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Reduction of 2- and 3-Acylpyrroles. A New Synthesis of the Pyrrolo[1,2-*b*]cinnolin-10-one Ring System from 1-(4-Methylphenyl)sulfonyl-1*H*-pyrrole

Athanasios Kimbaris and George Varvounis*

Department of Chemistry, University of Ioannina, 451 10, Ioannina, Greece

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Abstract—Reduction of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone **4** with zinc and ammonium chloride gave 5,10-dihydro-pyrrolo[1,2-*b*]cinnolin-10-one **5** and (2-hydroxylaminophenyl)(1*H*-pyrrol-2-yl)methanone **6** whereas reduction of **4** with zinc and sodium hydroxide gave only **5**. Reaction of (2-nitrophenyl)(1*H*-pyrrol-3-yl)methanone **10** with zinc and ammonium chloride or zinc and sodium hydroxide afforded (2-nitrosophenyl)(1*H*-pyrrol-3-yl)methanone **11** and 2-aminophenyl)(1*H*-pyrrol-3-yl)methanone **12** or **12** as a single product, respectively. Sodium borohydride reduction of (2-nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone **13** or (2-nitrophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone **19** gave a mixture of the corresponding alcohols **15** or **21** and nitroso-ketones **18** or **22**. Reduction of alcohols **15** or **21** with zinc and sodium hydroxide afforded nitroso-ketones **18** or **22**, respectively.

Reactions involving the intramolecular capture of electrophilic nitrene or nitroso species by an adjacent aromatic or heteroaromatic ring have been exploited in the synthesis of fused heteroaromatic systems, the reactions require reduction of appropriate aromatic nitro compounds. Cadogan et al.[1] were the first to introduce triethyl phosphite for the reduction of for example 2-nitrobiaryls into carbazoles, 1-*o*-nitrophenylnaphthalene into 3,4-benzocarbazole, *o*-nitroanils into indazoles and 2-nitroazobenzenes into benzotriazoles. Similar conditions were used by Klemm et al.[2] to transform 1-nitrotriphenylene into 4*H*-naphthol[1,4-*def*]carbazole. These cyclisations require heating with neat triethyl phosphite or in a solvent such as toluene and are believed to proceed via nitrene intermediates, pyrroles polymerise easily under these conditions. The only successful cyclisation involving a pyrrole was the conversion of 1-(2-nitrophenyl)-1*H*-pyrrole into 9*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole, reported by Lindley et al.[3] An alternative reductive process from nitro compounds involves intramolecular trapping of in situ generated nitroso species. The reductive procedures employed here are milder compared to those of triethyl phosphite. For example, zinc dust and sodium hydroxide in refluxing aqueous ethanol has been used by Bruneau et al.[4] to cyclise *N*1-(alkyl or aryl)-2-nitrobenzamides into 2-(alkyl or aryl)-2,3-dihydro-1*H*-3-indazolones. Even milder conditions, zinc dust and ammonium chloride in water and an organic solvent at ambient temperature, were used by Bird and Latif[5] for the cyclisation of substituted 3-(2-nitrophenoxy)phenols into 3*H*-phenoxazin-3-ones and by Mann and co-workers[6] for the cyclisation of ethyl 2-nitrophenylacetate into 4-hydroxy-1,4-benzoxazine-3(4*H*)-one.

Here we report our findings on the reduction of compounds **4**, **13**, **15**, **19** and **21** with zinc dust in the presence of either weak or relatively strong base. The starting materials **2** and **3** were not reported in the literature but were conveniently prepared using the methods described by Kakushima et al.[7] Thus 1-tosyl-1*H*-pyrrole **1**[8] was acylated by *o*-nitrobenzoyl chloride in 1,2-dichloroethane using either stannic chloride or aluminium trichloride as catalyst. With stannic chloride compounds **2** and **3** were isolated by column chromatography in 56 and 11% yield, respectively. The use of aluminium trichloride gave, after column chromatography, compounds **2** and **3** in 13 and 52% yield, respectively. Kakushima et al.[7] obtained better overall regioselectivity synthesising a range of 2-acyl-1-phenylsulfonyl-1*H*-pyrroles from 1-phenylsulfonyl-1*H*-pyrrole with boron trifluoride etherate as catalyst. No identifiable product could be obtained when we used boron trifluoride etherate. A similar observation was reported[9] during attempted Friedel–Crafts acylation of 1-(phenylsulfonyl)pyrrole with 2-(ethylthio)benzoyl chloride.

The substitution pattern in acyl pyrroles **2** and **3** was determined by the use of pyrrole coupling constants and chemical shifts.[10] The most important distinction between the two isomers is on one hand, H-5 is the most downfield pyrrole proton at δ=7.91 ppm of compound **2** and in the

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* Corresponding author. Tel.: +30-651-98-382; fax: +30-651-919-66; e-mail: gvarvoun@cc.uoi.gr

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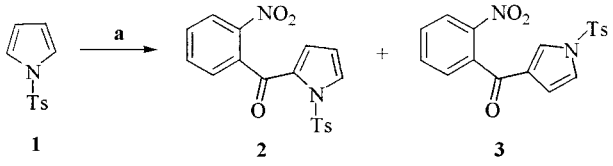


Catalyst	Compound	Yield %
$SnCl_4$	2	56
	3	11
$AlCl_3$	2	13
	3	52

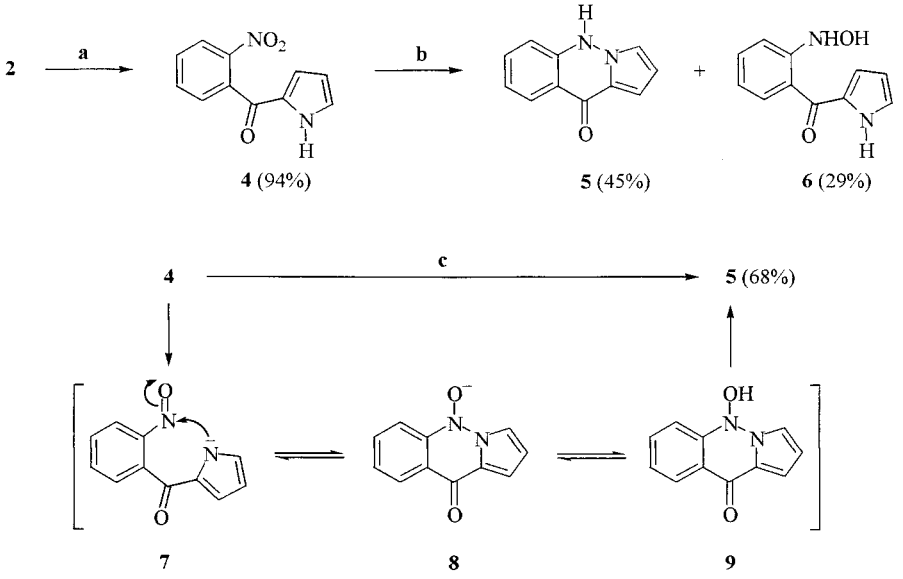
Scheme 1. Reagents: (a) 2-$NO_2C_6H_4COCl$, $ClCH_2CH_2Cl$, catalyst, 22°C.

other $J_{2,5}$=2.5 Hz of compound **3**. Both these values are comparable with the corresponding values δ=7.80–7.91 and $J_{2,5}$=2.1–2.3 Hz found in a range of 2- and 3-acyl(1-phenylsulfonyl or tosyl)pyrroles (Scheme 1).[7,11]

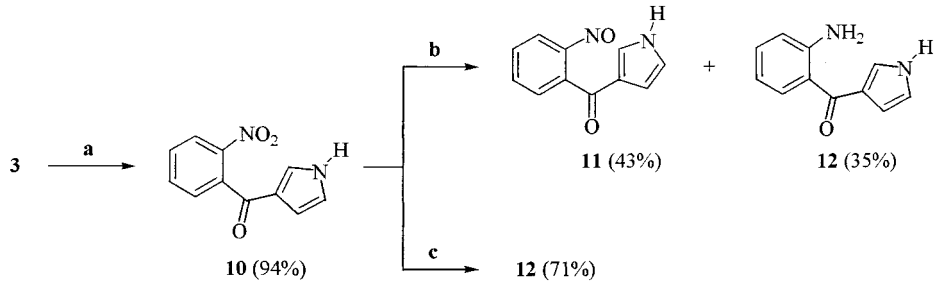
Encouraged by the reported reductive cyclisation of 1-(2-nitrophenyl)-1*H*-pyrrole with triethyl phosphite[3] we decided to try similar reaction conditions on compounds **2** and **3**, assuming that the -I/-M effects of the carbonyl and tosyl groups in these compounds will tune down the reactivity of the pyrrole rings. However, when compounds **2** and **3** were heated in neat triethyl phosphite, black tars were produced, and when heated in toluene containing two equivalents of triethyl phosphite, TLC examination of the black mass revealed a faint spot that corresponded to starting material. Failing to apply this method we turned to the alternative reductive cyclisation based on intramolecular capture of in situ generated aromatic nitroso compounds. For this purpose we required methanones **4** and **10** since the deprotected pyrrole rings of these compounds are more nucleophilic in character than the pyrrole rings of **2** and **3**. The latter were detosylated by refluxing in methanol containing 2N aqueous sodium hydroxide to give **4** and **10** in 94 and 87% yield, respectively. Compound **4**, was first reported by Khan and Morgan,[12] and was prepared by the action of pyrrolylmagnesium iodide on 2-nitrobenzoyl chloride.

Reduction of **4** with zinc dust and ammonium chloride in aqueous ethanol from 0°C to room temperature, gave a mixture consisting of pyrrolo[1,2-*b*]cinnolin-10-one **5** (45%) and hydroxylamine **6** (29%) (Scheme 2). Hamer et al.[12] reported the preparation of **5** by intramolecular aromatic fluoride displacement in 2-(2-fluorobenzoyl)-1*H*-pyrrol-1-ylcarbamic acid ethyl ester. Refluxing **4** in aqueous ethanol containing zinc dust and sodium hydroxide gave **5** in 68% yield. A plausible mechanism for the reductive cyclisation of **4** into **5** is deoxygenation and deprotonation to nitroso intermediate **7**, intramolecular cyclisation to *N*-oxide **8**, protonation to *N*-hydroxy compound **9** and reduction to **5**. In the reaction of **4** with zinc and ammonium chloride the formation of hydroxylamine **6** together with **5** is probably due to the relatively weak basic conditions of the redox reaction. The concentration of ammonia released may be insufficient to produce stoichiometrically deprotonated intermediate **7**, so that further reduction of protonated **7** leads to **6**. No trace of the isomeric pyrrolo[3,2-*b*]quinoline-9-one was observed in any of these reactions.

Contrary to the previous result, treating **10** with the zinc and ammonium chloride gave a mixture of nitroso compound **11** (43%) and amine **12** (35%) (Scheme 3). Since nitroso compounds are unstable under these conditions we assume that the isolation of **11** results because of depletion of



Scheme 2. Reagents: (a) MeOH, NaOH, reflux; (b) Zn, NH_4Cl, H_2O, EtOH, 0–22°C; (c) Zn, NaOH, H_2O, EtOH, reflux.

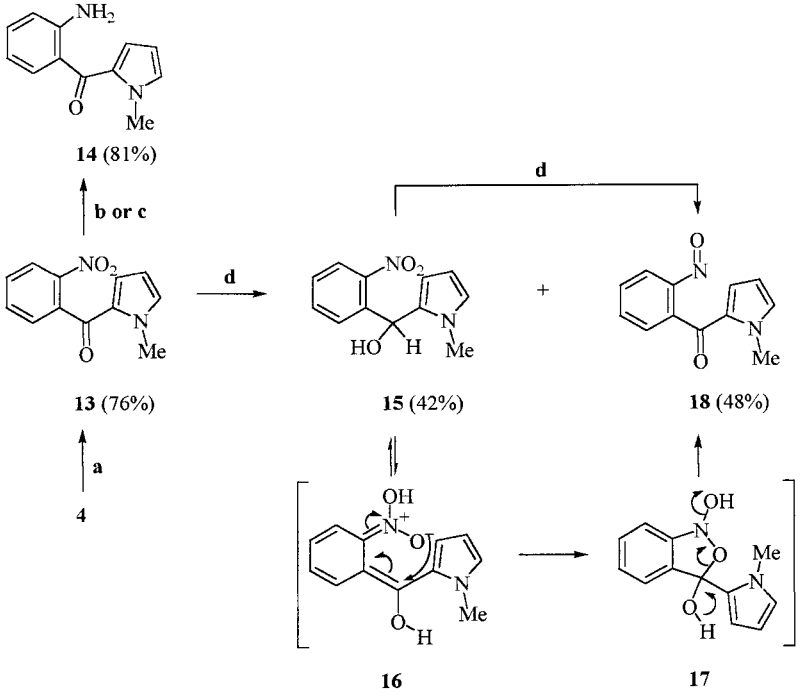


Scheme 3. Reagents: (a) MeOH, KOH, reflux; (b) Zn, NH_4Cl, H_2O, EtOH, −5–22°C; (c) Zn, NaOH, H_2O, EtOH, reflux.

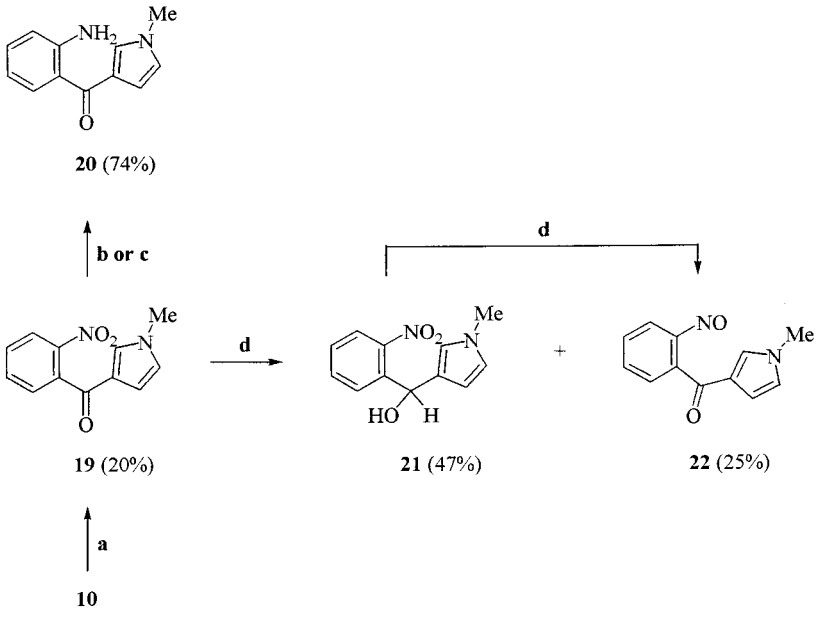
reducing agent from reduction of **11** to **12**. Treating **10** with zinc and sodium hydroxide afforded the amine **12** in 71% yield. Contrary to our expectations, no trace of the isomeric compounds pyrrolo[2,3-*b*]quinolin-4-one and pyrrolo-[3,4-*b*]quinoline-9-one were detected in these reactions.

An attempt to cyclise **11**, by heating in *p*-xylene for 6 h resulted in the recovery of starting material. Bates and Tafel[9] used similar reaction conditions to cyclise 3-[2-(ethylsulfinyl)benzoyl]pyrrole into 1,2-dihydro-thiochromeno[2,3-*b*]pyrrol-4-one. It is therefore highly unlikely that restricted rotation about the phenyl-acyl and pyrrole-acyl bonds of **11** is responsible for locking the molecule into a conformation where pyrrole ring and nitroso group are too far apart for reaction. A plausible explanation is, on one hand, that C-2 and C-4 of **11** are considerably less nucleophilic than N-1, and in the other, that the nitroso group of **11** is less electrophilic than the sulfoxide group of 3-[2-(ethylsulfinyl)benzoyl]pyrrole.

In order to synthesise *N*-methylated derivatives **13** and **19** (Schemes 4 and 5), an alternative route instead of the obvious methylation of compounds **4** and **10** was investigated. Friedel–Crafts acylation of 1-methylpyrrole with 2-nitrobenzoyl chloride in the presence of stannic chloride was chosen by analogy to the synthesis of compounds **2** and **3**. This route was abandoned since only 10% of compound **13** was isolated and a trace of compound **19** detected. On the other hand, methylation of compounds **4** and **10** by dissolving in dimethyl sulfoxide containing potassium hydroxide and then treating with methyl iodide gave **13** and **19** in 76 and 80% yield, respectively. No trace of *C*-alkylation was observed. Our initial thought was that the +I effect of the methyl group of compounds **13** and **19** would slightly increase the nucleophilic character of the pyrrole ring and possibly facilitate cyclisation. However, reduction of **13** and **19** with zinc and ammonium chloride or zinc and sodium hydroxide afforded the amines **14** and **20**, respectively. No trace of the anticipated 4,9-dihydro-1*H*-1-methylpyrrolo[3,2-*b*]quinolin-9-one and 4,9-dihydro-1*H*-1-methylpyrrolo[2,3-*b*]quinolin-9-one was detected in these reactions.



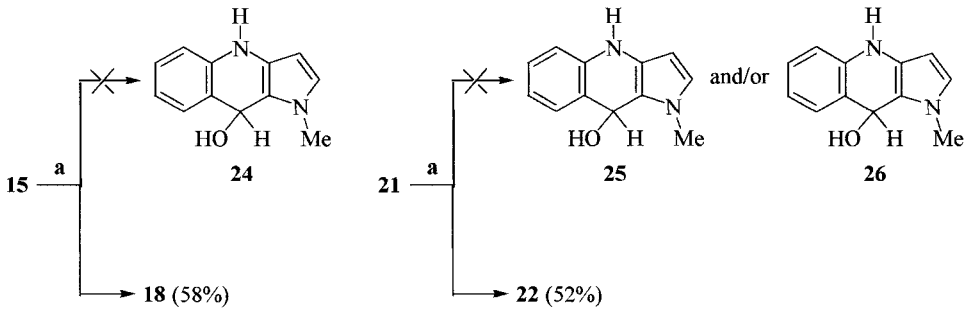
Scheme 4. Reagents: (a) KOH, DMSO, MeI; (b) Zn, NH_4Cl, H_2O, EtOH, 0–22°C; (c) Zn, NaOH, H_2O, EtOH, reflux; (d) $NaBH_4$, IPA, reflux.



Scheme 5. Reagents: (a) KOH, DMSO, MeI; (b) Zn, NH_4Cl, H_2O, EtOH, 0–22°C; (c) Zn, NaOH, H_2O, EtOH, reflux; (d) $NaBH_4$, IPA, reflux.

Next we considered that alcohols **15** and **21** are good candidates for reductive cyclisation since the −I/−M effects exercised by the carbonyl group in ketones **13** and **19** (Schemes 4 and 5) are absent in these compounds. The pyrrole rings of **15** and **21** should therefore be more nucleophilic than the corresponding pyrrole rings of compounds **13** and **19**. A literature search revealed that there are very few reports on the reduction of acyl pyrroles to alcohols. Salvadori and co-workers[13] reduced 3-acetyl-1-tosyl-1*H*-pyrrole with sodium borohydride and propan-2-ol in boiling dioxane and obtained 3-(1-hydroxyethyl)-1-tosyl-1*H*-pyrrole in 70% yield together with 3-ethyl-1-tosylpyrrole in 20% yield. More recently, Xiao and Ketcha[14] reported that reduction of 3-acetyl-1-(phenylsulfonyl)-1*H*-pyrrole by sodium borohydride in ethanol gave near quantitative yield of 3-(1-hydroxyethyl)-1-(phenylsulfonyl)-1*H*-pyrrole. The reduction of compounds **13** and **19** required heating under reflux in propan-2-ol with 1.5 equiv. of sodium borohydride and gave a mixture consisting of nitro-alcohol and nitroso-ketone, **15** and **21** and **18** and **22** (Schemes 4 and 5), respectively. The compounds in these mixtures were easily separated by column chromatography. We suggest that the initial step in these reactions is straightforward reduction of ketone to alcohol. In the presence of excess base the alcohol, for example compound **15**, tautomerises to the aci-nitro intermediate **16** (Scheme 4). The latter rearranges to the intermediate benzisoxazole **17** from which a molecule of water is lost to afford nitroso compound **18**. To our knowledge, this transformation is unprecedented in the literature. The closest analogy is the reaction of 2-nitrobenzehydrol with *p*-toluenesulfonyl chloride to give 2-nitrosobenzophenone[15] where an analogous benzisoxazole intermediate was proposed. Further confirmation of our reaction path is provided by the quantitative conversion of nitro-alcohols **15** and **21** into the corresponding nitroso-ketones **18** and **22** by heating in propan-2-ol with excess sodium borohydride.

In an attempt to produce tricycle **24** by treating nitro-alcohol **15** with zinc and sodium hydroxide, the reaction afforded instead nitroso-ketone **18**. Similar treatment of alcohol **21** afforded nitroso-ketone **22** (Scheme 6). We suggest that a mechanism similar to the one depicted in Scheme 4 for the conversion of **15** to **18** is taking place. The reason why neither nitro group in **15** nor nitroso group in **18** are reduced by the reductive reaction conditions is probably the rapid



Scheme 6. Reagents: (a) Zn, NaOH, H_2O, EtOH, reflux.

interconversion of **15** to aci-nitro intermediate **16** and the slow conversion of the latter to intermediate benzoisoxazole **17**. Both **16** and **17** are not reduced under these conditions during which time the redox reaction between zinc and ethanol goes to completion. A similar explanation can be given for the conversion of **21** to **22**, where tricycles **25** and/or **26** were not formed. Nitroso compounds **18** and **22** were also subjected to thermal activation in neutral or acidic conditions, since it seemed to present a good possibility for intramolecular electrophilic aromatic substitution because the high temperature would offer the greatest rotational freedom. Refluxing **18** or **22** in xylene, DMF or diglyme, subliming at 65°C/0.05 Torr or heating in PPA at 100°C left the compounds unchanged. No products were detected even when **18** or **22** were quenched in *t*-BuLi/Et_2O at 25°C.

Further work is under way in order to exploit the intramolecular capture of in situ generated nitroso species as a means of synthesising fused heteroaromatic systems.

Experimental

General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer solids were taken as Nujol mulls and liquids as thin films between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Nuclear magnetic resonance spectra were measured at 360 MHz on a Brüker AM 360 spectrometer or at 400 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a JEOL JMS-AX 505W (high-resolution) machine using EI.

Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out throughout using Merck 9385 silica gel. Light petroleum refers to the fraction with bp 40–60°C. Solvents and reagents were used as received from the manufacturers except for dichloromethane, ethanol, ethyl acetate, methanol and light petroleum, which were purified according to recommended procedures.[17]

Reaction of 1-(4-methylphenyl)sulfonyl-1*H*-pyrrole with benzoyl chloride and stannic chloride

The procedure of Kakushima et al.[7] was essentially used. To a stirred solution of stannic chloride (0.7 mL, 6 mmol) in anhydrous 1,2-dichloroethane (30 mL) at −10°C and under argon, was added slowly freshly distilled *o*-nitrobenzoyl chloride (0.72 mL, 5.6 mmol). The resulting mixture was stirred for 10 min. A solution of 1-(4-methylphenyl)sulfonyl-1*H*-pyrrole[8] (0.9 g, 4.07 mmol) in anhydrous 1,2-dichloroethane (20 mL) was added dropwise, and the mixture stirred for 30 min at −10°C and at 25°C for 90 min. The reaction was poured onto ice water (100 mL) and the aqueous layer extracted with chloroform (3×20 mL). The combined organic layers were treated with saturated $NaHCO_3$, washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give a dark oil. Column chromatography of the oily residue (11% ethyl acetate/light petroleum) gave two fractions. The first fraction gave *{1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-2-yl}(2-nitrophenyl)methanone* **2** and the second fraction gave *{1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-3-yl}(2-nitrophenyl)methanone* **3**.

{1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}(2-nitrophenyl)methanone (2). (0.84 g, 56%) as colourless plates (toluene), mp 151–152°C (photosensitive); [Found: C, 58.35; H, 3.77; N, 7.55. $C_{18}H_{14}N_2O_5S$ requires C, 58.37; H, 3.81; N, 7.57%]; ν_{max} (Nujol) 1660, 1520, 1340, 1320, 1160 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 2.43 (3H, s, Me), 6.28 (1H, t, *J*=3.8 Hz, H-4), 6.46 (1H, dd, *J*=3.8, 1.8 Hz, H-3), 7.35 (2H, d, *J*=8.4 Hz, H-3″, H-5″), 7.47 (1H, dd, *J*=7.5, 1.5 Hz, H-6′), 7.61 (1H, td, *J*=8.1, 1.5 Hz, H-4′), 7.69 (1H, td, *J*=7.5, 1.2 Hz, H-5′), 7.91 (1H, dd, *J*=3.8 Hz, H-5), 7.97 (2H, d, *J*=8.4 Hz, H-2″, H-6″), 8.01 (1H, dd, *J*=8.1, 1.2 Hz, H-3′); δ_C (90.5 MHz; $CDCl_3$) 21.7 (Me), 110.6 (C-4), 124.4 (C-3), 126.8 (C-4′), 128.6 (C-3″, C-5″), 129.4 (C-5′), 129.5 (C-2″, C-6″), 130.8 (C-6′), 131.4 (C-5), 131.9 (C-2), 133.7 (C-3′), 135.1(C-1′), 135.4 (C-2′), 143.3 (C-4″), 146.8 (C-1″), 179.8 (CO); *m/z* (EI) 370 (44, M^+), 340 (19), 155 (100), 134 (23), 91 (88%).

{1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}(2-nitrophenyl)methanone (3). (0.16 g, 11%) as colorless microcrystals (toluene), mp 163–165°C; [Found: C, 58.41, H, 3.78, N, 7.54. $C_{18}H_{14}N_2O_5S$ requires C, 58.37, H, 3.98, N, 7.57%]; ν_{max} (Nujol) 1670, 1530, 1350, 1330, and 1180 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 2.43 (3H, s, Me), 6.70 (1H, dd, *J*=3.4, 1.7 Hz, H-4), 7.15 (1H, dd, *J*=3.4, 2.0 Hz, H-5), 7.34 (2H, d, *J*=8.5 Hz, H-3″, H-5″), 7.40 (1H, t, *J*=1.8 Hz, H-2), 7.49 (1H, dd, *J*=7.4, 1.5 Hz, H-6′), 7.67 (1H, td, *J*=8.2, 1.5 Hz, H-4′), 7.75 (2H, d, *J*=8.5, H-2″, H-6″), 7.76 (1H, td, *J*=7.4, 1.2 Hz, H-5′), 8.15 (1H, dd, *J*=8.2, 1.2 Hz, H-3′); δ_C (90.5 MHz; $CDCl_3$) 21.7 (Me) 112.8 (C-4) 122.1 (C-5), 124.6 (C-4′), 125.9 (C-2), 127.3 (C-3″, C-5″), 128.1 (C-3), 128.7 (C-5′), 130.5 (C-2″, C-6″), 130.8 (C-6′), 134.0 (C-3′), 134.7 (C-1′), 136.0 (C-2′), 146.3 (C-4″), 146.8 (C-1″), 187.3 (CO); *m/z* (EI) 370 (18, M^+), 342 (17), 236 (13), 215 (12), 187 (23), 155 (76), 91 (100%).

Reaction of 1-(4-methylphenyl)sulfonyl-1*H*-pyrrole with benzoyl chloride in the presence of aluminium trichloride

The procedure of Kakushima et al.[7] was essentially used. To a stirred suspension of anhydrous aluminium trichloride (1 g, 75 mmol) in 1,2-dichloroethane (60 mL) at −10°C and under argon, was added *o*-nitrobenzoyl chloride (1.3 mL, 7 mmol) and the mixture was stirred for 10 min. A solution of 1-(4-methylphenyl)sulfonyl-1*H*-pyrrole[8] (1.12 g, 5.09 mmol) in anhydrous 1,2-dichloroethane (30 mL) was added dropwise, and the temperature allowed to reach 25°C while stirring was continued. The reaction mixture was poured onto ice water (130 mL), and the aqueous layer extracted with chloroform (3×30 mL). The combined organic layers were treated with saturated $NaHCO_3$, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a dark oil. The oily residue was subjected to column chromatography (11% ethyl acetate/light petroleum) to give two fractions. The

first fraction gave *{1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-3-yl}(2-nitrophenyl)methanone* **3** (0.96 g, 52%). The second fraction gave *{1-[(4-methylphenyl)sulfonyl]-1H-pyrrol-2-yl}(2-nitrophenyl)methanone* **2** (0.23 g, 13%). Compounds **2** and **3** obtained by this method were identical in all respects with the corresponding compounds prepared in the previous experiment.

General procedure for the detosylation of {1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}(2-nitrophenyl)-methanone and {1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}(2-nitrophenyl)methanone

To a solution of **2** or **3** (0.93 g, 2.5 mmol) in methanol (50 mL) was added 2N aqueous sodium hydroxide solution (2 mL) and the resulting mixture was stirred under reflux for 5 h. After cooling to room temperature the solvent was evaporated in vacuo to near dryness, water (30 mL) was added and the pH adjusted to 4–5 by dropwise addition of 2N aqueous hydrogen chloride solution. The suspension was extracted with chloroform (3×10 mL) the combined organic extracts washed with brine, dried (Na_2SO_4) and concentrated to give a light brown residue of crude *(2-nitrophenyl)(1H-pyrrol-2-yl)methanone* **4** or *(2-nitrophenyl)(1H-pyrrol-3-yl)methanone* **10**.

(2-Nitrophenyl)(1*H*-pyrrol-2-yl)methanone (4). (0.51 g, 94%) as colourless needles (toluene); mp=138–140°C [Found: C, 61.14; H, 3.71; N, 12.95. $C_{11}H_8N_2O_3$ requires C, 61.10; H, 3.73; N, 12.96%]; ν_{max} (Nujol) 3300, 1630, 1490, 1350 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.27 (1H, td, *J*=3.9, 2.4 Hz, H-4), 6.51 (1H, td, *J*=3.9, 2.4, 1.3 Hz, H-3), 7.21 (1H, td, *J*=2.4, 1.3 Hz, H-5), 7.62 (1H, td, *J*=7.5, 1.6 Hz, H-4′), 7.66 (1H, dd, *J*=7.5, 1.6 Hz, H-6′), 7.73 (1H, td, *J*=8.0, 1.2 Hz, H-5′), 8.14 (1H, dd, *J*=8.0, 1.2 Hz, H-3′), 10.24 (1H, s, br, NH); δ_C (90.5 MHz; $CDCl_3$) 111.4 (C-4), 119.9 (C-3), 124.6 (C-4′), 127.0 (C-5), 129.5 (C-5′), 130–6 (C-6′), 130–8 (C-2), 133.4 (C-3′), 135.2 (C-1′), 130.6 (C-6′), 130.8 (C-2), 133.4 (C-3′), 135.2 (C-1′), 147.5 (C-2′), 182.1 (CO); *m/z* (EI) 216 (21, M^+), 134 (49), 104 (64), 94 (25), 82 (100%).

(2-Nitrophenyl)(1*H*-pyrrol-3-yl)methanone (10). (0.47 g, 87%) as colourless needles (2-propanol) mp 148–149°C; [Found: C, 61.18, H, 3.74; N, 12.92. $C_{11}H_8N_2O_3$ requires C, 61.09; H, 3.73; N, 12.96%]; ν_{max} (Nujol) 3380, 1640, 1520, 1340 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.61 (1H, td, *J*=3.0, 1.6 Hz, H-4), 6.81 (1H, td, *J*=3.0, 2.1 Hz, H-5), 7.15 (1H, dd, *J*=3.2, 1.6 Hz, H-2), 7.54 (1H, dd, *J*=7.5, 1.5 Hz, H-6′), 7.62 (1H, td, *J*=8.2, 1.5 Hz, H-4′), 7.72 (1H, td, *J*=7.5, 1.2 Hz, H-5′), 8.13 (1H, dd, *J*=8.2, 1.2 Hz, H-3′), 8.65 (1H, s, br, NH); δ_C (90.5 MHz; $CDCl_3$) 109.6 (C-4), 120.0 (C-5), 124.3 (C-3′), 124.9 (C-2), 128.9 (C-5′), 130.1 (C-6′), 112.64 (C-3), 132.47 (C-1′), 144.35 (C-2′), 176.76 (CO); *m/z* (EI) 216 (41, M^+), 199 (22), 188 (19), 171 (18), 144 (10), 104 (26), 94 (100), 82 (50%).

Reduction of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone and (2-nitrophenyl)(1*H*-pyrrol-3-yl)methanone with zinc dust and ammonium chloride in aqueous ethanol

General procedure A. To a solution of **4** or **10** (0.22 g, 1 mmol) in ethanol (10 mL) at 0°C was added zinc dust (0.20 g, 3 mmol) followed by a solution of ammonium chloride (0.32 g, 6 mmol) in water (5 mL). The reaction mixture was left to stir at room temperature for 1.5 h, filtered and the residue washed with hot ethanol (10 mL). The solvents were concentrated in vacuo to near dryness, water (30 mL) was added and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and the oily residue was purified by column chromatography (25% ethyl acetate/light petroleum) to give two fractions. The first fraction gave *5,10-dihydropyrrolo[1,2-b]cinnolin-10-one* **5**[16] or *(2-nitrosophenyl)(1H-pyrrol-3-yl)methanone* **11** and the second fraction gave *(2-hydroxyl-aminophenyl)(1H-pyrrol-3-yl)-methanone* **6** or *(2-aminophenyl)(1H-pyrrol-3-yl)-methanone* **12**, respectively.

5,10-Dihydropyrrolo[1,2-*b*]cinnolin-10-one (5). (0.08 g, 45%) as colourless needles (ethanol); mp=130–131°C (lit.[12] mp>300°C) [Found: C, 71.73; H, 4.38; N, 15.21. $C_{11}H_8N_2O$ requires C, 71.70; H, 4.39; N, 15.22%]; ν_{max} (Nujol) 3230, 1640 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.41 (1H, dd, *J*=3.5, 2.6 Hz, H-2), 6.93–6.97 (2H, m, H-1 and H-8), 7.07 (1H, dd, *J*=2.6, 1.2 Hz, H-3), 7.28 (1H, td, *J*=8.3, 2.5 Hz, H-7), 7.50 (1H, dd, *J*=8.3, 1.7 Hz, H-6), 7.69 (1H, dd, *J*=8.7, 2.5 Hz, H-9), 9.93 (1H, s, br, NH); δ_C (100.6 MHz; $CDCl_3$) 110.6 (C-2), 111 (C-1), 112.2 (C-5a), 114.4 (C-8), 120.6 (C-3), 120.8 (C-9a), 122.3 (C-7), 123.2 (C-6), 131.2 (C-9), 157.5 (C-10a), 158.8 (CO); *m/z* (EI) 184 (100, M^+), 167 (3), 155 (45), 129 (36), 103 (11), 92 (14), 66 (9%).

(2-Hydroxylaminophenyl)(1*H*-pyrrol-2-yl)methanone (6). (0.06 g, 29%) as pale-yellow microcrystals (toluene); mp=146–147°C [Found: C, 65.35; H, 4.99; N, 13.85. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.98; N, 13.83%]; ν_{max} (Nujol) 3320, 3250, 1620 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.28 (1H, dd, *J*=4.0, 2.4 Hz, H-4), 6.78 (1H, dd, *J*=4.0, 1.2 Hz, H-3), 6.88 (1H, td, *J*=8.0, 1.6 Hz, H-5′), 7.11 (1H, s, H-5), 7.35–7.46 (2H, m, H-3′, H-4′), 7.81 (1H, d, *J*=7.6, Hz, H-6′), 8.00 (1H, s, N*H*OH), 9.06 (1H, s, NHO*H*), 10.71 (1H, s, NH); *m/z* (EI) 202 (100, M^+), 181 (85), 165 (18), 156 (41%).

(2-Nitrosophenyl)(1*H*-pyrrol-3-yl)methanone (11). (0.09 g, 43%) as pale-yellow microcrystals (toluene); mp=151–153°C [Found: C, 66.02; H, 4.02; N, 13.97. $C_{11}H_8N_2O_2$ requires C, 65.99; H, 4.03; N, 13.99%]; ν_{max} (Nujol) 3320, 1640 cm^{-1}; δ_H (400 MHz; DMSO) 6.80 (1H, dd, *J*=2.8, 1.5 Hz, H-4), 6.90–6.95 (2H, m, H-4′, H-5), 6.26 (1H, dd, *J*=8.0, 0.8 Hz, H-5′), 7.48–7.52 (2H, m, H-2, H-6′), 7.73 (1H, dd, *J*=7.8, 0.8 Hz, H-3′), 10.56 (1H, s, NH); *m/z* (EI) 200 (2, M^+), 184 (100), 155 (82), 129 (85), 69 (80%).

(2-Aminophenyl)(1*H*-pyrrol-3-yl)methanone (12). (0.06 g, 35%) as off-yellow microcrystals (toluene); mp=120–121°C [Found: C, 70.92; H, 5.42; N, 15.03%. $C_{11}H_{10}N_2O$ requires C, 70.95; H, 5.41; N, 15.04 %]; ν_{max} (Nujol) 3510, 3480, 3280, 1630 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.41 (2H, NH_2), 6.46 (1H, dd, *J*=3.9, 2.4 Hz, H-4), 6.55 (1H, td, *J*=8.0, 1.0 Hz, H-5′), 6.76 (1H, d, *J*=8.0 Hz, H-3′), 6.86 (1H, dd, *J*=4.5, 2.2 Hz, H-5), 7.20 (1H, dd, *J*=8.0,

1.5 Hz, H-4′), 7.26 (1H, s, H-2), 7.61 (1H, dd, J=8.0, 1.5 Hz, H-6′), 11.46 (1H, s, NH); m/z (EI) 186 (100, M^+), 169 (82), 158 (12), 94 (38), 66 (11%).

Reduction of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone and (2-nitrophenyl)(1*H*-pyrrol-3-yl)methanone with zinc dust and sodium hydroxide in aqueous ethanol

General procedure B. To a stirred solution of **4** or **10** (0.22 g, 1.0 mmol) in ethanol (10 mL) was added a solution of sodium hydroxide (0.16 g, 4.0 mmol) in water (5 mL) and zinc dust (0.20 g, 3 mmol). The resulting mixture was heated under reflux over a period of 3 h, filtered, washed with hot ethanol and the filtrate evaporated to near dryness. Water (30 mL) was added to the oily residue and then extracted with dichloromethane (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give a residue either of *5,10-dihydropyrrolo[1,2-b]cinnolin-10-one* **5** (0.13 g, 68%) or *2-aminophenyl)(1H-pyrrol-3-yl)methanone* **12** (0.13 g, 71%). Compounds **5** and **12** prepared by this method were identical in all respects to the corresponding compounds obtained by General procedure A.

General procedure for the methylation of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone and (2-nitrophenyl)-(1*H*-pyrrol-3-yl)methanone

To a stirred solution of potassium hydroxide (0.22 g, 4 mmol) in dry dimethyl sulfoxide (10 mL) under argon, was added (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone or (2-nitrophenyl)(1*H*-pyrrol-3-yl)methanone (0.22 g, 1 mmol) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 10°C, methyl iodide was added dropwise and stirring continued at room temperature for 45 min. Water (50 mL) was added and extracted with diethyl ether (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give crude *(2-nitrophenyl)(1-methyl-1H-pyrrol-2-yl)methanone* **13** or *(2-nitrophenyl)(1-methyl-1H-pyrrol-3-yl)methanone* **19**.

(2-Nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (13). (0.17 g, 76%) as colourless microcrystals (toluene); mp=72–74°C [Found: C, 62.62; H, 4.36; N, 12.16. $C_{12}H_{10}N_2O_3$ requires C, 62.60; H, 4.38; N, 12.17%]; ν_{max} (Nujol) 1640, 1540, 1360 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.09 (3H, s, Me), 6.07 (1H, dd, J=4.0, 2.4 Hz, H-4), 6.32 (1H, dd, J=4.0, 1.6 Hz, H-3), 6.92 (1H, s, H-5), 7.56–7.70 (3H, m, H-4′, H-5′, H-6′), 8.12 (1H, d, H-3′); m/z (EI) 230 (100, M^+), 214 (35), 169 (82), 158 (22), 131 (58%).

(2-Nitrophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone (19). (0.18 g, 80%) as colourless microcrystals (toluene); mp=109–111°C [Found C, 62.59; H, 4.37; N, 12.20. $C_{12}H_{10}N_2O_3$ requires C, 62.60; H, 4.38; N, 12.17%]; ν_{max} (Nujol) 1640, 1530, 1360 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3,64 (3H, s, Me), 6.51 (1H, dd, J=2.8, 1.8 Hz, H-4), 6.59 (1H, dd, J=2.8, 2.4 Hz, H-5), 6.97 (1H, s, H-2), 7.52 (1H, dd, J=7.5, 1.0 Hz, H-6′), 7.60 (1H, td, J=8.1, 1.0 Hz, H-4′), 7.69 (1H, td, J=7.5, 1.2 Hz, H-5′), 8.11 (1H, dd, J=8.1, 1.2 Hz, H-3′); m/z (EI) 230 (M^+, 100), 214 (26), 169 (78), 144 (12), 131 (38%).

Reduction of (2-nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)-methanone and (2-nitrophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone with zinc dust and ammonium chloride in aqueous ethanol

Compound **13** or **19** (0.23 g, 1 mmol) was dissolved in ethanol (10 mL), the solution cooled to 0°C and treated with zinc dust (0.20 g, 3 mmol) and aqueous ammonium chloride (0.32 g, 6 mmol) according to General procedure A. The oily residue after work-up was purified by column chromatography (33% ethyl acetate/light petroleum) to give *(2-aminophenyl)(1-methyl-1H-pyrrol-2-yl)methanone* **14** or *(2-aminophenyl)(1-methyl-1H-3-pyrrolyl)methanone* **20**.

Reduction of (2-nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)-methanone and (2-nitrophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone with zinc dust and sodium hydroxide in aqueous ethanol

Compound **13** or **19** (0.23 g, 1 mmol) was dissolved in ethanol (10 mL) and treated with a solution of sodium hydroxide (0.16 g, 4.0 mmol) in water (5 mL) and zinc dust (0.20 g, 3 mmol) according to General procedure B. After work-up the residue obtained was purified by column chromatography (33% ethyl acetate/light petroleum) to give *(2-aminophenyl)(1-methyl-1H-pyrrol-2-yl)methanone* **14** (0.15 g, 77%) or *(2-aminophenyl)(1-methyl-1H-3-pyrrolyl)-methanone* **20** (0.14 g, 71%). Compounds **14** and **20** prepared by this method were identical in all respects to the corresponding compounds obtained by General procedure A.

(2-Aminophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (14). (0.16 g, 81%) as pale-yellow microcrystals (toluene); mp=123–124°C [Found C, 71.95; H, 6.02; N, 13.98. $C_{12}H_{12}N_2O$ requires C, 71.98; H, 6.04; N, 13.99%]; ν_{max} (Nujol) 3480, 3370, 1635 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.99 (3H, s, Me), 5.47 (2H, s, NH_2), 6.14 (1H, dd, J=4.0, 2.5 Hz, H-4), 6.65–6.71 (3H, m, H-3, H-3′, H-5′), 6.87 (1H, t, J=2.5 Hz, H-5), 7.25 (1H, td, J=8.2, 1.2 Hz, H-4′), 7.69 (1H, dd, J=7.9, 1.5 Hz, H-6′); m/z (EI) 200 (100, M^+), 183 (51), 172 (21), 119 (36), 81 (27%).

(2-Aminophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone (20). (0.15 g, 74%) as pale-yellow microcrystals (toluene); mp=137–138°C [Found C, 71.96; 7H, 6.05; N, 13.95. $C_{12}H_{12}N_2O$ requires C, 71.98; H, 6.04; N, 13.99%]; ν_{max} (Nujol) 3545, 3425, 1640 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.68 (3H, s, Me), 6.41 (2H, NH_2), 6.46 (1H, dd, J=3.9, 2.4 Hz, H-4), 6.55–6.67 (3H, m, H-3′, H-5, H-5′), 6.88 (1H, s, H-2), 7.21 (1H, dd, J=8.3, 1.3 Hz, H-4′), 7.63 (1H, dd, J=7.8, 1.3 Hz, H-6′); m/z (EI) 200 (M^+, 100), 183 (71), 171 (41), 157 (36), 108 (17), 81 (31%).

Reduction of (2-nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)-methanone and (2-nitrophenyl)(1-methyl-1*H*-3-pyrrolyl)methanone with sodium borohydride in 2-propanol

General procedure C. To a solution of **13** or **19** ((0.35 g, 1.5 mmol) in 2-propanol (25 mL) was added sodium borohydride ((0.08 g, 2.1 mmol). The reaction suspension was refluxed for 18 h, after which the solvent was evaporated to

dryness, water (30 mL) was added to the residue, and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give an oily yellow-brown residue which was purified by column chromatography (20% ethyl acetate/light petroleum) to give two fractions. The first fraction gave *(2-nitrophenyl)(1-methyl-1H-pyrrol-2-yl)methanol* **15** or *(2-nitrophenyl)(1-methyl-1H-pyrrol-3-yl)methanol* **21** and the second fraction gave *(2-nitrosophenyl)(1H-pyrrol-2-yl)methanone* **18** or *(2-nitrosophenyl)(1H-pyrrol-3-yl)methanone* **22**, respectively.

(2-Nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanol (15). (0.13 g, 42%) as a pale-yellow oil bp=134–137°C/12 Torr; ν_{max}(liquid film) 3380, 1530, 1355 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.29 (1H, s, br, OH), 3.75 (3H, s, Me), 5.53 (1H, s, C*H*OH), 5.94 (1H, d, *J*=2.8 Hz, H-5), 6.56–6.61 (2H, m, H-3, H-5), 7.47 (1H, t, *J*=6.0, 1.0 Hz, H-4′), 7.68 (1H, t, *J*=6.5, Hz, H-5′), 7.93–7.98 (2H, m, H-3′, H-6′); *m/z* (EI) 232 (25, M^+), 200 (19), 169 (17), 150 (29), 96 (100), 81 (12%); HRMS (EI): M^+, found 232.0831 $C_{12}H_{12}N_2O_3$ requires 232.0848.

(1-Methyl-1*H*-pyrrol-2-yl)(2-nitrosophenyl)methanone (18). (0.17 g, 48%) as pale-yellow microcrystals (diethyl ether) mp=59–61°C; ν_{max} (Nujol) 1640 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.02 (3H, s, Me), 6.31 (1H, dd, *J*=3.8, 2.7 Hz, H-4), 6.86–6.88 (2H, m, H-3, H-5), 6.98 (1H, t, *J*=8.8, 1.0 Hz, H-4′), 7.30 (1H, t, *J*=9.1, 0.8 Hz, H-5′), 7.53 (1H, dd, *J*=9.1, 1.0 Hz, H-3′), 7.68 (1H, dd, *J*=8.8, 0.8 Hz, H-3′); *m/z* (EI) 214 (11, M^+), 197 (100), 183 (61), 169 (73), 155 (58), 69 (48%); HRMS (EI): M^+, found 214.0745 $C_{12}H_{10}N_2O_2$ requires 214.0742.

(2-Nitrophenyl)(1-methyl-1*H*-pyrrol-3-yl)methanol (21). (0.17 g, 47%) as a pale-yellow oil bp 143–145°C/12 Torr; ν_{max}(liquid film) 3525, 1555, 1360 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.49 (1H, s, br, OH), 3.59 (3H, s, Me), 6.02 (1H, t, *J*=2.2 Hz, H-4), 6.41 (1H, s, C*H*OH), 6.49–6.52 (2H, m, H-2, H-5), 7.44 (1H, td, *J*=8.4, 1.4 Hz, H-4′), 7.65 (1H, td, *J*=7.9, 1.2 Hz, H-5′), 7.90 (1H, dd, *J*=8.4, 1.4 Hz, H-6′), 7.97 (1H, dd, *J*=7.9, 1.2 Hz, H-3′); *m/z* (EI) 232 (17, M^+), 197 (51), 184 (60), 170 (89), 155 (69), 128 (42), 108 (98), 81 (100%); HRMS (EI): M^+, found 233.0882 $C_{12}H_{12}N_2O_3$ requires 233.0881.

(1-Methyl-1*H*-pyrrol-3-yl)(2-nitrosophenyl)methanone (22). (0.08 g, 25%) as pale-yellow microcrystals (diethyl ether) mp=49–50°C; ν_{max} (Nujol) 1650 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.77 (3H, s, Me), 6.73–6.76 (2H, m, H-4, H-5), 6.93 (1H, td, *J*=8.8, 1.0 Hz, H-4′), 7.27 (1H, td, *J*=9.1, 0.9 Hz, H-5′), 7.32 (1H, t, *J*=1.8, Hz, H-2), 7.51 (1H, dd, *J*=9.1, 4.0 Hz, H-6′), 7.69 (1H, dd, *J*=8.8, 0.9 Hz, H-3′); *m/z* (EI) 214 (21, M^+), 198 (100), 183 (78), 169 (82), 108 (71), 69 (79%). HRMS (EI): M^+, found 214.0741 $C_{12}H_{10}N_2O_2$ requires 214.0742.

Reduction of (2-nitrophenyl)(1-methyl-1*H*-pyrrol-2-yl)-methanol and (2-nitrophenyl)(1-methyl-1*H*-pyrrol-3-yl)-methanol with zinc dust and sodium hydroxide in aqueous ethanol

Compound **15** or **21** (0.43 mmol) was dissolved in ethanol (20 mL) and treated with a solution of sodium hydroxide (0.07 g, 4.0 mmol) in water (5 mL) and zinc dust (0.06 g, 0.86 mmol) according to General procedure B. After work-up the residue obtained was purified by column chromatography (11% ethyl acetate/light petroleum) to give *(1-methyl-1H-pyrrol-2-yl)(2-nitrosophenyl)methanone* **18** (0.06 g, 58%) or *(1-methyl-1H-pyrrol-3-yl)(2-nitrosophenyl)methanone* **22** (0.05 g, 52%). Compounds **18** and **22** prepared by this method were identical in all respects to the corresponding compounds obtained by the previous experiment.

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