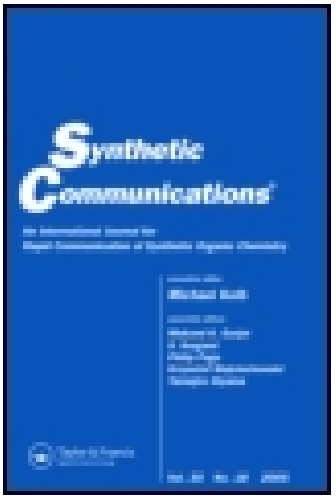

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Synthesis of 3-Aryl-5h-Pyrido[4,3-b]indoles

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SYNTHESIS OF 3-ARYL-5H-PYRIDO[4,3-b]INDOLES

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ABSTRACT : 3-aryl-γ-carbolines (**8**) were synthesised by the thermal decomposition of 3-azidomethyl-2-(β-arylvinyl)-1-phenylsulfonyl indole (**6**).

Due to the promising medicinal properties of β and γ carbolines[1-3], there is plethora of reports[4,5] for the synthesis of these compounds involving the thermal decomposition of vinylic azides. The synthesis of genotoxic heterocyclic amines, a γ-carboline derivative has been reported[6] using the thermal electrocyclisation of 1-azahexa-1,3,5-triene system involving the indole (b) bond. To the best of our knowledge there is no report of γ-carboline synthesis involving an intramolecular addition of nitrene to a carbon-carbon double bond. In continuation of our studies of extended heterocyclic systems with potential DNA intercalating properties[7], we report here a new synthesis of 3-aryl γ-carbolines by the thermal decomposition of indol-3-yl methylazide.

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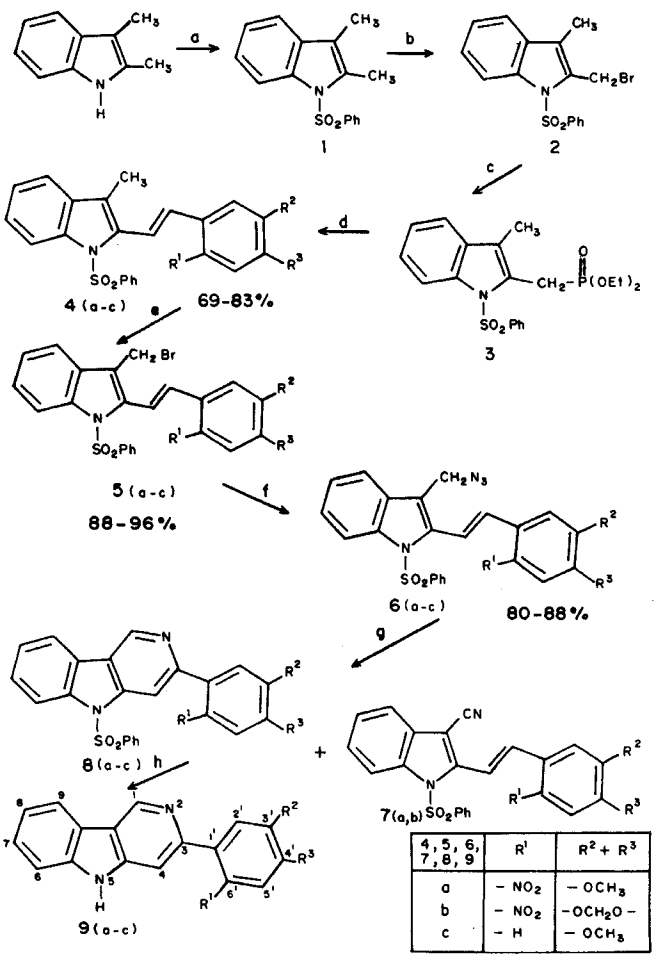
2,3-dimethylindole was N-benzenesulfonylated and then brominated with 1 eq.NBS to give exclusively the 2-bromomethyl derivative[8] (**2**). The Arbuzov reaction of (**2**) followed by Wittig-Horner reaction[9] at rt gave (**4**) in 69-83 % yields. The structure of the arylvinyl indoles (**4**) were confirmed by IR and ^1H NMR. The bromination of (**4**) with 1 eq.NBS gave the 3-bromomethyl compound (**5**). This bromo compound (**5**) was converted to the corresponding azide (**6**) by stirring with 1.5 eq. of NaN_3 in dry DMF. The thermolysis of azide (**6**) in refluxing xylene in the presence of 10 % Pd-C gave the expected carboline (**8**). When R^1 = $-NO_2$ ie in the case of (**6a**) & (**6b**) 3-cyano-2-arylvinylindoles (**7**) were also obtained in addition to the carbolines. But in the case of (**6c**) only the carboline (**8c**) was the exclusive product. Finally the benzenesulfonyl group of the carbolines (**8**) was cleaved by 10% NaOH in DMSO. The compound (**7**) showed a -C≡N stretching frequency at 2250Cm^{-1} and $-NO_2$ stretching frequency at 1500 & 1320Cm^{-1} in IR and the vinylic proton pattern was confirmed by ^1H NMR. The compounds (**8**) and (**9**) showed satisfactory spectral data.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 instrument. PMR spectra were recorded at 90 or 400 MHz instrument and the chemical shifts were given in ppm downfield from TMS. HRMS data were obtained using Finnigan MAT 8230 Mass Spectrometer. TLC was developed on a glass plates coated with silica gel (ACME) of 0.25mm thickness and visualised with iodine. Chromatographic separations were performed on alumina (neutral).

Scheme



Reagents and Conditions: (a) NaH/THF, $PhSO_2Cl$, 81%; (b) NBS/CCl_4, Δ, 92%; (c) $(EtO)_3P$, Δ, 91%; (d) NaH/THF, ArCHO; (e) NBS/CCl_4, Δ; (f) NaN_3/DMF; (g) Pd-C/xylene, Δ; (h) 10% NaOH, DMSO.

1-(phenylsulfonyl)-2,3-dimethylindole (1). 2,3-dimethylindole (7.25g, 50 mmol) in dry THF (100 mL) was slowly added to a stirred suspension of NaH (1.44g, 60mmol) in dry THF (50 mL) under N_2 at rt. After 2h it was cooled to -10°C, followed by the slow addition of a solution of $PhSO_2$ Cl (10.5 g, 60 mmol) in THF (50mL). The mixture was stirred at 0-5°C for 1 h. The solution was then poured over ice (500 g) and treated with saturated solution of NH_4Cl (50mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were washed with H_2O (200 mL), brine (2x150 mL) and dried (K_2CO_3) and concentrated in vacuo to give a sticky residue. Recrystallisation from MeOH gave 11.5 g (81%) of **1** as colorless crystal. mp 140°C; **IR (KBr)** 1380 and 1140 Cm^{-1} (SO_2); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 2 (s, 3 H, CH_3), 2.5 (S, 3 H, CH_3), 7 - 8.2 (m, 9 H, ArH).

1-(phenylsulfonyl)-3-methyl-2-bromomethylindole (2). A suspension of **1** (11.4g, 40 mmol) and benzoyl peroxide (50 mg) in dry CCl_4 (400 mL) containing finely powdered NBS (7.5 g, 42 mmol) was refluxed for 2h. The suspension was then cooled to rt filtered and the filtrate concentrated in vacuo to give bromo compound (**2**) as heavy crystals. Yield 13.4 g (92 %); mp 136°C (CCl_4); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 2.2 (s, 3 H, -OCH_3), 5.1 (S, 2 H, -CH_2Br), 7.4-8.1 (m, 9 H, ArH).

Diethyl[(1-phenylsulfonyl)-3-methylindol-2-yl]methyl phosphonate (3). A mixture of bromomethylindole **2** (3.64g, 10 mmol) and triethyl phosphite (4g, 24 mmol) was heated under N_2 at 160°C for 2h. The sticky oil was then poured over ice (200 g) and acidified with con-HCl (1 mL). The solid formed

was filtered and dried over $CaCl_2$. Yield 3.8g (91 %); mp 110°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 1.4 (t, 6 H, $-OCH_2\underline{CH_3}$), 2.4 (d, 3 H, $-CH_3$), 3.8 (s, 2 H, $-\underline{CH_2}-PO(OEt)_2$), 4.2 (q, 4 H, $-O\underline{CH_2}CH_3$), 7.1-8.2 (m, 9 H, ArH).

General procedure for Wittig-Horner reaction of the phosphonate ester (3) with aromatic aldehydes: To a suspension of NaH (150 mg, 6 mmol) in dry THF (20 mL) at rt, the phosphonate ester **3** (2.15g, 5 mmol) in dry THF (40 mL) was slowly added under N_2 and stirred for 2 h. A solution of arylaldehyde (7 mmol) in dry THF (20 mL) was slowly added to this. Stirring was continued for further 8 h. Then the pale yellow solution was poured over ice (200 g) and then acidified with con-Hcl (1 mL). The solid was filtered and washed with MeOH. The crude product was recrystallised from EtOAC or EtOH-$CHCl_3$.

3-methyl-1-phenylsulfonyl-2-[β(6'-nitroveratryl)vinyl]indole (4a). Yield 2 g (83 %); mp 200°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 2.4 (s. 3 H, $-CH_3$), 4 (s. 3 H, $-OCH_3$), 4.1 (s, 3 H, $-OCH_3$), 7.2-8.2 (m, 13 H, ArH & vinylic-CH).

3-methyl-1-phenylsulfonyl-2-[β(6'-nitropiperanyl)vinyl]indole (4b). Yield 1.7 g (74 %); mp 232°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 2.3 (s, 3 H, $-CH_3$), 6.1 (s, 2 H, $-OCH_2O-$), 7.1-8.2 (m, 13 H, ArH & vinylic-CH).

3-methyl-1-phenylsulfonyl-2-[β(3',4'-dimethoxyphenyl)vinyl] indole (4c). Yield 1.5 g (69 %) ; mp 176°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 2.4 (s, 3 H, $-CH_3$), 4.35-4.4 (2s, 6 H, $-OCH_3$), 6.6-8.4 (m, 14 H, ArH & vinylic-CH).

3-bromomethyl-1-phenylsulfonyl-2-[β(6'-nitroveratryl) vinyl] indole (5a). The procedure was similar to that of **2** except that the amount of CCl_4

was 400 mL for 5 mmol scale to avoid the solubility problem. Yield 5 g (90 %); mp 170°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4-4.3 (2s, 6 H,-OCH_3), 4.9 (s, 2 H, -CH_2Br), 7.2-8.2 (m, 13 H, ArH & vinylic-CH).

3-bromomethyl-1-phenylsulfonyl-2-[β(6'-nitropiperanyl)vinyl]indole (5b). Yield 5.2 g (96 %); mp 214°C; **^{1}H NMR** could not be recorded due to poor solubility of this compound.

3-bromomethyl-1-phenylsulfonyl-2-[β(3',4'-dimethoxyphenyl) vinyl]indole (5c). Yield 4.5 g (88 %). This compound did not crystallise and hence used as such for further reaction.

3-azidomethyl-1-phenylsulfonyl-2-[β(6'-nitroveratrayl)vinyl]indole (6a). To a solution of bromo compound **5a** (2.8 g, 5 mmol) in dry DMF (30 mL), NaN_3 (650 mg, 10 mmol) was added and stirred at rt for 10 h. Then it was poured over ice (100 g) and the solid was filtered and dried over $CaCl_2$. Yield 2.1 g (84 %); mp 168°C; **IR (KBr)** 2100 (N_3), 1500 and 1280 (NO_2), 1380 and 1170 Cm^{-1} (SO_2), **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4.1-4.2 (2s, 6 H, -OCH_3), 4.6 (s, 2 H, -CH_2N_3), 7-8.3 (m, 13 H, ArH & vinylic-CH).

3-azidomethyl-1-phenylsulfonyl-2-[β(6'-nitropiperanyl)vinyl]indole (6b). The procedure was similar to that of (**6a**); yield 2.2 g (88 %); mp 186°C; **IR (KBr)** 2100 (N_3), 1510 and 1290 (NO_2), 1380 and 1170 Cm^{-1} (SO_2); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4.6 (s, 2 H, -CH_2N_3), 6.1 (s, 2 H, -OCH_2O-), 7.2-8.2 (m, 13 H, ArH & vinylic-CH).

3-azidomethyl-1-phenylsulfonyl-2-[β(3',4'-dimethoxyphenyl)vinyl] indole (6c). Yield 1.9 g (80 %); **IR (KBr)** 2100 (N_3), 1500 and 1260 (NO_2),

1380 and 1160 Cm^{-1} (SO_2), **^{1}H NMR** (90 MHz, $CDCl_3$) δ 3.9-4 (2s, 6 H, $-OCH_3$), 4.5 (s, 2 H, $-CH_2N_3$), 6.7-8.4 (m, 14 H, ArH and vinylic-CH).

General procedure for the thermolysis of azide: A solution of azide **6** (2 mmol) in dry xylene (80 mL) containing 10% Pd-C (50 mg) was refluxed for 20 h. The Pd-C was filtered off and the xylene was removed completely. The residue was applied to a column of alumina and eluted with EtOAC-benzene (1:4).

3-cyano-1-phenylsulfonyl-2-[β (6'-nitroveratryl)vinyl]indole (7a). Yield 250 mg (26 %); mp 144°C; **IR (KBr)** 2260 (CN), 1520 and 1270 (NO_2), 1380 and 1180 Cm^{-1} (SO_2); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4-4.1 (2s, 6 H, $-OCH_3$), 7.3-8.5 (m, 13 H, ArH & vinylic-CH). **HRMS** Calcd for $C_{25}H_{19}N_3O_6S$ 489.0994, found M^+ 489.0962.

3-(6'-nitroveratryl)5-phenylsulfonylpyrido[4,3-b]indole (8a). Yield 400 mg (41 %); mp 118°C; **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4 (s, 6 H, $-OCH_3$), 7.2-8.2 (m, 11 H, ArH), 8.4 (s, 1 H, 4-H), 9.3 (s, 1 H, 1-H).

3-cyano-1-phenylsulfonyl-2-[β(6'-nitropiperanyl)vinyl]indole(7b).Yield 300 mg (32 %); mp 246°C; **IR (KBr)** 2240 (CN), 1490 and 1320 (NO_2), 1370 and 1170 Cm^{-1} (SO_2); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 6.1 (s, 2 H, $-OCH_2O-$), 7.2-8.3 (m, 13 H, ArH & vinylic-CH). **HRMS** Calcd for $C_{24}H_{15}N_3O_6S$ 473.0681, found M^+ 473.0656.

3-(6'-nitropiperanyl)5-phenylsulfonylpyrido[4,3-b]indole (8b). Yield 290 mg (31 %); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 6.2 (s, 2 H, $-OCH_2O-$), 7.1-8.3 (m, 11 H, ArH), 8.5 (s, 1 H, 4-H), 9.4 (s, 1 H, 1-H).

3-(3',4'-dimethoxyphenyl)5-phenylsulfonylpyrido[4,3-b]indole (8c). Yield 500 mg (56 %); **^{1}H NMR** (90 MHz, $CDCl_3$) δ 4-4.1 (2s, 6 H, $-OCH_3$), 7-8.5 (m, 12 H, ArH), 8.7 (s, 1 H, 4-H), 9.3 (s, 1 H, 1-H).

3-(6'-nitroveratryl)5H-pyrido[4,3-b]indole (9a). To a solution of **8a** (245 mg, 5 mmol) in DMSO (10 mL), 50 % NaOH (1 mL) was added stirred at rt for 6h. The solution was then poured over ice (100 g) and then slightly warmed to avoid emulsification. The solid was filtered and dried over $CaCl_2$. The crude **9a** was recrystallised from $CHCl_3$; 160 mg (91 %); mp 296°C; **IR (KBr)** 3500 (NH), 1600, 1500, 1330 Cm^{-1}; **^{1}H NMR** (400 MHz DMSO-d_6) δ 3.9-4 (2s, 6 H, $-OCH_3$), 7.3 (s, 2 H, 2'-11 & 5'-H), 7.5 (m, 1 H, 7-H), 7.6 (m, 2 H, 6-H & 8-H), 7.75 (s, 1 H, 4-H), 8.25 (d, 1 H, 9-H), 9.3 (s, 1 H, 1-H), 11.85 (bs, 1 H, NH). **HRMS** Calcd for $C_{19}H_{15}N_3O_4$ 349.1062, found M^+ 349.1025.

3-(6'-nitropiperanyl)5H-pyrido[4,3-b]indole (9b). The procedure was similar to that of **9a**. Yield 150 mg (90 %); mp 286°C; **IR (KBr)** 3420 (NH), 1600, 1460, 1340, 1250 Cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.3 (s, 2 H, $-OCH_2O-$), 7.3 (t, 1 H, 7-H), 7.38 (s, 1 H, 2'-H), 7.5 (t, 1 H, 8-H), 7.6 (m, 2 H, 5'-H & 6-H), 7.68 (s, 1 H, 4-H), 8.25 (d, 1 H, 9-H), 9.3 (s, 1 H, 1-H), 11.9 (bs, 1 H, NH). **HRMS** Cacld for $C_{15}H_{11}N_3O_4$ 333.1749 found M^+ 333.1694.

3-(3',4'-dimethoxyphenyl)5H-pyrido[4,3-b]indole (9c). Yield 140 mg (89 %); mp 200°C; **IR (KBr)** 3400 (NH), 1600 Cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.8-3.95 (2s, 6 H, $-OCH_3$), 7.05 (m, 1 H, 6'-H), 7.25 (m, 1 H, 5'-H), 7.45 (m, 1 H, 7-H), 7.55 (m, 1 H, 8-H), 7.7 (d, 1 H, 6-H), 7.8 (s, 1 H,

2'-H), 7.9 (s, 1 H, 4-H), 8.2 (d, 1 H, 9-H), 9.38 (s, 1 H, 1-H), 11.6 (bs, 1 H, NH). **HRMS** Cacld for $C_{19}H_{16}N_2O_2$ 304.1212, found M^+ 304.1197.

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