A Short Way to Pyrroloquinoxalinones via a Cascade Reaction of N-Aryl-5-alkylamino-2-nitrosoanilines with Methyl 2-Cyanoalkanoates. Unexpected direction of Nucleophilic Substitution of Hydrogen.

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1. General information.

Melting points are uncorrected. 1H and 13C NMR spectra were recorded on a Varian-NMR-vnmrs500 (500 MHz for 1H and 125 MHz for 13C spectra) instrument at 298 K. Chemical shifts δ are expressed in ppm referred to TMS, coupling constants in Hertz. Mass spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. Silica gel Merck 60 (230-400 mes H) was used for column chromatography. MeCN and DMF were dried over CaH2, distilled and stored over molecular sieves. THF was distilled from a sodium benzophenone ketyl solution. Known N-aryl-2-nitrosoanilines 1 were obtained as it was described in the previous papers.1, 2

2. Reaction procedures

Synthesis of the new 2-nitrosoanilines 1. General procedure:1
To a cooled solution of t-BuOK (695 mg, 6.2 mmol) in dry THF (10 ml) was added dropwise at -70-78 ºC a solution of the aniline (1.77 mmol) in THF (2 ml), then the nitroarene (1.77 mmol) in THF (2 ml). The mixture was stirred at that temperature for 30 min, poured into saturated aq NH4Cl and extracted with EtOAc (3x50 ml). The extract was washed with water and brine, dried with Na2SO4 and the solvent was evaporated. The product was isolated by column chromatography.
Synthesis of N-aryl-2-nitrosoanilines 1 bearing amino substituents at C-5. General procedure: \(^2\)

5-Fluoro- or 5-chloro-N-aryl-2-nitrosoaniline (0.5 mmol) was dissolved (or suspended in case of low solubility) in MeCN (10 mL), and the appropriate amine (2.5 mmol) was added. The mixture was stirred at ambient temperature for 2 to 48 h (tlc controlled). After the reaction was complete the mixture was poured into water and extracted three times with AcOEt. The combined extracts were washed with water, brine and the solvent was evaporated. The crude product was purified by column chromatography (SiO\(_2\), hexane/AcOEt).

A slightly different procedure was applied for the reaction of methyamine which was performed as follows: \(N\)-(4-chlorophenyl)-5-fluoro-2-nitrosoaniline (2 mmol) was treated with 33% methyamine solution in ethanol (10 mL). The reaction vial was stoppered and the mixture was stirred until completion (ca. 2 h, tlc control). The mixture was evaporated to dryness, dissolved in EtOAc (20mL), washed with water, dried (Na\(_2\)SO\(_4\)) and the solvent was evaporated. The crude product was sufficiently pure for further transformations.

General procedure for the reactions of 2-nitrosoanilines 1 with alkylcyanoacetic acid methyl esters 2.

\(N\)-Aryl-2-nitrosoaniline 1 (0.5 mmol) and alkylcyanoacetic acid methyl ester (1.2 mmol) were dissolved in dry MeCN (5mL). DBU (2.68 mmol, 0.4mL) was added, the reaction vial was stoppered and the reaction mixture was stirred until the whole nitroso compound was consumed (tlc control). The reaction mixture was poured into satd. aqueous NH\(_4\)Cl (20mL), extracted with EtOAc (3 x 20mL), dried (Na\(_2\)SO\(_4\)) and chromatographed on silica gel using hexane – EtOAc (4:1 to 1:1) as eluent. In the cases when a mixture of products 3 and 4 were formed, a toluene – ethyl acetate (10:1 to 4:1) eluent was used.
3. Physical and spectral data for the new compounds:

5-Benzyl oxy-N-(4-methylphenyl)-2-nitrosoaniline: brown solid; yield: 44%; mp 140 – 142 °C (hexane – ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ = 2.30 (s, 3 H), 5.02 (s, 2 H), 6.40 (br s, 1 H), 6.62 – 6.66 (m, 1 H), 7.02 – 7.06 (m, 2 H), 7.17 – 7.20 (m, 2 H), 7.31 – 7.34 (m, 2 H), 7.35 – 7.41 (m, 3 H), 8.51 (d, J = 9.1 Hz, 1 H), 12.95 (br s, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 21.1, 70.5, 95.0, 110.0, 115.8, 124.8, 126.1, 127.4, 128.5, 128.7, 130.2, 135.3, 142.5, 153.5, 166.1 [one signal invisible]. HRMS (ESI): m/z calcd for C₂₀H₁₉N₂O₂: 319.1447; found: 319.1448.

5-Fluoro-N-(4-methylphenyl)-2-nitrosoaniline: green solid; yield: 57%; mp 112-115 °C. ¹H NMR (400 MHz, CDCl₃): δ = 2.38 (s, 3 H), 6.64 – 6.74 (m, 2 H), 7.10 – 7.15 (m, 2 H), 7.22 – 7.25 (m, 2 H), 8.81 (br s, 1 H), 12.31 (br s, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 21.0, 99.7 (d, J_C-F = 26.4 Hz), 107.4 (d, J_C-F = 25.6 Hz), 124.9, 130.4, 133.6, 136.9, 144.6, 154.8, 168.1 (d, J_C-F = 260 Hz) (one signal invisible). MS (EI): m/z 230 (6), 229 (14), 215 (20), 214 (27), 213 (100), 199 (34), 198 (40), 186 (27). HRMS (SI): m/z calcd. for C₁₃H₁₂N₃OF (M + 1)⁺: 231.0934; found: 231.0935.

1-N-Propyl-3-N-(4-methylphenyl)-4-nitrosobenzene-1,3-diamine: from 5-chloro-N-(4-methylphenyl)-2-nitrosoaniline, yield: 38%; green solid; mp 128-132 °C. ¹H NMR (400 MHz, CDCl₃): δ = 0.97 (t, J = 7.4 Hz, 3 H), 1.60 – 1.68 (m, 2 H), 2.36 (s, 3 H), 3.07 – 3.12 (m, 2 H), 5.03 (broad s, 1 H), 5.91 (d, J = 2.4 Hz, 1 H), 6.24 (dd, J = 9.2, 2.4 Hz, 1 H), 7.14 – 7.21 (m, 4 H), 8.07 (d, J = 9.2 Hz, 1 H), 13.37 (br s, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 11.4, 21.0, 22.3, 44.9, 124.6, 130.0, 134.9, 135.6, 140.5, 141.5, 152.1, 155.3 (two signals invisible). MS
1-N-tert-Butyl-3-N-(4-chlorophenyl)-4-nitrosobenzene-1,3-diamine: from N-(4-chlorophenyl)-5-fluoro-2-nitrosoaniline, yield: 74%; green solid; mp 158-162 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.38\) (s, 9 H), 5.19 (br s, 1 H), 6.04 (d, \(J = 2.3\) Hz, 1 H), 6.28 (dd, \(J = 9.2, 2.3\) Hz, 1 H), 7.19\textendash7.22 (m, 2 H), 7.34\textendash7.37 (m, 2 H), 8.07 (d, \(J = 9.2\) Hz, 1 H), 13.26 (br s, 1 H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 29.5, 52.3, 89.9, 110.9, 125.9, 129.5, 130.9, 136.4, 139.2, 141.2, 151.4, 154.4\). MS (EI): \(m/z\) 305 (43), 304 (39), 303 (100), 302 (61), 269 (17), 246 (47), 232 (46), 231 (24), 230(100), 229 (11). HRMS (EI): \(m/z\) calcd. for C\(_{16}\)H\(_{18}\)N\(_3\)OCl: 303.1138; found: 303.1149.

3-N-(4-Chlorophenyl)-1-N-methyl-4-nitrosobenzene-1,3-diamine: from N-(4-chlorophenyl)-5-fluoro-2-nitrosoaniline, yield: 99%; green solid; mp 178-182 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.88\) (d, \(J = 4.5\) Hz, 3 H), 5.88 (d, \(J = 2.1\) Hz, 1 H), 6.34 (dd, \(J = 9.1, 2.1\) Hz, 1 H), 7.21 \textendash 7.25 (m, 2 H), 7.34 \textendash 7.38 (m, 2 H), 8.06 (d, \(J = 9.1\) Hz, 1 H), 13.34 (br s, 1 H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 29.9, 87.5, 109.6, 126.1, 129.6, 130.0, 131.1, 136.3, 141.3, 151.6, 156.5\). MS (EI): \(m/z\) 263 (40), 262 (39), 261 (100), 260 (61), 247 (13), 246 (32), 245 (19), 244 (89), 232 (31), 231 917), 230 (82), 229 (11). HRMS (EI): \(m/z\) calcd. for C\(_{13}\)H\(_{12}\)N\(_3\)OCl: 261.0669; found: 261.0673.

1-N-Butyl-3-N-(4-ethoxyphenyl)-4-nitrosobenzene-1,3-diamine: from N-(4-ethoxyphenyl)-5-fluoro-2-nitrosoaniline, yield: 32%; brown solid; mp 152-153 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.92\) (t, \(J = 7.4\) Hz, 3 H), 1.33 \textendash 1.40 (m, 2 H), 1.43 (t, \(J = 7.1\) Hz, 3 H), 1.55 –
1.62 (m, 2 H), 3.08 – 3.14 (m, 2 H), 3.04 (q, J = 7.1 Hz, 2 H), 5.40 (br s, 1 H), 5.77 (d, J = 2.2 Hz, 1 H), 6.30 (dd, J = 9.2, 2.2 Hz, 1 H), 6.90 – 6.93 (m, 2 H), 7.16 – 7.19 (m, 2 H), 7.98 (d, J = 9.2 Hz, 1 H), 13.26 (br s, 1 H). 13C NMR (100 MHz, CDCl3): δ = 13.7, 14.8, 20.0, 30.9, 63.7, 87.5, 109.8, 115.2, 115.5, 126.4, 129.9, 140.9, 155.5, 157.1 [two signals invisible]. MS (El): m/z 314 (25), 313 (99), 312 (76), 297 (28), 296 (100), 284 (23), 268 (60). HRMS (El): m/z calcd. for C18H23N3O: 313.1790; found: 313.1797.

1-N-Butyl-3-N-(2,6-dimethylphenyl)-4-nitrosobenzene-1,3-diamine: from N-(2,6-dimethylphenyl)-5-chloro-2-nitrosoaniline, yield: 48%; green solid; mp 125-128 °C. 1H NMR (400 MHz, CDCl3): δ = 0.87 (t, J = 7.4 Hz, 3 H), 1.26-1.36 (m, 2 H), 1.48-1.56 (m, 2 H), 2.16 (s, 6 H), 2.98-3.18 (m, 2 H), 5.02 (d, J = 2.5 Hz, 1 H), 5.30-5.50 (br s, 1 H), 6.32 (dd, J = 10.0, 2.5 Hz, 1 H), 7.12-7.17 (m, 3 H), 8.02 (d, J = 10.0 Hz, 1 H), 12.89 (br s, 1 H). 13C NMR (100 MHz, CDCl3): δ = 13.6, 18.2, 19.9, 30.8, 42.8, 87.6, 108.9, 127.4, 128.4, 128.8, 134.3, 135.7, 140.7, 151.4, 155.7. MS (El): m/z 297 (15), 283 (29), 282 (100). HRMS (El): m/z calcd. for C18H23N3O: 297.1841; found: 297.1848.

3-N-(4-Fluorophenyl)-4-nitroso-1-N-(propan-2-yl)benzene-1,3-diamine: from 5-fluoro-N-(4-fluorophenyl)-2-nitrosoaniline, yield: 98%; dark-green solid; mp 124-126 °C. 1H NMR (400 MHz, CDCl3): δ = 1.23 (d, J = 6.4 Hz, 6 H), 3.58 – 3.66 (m, 1 H), 5.23 (d, J = 6.6 Hz, 1 H), 5.77 (d, J = 2.2 Hz, 1 H), 6.28 (dd, J = 9.1, 2.2 Hz, 1 H), 7.06 – 7.12 (m, 2 H), 7.20 – 7.25 (m, 2 H), 8.06 (d, J = 9.1 Hz, 1 H), 13.23 (br s, 1 H). 13C NMR (100 MHz, CDCl3): δ = 22.5, 44.5, 88.1, 109.5, 116.3 (d, Jcf = 22.9 Hz), 126.8 (d, Jcf = 7.6 Hz), 133.6, 140.8, 141.6, 151.7, 154.6, 160.6 (d, Jcf = 244.6 Hz). MS (El): m/z 274 (26), 273 (100), 256 (30), 227 (53). HRMS (El): m/z calcd. for C15H16N3OF: 273.1277; found: 273.1283.
2-Butyl-6-methoxy-4-(4-methylphenyl)-3,4-dihydro-12,5,4-quinoxaline-1,3-dione (3b): yellow crystals; mp. 165-168 °C (hexane-ethyl acetate). IR (KBr): 1648. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.96\) (t, \(J = 7.2\) Hz, 3 H), 1.44 – 1.52 (m, 2 H), 1.67 - 1.73 (m, 2 H), 2.47 (s, 3 H), 3.07 – 3.11 (m, 2 H), 3.72 (s, 3 H), 6.21 (d, \(J = 2.5\) Hz, 1 H), 6.89 m(dd, \(J = 9.3, 2.5\) Hz, 1 H), 7.17 – 7.20 (m, 2 H), 7.39 – 7.42 (m, 2 H), 8.39 (d, \(J = 9.3\) Hz, 1 H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 13.83, 21.3, 23.0, 25.4, 26.9, 55.7, 100.1, 110.6, 122.2, 125.4, 128.2, 130.9, 132.8, 135.1, 139.6, 141.9, 157.1, 161.8. MS (EI): \(m/z\) 339 (3), 323 (9), 322 (37), 321(23), 294 (9), 293 (16), 281 (20), 280 (100), 279 (30), 266 (18), 265 (13), 252 (10), 251 (13). HRMS (EI): \(m/z\) calcd. for C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\): 322.1681; found: 322.1678. Anal. Calcd for C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\): C, 70.99; H, 6.55; N, 8.28; found: C, 70.54; H, 6.83; N, 8.40.

6-(Benzyloxy)-2-ethy1-4-(4-methylphenyl)-3,4-dihydro-12,5,4-quinoxaline-1,3-dione (3d): yellow crystals; mp 135-138 °C (hexane – ethyl acetate). IR (KBr): 1653. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.27\) (t, \(J = 7.4\) Hz, 3 H), 2.48 (s, 3 H), 3.11 (q, \(J = 7.4\) Hz, 2 H), 4.95 (s, 2 H), 6.25 (d, \(J = 2.5\) Hz, 1 H), 6.94 (dd, \(J = 9.2, 2.5\) Hz, 1 H), 7.11 – 7.14 (m, 2 H), 7.23 – 7.26 (m, 2 H), 7.30 – 7.35 (m, 3 H), 7.37 – 7.40 (m, 2 H), 8.38 (d, \(J = 9.2\) Hz, 1 H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 9.1, 19.1, 21.3, 70.5, 101.2, 111.6, 122.1, 125.4, 127.5, 128.1, 128.3, 128.6, 131.0, 132.8, 135.1, 135.5, 139.6, 142.6, 156.8, 160.8. MS (EI): \(m/z\) 387 (6), 386 (21), 370 (42), 369 (38), 91 (100). HRMS (EI): \(m/z\) calcd. for C\(_{24}\)H\(_{22}\)N\(_2\)O\(_3\): 386.1630; found: 386.1630.
6-(tert-Butylamino)-4-(4-chlorophenyl)-2-methyl-3,4-dihydro-1H\textsuperscript{5},4-quinoxaline-1,3-dione (3e): yellow crystals; mp 246 °C (dec.) (hexane-EtOAc). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 1.24 \) (s, 9 H), 2.54 (s, 3 H), 4.15 (s, 1 H), 5.77 (d, \( J = 2.1 \) Hz, 1 H), 6.59 (dd, \( J = 9.2, 2.1 \) Hz, 1 H), 7.26-7.29 (m, 2 H), 7.58-7.61 (m, 2 H), 8.17 (d, \( J = 9.2 \) Hz, 1 H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 11.7, 29.4, 51.4, 97.7, 112.3, 121.5, 122.6, 130.1, 130.5, 134.6, 134.8, 135.4, 135.9, 149.5, 157.2. 
MS (ESI): \( m/z \) 380 [M + Na]\textsuperscript{+}, 358 [M + H]\textsuperscript{+}. HRMS (ESI): \( m/z \) calcd. for C\textsubscript{19}H\textsubscript{21}N\textsubscript{3}O\textsubscript{2}\textsuperscript{35}Cl [M+H]\textsuperscript{+}: 358.1322; found: 358.1234.

Methyl 2-cyano-2-[3-ethyl-7-methoxy-1-(4-methylphenyl)-2-oxo-1,2-dihydroquinoxalin-6-yl]butanoate (4a): white crystals; mp 179-180 °C (hexane – ethyl acetate). IR (KBr): 2236 (CN), 1755, 1672, 1621. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 1.17 \) (t, \( J = 7.4 \) Hz, 3 H), 1.35 (t, \( J = 7.4 \) Hz, 3 H), 2.38 – 2.45 (m, 2 H), 2.46 (s, 3 H), 2.96 (q, \( J = 7.4 \) Hz, 2 H), 3.64 (s, 3 H), 3.78 (s, 3 H), 6.11 (s, 1 H), 7.14 – 7.18 (m, 1 H), 7.38 – 7.43 (m, 1 H), 7.92 (s, 1 H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 9.7, 10.8, 21.3, 27.1, 28.5, 50.0, 54.5, 56.0, 97.7, 118.1, 120.6, 126.9, 127.7, 127.8, 128.6, 130.9, 131.0, 132.9, 135.8, 139.7, 154.8, 156.9, 160.4, 168.7.

\textsuperscript{1}H (\textsuperscript{13}C) and \textsuperscript{15}N chemical shifts
Methyl 2-[3-butyl-7-methoxy-1-(4-methylphenyl)-2-oxo-1,2-dihydroquinoxalin-6-yl]-2-cyanohexanoate (4b): white crystals; mp 130-132 °C (hexane). IR (KBr): 2249 (CN), 1746, 1660, 1616. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.97 (t, $J$ = 7.1 Hz, 3 H), 0.98 (t, $J$ = 7.3 Hz, 3 H), 1.41 - 1.51 (m, 5 H), 1.54 - 1.63 (m, 1 H), 1.76 - 1.83 (m, 2 H), 2.31 - 2.41 (m, 2 H), 2.47 (s, 3 H), 2.92 - 2.95 (m, 2 H), 3.64 (s, 3 H), 3.78 (s, 3 H), 6.12 (s, 1 H), 7.14 - 7.18 m, 2 H), 7.38 - 7.43 (m, 2 H), 7.91 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 13.7, 13.9, 21.3, 22.5, 22.7, 27.2, 29.0, 33.7, 34.9, 49.1, 53.4, 56.0, 97.7, 118.3, 121.0, 126.8, 127.7, 127.7, 128.4, 130.9, 131.0, 132.9, 135.8, 139.6, 154.8, 156.9, 159.8, 168.9. MS (EI): m/z 476 (19), 475 (61), 434 (29), 433 (100), 416 (13). HRMS (EI): m/z calcd. for C$_{28}$H$_{33}$N$_3$O$_4$: 475.2471; found: 475.2468.

Methyl 2-cyano-2-[7-methoxy-1-(4-methylphenyl)-2-oxo-3-(propan-2-yl)-1,2-dihydroquinoxalin-6-yl]-3-methylbutanoate (4c): yellow oil. IR (KBr): 2242 (CN), 1755, 1666, 1619. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.14 (d, $J$ = 6.7 Hz, 3 H), 1.25 (d, $J$ = 6.7 Hz, 3 H), 1.33 (d, $J$ = 6.8 Hz, 6 H), 2.47 (s, 3 H), 2.96 (sept. $J$ = 6.7 Hz, 1 H), 3.54 - 3.64 (m, 1 H), 3.62 (s, 3 H), 3.74 (s, 3 H), 6.10 (s, 1 H), 7.15 - 7.18 (m, 2 H), 7.38 - 7.42 (m, 2 H), 7.96 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 19.2, 19.3, 20.2, 21.3, 31.0, 31.9, 53.2, 55.3, 55.9, 97.7, 117.1, 119.9, 126.9, 127.7, 129.7, 130.9, 130.9, 133.0, 135.4, 139.5, 154.4, 157.3, 163.4, 168.0. MS (EI): m/z 448 (34), 447 (82), 419 (25), 405 (72), 404 (100), 388 (31), 377 (9), 376 (28), 374 (13), 373 (45), 361 (32). HRMS (EI): m/z calcd. for C$_{29}$H$_{30}$N$_3$O$_4$: 447.2158; found: 447.2164.
Methyl 2-[7-(benzyloxy)-3-ethyl-1-(4-methylphenyl)-2-oxo-1,2-dihydroquinoxalin-6-yl]-2-cyanobutanoate (4d): white solid; mp 144-148 °C (hexane - ethyl acetate). IR (KBr): 2242(CN), 1749, 1668, 1618. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.19$ (t, $J = 7.4$ Hz, 3 H), 1.33 (t, $J = 7.4$ Hz, 3 H), 2.37 – 2.44 (m, 1 H), 2.49 – 2.56 (m, 1 H), 2.50 (s, 3 H), 2.95 (q, $J = 7.4$ Hz, 2 H), 3.48 (s, 3 H), 4.81 (d, $J = 11.7$ Hz, 1 H), 4.91 (d, $J = 11.7$ Hz, 1 H), 6.16 (s, 1 H), 7.05 – 7.09 (m, 2 H), 7.20 – 7.24 (m, 2 H), 7.29 – 7.32 (m, 3 H), 7.37 – 7.40 (m, 2 H), 7.91 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 9.7$, 10.8, 21.3, 27.0, 28.6, 49.7, 53.0, 71.1, 98.9, 118.3, 120.8, 126.8, 127.6, 127.7, 128.3, 128.4, 128.5, 130.9, 131.0, 132.9, 134.8, 135.6, 139.5, 154.7, 155.8, 160.4, 168.8. MS (EI): $m/z$ 496 (12), 495 (62), 467 (11), 437 (27), 436 (94), 91 (100). HRMS (EI): $m/z$ calcd. for C$_{30}$H$_{29}$N$_3$O$_4$: 495.2158; found: 495.2156.

2,8-Diethyl-4-(4-methylphenyl)-3,7-dioxo-6-propyl-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6a): yellow crystals; mp 148-151 °C (hexane – ethyl acetate). IR (KBr): 2243 (CN), 1733, 1670, 1631. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.82$ (t, $J = 7.4$ Hz, 3 H), 1.02 (t, $J = 7.4$ Hz, 3 H), 1.37 (t, $J = 7.4$ Hz, 3 H), 1.49 – 1.58 (m, 2 H), 2.17 – 2.24 (m, 1 H), 2.28 – 2.34 (m, 1 H), 2.50 (s, 3 H), 2.90 – 3.02 (m, 2 H), 3.41 – 3.50 (m, 1 H), 3.56 – 3.62 (m, 1 H), 6.06 (s, 1 H), 7.14 – 7.18 (m, 2 H), 7.41 – 7.46 (m, 2 H), 7.90 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 8.3$, 10.5, 11.2, 20.4, 21.3, 27.0, 30.8, 42.3, 46.4, 95.7, 116.6, 120.8, 125.4, 127.6, 127.7, 128.9, 131.0, 131.1, 132.9, 136.3, 139.9, 143.2, 154.6, 160.6, 170.4. MS (EI): $m/z$ 415 (41), 414 (100), 386 (19), 385 (38), 358 (915), 357 (38). HRMS (EI): $m/z$ calcd. for C$_{25}$H$_{26}$N$_4$O$_2$: 414.2056; found: 414.2047.
6-tert-Butyl-4-(4-chlorophenyl)-2,8-diethyl-3,7-dioxo-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6b): yellow crystals; mp 148-151 °C (hexane – ethyl acetate).
IR (KBr): 2241 (CN), 1731, 1670, 1627. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.95$ (t, $J = 7.4$ Hz, 3 H), 1.36 (t, 7.4 Hz, 3 H), 1.51 (s, 9 H), 2.18 – 2.30 (m, 2 H), 2.93 – 3.02 (m, 2 H), 6.51 (s, 1 H), 7.25 – 7.29 (m, 2 H), 7.61 – 7.65 (m, 2 H), 7.85 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 8.0$, 10.5, 27.0, 28.7, 31.6, 47.2, 59.3, 99.9, 117.0, 121.6, 124.9, 128.3, 129.5, 129.6, 130.6, 130.7, 134.2, 135.0, 135.8, 144.1, 154.4, 160.9, 170.9. MS (EI): $m/z$ 450 (16), 449 (17), 448 (34), 395 (15), 394 (47), 393 (40), 392 (100), 365 (17), 364 (19), 363 (27), 337 (21), 336 (20), 335 (43). HRMS (EI): $m/z$ calcd. for C$_{25}$H$_{25}$N$_4$O$_2$Cl: 448.1666; found: 448.1687.

6-t-Butyl-4-(4-chlorophenyl)-3,7-dioxo-2,8-bis(propan-2-yl)-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6c): yellow crystals; mp 186-191 °C (hexane – ethyl acetate). IR (KBr): 2242 (CN), 1726, 1666, 1627. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.92$ (d, $J = 6.9$ Hz, 3 H), 1.26 (d, $J = 6.9$ Hz, 3 H), 1.33 (d, $J = 6.9$ Hz, 3 H), 1.34 (d, $J = 6.9$ Hz, 3 H), 1.50 (s, 9 H), 2.54 – 2.63 (m, 1 H), 3.54 – 3.63 (m, 1 H), 6.49 (s, 1 H), 7.26 – 7.29 (m, 2 H), 7.60 7.65 (m, 2 H), 7.86 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.2$, 17.5, 20.1, 20.2, 28.7, 31.1, 37.0, 51.3, 59, 2, 99.7, 117.1, 120.4, 125.6, 128.1, 129.5, 129.6, 130.6, 130.7, 134.4, 143.9, 135.7, 144.4, 154.0, 164.0, 170.8 (1 missing). MS (EI): $m/z$ 478 (14), 477 (12), 476 (37), 422 (37), 421 (29), 420 (94), 392 (20), 380 (39), 379 (29), 378 (100), 350 (30). HRMS (EI): $m/z$ calcd. for C$_{27}$H$_{29}$N$_4$O$_2$Cl: 476.1979; found: 476.1981.
6-Butyl-4-(4-chlorophenyl)-2,8-diethyl-3,7-dioxo-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6d): yellow crystals; mp 128-130 °C (hexane – ethyl acetate). IR (KBr): 2241 (CN), 1733, 1670, 1631. 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.84$ (t, $J = 7.4$ Hz, 3 H), 1.01 (t, $J = 7.4$ Hz, 3 H), 1.19 – 1.28 (m, 2 H), 1.36 (t, $J = 7.4$ Hz, 3 H), 1.45 – 1.52 (m, 2 H), 2.17 – 2.25 (m, 1 H), 2.26 – 2.34 (m, 1 H), 2.92 – 3.02 (m, 2 H), 3.46 – 3.53 (m, 1 H), 3.59 – 3.67 (m, 1 H), 6.02 (s, 1 H), 7.24 – 7.28 (m, 2 H), 7.60 – 7.66 (m, 2 H), 7.91 (s, 1 H). 

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 8.3$, 10.5, 13.4, 19.7, 27.0, 28.9, 30.8, 40.4, 46.3, 95.3, 116.5, 121.1, 125.6, 128.8, 129.5, 129.6, 130.7, 130.8, 143.1, 143.4, 154.3, 154.8, 160.5, 170.2. MS (EI): $m/z$ 451 (18), 450 (46), 449 (41), 448 (100), 421 (18), 420 (18), 419 (34), 393 (13), 392 (13), 391 (29). HRMS (EI): $m/z$ calcd. for C$_{25}$H$_{25}$N$_4$O$_2$Cl: 448.1666; found: 448.1652. 

6-Butyl-4-(4-ethoxyphenyl)-2,8-diethyl-3,7-dioxo-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6e): yellow crystals; mp 155-157 °C (hexane – ethyl acetate). IR (KBr): 2239 (CN), 1733, 1665, 1630. 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.83$ (t, $J = 7.4$ Hz, 3 H), 1.01 (t, $J = 7.4$ Hz, 3 H), 1.19 – 1.27 (m, 2 H), 1.36 (t, $J = 7.4$ Hz, 3 H), 1.44 – 1.51 (m, 2 H), 1.48 (t, $J = 7.1$ Hz, 3 H), 2.16 – 2.25 (m, 1 H), 2.26 – 2.34 (m, 1 H), 2.93 – 3.03 (m, 2 H), 3.46 – 3.52 (m, 1 H), 3.58 – 3.65 (m, 1 H), 4.13 (q, $J = 7.1$ Hz, 2 H), 6.10 (s, 1 H), 7.09 – 7.14 (m, 2 H), 7.17 – 7.21 (m, 2 H), 7.90 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 8.33$, 10.57, 13.44, 14.73, 19.77, 27.04, 28.91, 30.88, 40.46, 46.42, 63.95, 95.78, 116.08, 116.18, 116.64, 120.87, 125.4, 127.9, 128.9, 129.0, 136.6, 143.2, 154.8, 159.6, 160.6, 170.3. MS (EI): $m/z$ 459 (31), 458 (100), 430 (16), 429 (29), 402(11), 401 (28). HRMS (EI): $m/z$ calcd. for C$_{27}$H$_{30}$N$_4$O$_3$: 476.1979; found: 458.2322.
6-Butyl-4-(2,6-dimethylphenyl)-2,8-diethyl-3,7-iodo-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinazoline-8-carbonitrile (6f) oil; IR (KBr): 2242 (CN), 1736, 1608, 1630. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.79$ (t, $J = 7.2$ Hz, 3 H), 1.05 (t, $J = 7.2$ Hz, 3 H), 1.15-1.22 (m, 2 H), 1.38 (t, $J = 7.2$ Hz, 3 H), 1.40-1.43 (m, 2 H), 1.98 (s, 6 H), 2.16-2.24 (m, 1 H), 2.27-2.34 (m, 1 H), 2.98-3.05 (m, 2 H), 3.42-3.49 (m, 1 H), 3.53-3.60 (m, 1 H), 5.87 (s, 1 H), 7.26-7.31 (m, 2 H), 7.34-7.39 (m, 2 H), 7.93 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 8.4, 10.5, 13.4, 17.5, 17.6, 19.8, 27.0, 28.9, 30.9, 40.4, 46.5, 94.3, 116.6, 121.1, 125.6, 129.1, 129.2, 129.3, 129.8, 133.7, 134.9, 135.2, 135.3, 143.8, 153.5, 161.1, 170.3. MS (EI): $m/z$ 442 (100), 413 (40), 385 (32). HRMS (EI): $m/z$ calcd. for C$_{27}$H$_{30}$N$_4$O$_2$: 442.2369; found: 442.2384.

4-(4-Chlorophenyl)-3,7-diodo-2,8-bis(propan-2-yl)-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinazoline-8-carbonitrile (6g) yellow solid; mp 206-208 °C. IR (KBr): 2237 (CN), 1749, 1722, 1634, 1490. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.97$ (d, $J = 6.8$ Hz, 3 H), 1.29 (d, $J = 6.8$ Hz, 3 H), 1.33 (d, $J = 6.8$ Hz, 3 H), 1.34 (d, $J = 6.8$ Hz, 3 H), 2.61 (sept, $J = 6.8$ Hz, 1 H), 3.56 (sept, $J = 6.8$ Hz, 1 H), 6.15 (s, 1 H), 7.22-7.26 (m, 2 H), 7.58-7.63 (m, 2 H), 7.90 (s, 1 H), 8.34 (br s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.5, 17.5, 20.1, 20.2, 26.9, 31.1, 36.3, 51.2, 96.6, 116.4, 120.4, 126.6, 129.0, 129.7, 130.8, 130.9, 134.1, 135.7, 135.9, 141.2, 154.0, 163.9, 171.8. MS (EI): $m/z$ 420 (57), 378 (100), 350 (53), 335 (27). HRMS (EI): $m/z$ calcd. for C$_{23}$H$_{21}$N$_4$O$_2^{35}$Cl: 420.1353; found: 420.1339.
4-(4-Chlorophenyl)-1,3,7-trio xo-2,8-bis(propan-2-yl)-3H,4H,6H,7H,8H-1,5,4,6-pyrrolo[2,3-g]quin o naline-8-carbonitrile (6ox): white solid; mp 188-193 °C. IR (KBr): 2255 (CN), 1719, 1668, 1628, 1324. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.16 (d, $J$ = 6.8 Hz, 3 H), 1.31 (d, $J$ = 6.8 Hz, 3 H), 1.32 (d, $J$ = 6.8 Hz, 6 H), 2.63 (sept, $J$ = 6.8 Hz, 1 H), 3.56 (sept, $J$ = 6.8 Hz, 6 H), 6.06 (s, 1 H), 7.19-7.25 (m, 2 H), 7.56-7.60 (m, 2 H), 7.64 (s, 1 H), 8.37 (br s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.2, 16.1, 16.8, 20.1, 20.2, 22.6, 26.9, 31.2, 33.6, 79.8, 101.2, 114.5, 118.0, 126.7, 129.6, 129.8, 130.7, 130.8, 130.9, 134.2, 135.8, 137.2, 153.7, 160.5, 165.6. MS (EI): m/z 436 (100), 421 (23), 408 (48). HRMS (EI): m/z calcd. for C$_{23}$H$_{21}$N$_4$O$_3$Cl: 436.1302; found: 436.1289.

6-tert-Butyl-4-(4-chlorophenyl)-2,8-dimethyl-3-methylidene-7-oxo-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6i): white crystals; mp 244-246 °C (hexane-EtOAc). IR (KBr): 2245 (CN), 1716, 1679, 1628. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.51 (s, 9 H), 1.81 (s, 3 H), 2.60 (s, 3 H), 6.50 (s, 1 H), 7.22-7.29 (m, 2 H), 7.61-7.66 (m, 2 H), 7.82 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.2, 24.2, 28.7, 42.4, 59.3, 100.2, 117.5, 123.6, 124.5, 128.3, 129.4, 129.5, 130.7, 130.8, 134.2, 135.3, 135.9, 143.5, 154.7, 157.4, 171.5. MS (EI): m/z 420 (20), 364 (100), 312 (24), 308 (26). HRMS (EI): m/z calcd. for C$_{23}$H$_{21}$N$_4$O$_2$Cl: 420.1353; found: 420.1360.

4-(4-Chlorophenyl)-2,8-dimethyl-3,7-dioxo-6-(propan-2-yl)-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6i): pale yellow crystals; mp 285-289 °C/dec. (EtOAc). IR (KBr): 2244, (CN), 1727, 1672, 1629. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.85 (s, 3 H), 2.60 (s, 3 H), 3.11 (s, 3 H), 6.03 (s, 1 H), 7.18-7.28 (m, 2 H), 7.60-7.65 (m, 2 H), 7.88
(s, 1 H). $^13$C NMR (100 MHz, CDCl$_3$): $\delta = 21.2, 23.4, 27.3, 41.4, 95.3, 116.9, 122.8, 125.1,$
$129.1, 129.5, 129.6, 130.9, 131.0, 134.0, 136.0, 143.4, 154.7, 157.1, 170.8$ (two
additional signals apparently due to the aryl rotation hindrance). MS (EI): m/z 380 (49), 379
(40), 378 (100), 363 (11), 350 (21), 337 (30), 336 (22), 335 (57). HRMS (EI): m/z calcd. for
C$_{20}$H$_{15}$N$_4$O$_2$Cl: 378.0884; found: 378.0889.

![Chemical structure of 2,8-Dibutyl-4-(4-fluorophenyl)-3,7-dioxo-6-(propan-2-yl)-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6j)](image)

2,8-Dibutyl-4-(4-fluorophenyl)-3,7-dioxo-6-(propan-2-yl)-3H,4H,6H,7H,8H-pyrrolo[2,3-g]quinoxaline-8-carbonitrile (6j): oil. IR (KBr): 2240 (CN), 1729, 1671, 1631, 1509. $^1$H
NMR (400 MHz, CDCl$_3$): $\delta = 0.87$ (t, $J = 6.9$ Hz, 3 H), 0.99 (t, $J = 7.4$ Hz, 3 H), 1.27-1.32
(m, 10 H), 1.47-1.53 (m, 2 H), 1.77-1.84 (m, 2 H), 2.10-2.25 (m, 2 H), 2.90-3.02 (m, 2 H),
4.36 (sept, $J = 6.8$ Hz, 1 H), 6.16 (s, 1 H), 7.24-7.37 (m, 4 H), 7.88 (s, 1 H). $^13$C NMR (100
MHz, CDCl$_3$): $\delta = 13.6, 13.9, 19.0, 19.1, 22.2, 22.7, 25.6, 28.7, 33.6, 37.2, 45.3, 45.9, 96.5,$
116.8, 117.6 (d, $J_{CF} = 22.9$ Hz), 117.7 (d, $J_{CF} = 22.9$ Hz), 121.7, 125.5, 128.5, 130.0 (d, $J_{CF} =$
9.5 Hz), 130.1 (d, $J_{CF} = 9.5$ Hz), 131.5 (d, $J_{CF} = 3.5$ Hz), 135.9, 142.6, 154.6, 160.1, 163.0 (d, $J_{CF} = 249.5$ Hz), 170.1. MS (EI): m/z 474 (66), 432 (100), 305 (32). HRMS (EI): m/z calcd. for C$_{28}$H$_{31}$N$_4$O$_2$F: 474.2431; found: 474.2449.
4. References
