Supporting Information

for

Functionalization of 4-bromobenzo[c][2,7]naphthyridine via regioselective direct ring metalation. A novel approach to analogues of pyridoacridine alkaloids

Benedikt C. Melzer, Alois Plodek and Franz Bracher


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General information

Solvents used were of HPLC grade or p.a. grade and/or purified according to standard procedures. Melting points were determined by open tube capillary method with a Büchi melting point B-450 apparatus. IR measurements were carried out with a Perkin–Elmer FTIR Paragon 1000 spectrometer. NMR spectra were recorded with Jeol J NMR GX (400 or 500 MHz) and Avance III HD Bruker BioSpin (400 or 500 MHz) spectrometers with residual non-deuterated solvent as internal standard. Spectra were recorded in deuterated solvents and chemical shifts are reported in parts per million (ppm). J values are given in Hertz. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet. Signal assignments were carried out based on $^1$H, $^{13}$C, HMBC, HMQC and COSY spectra. NMR spectra were analyzed with the NMR software MestReNova, Version 5.1.1-3092 (Mestrelab Research S.L.) HRMS were performed by electron impact (EI) at 70 eV with a Thermo Finnigan MAT 95 or a Jeol GCmate II spectrometer or by electrospray ionization (ESI) with a Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron resonance mass spectrometer. Chromatographic purification of products was performed by using flash column chromatography on Merck silica gel 60 (0.015–0.040 mm) as stationary phase. Purity of the synthesized compounds was typically >95%, as determined by HPLC on a Merck Hitachi LaChrom HPLC system equipped with a Poroshell 120 EC-C18 column (3.0 × 100 mm) with acetonitrile/water/THF (700:298:2) as the eluent or with a Luna 5 µm CN 100 Å Column 4.6 × 250 mm) with acetonitrile/water/THF (800:199:1) as the eluent (for compounds 14, 20a, 20b, 22), and UV detection at 210 and 254 nm.

General procedure A: regioselective metalation of 4-bromobenzo[c][2,7]naphthyridine (9d)

A dry and nitrogen flushed 25 or 50 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with TMPMgCl∙LiCl (1.0 M in THF/toluene, 1.1 equiv) and cooled to −40 °C. A solution of 4-bromobenzo[c][2,7]benzonaphthyridine (9d; 1.0 equiv) in dry THF (10 mL per mmol 9d) was added and the reaction mixture was stirred at −40 °C for 2 h. The obtained metalated species was reacted immediately with the respective electrophiles, as described in detail below.
Deuteration experiment with 4-bromobenzo[c][2,7]naphthyridine (9d)
After metalation (see General Procedure A) the mixture was quenched with D₂O, lipophilic components separated and analysed by ¹H NMR. The singlet of 5-H at 9.7 ppm showed an integral of 0.4 H. Other proton signals were not reduced in integration. The complete absence of proton signals not arising from compound 9d-D further indicates, that under the applied metalation conditions no subsequent reactions, e.g., halogen dance reactions, took place.

For comparison: non-deuterated 9d:
Compounds

4-Bromobenzo[c][2,7]napthyridine (9d)

Easily available 3-cyano-4-methylquinoline was reacted with Bredereck’s reagent (tert-butoxybis(dimethylamino)methane) to give a crude enamine, which was treated with HBr in glacial acetic acid to give 9d in excellent yield. For details, see ref. 1.

(±)-(4-Bromobenzo[c][2,7]napthyridin-5-yl)(phenyl)methanol (12a)

9d (0.150 g, 0.581 mmol) was metalated according to General Procedure A with TMPMgCl·LiCl (1.0 M in THF/toluene; 0.640 mL, 0.640 mmol) in dry THF (6 mL). After the metalation period benzaldehyde (11a; 0.065 mL, 0.640 mmol) dissolved in dry THF (0.5 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 12a (0.106 g, 50%) as a pale brown solid. mp 188–190 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.58 (d, J = 5.5 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.43 (d, J = 5.8 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.95 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.81 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.23-7.10 (m, 5H), 6.44 (d, J = 7.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) = 158.8, 147.4, 143.2, 142.5, 142.3, 141.6, 132.1, 129.7, 128.7, 128.6, 128.3, 127.9, 123.0, 122.0, 120.9, 115.8, 72.9; IR (KBr): ν (cm⁻¹) = 3424, 2856, 1591, 1551, 1391, 1201, 1164, 1113, 1089, 945, 763; HRMS (EI): m/z = 364.0206 (calcd for C₁₉H₁₃N₂OBr: 364.0211).
(±)-(4-Bromobenzo[c][2,7]naphthyridin-5-yl)(thiazol-5-yl)methanol (12b)

9d (0.433 g, 1.68 mmol) was metalated according to General Procedure A with TMPMgCl⋅LiCl (1.0 M in THF/toluene; 1.84 mL, 1.84 mmol) in dry THF (17 mL). After the metalation period 5-thiazolecarbaldehyde (11b; 0.174 mL, 2.02 mmol) dissolved in dry THF (0.5 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 12b (0.386 g, 61%) as a slightly yellow solid. mp 185–187 °C; ¹H NMR (400 MHz, MeOD-d₃ : CDCl₃ = 1 : 2): δ (ppm) = 8.85 (s, 1H), 8.70 (d, J = 8.1 Hz, 1H), 8.68-8.62 (m, 2H), 8.28 (d, J = 8.2 Hz, 1H), 8.00 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.92-7.82 (m, 2H), 7.53 (s, 1H); ¹³C NMR (101 MHz, MeOD-d₃ : CDCl₃ = 1 : 2): δ (ppm) = 157.0, 154.9, 147.3, 142.9, 142.6, 142.4, 140.8, 140.7, 132.3, 129.5, 129.2, 123.4, 122.1, 120.1, 116.6, 66.4; IR (KBr): ν (cm⁻¹) = 3422, 1586, 1541, 1391, 1300, 1254, 1039, 989, 876, 762; HRMS (EI): m/z = 370.9715 (calcd for C₁₆H₁₀N₃OSSBr: 370.9728).

(±)-(4-Bromobenzo[c][2,7]naphthyridin-5-yl)(2-bromophenyl)methanol (12c)

9d (0.300 g, 1.16 mmol) was metalated according to General Procedure A with TMPMgCl⋅LiCl (1.0 M in THF/toluene; 1.28 mL, 1.28 mmol) in dry THF (12 mL). After the metalation period 2-bromobenzaldehyde (11c; 0.176 mL, 1.51 mmol) dissolved in dry THF (0.5 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 12c (0.265 g, 52%) as a brown solid. mp 214–216 °C; ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.63-8.55 (m, 2H), 8.47 (d, J = 5.6 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.97 (ddd, J = 8.0, 7.1, 1.3 Hz, 1H), 7.84 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.69 (dd, J = 8.0, 1.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 7.09 (td, J = 7.7, 1.7
Hz, 1H), 6.93 (td, J = 7.6, 1.3 Hz, 1H), 6.48 (d, J = 6.8 Hz, 1H), 6.16 (dd, J = 7.8, 1.6 Hz, 1H);

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) = 157.7, 147.6, 142.9, 142.5, 142.1, 141.8, 133.7, 132.2, 129.8, 129.4, 128.9, 127.9, 126.6, 123.0, 122.1, 121.1, 115.9, 72.8; IR (KBr): ν (cm$^{-1}$) = 3426, 1589, 1545, 1392, 1296, 1042, 994, 762; HRMS (EI): m/z = 443.9308 (calcd for C$_{19}$H$_{12}$N$_2$OBr$_2$: 441.9316).

(±)-(4-Bromobenzo[c][2,7]naphthyridin-5-yl)(2-bromopyridin-3-yl)methanol (12d)

![Chemical structure](image)

9d (0.400 g, 1.55 mmol) was metalated according to General Procedure A with TMPMgCl⋅LiCl (1.0 M in THF/toluene; 1.71 mL, 1.71 mmol) in dry THF (15 mL). After the metalation period 2-bromo-3-pyridincarbaldehyde (11d; 0.346 mg, 1.86 mmol) dissolved in dry THF (0.5 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH$_4$Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 12d (0.451 g, 66%) as a brown solid. mp 201–203 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.64 (d, J = 5.5 Hz, 1H), 8.60 (d, J = 8.2 Hz, 1H), 8.50 (d, J = 5.6 Hz, 1 H), 8.32-8.19 (m, 2 H), 7.99 (t, J = 7.6 Hz, 1 H), 7.87 (d, J = 7.7 Hz, 1 H), 7.53 (s, 1 H), 6.96 (dd, J = 7.6, 4.7 Hz, 1 H), 6.59 (dd, J = 7.6, 1.8 Hz, 1 H), 6.40 (s, 1 H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ (ppm) = 156.5, 148.9, 147.8, 146.2, 142.7, 142.1, 141.5, 140.2, 135.8, 132.4, 129.8, 129.2, 123.1, 122.8, 122.2, 120.8, 116.0, 72.3; IR (KBr): ν (cm$^{-1}$) = 3406, 1588, 1560, 1546, 1393, 1050, 994, 762; HRMS (EI): m/z = 442.9265 (calcd for C$_{18}$H$_{11}$N$_3$OBr$_2$: 442.9269).

4-Bromo-5-iodobenzo[c][2,7]naphthyridine (13)

![Chemical structure](image)

9d (0.300 g, 1.16 mmol) was metalated according to General Procedure A with TMPMgCl⋅LiCl (1.0 M in THF/toluene; 1.28 mL, 1.28 mmol) in dry THF (12 mL). After the metalation period a solution of iodine (1.0 M in THF; 1.51 mL, 1.51 mmol) was added. The reaction mixture was
slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 13 (0.361 g, 71%) as a brown solid. mp 141–143 °C; ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.60 (d, J = 5.5 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 8.33 (d, J = 5.5 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 147.0, 145.5, 144.1, 141.2, 132.2, 129.7, 128.8, 122.9, 122.3, 120.9, 117.8, 115.5; IR (KBr): ν (cm⁻¹) = 3430, 3066, 1581, 1519, 1447, 1380, 1242, 1184, 1112, 916, 837, 755; HRMS (EI): m/z = 383.8753 (calcd for C₁₂H₆N₂IBr: 383.8759).

**Ethyl 4-bromobenzo[a][2,7]naphthyridine-5-carboxylate (14)**

9d (0.100 g, 0.386 mmol) was metalated according to General Procedure A with TMPMgCl-LiCl (1.0 M in THF/toluene; 0.425 mL, 0.425 mmol) in dry THF (4 mL). After the metalation period neat diethyl carbonate (0.234 mL, 0.425 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 16 h. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (5 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 10:1) to give 14 (0.045 g, 37%) as a white solid. mp 207 °C (ref. 1: 206 °C); ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.66 (d, J = 5.6 Hz, 1H), 8.53 (dd, J = 8.2, 1.3 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.28 (dd, J = 8.2, 1.3 Hz, 1H), 7.92 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.82 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 4.61 (q, J = 7.2 Hz, 2H), 1.50 (t, J = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 166.9 (C=O), 152.2, 147.9, 143.9, 142.4, 141.5, 132.2, 130.9, 129.4, 123.0, 122.0, 119.1, 115.6, 63.4, 14.0; IR (KBr): ν (cm⁻¹) = 2985, 2938, 1740, 1587, 1547, 1462, 1395, 1379, 1320, 1238, 1189, 1117, 1095, 1020, 795, 763, 741, 628; HRMS (EI): m/z (%) = 330.0017 (calcd for C₁₅H₁₁BrN₂O₂: 330.0004).
4-(Dimethylamino)benzo[c][2,7]naphthyridine-5-carbaldehyde (16)

9d (0.258 g, 1.00 mmol) was metalated according to General Procedure A with TMPMgCl-LiCl (1.0 M in THF/toluene; 1.10 mL, 1.10 mmol) in dry THF (10 mL). After the metalation period dry DMF (0.10 mL, 1.30 mmol) dissolved in dry THF (0.5 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for 20 min. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 1:1) to give 16 (0.103 g, 41%) as a brown solid. mp 125–127 °C; ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 10.47 (s, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.47 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.87 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.76 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 3.00 (s, 6H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 189.9, 161.9, 155.2, 147.6, 144.8, 142.0, 131.2, 128.7, 123.1, 123.0, 111.2, 109.4, 43.2 (2C); IR (KBr): ν (cm⁻¹) = 3442, 2857, 1703, 1588, 1575, 1545, 1485, 1396, 1077, 966, 776; HRMS (ESI): m/z = 252.1131 [M + H]⁺ (calcd for C₁₅H₁₄N₃O⁺: 252.1131).

5-Allyl-4-bromobenzo[c][2,7]naphthyridine (18)

9d (0.100 g, 0.386 mmol) was metalated according to General Procedure A with TMPMgCl-LiCl (1.0 M in THF/toluene; 0.425 mL, 0.425 mmol) in dry THF (4 mL). After the metalation period allyl iodide (0.071 g, 0.425 mmol) was added to the reaction mixture directly followed by CuCN-2LiCl (1.0 M in THF; 0.04 mL, 0.040 mmol). The mixture was stirred at −40 °C for 2 h, then quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 5:1) to give 18 (0.043 g, 37%) as an orange solid, which decomposed rapidly on storage. mp 65–66 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.58 (d, J = 5.5 Hz, 1H), 8.47 (d, J = 8.3 Hz, 1H), 8.40 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.85 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.69 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 6.38 (ddt, J = 17.2, 10.3, 6.1 Hz, 1H), 5.18 (dq, J = 10.3, 1.5 Hz, 1H), 5.10 (dq, J = 17.2, 1.7 Hz, 1H), 4.65 (dt, J = 6.1, 1.6 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) = 158.5, 146.7, 144.5, 142.2, 142.2, 135.9,
131.6, 130.0, 127.7, 122.8, 121.9, 116.6, 115.8, 44.3; IR (KBr): ν (cm⁻¹) = 3062, 2924, 1608, 1584, 1540, 1457, 1387, 1305, 1253, 1198, 1175, 1152, 1117, 1041, 1017, 836, 786, 762, 737, 628; HRMS (EI): m/z (%) = 298.0109 (calcd for C₁₅H₁₁BrN₂: 298.0106).

**Methyl 2-(4-bromobenzo[c][2,7]naphthyridin-5-yl)benzoate (20a)**

9d (0.200 g, 0.772 mmol) was metalated according to General Procedure A with TMPMgCl·LiCl (1.0 M in THF/toluene; 0.849 mL, 0.849 mmol) in dry THF (8 mL). After the metalation period anhydrous ZnCl₂ (1.0 M in THF; 0.849 mL, 0.849 mmol) was added and the mixture stirred at −40 °C for further 60 min. Then Pd(dbac)₂ (0.022 g, 0.039 mmol, 5 mol %) and P(2-furyl)₃ (0.018 g, 0.077 mmol, 10 mol %) dissolved in dry THF (4 mL) were transferred to the reaction mixture, directly followed by the addition of methyl 2-iodobenzoate (19a; 0.162 g, 0.618 mmol) dissolved in dry THF (2 mL). The reaction mixture was slowly warmed to room temperature, stirred for 72 h at this temperature, then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 5:1) to give 20a (0.057 g, 26%) as a red solid. mp 205–206 °C; ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.62 (d, J = 5.6 Hz, 1H), 8.58 (dd, J = 8.3, 1.3 Hz, 1H), 8.49 (d, J = 5.6 Hz, 1H), 8.18 (ddd, J = 7.9, 5.1, 1.0 Hz, 2H), 7.88 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.76 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.69 (td, J = 7.5, 1.4 Hz, 1H), 7.59 (td, J = 7.7, 1.3 Hz, 1H), 7.45 (dd, J = 7.6, 1.3 Hz, 1H), 3.57 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 166.7 (C=O), 160.2, 147.1, 144.3, 143.6, 143.3, 141.3, 132.7, 131.7, 130.7, 130.6, 130.4, 128.2, 128.8, 128.1, 123.0, 121.7, 121.7, 115.8, 52.1; IR (KBr): ν (cm⁻¹) = 1712, 1587, 1541, 1433, 1392, 1322, 1263, 1184, 1132, 1090, 1044, 949, 845, 790, 770, 704, 633; HRMS (EI): m/z (%) = 392.0150 (calcd for C₂₀H₁₃BrN₂O₂: 392.0160).
4-(4-Bromobenzo[c][2,7]naphthyridin-5-yl)nicotinonitrile (20b)

![Chemical Structure](image)

9d (0.259 g, 1.00 mmol) was metalated according to General Procedure A with TMPMgCl·LiCl (1.0 M in THF/toluene; 1.10 mL, 1.10 mmol) in dry THF (10 mL). After the metalation period anhydrous ZnCl₂ (1.0 M in THF; 1.10 mL, 1.10 mmol) was added and the reaction mixture stirred at −40 °C for further 60 min. Then Pd(dba)₂ (0.029 g, 0.050 mmol, 5 mol %) and P(2-furyl)₃ (0.023 g, 0.100 mmol, 10 mol %) dissolved in dry THF (8 mL) were transferred to the reaction mixture, directly followed by the addition of 2-iodonicotinonitrile (19b; 0.184 g, 0.800 mmol) dissolved in dry THF (4 mL). The reaction mixture was slowly warmed to 50 °C and stirred for 16 h at this temperature. Then the reaction mixture was quenched with satd. aqueous NH₄Cl solution (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 2:1) to give 20b (0.132 g, 46%) as a brown solid. mp > 300 °C (decomposition); ¹H NMR (500 MHz, CD₂Cl₂): δ (ppm) = 9.05 (d, J = 0.8 Hz, 1H), 8.93 (d, J = 5.1 Hz, 1H), 8.71 (d, J = 5.6 Hz, 1H), 8.66 (dd, J = 8.3, 1.3 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 8.26 – 8.23 (m, 1H), 7.99 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.90 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.60 (dd, J = 5.1, 0.8 Hz, 1H); ¹³C NMR (126 MHz, CD₂Cl₂): δ (ppm) = 153.9 (CN), 153.5, 153.2, 153.1, 148.5, 144.5, 142.5, 142.3, 132.8, 131.1, 130.0, 125.0, 123.7, 122.3, 120.7, 116.4, 116.3, 110.7; IR (KBr): ν (cm⁻¹) = 2232, 1584, 1533, 1456, 1392, 1321, 1185, 1154, 1040, 959, 869, 840, 787, 770, 637; HRMS (EI): m/z (%) = 360.0010 (calcd for C₁₈H₉BrN₄: 360.0010).

(4-Bromobenzo[c][2,7]naphthyridin-5-yl)(thiazol-5-yl)methane (21)

![Chemical Structure](image)

A mixture of 12b (0.180 g, 0.485 mmol) and MnO₂ (0.218 g, 2.50 mmol) in THF (10 mL) was heated to reflux for 24 h. After cooling to room temperature residual solids were filtered off and water (20 mL) was added to the filtrate. The mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 4:1) to give 21 (0.166 g, 92%) as a white solid. mp 220 – 222 °C; ¹H NMR (500 MHz,
CDCl₃): δ (ppm) = 9.18 (s, 1 H), 8.71 (d, J = 5.6 Hz, 1 H), 8.61 (d, J = 7.3 Hz, 1 H), 8.48 (d, J = 5.7 Hz, 1 H), 8.45 (s, 1 H), 8.26 (d, J = 7.2 Hz, 1 H), 7.97 (ddd, J = 8.3, 7.1, 1.3 Hz, 1 H), 7.88 (ddd, J = 8.3, 7.1, 1.3 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 185.3, 160.3, 155.7, 150.8, 148.2, 143.5, 142.3, 142.0, 139.3, 132.4, 130.9, 129.8, 123.1, 122.1, 119.9, 115.5; IR (KBr): ν (cm⁻¹) = 3432, 3074, 1655, 1585, 1501, 1384, 1187, 1128, 894, 837, 770, 601; HRMS (ESI): m/z = 369.9642 [M + H]+ (calcd for C₁₇H₉N₃OSBr+: 369.9644).

8H-Benzo[c]pyrido[4,3,2-mn]acridin-8-one (22)

A dry and nitrogen flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with a solution of 20a (0.050 g, 0.127 mmol) in dry THF (2 mL) and cooled to 0 °C. iPrMgCl·LiCl (1.3 M in THF; 0.22 mL, 0.27 mmol) was slowly added and the reaction mixture was stirred at 0 °C for 2 h. Then the mixture was allowed to warm to room temperature, quenched with satd. aqueous NH₄Cl solution (5 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate = 4:1) to give 22 (0.010 g, 28%) as a yellow solid. mp 312 – 314 °C (ref. 2: >300 °C); ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 9.30 (d, J = 4.1 Hz, 1H), 9.01 (d, J = 7.8 Hz, 1H), 8.61 (d, J = 4.1 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 8.50 (d, J = 7.7 Hz, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.92 (t, J = 7.5 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 182.4, 150.1, 149.2, 147.5, 145.8, 138.2, 135.8, 134.7, 132.8, 131.9, 131.6, 131.5, 128.8, 128.4, 125.8, 123.0, 121.9, 119.6, 118.7; IR (KBr): ν (cm⁻¹) = 1677, 1593, 1575, 1353, 1325, 1297, 1195, 1098, 964, 951, 872, 762, 708, 580; HRMS (ESI): m/z = 282.0803 (calcd for C₁₉H₁₀N₂O: 282.0793).

References:
NMR spectra

12a
12b
12c
12d
20a
20b