Synthesis and cycloaddition of 2,4-dihydropyrrolo[3,4-*b*]indoles

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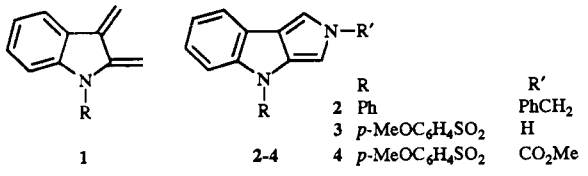
Friedel–Crafts acylation of 2-methyl-1-phenylsulfonylindole **6** gave the 3-acyl derivatives **7** which upon side chain bromination with *N*-bromosuccinimide (NBS) followed by treatment with primary amines afforded the title compounds **9**. Diels–Alder reaction of **9** with dimethyl acetylenedicarboxylate (DMAD) gave the polysubstituted carbazoles **12**.

Indole-2,3-quinodimethane **1**, a widely studied heterocyclic reactive intermediate,[1] has been used in inter- and intramolecular Diels–Alder reactions to synthesize[2–6] many alkaloids. Our interest was the synthesis of stable analogues of **1** with greater regioselectivity in cycloadditions.



1 2-4

The synthesis of furo[3,4-*b*]indoles and their cycloaddition to carbazoles and pyridocarbazoles have been reported by Gribble *et al.*,[7] whilst the synthetic use of pyrano[3,4-*b*]indole-3-ones has been illustrated by Moody[8] and Pindur.[9] The first synthesis of 2,4-dihydropyrrolo[3,4-*b*]indole **2** with a phenyl substituent on the indole nitrogen was reported[10] by Welch whilst Sha and co-workers synthesized[11] the two pyrroloindoles **3** and **4**. The corresponding adduct of **4** with dienophiles from Diels–Alder reactions has also been reported.[11]

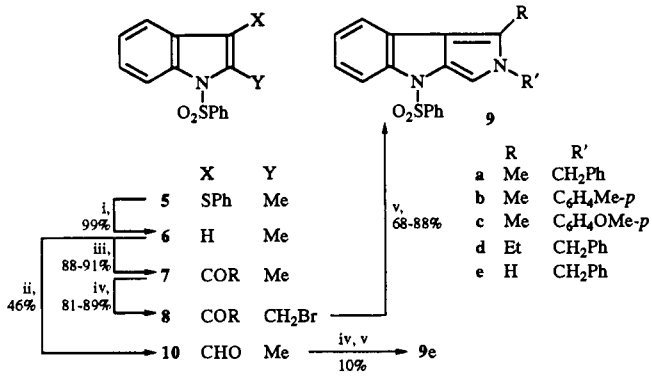
Results and discussion

Compound **5** has been extensively used for the synthesis[12] of 2-substituted indoles with a vacant 3-position. Desulfurization of **5** using Raney nickel in boiling ethanol gave **6**, acylation of which with acid anhydrides afforded the corresponding 3-acyl derivatives **7**. Bromination of **7** with *N*-bromosuccinimide (NBS) in CCl_4 gave the corresponding 2-bromomethyl derivatives **8**, treatment of which with a primary amine in chloroform at 30 °C gave pyrrolo[3,4-*b*]indoles **9a–d** (66–88%). In order to prepare the pyrroloindole **9e** unsubstituted at the C-1 position, formylation of **6** was carried out to give **10**. A similar sequence of reactions gave **9e** in an overall yield of only 10%.

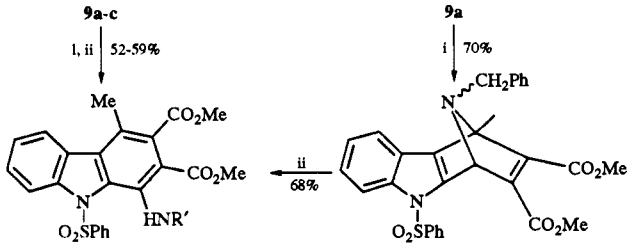
This is a facile and general route for the synthesis of stable analogues of **1** from readily available and inexpensive starting materials using mild reaction conditions

A one-pot synthesis of carbazoles **12a–c** was achieved by carrying out the Diels–Alder reaction of **9a–c** with dimethyl acetylenedicarboxylate (DMAD) followed by the addition of toluene-*p*-sulfonic acid to the boiling solution. Only in the case of **9a** was the cycloadduct **11** isolated and characterized.

Although there are reports[7,11,13] for aromatization of adducts of similar ring system, they suffer extrusion of the heteroatom at the bridging position. But in this case PTS in boiling THF liberated the nitrogen from the bridge to give the corresponding 1-arylamino- or 1-benzylamino-carbazoles **12**. Although there are many syntheses for functionalized carbazoles, there are few reports for the synthesis of amino substituted carbazoles.[14] This methodology constitutes an attractive route for the synthesis of such compounds.



Reagents: i, Raney Ni, EtOH; ii, $DMF–POCl_3$; iii, $(RCO)_2O$, CH_2Cl_2, $AlCl_3$; iv, N B S, CCl_4, $(PhCO_2)_2$ v, R^1NH_2, $CHCl_3$, K_2CO_3



Reagents: i, DMAD, THF; ii, PTS. **12a** (R^1 = CH_2Ph); **12b** (R^1 = C_6H_4Me-*p*); **12c** (R^1 = C_6H_4OMe-*p*)

Experimental

General directions

^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) or a Hitachi R-1100 (60 MHz) spectrometer using tetramethylsilane as reference. ^{13}C NMR spectra were recorded using Bruker MSL 300P (75 MHz). High-resolution mass spectra were recorded on a Finnigan MAT 8230 mass spectrometer. IR spectra were recorded either on a Perkin-Elmer 598 or Philips model PU 9716 spectrophotometer. Reagents and solvents were purified by standard methods. Silica gel used for chromatography was Acme's 100–200 mesh.

Desulfurization of 5

Compound **5** (4 g, 10.55 mmol) and Raney Nickel ($\approx$ 12 g) were taken in dry ethanol (120 cm^3) and refluxed for 8 h. The catalyst

was filtered off and washed with hot ethanol (3 × 30 cm^3). The combined filtrates were concentrated and the residue was taken up in ethyl acetate (60 cm^3), dried (Na_2SO_4), and evaporated to give the product **6** as a thick syrup (2.7 g, 99%).[7]

3-Acyl-2-methyl-1-phenylsulfonylindoles 7

General procedure. The appropriate acid anhydride (20 mmol) was added dropwise under nitrogen to a stirred solution of anhydrous aluminium chloride (2.05 g, 20 mmol) in dry methylene dichloride (60 cm^3) and stirring was continued for 30 min at 30 °C. After this, a solution of **6** (9.6 mmol) in methylene dichloride (100 cm^3) was added dropwise to the mixture which was then stirred for 12h before being poured over ice and acidified with 12 mol dm^{-3} HCl. The organic layer was separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic layer and extracts were washed with aqueous sodium hydrogen carbonate (2 × 30 cm^3) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was recrystallized to give compound **7**.

3-Acetyl-2-methyl-1-phenylsulfonylindole 7a. (1.4 g, 89%); mp 118–119 °C (ethyl acetate) (lit.,[7] mp 118–121 °C).

2-Methyl-1-phenylsulfonyl-3-propionylindole 7b. (2.27 g, 91%); mp 114 °C (benzene–hexane); ν_{max}(KBr)/cm^{-1} 1670 (C=O), 1150 and 1360 (SO_2); δ_H($CDCl_3$) 1.2 (3 H, t, CH_2CH_3), 2.8 (2 H, q, CH_2CH_3), 2.9 (3 H, s, CH_3) and 7.4–8.6 (9 H, m, ArH) (Found: M^+, 327.0886. $C_{18}H_{17}NSO_3$ requires M^+, 327.0929).

3-Acyl-2-bromomethyl-1-phenylsulfonylindoles 8

General procedure. A solution of 3-acylindole **7** (4 mmol) in CCl_4 (50 cm^3) containing finely powdered NBS (4 mmol) and dibenzoyl peroxide (10 mg) was refluxed for 5 h and then cooled. The succinimide was filtered off and the filtrate was concentrated to 20 cm^3 and left at room temperature to afford the pure bromo compound **8a,b** as a crystalline solid.

Compound **8a.** (1.4 g, 89%), mp 132–133 °C, ν_{max}(KBr)/cm^{-1} 1665 (CO), 1170 and 1370 (SO_2); δ_H($CDCl_3$) 2.7 (3 H, s, $COCH_3$), 5.35 (2 H, s, CH_2 Br) and 7.4–8.5 (9 H, m, ArH). Compound **8b** (1.3 g, 81%), mp 120 °C, ν_{max}(KBr)/cm^{-1} 1670 (CO), 1170 and 1370 (SO_2); δ_H($CDCl_3$) 1.3 (3 H, t, CH_2CH_3), 3.0 (2 H, q, CH_2CH_3), 5.4 (2 H, s, CH_2Br) and 7.2–8.4 (9 H, m, ArH).

Pyrrolo[3,4-*b*]indoles 9a–d

General procedure. A solution of **8** (2.5 mmol) and the appropriate amine (5.1 mmol) in $CHCl_3$ (50 cm^3) containing K_2CO_3 (1 g) was stirred for 12 h at 30 °C. The mixture was poured over ice and acidified (pH 6) by dil. HCl. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (30 cm^3). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The residue was passed through a column of silica gel to afford **9a–d** in 68–88% yield.

2-Benzyl-1-methyl-4-phenylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole 9a. (0.9 g, 88%); mp 190 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 1180 and 1370 (SO_2); δ_H($CDCl_3$) 2.4 (3 H, s, CH_3), 5.2 (2 H, s, CH_2Ph) and 6.8–8.4 (15 H, m, ArH); δ_C($CDCl_3$) 11.42, 51.11, 96.41, 103.14, 114.52, 115.35, 117.74, 119.56, 120.92, 124.29, 124.89, 126.97, 127.47, 128.57, 129.37, 130.46, 137.45, 139.70, 142.30 and 142.27 (Found: M^+, 400.1245. $C_{24}H_{20}N_2SO_2$ requires, M^+, 400.1245).

1-Methyl-4-phenylsulfonyl-2-(*p*-tolyl)-2,4-dihydropyrrolo[3,4-*b*]indole 9b. (0.75 g, 74%); mp 218 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 1170 and 1360 (SO_2); δ_H($CDCl_3$) 2.4 (3 H, s, CH_3), 2.5 (3 H, s, CH_3) and 7.1–8.2 (14 H, m, ArH) (Found: M^+, 400.144. $C_{24}H_{20}N_2SO_2$ requires M^+, 400.1245).

2-(*p*-Methoxyphenyl)-1-methyl-4-phenylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole 9c. (0.8 g, 75%); mp 190–192 °C (CCl_4); ν_{max}(KBr)/cm^{-1} 1160 and 1350 (SO_2); δ_H($CDCl_3$) 2.4 (3 H, s, CH_3), 3.85 (3 H, s, OCH_3) and 6.9–8.2 (14 H, m, ArH) (Found: M^+, 416.1110. $C_{24}H_{20}N_2SO_3$ requires M^+, 416.1194).

2-Benzyl-1-ethyl-4-phenylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole 9d. (0.72 g, 68%); mp 154–156 °C (MeOH); ν_{max}(KBr)/cm^{-1} 1180 and 1360 (SO_2); δ_H($CDCl_3$) 1.2 (3 H, t, CH_2CH_3), 2.75 (2 H, q, CH_2CH_3), 5.15 (2 H, s, CH_2Ph) and 6.8–8.3 (15 H, m, ArH) (Found: M^+, 414.1361. $C_{25}H_{22}N_2SO_2$ requires M^+, 414.1402).

2-Methyl-1-phenylsulfonylindole-3-carbaldehyde 10. Dry *N*,*N*-dimethylformamide (10 cm^3) was cooled to 0 to −5 °C for 20 min after which freshly distilled phosphorus oxychloride (3 cm^3) was added dropwise to it with stirring. After 0.5 h, a solution of **6** (2 g, 7.4 mmol) in DMF (10 cm^3) was added dropwise to the mixture which was left for 1 h and then heated at 90 °C for 1 h. The reaction mixture was cooled and poured over ice to which aqueous sodium hydroxide (12% 50 cm^3) was then added. After being heated at 90 °C for 0.5 h, the reaction mixture was cooled and extracted with ethyl acetate (3 × 50 cm^3). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Column chromatographic purification of the residue yielded **10** as a yellow crystalline solid (0.96 g, 46%); mp 165 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 1670 (CO), 1135 and 1355 (SO_2); δ_H($CDCl_3$) 2.9 (3 H, s, CH_3), 7.3–8.5 (9 H, m, ArH) and 10.5 (1 H, s, CHO).

2-Benzyl-4-phenylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole 9e. To a solution of **10** (0.45 g, 1.5 mmol) in CCl_4 (35 cm^3) was added powdered NBS (0.27 g, 1.5 mmol) and dibenzoyl peroxide (10 mg). The mixture was refluxed for 2 h and then cooled. The succinimide formed was filtered off and the filtrate was treated with benzylamine (0.33 g, 3 mmol) and K_2CO_3 (0.42 g, 3 mmol) under the conditions employed for **9a–d** to give **9e** (0.06 g, 10%); mp 152–154 °C (ethyl acetate–hexane); ν_{max}(KBr)/cm^{-1} 1170 and 1370 (SO_2); δ_H($CDCl_3$) 5.1 (2 H, s, CH_2 Ph) and 6.6–8.1 (16 H, m, ArH) (Found: M^+, 386.1047. $C_{23}H_{18}N_2SO_2$ requires M^+, 386.1089).

Cycloaddition of 9a

A solution of **9a** (0.2 g, 0.5 mmol) and DMAD (0.15 g, 1 mmol) in THF (20 cm^3) was heated under reflux for 6 h and then evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) to yield the adduct **11** as a pale yellow solid (0.19 g, 70%); mp 148 °C (benzene–EtOAc–hexane); ν_{max}(KBr)/cm^{-1} 1710 (CO), 1350 and 1160 (SO_2); δ_H($CDCl_3$) 2.3 (3 H, s, CH_3), 3.5 (3 H, s, CO_2Me), 3.7 (3 H, s, CO_2Me), 5.15 (2 H, s, CH_2Ar), 6.15 (1 H, s, bridgehead H) and 6.6–8.4 (14 H, m, ArH).

Carbazoles 12a–c

General procedure. A solution of **9** (0.5 mmol) and DMAD (0.6 mmol) in THF (20 cm^3) was refluxed for 6 h after which toluene-*p*-sulfonic acid (10 mg) was added to it and refluxing was continued for a further 4 h. After evaporation of the mixture under reduced pressure, the residue was taken in ethyl acetate (50 cm^3) and the solution washed with 10% aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated. The residue was chromatographed (1 : 9; ethyl acetate–hexane) on a column of silica gel to give **12** which was crystallized from ethyl acetate–hexane.

Dimethyl 4-benzylamino-1-methyl-5-phenylsulfonylcarbazole-2,3-dicarboxylate 12a. (0.95 g, 57%); mp 135 °C; ν_{max}(KBr)/cm^{-1} 3320 (NH), 1710 (CO), 1350 and 1170 (SO_2); δ_H($CDCl_3$) 2.25 (3 H, s, CH_3), 3.8 (3 H, s, CO_2Me), 3.9 (3 H, s, CO_2Me), 4.75 (2 H, s, CH_2Ph) and 6.9–8.6 (14 H, m, ArH); δ_C($CDCl_3$) 16.44, 50.87, 52.25, 52.39, 113.54, 115.53, 117.42, 120.12, 123.02, 125.08, 127.04, 127.74, 128.43, 129.72, 130.46,

132.95, 133.52, 134.39, 134.98, 137.45, 139.70, 142.08, 142.79, 169.58 and 169.95 (Found: M^+, 542.1554. $C_{30}H_{26}N_2SO_6$ requires M^+, 542.1511) (Found: C, 66.5; H, 4.8; N, 5.1. Calc. for $C_{30}H_{26}N_2SO_6$: C, 66.40; H, 4.83; N, 5.16%).

Dimethyl 1-methyl-5-phenylsulfonyl-4-(*p*-tolylamino)-carbazole-2,3-dicarboxylate 12b. (0.16g, 59%); mp 168–170 °C; ν_{max}(KBr)/cm^{-1} 3300 (NH), 1710(CO), 1360 and 1170 (SO_2); δ_H($CDCl_3$) 2.2 (3 H, s, CH_3), 2.6 (3 H, s, CH_3), 3.45 (3 H, s, CO_2Me), 3.9 (3 H, s, CO_2Me), 6.4–7.0 (4 H, q, ArH) and 7.1–8.4 (9 H, m, ArH) (Found: M^+, 542.1471. $C_{30}H_{26}N_2SO_6$ requires M^+, 542.1511) (Found: C, 66.3; H, 5.0; N, 4.7. Calc. for $C_{30}H_{26}N_2SO_6$ C, 66.40; H, 4.83; N, 5.16%).

Dimethyl 4-(*p*-methoxyphenylamino)-1-methyl-5-phenylsulfonylcarbazole-2,3-dicarboxylate 12c. (0.14 g, 52%); mp 120 °C; ν_{max}(KBr)/cm^{-1} 1720 (CO), 1350 and 1170 (SO_2); δ_H($CDCl_3$) 2.5 (3 H, s, CH_3), 3.7 (3 H, s, CO_2Me), 3.8 (6 H, s, CO_2Me and OCH_3), 6.8 (4 H, br s, ArH) and 7.2–8.4 (9 H, m, ArH) (Found: M^+, 558.1362. $C_{30}H_{26}N_2SO_7$ requires M^+, 558.1460) (Found: C, 64.35; H, 4.6; N, 5.2. Calc. for $C_{30}H_{26}N_2SO_7$: C, 64.50; H, 4.69; N, 5.01%).

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References

1 For reviews, see: U. Pindur and H. Erfanian-Abdoust, *Chem. Rev.*, 1989, **89**, 1681.
2 E. R. Marinelli, *Tetrahedron Lett.*, 1982, **23**, 2745.
3 B. Saroja, P. C. Srinivasan, *Tetrahedron Lett.*, 1984, **25**, 5429.
4 S. F. Vice, H. N. de Carvalho, N. G. Taylor and G. I. Dimitrienko, *Tetrahedron Lett.*, 1989, **30**, 7289.
5 M. Haber and U. Pindur, *Tetrahedron*, 1991, **47**, 1925.
6 P. Magnus, T. Gallagher, P. Brown and P. Pappalardo, *Acc. Chem. Res.*, 1984, **17**, 35 and references cited therein.
7 G. W. Gribble, D. J. Keavy, D. A. Davis, M. G. Saulnier, B. Peleman and C. Timothy, *J. Org. Chem.*, 1992, **57**, 5878.
8 C. J. Moody and P. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1989, 376; 1989, 2463; C. J. Moody and K. F. Rahimtoola, *J. Chem. Soc., Chem. Comuun.*, 1990, 1667.
9 U. Pindur and H. Erfanian-Abdoust, *Heterocycles*, 1990, **31**, 1751.
10 W. M. Welch, *J. Org. Chem*, 1976, **41**, 2031.
11 C. K. Sha, K. S. Chung and S. J. Wey, *J. Chem. Soc., Perkin Trans. 1*, 1987, 977.
12 D. Nagarathnam, M. Vedachalam and P. C. Srinivasan *Synthesis*, 1983, 156.
13 G. W. Gribble, R. W. Allen, R. S. Anderson, M. E. Christy and C. D. Colton, *Tetrahedron Lett.*, 1976, **17**, 3673; G. W. Gribble, R. W. Allen, C. S. Le Houllier, J. T. Eaton, N. R. Jr. Eaton, R. I. Slayton and M. P. Sibi, *J. Org. Chem.*, 1981, **46**, 1025.
14 U. Pindur and C. Otto, *Tetrahedron*, 1992, **48**, 3515; J. Moron, C. Landras and E. Bisagni, *J. Heterocycl. Chem.*, 1992, **29**, 1573; H. H. Wasserman, J. H. Van Duzer and B. Vu.Chi. *Tetrahedron Lett.*, 1990, **31**, 1609.

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