Exploring a new, connective Pummerer reaction: Formation of oxindoles by the reaction of thiols with glyoxamides

Marc Miller, a William Tsang, a Andrew Merrittb and David J. Procter* a

a School of Chemistry, University of Manchester, Oxford Rd., Manchester, M13 9PL, UK. Email: david.j.procter@manchester.ac.uk
b GlaxoSmithKline, Gunnelswood Rd., Stevenage, SG1 2NY, UK.

Supporting Information

S2 General considerations

S3 Representative procedure for the connective Pummerer cyclisation with monoglyoxamides – preparation of 12

S4 Representative procedure for the connective Pummerer cyclisation with 1,3-bisglyoxamides – preparation of 19

S5 Representative procedure for the connective Pummerer cyclisation with 1,4-bisglyoxamides – preparation of 29

S7 Selected 1H and 13C NMR spectra
General considerations

All experiments were performed under an atmosphere of N\textsubscript{2} using anhydrous solvents unless otherwise stated. Reactions were carried out using oven dried glassware. THF was distilled from sodium/benzophenone, CH\textsubscript{2}Cl\textsubscript{2} was distilled from CaH\textsubscript{2}, NEt\textsubscript{3} was distilled from CaH\textsubscript{2} and stored over KOH under N\textsubscript{2}. DMSO was distilled from CaH\textsubscript{2}, stored over molecular sieves and under N\textsubscript{2}. DMPU was distilled from CaH\textsubscript{2}, stored over molecular sieves and under N\textsubscript{2}.

\textsuperscript{1}H NMR and \textsuperscript{13}C NMR were recorded on a Fourier transform spectrometer, with chemical shift values being reported in ppm relative to residual chloroform (\textdelta\textsubscript{H} 7.27 or \textdelta\textsubscript{C} 77.2) as an internal standard unless otherwise stated. NMR signals were assigned using DEPT – 135, HMQC and COSY spectra. All coupling constants are reported in Hertz (Hz). Mass spectra were recorded using a Waters Trio 2000 and a Thermo Finnigan MAT 95 XP at the University of Manchester. IR spectra were recorded using a Bio-Rad Excalibur.

Column chromatography was carried using Fischer Matrix silica gel 60 and FluoroFlash silica. Macherey-Nagel aluminium backed plates, precoated with silica gel 60 (UV\textsubscript{254}) were used for thin-layer chromatography and were visualised by UV or staining with KMnO\textsubscript{4}.
Representative procedure for the connective Pummerer cyclisation with mono-glyoxamides

Methyl 3-(5-fluoro-2-oxo-1-proplindolin-3-ylthio) propanoate 12

To a solution of oxalyl chloride (203 µl, 2.13 mmol, 1.1 eq) in CH₂Cl₂ (6 ml) was added DMSO (302 µl, 4.25 mmol, 2 eq) in CH₂Cl₂ (3 ml) at –78 °C. After 0.5 h, N-(4-fluorophenyl)-N-propyl-2-hydroxyacetamide (449 mg, 2.13 mmol, 1 eq) in CH₂Cl₂ (5 ml) was added. After a further 1 h, Et₃N (1.48 ml, 10.62 mmol, 5 eq) was added and reaction allowed to warm to room temp. After 1 h, CH₂Cl₂ (15 ml) was added to reaction mixture. Organic layer was washed with NaHCO₃ (3 × 15 ml) then dried (MgSO₄), filtered and concentrated in vacuo to give the crude glyoxamide, which was used without further purification. CH₂Cl₂ (8 ml) was added to crude glyoxamide (197 mg, 0.93 mmol, 1 eq) followed by thiol ester (101 µl, 0.93 mmol, 1 eq) and reaction allowed to stir at room temp for 18 h. TFAA (1.19 ml, 8.39 mmol, 9 eq) was then added and after a further 1 h BF₃·OEt₂ (574 µl, 4.66 mmol, 5 eq). After stirring for 1 h, reaction was quenched with NaHCO₃ (15 ml), the organic layer was washed with NaHCO₃ (2 × 15 ml), dried (MgSO₄), filtered and concentrated in vacuo to give an orange oil. The crude mixture was then purified by column chromatography using 20% EtOAc in petroleum ether as eluant to give methyl 3-(5-fluoro-2-oxo-1-proplindolin-3-ylthio) propanoate 12 (197 mg, 0.62 mmol, 67% for 2 steps) as a light orange oil.

¹H NMR (300 MHz, CDCl₃) δ 0.98 (3H, t, J = 7.4 Hz, CH₃), 1.53 (2H, sextet, J = 7.4Hz, CH₂), 2.63 (3H, t, J = 7.1 Hz, SCH₂CH₂C=O), 2.77-2-86 (1H, m, 1H of CH₂S), 2.98-3.07 (1H, m, 1H of CH₂S), 3.58-3.69 (2H, m, CH₂N), 3.67 (3H, s, CO₂CH₃), 4.30 (1H, s, CHS), 4.74 (1H, dd, J = 4.1, 8.5 Hz, ArCH), 6.85 (1H, dt, J = 2.6, 8.5 Hz, ArCH), 7.15 (1H, ddd, J = 0.9, 2.6, 7.8 Hz, ArCH).

¹³C NMR (75 MHz, CDCl₃) δ 11.6 (CH₃), 20.9 (CH₂), 25.2 (CH₂S), 34.5 (CH₂C=O), 42.1 (CH2N), 45.0 (CHS), 52.1 (CO₂CH₃), 109.3 (ArCH, d, J = 8.1 Hz), 113.5 (ArCH, d, J = 25.0 Hz), 115.6 (ArCH, d, J = 23.3 Hz), 127.6 (ArC, d, J = 8.3 Hz), 139.6 (ArC, d, J = 2.0 Hz), 159.4 (ArCF, d, J = 243.6 Hz), 172.2 (C=O amide), 175.1 (C=O ester).
Representative procedure for the connective Pummerer cyclisation with a 1,3–**bis**–glyoxamides

**3,5-Bis benzylsulfonyl-1,7-dipropyl-5,7-dihydro-1H, 3H-pyrrolo[3,2-f] indole-2,6-dione 19**

![Chemical Structure](image)

To a solution of oxalyl chloride (120 µl, 1.37 mmol, 2.2 eq) in CH₂Cl₂ (2 ml) at −78 °C was added a solution of DMSO (177 µl, 2.50 mmol, 4 eq) in CH₂Cl₂ (2 ml). After stirring for 30 min a solution of 2-hydroxy-N-3-(hydroxy acetyl-propyl amine)-phenyl]-N-propyl acetamide (194 mg, 0.62 mmol, 1 eq) in CH₂Cl₂ (3 ml) was added. After stirring for a further 1 h at −78 °C, NEt₃ (863 µl, 6.20 mmol, 10 eq) was added and the reaction allowed to stir at room temperature for 1.5 h. CH₂Cl₂ (15 ml) was added to the reaction mixture and the organic layer washed with NaHCO₃ (3 × 20 ml), dried (MgSO₄) and concentrated *in vacuo* to give the crude bis-glyoxamide, which was used without further purification. CH₂Cl₂ (4 ml) was added to the crude bis-glyoxamide (90 mg) followed by benzyl mercaptan (48 µl, 0.41 mmol, 1.4 eq) and the reaction was allowed to stir at room temperature for 18 h. TFAA (761 µl, 5.27 mmol, 18 eq) was then added and after a further 1 h, BF₃•Et₂O (410 µl, 2.93 mmol, 10 eq). After stirring for 1 h the reaction was quenched with NaHCO₃ (20 ml), the organic layer was washed with NaHCO₃ (2 × 30 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a blue oil. The crude reaction mixture was then purified by flash chromatography using 30 % EtOAc in petroleum ether as eluant to give 3,5-bis benzylsulfonyl-1,7, dipropyl-5,7-dihydro 1H, 3H-pyrrolo[3,2-f] indole-2,6-dione 19 (769 mg, 0.15 mmol, 51% over 2 steps) as a dark purple oil.

¹H NMR (500 MHz, CDCl₃) δ 0.92 (6H, t, J = 7.4 Hz, 2 × CH₃), 1.60-1.66 (4H, m, 2 × CH₂), 3.53- 3.58 (4H, m, 2 × NCH₂), 3.65 (1H, d, J = 13.2 Hz, 1H of CH₂S), 3.69 (1H, d, J = 13.1 Hz, 1H of CH₂S), 4.01 (1H, s, CHS), 4.03 (1H, s, CHS), 4.13 (1H, d, J = 13.2 Hz, 1H of CH₂S), 4.14
(1H, d, J = 13.1 Hz, 1H of CH$_2$S), 6.14 (1H, s, ArH), 7.14-7.31 (11H, m, 1H ArH and 10H of benzyl groups).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 11.7 (2´CH$_3$), 21.2 (2´CH$_2$), 34.6 (2´CH$_2$S), 42.1 (2´CH$_2$N), 43.0 (2´CHS), 91.0 (ArCH), 118.9 (2´ArC), 122.5 (2´ArCH), 127.5 (ArCH), 127.6 (ArCH), 128.7 (2´ArCH), 128.8 (2´ArCH), 129.5 (2´ArCH), 129.6 (ArCH), 137.5 (ArC), 137.6 (ArC), 144.8 (ArC), 144.9 (ArC), 176.3 (2 x C=O),

IR $\nu_{max}$/cm$^{-1}$ 3410, 3061, 2966, 1714 (C=O), 1614, 1487, 1372, 1208, 1129.

MS m/z (EI$^+$ mode) 516 (M$^+$, 7%), 393 (16%), 124 (8%), 91 (100%), 77 (16%), 65 (43%).

C$_{30}$H$_{33}$O$_2$N$_2$S$_2$ requires 517.1987. Found 517.1978.

Representative procedure for the connective Pummerer cyclisation with a 1,4–bis–glyoxamides

3,7-Bis-(4-bromo-benzylsulfanyl)-1,5-dihexyl-5,7-dihydro-1$^H$,3$^H$-pyrrolo[2,3-f]indole-2,6-dione 29

To a solution of oxalyl chloride (223 µl, 2.56 mmol, 2.2 eq) in CH$_2$Cl$_2$ (6 ml) at -78°C was added DMSO (330 µl, 4.65 mmol, 4 eq) in CH$_2$Cl$_2$ (5 ml). After stirring for 30 min a solution of N,N'- (1,4-phenylene)bis(N-hexyl-2-hydroxyacetamide) (456 mg, 1.16 mmol, 1 eq) in CH$_2$Cl$_2$ (5 ml) was added. After a further 1 h at -78 °C, NEt$_3$ (1.62 ml, 11.62 mmol, 10 eq) was added and the reaction allowed to stir at room temperature for 1 h. CH$_2$Cl$_2$ (10 ml) was added to the reaction mixture and the organic layer washed with aqueous saturated NaHCO$_3$ (3 x 25 ml), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to give the crude bis–glyoxamide, which was used without further purification. CH$_2$Cl$_2$ (6 ml) was added to a portion of crude bis-glyoxamide (227 mg, 0.58 mmol, 1 eq) followed by 4-bromobenzyl mercaptan (236 mg, 1.16 mmol, 2 eq) in CH and the reaction was allowed to stir at room temperature for 18 h. TFAA (1.47 ml, 10.44 mmol, 18 eq) was then added and after a further 1 h BF$_3$•OEt$_2$ (713 µl, 5.80 mmol, 10 eq) was also added. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated NaHCO$_3$.
(20 ml) and CH₂Cl₂ (15 ml) added and the organic layer separated. The organic fraction was washed with aqueous saturated NaHCO₃ (2 × 20 ml), dried (Na₂SO₄), filtered and concentrated in vacuo to give the crude mixture as a red solid. The crude reaction mixture was then purified by flash chromatography using 15% EtOAc in petroleum ether as eluant to afford 3,7-bis-(4-bromo-benzylsulfanyl)-1,5-dihexyl-5,7-dihydro-1H,3H-pyrrolo[2,3-f]indole-2,6-dione 29 as a 1:1 mixture of diastereoisomers (238 mg, 0.31 mmol, 54%).

¹H NMR (500 MHz, CDCl₃) δ 0.81 (12H, t, J = 7.2 Hz, 4 × CH₃ of both diastereoisomers), 1.18-1.29 (24H, m, 4 × CH₂CH₂CH₂CH₃ of both diastereoisomers), 1.67-1.69 (4H, quin, J = 7.2 Hz, 4 × NCH₂CH₂ of both diastereoisomers), 3.46-3.53 (2H, m, 2 × 1H from CH₂N of both diastereoisomers), 3.55-3.61 (2H, m, 2 × 1H from CH₂N of both diastereoisomers), 3.59 (1H, d, J = 13.2 Hz, 1H from CH₂S of one diastereoisomer), 3.62 (1H, d, J = 13.2 Hz, 1H from CH₂S of one diastereoisomer), 4.04 (1H, s, CH₃S of one diastereoisomer), 4.05 (1H, d, J = 13.2 Hz, 1H from CH₂S of one diastereoisomer), 4.07 (1H, s, CH₃S of one diastereoisomer), 4.13 (1H, d, J = 13.2 Hz, 1H from CH₂S of one diastereoisomer), 6.57 (4H, s, 4 × ArH of both diastereoisomers), 7.12-7.16 (8H, m, 8 × ArH of both diastereoisomers), 7.29-7.34 (8H, m, 8 × ArH of both diastereoisomers).

¹³C NMR (125 MHz, CDCl₃) δ 14.1 (4 × CH₃), 22.6 (4 × CH₂), 26.5 (4 × CH₂), 27.4 (4 × CH₂), 29.7 (4 × CH₂), 33.6 (4 × CH₂S), 40.4 (4 × CH₂N), 43.5 (4 × CHS), 106.9 (4 × ArCH), 121.2 (4 × ArC), 126.0 (4 × ArC), 130.9 (4 × ArCH), 131.5 (4 × ArCH), 136.3 (4 × ArC), 139.1 (4 × ArC), 174.2 (4 × C=O).

IR νₓ(cm⁻¹) 2924, 1681, 1465, 1346, 1226, 1124, 1095, 1009, 987

MS m/z (ES⁻ mode) 757 ((M−H)⁺, 43%), 569 (100%), 415.2 (35%), 339.7 (18%), 273 (10%).
Selected $^1$H and $^{13}$C NMR spectra

$^1$H NMR of 19

$^{13}$C NMR of 19
$^1$H NMR of 21

$^{13}$C NMR of 21
$^1$H NMR of 11

mm4-79-1
mPROTONnight CDCl3 /opt/topspin djp 37

$^{13}$C DEPT NMR of 11

mm4-79-1
mDEPT135night CDCl3 /opt/topspin djp 37
$^1{H}$ NMR of 29

mm4-65- mPROTONnight CDCl3 /opt/topspin djp 36

$^{13}C$ NMR of 29

mm4-65- mCARBONnight CDCl3 /opt/topspin djp 36
$^1$H NMR of 30
mecd-77-88-1
nMROTON CDC03 /opt/topspin djp 22

$^1$H NMR of 32
mecd-86-2
nMROTON CDC03 /opt/topspin djp 39