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Ortho-METALLATION REACTIONS OF VARIOUS *N*-SUBSTITUTED PYRROLES

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Summary

Two routes for the preparation of 2,3-disubstituted pyrroles have been explored. The first involves the directed palladation of a 2-dimethylaminomethylpyrrole and the second the lithiation of a 2-oxazolinopyrrole.

Introduction

In general, electrophilic substitution of pyrrole and its 1-substituted derivatives occurs predominantly at the 2-position [1]. The reactivity of the β-position in pyrrole can be enhanced by the presence of an electron-withdrawing group in the 2-position leading to substantial amounts of 2,4-disubstituted products [2,3]. Furthermore, large alkyl groups on nitrogen sterically hinder attack of the electrophile at the α-position, so that β-substitution can predominate in some cases [4]. However, where a 2,3-disubstitution pattern has been sought, recourse has usually been made to synthesis of the pyrrole ring from acyclic precursors in which the desired groups or suitable equivalents are already present [5]. The present study describes application of the directed metallation reaction towards the synthesis of 2,3-disubstituted pyrroles since this substitution pattern is not readily available by existing methodology.

Discussion

Heterocyclic substrates with *ortho* directing substituents may undergo competitive α- or *ortho*-lithiation depending on the choice of directing group and reaction conditions [6,7]. In general, however, most *ortho* directing groups are unable to compete with α-activation [6]. In accord with this expectation, we have found that lithiation of 2-dimethylaminomethyl-1-methylpyrrole (I) with n-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine

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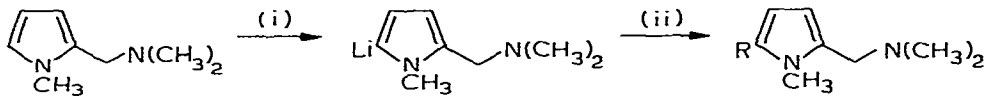
(TMEDA) followed by treatment with deuterium oxide or benzophenone gave the 2,5-disubstituted pyrroles II and III as major products (eq. 1).



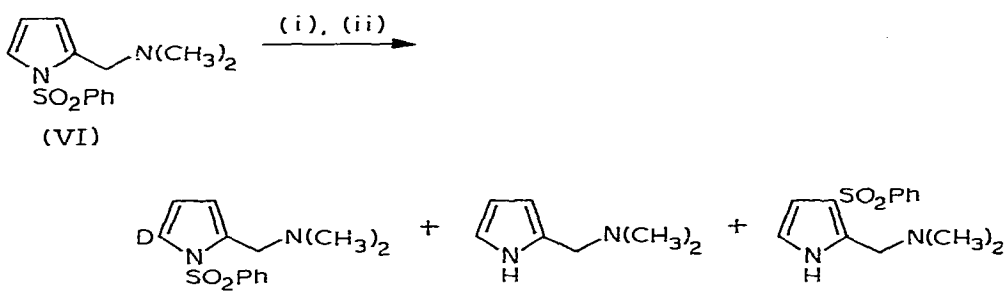
(I) (II R = D; III R = C(OH)Ph_2) (1)

((i) n-BuLi/TMEDA, (ii) D_2O or Ph_2CO)

Analysis of reaction products from the deuterium oxide experiment by ^2H NMR indicated 31% deuteration at the 5-position. Furthermore, the presence of minor amounts of products deuterated at the *N*-methyl (IV) and methylene groups (V) was inferred from the ^2H NMR spectrum.

(IV) (V)

The Mannich base VI was prepared from the potassium salt of 2-dimethylaminomethylpyrrole and benzenesulphonyl chloride in THF [8]. Lithiation of pyrrole VI with n- or t-butyllithium under a variety of reaction conditions resulted in substantial amounts of products arising from cleavage of the 1-benzenesulphonyl protecting group [9] (eq. 2). In one case (4 molar excess of t-butyllithium) quenching of the reaction mixture with D_2O gave a low yield of the 2,5-disubstituted pyrrole (VII).



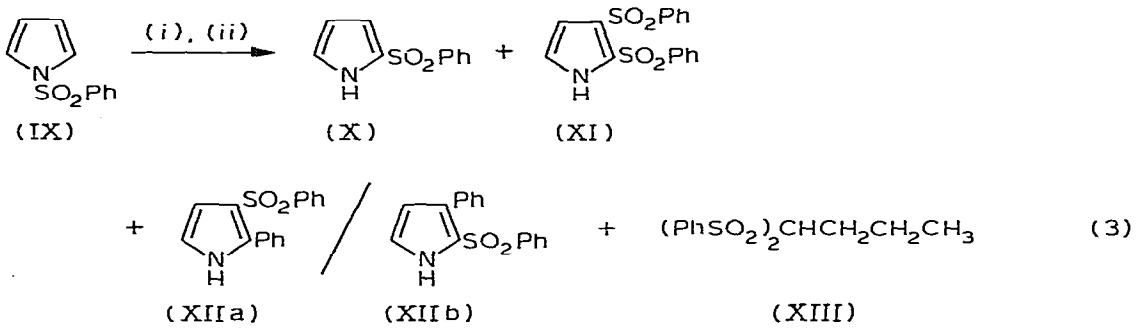
(VI) (VII) (VIII) (2)

((i) t-BuLi/TMEDA, (ii) D_2O)

The magnitude of the coupling of the pyrrolic hydrogens (2.7 Hz) tends to support the 2,3-disposition of substituents in the cleavage product (VIII).

In view of the low reactivity of the pyrrole VI towards lithiating reagents, the behaviour of 1-benzenesulphonyl pyrrole IX was investigated. Concurrently with our work in this area, Levy et al. [10] reported that 1-benzenesulphonylpyrrole undergoes cleavage reactions upon treatment with various lithiating reagents. We have isolated in low yield several novel cleavage products arising

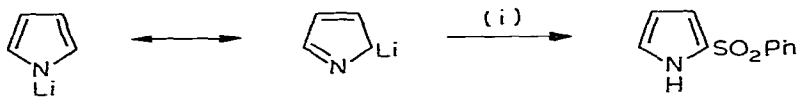
from these reactions (eq. 3).



(IX) (X) (XI) (XIIa) (XIIb) (XIII) (3)

((i) n-BuLi/TMEDA, (ii) D_2O)

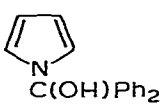
The formation of 2-benzenesulphonylpyrrole X may be rationalised through the reaction of the pyrryl anion XIV with a second molecule of 1-benzenesulphonyl pyrrole (eq. 4).



(XIV) (X) (4)

((i) 1-benzenesulphonylpyrrole)

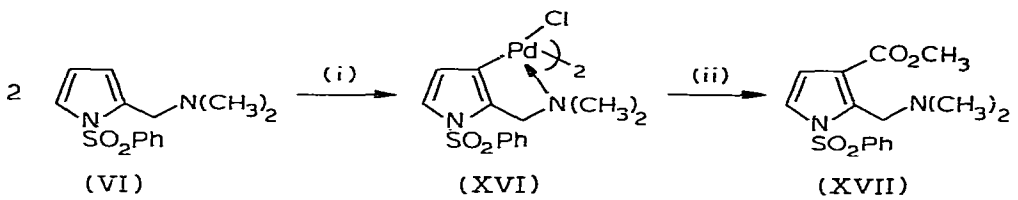
Lithiation of 2-benzenesulphonylpyrrole X then leads to the formation of 2,3-dibenzenesulphonylpyrrole XI. The 2-benzenesulphonyl group would be expected to inductively activate the adjacent 3-position in the pyrrole ring. An unexpected product XIIa or its positional isomer XIIb was also isolated in addition to the previously reported side-product, 1,1-dibenzenesulphonylbutane XIII [9]. Treatment of 1-benzenesulphonylpyrrole with n-butyllithium followed by quenching with benzophenone led to the isolation of the 1-diphenylcarbinol XV.



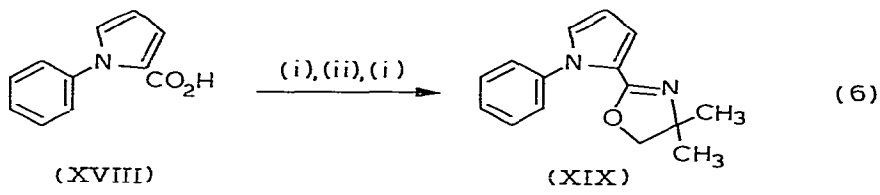
(XV)

The *ortho* palladation reaction has provided a convenient route to selectively *ortho*-disubstituted aromatic compounds difficult to prepare by conventional methods [11,12]. The 1-benzenesulphonylpyrrole Mannich base VI was readily *ortho* palladated with lithium tetrachloropalladate. The palladium complex XVI gave the correct elemental analysis and the ^1H NMR spectrum of the compound revealed two doublets at δ 7.0 and 6.1 ppm ($J_{4,5}$ ca. 3.3 Hz). Carbonylation of XVI with carbon monoxide in methanol [12a] gave an ester XVII in good yield (eq. 5).

The *ortho* palladation of suitably substituted pyrroles is an unexplored area and the potential of this reaction is currently under investigation in these laboratories.



The *ortho* lithiation of thiophen and pyridine nuclei has been successfully achieved with a 2-oxazoline substituent [7,13]. Accordingly, 2-(1-phenyl-2-pyrrolyl)-oxazoline (XIX) was prepared from 1-phenylpyrrole-2-carboxylic acid (XVIII) [14] (eq. 6).



Treatment of the oxazoline XIX with n-butyllithium in ether or THF followed by reaction with several electrophiles gave a mixture of 3- and 5-substituted products (eq. 7). Results of these lithiation reactions are summarised in Table 1.

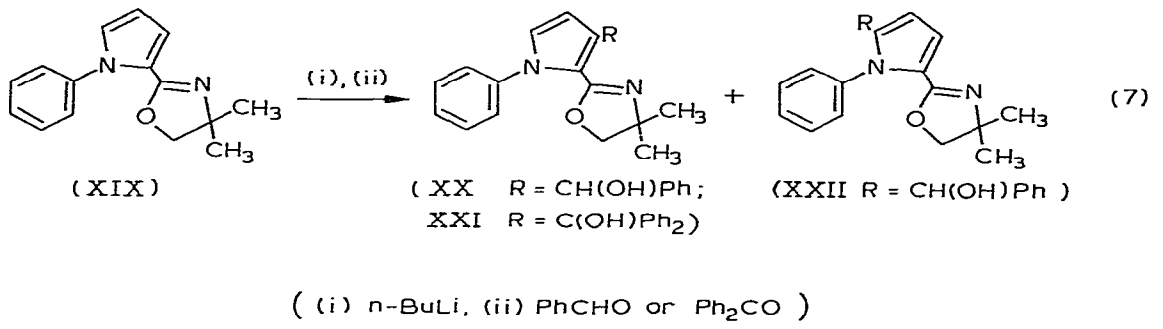


TABLE 1

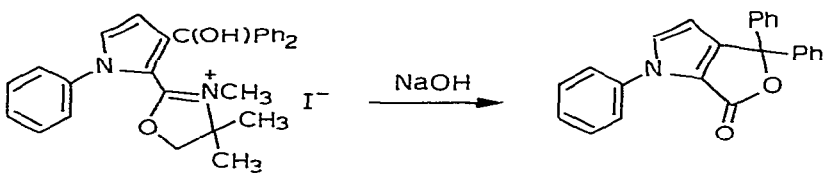
LITHIATION REACTIONS OF THE OXAZOLINE XIX

Solvent	Electrophile	% Recovered Oxazoline	% Adducts	
			3-isomer	5-isomer
THF	Benzaldehyde	33	32	5
Et_2O	Benzaldehyde	52	39	11
THF	Benzophenone [a]	51	22	—

[a] The lithiating reagent was n-BuLi-TMEDA.

Lithiation of the oxazoline XIX followed by condensation with benzaldehyde gave mixtures of products with the desired isomer XX being favoured. The isomers XX and XXII were readily separated by column chromatography and fully-coupled ^{13}C NMR spectra revealed $^{1}J(CH)$ values of 188 Hz (α-carbon) and 173/174 Hz (β-carbons) which supports the structural assignment [15].

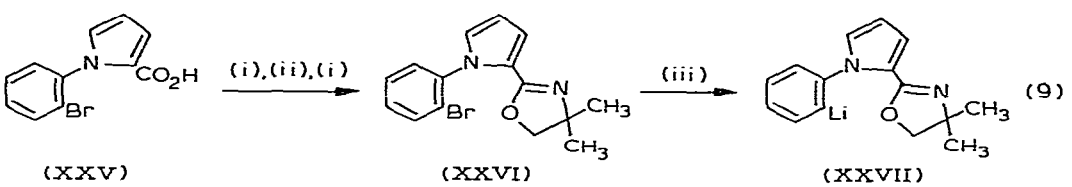
Removal of the oxazoline protecting-group was effected by conversion to the methyl iodide salt followed by basic hydrolysis with sodium hydroxide [16]. In this way the oxazoline XIX was hydrolysed to the parent acid XVIII in moderate yield. Conversion of the benzophenone adduct XXI to the methyl iodide salt XXIII followed by basic hydrolysis gave an intermediate acid which cyclised spontaneously to the lactone XXIV during the isolation procedure (eq. 8).



(XXIII) (XXIV) (8)

However, hydrolysis of the methiodide of the benzaldehyde adduct XX gave a product from which neither the pure acid nor the corresponding lactone could be isolated.

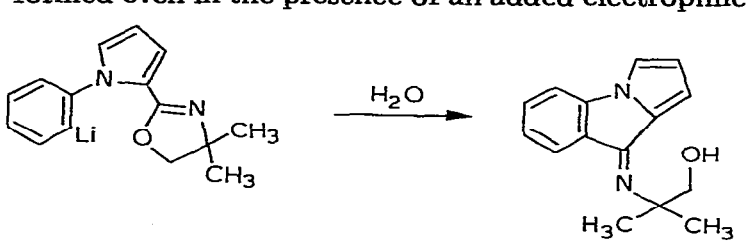
Meyers has demonstrated that bromophenyloxazolines may be converted into the Grignard reagents with the carboxyl group safely protected [14]. It was anticipated that similar masking of the carboxyl group in the pyrrole XXV [17] followed by lithium—bromine exchange and reaction with a suitable electrophile might lead to selective substitution on the phenyl ring (eq. 9).



(XXV) (XXVI) (XXVII) (9)

((i) $SOCl_2$, (ii) 2-amino-2-methylpropanol, (iii) n-BuLi)

However, the aryl lithium XXVII reacted intramolecularly, cleaving the carbon—oxygen bond in the oxazoline ring (eq. 10). The cyclic imine XXVIII was formed even in the presence of an added electrophile such as benzaldehyde.



(XXVII) (XXVIII) (10)

Experimental

All reactions involving organolithium reagents were performed under dry nitrogen in a two-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and rubber septum cap. Tetrahydrofuran was dried by distilling from sodium benzophenone ketyl.

M.p's were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Unicam SP200 spectrometer for potassium bromide discs, unless otherwise specified. ^{1}H NMR spectra were recorded at 60 MHz on a Perkin—Elmer R12B spectrometer unless stated otherwise, with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker WP 60 spectrometer operating at 15.08 MHz with wide band decoupling unless otherwise specified.

Mass spectra were recorded at 70 eV on an AEI MS 30 mass spectrometer. Column chromatography was carried out with Merck silica gel 60, particle size 0.063—0.200 mm, 70—230 mesh ASTM, catalogue no. 7734. Preparative layer chromatography was performed with Schleicher and Schüll Kieselgel (F 1500 LS 254).

Lithiation of 2-dimethylaminomethyl-1-methylpyrrole (I) with the n-butyllithium/TMEDA complex

The n-butyllithium/TMEDA complex was generated at 0°C by adding n-butyllithium (17.9 ml of a 1.57 *M* solution in hexane, 0.028 mol) to a solution of TMEDA (3.3 g, 0.028 mol) in dry diethyl ether (7 ml). After stirring at 0°C/10 min, the pyrrole I (3.5 g, 0.025 mol) [18] in dry diethyl ether (30 ml) was added and stirring continued at 0°C/30 min and room temperature/3 h. The reaction was quenched with benzophenone (4.7 g, 0.026 mol) in diethyl ether (30 ml). The reaction was stirred at room temperature/16 h, poured into water (150 ml) and the ether and water layers separated. The aqueous layer was extracted with diethyl ether (2 × 60 ml) and the ether extracts were combined, dried and evaporated giving the crude diphenylcarbinol III which crystallised from methanol/hexane as white needles (2.6 g, 32%), m.p. 155—156°C. Concentration of the mother liquor gave further product (0.69 g) (total yield 41%). Anal. Found: C, 78.8; H, 7.6; N, 8.8; $C_{21}H_{24}N_2O$ calcd.: C, 78.8; H, 7.5; N, 8.8%. IR: 3000br (O—H).

^{1}H NMR (DMSO-d_6): 7.3(s, 10H, benzenoid H); 6.5(s, 1H, O—H) exchangeable with D_2O); 5.8(d, $J_{3,4}$ 4 Hz, 1H, H(3)); 5.1(d, $J_{3,4}$ 4 Hz, 1H, H(4)); 3.3(br, 5H, methylene H and N(1)—CH_3); 2.1(s, 6H, $N(CH_3)_2$).

^{13}C NMR (DMSO-d_6): 146.4, 139.4, 127.5, 126.8(benzenoid C) 123.3(C(5)); 111.1, 110.3(C(3) and C(4)); 77.2(methylene C); 50.6(N(1)—CH_3); 32.7 ($N(CH_3)_2$).

m/e: 320(11%, M^+), 276(100%, $M^+ - N(CH_3)_2$), 198(16%, $M^+ - N(CH_3)_2 - C_6H_6$), 170(23%, $M^+ - N(CH_3)_2 - PhCOH$), 105(66%, $C_6H_5CO^+$), 94(67%, $M^+ - N(CH_3)_2 - (C_6H_5)_2CO$).

2-Dimethylaminomethyl-1-benzenesulphonylpyrrole (VI)

A stirred mixture of 2-dimethylaminomethylpyrrole (10.2 g, 0.08 mol) [19], potassium (3.5 g, 0.09 mol) and dry THF (120 ml) was refluxed under

nitrogen until all the potassium had reacted (5 h). The suspension was cooled in an ice bath and benzenesulphonyl chloride (14.5 g, 0.08 mol) in dry THF (40 ml) was added dropwise over 30 min. The mixture was stirred overnight at room temperature, filtered and filtrate concentrated. The resultant reddish oil was chromatographed on silica gel using chloroform as eluent. The product (crude yield 81%) was recrystallised from hexane giving white needles (9.6 g, 44%), m.p. 67—68°C. R_f 0.61 (methanol). Anal. Found: C, 59.1; H, 6.2; N, 10.6; $C_{13}H_{16}N_2SO_2$ calcd.: C, 59.1; H, 6.1; N, 10.6%.

IR: 1350s, 1170s (SO_2—N).

^{1}H NMR ($CDCl_3$): 7.8—8.1(m, 2H, benzenoid H); 7.3—7.7(m, 4H, benzenoid H and H(5)); 6.2(m, 2H, H(3) and H(4); 3.5(s, 2H, methylene H); 1.9(s, 6H, $N(CH_3)_2$).

^{13}C NMR (DMSO-d_6): 138.9 (quaternary benzenoid C); 133.7, 128.9, 126.7 (benzenoid C); 132.3(C(2)); 123.3(C(5)); 114.9(C(3)); 111.0(C(4)), 54.2 (methylene C); 43.8($N(CH_3)_2$).

m/e: 264(28%, M^+), 220(84%, $M^+ - N(CH_3)_2$), 141(77%, $SO_2C_6H_5^+$), 123(33%, $M^+ - SO_2C_6H_5$), 77(100%, $C_6H_5^+$).

Lithiation of 2-dimethylaminomethyl-1-benzenesulphonyl-pyrrole (VI) with the t-butyllithium/TMEDA complex

The t-butyllithium/TMEDA complex was formed at 0°C from t-butyllithium (12.6 ml of a 1.47 *M* solution in pentane, 18.6 mmol) and TMEDA (2.2 g, 18.6 mmol) in dry THF (8 ml). After 15 min, a solution of the pyrrole VI (1.2 g, 4.6 mmol) in THF (30 ml) was added and stirring was continued at 0°C/15 min and room temperature/3 h. The dark orange solution was cooled in ice and was quenched with D_2O (3 ml). The mixture was stirred at room temperature/30 min, poured into water (50 ml), diluted with ether (50 ml) and the layers separated. The aqueous layer was extracted with ether (50 ml) and the combined ether extracts were dried and evaporated giving a brown oil (1.3 g). Chromatography on silica gel (40 g) using chloroform followed by methanol as eluent, gave the following components, listed in order of elution:

(i) 2-Dimethylaminomethyl-1-benzenesulphonylpyrrole. Obtained in 34% yield (0.4 g). ^{1}H NMR integration indicated 11% deuterium incorporation.

(ii) 2-Dimethylaminomethyl-3-benzenesulphonylpyrrole (VIII). This cleavage product was obtained as a brown oil (0.1 g, ca. 11%) which resisted further purification.

IR (film): 3400s (N—H), 1360s, 1180s (SO_2—N)

^{1}H NMR (CD_3OD/D_2O): 7.4—8.1(m, 6H, benzenoid H and H(5)); 6.3 (d, $J_{4,5}$ 2.7 Hz, 1H, H(4)); 3.7(s, 2H, methylene H); 1.2(s, 6H, $N(CH_3)_2$).

m/e: 264(3%, M^+), 220(11%, $M^+ - N(CH_3)_2$), 141(37%, $SO_2C_6H_5^+$), 123(27%, $M^+ - SO_2C_6H_5$), 77(100%, $C_6H_5^+$).

Lithiation of 1-benzenesulphonylpyrrole (IX) with the n-butyllithium/TMEDA complex

The butyllithium/TMEDA complex was formed at 0°C by adding n-butyllithium (1.2—2.5 molar excess) to a solution of TMEDA in THF (5 ml). The pyrrole IX (1.4—1.6 g, 7—8 mmol) [8] in THF (20—30 ml) was added to the butyllithium/TMEDA complex and the reaction mixture was stirred at 0°C/

30 min and room temperature/3 h. The reaction was quenched with D_2O (2—5 ml) and stirring continued at room temperature/30 min. The mixture was poured into water (60 ml) and the layers separated. The aqueous layer was extracted with ether (2 × 50 ml) and the combined extracts were dried and evaporated. The crude mixture was subjected to chromatography on silica gel (40—100 g) using chloroform followed by methanol as eluent.

(a) With n-butyllithium/TMEDA (1.2 mol). In addition to unreacted 1-benzenesulphonylpyrrole IX (37%) the following cleavage/rearrangement products were isolated:

(i) 2-Benzenesulphonylpyrrole (X). Purified by preparative layer chromatography in chloroform, followed by sublimation at 80—85°C/0.5 mmHg, giving a white solid (58 mg, 3%), m.p. 101—102°C. R_f 0.19 (chloroform). Anal. Found: C, 58.2; H, 4.6; N, 6.4; $C_{10}H_9NSO_2$ calcd.: C, 58.0; H, 4.3; N, 6.7%.

IR (film): 3300s(N—H), 1320s, 1160s (SO_2—N).

^{1}H NMR ($CDCl_3/D_2O$): 7.4—8.0(m, 5H, benzenoid H); 6.9(m, 2H, H(3) and H(5); 6.3(m, 1H, H(4)).

m/e: 207(37%, M^+), 143(21%, $M^+ - SO_2$), 125(9%), 82(100%).

(ii) 2-Benzenesulphonyl-3-phenylpyrrole (XIIa) or its positional isomer (XIIb). Obtained as a reddish oil which was purified by preparative layer chromatography in chloroform and recrystallised from diethyl ether giving white needles (50 mg, 2%), m.p. 138—141°C. R_f 0.35 (chloroform). Anal. Found: C, 67.4; H, 4.7; N, 4.8; $C_{16}H_{13}NSO_2$ calcd.: C, 67.8; H, 4.6; N, 4.9%.

IR: 3250s (N—H), 1310s, 1140s (SO_2—N).

^{1}H NMR ($CDCl_3/D_2O$): 8.0(m, 2H, benzenoid H); 7.5(m, 8H, benzenoid (H); 7.0(d, $J_{4,5}$ 3 Hz, 1H, H(5)); 6.6(d, $J_{4,5}$ 3 Hz, 1H, H(4)).

m/e: 283(73%, M^+), 219(24%, $M^+ - SO_2$), 158(70%), 115 (100%, $M^+ - SO_2 - C_6H_5 - HCN$).

(b) With n-butyllithium/TMEDA (2.5 mol). The following components were isolated:

(i) 1-Benzenesulphonylpyrrole (IX). Obtained in 37% yield (0.85 g). Mass spectral analysis indicated that the product was polydeuterated.

(ii) 2,3-Dibenzenesulphonylpyrrole (XI). Crystallised from diethyl ether to give faintly pink needles (46 mg, ca. 1%), m.p. 142—144°C. R_f 0.28 (chloroform). Anal. Found: C, 55.2, H, 3.8; N, 4.3; $C_{16}H_{13}NS_2O_4$ calcd.: C, 55.3; H, 3.7; N, 4.0%.

IR: 3400w(N—H), 1380s, 1320s, 1180s, 1140s, (SO_2—N).

^{1}H NMR (250 MHz, $CDCl_3$): 8.0(m, 4H, benzenoid H); 7.6(m, 6H, benzenoid H); 7.3(d, $J_{4,5}$ 3.3 Hz, 1H, H(5)); 6.4(d, $J_{4,5}$ 3.3 Hz, 1H, H(4)).

m/e: 347(11%, M^+), 206(3%, $M^+ - SO_2C_6H_5$), 141(57%, $SO_2C_6H_5^+$), 77(100%, $C_6H_5^+$).

Lithiation of 1-benzenesulphonylpyrrole (IX) with n-butyllithium

To a stirred, cooled solution of pyrrole IX (1.4—1.6 g, 7—8 mmol) in dry ether (30 ml) was added n-butyllithium (10% molar excess in hexane). The solution was maintained at 35°C for 18 h and quenched with benzophenone (1.3—1.4 g, 7—8 mmol) in ether (20 ml). Stirring was continued at room temperature for 3.5 h. The reaction mixture was poured into water (20 ml) and extracted with ether (2 × 30 ml). The combined ether extracts were

dried and evaporated giving a yellow oil which was chromatographed on silica gel (120 g) using chloroform followed by methanol as eluent. In addition to unreacted 1-benzenesulphonylpyrrole IX (0.3—0.4 g, 20—28%) and 1,1-dibenzenesulphonylbutane XIII (0.7—0.8 g, 57—67%) [9], the diphenyl (1-pyrryl) carbinol XV was isolated from the reaction mixture. This product was purified by sublimation at 110—120°C/0.1 mmHg, giving a white solid (0.22 g, 11%), m.p. 120—124°C. R_f 0.30 (benzene). Anal. Found: C, 81.7; H, 6.2; N, 5.6; $C_{17}H_{15}NO$ calcd.: C, 81.9; H, 6.0; N, 5.6%.

IR: 3400s (O—H).

^{1}H NMR ($CDCl_3$): 7.3(m, 10H, benzenoid H); 6.6(m, 2H, H(2) and H(5)); 6.2(m, 2H, H(3) and H(4)).

m/e: 249(15%, M^+), 232(43%, $M^+ - OH$), 182(22%, $(C_6H_5)_2CO^+$), 105(100%, $C_6H_5CO^+$), 77(60%, $C_6H_5^+$).

Di-μ-chloro-bis(2-dimethylaminomethyl-1-benzenesulphonylpyrrole-3-C,N)-dipalladium (II) (XVI).

A solution of 2-dimethylaminomethyl-1-benzenesulphonylpyrrole VI (1.25 g, 4.72 mmol) in methanol (20 ml) was mixed with a solution of lithium tetrachloropalladate (II) (2.36 mmol) in methanol (20 ml). The red solution rapidly became lighter in colour and a yellow precipitate was formed. After stirring at room temperature/21 h the complex XVI was filtered and recrystallised from chloroform/hexane giving yellow prisms (0.87 g, 91%), m.p. 156—158°C (dec.). Concentration of the mother liquor gave further product (0.063 g, total yield 98%). Anal. Found: C, 39.0; H, 3.9; N, 6.7; $C_{13}H_{15}N_2SO_2PdCl$ calcd.: C, 38.5; H, 3.7; N, 6.9%.

^{1}H NMR ($CDCl_3$): 7.6(m, 5H, benzenoid H); 7.0(d, $J_{4,5}$ 3.3 Hz, 1H, H(5)); 6.1(d, $J_{4,5}$ 3.3 Hz, 1H, H(4)); 3.9(s, 2H, methylene H); 2.8(s, 6H, $N(CH_3)_2$).

In a similar run using equimolar amounts of the pyrrole VI (1.13 g, 4.30 mmol) and lithium tetrachloropalladate (II) (4.33 mmol) in the presence of triethylamine (0.87 g, 8.60 mmol), there was obtained after 19 h a grey solid which was dissolved in hot chloroform. Chloroform-insoluble material was removed by filtration and the filtrate gave the crude palladium complex XVI (1.10 g, 63%). Recrystallisation from chloroform/hexane afforded yellow prisms (0.72 g, 41%).

Carbonylation of the palladium complex (XVI)

The palladium complex XVI (0.31 g, 0.77 mmol) was suspended in methanol (20 ml) and carbon monoxide was bubbled into the suspension at room temperature/1 atmosphere/1 h. The suspension darkened within minutes. The palladium residue was filtered and the solvent was removed from the filtrate. The oily residue thus obtained, was dissolved in chloroform (50 ml) and washed with dilute sodium bicarbonate. The chloroform layer was dried and evaporated giving the ester XVII as an oil which crystallised from pentane as white needles (0.17 g, 69%), m.p. 86—87°C. Anal. Found: C, 55.8; H, 5.6; N, 8.6; $C_{15}H_{18}N_2SO_4$ calcd.: C, 55.9; H, 5.6; N, 8.7%.

IR (film): 1710s (C=O).

^{1}H NMR ($CDCl_3$): 7.5—8.0(m, 6H, benzenoid H and H(5)); 6.6(d, $J_{4,5}$ 3.3 Hz, 1H, H(4)); 4.0(s, 2H, methylene H); 3.7(s, 3H, $COOCH_3$); 1.8(s, 6H, $N(CH_3)_2$).

m/e: 322(11%, M^+), 307(100%, $M^+ - CH_3$), 291(22%, $M^+ - OCH_3$), 275(42%), 264(14%, $M^+ - CH_2N(CH_3)_2$), 220(78%, $M^+ - CH_2N(CH_3)_2 - CO_2$), 181(51%, $M^+ - SO_2C_6H_5$), 137(27%, $M^+ - SO_2C_6H_5 - CO_2$), 77(49%, $C_6H_5^+$).

1-Phenylpyrrole-2-carboxylic acid (XVIII)

1-Phenyl-2-trifluoroacetylpyrrole [4] was hydrolysed by refluxing for 3 h with sodium hydroxide (10 fold molar excess) in aqueous ethanol (1/1) according to the procedure described by Sonnet [20]. The solution was concentrated to approximately 50% volume and acidified with 5 *M* hydrochloric acid. Extraction was performed with ether, and the combined ether extracts were dried and evaporated giving a buff-coloured solid which was used without further purification.

IR: 1660s (C=O).

2-(1-Phenyl-2-pyrrolyl)-4,4-dimethyl-oxazoline (XIX)

To a suspension of 1-phenylpyrrole-2-carboxylic acid (XVIII) (30.1 g, 0.16 mol) in benzene (100 ml) was added over 15 min a solution of thionyl chloride (192 g, 1.6 mol) in benzene (80 ml). The mixture was stirred at 75°C/45 min. Excess thionyl chloride and solvent was removed under reduced pressure giving the crude acid chloride as a brownish oil (γ(C=O) 1730 cm^{-1}). The acid chloride in dichloromethane (200 ml) was added dropwise to a stirred solution of 2-amino-2-methyl-1-propanol (46.7 g, 0.52 mol) in dichloromethane (200 ml) at 0°C. The mixture was stirred at room temperature/2 h. The white precipitate was filtered and washed with dichloromethane. The filtrate was washed with water, dried and concentrated giving the crude amide (γ(C=O) 1630 cm^{-1}). A stirred suspension of the amide in benzene (200 ml) was cooled in ice and thionyl chloride (67.0 g, 0.56 mol) in benzene (100 ml) was added dropwise. Stirring was continued at room temperature/1 h. The mixture was concentrated to one-third volume and the hydrochloride salt was neutralised with 1 *M* sodium hydroxide (500 ml) and extracted with ether (3 × 300 ml). The ether layer was dried and evaporated giving the oxazoline XIX as a pale yellow solid (35.8 g, 93% crude yield). Trituration with ether/hexane gave chromatographically-pure yellow solid (26.6 g, 69%). Analytically-pure oxazoline XIX, m.p. 87—90°C, was obtained by recrystallisation from hexane. Anal. Found: C, 74.9; H, 6.7; N, 11.6; $C_{15}H_{16}N_2O$ calcd.: C, 75.0, H, 6.7; N, 11.7%.

IR: 1660s (C=N).

^{1}H NMR ($CDCl_3$): 7.4(s, 5H, benzenoid H); 6.9(m, 2H, H(3) and H(5)); 6.3(m, 1H, H(4)); 3.8(s, 2H, methylene H); 1.2(s, 6H, 2 × CH_3).

^{13}C NMR ($CDCl_3$): 156.2(C=N); 140.7(quaternary benzenoid C); 128.5, 127.1, 125.6 (benzenoid C and C(5)); 121.7(C(2)); 116.1(C(3)); 109.3(C(4)); 78.4(CH_2); 67.3($C(CH_3)_2$); 28.0(CH_3).

m/e: 240(41%, M^+), 239(67%, $M^+ - 1$), 225(100%, $M^+ - CH_3$), 197(37%, $M^+ - C(CH_3)_2 - H$), 168(24%, $M^+ - C_4H_8O$), 154(43%, $M^+ - C_4H_8NO$), 115(27%, $M^+ - C_5H_8NO - HCN$), 77(43%, $C_6H_5^+$).

Lithiation of the oxazoline (XIX) (Table 1)

To a solution of the oxazoline (XIX) (0.96—1.2 g, 4—5 mmol) in ether or THF (30 ml) cooled to 0°C, was added n-butyllithium (10% molar excess) in

hexane. After stirring at 0°C/3 h, the reaction was quenched with the appropriate electrophile and finally poured into water (80 ml) and extracted with diethyl ether (2 × 80 ml). The ether extracts were combined, dried and evaporated. The reaction mixture was further purified as described below.

(a) Quenched with benzaldehyde. The reaction was quenched with benzaldehyde (0.5—1.0 g) (20% molar excess) in ether or THF (15 ml) and stirred at room temperature/1.5 h. The mixture was then treated as described above under the general procedure. The crude products were separated by chromatography on silica gel (120 g), elution being performed with dichloromethane/ethyl acetate 9/1. The following products were obtained:

(i) 3-isomer (XX). Obtained in 32—39% yield (0.5—0.6 g). Recrystallisation from hexane gave white prisms, m.p. 97—100°C. Anal. Found: C, 76.0; H. 6.5; N, 8.0; $C_{22}H_{22}N_2O_2$ calcd.: C, 76.3; H, 6.4; N, 8.1%.

IR (film): 3200s (O—H), 1640s (C=N).

^{1}H NMR ($CDCl_3$): 7.3(m, 10H, benzenoid H); 6.7(d, $J_{4,5}$ 3 Hz, 1H, H(5)); 6.3(s, 1H, O—H, exchangeable with D_2O); 5.9(d, $J_{4,5}$ 3 Hz, 1H, H(4)); 5.7(s, 1H, PhC*H*-); 3.6(s, 2H, methylene H); 1.2(s, 3H, CH_3); 1.0(s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): 153.0(C=N); 143.5, 140.7, 136.8(quaternary benzenoid C and C(2)/C(3)); 128.6, 127.8, 127.4, 126.7, 125.2(benzenoid C); 125.8(C(5)); 118.3(C(2)/C(3)); 110.7(C(4)); 79.2(CH_2); 69.5(CH(OH)); 66.4($C(CH_3)_2$); 28.2, 27.7(CH_3).

A fully-coupled spectrum of XX gave the following ^1J(CH) values: $^1J(C_5H)$ 188, $^1J(C_4H)$ 174 Hz.

m/e: 346(49%, M^+), 328(54%, $M^+ - H_2O$), 315(29%, $M^+ - (CH_3)_2 - H$), 274(32%, $M^+ - C_4H_8O$), 240(41%, $M^+ - C_6H_6CO$), 197(38%, $M^+ - C_6H_5 - C_4H_8O$), 105(51%, $C_5H_5CO^+$), 93(59%), 77(100%, $C_6H_5^+$).

(ii) 5-isomer (XXII). Isolated as an orange oil (150—300 mg, 5—11%) which was further purified by preparative layer chromatography using dichloromethane/ethyl acetate 9/1 as eluent. The product failed to give a satisfactory elemental analysis.

IR (film): 1650s (C=N).

^{1}H NMR ($CDCl_3$): 7.3(m, 10H, benzenoid H); 6.8(d, $J_{3,4}$ 4 Hz, 1H, H(3)); 6.1(d, $J_{3,4}$ 4 Hz, 1H, H(4)); 5.4(s, 1H, PhC*H*-); 3.6(s, 2H, methylene H); 1.0(s, 6H, 2 × CH_3).

^{13}C NMR ($CDCl_3$): 156.5(C=N); 142.4, 141.2, 138.7(quaternary benzenoid C and C(2)/C(5)); 128.4; 128.2; 128.0; 127.3, 126.7(benzenoid C); 123.1(C(2)/C(5)); 114.5(C(3)); 108.5(C(4)); 78.4(CH_2); 68.7(CH(OH)); 66.8($C(CH_3)_2$); 27.8(CH_3).

From a fully coupled spectrum of XXII the following ^1J(CH) values were obtained: $^1J(C_3H)$ 174; $^1J(C_4H)$ 173 Hz.

m/e: 346(52%, M^+), 331(100%, $M^+ - CH_3$), 315(14%, $M^+ - (CH_3)_2 - H$), 241(21%, $M^+ - C_6H_5CO$), 105(35%, $C_6H_5CO^+$), 77(54%, $C_6H_5^+$).

(b) Quenched with benzophenone. The reaction was quenched with benzophenone (10% molar excess) (1.0 g, 5.8 mmol) in THF (20 ml) and stirred at room temperature/22 h. The mixture was then treated as described above under the general procedure. The reaction mixture was chromatographed on silica gel (130 g) using dichloromethane/ethyl acetate 9/1 as eluent. The following product was isolated:

3-isomer (XXI). Obtained in 22% yield (0.50 g) and recrystallised from diethyl ether giving white prisms, m.p. 187—190°C. Anal. Found: C, 79.6; H, 6.2; N, 6.5; $C_{28}H_{26}N_2O_2$ calcd.: C, 79.6; H, 6.2; N, 6.6%.

IR: 1640s (C=N).

^{1}H NMR ($CDCl_3$): 8.6(s, 1H, O—H, exchangeable with D_2O); 7.3 (m, 15H, benzenoid H); 6.7(d,$J_{4,5}$ 2.7 Hz, 1H, H(5)); 5.5(d, $J_{4,5}$ 2.7 Hz, 1H, H(4); 3.5(s, 2H, methylene H); 1.2(s, 6H, 2 × CH_3).

^{13}C NMR ($CDCl_3$): 157.7(C=N); 148.0, 140.7, 140.2 (quaternary benzenoid C and C(2)/C(3); 128.7, 128.2, 127.6, 127.4, 126.5, 124.6, 124.4(benzenoid C, C(2)/C(3) and C(5)); 112.6(C(4)); 78.9(CH_2); 77.6(C(OH)); 66.2($C(CH_3)_2$); 27.0(CH_3).

m/e: 422(95%, M^+), 345(60%, $M^+ - C_6H_5$), 273(81%, $M^+ - C_6H_5 - C_4H_8O$), 195(37%, $M^+ - 2 \times C_6H_5 - H - C_4H_8O$), 105(100%, $C_6H_5CO^+$), 77(83%, $C_6H_5^+$).

Hydrolysis of the benzophenone adduct (XXI)

The methyl iodide salt XXIII was prepared by heating a solution of XXI (0.42 g, 0.99 mmol) and methyl iodide (1.14 g, 8.0 mmol) in nitromethane (4 ml) under nitrogen at 70°C/20 h. Removal of the solvent gave an oil which dissolved in acetonitrile and was precipitated with diethyl ether. The resultant yellow solid was filtered giving the methyl iodide salt XXIII (0.12 g), m.p. 190°C (dec.), γ(C=N)1660 cm^{-1}. The filtrate contained a substantial amount of unreacted oxazoline and was subjected to further treatment with methyl iodide, as described above. The methyl iodide salt obtained from the second treatment failed to solidify and was used without further purification. The methyl iodide salt XXIII was hydrolysed with excess sodium hydroxide in ethanol/water 2/1 at 70—80°C/1.5 h. The solvent was removed, and the residue was dissolved in water (50 ml) and extracted with diethyl ether (2 × 50 ml). The aqueous phase was acidified with dilute hydrochloric acid and extracted with diethyl ether (2 × 50 ml). The ether extracts were combined, dried and evaporated giving a white solid (79 mg, 29%), m.p. 170—172°C, identified as the lactone. Anal. Found: C, 81.5; H, 5.0; N, 4.0; $C_{24}H_{17}NO_2$ calcd.: C, 82.0; H, 4.8; N, 4.0%.

IR: 1760s (C=O).

^{1}H NMR ($CDCl_3$): 7.2—7.8(m, 16H, benzenoid H and H(5)); 6.5 (d, $J_{4,5}$ 2.8 Hz, 1H, H(4)).

m/e: 307(98%, $M^+ - CO_2$), 230 (27%, $M^+ - CO_2 - C_6H_5$), 77(100%, $C_6H_5^+$).

2-[1-(2'-Bromophenyl)-2-pyrrolyl]-4,4-dimethyloxazoline (XXVI)

The oxazoline XXVI was prepared from 1-(2'-bromophenyl)pyrrole-2-carboxylic acid XXV (49.3 g, 0.18 mol) [17] according to the method described above for the oxazoline XIX. The product XXVI was obtained as a darkly-coloured solid (57.2 g, 97%). Recrystallisation from pentane afforded an off-white solid (41.0 g, 69%), m.p. 59—64°C. Anal. Found: C, 56.6; H, 4.7; N, 9.0; $C_{15}H_{15}BrN_2O$ calcd.: C, 56.4; H, 4.7; N,8.8%.

IR (film): 1660s (C=N).

^{1}H NMR ($CDCl_3$): 7.3—7.8(m, 4H, benzenoid H); 7.0(dd, $J_{3,4}$ 4Hz, $J_{3,5}$ 2 Hz, 1H, H(3)); 6.8(dd, $J_{3,5}$ 2 Hz, $J_{4,5}$ 3.3 Hz, 1H, H(5)); 6.3(dd, $J_{3,4}$ 4 Hz, $J_{4,5}$ 3.3

Hz, 1H, H(4)); 3.8(s, 2H, methylene H); 1.1(s, 6H, 2 × CH_3).

m/e: 318(5%, $M^+[^{79}Br]$), 303(19%, $M^+[^{79}Br] - CH_3$), 275(11%, $M^+[^{79}Br] - C(CH_3)_2 - H$), 239(100%, $M^+ - Br$), 197(11%, $M^+ - Br - C(CH_3)_2$), 168(21%, $M^+ - Br - C_4H_7O$).

Lithiation of the bromo oxazoline (XXVI) with n-butyllithium

To a solution of the bromo oxazoline XXVI (1.2 g, 3.9 mmol) in THF (30 ml) cooled to −80°C, was added n-butyllithium (2.84 ml of a 1.64 *M* solution in hexane). The anion solution was stirred at −80°C/3.5 h and then at room temperature/21 h. The reaction was quenched by pouring into water (60 ml) and extracted with diethyl ether (2 × 50 ml). The ether extracts were combined, dried and evaporated giving a reddish solid. Trituration of the crude product with diethyl ether gave the cyclic imine XXVIII as a yellowish solid (0.54 g, 58%) and chromatography of the supernatant liquid on silica gel (20 g) with dichloromethane/ethyl acetate 9/1 gave further product (0.29 g, 32%). Sublimation at 120°C/1 mmHg gave analytically pure imine (0.59 g, 63%), m.p. 136—138°C. Anal. Found: C, 74.6; H, 6.8; N, 11.7; $C_{15}H_{16}N_2O$ calcd.: C, 75.0; H, 6.7; N, 11.7%.

IR: 3300s (O—H), 1620s (C=N).

^{1}H NMR ($CDCl_3$): 6.9—7.8(m, 5H, benzenoid H and H(3)); 6.6(dd, $J_{1,2}$ 3.8 Hz, $J_{1,3}$ 0.9 Hz, 1H, H(1)); 6.3(dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 2.6 Hz, 1H, H(2)); 3.6(s, 2H, methylene H); 1.4(s, 6H, 2 × CH_3).

^{13}C NMR ($CDCl_3$): 151.0 (C=N); 140.6, 133.8(quaternary benzenoid C); 130.8, 127.8, 124.5, 122.9(benzenoid C and C(9a)); 115.0(C(3)); 114.6(C(1)); 109.3(C(2)); 73.4(CH_2); 58.6($C(CH_3)_2$); 19.4(CH_3).

m/e: 240(1%, M^+), 209(100%, $M^+ - 2 \times CH_3 - H$), 167(45%, $M^+ - C_4H_9O$), 153(28%, $M^+ - C_4H_9NO$).

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