Facile Synthesis of 1-Substituted 2-Amino-3-cyanopyrroles: New Synthetic Precursors for 5,6-Unsubstituted Pyrrolo[2,3-*d*]pyrimidines

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Experimental Section

1-Benzyl-2-methoxycarbonylamino-3-cyanopyrrole (**6a**)

To a solution of 1-benzyl-3-cyanopyrrole-2-carboxylic acid¹ (**4**, 7.04 g, 31.12 mmol) in *N,N*-dimethylformamide (75 mL) at 0 °C was added diphenylphosphoryl azide (DPPA, 7.65 mL, 9.72 g, 35.30 mmol, 1.1 eq) and triethylamine (4.75 mL, 3.42 g, 33.80 mmol, 1.1 eq). The solution was allowed to stir at room temperature for 6 hr. Methanol (7 mL) was added and the reaction mixture was heated at 65 °C for 8 hr. The solvents were evaporated *in vacuo* then the resulting residue was dissolved in EtOAc (140 mL). The solution was extracted with 1 N aqueous HCl solution (3 x 80 mL), saturated NaHCO₃ solution (3 x 80 mL), dried over anhydrous MgSO₄ then concentrated to dryness. The residue was recrystallized from ethanol to give **6a** (4.695 g, 18.39 mmol, 59%). mp 140 – 142 °C (EtOH); ¹H NMR (DMSO-*d*₆, 500 MHz) δ 9.57 (bs, 1 H, NH), 7.36 – 7.28 (m, 3

H, Ph), 7.16 – 7.15 (m, 2 H, Ph), 6.87 (d, 1 H, $J = 2.9$ Hz), 6.46 (d, 1 H, $J = 3.3$ Hz), 5.05 (s, 2 H, CH₂), 3.63 (bs, 3 H, CH₃); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 155.8, 137.6, 133.6, 129.4 (CH), 128.5 (CH), 128.2 (CH), 121.3 (CH), 116.7, 110.4 (CH), 89.0, 53.3 (CH₃), 50.0 (CH₂); IR (KBr, cm⁻¹) 3281, 3141, 3125, 2226, 1735, 1679, 1570, 1507; Anal. Calcd for C₁₄H₁₃N₃O₂: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.94; H, 5.08; N, 16.30.

1-Benzyl-2-benzyloxycarbonylamino-3-cyanopyrrole (6b)

To a solution of **4** (22.62 g, 100.0 mmol) in *N,N*-dimethylformamide (200 mL) at 0 °C was added diphenylphosphoryl azide (24.6 mL, 31.24 g, 113.53 mmol, 1.1 eq) and triethylamine (15.2 mL, 10.94 g, 108.15 mmol, 1.1 eq). The solution was allowed to stir at room temperature for 1 hr. Benzyl alcohol (16.2 mL, 16.85 g, 155.80 mmol, 1.6 eq) was added and the reaction mixture was heated at 80 °C for 10 hr. The solvents were evaporated *in vacuo* then the resulting residue was dissolved in EtOAc (300 mL). The solution was extracted with 1 N aqueous HCl solution (300 mL), saturated NaHCO₃ solution (2 x 300 mL), dried over anhydrous MgSO₄ then concentrated to dryness. The residue was recrystallized from diethyl ether to give **6b** (28.35 g, 85.55 mmol, 86%). mp 170 – 172 °C (ether); ¹H NMR (DMSO-*d*₆, 500 MHz) δ 9.23 (bs, 1 H, NH), 6.93 – 6.83 (m, 8 H, Ph), 6.67 – 6.66 (m, 2 H, Ph), 6.42 (d, 1 H, $J = 3.3$ Hz), 6.00 (d, 1 H, $J = 3.3$ Hz), 4.65 (s, 2 H, CH₂), 4.59 (s, 2 H, CH₂); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 154.9, 137.2, 136.8, 133.7, 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 120.7 (CH), 116.4, 109.9 (CH), 88.2 (CH₂), 66.9 (CH₂); IR (KBr, cm⁻¹) 3234,

3065, 3030, 2222, 1701, 1567, 1546, 1504; MS (ESI) m/z 354 (100) (M + Na); HRMS Calcd for $C_{20}H_{17}N_3O_2 \cdot Na$ (M + Na): 354.1218. Found: 354.1223.

1-Benzyl-2-*tert*-butoxycarbonylamino-3-cyanopyrrole (6c)

To a solution of **4** (4.0 g, 17.68 mmol) in *tert*-butyl alcohol (90 mL) at 0 °C was added diphenylphosphoryl azide (3.80 mL, 4.83 g, 17.54 mmol, 1.0 eq), and triethylamine (2.44 mL, 1.76 g, 17.36 mmol, 1.0 eq). The solution was allowed to stir at room temperature for 1 hr then the reaction mixture was heated at reflux temperature for 21 hr. The solvent was evaporated under reduced pressure then the resulting residue was dissolved in EtOAc (80 mL). The solution was extracted with 1 N aqueous HCl solution (3 x 50 mL), saturated $NaHCO_3$ solution (3 x 50 mL), dried over anhydrous $MgSO_4$ then concentrated to dryness. The residue was recrystallized from diethyl ether to give **6c** (3.90 g, 13.12 mmol, 74%). mp 154 - 155 °C (ether); 1H NMR ($DMSO-d_6$, 270 MHz) δ 9.20 (bs, 1 H, NH), 7.30 – 6.40 (m, 7 H, Ph), 5.05 (s, 2 H, CH_2), 1.35 (s, 9 H, CH_3); IR (KBr, cm^{-1}) 3276, 2981, 2221, 1722, 1574; Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.40; H, 6.47; N, 13.97.

2-Amino-1-benzyl-3-cyanopyrrole (1a)

[Method A] To a suspension of **6a** (4.69 g, 18.37 mmol) in ethylene glycol (115 mL) was added potassium hydroxide (2.05 g, 36.54 mmol, 2.0 eq). The mixture was heated at 110 – 115 °C for 90 min. After the solution was cooled to room temperature, EtOAc (80 mL) was added and the solution was extracted with H_2O (100 mL). The aqueous layer was extracted with some additional EtOAc (80 mL). Two organic portions were

combined, dried over anhydrous MgSO_4 , and the solvents were evaporated under reduced pressure. The resulting oil was purified by column chromatography (CH_2Cl_2 , $R_f = 0.12$) to give **1a** (2.12 g, 10.75 mmol, 59%). An analytical sample of **1a** was obtained by recrystallization from ether. mp 100 – 102 °C (ether).

[Method B] To a solution of **6b** (0.199 g, 0.60 mmol) in methanol (10 mL) was added 10% Pd / C (63.8 mg, 0.06 mmol, 0.1 eq) and the mixture was hydrogenated on a *Parr* shaker under 40 psi of hydrogen at room temperature for 90 min. After hydrogenolysis, the catalyst was removed by filtration through Celite and quickly washed with methanol (3 x 15 mL). The combined filtrates were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex / EtOAc = 7 : 3) to give **1a** (88.8 mg, 0.45 mmol, 75%, $R_f = 0.31$ (Hex / EtOAc = 6 : 4)). The compound was recrystallized from Hex / EtOAc to give an analytical sample of **1a** (41.0 mg, 0.21 mmol, 35%). mp 104 - 106 °C (Hex / EtOAc).

[Method C] *Preparation of N-benzylaminoacetaldehyde dimethyl acetal (7a)*: To a solution of aminoacetaldehyde dimethyl acetal (1.10 mL, 1.05 g, 10 mmol) in benzene (100 mL) was added benzaldehyde (1.02 mL, 1.06 g, 10 mmol, 1 eq). The mixture was heated at reflux temperature for 2 hr and H_2O generated from the reaction was continuously removed by a Dean-Stark apparatus. After the reaction was cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue was dissolved in ethanol (100 mL). The mixture was stirred, cooled in an ice bath and sodium borohydride (0.756 g, 20 mmol, 2 eq) was added portionwise. After completion of the addition, the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the white residue was dissolved in EtOAc (150 mL), washed

with water (2 x 80 mL), saturated NaCl solution (80 mL), dried over anhydrous Na₂SO₄, and the solvent was then evaporated under reduced pressure to give the crude product as a colorless oil that was used without further purification.

To a mixture of *N*-benzylaminoacetaldehyde dimethyl acetal (**7a**, prepared from 10 mmol of aminoacetaldehyde dimethyl acetal and benzylaldehyde) and malononitrile (1.39 g, 21 mmol, 1.05 eq) in methylene chloride (200 mL) was added *p*-toluenesulfonic acid monohydrate (7.61 g, 40 mmol, 2 eq). The reaction mixture was stirred at room temperature for 24 hr. The solvent was then evaporated to dryness under reduced pressure. The resulting residue was dissolved in EtOAc (200 mL), washed with saturated Na₂CO₃ solution (100 mL), saturated NaCl solution (100 mL), dried over anhydrous Na₂SO₄, and the solvent was then evaporated under reduced pressure. The resulting oil was purified by flash column chromatography (Hex / EtOAc = 7 : 3, R_f = 0.27) to give **1a** (1.37 g, 6.87 mmol, 35% from benzaldehyde). mp 104 - 106 °C (Hex / EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 7.40 – 7.32 (m, 3H, Ph), 7.13 – 7.11 (m, 2 H, Ph), 6.24 (d, 1 H, *J* = 3.4 Hz), 6.17 (d, 1 H, *J* = 3.4 Hz), 4.95 (s, 2 H, CH₂), 3.84 (bs, 2 H, NH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 145.1, 136.2, 129.6 (CH), 128.6 (CH), 127.1 (CH), 118.1, 116.7 (CH), 108.6 (CH), 76.1, 50.0 (CH₂); IR (KBr, cm⁻¹) 3375, 3325, 2187, 1636, 1548, 1505; MS (EI / 70 eV) *m/z* 91 (100), 197 (41) (M⁺); HRMS Calcd for C₁₂H₁₁N₃ (M⁺): 197.0953. Found: 197.0952. Anal. Calcd for C₁₂H₁₁N₃: C, 73.07; H, 5.62; N, 21.30. Found: C, 73.00; H, 5.58; N, 21.47.

2-Amino-1-(2-furfuryl)-3-cyanopyrrole (1b)

N-(2-Furfuryl)aminoacetaldehyde dimethyl acetal (**7b**) was prepared from 2-furaldehyde (1.24 mL, 1.44 g, 15 mmol) and aminoacetaldehyde dimethyl acetal (1.64 mL, 1.58 g, 15 mmol, 1.0 eq) by the method described for **7a** and was used without further purification.

Compound **1b** (0.533 g, 2.85 mmol, 19% from 2-furaldehyde) was prepared from *N*-(2-furfuryl)aminoacetaldehyde dimethyl acetal (**7b**, prepared from 15 mmol of aminoacetaldehyde dimethyl acetal and 2-furaldehyde) using malononitrile (0.99 g, 15 mmol, 1.0 eq), *p*-toulenesulfonic acid monohydrate (5.71 g, 30 mmol, 2.0 eq), and CH₂Cl₂ (150 mL) by the method described for **1a**. The product was purified by flash column chromatography (Hex / EtOAc = 7 : 3, R_f = 0.26). An analytical sample of **1b** was obtained by recrystallization from Hex / EtOAc. mp 86 - 87 °C (Hex / EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 7.41 (d, 1 H, *J* = 1.1 Hz, furan 5'-H), 6.37 (dd, 1 H, *J* = 1.9 & 3.1 Hz, furan 4'-H), 6.31 (d, 1 H, *J* = 3.1 Hz), 6.24 (d, 1 H, *J* = 3.4 Hz, pyrrole), 6.15 (d, 1 H, *J* = 3.4 Hz, pyrrole), 4.90 (s, 2 H, CH₂), 4.01 (bs, 2 H, NH₂); ¹³C NMR (CDCl₃, 125 MHz) δ 149.5, 144.7, 143.7 (CH), 117.8, 116.1 (CH), 111.1 (CH), 109.1 (CH), 108.7 (CH), 76.9, 43.0 (CH₂); IR (KBr, cm⁻¹) 3415, 3338, 3238, 2204, 1631, 1555, 1504; Anal. Calcd for C₁₀H₉N₃O: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.84; H, 4.82; N, 22.37.

2-Amino-3-cyano-1-methylpyrrole (**1c**)

Compound **1c** (0.150 g, 1.24 mmol, 12%) was prepared from *N*-methylaminoacetaldehyde dimethyl acetal (**7c**, 1.30 mL, 1.19 g, 10 mmol) using malononitrile (0.661 g, 10 mmol, 1.0 eq), *p*-toulenesulfonic acid monohydrate (3.80 g, 20 mmol, 2.0 eq), and CH₂Cl₂ (100 mL) by the method described for **1a**. The product was

purified by flash column chromatography (Hex / EtOAc = 6 : 4, R_f = 0.19). An analytical sample of **1c** was obtained by recrystallization from Hex / EtOAc. mp 98 - 100 °C (Hex / EtOAc); ¹H NMR (CDCl₃, 500 MHz) δ 6.14 (d, 1 H, *J* = 3.3 Hz), 6.11 (d, 1 H, *J* = 3.3 Hz), 3.90 (bs, 2 H, NH₂), 3.44 (s, 3 H, CH₃); ¹³C NMR (CDCl₃, 125 MHz) δ 145.0, 118.1, 116.7 (CH), 108.3 (CH), 75.6, 32.8 (CH₃); IR (KBr, cm⁻¹) 3334, 3240, 3130, 2942, 2196, 1635, 1540, 1507; Anal. Calcd for C₆H₇N₃: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.39; H, 5.80; N, 34.82.

4-Amino-7-benzylpyrrolo[2,3-*d*]pyrimidine (8)

To a solution of **1a** (1.78 g, 9 mmol), tetrabutylammonium hydrogen sulfate (0.153 g, 0.45 mmol, 0.05 eq) in acetonitrile (45 mL) was added diethoxymethyl acetate² (3.7 mL, 3.65 g, 22.5 mmol, 2.5 eq). The mixture was heated at reflux temperature for 3 hr. After cooled to room temperature, the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and H₂O. The organic layer was washed with saturated aqueous NaHCO₃ solution, saturated aqueous NaCl solution, dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure to dryness. The resulting residue was dissolved in methanolic ammonia (45 mL) and the reaction mixture was sealed in a stainless reaction vessel. The mixture was heated at 60 °C for 4 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure to dryness. The resulting residue was recrystallized from ethanol and H₂O to give **8**³ (1.14 g, 5.08 mmol, 56%). mp 174 – 176 °C (EtOH / H₂O) [*lit.*³ 177 – 179 °C (EtOH)]; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 8.09 (s, 1 H, 2-H), 7.32 – 7.29 (m, 2 H, Ph), 7.26 – 7.24 (m, 1 H, Ph), 7.23 – 7.21 (m, 2 H, Ph), 7.20 (d, 1 H, *J* = 3.4 Hz, 6-H), 7.01

(bs, 2 H, NH₂), 6.58 (d, 1 H, $J = 3.4$ Hz, 5-H), 5.33 (s, 2 H, CH₂); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 158.4 (4-C), 152.7 (2-CH), 150.5 (7a-C), 139.2, 129.4 (CH), 128.2 (CH), 128.1 (CH), 125.0 (6-CH), 103.2 (4a-C), 99.8 (5-CH), 47.9 (CH₂).

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