Supporting Information
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Supporting Information for

Concise Entries to 4-Halo-2-pyridones and 3-Bromo-4-halo-2-pyridones

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General information

All reactions were carried out under air. All the reagents were obtained commercially and used without any further purification. Yields refer to isolated material following silica gel column chromatography, unless otherwise specified. Reactions were monitored by thin-layer chromatography TLC on aluminium backed 60 F254 silica plates. Visualisation was achieved by UV fluorescence and/or a basic KMnO4 solution and heat. Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or films in the range 4000-600 cm⁻¹. Nuclear magnetic resonance spectroscopy was carried out at ambient temperature (unless otherwise stated) in the solvent indicated, on Varian 400-MR, Jeol Lambda 300 and Jeol JNM-ECP 400 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm), coupling constants (J) in Hz. ¹H and ¹³C NMR spectra are referenced to the deuterated solvent peak, ¹⁹F NMR spectra to external sample of CFCl₃. Other abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Melting points were determined from recrystallized material using Stuart SMP3 apparatus.

Experimental Section

General procedure for the synthesis of substrates (1b-d)[¹]

![Diagram of synthesis](attachment:diagram.png)

To a mixture of copper source (1.2 eq., CuBr₂ for 4b, CuCl₂ for 4c, Cul for 4d) in acetonitrile (0.4M) was slowly added tBuONO (1.5 eq.). The mixture was stirred for 15 min and then cooled to 0°C. A solution of 2-chloro-4-aminopyridine 3 (1.0 eq.) in acetonitrile (0.5M) was slowly added. The mixture was stirred for 1h at 0°C and then allowed to warm to r.t. for 16h. After concentration in vacuo, aq. 15% ammonia
solution (1.3 mL/mmol) was added, and the aqueous layer was extracted with dichloromethane (10 mL/mmol; 3x). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and carefully concentrated under reduced pressure (CAUTION: volatile products) to give the crude 4b-d, which was used in the next step without purification.

To 4b/c/d (prepared above) and sodium acetate (2.0 eq.) in acetic acid (1.0M) was heated at 150°C in a sealed tube for 72h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (3 mL/mmol) and cold water (3mL/mmol). The aqueous layer was extracted with ethyl acetate (3mL/mmol; 4x). The combined organic layers were successively washed with sat. NaHCO₃ (1 mL/mmol), brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel to give products 1b/c/d, and details of individual compounds are provided below.

**4-Chloro-3-chloropyridine (4b)[²]**
Carried out on 5.0 mmol scale; pale yellow liquid (465 mg, 62%). ¹H NMR (400 MHz, CDCl₃,) δ 8.31 (d, 1H, J = 5.4 Hz), 7.38 (d, 1H, J = 1.60 Hz), 7.25 (dd, 1H, J = 5.4 Hz, J = 1.6 Hz).

**4-Bromo-3-chloropyridine (4c)[³]**
Carried out on 60.0 mmol scale; yellow liquid (9.21 g, 96%). ¹H NMR (400 MHz, CDCl₃,) δ 8.23 (dd, 1H, J = 5.4 Hz, J = 0.5 Hz), 7.54 (dd, 1H, J = 1.60 Hz, J = 0.5 Hz), 7.40 (dd, 1H, J = 5.4 Hz, J = 1.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 152.2, 150.1, 134.2, 127.3, 125.9.
**4-Iodo-3-chloropyridine (4d)**

Carried out on 3.3 mmol scale; yellow liquid (242 mg, 34%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (d, 1H, $J = 5.2$ Hz), 7.74 (d, 1H, $J = 1.2$ Hz), 7.58 (dd, 1H, $J = 5.2$ Hz, $J = 1.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.7, 149.7, 133.1, 131.6, 106.6.

**4-Chloro-2-pyridone (1b)**

Carried out on 5.0 mmol scale. Purification by flash chromatography on silica gel (EtOAc/MeOH: 95/5), followed by recrystallization from toluene gave 1b (380 mg, 59% from 3) as an off-white solid. mp: 183-184 °C (toluene), lit.$^{[5a]}$: 184.5-185.5°C (no solvent reported); $^1$H NMR (400 MHz, DMSO-D$_6$) $\delta$ 11.82 (br s, 1H, NH), 7.42 (d, 1H, $J = 7.0$ Hz), 6.43 (d, 1H, $J = 2.1$ Hz), 6.25 (dd, 1H, $J = 7.0$ Hz, $J = 2.1$ Hz); $^{13}$C NMR (100 MHz, DMSO-D$_6$) $\delta$ 162.1, 147.0, 137.1, 118.9, 106.7; IR (neat): 3105, 3059, 2919, 2693, 1669, 1606 cm$^{-1}$; HRMS (ESI$^+$) Calcd for C$_5$H$_5^{35}$ClNO [M+H]$^+$: 130.0054, Found: 130.0059; C$_5$H$_4^{35}$ClNaO[M+Na]$^+$: 151.9874; Found: 151.9876. Anal. Calcd for C$_5$H$_4$ClNO: C, 46.36; H, 3.40; N, 10.81; Found: C, 46.74; H, 3.41; N, 10.66).

**4-Bromo-2-pyridone (1c)**

Carried out on 49.1 mmol scale. Purification by flash chromatography on silica gel (DCM/MeOH/NH$_4$OH: 89/10/1) gave 1c (7.04 g, 82%) as an off-white solid.: mp: 207-208 °C (toluene); $^1$H NMR (400 MHz, DMSO-D$_6$) $\delta$ 11.84 (br s, 1H, NH), 7.33 (d, 1H,
\[ J = 7.0 \text{ Hz}, \ 6.62 \ (d, \ 1H, \ J = 1.8 \text{ Hz}), \ 6.35 \ (dd, \ 1H, \ J = 7.0 \text{ Hz}, \ J = 1.8 \text{ Hz}); \ \ ^{13}\text{C} \text{ NMR (100 MHz, DMSO-D}_6) \ \delta \ 161.8, \ 136.8, \ 136.5, \ 122.4, \ 109.2; \ \text{IR (neat): 2752, 2693, 1682, 1590, 1428, 1058, 956, 871, 756 cm}^{-1}; \ \text{HRMS (EI}^+) \ \text{Calcd for C}_5\text{H}_4\text{BrNO \ [M}^{+}]^{\#}: \ 172.9476; \ \text{Found: 172.9474.}

4-Iodo-2-pyridone (1d)[6]
Carried out on 1.8 mmol scale. Purification by flash chromatography on silica gel (DCM/MeOH: 95/5) gave 1d (328 mg, 83%) as pale yellow solid. mp: 198-199 °C (toluene); \(^1\text{H NMR (400 MHz, DMSO-D}_6) \ \delta \ 11.77 \ (br \ s, \ 1H, \ \text{NH}), \ 7.12 \ (d, \ 1H, \ J = 6.8 Hz), \ 6.85 \ (d, \ 1H, \ J = 1.6 Hz), \ 6.47 \ (dd, \ 1H, \ J = 6.8 \text{ Hz}, \ J = 1.6 \text{ Hz}); \ ^{13}\text{C NMR (100 MHz, DMSO-D}_6) \ \delta \ 161.3, \ 136.0, \ 129.3, \ 114.3, \ 112.1; \ \text{IR (neat): 2687, 1668, 1590, 1424, 1230, 955, 878, 761 cm}^{-1}; \ \text{HRMS (EI}^+) \ \text{Calcd for C}_5\text{H}_4\text{INO \ [M}^{+}]^{\#}: \ 220.9338; \ \text{Found: 200.9330.}

Procedure for the synthesis of 4-amino-2-pyridone (5)[7]
A mixture of 2-chloro-4-aminopyridine 3 (127 mg, 1.0 mmol) and KOH (280.6 mg, 5.0 mmol) in toluene (4.0 mL) was heated at 170°C in a sealed tube for 72h. The mixture was cooled to r.t. and the toluene was removed. The residue was purified by flash chromatography on silica gel (DCM/MeOH/NH\_4OH: 78/20/2) to give 5 (107 mg, 97%) as a pale yellow solid. mp: 213-214°C (acetone) (lit.[7b] (acetone): 219-221°C); \(^1\text{H NMR (400 MHz, DMSO-D}_6) \ \delta \ 10.25 \ (br \ s, \ 1H, \ \text{NH}), \ 6.95 \ (d, \ 1H, \ J = 7.1 \text{ Hz}), \ 5.94 \ (br \ s, \ 2H, \ \text{NH}_2), \ 5.58 \ (dd, \ 1H, \ J = 7.1 \text{ Hz}, \ J = 2.2 \text{ Hz}), \ 5.12 \ (d, \ 1H, \ J = 2.2 \text{ Hz}); \ ^{13}\text{C NMR (100 MHz, DMSO-D}_6) \ \delta \ 164.1, \ 158.4, \ 135.0, \ 98.8, \ 93.4; \ \text{IR (neat): 3217, 1645, 1623, 1600, 1581, 1501 cm}^{-1};
**4-Fluoro-2-pyridone 1a**

![Image of 4-Fluoro-2-pyridone 1a](image)

To a cooled solution of HF-pyridine complex (70%, 13.1 mL) at 0°C was slowly added 4-amino-2-pyridone 5 (1.85 g, 16.8 mmol). The mixture was cooled to -20°C and tBuONO (3.0 mL, 25.2 mmol) was slowly added. The reaction mixture was stirred at -20°C for 0.5h, then allowed to warm to r.t. for 2h and finally heated at 60°C for 1h. The mixture was cooled to 0°C and sat. aq. Na₂CO₃ was added. The aqueous layer was extracted with ethyl acetate (5x), and the combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (DCM/MeOH: 95/5) to give 1a (1.14 g, 60%) as a colorless solid. mp: 174-175°C (DCM/Et₂O) (lit. [8] (DCM/Et₂O): 176-177°C); ¹H NMR (400 MHz, DMSO-D₆) δ 11.72 (br s, 1H, NH), 7.47 (app t, 1H, J = 7.9 Hz), 6.15 (app td, 1H, J₁ = 7.0 Hz, J₂ = 2.5 Hz), 6.04 (dd, 1H, J₁ = 2.5 Hz); ¹³C NMR (100 MHz, DMSO-D₆) δ 171.1 (d, J = 263.9 Hz), 164.3 (d, J = 18.3 Hz), 138.6 (d, J = 14.8 Hz), 102.7 (dd, J₁ = 15.1 Hz, J₂ = 1.5 Hz), 97.4 (d, J = 26.8 Hz); ¹⁹F NMR (282 MHz, DMSO-D₆) δ -97.5 (m); IR (neat): 3378, 2913, 2845, 1675, 1616, 1468, 1181, 1012, 901, 837, 768.

**Procedure for the synthesis of 2-benzyloxy-4-aminopyridine 6**

![Image of 2-benzyloxy-4-aminopyridine 6](image)

A mixture of 2-chloro-4-aminopyridine 3 (6.43g, 50.0 mmol), benzyl alcohol (10.4 mL, 100.0 mmol) and potassium hydroxide (8.42 g, 150 mmol) in toluene (100 mL) was heated overnight to reflux in a round bottom flask equipped with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer
was extracted with dichloromethane twice. The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/EtOAc: 60/40) to give 6 (5.57 g, 56%) as an off-white solid. mp: 97-98 °C (toluene); ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, 1H, J = 5.7 Hz), 7.45-7.42 (m, 2H), 7.38-7.34 (m, 2H), 7.32-7.28 (m, 1H), 6.22 (dd, 1H, J = 5.7 Hz, J = 2.1 Hz), 6.01 (d, 1H, J = 2.1 Hz), 5.33 (s, 2H), 4.05 (br s, 2H, NH₂); ¹³C NMR (100 MHz, CDCl₃) δ 165.2, 155.1, 147.2, 137.7, 128.4 (2C), 127.8 (2C), 127.7, 105.7, 94.1, 67.4. IR (neat): 3457, 3356, 1633, 1598, 1556, 1445, 1345, 1191, 1174, 1004, 838, 812, 751 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₂H₁₁N₂O [M+H]⁺: 201.1028; Found: 201.1025. Anal. Calcd for C₁₂H₁₂N₂O: C, 71.98; H, 6.04; N, 13.99; Found C, 72.32; H, 6.08; N, 13.93.

Procedure for the synthesis of 2-benzyloxy-4-bromopyridine 7a; isolation of 2-benzyloxy-3,4-dibromopyridine 7b and 2-benzyloxy-3,4,5-bromopyridine 7c.

![Chemical structures](image)

To a solution of CuBr₂ (536 mg, 2.4 mmol) in acetonitrile (6 mL) was added tBuONO (356 μL, 3.0 mmol) and the mixture was stirred for 15 min. A solution of 2-benzyloxy-4-aminopyridine 6 (400.5 mg, 2.0 mmol) in acetonitrile (4 mL) was added and the mixture was stirred for 16h. After concentration under reduced pressure, aq. 15% ammonia solution was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (hexane/DCM: 80/20) first yielded 2-benzyloxy-3, 4, 5-tribromopyridine 7c (97 mg, 12%) as a colorless solid.

Analytical data for 7c: mp: 105-107 °C (toluene); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.48-7.45 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 5.43 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.5, 146.1, 138.9, 136.2, 128.5 (2C), 128.0, 127.5 (2C), 115.2,
111.6, 69.4; IR (neat): 1546, 1422, 1339, 1005, 746, 739 cm⁻¹; HRMS (EI⁺) Calcd for C₁₂H₈Br₃NO [M⁺]: 418.8156; Found: 418.8144.

Further elution (hexane/DCM: 80/20) gave 2-benzyloxy-3, 4-dibromopyridine 7b (92 mg, 13%) as a pale yellow oil.

Analytical data for 7b: ¹H NMR (400 MHz, CDCl₃,) δ 7.90 (d, 1H, J = 5.4 Hz), 7.50-7.47 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 7.15 (d, 1H, J = 5.4 Hz), 5.45 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 160.7, 145.0, 136.6, 128.4 (2C), 127.9, 127.4 (2C), 122.0, 110.6, 100.0, 69.0; IR (neat): 1558, 1434, 1407, 1345, 1034, 988, 804, 731 cm⁻¹; HRMS (EI⁺) Calcd for C₁₂H₉Br₂NO [M⁺]: 340.9051; Found: 340.9040.

Further purification by flash chromatography (hexane/DCM: 80/20) yielded 7a (327 mg, 62%) as a pale yellow oil.

Analytical data for 7a: ¹H NMR (400 MHz, CDCl₃,) δ 8.00 (d, 1H, J = 5.5 Hz), 7.46-7.43 (m, 2H), 7.40-7.36 (m, 2H), 7.30-7.31 (m, 1H), 7.05 (dd, 1H, J = 5.5 Hz, J = 1.6 Hz), 7.03 (d, 1H, J = 1.6 Hz), 5.38 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 147.4, 136.8, 133.9, 128.5 (2C), 128.0, 127.9 (2C), 120.5, 114.5, 68.0; IR (neat): 1574, 1553, 1349, 1218, 995, 981 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₂H₁₁BrNO [M+H⁺]: 264.0017; Found: 264.0019.

Alternative procedure for the synthesis of 4-bromo-2-pyridone 1c from 6

To a solution of 2-benzyloxy-4-bromopyridine 6 (201 mg, 0.8 mmol) in MeOH (4.5 mL) was added conc. HCl (2.3 mL). The mixture was heated at reflux overnight. Then the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was poured into cold water and carefully quenched with aq. sat. Na₂CO₃. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was purified by flash...
chromatography on silica gel (EtOAc/MeOH: 98/2) to give 1c (109 mg, 82%) as a colorless solid. Data for 1c are reported above.

**Procedure for the synthesis of 2-benzyloxy-3-bromo-4-aminopyridine 7d.**

![Chemical structure of 6 and 7d](image)

To a solution of 2-(benzyloxy)-4-aminopyridine 6 (1.72 g, 8.6 mmol) in acetonitrile (43 mL) was added CuBr₂ (2.12 g, 9.5 mmol). The mixture was stirred at r.t. for 7 days. After concentration under reduced pressure, aq. 15% ammonia solution was added and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure, and purification by flash chromatography on silica gel (hexane/EtOAc: 80/20) gave 7d (1.62 g, 75%) as an off-white solid. mp: 86-87°C (toluene); "H NMR (400 MHz, CDCl₃) δ 7.73 (d, 1H, J = 5.6 Hz), 7.50-7.48 (m, 2H), 7.39-7.36 (m, 2H), 7.32-7.28 (m, 1H), 6.29 (d, 1H, J = 5.6 Hz), 5.43 (s, 2H), 4.60 (br s, 2H, NH₂); "C NMR (100 MHz, CDCl₃) δ 160.3, 152.1, 144.7, 137.4, 128.4, 127.6, 127.3, 105.5, 91.3, 68.1; IR (neat): 3443, 3297, 3182, 1625, 1593, 1413, 1307, 1054, 727 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₂H₁₂BrN₂O [M+H]⁺: 279.0128; Found: 279.0133; Anal. Calcd for C₁₂H₁₁BrN₂O: C, 51.63; H, 3.97; N, 10.04; Found C, 51.94, H, 3.97, N, 10.04.

**General procedure for the synthesis of 7b-c, 7e and 7f.**

![Chemical structure of 7d and 7b-c, e-f](image)

To a mixture of copper source (1.2 eq., CuBr₂ for 7b and 7c, CuCl₂ for 7e, Cul for 7f) in acetonitrile (0.4M) was slowly added tBuONO (1.5 eq.). The mixture was stirred for 15 min and then cooled to 0°C. A solution of 2-benzyloxy-3-bromo-4-aminopyridine 7d (1.0 eq.) in acetonitrile (0.5M) was slowly added. The mixture was stirred for 1h at 0°C and then allowed to warm to r.t. for 16h. After concentration
under reduced pressure, aq. 15% ammonia solution (2 mL/mmol) was added, and the aqueous layer was extracted with dichloromethane (5 mL/mmol; 3x). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to give the product(s) 7b-c, 7e and 7f.

4-Benzylxoy-3, 4-bromopyridine 7b and 4-benzylxoy-3, 4, 5-tribromopyridine 7c
Carried out on 1.0 mmol scale. Purification by flash chromatography on silica gel (hexane/DCM: 75/25) first yielded 4-benzylxoy-3, 4, 5-tribromopyridine 7c (141 mg, 33%) as a colorless solid. Further purification by flash chromatography (hexane/DCM: 75/25) yielded 2-benzyloxy-3, 4-dibromopyridine 7b (185 mg, 54%) as a pale yellow oil. Data for 7b and 7c are described earlier.

4-Benzyloxy-3-bromo-4-chloropyridine 7e
Carried out on 1.0 mmol scale. Purification by flash chromatography on silica gel (hexane/DCM: 70/30) gave 7e (256 mg, 86%) as a pale yellow solid. mp: 53-54°C (toluene); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (d, 1H, $J = 5.4$ Hz), 7.50-7.48 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.30 (m, 1H), 7.00 (d, 1H, $J = 5.4$ Hz), 5.47 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.0, 145.7, 145.0, 136.6, 128.4 (2C), 127.9, 127.5 (2C), 118.9, 108.1, 69.0; IR (neat): 1567, 1539, 1438, 1411, 1336, 1035, 996, 753, 699 cm$^{-1}$; HRMS (ESI$^+$) Calcd for C$_{12}$H$_{10}$Br$_3$ClNO [M+H]$^+$: 297.9629; Found: 297.9630.
4-Benzylxy-3-bromo-4-iodopyridine 7f
Carried out on 0.7 mmol scale. Purification by flash chromatography on silica gel (hexane/DCM: 70/30) gave 7f (157 mg, 55%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$,) $\delta$ 7.73 (d, 1H, $J = 5.2$ Hz), 7.49-7.47 (m, 2H), 7.40-7.36 (m, 3H), 7.33-7.29 (m, 1H), 5.44 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.7, 145.0, 136.6, 128.4 (2C), 128.2, 127.8, 127.5 (2C), 115.6, 114.5, 69.0; IR (neat): 3031, 2942, 1527, 1554, 1431, 1400, 1342, 1310, 1026, 980, 731, 693 cm$^{-1}$; HRMS (ESI$^+$) Calcd for C$_{12}$H$_{9}$BrINO $[M+H]^+$: 389.8995; Found: 389.8979; C$_{12}$H$_{9}$BrINO $[M+Na]^+$: 411.8804; Found: 411.8793.

General procedure for the synthesis of 4-substituted-3-halopyrid-2-ones 8-11 and 13

To a solution of the appropriate pyridine (7b-f) in MeOH (0.1M) was added conc. HCl (10 eq.). The mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, added to cold water (4 mL/mmol) and carefully quenched with aq. sat. Na$_2$CO$_3$ (4 mL/mmol). The aqueous layer was extracted with ethyl acetate (15 mL/mmol; 5x). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to give pyridones 8-11 and 13, details of each of which are provided below.

2, 3-Dibromopyrid-2-one 8
Carried out on 0.54 mmol scale. Purification by flash chromatography on silica gel (EtOAc) gave 8 (130 mg, 95%) as a pale yellow solid. mp: $>250^\circ$C (decomp., toluene); $^1$H NMR (400 MHz, DMSO-D$_6$) $\delta$ 12.28 (br s, 1H, NH), 7.38 (d, 1H, $J = 6.9$
2, 3, 4-Tribromopyrid-2-one 9

Purification by flash chromatography on silica gel (DCM/MeOH: 95/5) gave 9 (103 mg, 97%) as a pale yellow solid. Mp: >250°C (decomp., toluene); \( ^1 \)H NMR (400 MHz, DMSO-D\(_6\)) \( \delta \) 12.62 (br s, 1H, NH), 7.92 (s, 1H); \( ^{13} \)C NMR (100 MHz, DMSO-D\(_6\)) \( \delta \) 157.4, 140.6, 136.2, 119.8, 100.5; IR (neat): 2775, 1636, 1584, 1364, 911, 857 cm\(^{-1}\); HRMS (EI\(^+\)) Calcd for C\(_5\)H\(_2\)\(^{79}\)Br\(_3\)NO [M\(^{+}\)]: 328.7686; Found: 328.7690.

3-Bromo-4-chloropyrid-2-one 10

Carried out on 0.75 mmol scale. Purification by flash chromatography on silica gel (DCM/MeOH: 95/5) gave 10 (151 mg, 96%) as a pale yellow solid. mp: 245-246 °C (toluene); \( ^1 \)H NMR (400 MHz, DMSO-D\(_6\)) \( \delta \) 12.29 (br s, 1H, NH), 7.47 (d, 1H, J = 7.0 Hz), 6.42 (d, 1H, J = 7.0 Hz); \( ^{13} \)C NMR (100 MHz, DMSO-D\(_6\)) \( \delta \) 158.9, 146.8, 135.1, 115.8, 107.4; IR (neat): 2797, 1605, 1421, 1138, 933, 772 cm\(^{-1}\); HRMS (EI\(^+\)) Calcd for C\(_5\)H\(_3\)\(^{79}\)Br\(_3\)ClNO [M\(^{+}\)]: 206.9087; Found: 206.9093.

4-Iodo-3-bromopyrid-2-one 11
Carried out on 0.34 mmol scale. Purification by flash chromatography on silica gel (DCM/MeOH: 95/5) gave 11 (91 mg, 89%) as a pale yellow solid. mp: >250 °C (toluene); ^1^H NMR (400 MHz, DMSO-D$_6$) $\delta$ 12.17 (br s, 1H, NH), 7.18 (d, 1H, $J =$ 6.8 Hz), 6.64 (d, 1H, $J =$ 6.8 Hz); ^13^C NMR (100 MHz, DMSO-D$_6$) $\delta$ 157.3, 134.5, 124.5, 118.5, 115.7; IR (neat): 2802, 1633, 1589, 1230, 1017, 774 cm$^{-1}$; HRMS (EI$^+$) Calcd for C$_5$H$_3$BrINO [M]$^+$: 298.8443; Found: 298.8438.

4-Amino-3-bromopyrid-2-one 13\textsuperscript{[10]}

Purification by flash chromatography on silica gel (DCM/MeOH/NH$_4$OH: 89/10/1) gave 13 (74 mg, 78%) as an off-white solid. mp: >250°C (toluene) lit.\textsuperscript{[10]}: 255-258°C (no solvent cited); ^1^H NMR (400 MHz, DMSO-D$_6$) $\delta$ 10.79 (br s, 1H, NH), 7.03 (d, 1H, $J =$ 7.1 Hz), 6.26 (br s, 2H, NH$_2$), 5.78 (d, 1H, $J =$ 7.1 Hz); ^13^C NMR (100 MHz, DMSO-D$_6$) $\delta$ 159.6, 154.8, 133.4, 97.9, 90.4; IR (neat): 3452, 3283, 3172, 2924, 2827, 1602, 1476, 1447, 1023, 783 cm$^{-1}$; HRMS (EI$^+$) Calcd for C$_5$H$_5$BrN$_2$O [M]$^+$: 187.9585; Found: 187.9588.

Procedure for the synthesis of 4-fluoro-3-bromopyrid-2-one 12

![Formula](https://i.imgur.com/3Q5Q5Q.png)

To a cooled solution of HF-pyridine complex (70%, 1 mL) at 0°C was slowly added 2-benzyloxy-3-bromo-4-aminopyridine 7d (279 mg, 1.0 mmol). The mixture was cooled to -20°C and tBuONO (180 μL, 1.5 mmol) was slowly added. The reaction mixture was stirred at -20°C for 0.5h, then allowed to warm to r.t. for 2h and finally heated at 60°C for 2h. The mixture was cooled to 0°C and quenched to pH 10 with aq. sat. Na$_2$CO$_3$. The aqueous layer was extracted with ethyl acetate (5x). The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (DCM/MeOH: 95/5) to
give 12 (114 mg, 59%) as a beige solid. mp: 214-215°C (toluene); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 12.25 (br s, 1H, NH), 7.57 (t, 1H, \(J = 7.5\) Hz), 6.36 (t, 1H, \(J = 7.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.9 (d, \(J = 263.8\) Hz), 160.7 (d, \(J = 9.0\) Hz), 137.1 (d, \(J = 14.5\) Hz), 98.6 (d \(J = 14.4\) Hz), 97.8 (d \(J = 27.2\) Hz); \(^19\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -88.2 (t, \(J = 14.5\) Hz); IR (neat): 2815, 1634, 1458, 1220, 1043, 783, 776 cm\(^{-1}\); HRMS (El\(^+\)) Calcd for C\(_5\)H\(_3\)\(^{35}\)BrFNO \([M]^+\): 190.9382; Found: 190.9385.

2-Benzylxoy-3-iodo-4-aminopyridine (see footnote 15, main text).

![Chemical Structure](attachment:image.png)

To a solution of 2-(benzyloxy)-4-aminopyridine (100 mg, 0.50 mmol) in acetonitrile (2.5 mL) was added Cul (104.7 mg, 0.55 mmol). The mixture was stirred at r.t. for 7 days. After concentration under reduced pressure, an aq. 15% NH\(_4\)OH solution was added and the aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated under reduced pressure. The crude (28% conversion by \(^1\)H NMR) was purified by flash chromatography on silica gel (hexane/EtOAc: 80/20) to give the title product (39 mg, 24%) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.71 (d, 1H, \(J = 5.6\) Hz), 7.52-7.50 (m, 2H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 1H), 6.25 (d, 1H, \(J = 5.6\) Hz), 5.42 (s, 2H), 4.66 (br s, 2H, NH\(_2\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.5, 155.1, 146.1, 137.4, 128.4 (2C), 127.5, 127.1 (2C), 104.8, 68.4, 66.9; IR (neat): 3425, 3293, 3180, 1625, 1586, cm\(^{-1}\); HRMS (ESI\(^+\)) Calcd for C\(_{12}\)H\(_{12}\)I\(_2\)N\(_2\)O \([M+H]^+\): 326.9989, Found: 326.9983; C\(_{12}\)H\(_{11}\)I\(_2\)N\(_2\)NaO \([M+Na]^+\): 348.9808; Found: 348.9811.

References


Copies of NMR Spectra

$^1$H NMR for 4b
$^1$H NMR for 4c

$^{13}$C NMR for 4c
$^1$H NMR for 4d

$^{13}$C NMR for 4d
$^1$H NMR for 1b

$^{13}$C NMR for 1b
$^{1}H$ NMR for 1d

$^{13}C$ NMR for 1d
$^{19}$F NMR for 1
$^1$H NMR for 6

$^{13}$C NMR for 6
$^1$H NMR for 7e

$^{13}$C NMR for 7e
$^1$H NMR for 7f

$^{13}$C NMR for 7f
$^1$H NMR for 8

$^{13}$C NMR for 8
$^1$H NMR for 9

$^{13}$C NMR for 9
$^1$H NMR for 10

$^{13}$C NMR for 10
$^1$H NMR for 11

$^{13}$C NMR for 11
$^1$H NMR for 12

$^{13}$C NMR for 12
$^{19}$F NMR for 12
$^1$H NMR for 2-benzyloxy-3-iodo-2-aminopyridine

$^{13}$C NMR for 2-benzyloxy-3-iodo-2-aminopyridine