Investigations into the Parallel Synthesis of Novel Pyrrole-Oxazole Analogues of the Insecticide Pirate

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Abstract: Investigations into the parallel synthesis of selected analogues of a structurally unique pyrrole-oxazole analogue of the pyrrole insecticide pirate, are reported. Acylaminoketone salts were obtained from ketobromides in moderate to high yields and excellent purity. A number of N-tosyl pyrroles were obtained; however, formation of the target acyl tosyl pyrroles was thwarted by the stereoelectronic effects of the pyrrole substituents. During the pyrrole subunit chemistry, an interesting pyrrole derivative, vinyl pyrrole, was isolated. By restricting diversity to the aryl subunit, the parallel synthesis of selected pyrrole-oxazoles in moderate purity, was achieved when electron-donating or no groups were present on the aryl ring.

Key words: pyrroles, oxazoles, amines, cyclizations, parallel synthesis

The natural product antibiotic, dioxapyrrolomycin (**1**) isolated from Streptomyces MG796-AF7,[1] displays moderate insecticidal and acaricidal activity against arachnids, mites and ticks[2] and has been found to be a potent uncoupler of oxidative phosphorylation.[3] Using **1** as a lead compound, 2-arylpyrroles, have been developed through QSAR studies[4] and identified as a novel class of insecticides and acaricides. In particular, Pirate™ **2** has been commercially developed as a broad-spectrum insecticide/miticide.[3] The N-dealkylated analogue **3**, of pirate, is the metabolically active compound,[5] where the activity of the pyrrole insecticides is primarily a function of lipophilicity (Log P) and acidity (pK_a).[2,6]

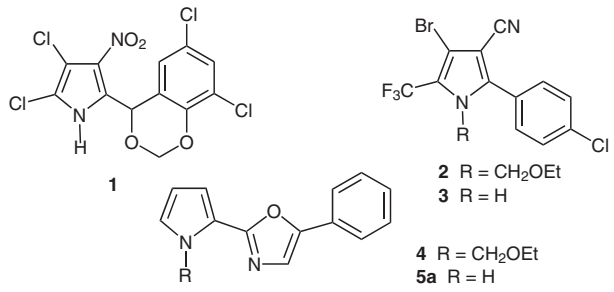
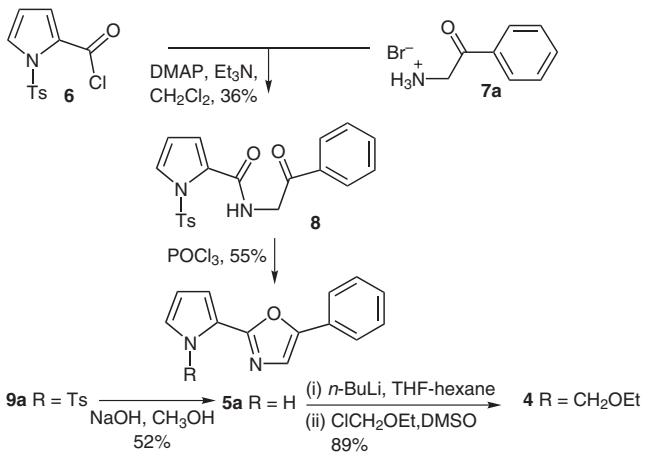


Figure 1 Structures of known insecticides **1**–**3** and potential lead compounds **4** and **5**

As part of a study aimed at identifying new potential insecticides, we sought to synthesize novel, structurally unique analogues of pirate **2**, that might ultimately deliver improved dosage rates and selectivity in the field, while reducing negative ecological impact. Previously[7] we generated simple pyrrole-oxazoles **4** and **5**, and established that they displayed moderate cytotoxicity.

During these investigations,[7] we established a viable synthetic route to pyrrole-oxazole **5** via coupling of **6** and **7a** and subsequent conversion to the target pyrrole-oxazole **5** (Scheme 1) without any purification steps, in 21% yield (cf. 10% with purification steps).[7] This suggested that the sequence was robust enough for the generation of analogues using solution-phase parallel synthesis. In the present work we wish to report the results of our investigations on the parallel synthesis of selected analogues of pyrrole-oxazole **5**.



Scheme 1

We examined the parallel synthesis of acylaminoketone salts, choosing commercially available ketobromides **10a–k**, which varied in the steric and electronic influences of the group α to the ketone. Acylaminoketone salts **7a–k** were obtained, in moderate to high yields and excellent purity (with the exception of **7j** which, though high yielding, was impure), via a Delépine reaction in which the ketobromides **10a–k** were reacted with hexamethylenetetramine[9] followed by cleavage of the resulting salt **11a–k** with hydrobromic acid (Scheme 2).[10]

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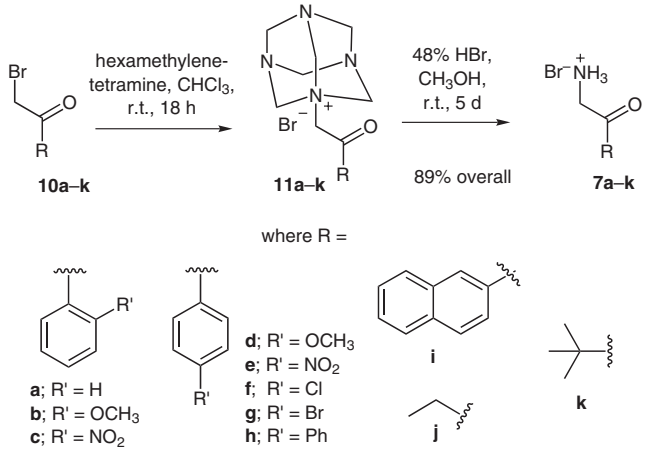
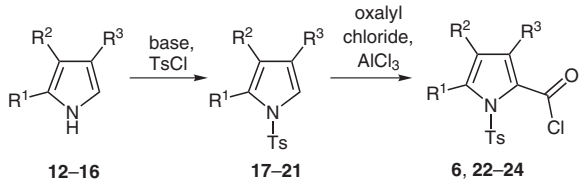


where yield = **7a**, 63%; **7b**, 93%; **7c**, 99%; **7d**, 67%; **7e**, 99%; **7f**, 54%; **7g**, 99%; **7h**, 50%; **7i**, 68%; **7j**, 97% (impure); **7k**, 76%.

Scheme 2

Synthesis of selected pyrrole subunits was examined using commercially available pyrroles with representative combinations of electron donating and withdrawing groups.

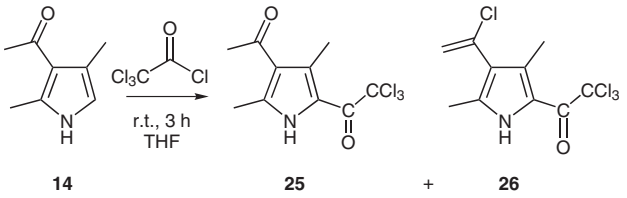
Generation of the potassium anion of pyrroles **12**–**14**, followed by treatment with tosyl chloride[11] gave the corresponding *N*-tosyl pyrroles **17**–**19** (Scheme 3). A modified procedure, using methyllithium and DMSO (to aid solubility of **15**), was used to generate *N*-tosyl pyrrole **20** (35%) from **15**. Acylation of N-tosyl pyrroles **17**–**20** was then examined. Unfortunately, though the unsubstituted pyrrole **17** underwent regioselective $AlCl_3$-catalyzed Friedel–Crafts acylation[12] to give *N*-tosylpyrrolecarbonyl chloride (**6**) (Scheme 3), pyrroles **18**–**20** were not acylated to the corresponding acylpyrroles **22**–**24**, with only starting materials being recovered. Pyrrole **19** was also quantitatively recovered even upon heating at reflux for 48 hours. These results suggest the balance of steroelectronic effects deactivate the 2-position to direct acylation.



6,**12**,**17**; $R^1 = R^2 = R^3 = H$ **13**,**18**,**22**; $R^1 = R^3 = CH_3$, $R^2 = H$
14,**19**,**23**; $R^1 = R^3 = CH_3$, $R^2 = C(O)CH_3$ **15**,**20**,**24**; $R^1 = H$, $R^2 = R^3 = CO_2Et$
16,**21**; $R^1 = C(O)CCl_3$, $R^2 = R^3 = H$

Scheme 3

At this point the synthetic route to *N*-tosylpyrrolecarbonyl chloride **6** was reconsidered. We previously showed that conversion of *N*-tosylpyrrole carboxylic acid to **6** was complicated by decomposition of the starting material.[7] In contrast, it has been reported[13] that acylation of 2-methyl-3-ethylpyrrole carboxylate with trichloroacetyl chloride does occur upon heating at 65 °C. Since trichloroacetyl pyrroles can be coupled with amines,[14] we treated acetyl dimethylpyrrole **14** with trichloroacetyl chloride in THF at room temperature for 3 hours and found that, along with trichloroacetyl pyrrole **25** (19%), the vinyl pyrrole **26** was also formed, albeit in low yield (7%). The structure of **26** was unambiguously assigned using g-COSY, g-HMBC, g-HSQC, GC-Mass spectrometry and micro analysis. A key correlation between protons at $\delta = 5.29$ and 5.71 ppm ($^2J = 1$ Hz) and the carbon at $\delta = 118.2$ ppm in the g-HSQC indicated a disubstituted olefinic group external to the pyrrole ring. Chlorine isotope peaks were observed for fragments at 182 [M – CCl_3] and 264 [M – Cl] in the GC-MS (+) spectrum. Reaction of the enol of trichloroacetyl pyrrole **25** with trichloroacetyl chloride followed by displacement of trichloroacetate ion with a chloride ion would account for formation of vinyl pyrrole **26**.



Scheme 4

As side products were observed in the formation of **25**, trichloroacetyl pyrrole **16** was used for a trial tosylation reaction. Treatment of **16** with potassium and tosyl chloride, however, gave complex mixtures and none of *N*-tosyl pyrrole **21**. A modified procedure using butyllithium in DMSO–THF (~1:1) also gave a mixture of which starting pyrrole **13** was the major component (~90%).

With the complications of substituent effects and the side reactions observed for the pyrrole subunit, we pursued the parallel synthesis of the carboxamides, incorporating representative points of diversity only in the aryl subunit. A set of acylaminoketone salts was selected with a range of substituents; phenyl (**7a**), methoxyphenyl (**7d**), nitrophenyl (**7e**), and chlorophenyl (**7f**). A parallel set of reactions were carried out using the sequence of coupling, cyclization and deprotection (Scheme 1, **7** to **5**).

To streamline the parallel synthesis, purification of intermediate compounds was not carried out, reactions were carried out on a smaller scale and minimal reaction work-up steps were used. Aliquots were taken at the conclusion of some steps for analysis by mass spectrometry to monitor the progress of the synthesis. After the coupling step, it was found necessary to thoroughly dry the crude carboxamides (**8a**–**d**) so as to prevent hydrolysis of phosphorus oxychloride during the subsequent cyclodehydration.

Using acylaminoketone salts **7a**, **7d** and **7f**, coupling with acylpyrrole **6** gave carboxamides **8a**, **8b** and **8d**, which were successfully cyclized to the tosyl pyrrole-oxazoles **9a**, **9b** and **9d**, deprotection of which gave the corresponding pyrrole-oxazoles **5a**, **5b** and **5d**, as confirmed by mass spectrometry (Figure 2). Mass spectral monitoring also provided evidence that coupling of acylaminoketone salt

7e with **6** did not proceed under standard conditions to form the carboxamide **8c**. The purity of the crude products (**5a**, **5b** and **5d**) was estimated by ^{1}H NMR spectroscopy and by comparison with the spectra of authentic samples where possible (**5a** and **5b**). The lower overall yield (eg: **7a** to **5a**, ~12% cf. larger scale 21%) was attributed to the smaller scale of reaction used in the parallel procedure. Typical purity of the final pyrrole-oxazole was only moderate (50–65%) with complex mixtures of by-products being observed, particularly for chloropyrrole-oxazole **5d**. Full characterization was not carried out due to the moderate purities observed. Notably, when carboxamide **8d** was purified by column chromatography before the dehydration and deprotection steps were carried out (with no further purification and minimal workup) the purity of pyrrole-oxazole **5d** increased to 74%.

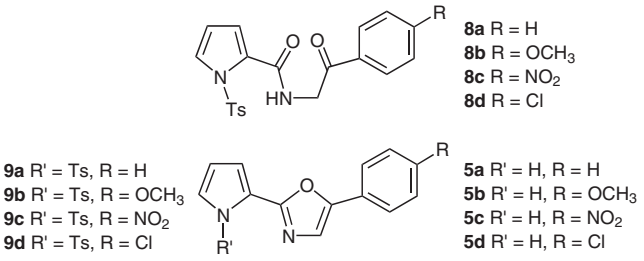


Figure 2 Carboxamides and pyrrole-oxazoles

In summary, the parallel synthesis of the arylamino salt subunit **7a**–**k** has been achieved in moderate to high yields and excellent purity (with the exception of **7j**). The synthetic route constitutes a reliable methodology for access to such salts. Whereas the *N*-tosyl pyrroles **17**–**19** were synthesized, the pyrrole acyl chloride subunits **22**–**24** could not be obtained using parallel chemistry, as this was thwarted by the stereoelectronic effects of the pyrrole substituents. Examination of an alternate route to the pyrrole subunit revealed the formation of the interesting pyrrole derivative, vinyl pyrrole **26**.

By restricting diversity to the aryl subunit, the parallel synthesis of target pyrrole-oxazoles **5a**, **5b** and **5d** with either no groups, or electron-donating groups on the aryl ring, was achieved. The parallel synthesis of these pyrrole-oxazoles, easily monitored by mass spectrometry, exploited modified workup procedures with no intermediate purification steps and gave moderate purity of the target compounds. Using one example, purification after the coupling step was shown to increase the purity of the final pyrrole-oxazole. From the above preliminary study, the scope and limitations for the parallel synthesis of arylamino salts, pyrrole acyl chlorides and pyrrole-oxazole units were assessed and presented for organic chemists considering using such methodology.

Instrumental details, the preparation of compounds **4**, **5a**, **5b**, **6**, **7a**, **8a**, **8b**, **9a**, **9b** and the parallel synthesis procedures used, are described elsewhere.[7,11,15]

Arylamino Ketone Salts 7a–k; General Procedure

In parallel, each bromo ketone (1.0 equivalent; **10a**, 20.0 g, 0.1 mol; **10b**, 2.0 g, 8.76 mmol; **10c**, 0.5g, 2.0 mmol; **10d**, 2.0 g, 8.7 mmol; **10e**, 2.0 g, 8.2 mmol; **10f**, 1.0 g, 4.3 mmol; **10g**, 1.0 g, 3.6 mmol; **10h**, 1.0 g, 3.6 mmol; **10i**, 1.0 g, 4.5 mmol; **10j**, 1.5 g, 9.9 mmol; **10k**, 2.0 g, 11.2 mmol) was added to a solution of hexamethylenetetramine (1.1 equiv) dissolved in $CHCl_3$ (**10a**, 200 mL; **10b**,**d**,**e**,**k** 20 mL; **10j**, 15 mL; **10f**–**i**, 10 mL; **10c**, 5 mL). After stirring at r.t. for 12 h a precipitate formed. tert-Butyl methyl ether (**10a**, 100 mL; **10b**, **d**,**e**,**k** 10 mL; **10j**, 7.5 mL; **10f**–**i**, 5 mL; **10c**, 2.5 mL) was added to the suspension and the solid was filtered, washed with a minimal amount of Et_2O and dried under high vacuum to give the quaternary salts **11a**–**k**. The salts **11a**–**k** were then added to a solution of MeOH (**11a**, 200 mL; **11b**,**d**,**e**, 20 mL; **11j**, 17 mL; **11f**, **h**–**i**, **k** 10 mL; **11g**, 8 mL; **11c**, 5 mL) and HBr (48%; **11a**, 38.82 mL; **11b**, 3.3 mL; **11c** 0.73 mL; **11d**, 3.5 mL; **11e**, 3.6 mL; **11f**, 1.92 mL; **11g**, 1.32 mL; **11h**, 1.6 mL; **11i**, 1.72 mL; **11j**, 3.11 mL; **11k**, 1.04 mL). The mixtures were stirred at r.t. for 5 d then the solvent volume was reduced in vacuo to a slurry, which was cooled to –15 °C. The resultant solid was filtered, washed with sat. aq KBr and air dried. The solid was recrystallised from *n*-BuOH and dried under high vacuum to give the arylamino ketone salts **7a**–**k**.

(2-Phenyl-2-oxoethyl)ammonium Bromide (7a)

Yield: 13.52 g (63%); white solid; mp 234–235 °C (Lit.[16] 198–200 °C [HBr + HCl salt]).

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.8 (br s, 2 H, CH_2), 7.55 (dd, *J* = 8.2, 8.2 Hz, 2 H, H-3′, H-5′), 7.75 (dd, *J* = 7.1, 7.1 Hz, 1 H, H-4′), 7.94 (d, *J* = 7.1 Hz, 2 H, H-2′, H-6′).

NH_3 not observed.

MS (ESI, +): *m*/*z* (%) = 136 (100) $[M + H]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (99) $[Br]^-$.

[2-(2′-Methoxyphenyl)-2-oxoethyl]ammonium Bromide (7b)

Yield: 1.19 g (93%); orange solid; mp 249–250 °C.

IR (KBr): 1671, 1399 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.01 (s, 3 H, OCH_3), 4.67 (br s, 2 H, CH_2), 7.05–7.18 (m, 2 H, H-3′, H-5′), 7.71 (dd, *J* = 7.0, 7.0 Hz, 1 H, H-4′), 7.98 (dd, *J* = 7.5, <1.0 Hz, 1 H, H-6′).

NH_3 not observed.

^{13}C NMR (50 MHz, $CDCl_3$–TFA): δ = 49.2, 56.8, 113.8, 122.2, 124.4, 131.8, 137.6, 162.1, 198.4.

MS (ESI, +): *m*/*z* (%) = 166 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (98) $[Br]^-$.

HRMS: *m*/*z* calcd for $C_9H_{12}NO_2^+$: 166.0863; found 166.0841.

[2-(2′-Nitrophenyl)-2-oxoethyl]ammonium Bromide (7c)

Yield: 0.296 g (67%); beige solid; mp 209–211 °C.

IR (KBr): 1723, 1524, 1399, 1343 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.57 (br s, 2 H, CH_2), 7.56 (d, *J* = 6.9 Hz, 1 H, H-4′), 7.75–7.92 (m, 2 H, H-5′, H-6′), 8.26 (d, *J* = 6.9 Hz, 1 H, H-3′).

NH_3 not observed.

^{13}C NMR (50 MHz, $CDCl_3$–TFA): δ = 48.8, 125.2, 129.9, 132.6, 132.9, 135.6, 145.6, 194.9.

MS (ESI, +): *m*/*z* (%) = 181 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (98) $[Br]^-$.

HRMS: *m*/*z* calcd for $C_8H_9N2O_3^+$: 181.0608; found 181.0606.

[2-(4′-Methoxyphenyl)-2-oxoethyl]ammonium Bromide (7d)
Yield: 1.99 g (99%); pale yellow solid; mp 207.5–209 °C (Lit.[10] 204–205 °C).

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 3.92 (s, 3 H, OCH_3), 4.7 (br s, 2 H, CH_2), 7.01 (d, *J* = 9.75 Hz 2 H, H-3′, H-5′), 7.92 (d, *J* = 9.75 Hz, 2 H, H-2′, H-6′).

NH_3 not observed.

MS (ESI, +): *m*/*z* (%) = 166 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (98) $[Br]^-$.

[2-(4′-Nitrophenyl)-2-oxoethyl]ammonium Bromide (7e)
Yield: 0.296 g (67%); brown solid; mp 258–260 °C (dec.).

IR (KBr): 1683, 1520, 1472, 1340 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.76 (br s, 2 H, CH_2), 8.16 (d, *J* = 9.1 Hz, 2 H, H-2′, H-6′), 8.44 (d, 2 H, *J* = 9.1 Hz, 2 H, H-3′, H-5′).

NH_3 not observed.

^{13}C NMR (50 MHz, $CDCl_3$–TFA): δ = 46.3, 124.6, 129.8, 136.8, 149.0, 190.3.

MS (ESI, +): *m*/*z* (%) = 181 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (98) $[Br]^-$.

HRMS: *m*/*z* calcd for $C_8H_9N2O_3^+$: 181.0608; found 181.0600.

[2-(4′-Chlorophenyl)-2-oxoethyl]ammonium Bromide (7f)[17]
Yield: 0.608 g (54%); white solid; mp 279–280 °C.

IR (KBr): 1682, 1464, 826 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.74 (br s, 2 H, CH_2), 7.56 (d, *J* = 6.5 Hz, 2 H, H-2′, H-6′), 7.90 (d, *J* = 6.5 Hz, 2 H, H-3′, H-5′).

NH_3 not observed.

^{13}C NMR (50 MHz, CD_3OD): δ = 45.7, 122.8, 129.9, 143.4, 154.8, 191.5.

MS (ESI, +): *m*/*z* (%) = 172 (34) $[M]^+$, 170 (100).

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (98) $[Br]^{\&\ ndash;}$.

[2-(4′-Bromophenyl)-2-oxoethyl]ammonium Bromide (7g)
Yield: 0.81 g (99%); white solid; mp 267 °C (dec.) [Lit.[18] 273–277 (dec.); Lit.[10] 260 °C (dec.)].

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.71 (br s, 2 H, CH_2), 7.73 (d, *J* = 8.7 Hz, 2 H, H-3′, H-5′), 7.82 (d, *J* = 8.3 Hz, 2 H, H-2′, H-6′).

NH_3 not observed.

MS (ESI, +): *m*/*z* (%) = 216 (38) $[M]^+$, 214 (38).

MS (ESI, –): *m*/*z* (%) = 81 (99) $[Br]^-$, 79 (100) $[Br]^-$.

2-[1,1′-Biphenyl]-4-yl-2-oxoethylammonium Bromide (7h)
Yield: 1.04 g (50%); beige solid; mp 271–273 °C (dec.) (Lit.[19] 240 °C char, not melted at 300 °C).

^{1}H NMR (200 MHz, $CDCl_3$,/TFA): δ = 4.77 (br s, 2 H, CH_2), 7.40–7.65 (m, 5 H, H-2″, H-3″, H-4″, H-5″, H-6″), 7.80 (d, *J* = 8.1 Hz, 2 H, H-3′, H-5′), 8.03 (d, *J* = 8.1 Hz, 2 H, H-2′, H-6′).

NH_3 not observed.

MS (ESI, +): *m*/*z* (%) = 212 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (99) $[Br]^-$.

[2-(2′-Naphthalyl)-2-oxoethyl]ammonium Bromide (7i)
Yield: 0.7 g (68%); white solid; mp 236–238 °C.

IR (KBr): 1693, 1486 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 4.91 (br s, 2 H, CH_2), 7.60–7.80 (m, 3 H, H-5′, H-6′, H-7′), 7.90–8.05 (m, 3 H, H-3′, H-4′, H-8′), 8.52 (br s, 1 H, H-1′).

NH_3 not observed.

^{13}C NMR (50 MHz, CD_3OD): δ = 46.36, 124.0, 128.3, 128.9, 130.0, 130.8, 131.8, 132.3, 133.9, 137.6, 193.1.

MS (ESI, +): *m*/*z* (%) = 116 (7) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (96) $[Br]^-$.

HRMS: *m*/*z* calcd for $C_9H_{12}NO^+$: 186.0913; found 186.0912.

(2-Ethyl-2-oxoethyl)ammonium Bromide (7j)
Yield: 1.045 g (97%); brown solid; mp 372–373 °C (dec.).

IR (KBr): 1638, 1399 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$–TFA): δ = 1.16 (t, *J* = 7.4 Hz, 3 H, CH_3), 2.62 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.11 (br s, 2 H, CH_2).

NH_3 not observed.

^{13}C NMR (50 MHz, CD_3OD): δ = 14.4, 26.4, 58.2, 173.3.

MS (ESI, +): *m*/*z* (%) = 188 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (99) $[Br]^-$.

HRMS: *m*/*z* calcd for $C_9H_{12}NO^+$: 188.0768; found: $[M + H]^+$ peak unable to be measured.

(2-*tert*-Butyl-2-oxoethyl)ammonium Bromide (7k)
Yield: 1.045 g (97%); white solid; mp 390 °C (dec.).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.20 (s, 9 H, 3 × CH_3), 4.14 (br s, 2 H, CH_2).

NH_3 not observed.

MS (ESI, +): *m*/*z* (%) = 186 (100) $[M]^+$.

MS (ESI, –): *m*/*z* (%) = 81 (100) $[Br]^-$, 79 (95) $[Br]^-$.

Tosyl Pyrroles; General Procedure
Potassium [(a) 1.369 g, 35 mmol; (b) 0.891 g, 23 mmol; 1.1 equiv] was added to a solution of pyrrole [(a) **13**, 3.000 g, 32 mmol; (b) **14**, 3.006 g, 22 mmol; 1 equiv] in THF [(a) 25 mL, (b) 17 mL]. The solution was gently heated at reflux until all of the potassium had reacted. A solution of TsCl [(a) 6.101 g, 32 mmol; (b) 3.516 g, 22 mmol; 1 equivalent] in THF [(a) 15 mL; (b) 11 mL] was added dropwise over 20 minutes. The reaction was stirred at r.t. for 12 h. H_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. The crude product was recrystallised (MeOH–hexane) and dried under high vacuum.

2,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole (18)
Yield: 6.761 g (84%); light brown solid; mp 80.1–82.0 °C (Lit.[21] 85 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (d, *J* = 1 Hz, 3 H, 2-CH_3), 2.26 (d, *J* = 1 Hz, 3 H, 4-CH_3), 2.41 (s, 3 H, $PhCH_3$), 5.80 (br s, 1 H, H3), 7.00 (br s, 1 H, H5), 7.29 (d, *J* = 8.2 Hz, 2 H, *m*-$SO_2C_6H_4$), 7.66 (d, *J* = 8.2 Hz, 2 H, *o*-$SO_2C_6H_4$).

1-{2,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}ethanone (19)
A residue of **19** (66%) and starting material **14** (34%) was obtained. Purification by column chromatography (CH_2Cl_2–hexane, 2:1) gave pure **19**.

Yield: 1.34 g (26%); colourless crystals; mp 111–112 °C.

IR (KBr): 2926, 1670, 1365, 1174 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.20 (d, *J* = 1 Hz, 3 H, 4-CH_3), 2.38 (s, 3 H, 2-CH_3), 2.41 (s, PhCH_3, 3 H), 2.52 (s, 3 H, $COCH_3$), 7.08 (d, *J* = 1 Hz, 1 H, H5), 7.31 (d, *J* = 8.1 Hz, 2 H, *m*-$SO_2C_6H_4$), 7.70 (d, *J* = 8.1 Hz, 2 H, *o*-$SO_2C_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (2-CH_3), 13.3 (4-CH_3), 21.6 (PhCH_3), 31.6 ($COCH_3$), 119.4 (C5), 120.6 (C3), 126.5 (C4), 127.1 (*o*-$SO_2C_6H_4$), 130.1 (*m*-$SO_2C_6H_4$), 135.7 (*i*-$SO_2C_6H_4$), 141.7 (2), 145.4 (*p*-$SO_2C_6H_4$), 196.8 (C=O).

MS (ESI, +): *m*/*z* (%) = 292 (23) $[M]^+$.

HRMS: *m*/*z* calcd for $C_{15}H_{18}NO_3S^+$: 292.1002; found 292.1002.

Diethyl 1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate (20)

n-Methyllithium (5.90 mL, 7.1 mmol) was added dropwise at 0–5 °C to a solution of diethyl 3,4-pyrrole dicarboxylate **15** (1.5 g, 1.5 mmol) in dry THF (15 mL) under an atmosphere of nitrogen. The reaction mixture was stirred at 0 °C for 15 min, and warmed to r.t. Dry DMSO (30 mL) was added, followed by dropwise addition of TsCl (1.22 g, 6.39 mmol) in THF (10 mL). The solution was stirred at r.t. for 12 h then H_2O was added and the reaction mixture was worked up according to the reference given in the general procedure.

Yield: 0.9 g (35%) (~95% purity); amber oil; Lit.[22] mp 67–68 °C.

IR (KBr): 1747, 1380, 1066 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 8.0 Hz, 6 H, 2 × CH_3), 2.45 (s, 3 H, 4′-CH_3), 4.29 (q, *J* = 8.6 Hz, 4 H, 2 × CH_2), 7.37 (d, *J* = 10.3 Hz, 2 H, H3′, H5′), 7.65 (s, 2 H, H2, H5), 7.83 (d, *J* = 10.3 Hz, 2 H, H2′, H6′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.25, 21.75, 61.0, 119.9, 125.5, 127.6, 130.5, 134.5, 149.5, 164.7.

MS (GCMS): *m*/*z* (%) = 365 (8) $[M]^+$.

Pyrroles 25 and 26

3-Acetyl-2,4-dimethylpyrrole **14** (100 mg, 0.78 mmol) in THF (10 mL) was added dropwise over 20 min to a solution of trichloroacetyl chloride (0.162 g, 0.78 mmol, 0.1 mL) in dry THF (10 mL). The solution was stirred at r.t. for 3 h, then a sat. soln of $NaHCO_3$ (50 mL) was added dropwise over 1 h. The organic phase was collected and washed with brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product mixture was purified by silica column chromatography (EtOAc–CH_2Cl_2, 4:94).

1-(4-Acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)-2,2,2-trichloroethanone (25)

Yield: 28 mg (13%); yellow solid; mp 125–127 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, 3-CH_3), 2.59 (s, 3 H, 5-CH_3), 2.69 (s, 3 H, C(O)CH_3), 9.10 (br s, $W_{h/2}$ = 20 Hz, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (3-CH_3), 15.7 (5-CH_3), 31.8 (C(O)*C*H_3), 96.17 (CCl_3), 118.4 (C4), 124.9 (C3), 139.0 (C2), 140.6 (C5), 170.3 (*C*(O)CCl_3), 195.3 (*C*(O)CH_3).

MS (ESI, +): *m*/*z* (%) = 281 (100) $[M + 1]^+$.

HRMS: *m*/*z* calcd for $C_{10}H_{10}Cl_3NO_2$: 280.9777; found 280.9775.

2,2,2-Trichloro-1-[4-(1-chlorovinyl)-3,5-dimethyl-1*H*-pyrrol-2-yl]ethanone (26)

Yield: 15 mg (7%); colorless solid; mp 138–140 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, 5-CH_3), 2.45 (s, 3 H, 3-CH_3), 5.29 (d, *J* = 1 Hz, 1 H, C=C*H*H), 5.71 (d, *J* = 1 Hz, 1 H, C=CH*H*), 8.90 (br s, $W_{h/2}$ = 25 Hz, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.9 (CH_3), 13.0 (CH_3), 96.2 (CCl_3), 118.2 (=CCl), 118.7 (=CH_2), 124.0 (C3), 132.2 (C4), 135.2 (C2), 136.9 (C5), 169.8 (C=O).

MS (ESI, +): *m*/*z* (%) = 301 (30) $[M + 1]^+$.

GCMS: (%) = 182 (100) [M – CCl_3].

Anal. Calcd for $C_{10}H_9Cl_4NO$: C, 39.90; H, 3.01; N, 4.65. Found: C, 40.29; H, 3.10; N, 4.36.

Parallel Synthesis; Coupling Step

N-Tosylpyrrole-2-carbonyl chloride **6** (80 mg, 0.28 mmol), DMAP (0.15 mg, 1.2 μmol) and Et_3N (85 mg, 0.84 mmol, 0.12 mL) in CH_2Cl_2 (3 mL) were added to each of four reacti-vials containing one arylamino ketone salt in each. Vial A, **7a** (60 mg, 0.28 mmol); vial B, **7d** (69 mg, 0.28 mmol); vial C **7e** (73 mg, 0.28 mmol); vial D, **7f** (70 mg, 0.28 mmol). The solutions were stirred for 48 h at r.t. then H_2O (2 mL) was added to each reacti-vial and the aqueous phase was removed by pasteur pipette. The organic phase from each vessel was passed through a separate column of anhydrous Na_2SO_4 and the organic phases were collected and evaporated in vacuo.

Compound **8a**

MS (ESI, +): *m*/*z* (%) = 405 (100) $[M + Na]^+$.

Compound **8b**

MS (ESI, +): *m*/*z* (%) = 435 (100) $[M + Na]^+$.

Compound **8c**

No peaks detected in the MS (ESI, +).

(2′-(4″-Chlorophenyl-2′-oxoethyl)-1-tosyl-1H-pyrrole-2-carboxamide (8d)

Obtained as a crude product.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 4.85 (d, 2 H, H1′), 6.30 (dd, 1 H, H4), 6.82 (dd, 1 H, H3), 7.31 (d, 2 H, *m*-$SO_2C_6H_4$), 7.49 (m, 2 H, H3″, H5″), 7.54 (dd, 1 H, H5), 7.91 (d, 2 H, *o*-$SO_2C_6H_4$), 7.93 (d, 2 H, H2″, H6″).

NH not apparent.

MS (ESI, +): *m*/*z* (%) = 423 (100) $[M + Li]^+$.

Parallel Synthesis; Cyclodehydration

Phosphorus oxychloride (3 mL) was added to each reacti-vial (A–D) containing the residues from the coupling step described above, and the solutions were heated at reflux for 2 h. The reacti-vials were allowed to cool to r.t. and stirred for a further 2 h before H_2O (2 mL) was added, and the solutions made basic by the addition of aq NH_3 (28%) and worked up as described above.

5-(4″-Chlorophenyl)-2-(1′-tosyl-1H-pyrrol-2′-yl)-1,3-oxazole (9d)

Obtained as a crude product.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 6.40 (dd, 1 H, H4′), 6.90 (dd, 1 H, H3′), 7.27 (m, 2 H, H4 of *m*-$SO_2C_6H_4$), 7.41 (m, 2 H, H3″, H5″), 7.53–7.56 (m, 2 H, H5′, H2″, H6″), 7.77 (d, 2 H, *o*-$SO_2C_6H_4$).

Parallel Synthesis; Deprotection

MeOH (3 mL) and NaOH (5M, 0.5 mL) were added to each reacti-vial (A-D) containing the residues from the cyclodehydration. The solutions were heated at reflux for 3 h then H_2O (1 mL) was added and the aqueous phase worked up with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine (3 × 3 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude residues were obtained as black solids; vial A (**5a**, 7 mg, ~12% from **6**), vial B (complex mixture, 12 mg), vial C (**5b**, 10 mg, ~15% from **6**), vial D (**5d**, 8 mg, ~12% from **6**). The crude residues were analysed by mass spectrometry and ^{1}H NMR spectroscopy.

Purity as estimated by ^{1}H nmr of crude product: **5a**[7] (55%); **5b**[11] (65%); **5d** (50% without purification of **8d**); **5d** (74% with purification of **8d**)

5-(4″-Chlorophenyl)-2-(1H-pyrrol-2′-yl)-1,3-oxazole (5d)
Obtained as a crude product.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.32–6.38 (m, 1 H, H4′), 6.90–6.95 (m, 1 H, H3′), 6.95–6.01 (m, 1 H, H5′), 7.33 (s, 1 H, H4), 7.40 (2 H, d, H2″, H6″, 7.61 (d, 2 H, H3″ H5″), 9.48 (br s, 1 H, NH).

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