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# Palladium Catalysed Synthesis of Spiroindolines.

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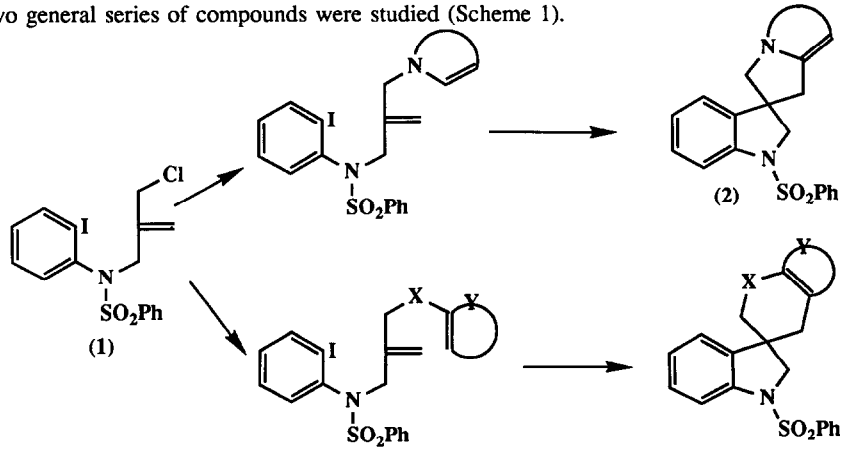
*Abstract: A series of palladium catalysed consecutive bis(5-exo trig)-, 5-exo trig-6-exo trig-, and 5-exo trig-7-endo trig-cyclisations via an alkene relay onto benzene or a wide range of heterocycles (pyrrole, furan, thiophen, indole, pyridine, pyridones) generates 5,5-, 5,6- and 5,7-spiroindolines in good yield.*

We recently described a range of facile palladium catalysed Heck-type cyclisation reactions generating spirocyclic products.[1] Other groups subsequently provided further examples of such processes.[2] The methodology has continued to develop with Tl(I) salts being shown to be particularly beneficial in preventing double bond isomerisation in the products[3] and silver phosphate exerting control over the stereoselection in cyclisations of caged gelsemine intermediates.[4] All these cyclisations involve intramolecular attack of an arylpalladium species onto a proximate cyclo-olefin. Thus one of the two spirocyclic rings is present in the precursor. It was of interest to develop a general protocol in which **both** constituent rings of the spirocycle are created via a palladium catalysed biscyclisation process.

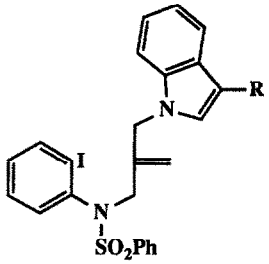
In this study our interest lay in spiroindolines and the common starting material for our studies was (1). Two general series of compounds were studied (Scheme 1).



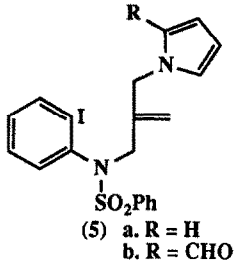

**Scheme 1**

In the first series the allylic chloride (1) was used to N-alkylate a series of aromatic or unsaturated nitrogen heterocycles. These products subsequently led to 5,5-spirocycles (2) (Scheme 1). In the second series the allylic chloride was attached to an aromatic or heteroaromatic ring via an oxygen or aminomethyl spacer leading subsequently to 5,6- and 5,7-spirocycles (3) respectively (Scheme 1). These various spirocyclic combinations are now considered in turn.

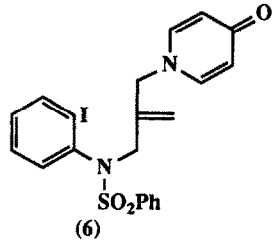
**5,5-Spirocycles.** The cyclisation substrates (4a-c), (5a,b), (6) and (7) were prepared from (1) and the appropriate heterocycle in good yield using one of three base/polar solvent combinations. (Table 1).



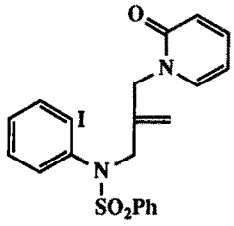

(4) a. R = H
b. R = CHO
c. R = Me




(5) a. R = H
b. R = CHO




(6)

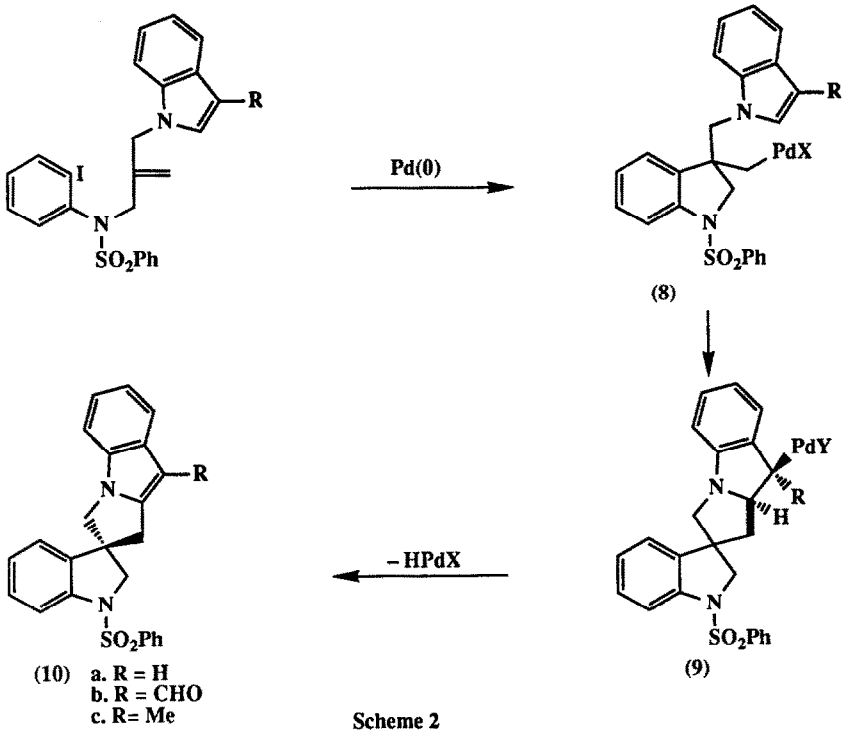



(7)

**Table 1.** Preparation of cyclisation precursors (4) - (7).

| Compound | Base | Solvent | Temp(°C) | Time(h) | Yield(%) |
|---|---|---|---|---|---|
| 4a | KOH | DMSO | 25 | 2 | 64 |
| 4b | $K_2CO_3$ | MeCN | 80 | 24 | 73 |
| 4c | KOH | DMSO | 25 | 6 | 76 |
| 5a | KOH | DMSO | 25 | 2 | 74 |
| 5b | $K_2CO_3$ | MeCN | 80 | 36 | 80 |
| 6 | $K_2CO_3$ | DME | 85 | 17.5 | 86 |
| 7 | $K_2CO_3$ | DME | 85 | 65 | 96 |

In the cyclisation of precursors (4a-c) and (5a,b) the second ring forming process, illustrated for (4a-c) in Scheme 2, involves attack of an alkylpalladium (II) species (8) on an aromatic ring. Moreover, the indole and pyrrole moieties even when bearing a carboxaldehyde substituent are "electron-rich" species. The spirocyclisations occurred in good to excellent yield, (Table 2), by two successive 5-exo trig processes.



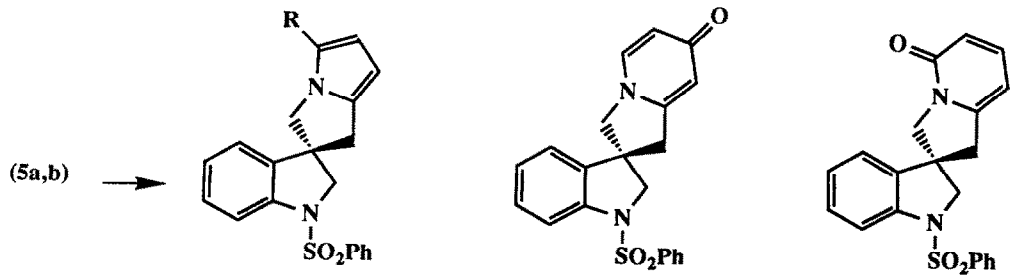

Scheme 2

**Table 2.** 5,5-Spirocyclisation Processes.[a]

| Substrate | Solvent | Base | Temp(°C) | Time(h) | Product (Yield %) |
|---|---|---|---|---|---|
| 4a | MeCN | $K_2CO_3$ | 60 | 15 | 10a (74)[b] |
| 4b | anisole | KOAc | 130 | 24 | 10b (91) |
| 4c | anisole | KOAc | 130 | 24 | 10c (77) |
| 5a | anisole | KOAc | 130 | 64 | 11a (59) |
| 5b | anisole | KOAc | 130 | 24 | 11b (81) |
| 6 | MeCN | $K_2CO_3$ | 80 | 3 | 12 (75)[b] |
| 7 | MeCN | $K_2CO_3$ | 80 | 3.5 | 13 (80)[b] |

a. In all cases the Pd(0) catalyst was generated *in situ* from 10mol % $Pd(OAc)_2$ and 20mol % $PPh_3$.

b. In these reactions $Et_4NCl$ (1 eq.) was also present.[5]

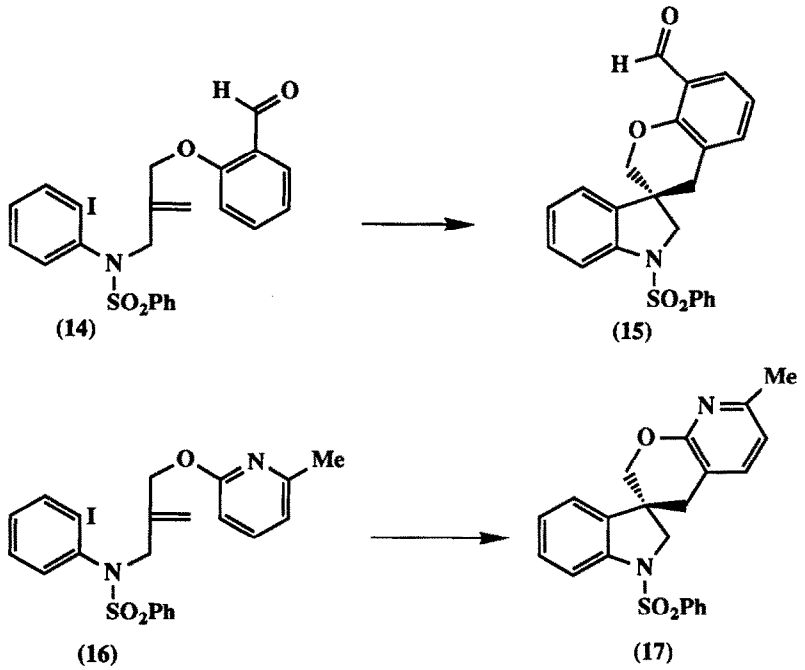



The moderate yield of (11a) reflects the longer reaction time involved in this case together with the tendency

of (5a) to undergo slow (oxidative?) decomposition in hot solvent. Subsequently it was discovered that addition of tetraethylammonium chloride (1 eq.) promoted a faster, cleaner, reaction. Thus (4a) furnished (10a) in only 38% yield when the cyclisation was carried out in anisole ($K_2CO_3$, 130°C, 52h). It is therefore probable that this combination will reduce reaction times and improve yields when applied to (4b,c) and (5a,b).

The second cyclisation step, e.g. (8) → (9) (Scheme 2), is expected to occur with cis-stereochemistry and, similarly, the β-hydride elimination step, e.g. (9) → (10), normally occurs with cis-stereochemistry. Clearly this latter process is not possible in (9). Similar, formally forbidden, eliminations are not uncommon especially when the Pd(II) species is located at a benzylic position and may involve prior stereomutation of the Pd(II) moiety or a slower trans-elimination.[6]

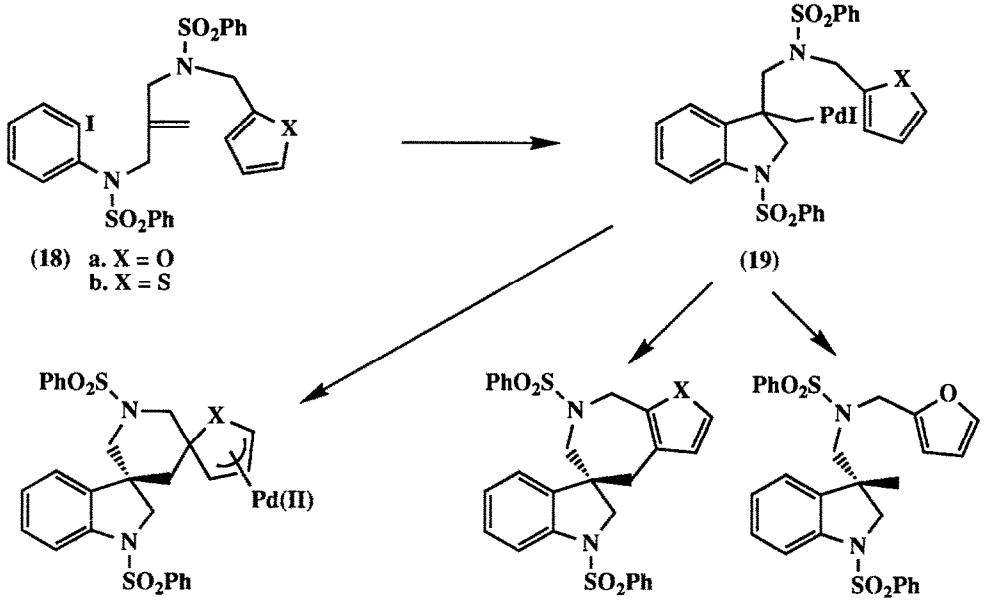
**5,6-Spirocycles.** Alkylation of salicylaldehyde and 6-methyl-2-pyridone afforded the representative cyclisation substrates (14) (51%) and (16) (58%) respectively. Catalytic spirocyclisation of (14), under analogous conditions to those used for (6) and (7), afforded (15) (68%). In a similar fashion (16) cyclised to (17) (68%).



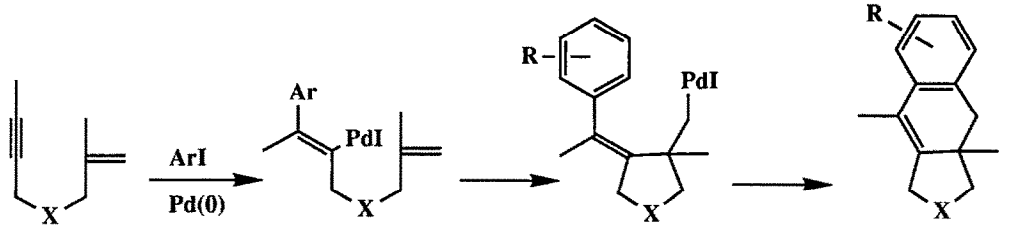

Thus the spirocyclisation can be effected onto both "electron rich" and "electron poor" heteroaromatic rings.

**5,7-Spirocyclisations.** Two substrates (18a,b) were prepared by the N-alkylation of N-phenylsulphonylfurfurylamine and N-phenylsulphonyl-2-aminomethylthiophen using compound (1) and sodium hydride as the base. The substrates (18a,b) underwent cyclisation [10mol % $Pd(OAc)_2$, 20mol % $PPh_3$] to (20a,b) (Scheme 3) in DMF at 100°C in the presence of tetraethylammonium chloride (1 eq.) and potassium carbonate in poor yield (24-26%). Using more severe (anisole, 130°C) or less severe (MeCN, 80°C) conditions did not result in any improvement. However, the furan (18a) cyclised in acetonitrile at 80°C in the presence of TlOAc (1mol) to afford (20a) in 64% yield whilst the thiophen (18b) afforded (20b) in 41% yield when

cyclised in DMF at 100°C in the presence of TlOAc (2 eq.). We have previously reported on the beneficial effects of Tl(I) additives on a range of palladium catalysed processes.[7-9]. The intermediate alkylpalladium (II) species (19) thus undergoes a 7-endo trig cyclisation to (20a,b). The alternative 6-exo trig cyclisation would furnish a π-allylpalladium (II) species which lacks a β-hydride elimination pathway (Scheme 3). The cyclisation of (18a) was carried out in the presence of sodium formate (MeCN, 80°C, 15h) to see if this latter intermediate could be trapped by hydride ion transfer. The product proved to be the monocyclisation-hydride capture compound (21) (60%).




Scheme 3




In summary, alkylpalladium (II) species, generated via initial palladium catalysed cyclisation of an aryl iodide onto a proximate alkene, are highly reactive and will attack proximate aromatic and heteroaromatic rings (both "electron rich" and "electron poor") leading to spirocycles usually in good yield. The reactive alkylpalladium (II) species can be generated in other ways. Thus we have recently shown that the palladium catalysed addition of aryl iodides to (22) sets off a cascade process leading via (23) and (24) to (25).[10] The potential for incorporation of heterocyclic rings in this latter process is currently under investigation.

**Experimental.** General experimental details were as previously described.[11] 3-(2'-Iodo-N-phenylsulphonylanilinyl)-2-chloromethylpropene (1) was prepared as previously described.[8]

**Cyclisation Substrates.**

**Indole (4a).** 3-(2'-Iodo-N-phenylsulphonylanilinyl)-2-chloromethylpropene (1) (1.5g, 3.4mmol) was added to stirred mixture of indole (0.40g, 3.4mmol) and powdered potassium hydroxide (0.57g, 10mmol) in dry DMSO (25ml) and stirring continued for 2h. at room temperature. Water (75ml) was then added to the mixture followed by dilute HCl until the solution was slightly acidic to litmus. The mixture was then extracted with ether (2 x 75ml) and the combined ether extracts washed with sodium bicarbonate solution (50ml) and water (50ml), dried ($Na_2SO_4$) and evaporated to afford a brown gum. Crystallisation from ether afforded the **product** as colourless needles (1.1g, 64%), m.p. 123-125°C. (Found: C, 54.25; H, 3.8; N, 5.35. $C_{24}H_{21}IN_2S$ requires C, 54.55; H, 4.0; N, 5.3%); δ 8.0-6.8 (m, 14H, ArH), 6.51 (d, 1H, 3.5Hz, NC=CH), 5.02 (d, 1H, J 16.5Hz, CHNC=), 4.94 (d, 1H, 16.6Hz, CHNC=) 4.75 and 4.69 (2 x s, 2 x 1H, C=$CH_2$), 4.31 and 3.83 (2xd, 2x 1H, 14.0 Hz, $SNCH_2$); m/z (%) 528 ($M^+$, 81), 387 (43), 170 (100), 130 (97) and 77 (64).

**Indole (4b).** A mixture of 3-(2'-iodo-N-phenylsulphonylanilinyl)-2-chloromethylpropene (1) (0.81g, 1.8mmol), indole-3-carboxaldehyde (0.27g, 1.8mmol), and anhydrous potassium carbonate (0.5g, 3.6mmol) in dry acetonitrile (100ml) was boiled under reflux for 24h. The solvent was then removed under reduced pressure and the residue partitioned between methylene chloride and water. The water layer was separated, washed with methylene chloride, and the combined methylene chloride extracts dried ($Na_2SO_4$) and evaporated. Crystallisation of the residue from ethyl acetate afforded the **product** (0.73g, 73%) as colourless needles, m.p.195-198°C. (Found: N, 4.7. $C_{25}H_{21}IN_2O_3S$ requires N, 5.05%); δ 10.03 (s, 1H, CHO), 8.4-6.8 (m, 14H, ArH), 5.20 and 5.05 (2xd, 2x1H, J 16.0Hz, $CH_2NC$=), 4.88 and 4.85 (2 x s, 2 x 1H, C=$CH_2$), 4.29 and 3.80 (2xd, 2x1H, J 14.1Hz, $SNCH_2$); m/z(%), 556 ($M^+$, 81), 168 (74), 144 (68), 130 (81) and 77 (100).

**Indole (4c).** Prepared from 3-methylindole using the same procedure as that employed for the synthesis of (4a). The reaction was complete in 6h. After work-up the residue was purified by flash chromatography ($SiO_2$) to afford an orange powder which crystallised from ether as colourless plates (76%), m.p.122-123°C. (Found: C, 55.5; H, 4.3; N, 5.15. $C_{25}H_{23}IN_2O_2S$ requires C, 55.35; H, 4.25; N, 5.15%); δ 8.0-6.8 (m, 14H, ArH), 4.88 (m, 2H, $CH_2NC$=), 4.76 and 4.70 (2 x s, 2 x 1H, C=$CH_2$), 4.29 and 3.87 (2xd, 2x1H, J 14.1Hz, $SNCH_2$) and 2.31 (s, 3H, $CH_3$); m/z(%) 542 ($M^+$, 90), 401 (42), 184 (80), 144 (100) and 77 (59).

**Pyrrole (5a).** Prepared from pyrrole using the same procedure as that employed for the synthesis of (4a). The reaction was complete in 2h. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:1 v/v ether-petroleum ether to afford the **product** (74%) as an yellow gum which crystallised from petroleum ether as colourless plates, m.p.91-94°C. (Found: C, 50.05; H, 3.9; N, 5.75. $C_{20}H_{19}IN_2S$ requires C, 50.2; H, 4.0; N, 5.85%); δ 8.0-6.8 (m, 9H, ArH), 6.65 (s, 2H, 2 x NCH=), 6.14 (s, 2H, 2 x NC=CH), 4.8-4.6 (m, 4H, $CH_2NC$= and C=$CH_2$), 4.25 and 3.81 (2xd, 2x1H, J 13.8Hz, SNCH); m/z(%), 478 ($M^+$, 8), 337 (100), 209 (24), 120 (62) and 80 (63).

**Pyrrole (5b).** Prepared from pyrrole 2-carboxaldehyde using the same procedure as that employed for the synthesis of (4b). The reaction was complete after 36h. The solvent was then removed under reduced pressure and the residue partitioned between ether and water. The water layer was extracted with ether and the

combined ether extracts dried ($Na_2SO_4$) and evaporated to afford the **product** (80%) as a colourless powder which crystallised from ether as colourless plates, m.p.123-125°C. (Found: C, 49.65; H, 3.6; N, 5.55. $C_{21}H_{19}IN_2O_3S$ requires C, 49.8; H, 3.8; N, 5.55%); δ 9.48 (s, 1H, CHO), 8.0-6.8 (m, 11H, ArH), 6.26 (m, 1H, CH-C=C-C=O), 5.19 (s, 2H, $NCH_2C$=), 4.69 and 4.54 (2 x s, 2 x 1H, C=$CH_2$), 4.33 and 3.90 (2xd, 2x1H, J 14.1Hz, $SNCH_2$); m/z(%) 507 ($M^+$1, 0.1), 365 (100), 118 (62) and 77 (88).

**4-Pyridone (6).** A mixture of 3-(2′-iodo-N-phenylsulphonylanilinyl)-2-chloromethylpropene (1.9g, 4.3mmol), 4-pyridone (0.43g, 95% purity, 4.3mmol), and anhydrous potassium carbonate (1.3g, 9.2mmol) in dry DME (60ml) was boiled under reflux for 17.5h. The solvent was then removed under reduced pressure and the residue partitioned between methylene chloride (100ml) and water (100ml). The water layer was extracted with methylene chloride (100ml) and the combined methylene chloride extracts dried ($Na_2SO_4$) and evaporated. The residue was crystallised from ether to afford the **product** (1.9g, 86%) as yellow prisms, m.p. 75-80°C. (Found: C, 49.75; H, 3.9; N, 5.45. $C_{21}H_{19}IN_2O_3S$ requires C, 49.8; H, 3.8; N, 5.55%); δ 8.0-6.8 (m, 11H, ArH and 2 x CHC=O), 6.44 and 6.41 (2 x s, 2 x 1H, 2 x NC=CH), 4.93 and 4.85 (2 x s, 2 x 1H, C=$CH_2$), 4.80 and 4.67 (2xd, 2x1H, J 16.0Hz, $CH_2NC$=), 4.27 and 3.76 (2xd, 2x1H, J 14.2Hz, $SNCH_2$); m/z(%) 506 ($M^+$, 38), 365 (21), 148 (100), 134 (50) and 77 (63).

**2-Pyridone** (7). Prepared from 2-pyridone by the same method employed for (6). The reaction was complete in 65h. After work-up the residue purified by flash chromatography ($SiO_2$) eluting with 1:3.5 v/v methanol-ether to afford the **product** (96%) as colourless plates, m.p. 45-50°C. (Found: C, 49.95; H, 3.85; N, 5.5. $C_{21}H_{19}IN_2O_3S$ requires C, 49.8; H, 3.8; N, 5.55%); δ 8.0-6.9 (m, 11H, ArH and NCH= and C<u>H</u>=CHCO), 6.6-6.1 (m, 2H, CHCO and C<u>H</u>=CHN), 4.9-4.7 (m, 4H, $CH_2NC$= and C=$CH_2$), 4.38 and 3.94 (2xd, 2x1H, J 14.3Hz, $SNCH_2$); m/z(%) 507 (M+1, 59), 365 (100, 270 (67), 148 (87) and 77 (76).

**Salicylaldehyde ether (14).** Prepared from salicylaldehyde using the same procedure as that employed for the synthesis of (4b). After the usual work-up the residue was crystallised from ether-petroleum ether to afford the **product** (51%) as colourless prisms, m.p. 112-113°C (Found: C, 51.5; H, 3.8; N, 2.7. $C_{23}H_{20}INO_4S$ requires C, 51.7; H, 3.75; N, 2.6%); δ 10.4 (s, 1H, CHO), 7.9-7.0 (m, 13H, ArH), 5.3 and 5.0 (2xs, 2x1H, C=$CH_2$), 4.8 (s, 2H, $OCH_2$), and 4.4 and 4.2 (2xd, 2x1H, $NCH_2$); m/z(%). 534 (M+1, 0.5), 504 (2), 412 (30), 393 (28), 392 (100), 284 (65), 271 (62), 230 (40), 143 (78), 142 (23), 91 (11) and 77 (60).

**Pyridyl ether (16).** Prepared from 6-methyl-2-pyridone using the method employed for the synthesis of (4b). The reaction was complete in 34h. After the usual work-up the residue was purified by flash chromatography ($SiO_2$) eluting with dichloromethane to afford the **product** (2.3g, 58%) as a pale yellow gum which crystallised upon standing for several days as pale yellow prisms, m.p. 76-78°C. (Found: C, 50.55; H, 3.8; N, 5.55. $C_{22}H_{21}IN_2O_3S$ requires C, 50.75; H, 4.05; N, 5.4%); δ 7.9-6.9 (m, 10H, ArH and $CH_3C$=C-C<u>H</u>, 6.70 (d, 1H, J 7.1Hz, OCCH), 6.49 (d, 1H, J 8.2Hz, $CH_3CCH$), 5.19 and 4.93 (2xs, 2x1H, C=$CH_2$), 4.88 (d, 1H, J 13.4Hz, OCH), 4.77 (d, 1H, J 13.3Hz, OCH), 4.41 and 4.28 (2xd, 2x1H, J 14.4Hz, $NCH_2$) and 2.42 (s, 3H, $CH_3$); m/z(%) 521 (M+1, 18), 379 (81), 162 (80), 143 (77) and 77 (100).

**Furan (18a).** N-Phenylsulphonylfurfurylamine (0.22g, 0.93mmol) was dissolved in dry DMF (10ml) and sodium hydride (0.059g, 50% in mineral oil, 1.3mmol) added portionwise with stirring in an ice bath. The mixture was stirred for 1h. at room temperature and then 3-(2′-iodo-N-phenylsulphonylanilinyl)-2-

chloromethylpropene (0.42g 0.93mol) was added. The mixture was stirred for 1 day at room temperature. The solvent was then removed under reduced pressure and the residue partitioned between ether (50ml) and water (50ml). The water layer was extracted with ether (50ml) and the combined ether extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:1 v/v ether-petroleum ether to afford the **product** (0.46g, 76%) as a colourless glass. (Found: C, 49.75; H, 3.85; N, 4.2. $C_{27}H_{25}IN_2O_5S_2$ requires C, 50.0; H, 3.9; N, 4.3%); δ 7.9-6.9 (m, 15H, ArH and OCH), 6.18 (d, 1H, J 3.1Hz, $OC(CH_2)=C\underline{H}$, 6.04 (d, 1H, J 2.9Hz, $OCH=C\underline{H}$), 5.19 and 5.15 (2xs, 2x1H, $C=CH_2$), 4.32 (s, 2H, $CH_2C$-O), 4.29 and 410 (2xd, 2x1H, J 15.6Hz, $CH_2NC\underline{H}_2C=CH_2$) and 3.94 and 3.84 (2xd, 2x1H, J 15.9Hz, $ArNCH_2$); m/z(%) 648 ($M^+$, 0.2), 507 (51), 338 (14), 81 (100) and 77 (38).

**Thiophen (18b).** Prepared from 3-(2′-iodo-N-phenylsulphonylanilinyl)-2-chloromethylpropene (0.41g, 0.91mmol) and N-phenylsulphonyl-2-aminomethylthiophen (0.23g, 0.91mol) using the same procedure as that described above. The residue was purified by flash chromatography ($SiO_2$) eluting with 3:1 v/v ether-petroleum ether to afford the product (0.47g, 78%) as a colourless glass. (Found: C, 48.55; H, 3.55; N, 3.95. $C_{27}H_{25}IN_2O_4S_3$ requires C; 48.8; H, 3.8; N, 4.2%); δ 7.9-6.7 (m, 17H, ArH and SCH=CHCH), 5.17 and 5.11 (2xs, 2x1H, $C=CH_2$), 4.53 (s, 2H, $CH_2CS$), 4.21 (d, 1H, J 15.2Hz, $CH_2NC\underline{H}C=CH_2$), 4.04-3.82 (m, 3H, $CH_2NC\underline{H}C=CH_2$ and $ArNCH_2$); m/z(%) 664 ($M^+$, 0.2), 523 (35), 381 (8), 97 (100) and 77 (39).

**Spirocyclisation Products.**

**Spirocycle (10a).** Indole (4a) (1.018g, 1.9mmol) was dissolved in dry acetonitrile (40ml) and palladium acetate (0.043g, 0.19mmol), triphenyl phosphine (0.109g, 0.42mmol) tetraethylammonium chloride (0.321g, 1.9mmol), and potassium carbonate (0.533g, 3.9mmol) added. The mixture was stirred and heated at 60°C under an atmosphere of argon for 15h. The solvent was then removed under reduced pressure and the residue partitioned between water (50ml) and ethyl acetate (50ml). The water layer was extracted with ethyl acetate (50ml) and the combined ethyl acetate extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:2 v/v ether-petroleum ether to afford the **product** (0.569g, 74%) as a brown powder which crystallised from ether as off-white needles, m.p. 198-202°C. (Found: N, 6.55; S, 7.75. $C_{24}H_{20}N_2O_2S$ requires N, 7.0; S, 8.0%). Accurate mass: 400.125. $C_{24}H_{20}N_2O_2S$ requires 400.125; δ 7.9-6.7 (m, 13H, ArH), 6.13 (s, 1H, NC=CH), 3.98 and 3.89 (2xd, 2x1H, J 11.3Hz, $SNCH_2$), 3.78 (s, 2H, $CH_2NC=$) and 2.97 (m, 2H, $CH_2C=$); m/z(%) 400 ($M^+$, 63), 277 (56), 270 (100), 130 (94) and 77 (49).

**Spirocycle (10b).** A mixture of indole (4b) (0.20g, 0.36mmol), palladium acetate (0.010g, 0.044mmol), triphenylphosphine (0.022g, 0.084mmol), and potassium acetate (0.073g, 0.75mmol) in anhydrous anisole (15ml) was stirred and heated at 130°C under an atmosphere of dry nitrogen for 24h. The solvent was then removed under reduced pressure and the residue partitioned between ether (50ml) and water (50ml). The aqueous layer was further extracted with ether (50ml) and the combined ether extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with ether to afford the **product** (0.14g, 91%) as a yellow powder which crystallised from ether as yellow plates, m.p. 193-196°C. (Found: C, 69.3; H, 4.8; N, 6.2; S, 7.2. $C_{25}H_{20}O_3S$ requires C, 70.05; H, 4.7; N, 6.55; S, 7.5%). Accurate mass: 428.121. $C_{25}H_{20}N_2O_3S$ requires 428.119; δ 9.96 (s, 1H, CHO), 8.3-6.8 (m, 13H, ArH), 4.2-3.9 (m, 4H, $SNCH_2$ and $CH_2NC=$) and 3.35 and 3.22 (2xd, 2x1H, J 17.5Hz, $CH_2C=$); m/z(%) 428 ($M^+$, 35), 287 (70), 270 (100), 130 (87) and 77 (64).

**Spirocycle (10c).** Prepared from (4c) (0.20g, 0.37mmol) using the same procedure as that used above. The reaction was performed under nitrogen and was complete in 24h. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:2 v/v ether-petroleum ether to afford the product (0.12g, 77%) as off-white powder, m.p. 195-197°C. (Found: C, 70.25; H, 5.25; N, 6.45. $C_{25}H_{22}N_2O_2S$. $0.75H_2O$ requires C, 70.15; H, 5.55; N, 6.55%); δ 7.9-6.8 (m, 13H, ArH), 4.02 and 3.95 (2xd, 2x1H, J 11.1Hz, $SNCH_2$), 3.81 (s, 2H, $CH_2NC$=), 2.99 and 2.88 (2xd, 2x1H, J 15.8Hz, $CH_2C$=) and 2.21 (s, 3H, $CH_3$); m/z(%) 414 ($M^+$, 72), 270 (100), 144 (38), 130 (72) and 77 (51).

**Spirocycle (11a).** Prepared from (5a) (0.20g, 0.42mmol) using the same procedure as that above. The reaction was performed under argon and was complete in 64h. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:2 v/v ether-petroleum ether to afford the product (0.087g, 59%) as a pale yellow powder, which crystallised from ether-petroleum ether as yellow rods, m.p. 144-148°C. (Found: C, 68.55; H, 5.25; N, 7.85. $C_{20}H_{18}N_2O_2S$ requires C, 68.55; H, 5.2; N, 8.0%); δ 8.0-6.8 (m, 9H, ArH), 6.7-5.8 (m, 3H, NCH=CHCH), 3.95 and 3.78 (2x2d, 2x2H, $CH_2NC$= and $SNCH_2$) and 2.89 and 2.77 (2xd, 2x1H, J 15.4Hz, $CH_2C$=); m/z(%) 350 ($M^+$, 70), 270 (86), 166 (41), 130 (100) and 77 (38).

**Spirocycle (11b).** Prepared from (5b) (0.20g, 0.39mmol) using the same procedure as that used above. The reaction was performed under nitrogen and was complete in 24h. The residue was purified by flash chromatography ($SiO_2$) eluting with 2:1 v/v ether-petroleum ether to afford the product (81%) as a pale yellow powder, m.p. 137-139°C. (Found: C, 66.7; H, 4.8; N, 7.25. $C_{21}H_{18}N_2O_3S$ requires C, 66.65; H, 4.79; N, 7.4%); δ 9.40 (s, 1H, CHO), 7.9-6.8 (m, 10H, ArH), 5.99 (d, 1H, J 3.6Hz, $CH_2C$=C<u>H</u>), 4.15 and 4.14 (2xs, 2x1H, $CH_2NC$=), 4.01 and 3.92 (2xd, 1x1H, J 11.1Hz, $SNCH_2$) and 2.89 (s, 2H, $CH_2C$=); m/z(%) 378 ($M^+$, 37), 270 (100), 237 (71), 130 (99) and 77 (66).

**Spirocycle (12).** The N-substituted 4-pyridone (6) (0.20g, 0.39mmol) was dissolved in dry acetonitrile (25ml) and palladium acetate (0.0098g, 0.044mmol), triphenyl phosphine (0.022g, 0.085mmol), potassium carbonate (0.11g, 0.83mmol) and tetraethylammonium chloride (0.068g, 0.41mmol) added. The mixture was boiled under reflux under an atmosphere of nitrogen for 3h. The solvent was then removed under reduced pressure and the residue partitioned between water (50ml) and dichloromethane (50ml). The water layer was extracted with dichloromethane (50ml) and the combined dichloromethane extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with 1:1 v/v methanol-ether to afford the **product** (0.11g, 75%) as a yellow powder which crystallised from methanol ether as pale yellow needles, m.p. 141-143°C. (Found: N, 7.05. $C_{21}H_{18}N_2O_3S$ requires N, 7.40%); δ 7.9-6.9 (m, 10H, ArH and NCH=), 6.4-6.2 (m, 2H, 2xCHC=O), 4.02 and 3.79 (2xd, 2x1H, J 11.1Hz, $CH_2NC$=), 3.92 and 3.85 (2xd, 2x1H, J 11.1Hz, $SNCH_2$) and 3.09 and 2.88 (2xd, 2x1H, J 17.0Hz, $CH_2C$=); m/z(%) 378 ($M^+$, 96), 237 (100), 217 (49), 130 (55) and 77 (96); accurate mass: 378.103. $C_{21}H_{18}N_2O_3S$ requires 378.104.

**Spirocycle (13).** Prepared from the N-substituted 2-pyridone (7) (0.21g, 0.41mmol) using the same procedure as that used for (12) above. The reaction was complete in 3.5h. and the residue purified by flash chromatography ($SiO_2$) eluting with 1:5 v/v methanol-ether to afford the **product** (0.12g, 80%) as yellow plates, m.p. 81-85°C. (Found: C, 66.35; H, 4.65; N, 7.0. $C_{21}H_{18}N_2O_3S$ requires C, 66.64; H, 4.79; N, 7.40%); δ 7.9-6.9 (m, 10H, ArH and C<u>H</u>=CHCO), 6.44 and 6.09 (2xd, 2x1H, J 9.0Hz and J 6.5Hz, 2xC=CH), 4.03 (s, 2H, $CH_2NCO$), 3.97 and 3.81 (2xd, 2x1H, J 10.9Hz, $SNCH_2$) and 3.06 (s, 2H, $CH_2C$=); m/z(%) 378 ($M^+$, 54), 270

(72), 237 (100), 141 (41) and 77 (55).

**Spirocycle (15).** Prepared from (14) by the procedure used for (12) above. The reaction was complete after 16h. Work-up in the usual way followed by preparative t.l.c. eluting with ether-petroleum ether afforded a pale yellow solid. Crystallisation from ether-petroleum ether afforded the product (0.25g, 68%) as pale yellow prisms, m.p. 176-178°C. (Found: C, 67.9; H, 4.7; N, 3.55. $C_{23}H_{19}NO_4S$ requires C, 68.15; H, 4.7; N, 3.45%); δ 10.4 (s, 1H, CHO), 7.8-6.9 (m, 12H, ArH), 4.01 (d, 1H, J 10.1Hz, OCH), 3.92 and 3.74 (2xd, 2x1H, J 10.75Hz, $NCH_2$), 3.6 (d, 1H, OCH), 3.04 and 2.5 (2xd, 2x1H, $ArCH_2$); m/z(%) 405 ($M^+$, 77), 271 (45), 270 (45), 264 (47), 235 (16), 204 (14), 148 (15), 130 (100), 129 (21), 117 (10), 103 (20), 91 (23) and 77 (72).

**Spirocycle (17).** Pyridyl ether (16) (0.14g, 0.27mmol) was dissolved in dry acetonitrile (20ml) and palladium acetate (0.0068g, 0.030mmol), triphenyl phosphine (0.015g, 0.056mmol), potassium carbonate (0.075g, 0.54mmol) and tetraethylammonium chloride (0.047g, 0.28mmol) added. The mixture was boiled under reflux under an atmosphere of nitrogen for 17h. The solvent was then removed under reduced pressure and the residue partitioned between water (30ml) and ether (30ml). The aqueous layer was extracted with ether (30ml) and the combined ether extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with ether to afford the **product** (0.72g, 68%) as a pale yellow powder, m.p. 90-94°C. (Found: C, 67.2; H, 5.6. $C_{22}H_{20}N_2O_3S$ requires C, 67.3; H, 5.15%); δ 7.9-6.9 (m, 10H, ArH and $CH_3C$=C-C<u>H</u>), 6.78 (d, 1H, J 7.4Hz, $CH_3CC$<u>H</u>), 4.03 and 3.95 (2xd, 2x1H, J 11.2Hz, $NCH_2$), 3.64-3.58 (m, 2H, $OCH_2$), 3.00 and 2.49 (2xd, 2x1H, J 15.2Hx, OC=$CCH_2$) and 2.46 (s, 3H, $CH_3$); m/z(%) 392 ($M^+$,25), 270 (47), 251 (58), 130 (100) and 77 (73).

**Spirocycle (20a).** The N-substituted 2-aminomethylfuran (18a) (0.41g, 0.63mmol) was dissolved in dry acetonitrile (30ml) and palladium acetate (0.015g, 0.066mmol), triphenyl phosphine (0.034g, 0.13mmol), thallium acetate (0.169g, 0.64mmol) and tetraethylammonium chloride (0.106g, 0.64mmol) added. The mixture was boiled under reflux under an atmosphere of nitrogen with stirring for 15h. The solvent was then removed under reduced pressure and the residue partitioned between water (50ml) and ethyl acetate (50ml). The water layer was extracted with ethyl acetate (50ml) and the combined ethyl acetate extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$) eluting with 4:1 v/v ether-petroleum ether to afford the **product** (0.211g, 64%) as a pale yellow powder which crystallised from ether-petroleum ether as colourless needles, m.p. 219-222°C. (Found: C, 62.3; H, 4.6; N, 5.35. $C_{27}H_{24}N_2O_5S_2$ requires C, 62.3; H, 4.65; N, 5.4%); δ 8.0-6.9 (m, 15H, ArH and OCH), 6.02 (s, 1H, CH=CO), 4.85 and 3.88 (2xd, 2x1H, J 15.0Hz, $ArCC$<u>$H_2$</u>$NCH_2$), 4.20 and 3.74 (2xd, 2x1H, J 11.2Hz, $ArNCH_2$), 3.71 and 2.99 (2xd, 2x1H, J 13.9Hz, $CH_2C$=CO) and 2.53 (s, 2H, $CH_2CO$); m/z(%) 520 ($M^+$, 18), 349 (64), 208 (98), 180 (55) and 77 (100).

**Spirocycle (20b).** The N-substituted 2-aminomethylthiophen (18b) (0.628g, 0.95mmol), was dissolved in dry DMF (30ml) and palladium acetate (0.23g, 0.10mmol), triphenylphosphine (0.051g, 0.19mmol), tetraethylammonium chloride (0.157g, 0.95mmol) and thallium acetate (0.501g, 1.9mmol) added. The mixture was stirred and heated at 100°C under an atmosphere of nitrogen for 9h. Work up as above followed by flash chromatography eluting with 10:1 v/v toluene-diethyl ether afforded the **product** (0.208g, 41%) as a pale yellow powder which crystallised from ether-petroleum ether as colourless needles, m.p. 232-233°C. (Found: C, 60.35; H, 4.45; N, 5.15. $C_{27}H_{24}N_2O_4S_3$ requires C, 60.4; H, 4.5; N, 5.2%); δ 8.0-6.8 (m, 15H, ArH and SCH, 6.57 (d, 1H, J 5.0Hz, CH=CS), 4.85 and 4.05 (2xd, 2x1H, J 15.3Hz, $ArCC$<u>$H_2$</u>$NCH_2$), 4.03 and 3.64 (2xd, 2x1H, J

11.2Hz, $ArNCH_2$), 3.72 and 3.10 (2xd, 2x1H, J 13.6Hz, $CH_2C{=}CS$) and 2.84 (s, 2H, $CH_2CS$); m/z(%) 536 ($M^+$, 10), 365 (52), 224 (100), 110 (44) and 77 (72).

**Monocyclisation Product (21).** A mixture of the N-substituted 2-aminomethylfuran (18a) (1.5g, 1.6mmol), palladium acetate (0.037g, 0.17mmol), triphenylphosphine (0.086g, 0.33mmol), tetraethylammonium chloride (0.271g, 1.6mmol) and sodium formate (0.111g, 1.6mmol) in anhydrous acetonitrile (45ml) was boiled under reflux with stirring under an atmosphere of nitrogen for 15h. The solvent was then removed under reduced pressure and the residue partitioned between ethyl acetate (50ml) and water (50ml). The aqueous layer was further extracted with ethyl acetate (50ml) and the combined ethyl acetate extracts dried ($Na_2SO_4$) and evaporated. The residue was purified by flash chromatography eluting with ether to afford the **product** (0.511g, 60%) as colourless prisms from ether, m.p. 102-104°C (Found: C, 61.9; H, 5.0; N, 5.0; S, 12.05. $C_{27}H_{28}N_2O_5S_2$ requires C, 62.05; H, 5.0; N, 5.35; S, 12.25%); δ 8.0-6.9 (m, 15H, ArH and furan-H), 6.11 and 5.77 (m and d, 2 x 1H, furan-H), 4.24 and 3.37 (2 x d, 2 x 1H, J 10.6Hz, $NCH_2$), 4.04 and 3.78 (2 x d, 2 x 1H, J 16.3Hz, $NCH_2$), 3.45 and 3.28 (2 x d, 2 x 1H, J 15.0Hz, $NCH_2$) and 1.23 (s, 3H, Me).

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