 1.2 g (94%) of compound 7 as a yellow solid, mp 203–205°C; ¹H NMR (400 MHz, DMSO-d₆): δ 3.98 (s, 3H), 4.27 (s, 2H), 4.46 (d, J = 6 Hz, 2H), 6.17 (d, J = 6 Hz, 1H), 6.75 (t, J = 5 Hz, 1H), 7.20–7.24 (m, 10H), 7.83 (d, J = 6 Hz, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 158.3, 152.2, 146.4, 140.2, 137.2, 128.6, 127.6, 127.3, 126.5, 126.1, 124.7, 118.9, 116.2, 58.2, 33.0, 31.8; LC-MS: m/z 329.2 (M+H)⁺; HRMS (ESI) m/z calcd for C₁₇H₁₅N₁ClO (M+H)⁺: 329.1766, found: 329.1762.

2-Benzyl-1-methyl-1H-imidazo[4,5-b]pyridine-7-amine, a salt with trifluoroacetic acid (8)

To a solution of 7 (0.6 g, 1.8 mmol) in a mixture of MeCN (10 mL) and H₂O (2 mL) was added CAN (3.0 g, 5.5 mmol), and the mixture was stirred at 8–14°C overnight. The mixture was concentrated and the residue was treated with water (10 mL) and dichloromethane (10 mL). The resultant solid was filtered, suspended in methanol (30 mL), and the mixture was stirred for 10 min. After filtration the filtrate was collected and then concentrated. The residue was purified by preparative HPLC with 0.1% trifluoroacetic acid as additive to afford 0.19 g (44%) of 8 as a yellow solid with trifluoroacetic acid, mp 186–188°C (dec); ¹H NMR (400 MHz, DMSO-d₆): δ 4.01 (s, 3H), 4.35 (s, 2H), 6.61 (d, J = 7 Hz, 1H), 7.25–7.36 (m, 5H), 7.95–8.01 (m, 3H), 14.03 (br, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 151.1, 149.4, 166.2, 137.3, 1276, 1273, 1271, 126.2, 118.6, 115.3, 33.2, 31.4; LC-MS: m/z 239.2 (M+H)⁺; HRMS (ESI) m/z calcd for C₁₇H₁₅N₁O (M+H)⁺: 239.1297. Found: 239.1299.

N-(2-Benzyl-1-methyl-1H-imidazo[4,5-b]pyridine-7-yl)-3,3-dimethylbutanamide, a salt with trifluoroacetic acid (9)

To a solution of 6 (200 mg, 0.78 mmol), 3,3-dimethylbutanamide (104 mg, 0.9 mmol) and Pd(dba)₃ (13 mg, 0.01 mmol) in 1,4-dioxane (7 mL) was added Cs₂CO₃ (507 mg, 1.56 mmol) and xantophos (9 mg, 0.01 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 110°C for 16 h. After cooling, the mixture was concentrated and the residue was dissolved in ethyl acetate (150 mL), and the solution was washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by preparative HPLC with 0.1% trifluoroacetic acid as additive to afford 61 mg (23%) of 9 as an off-white salt with trifluoroacetic acid, mp 192–194°C (dec); ¹H NMR (300 MHz, CDCl₃): δ 1.09 (s, 9H), 2.49 (s, 2H), 3.91 (s, 3H), 4.23 (s, 2H), 7.14–7.33 (m, 5H), 7.59–7.71 (m, 2H), 8.62 (br, 1H), 10.53 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 174.1, 149.7, 145.4, 138.6, 137.0, 127.5, 1271, 126.7, 126.1, 1179, 115.2, 52.5, 33.1, 31.8, 31.3, 29.2; LC-MS: m/z 336.5 (M)⁺; HRMS (ESI) m/z calcd for C₁₇H₁₇N₁O₂ (M+H)⁺: 337.2028, found: 337.2022. Anal. Calcd for C₁₇H₁₇N₁O₂ (M+H)⁺: C, 58.66; H, 5.59; N, 12.44. Found: C, 58.78; H, 5.71; N, 12.52.

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References


