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Chemo- and regioselectivity in the reactions of polyfunctional pyrroles

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ABSTRACT

The chemo- and regioselectivity of the reduction, oxidation and Wittig reaction of polyfunctional pyrroles, containing a variety of reactive centres was investigated. The reaction of 3,5-dichloropyrrole-2,4-dicarboxaldehydes with potassium permanganate leads to regioselective oxidation of the 2-formyl group, while the Wittig reaction with 1 equiv of a triphenylphosphorane produced the 2-alkenyl substituted pyrroles.

1. Introduction

Polyfunctional pyrroles represent important examples of synthetic agrochemicals and pharmaceuticals and many naturally occurring compounds also contain this structural moiety. Examples of polysubstituted pyrroles include; Atorvastatin (Lipitor®) **1**,[1] the insecticide, Chlorfenapyr **2**[2] and the *anti*-bacterial natural product, Pentabromopseudilin **3**, isolated from the marine bacterium *Pseudoalteromonas luteoviolaceus*,[3] (Fig. 1). These pyrroles are also interesting heterocyclic intermediates as they have a range of reactive centres and the chemo- and regioselectivity of their reactions under a range of conditions is, therefore, of much interest. Pyrroles containing a number of functional groups are relatively difficult to prepare and the selective reactions of polyfunctional pyrrole intermediates would allow the preparation of a wide variety of these substituted heterocyclic compounds. We now report the results of our studies on the chemo- and regioselective reduction, oxidation and Wittig reaction of multi-substituted pyrroles.

2. Results and discussion

For our study of the chemo- and regioselectivity of the reactions of polyfunctional pyrroles we employed the 3,5-dichloro-1*H*-pyrrole-2,4-dicarboxaldehydes **4** as the starting materials, as we have previously described the reactivity of these multi-functional pyrroles with a range of nucleophiles.[4] These pyrroles are particularly interesting as they contain a number of reactive sites and allow for the study of regioselectivity through the comparison of the

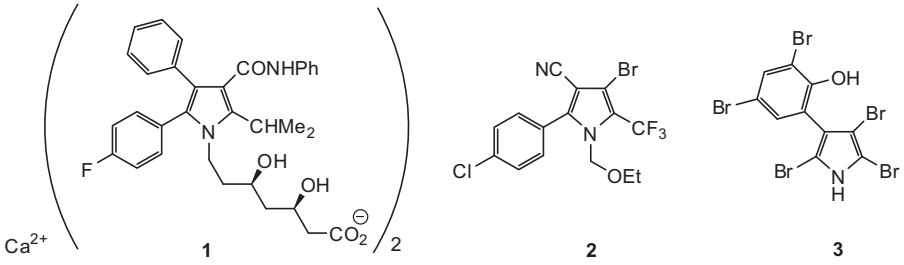

Figure 1.

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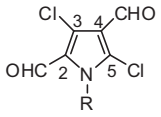
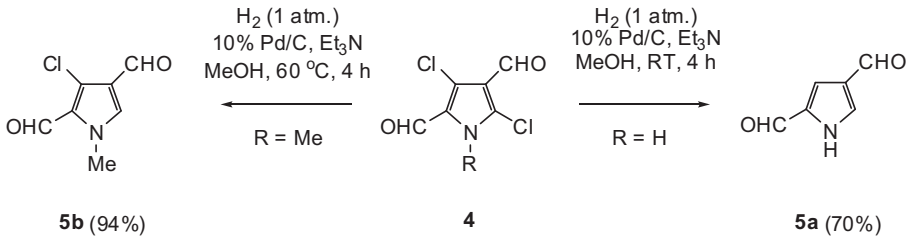
reactivity of substituents at different positions on the pyrrole ring e. g., through the comparison of the reactivity of the aldehyde groups at the α-(C-2) and β-positions (C-4) of the ring.



4a R = H
4b R = Me
4c R = Et

2.1. Reduction

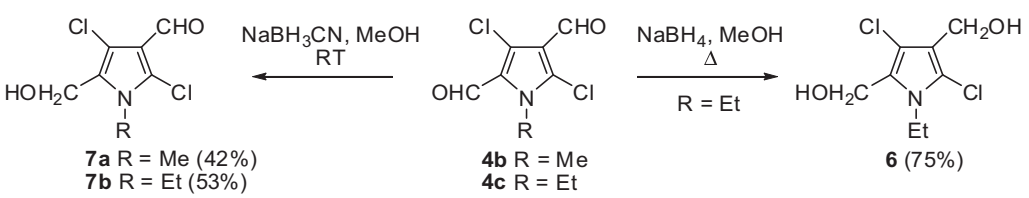
We first examined the catalytic hydrogenation of these pyrroles—complete dechlorination of 3,5-dichloro-1*H*-pyrrole-2,4-dicarboxaldehyde **4a** was observed with hydrogen (1 atm) over 10% Pd/C catalyst, in Et_3N and MeOH, to give the 1*H*-pyrrole-2,4-dicarboxaldehyde **5a** in 70% yield, Scheme 1, but the reaction of the methyl substituted pyrrole **4b** under similar conditions resulted in the selective dehalogenation at C-5, to give the 3-chloro derivative **5b** in an excellent yield. In each case, the structure of the aldehyde could be confirmed by spectroscopic analysis, for example, the ^1H NMR spectrum of the 3-chloro derivative **5b** showed the appearance of a singlet for H-5 at δ=7.36 and the DEPT 135 spectrum showed a new CH signal at δ=132.7, while it is obvious from the HMBC spectrum that the dehalogenation has taken place at the C-5 position, since the new H-5 proton shows connectivities to C-4 (^2J; **H**-C5-**C4**), at δ=127.0 and the *N*CH_3 (^3J; **H**-C5-N–**CH**$_3$), at δ=38.4.



5b (94%) **4** **5a** (70%)

Scheme 1.

We next attempted the reduction of the aldehyde groups in these pyrroles **4** with complex metal hydrides—reduction with lithium aluminium hydride gave an uncharacterisable product upon reaction with either the *N*-methylpyrrole **4b** or the *N*-ethylpyrrole **4c**, while the reduction of **4c** with sodium borohydride in methanol gave the diol **6** (surprisingly, even when using only 0.5 equiv of $NaBH_4$), Scheme 2. Selective reduction of the 2-formyl group in the methyl-**4b** and ethyl-substituted pyrroles **4c** was, however, achieved, using sodium cyanoborohydride in aqueous HCl/methanol (pH 3–4), to give the mono-hydroxymethylpyrrolecarboxaldehydes **7a**,**b**, (Scheme 2). Once again, the regioisomers were identified through indicative HMBC correlations. This selective reduction of the 2-formyl group with the milder reducing agent presumably arises as a result of the greater electrophilicity of the carbonyl carbon, compared to that of the C-4 formyl group, due to its proximity to the nitrogen of the pyrrole ring.



7a R = Me (42%)
7b R = Et (53%)
4b R = Me
4c R = Et
6 (75%)

Scheme 2.

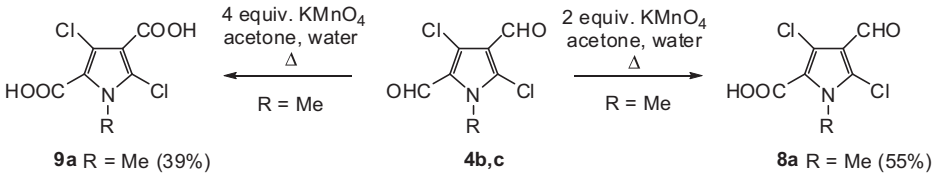
2.2. Oxidation

We next turned our attention to the investigation of the selective oxidation of the 2-formyl group of the unsubstituted pyrrole **4a**. The reaction with $KMnO_4$ in aqueous acetone was unsuccessful, with only starting material recovered, as was the oxidation of the *N*-methylpyrrole **4b** with $KMnO_4$ in aqueous acetone, at room temperature in the presence of a crown ether. Refluxing this mixture without the crown ether resulted in the formation of the 4-formylpyrrole-2-carboxylic acid **8a**, while under the same conditions the ethyl-substituted pyrrole **4c** always gave an inseparable mixture of the mono-**8b** and dicarboxylic acids **9b** (R=Et), (Scheme 3). The use of 4 equiv of $KMnO_4$ resulted in the oxidation of both aldehyde groups of the *N*-methylpyrrole **4b** to give the dicarboxylic acid **9a**.

Having achieved the regioselective oxidation of the *N*-methylpyrrole **4b** to the 4-formyl-1-methyl-1*H*-pyrrole-2-carboxylic acid **8a**, the functional group interconversion of the acid to the amides **12** and esters **13** was achieved using standard conditions, (Scheme 4). The 4-formyl-pyrrole-2-carboxylic acid **8a** and $SOCl_2$ were refluxed in toluene for 4 h to give the acid chloride **10**, which without purification, was dissolved in DCM and a solution of an amine **11** and Et_3N in DCM was added dropwise at 0 °C. After stirring at room temperature for 2 h, the amides **12** were obtained in good to high yields. The preparation of the ester derivatives of acid **8a** was again achieved via the acid chloride **10**, which was reacted with dry MeOH or EtOH or benzyl alcohol (and Et_3N in DCM) to give the esters, **13a**–**c**. Further oxidation of the methyl 4-formyl-pyrrole-2-carboxylate **13a** resulted in the dicarboxylic acid monoester **14**, in which the two carboxyl groups are capable of further independent tranformations. An alternative route to amide **12d** involved the in situ generation and reaction of an acyl bromide **15** from the dicarboxaldehyde **4b**,[5] (Scheme 5).

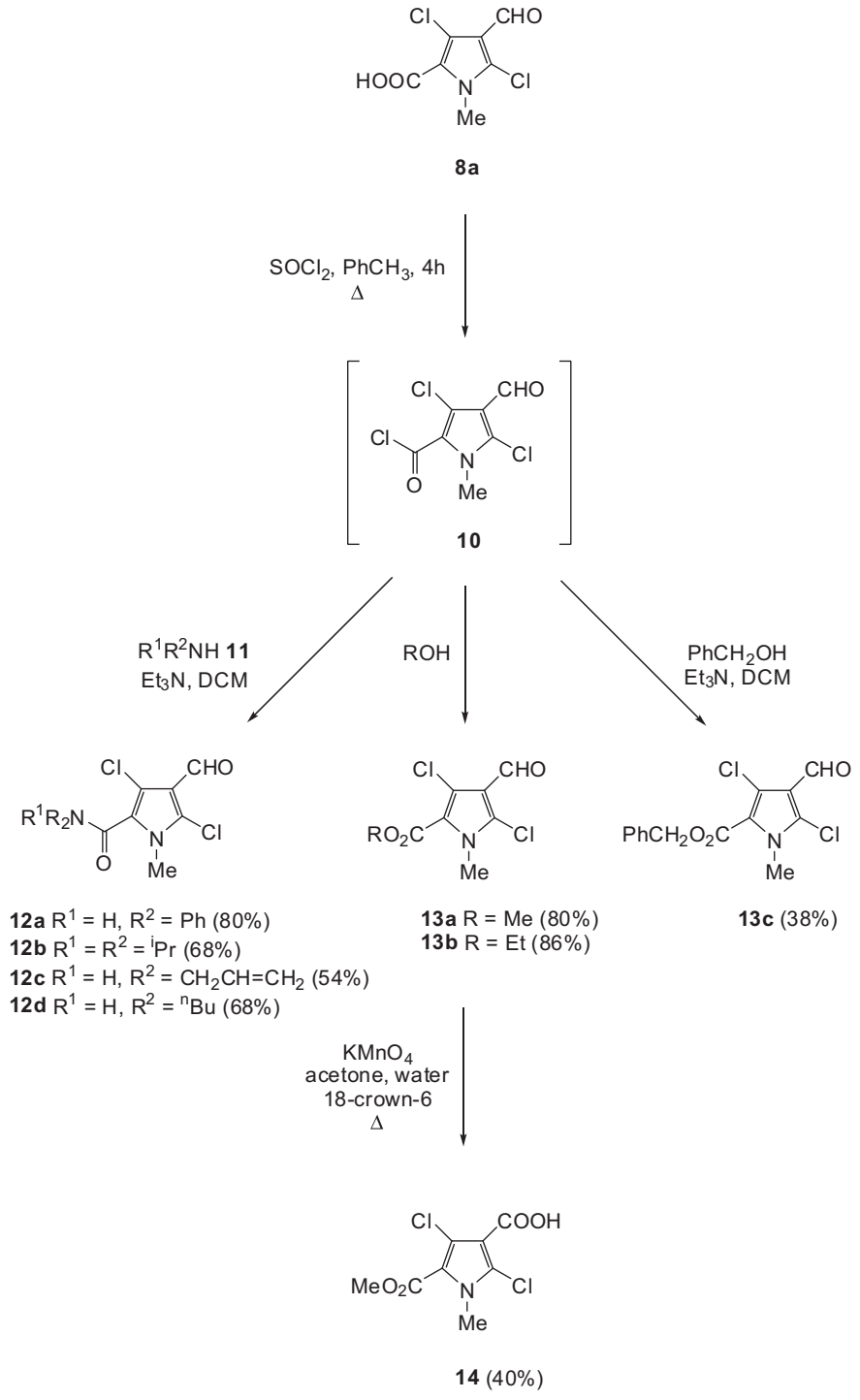
2.3. Wittig reaction and oxime formation

The Wittig reaction of the pyrroles **4** with 1.05 equiv of the phosphoranes **16** once again highlights the greater reactivity of the 2-formyl compared to the 5-formyl group, as the 2-alkenyl substituted

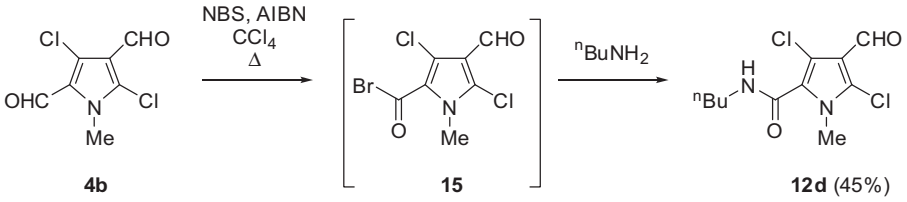


9a R = Me (39%) **4b,c** **8a** R = Me (55%)

Scheme 3.



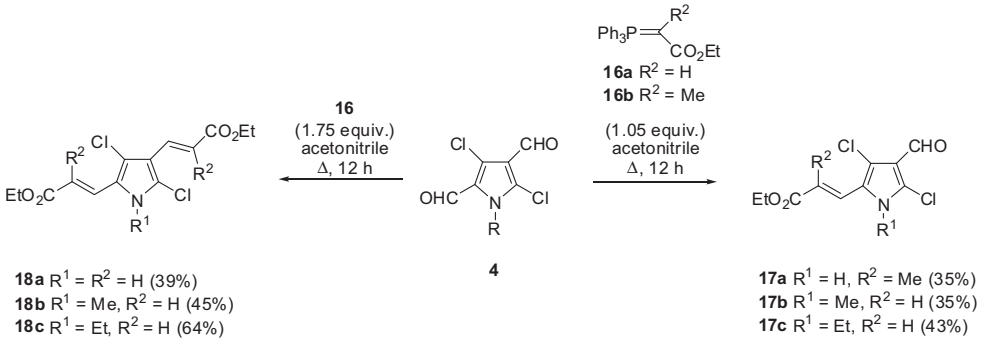
Scheme 4.



Scheme 5.

pyrroles **17a**–**c** were the sole regioisomers obtained, with only trace amounts of the 2,5-alkenyl adducts detectable in the ^{1}H NMR spectra and TLC; while treatment with 1.75 equiv gave the 2,5-dialkenyl adducts **18a**–**c**, with only trace amounts of the mono-alkenyl adducts being evident in this case, (Scheme 6).

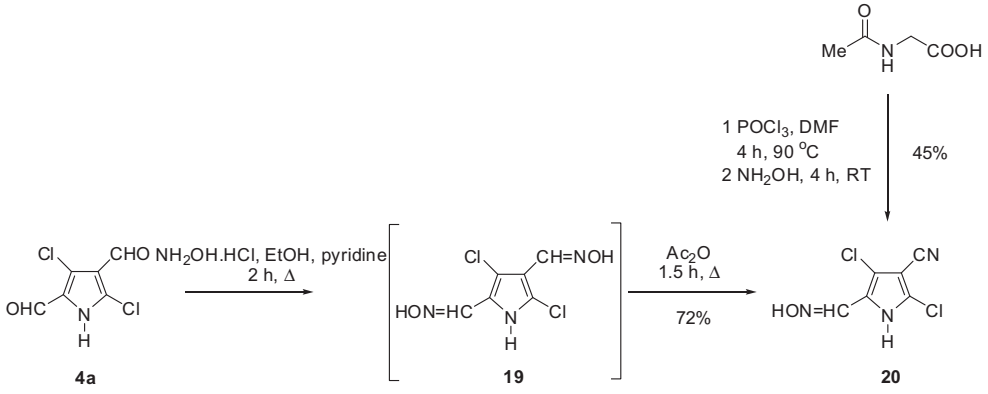
polyfunctional pyrroles **4** through their reactions with nucleophiles, which we have previously reported,[4] the two carboxaldehyde groups in the pyrroles **4** can also be differentiated successfully through a number of regioselective functional group interconversions, with a sequential oxidation/esterification/oxidation leading to the di-



Scheme 6.

Finally, the differentiation of the two aldehyde groups in pyrroles **4a** could also be achieved via the synthesis of the bisoxime **19**, through the chemoselective nucleophilic reaction with both aldehyde groups rather than the nucleophilic substitution of the chloro groups and its regioselective dehydration to give the nitrile–oxime **20**, (Scheme 7). Once again the regioisomer obtained was confirmed by 2D NMR, with

carboxylic acid monoester **14**, in which both carbonyl-containing groups are capable of further, independent, transformation. The combination of regioselective nucleophilic substitution with regioselective functional group interconversion of the aldehyde groups thus opens up the possibility for the synthesis of a range of substituted pyrroles.



Scheme 7.

a key correlation in the HMBC spectrum being that from the NH to the oxime CH. This nitrile–oxime **20** was also the only regioisomer obtained in a one-pot synthesis from *N*-acetylglycine using an adaptation of the method employed by Reddy and co-workers, Scheme 7.[6]

3. Conclusion

The transformations outlined in Schemes 3–7 show that, in addition to the differentiation of the two chloro substituents in the

4. Experimental

4.1. General

Melting points were determined using an Electrothermal 9100, a Gallenkamp melting point apparatus, or a Reichert hot stage microscope and are uncorrected. Microanalyses were carried out on an Exeter Analytical CE 440 Elemental Analyzer instrument. Infra-red spectra of liquid or solid samples were

obtained on a SpectrumBX fitted with PIKE MIRacle™. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVANCE DPX-300 (chemiSPEC, University of Sunderland). Chemical shifts are reported in δ units relative to internal tetramethylsilane (TMS) or the deuterated solvent. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75.5 MHz. Homonuclear correlation spectroscopy (^{1}H–^{1}H COSY) and heteronuclear (^{1}H–^{13}C) correlation spectroscopy (HMQC and HMBC) were obtained using the standard Bruker pulse sequences. Low-resolution electrospray mass spectra were obtained on an Esquire 3000+ ion trap mass spectrometer (chemiSPEC, University of Sunderland) in positive ion mode and high-resolution spectra were obtained by means of ESI-TOF-MS on a Synapt HDMS instrument (University of Warwick, UK). An internal standard of sodiated maltose in methanol was added at an appropriate level for mass correction using the ion at *m*/*z* 365.1060. Thin layer chromatography (TLC) was performed on Merck silica gel 60F_{254} plates and the components were detected under UV light (254 nm). Kieselgel 60 (Merck) was used for flash column chromatography.

All crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy prior to purification and, unless stated otherwise, no evidence was obtained for the formation of other regioisomers and only starting materials or uncharacterisable products were formed, in addition to the compounds listed below. All yields quoted are isolated yields, after purification.

*4.1.1. 1H-Pyrrole-2,4-dicarboxaldehyde (**5a**).* 3,5-Dichloro-1*H*-pyrrole-2,4-dicarboxaldehyde **4a** (0.80 g, 4.16 mmol), 10% palladium on carbon (0.024 g) and Et_3N (0.71 mL, 5.10 mmol) were dissolved in methanol (80 mL) then stirred under hydrogen (1 atm) at ambient temperature (ca. 23 °C). After 4 h the reaction mixture was filtered through Celite and the solution was removed in vacuo. The residue was extracted with ethyl acetate (3×40 mL) and the combined organic layer was washed with brine (70 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give **5a** (0.36 g, 70%) as a white solid, mp 103–104 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 7.42 (1H, s, H3), 7.97 (1H, s, H5), 9.62 (1H, s, CHO), 9.81 (1H, s, CHO), 12.85 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 118.9 (CH, C3), 127.6 (quat., C2), 133.5 (CH, C5), 134.6 (quat., C4), 181.5 (CHO), 186.4 (CHO); IR (cm^{-1}): 3117 (NH), 1666 (C=O), 1637 (C=O), 1540 (C=C). HRMS *m*/*z* calcd for $C_6H_6NO_2$ [MH$^+$]: 124.0393, found: *m*/*z* 124.0395.

*4.1.2. 3-Chloro-1-methyl-1H-pyrrole-2,4-dicarboxaldehyde (**5b**).* 3,5-Dichloro-1-methyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4b** (1.01 g, 4.90 mmol), 5% palladium on charcoal (0.024 g) and Et_3N (0.71 mL, 5.1 mmol) were dissolved in methanol (80 mL) then stirred in an autoclave under hydrogen (4 bar) at 60 °C. After 4 h the reaction mixture was filtered through Celite and the methanol was concentrated in vacuo. The residue was extracted with ethyl acetate (3×40 mL) and the combined organic layer was washed with brine (70 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and recrystallised from petroleum ether (60–80 °C) to give **5b** as a white powder (0.79 g, 94%), mp 100–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 3.91 (1H, s, CH_3), 7.36 (1H, s, H5), 9.80 (1H, s, CHO), 9.83 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 38.4 (CH_3), 121.6 (quat., C3), 127.0 (quat., C4), 127.6 (quat., C2), 132.7 (CH, C5), 178.6 (4-CHO), 183.4 (2-CHO); IR (cm^{-1}): 1715 (C=O), 1653 (C=O), 1508 (C=C). Anal. Calcd for $C_7H_6NO_2Cl$: C, 49.0; H, 3.5; N, 8.2. Found: C, 48.8; H, 3.5; N, 8.0%.

*4.1.3. 3,5-Dichloro-1-ethyl-2,4-bis(hydroxymethyl)-1H-pyrrole (**6**).* Methanol (15 mL) was added dropwise to sodium borohydride (0.037 g, 0.97 mmol) then the reaction mixture was stirred for 5 min at room temperature. 3,5-Dichloro-1-ethyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4c** (0.40 g, 1.82 mmol) was added to the solution which was then refluxed for 4 h. After completion of the reaction, as indicated by TLC, the solvent was evaporated under reduced pressure and the residue quenched with water (20 mL), extracted with ether (3×30 mL) and the combined organics dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (50:50) to give pyrrole **6** as a white solid (0.23 g, 75%), mp 139–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.25 (3H, t, J=7.2 Hz, CH_3), 4.01 (2H, q, J=7.2 Hz, CH_2), 4.24 (2H, s, 4-CH_2), 4.42 (2H, s, 2-CH_2), 4.71 (1H, br s, OH), 5.13 (1H, br s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 16.3 (CH_3), 39.9 (CH_2), 52.3 (4-CH_2), 53.1 (2-CH_2), 109.8 (quat., C3), 114.2 (quat., C5), 116.8 (quat., C4), 128.1 (quat., C2); IR (cm^{-1}): 3338 (broad OH). HRMS *m*/*z* calcd for $C_8H_{12}{}^{35}Cl_2NO_2$ [MH$^+$]: 224.0240, found: *m*/*z* 224.0244.

*4.1.4. 3,5-Dichloro-1-methyl-2-hydroxymethyl-1H-pyrrole-4-carboxaldehyde (**7a**).* 3,5-Dichloro-1-methyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4b** (0.50 g, 2.43 mmol) and sodium cyanoborohydride (0.15 g, 2.3 mmol) were dissolved in methanol (10 mL) and 2 M aq HCl/methanol (3 mL, 20:80) was added dropwise, with stirring, to the solution. Stirring was continued for an additional 1 h then the methanol was evaporated under reduced pressure, the residue was taken up in water (7 mL), saturated with sodium chloride, extracted with ether (3×20 mL) and the combined organics dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give **7a** as a yellow solid (0.21 g, 42%), mp 129–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.72 (3H, s, CH_3), 4.54 (2H, s, CH_2), 5.38 (1H, br s, OH), 9.84 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 31.9 (CH_3), 51.8 (CH_2), 109.8 (quat., C3), 115.3 (quat., C4), 124.7 (quat., C5), 131.8 (quat., C2), 182.7 (CHO); IR (cm^{-1}): 3353 (broad OH), 1710 (C=O), 1511 (C=C). $C_7H_8{}^{35}Cl_2NO_2$ [MH$^+$]: 207.9927, found: *m*/*z* 207.9937.

*4.1.5. 3,5-Dichloro-1-ethyl-2-hydroxymethyl-1H-pyrrole-4-carboxaldehyde (**7b**).* 3,5-Dichloro-1-ethyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4c** (0.40 g, 1.82 mmol) and sodium cyanoborohydride (0.08 g, 1.84 mmol) were dissolved in methanol (15 mL) and 2 M aq HCl/methanol (3 mL, 2:8) was added dropwise, with stirring, to the solution. Stirring was continued for an additional 1 h then the methanol was evaporated under reduced pressure, the residue was taken up in water (10 mL), saturated with sodium chloride, extracted with ether (3×20 mL) and the combined organics dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give pyrrole **7b** as a yellow solid (0.21 g, 53%), mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.24 (3H, t, J=7.2 Hz, CH_3), 4.38 (2H, q, J=7.2 Hz, CH_2), 4.50 (2H, s, CH_2), 9.60 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.8 (CH_3), 41.3 (CH_2CH_3), 52.5 (CH_2), 119.1 (quat., C4 or C5), 120.3 (quat., C3), 124.7 (quat., C4 or C5), 126.3 (quat., C2), 176.9 (CHO); IR (cm^{-1}): 3350 (broad OH), 1662 (C=O). HRMS *m*/*z* calcd for $C_8H_{10}{}^{35}Cl_2NO_2$ [MH$^+$]: *m*/*z* 222.0083, found: *m*/*z* 222.0092.

*4.1.6. 3,5-Dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxylic acid (**8a**).* 3,5-Dichloro-1-methyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4b** (0.50 g, 2.43 mmol) was dissolved in acetone (40 mL) and treated with a solution of $KMnO_4$ (0.78 g, 4.9 mmol) in H_2O (13 mL). The reaction mixture was refluxed for 12 h then decolourised with charcoal. After filtration, the solvent was evaporated under reduced

pressure, acidified with 2 M aq HCl and the crude product was recrystallised from methanol to give pyrrole **8a** as a white solid (0.30 g, 55%), mp 173–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.87 (3H, s, CH_3), 9.72 (1H, s, CHO), 13.15 (1H, br s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 33.6 (CH_3), 111.4 (quat., C4), 125.1 (quat., C3), 126.5 (quat., C5), 130.7 (quat., C2), 162.1 (C=O), 178.4 (CHO); IR (cm^{-1}): 2588 (broad OH), 1662 (C=O). HRMS *m*/*z* calcd for $C_7H_6{}^{37}Cl_2NO_3$ [MH$^+$]: *m*/*z* 225.9665, found: *m*/*z* 225.9657.

*4.1.7. 3,5-Dichloro-1-methyl-1H-pyrrole-2,4-dicarboxylic acid (**9a**).* This pyrrole was prepared, as described above, but using 4 M equiv of $KMnO_4$, to give pyrrole **9a** as a white solid (0.23 g, 39%), mp 179–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.84 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): 34.6 (CH_3), 111.3 (quat., C4), 118.9 (quat., C3), 121.5 (quat., C5), 126.7 (quat., C2), 160.8 (COOH), 162.6 (COOH); IR (cm^{-1}): 2591 (broad OH), 1661 (C=O). Anal. Calcd for $C_7H_5Cl_2NO_4$: C, 35.5; H, 2.1; N 5.9. Found: C, 35.9; H, 2.3; N, 5.5%.

4.2. General procedure for preparation of compounds (12a–d) and (13c)

A solution of 3,5-dichloro-4-formyl-1-methyl-1*H*-pyrrole-2-carboxylic acid **8a** (1.35 mmol) and $SOCl_2$ (0.49 mL) in toluene (5 mL) was refluxed for 4 h. After evaporation of the solvent, the crude mixture was dissolved in DCM (5 mL) and a solution of an amine **11** or benzyl alcohol (2.01 mmol) and TEA (0.19 mL) in DCM (1.6 mL) was added dropwise at 0 °C. The mixture was stirred for 2 h at room temperature then washed sequentially with 5% aq HCl (10 mL) and 5% aq NaOH (10 mL). The organic layer was dried over $MgSO_4$ and, after filtration, the solvent was evaporated under reduced pressure and purified by column chromatography or recrystallised.

*4.2.1. N-Phenyl-3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxamide (**12a**).* The crude product was recrystallised from methanol to give **12a** as colourless needles (0.32 g, 80%), mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 3.91 (3H, s, CH_3), 7.11 (1H, m, ArH), 7.31 (2H, m, ArH), 7.53 (2H, m, ArH), 7.91 (1H, br s, NH), 9.70 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 33.3 (CH_3), 114.5 (quat.), 120.2 (CH, Ar), 120.4 (quat.), 120.5 (CH, Ar), 122.8 (quat.), 124.9 (CH, Ar), 125.2 (quat.), 125.9 (quat.), 129.1 (CH, Ar), 129.2 (CH, Ar), 137.4 (C=O), 177.6 (CHO); IR (cm^{-1}): 3276 (NH), 1713 (aldehyde C=O), 1660 (amide C=O). Anal. Calcd for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.6; H, 3.4; N, 9.4. Found: C, 52.9; H, 3.8; N, 9.0%.

*4.2.2. N,N-Diisopropyl-3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxamide (**12b**).* The crude product was recrystallised from methanol to give **12b** as white crystals (0.28 g, 68%), mp 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (6H, m, 2×CH_3), 1.47 (6H, m, 2×CH_3), 3.45 (1H, m, CH), 3.76 (1H, m, CH), 3.85 (3H, s, CH_3), 9.62 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.4 (CH_3), 20.5 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 33.2 (*N*CH_3), 46.3 (CH), 51.7 (CH), 119.5 (quat., C3 or C4), 122.4 (quat., C3 or C4), 124.5 (quat., C5), 125.4 (quat., C2), 160.9 (C=O), 177.3 (CHO); IR (cm^{-1}): 1675 (aldehyde C=O), 1635 (amide C=O), 1536 (C=C). Anal. Calcd for $C_{13}H_{18}Cl_2N_2O_2$: C, 51.2; H, 5.9; N, 9.2. Found: C, 51.1; H, 5.9; N, 8.9%.

*4.2.3. N-Allyl-3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxamide (**12c**).* This pyrrole was prepared, as described above and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (40:60) to give **12c** as an orange solid (0.19 g, 54%), mp 125–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.88 (3H, s, CH_3), 4.01 (2H, m, CH_2), 5.13 (1H, t, *J*=1.8 Hz,=CH^{a}H), 5.19 (1H, t, *J*=1.8 Hz,=CH^{b}H), 5.86 (1H, m, CH), 6.27 (1H, br s, NH), 9.69 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 33.2 (CH_3), 41.9 (CH_2), 114.3 (quat.), 116.7 (=CH_2), 123.0 (quat.), 125.7 (quat.), 129.4 (quat.), 133.8 (=CH), 160.1 (C=O), 177.6 (CHO); IR (cm^{-1}): 3262 (NH), 1668 (aldehyde C=O), 1635 (amide C=O), 1535 (C=C). HRMS *m*/*z* calcd for $C_{10}H_{11}{}^{35}Cl_2N_2O_2$ [MH$^+$]: 261.0193, found: *m*/*z* 261.0203.

*4.2.4. N-Butyl-3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxamide (**12d**). 4.2.4.1. Method A.* 3,5-Dichloro-1-methyl-1*H*-pyrrole-2,4-dicarboxaldehyde **4b** (0.40 g, 1.96 mmol) was dissolved in dry CCl_4 (10 mL). To this solution was added AIBN (0.005 g, 0.033 mmol) and NBS (0.45 g, 2.52 mmol). The reaction mixture was refluxed for 15 min then cooled to 0 °C (ice-water bath) and *n*-butylamine (0.33 g, 4.50 mmol) was added dropwise. The ice-bath was removed and the suspension was stirred at room temperature for 10 min. The solid material was removed by filtration and washed with CCl_4 (10 mL). The filtrate was extracted with water (2×10 mL) and the combined organics dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80) to give **12d** as a yellow solid (0.24 g, 45%).

4.2.4.2. Method B. A solution of 3,5-dichloro-4-formyl-1-methyl-1*H*-pyrrole-2-carboxylic acid **8a** (0.30 g, 1.35 mmol) and $SOCl_2$ (0.49 mL) in toluene (5 mL) was refluxed for 4 h. After evaporation of the solvent, the crude mixture was dissolved in DCM (5 mL) and a solution of *n*-butylamine (0.31 mL, 3.1 mmol) and TEA (0.19 mL) in DCM (2 mL) was added dropwise at 0 °C. The mixture was stirred for 2 h at room temperature then washed sequentially with 5% aq HCl (10 mL) and 5% aq NaOH (10 mL). The organic layer was dried over $MgSO_4$ and, after filtration, the solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give **12d** as a yellow solid (0.28 g, 68%), mp 134–135 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 0.89 (3H, t, *J*=7.1 Hz, CH_3), 1.34 (2H, sextet, *J*=7.1 Hz, CH_2), 1.47 (2H, quintet, *J*=7.1 Hz, CH_2), 3.20 (2H, q, *J*=7.1 Hz, NCH_2), 3.86 (3H, s, CH_3), 8.21 (1H, br s, NH), 9.66 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.1 (CH_3), 19.9 (CH_2), 31.5 (CH_2), 33.4 (NCH_3), 39.0 (CH_2), 118.1 (quat.), 122.1 (quat.), 125.5 (quat.), 126.2 (quat.), 160.0 (C=O), 177.9 (CHO); 3273 (NH), 1671 (C=O), 1637 (C=O), 1554 (C=C). HRMS *m*/*z* calcd for $C_{11}H_{15}{}^{35}Cl_2N_2O_2$ [MH$^+$]: 277.0505, found: *m*/*z* 277.0515.

*4.2.5. Benzyl 3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxylate (**13c**).* This pyrrole was prepared, as described above, from benzyl alcohol and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (50:50) to give **13c** as a white solid (0.15 g, 38%), mp 124–125 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.89 (3H, s, CH_3), 5.34 (2H, s, CH_2), 7.39–7.45 (5H, m, ArH), 9.73 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 33.7 (CH_3), 66.4 (CH_2), 110.2 (quat.), 124.9 (quat.), 126.7 (quat.), 128.3 (2×CH), 128.5 (CH), 128.9 (2×CH), 130.9 (quat.), 136.3 (quat., C1′), 160.5 (C=O), 178.5 (CHO); IR (cm^{-1}): 1707 (C=O), 1664 (C=O). Anal. Calcd for $C_{14}H_{11}Cl_2NO_3$: C, 53.9; H, 3.6; N, 4.5. Found: C, 53.5; H, 3.8; N, 4.2%.

*4.2.6. Methyl 3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxylate (**13a**).* A solution of 3,5-dichloro-4-formyl-1-methyl-1*H*-pyrrole-2-carboxylic acid **8a** (0.26 g, 1.16 mmol) and $SOCl_2$ (0.49 mL) in toluene (5 mL) was refluxed for 4 h. After evaporation of the solvent, the crude mixture was cooled to 0 °C. Dry methanol (10 mL) was added and the solution stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure and the crude mixture was diluted with water (10 mL), extracted with EtOAc (3×20 mL) and the combined organic layers dried over $MgSO_4$. The product was purified by column chromatography on silica, eluting with petroleum ether/diethyl ether (60–80 °C) (60:40) to give a solid, which

was recrystallised from methanol to give **13a** as a white solid (0.22 g, 80%), mp 108–110 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.87 (3H, s, NCH_3), 3.94 (3H, s, OCH_3), 9.79 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 33.7 (NCH_3), 52.2 (OCH_3), 110.4 (quat.), 124.8 (quat.), 126.7 (quat.), 130.7 (quat.), 161.1 (C=O), 178.5 (CHO); IR (cm^{-1}): 1711 (C=O), 1654 (C=O), 1511 (C=C). Anal. Calcd for $C_8H_7Cl_2NO_3$: C, 40.7; H, 3.0; N, 5.9. Found: C, 40.5; H, 2.9; N, 5.7%.

*4.2.7. Ethyl 3,5-dichloro-4-formyl-1-methyl-1H-pyrrole-2-carboxylate (**13b**).* This ester was prepared as above and purified by column chromatography on silica, eluting with petroleum ether/diethyl ether (60–80 °C) (60:40) to give **13b** as white solid (0.25 g, 86%), mp 78–80 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.35 (3H, t, J=7.2 Hz, CH_2CH_3), 3.93 (3H, s, NCH_3), 4.35 (2H, q, J=7.2 Hz, CH_2), 9.76 (1H, s, CHO); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.5 (CH_2CH_3), 33.6 (NCH_3), 60.9 (CH_2), 110.5 (quat., C3 or C4), 124.8 (quat., C3 or C4), 126.6 (quat., C5), 130.6 (quat., C2), 160.6 (C=O), 178.4 (CHO); IR (cm^{-1}): 1706 (C=O), 1662 (C=O), 1512 (C=C). Anal. Calcd for $C_9H_9Cl_2NO_3$: C, 43.2; H, 3.6; N, 5.6. Found: C, 43.3; H, 3.8; N, 5.4%.

*4.2.8. Methyl 3,5-dichloro-4-carboxylic acid-1-methyl-1H-pyrrole-2-carboxylate (**14**).* Methyl 3,5-dichloro-4-formyl-1-methyl-1*H*-pyrrole-2-carboxylate **13a** (0.15 g, 0.64 mmol) was dissolved in acetone (15 mL) and treated with a solution of $KMnO_4$ (0.23 g, 1.5 mmol) in H_2O (5 mL). The reaction mixture was refluxed for 12 h then decolourised with charcoal. After filtration, the solvent was evaporated under reduced pressure, acidified with 2 M aq HCl and the crude product was recrystallised from methanol to give **14** as a white solid (0.064 g, 40%), mp 138–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.64 (3H, s, NCH_3), 3.70 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): 34.7 (NCH_3), 52.0 (OCH_3), 110.3 (quat.), 118.7 (quat.), 121.8 (quat.), 136.9 (quat.), 160.6 (C=O), 161.6 (C=O); IR (cm^{-1}): 1723 (ester C=O), 1659 (acid C=O), 1521 (C=C). Anal. Calcd for $C_8H_7Cl_2NO_4$: C, 38.1; H, 2.8; N, 5.6. Found: C, 37.9; H, 2.8; N, 5.5%.

4.3. General procedure for the Wittig reactions

The appropriate aldehyde **4b** or **4c** (2.91 mmol) was dissolved in CH_3CN (30 mL) and treated with (carbethoxymethylene)triphenylphosphorane **16a** (3.06 or 5.09 mmol) or (carbethoxyethylidene) triphenylphosphorane **16b** (3.06 or 5.09 mmol). The reaction mixture was refluxed for 9–12 h, then the solvent was removed under reduced pressure and the residue was treated with water (20 mL), extracted with EtOAc (3×30 mL) and the combined organic layers dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography.

*4.3.1. Ethyl 3-(3′,5′-dichloro-4′-formyl-1H-pyrrol-2′-yl)methacrylate (**17a**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give **17a** as a yellow solid (0.20 g, 35%), mp 149–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.35 (3H, t, J=7.2 Hz, CH_3), 2.13 (3H, d, J=1.5 Hz, CH_3), 4.28 (2H, q, J=7.2 Hz, CH_2), 7.37 (1H, q, J=1.5 Hz,=CH), 9.88 (1H, s, CHO), 12.96 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.6 (CH_3), 15.2 (CH_3), 61.3 (CH_2), 114.3 (quat., C4′), 116.7 (quat., C3′), 123.8 (CH, C3), 125.5 (quat., C5′), 126.1 (quat., C2′), 128.5 (quat., C2), 167.5 (C=O), 182.9 (CHO); IR (cm^{-1}): 3180 (NH), 1717 (C=O), 1666 (C=O). Anal. Calcd for $C_{11}H_{11}Cl_2NO_3$: C, 47.9; H, 4.0; N, 5.1. Found: C, 47.8; H, 4.0; N, 5.0%.

*4.3.2. Ethyl 3-(3′,5′-dichloro-4′-formyl-1′-methyl-1H-pyrrol-2′-yl) acrylate (**17b**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give **17b** as a pink solid (0.24 g, 35%), mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (3H, t, J=7.2 Hz, CH_3), 3.89 (3H, s, NCH_3), 4.19 (2H, q, J=7.2 Hz, CH_2), 6.61 (1H, d, J=16.0 Hz, H2), 7.48 (1H, d, J=16.0 Hz, H3), 9.69 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.4 (CH_3), 33.5 (CH_3), 60.6 (CH_2), 114.6 (quat., C3′), 119.1 (CH, C2), 125.3 (quat., C5′), 126.5 (quat., C3), 128.8 (quat., C4′), 131.8 (CH, C3), 167.1 (C=O), 177.5 (CHO); IR (cm^{-1}): 1701 (C=O), 1660 (C=O), 1634 (C=C). HRMS m/z calcd for $C_{11}H_{12}{}^{35}Cl_2NO_3$ [MH$^+$]: 276.0189, found: m/z 276.0196.

*4.3.3. Ethyl 3-(3′,5′-dichloro-1′-ethyl-4′-formyl-1H-pyrrol-2′-yl)acrylate (**17c**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give **19c** as a pale yellow solid (0.20 g, 43%), mp 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.28 (3H, t, J=6.9 Hz, NCH_2CH_3), 4.19 (2H, q, J=7.2 Hz, OCH_2CH_3), 4.41 (2H, q, J=6.9 Hz, NCH_2CH_3), 6.66 (1H, d, J=16.2 Hz, H2), 7.49 (1H, d, J=16.2 Hz, H3), 9.68 (1H, s, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.4 (CH_3), 15.3 (CH_3), 41.8 (NCH_2), 60.6 (OCH_2), 114.6 (quat., C-2′), 119.1 (CH, C2), 125.6 (quat., C3′ or C5′), 125.8 (quat., C3′ or C5′), 127.9 (quat., C4′), 131.8 (CH, C3), 167.1 (C=O), 177.2 (CHO); IR (cm^{-1}): 1706 (C=O), 1665 (C=O), 1634 (C=C), 1525 (C=C). HRMS m/z calcd for $C_{12}H_{14}{}^{35}Cl_2NO_3$ [MH$^+$]: 290.0346, found: m/z 290.0359.

*4.3.4. 3,5-Dichloro-2,4-bis(2′-ethoxycarbonylethenyl)-1H-pyrrole (**18a**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give diester **18a** as a pink solid (0.42 g, 39%), mp 168–169 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.29 (6H, t, J=6.9 Hz, 2×CH_3), 4.22 (4H, q, J=6.9 Hz, 2×CH_2), 6.46 (1H, d, J=16.0 Hz,=CH), 6.59 (1H, d, J=16.0 Hz,=CH), 7.39 (2H, m,=CH), 13.18 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.6 (2×CH_3), 60.5 (2×CH_2), 113.7 (quat.), 115.5 (CH), 115.6 (quat.), 116.7 (CH), 122.3 (quat.), 125.5 (quat.), 128.7 (CH), 132.6 (CH), 166.5 (C=O), 166.7 (C=O); IR (cm^{-1}): 3208 (NH), 1704 (C=O), 1667 (C=O), 1624 (C=C), 1542 (C=C). HRMS m/z calcd for $C_{14}H_{16}{}^{35}Cl_2NO_4$ [MH$^+$]: 332.0451, found: m/z 332.0438.

*4.3.5. 3,5-Dichloro-2,4-bis(2′-ethoxycarbonylethenyl)-1-methyl-1H-pyrrole (**18b**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give **18b** as a yellow solid (0.38 g, 45%), mp 113–114 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.30–1.36 (6H, m, 2×CH_3), 3.79 (3H, s, NCH_3), 4.24–4.28 (4H, m, 2×CH_2), 6.64 (1H, d, J=16.2 Hz,=CH), 6.67 (1H, d, J=16.2 Hz,=CH), 7.49 (1H, d, J=16.2 Hz,=CH), 7.57 (1H, d, J=16.2 Hz,=CH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.7 (2×CH_3), 33.1 (NCH_3), 60.6 (CH_2), 60.7 (CH_2), 113.6 (quat.), 114.6 (quat.), 116.9 (CH), 117.4 (CH), 123.8 (quat.), 125.8 (quat.), 129.4 (CH), 132.6 (CH), 166.7 (2×C=O); IR (cm^{-1}): 1698 (C=O), 1624 (C=C). HRMS m/z calcd for $C_{15}H_{18}{}^{35}Cl_2NO_4$ [MH$^+$] 346.0607, found: m/z 346.0618.

*4.3.6. 3,5-Dichloro-2,4-bis(2′-ethoxycarbonylethenyl)-1-ethyl-1H-pyrrole (**18c**).* The crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (20:80), to give **18c** as an orange solid (0.42 g, 64%), mp 84–86 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.30–1.36 (9H, m, 3×CH_3), 4.24–4.28 (6H, m, 3×CH_2), 6.65 (1H, d, J=16.0 Hz,=CH), 6.68 (1H, d, J=16.4 Hz,=CH), 7.49 (1H, d, J=16.0 Hz,=CH), 7.57 (1H, d, J=16.4 Hz,=CH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 14.6 (2×CH_3), 15.6 (CH_3), 40.8 (CH_2), 60.6 (CH_2), 60.8 (CH_2), 113.8 (quat.), 114.8 (quat.), 117.2 (CH), 117.6 (CH), 122.8 (quat.), 124.6 (quat.), 129.1 (CH), 132.5 (CH), 166.7 (2×C=O); IR (cm^{-1}): 1704 (C=O), 1624 (C=C). Anal. Calcd for $C_{16}H_{19}Cl_2NO_4$: C, 53.4; H, 5.3; N, 3.9. Found: C, 53.5; H, 5.4; N, 3.8%.

*4.3.7. 3,5-Dichloro-4-cyano-1H-pyrrole-2-carboxaldehyde oxime (**20**). 4.3.7.1. Method A.* $POCl_3$ (2.92 mL) was added dropwise to dry DMF (10 mL) at 0 °C. To this solution, *N*-acetylglycine (1.00 g,

8.54 mmol) was added and the mixture stirred for 1 h at room temperature then 4 h at 90 °C. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with DCM (12 mL), cooled to 0 °C and hydroxylamine hydrochloride (1.77 g, 25.5 mmol) in DMF (5 mL) was added. The mixture was stirred for 4 h at room temperature. After the reaction was complete, it was diluted with water (8 mL) and extracted with DCM (2×15 mL). The combined organic phases were washed with water (2×10 mL), saturated aq $NaHCO_3$ solution (8 mL) and water (15 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give **20** (0.72 g, 45%) as a yellow solid with identical spectral data to those given below.

4.3.7.2. Method B. 3,5-Dichloro-1*H*-pyrrole-2,4-dicarboxaldehyde **4a** (1.00 g, 5.21 mmol), hydroxylamine hydrochloride (0.38 g, 5.47 mmol) and pyridine (0.43 g, 5.43 mmol) were refluxed in EtOH for 2 h, to give the crude bisoxime **19**. To this solution was added Ac_2O (15 mL), the mixture was heated under reflux for 1.5 h, cooled, stirred with water (100 mL), extracted with DCM (3×30 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (60–80 °C) (30:70) to give **20** as a yellow solid (0.78 g, 72%), mp 158–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 4.98 (1H, s, NH), 7.89 (1H, s, CH=N), 11.53 (1H, s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6): 100.3 (quat., C4 or C5), 111.7 (quat., C4 or C5), 112.6 (quat., C2 or C3), 120.2 (quat., C2 or C3), 139.2 (CH=N); IR (cm^{-1}): 3170 (broad NH and OH), 2234 (C≡N). HRMS *m*/*z* calcd for $C_6H_4{}^{35}Cl_2N_3O$ [MH^+]: 203.9726, found: *m*/*z* 203.9732.

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Supplementary data

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