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A NEW ROUTE TO 3-HETEROARYLINDOLES

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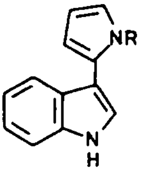
Abstract - The syntheses of 3-(2-pyrrolyl)- and 3-(2-furanyl)-indoles are described via the ring-closure of 2-(2-nitrophenylethenyl)-pyrroles or -furans, respectively, with triethylphosphite. The necessary starting compounds are obtained by Lewis acid mediated Michael type addition reactions of either pyrroles or furans to ß-nitrostyrene, followed by bromination/dehydrobromination. The ethenylpyrroles may also be prepared by similar additions of pyrroles to ß-bromo-ß-nitrostyrenes and dehydrobromination of the products.

3-(2-Pyrrolyl)- and 3-(2-furanyl)-indoles (1) and (2) are relatively unknown[1] structural types, and are not in our experience, accessible by the obvious Fischer indole approaches.[2] A general route to such systems is desirable because of their potential further applications in synthesis.



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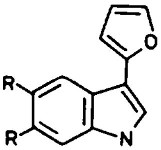

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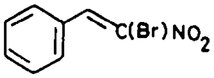
Here we describe a convenient synthesis, firstly, of 3-[2-(N-methylpyrrolyl)] indole (1,R=Me) in which the indole ring is formed in the last step. Thus N-methylpyrrole was reacted with ß-bromo-ß-nitrostyrene (3) at room temperature, in the presence of zinc iodide, to give the adduct (4,R=Me) (95%), which was dehydrobrominated by a suspension of finely divided calcium carbonate in N,N-dimethylacetamide to give the nitrostyrene (5,R=Me) (67%) as a mixture of E and Z-isomers. Cyclisation to the target indole (1,R=Me) was achieved by reaction with triethylphosphite at 160°, in 40% yield.[3] The yield, although modest, is compensated for by the brevity and convenience of the route. No compounds resulting from cyclisation with the more electron rich pyrrole ring were isolated, and when the reaction was repeated with the N-dealkyl-ß-nitrostyrene (5,R=H) a dark intractable tar formed. Since the structures, (6), or (7), to be expected from the alternative cyclisations to the five-membered ring are strained it is possible that they do not survive the relatively harsh conditions and lead, at least in part, to the large amounts of resinous material which always accompany the indoles in the reaction products.



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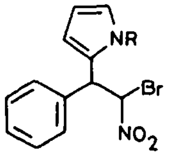

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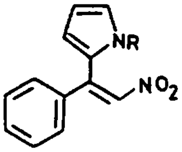

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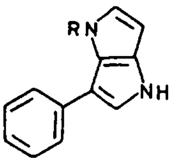

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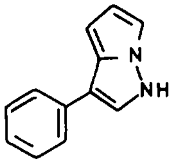

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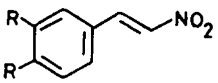

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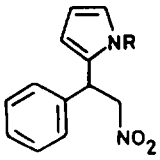
In variations of the reaction sequence pyrrole and N-methylpyrrole were reacted with β-nitrostyrene (8,R=R=H), in the absence of catalyst, to give the corresponding adducts (9) in 68.5 and 88% yields respectively. However, bromination-dehydrobromination attempts on these compounds, which should have led to the appropriate unsaturated derivatives (5), failed because of the facile formation of the corresponding 5-bromopyrroles (10).

Some differences emerged from a study of similar reactions in the furan series: thus whereas furan does not react with β-bromo-β-nitrostyrene (3), it adds to β-nitrostyrene (8,R=R=H) in the presence of zinc iodide to give the nitroethane derivative (11), apparently by a Michael type reaction. No Diels Alder adducts (12) were observed, which contrasts with the facile zinc iodide mediated 1,4-cycloaddition reaction which occurs between furan and nitroacrylates.[4] Reaction of the nitroethane (11,R=R=H) with N-bromosuccinimide together with AIBN as initiator led to the nitroethene (14,R=R=H) directly, in 43% yield, probably via the intermediate bromocompound (13). Cyclisation to the indole (2,R=R=H) was achieved by heating the nitroethene with triethylphosphite at 160°C.

This synthesis was easily extended to the preparation of 5,6-methylenedioxy-3-(2-furanyl) indole (2,R=R=OCH_2O) in 15% yield, although in this case the bromination-debromination step is best carried out by reaction of the nitroethane (11,R=OCH_2O) with bromine and sodium hydride. Once again no product stemming from ring closure to the five-membered ring was obtained.



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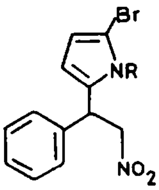

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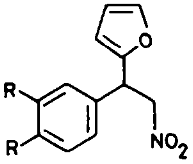

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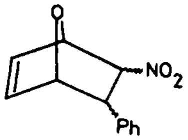

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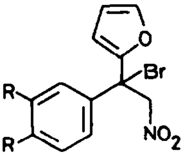

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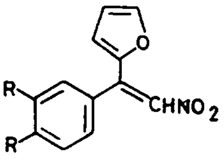

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Acknowledgement

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EXPERIMENTAL

All m.p. are uncorrected. ^{1}H N.M.R. spectra were recorded at 100 MHz and ^{13}C N.M.R. at 22.5 MHz; $CDCl_3$ was employed as solvent with TMS as an internal standard. Chromatography was conducted with silica using petroleum ether (60–80°C) and ethyl acetate mixtures as the eluting medium.

2-(2-Bromo-2-nitro-1-phenylethan-1-yl)-1-methylpyrrole (4,R=Me) A mixture of N-methylpyrrole ($5cm^3$), β-bromo-β-nitrostyrene (2.3g) and anhydrous zinc iodide (0.2g) was stirred for 3 hours under a protective atmosphere of nitrogen, then ethyl acetate ($20cm^3$) and water ($5cm^3$) were added. The organic phase was collected, washed with saturated brine ($5cm^3$), dried, and evaporated to afford a dark coloured oil which was purified by column chromatography. This gave the title compound as a straw coloured oil , 2.95g; 95% yield, based on the styrene; ν_{max} 1560, $1345cm^{-1}$, δ_H 3.35 (s,3H,NCH_3), 4.85 (d,1H,J=11Hz,PhCH), 6.1(m,2H, H-3,H-4), 6.35(d,1H,J=11Hz,$CHNO_2$), 6.45(m,1H,H-5), 7.25(m,5H,aryl protons);*m/z* 310(27%),308 (27%),170(100%) [Found C,50.45;H,4.0;N.9.2 $C_{13}H_{13}N_2O_2Br$ requires: C,50.5;H,4.2;N,9.1%]

2-(2-Bromo-2-nitro-1-phenylethan-1-yl) pyrrole (4,R=H) This compound was made in exactly the same way from β-bromo-β-nitrostyrene and pyrrole. Yield 88.5%; It is a pale brown solid, m.p. 76–80°C, which gradually darkens in air and light; ν_{max} 3470, 1565, 1355cm^{-1}; δ_H 4.92 (d,1H,*J*=11Hz,PhCH), 6.15 (m,2H,H-3,H-4), 6.35 (d,1H,*J*=11H$_z$,CHNO$_2$), 6.65 (m,1H,H-5), 7.3 (m,5H,aryl protons), 7.9 (bs,1H,NH); *m/z* 296 (18%), 156 (100%) [Found: C,48.9; H,4.0; N.9.6 $C_{12}H_{11}BrN_2O_2$ requires: C,48.8; H,3.8; N,9.5%

1-Methyl-2-(2-nitro-1-phenylethan-1-yl) pyrrole (9,R=Me) The title compound is a yellow oil; ν_{max} 1555 cm^{-1}; δ_H 3.25 (s,3H,CH$_3$), 4.80 (m,3H,PhCH,CH$_2$NO$_2$), 6.08 (d,2H,*J*=2.5Hz,H-3,H-4),6.52 (t,1H,*J*=2.5Hz H-5), 7.2 (m,5H,aryl protons); *m/z* 230 (100%), 183 (88%), 170 (63%) [Found: 230.1050 $C_{13}H_{14}N_2O_2$ requires: 230.1055] and 2-(2-nitro-1-phenylethan-1-yl) pyrrole 9, R=H , an off-white solid, m.p. 77–77.5°C; ν_{max} 3460, 1550 cm^{-1}, δ_H 4.70 (m,3H,PhCH,CH$_2$NO$_2$), 6.05 (m,2H,H-3,H-4), 7.1 (m,5H,aryl protons), 7.75 (bs,1H,NH); *m/z* 216 (24%), 169 (100%) [Found: C,66.6; H,5.5; N,12.9 $C_{12}H_{12}N_2O_2$ requires: C,66.65; H,5.6;N,12.95%] were similarly prepared from β-nitrostyrene and N-methylpyrrole and pyrrole, respectively. No catalyst was required. For the first compound the yield was 68.5% and for the second 88%.

1-Methyl-2-(2-nitro-1-phenylethen-1-yl) pyrrole (5,R=Me) The ethylpyrrole (4,R=Me) (2.4g) in *N*, *N*-dimethylacetamide (5cm^3) and ethanol (45cm^3) was stirred for 48 hours with finely divided calcium carbonate (1.5g), the mixture was then filtered. The filtrate was diluted with ethyl acetate (50cm^3) and washed with water (2 x 10cm^3), dried and evaporated to yield an oil which was chromatographed. This afforded the title compound, a mixture of *E* and *Z*-isomers, as a low m.p. solid (1.2g, 67% yield); λ_{max}230nm, ν_{max}1550cm^{-1}, δ_H 3.25(2xs,3H,CH$_3$), 6.23 (m,2H,H-3,H-4), 6.82 (m,1H,H-5), 7.32 (m,6H,CHNO$_2$, aryl protons), *m/z* 228 (42%), 185 (100%), 184 (62%) [Found 228.0890 $C_{13}H_{12}N_2O_2$ requires: 228.0899].

2-(2-Nitro-1-phenylethen-1-yl) pyrrole (5,R=H), an oil, was similarly prepared from the ethylpyrrole (4,R=H) in 63% yield; λ_{max} 235nm, ν_{max} 3440, 3340, 1555cm^{-1}, δ_H 6.22 (m,2H, H-3,H-4), 6.84 (s,1H,CHNO$_2$), 7.13 (m,1H,H-5), 7.32 (m,5H,aryl protons), 8.75 (bs,1H,NH), *m/z* 214 (57%), 171 (100%) [Found: 214.0738 $C_{12}H_{10}N_2O_2$ requires: 214.0742].

3-(1-Methylpyrrol-2-yl)indole (1,R=Me) The nitroethene (5,R=Me) (0.7g) and triethylphosphite (15cm^3) were heated to 160 ± 3°C for 6 hours under a nitrogen atmosphere. Excess reagent was then removed under reduced pressure and the residue chromatographed to afford the title compound as a pale yellow oil (0.24g, 40%) ; ν_{max} 3450, 1580, 1440 cm^{-1}; δ_H 3.51 (s,3H,NCH$_3$), 6.34 (d,2H,*J*=2.5H$_z$,H-3',H-4'), 6.75 (t,1H,*J*≈2.5H$_z$,H=5), 6.98 (bd,1H,J≈3H$_z$,H-2), 7.18 (m,3H,H-5,H-6,H-7), 7.70 (bm,2H,H-4,NH); 196 (100%), 195 (60%) [Found: 195.9996 $C_{13}H_{12}N_2$ requires: 196.0000].

2-(2-Nitro-1-phenylethan-1-yl) furan (11, R=R=H) A mixture of furan (25cm^3), β-nitrostyrene (6g) and zinc iodide (3.2g) was stirred, under a protective atmosphere of nitrogen, for 3 days at room-temperature. The reaction mixture was then partitioned between ethyl acetate (50cm^3) and water (10cm^3), and the organic phase, dried and evaporated to give the title compound as an oil. Purification was achieved by chromatography affording a pale yellow gum (6.8g, 78%); ν_{max} (liquid film) 1550; δ_H 4.85 (m,3H,PhC$\underline{H}$-C$\underline{H}_2$NO$_2$), 6.05 (d,1H,$\underline{J}$=3.5Hz, H-3) 6.24 (dd,1H,$\underline{J}_1$=3.5Hz,$\underline{J}_2$=3Hz,H-4), 7.22 (m,6H,H-5,aryl protons); *m/z* 217 (20%), 170 (100%) [Found: 217.0738 $C_{12}H_{11}NO_3$ requires: 217.07389].

2-[1-(3,4-Methylenedioxyphenyl ethan-1-yl)-2-nitro furan] (11, R=R=OCH$_2$O) was similarly prepared from 3,4-methylenedioxy-β-nitrostyrene and furan in 24% yield, as an oil: ν max 1550cm^{-1}; δ_H 4.9 (m,3H,Ar,C$\underline{H}$-C$\underline{H}_2$NO$_2$), 5.98 (s,2H,OC$\underline{H}_2$O), 6.15 (d,1H,$\underline{J}$=3.5Hz,H-3H), 6.35 (dd,1H,$\underline{J}$=3.5Hz,$\underline{J}_2$=3Hz,H-4), 6.78 (bs,3H,aryl protons), 7.36 (d,1H,$\underline{J}$=3Hz,H-5); δ_C43.3 (d,Ar$\underline{C}$H) 78.2 (t,$\underline{C}$H$_2$NO$_2$), 101.4 (t,O$\underline{C}$H$_2$O), 107.3 (d,C-3), 108.2 (d,C-2'), 108.7 (d,C-5'), 110.5 (d,C-4), 121.4 (d,C-6'), 130.7 (s,C-1'), 142.6 (d,C-5), 147.5 (s,C-3'), 148.2 (s,C-4'), 152.2 (s,C-2); *m/z* 261 (21%), 214 (100%) [Found: 261.0634 $C_{13}H_{11}NO_5$ requires: 261.0637].

(E/Z)-2-(2-Nitro-1-phenylethen-1-yl) furan (14, R=R=H) The furanylethane (11, R=R=H) (0.65g) in carbon tetrachloride (20cm^3) was treated with N-bromosuccinimide (0.54g) and azobisisobutryonitrile (0.67g). After stirring for 15 minutes at room-temperature, the mixture was heated at reflux for 1 hour, cooled and partitioned between ethyl acetate (20cm^3) and water (10cm^3). The organic phase was then collected, dried and evaporated to give an oil which was chromatographed to afford the title compounds as a pale yellow gum (0.28g, 43%); λ_{max} 343 nm; ν_{max} 1605, 1550cm^{-1}; δ_H 6.28 (d,1H,$\underline{J}$=3.5Hz,H-3), 6.48 (dd,1H,$\underline{J}_1$=3.5Hz,$\underline{J}_2$=3Hz,H-4), 7.4 (m,5H,aryl protons), 7.58 (d,1H,$\underline{J}$=3Hz,H-5), 7.71 (s,1H,C$\underline{H}$ =NO$_2$); *m/z* 215 (100%), 170 (67%) [Found: 215.0580 $C_{12}H_9NO_3$ requires: 215.0582].

(E/Z)-2-[1-(3,4-Methylenedioxyphenylethen)-2-nitroethen-1-yl] furan (14, R=R=OCH$_2$O) The furanylethane (11, R=R=OCH$_2$O) (2.35g) in dry tetrahydrofuran (60cm^3) maintained at 0°C was added slowly to a suspension of sodium hydride (0.72g) in the same solvent (20cm^3). After the addition, bromine (0.46cm^3) in carbon tetrachloride (80cm^3) was introduced and the reaction mixture was allowed to warm to room-temperature overnight. Next day the solvents were partly removed by evaporation and ethyl acetate (150cm^3) was added, together with aqueous sodium sulphite (2M,15cm^3). Water (100cm^3) was then introduced and the organic phase separated, washed with hydrochloric acid (2M, 2 x 50cm^3 and water 100cm^3), dried and evaporated to afford an oil. This was chromatographed to give a yellow gum 1.35g, 58%); ν_{max} 1600, 1550cm^{-1}; δ_H 6.02 (s2H,OC$\underline{H}_2$O), 6.38 (d,1H,$\underline{J}$=3.5Hz,H-3), 6.48 (dd,1H,$\underline{J}_1$=$\underline{J}_2$=3.5Hz,H-4), 6.76 (m,2H,H-2',H-6'), 6.86 (d,1H,$\underline{J}$=3Hz,H-5), 7.57 (d,1H,$\underline{J}$=8Hz, H-5'), 7.64 (s,1H,C$\underline{H}$NO$_2$); δ_C 101.4 (t,O$\underline{C}$H$_2$O), 108.2 (d,C-3), 109.1 (d,C-4), 111.9 (s,C-1'), 112.9 (d,C-6'), 119.3 (d,C-2'), 122.4 (d,C-5'), 125.8 (s,Ar$\underline{C}$), 131.4 (d,C-5), 138.0 (s,CNO$_2$), 145.9 (a,$\underline{C}$H=NO$_2$), 147.6, 148.5 (2 x s,C-3',C-4'); *m/z* 259 (100%), 227 (49%), 187 (39%) [Found: 259.0476 $C_{13}H_9NO_5$ requires: 259.0481].

3-(2-Furanyl) indole (2,R=R=H) The ethenylfuran (14,R=R=H) (0.16g) and triethyl phosphite (5cm^3) were heated at 160 ± 3°C for 6 hours under a nitrogen atmosphere. After this time excess reagent was removed under reduced pressure, and the residue partitioned between ethyl acetate (50cm^3) and water (20cm^3). The organic phase was then collected, dried and evaporated to yield a gum which was purified by chromatography to afford the title compound as a pale brown solid (0.04g, 30%), m.p. 90-91°C; λ_{max} 228, 265nm; ν_{max}, 3470, 1605cm^{-1}; δ_H 6.4 (m,2H,H-3',H-4'), 7.14 (m,3H,H-5,H-6,H-7), 7.32 (m,2H,H-2,H-5'), 7.85 (bm,2H,H-4,NH); *m/z* 183 (100%), 154 (64%) [Found: C, 78.6; H, 5.0; N, 7.5 $C_{12}H_9NO$ requires: C, 78.7; H, 4.95; N, 7.65%].

3-(2-Furanyl)-5,6-methylenedioxyindole (2,R=R=OCH$_2$O), an oil, was obtained in similar manner from the corresponding ethenylfuran (14, R=R=OCH$_2$O) in 40% yield; ν_{max} 3450, 1600cm^{-1}; δ_H 5.97 (s,2H,OCH$_2$O), 6.47 (d,1H,J=3.5H$_z$,H-3'), 6.51 (d,d,1H,J_1J_2=3.5H$_z$,H-4) 6.77 (s,1H,H-7), 7.32 (d,1H,*J*=3.5H$_z$,H-5'), 7.37 (s,1H,H-4), 7.46 (bs,1H,H-2), 8.04 (bs,1H,N-H); δ_C 91.9 (t,OCH$_2$O), 98.8 (d,C-4'), 100.6 (d,C-3'), 102.8 (d,C-4), 109.3 (s,C-3),110.9 (d,C-7), 118.1 (s,C-3a), 119.7 (d,C-2), 131.0 (s,C-7a), 139.9 (d,C-5'), 143.5 (s,C-6), 150.5 (s,C-2'); *m/z* 227 (100%) [Found: 227.0580 $C_{13}H_9NO_3$ requires: 227.0584].

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