

DIMERIZATION OF 1-BENZENESULFONYL-3-CYANOMETHYLINDOLE.
SYNTHESIS OF INDOLO[2,3-*a*]CARBAZOLES

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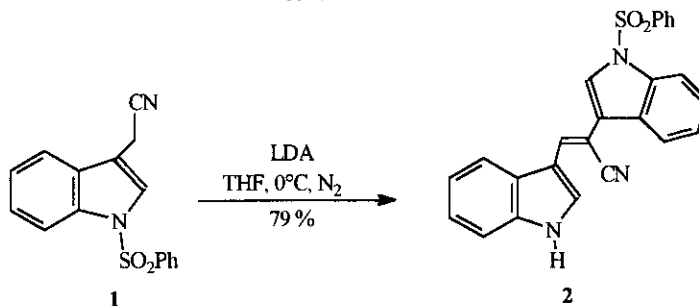
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Abstract - The treatment of 1-benzenesulfonyl-3-cyanomethylindole (**1**) with LDA, in THF at 0°C, affords 2-(1-benzenesulfonyl-1*H*-indol-3-yl)-3-(1*H*-indol-3-yl)acrylonitrile (**2**) in 79% yield. From **2**, the indolo[2,3-*a*]carbazole (**4**) has been obtained in 58% yield.

A number of diverse synthetic approaches¹ have been developed to prepare the indolocarbazole alkaloids, a biologically interesting class of natural products. 1,2-Bis(3-indolyl)ethylidene derivatives are a very good intermediates to obtain indolo[2,3-*a*]carbazoles by electrocyclic reaction.²

The key step of this synthetic path is the preparation of the 1,2-bis(3-indolyl)ethylidene derivatives.³ We describe here the results of the treatment of 1-benzenesulfonyl-3-cyanomethylindole (**1**)⁴ with LDA, in anhydrous THF at 0°C. In these conditions the dimeric compound (**2**) was obtained in good yield following an unusual mechanism. In fact a benzenesulfinate group and a cyano group were lost (Scheme 1).

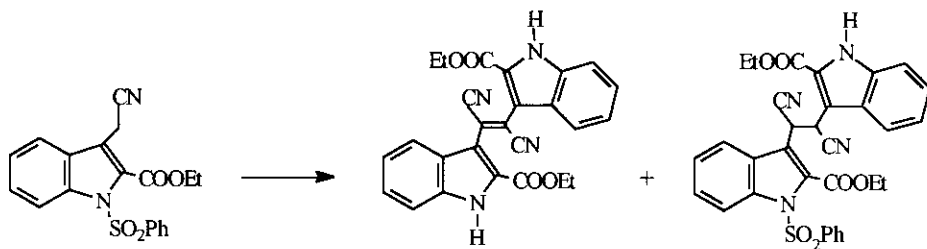
Scheme 1



The literature reports that the reaction of the ethyl 1-benzenesulfonyl-3-cyanomethyl-2-indolecarboxylate in THF with a base and a catalytic amount of 18-crown-6 gave a mixture of two dimeric derivatives, both retaining the cyano groups ⁵ (Scheme 2).

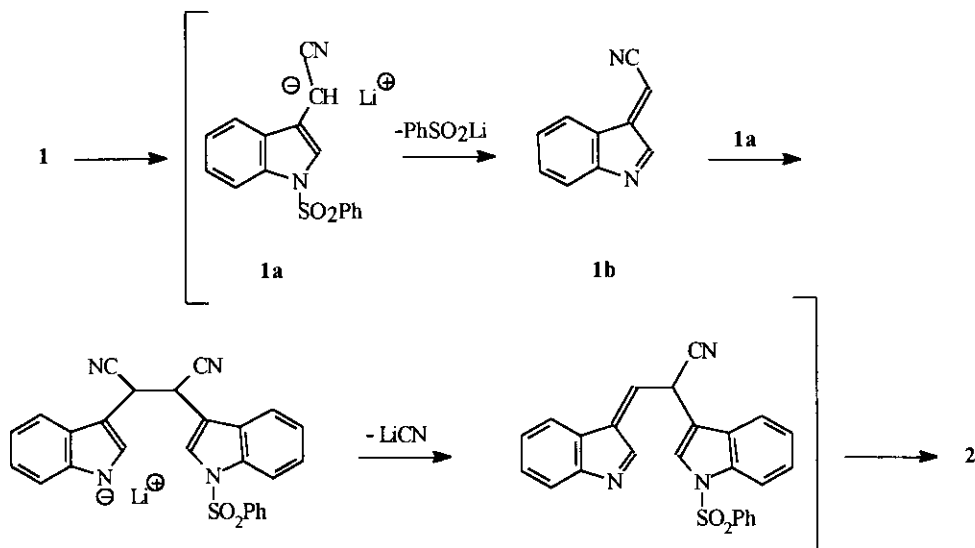
Besides, the anion of 1-benzenesulfonyl-3-cyanomethylindole (**1**) could be alkylated, at $-78\text{ }^{\circ}\text{C}$, with retention of the benzenesulfonyl group. These results suggested to the authors that the activation by a carboxyl group is essential for the elimination of benzenesulfinate.

Scheme 2

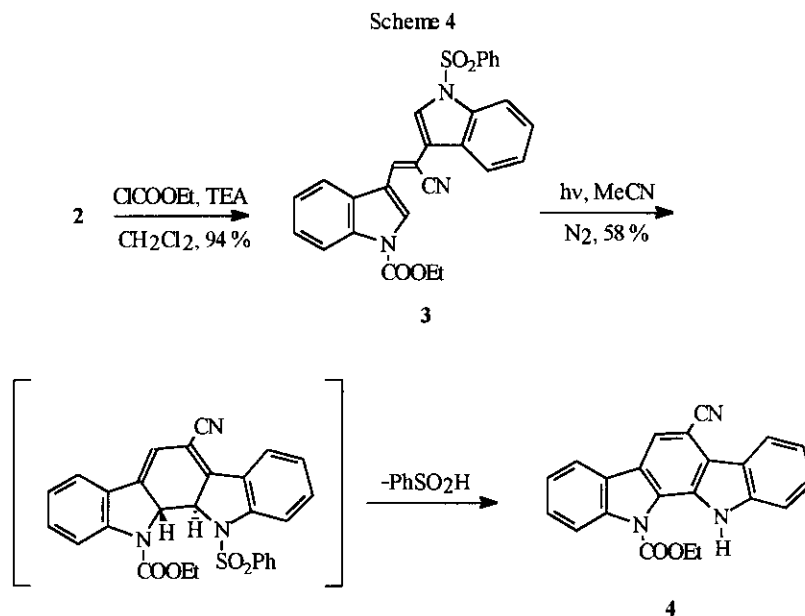


In our case, the absence of the carboxy group and the different experimental conditions, we lead to suppose the mechanism reported in Scheme 3. The base generates the anion (**1a**) which could eliminate benzenesulfinate to give the intermediate (**1b**). Intermediate (**1b**) could be attacked by another molecule of **1a** to form a new anion from which the final derivative (**2**) arises by elimination of cyanide ion and subsequent isomerization.

Scheme 3



Attempted photocyclization of compound (2) gave very poor results. Better results were obtained from the photocyclization, in acetonitrile solution of compound (3), prepared from 2 by reaction with ethyl chloroformate and triethylamine. The indolocarbazole (4) obtained, arises from the intermediate dihydroderivative *via* elimination of benzenesulfinic acid followed by isomerization (Scheme 4).



The structure of compound (2) was indirectly confirmed by an independent synthesis of compound (8), stereoisomer of compound (3) (Scheme 5).

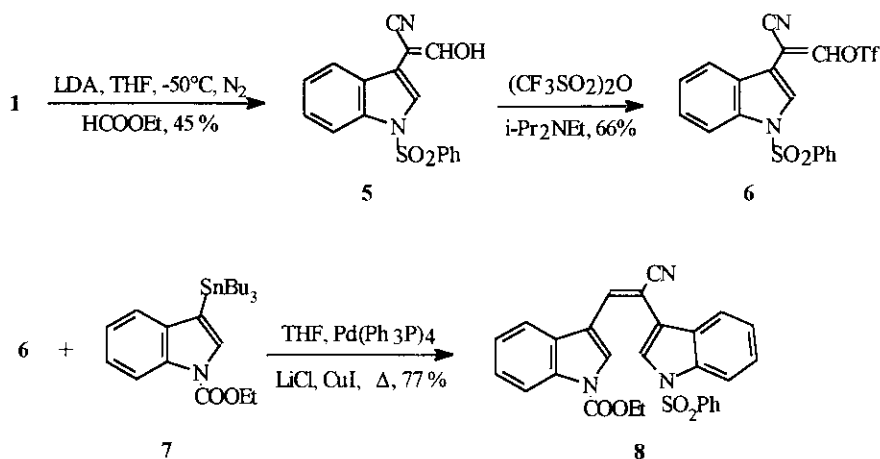
Compound (1), treated in THF solution at -50°C with LDA and ethyl formate, gave the corresponding formyl derivative (5) (enol form), from which the triflate (6) was prepared with trifluoromethanesulfonic anhydride and *N,N*-diisopropylethylamine.

The coupling between compound (6) and ethyl 3-tributylstannylindol-1-carboxylate (7)⁶ using the Stille conditions⁷ but in the presence of catalytic amount of CuI, gave compound (8) in 69% yield (Scheme 5).

The structure of new compounds follows from analytical and spectroscopic data (see Experimental).

Spectroscopic data suggest compound (8) is a stereoisomer of compound (3).

Scheme 5



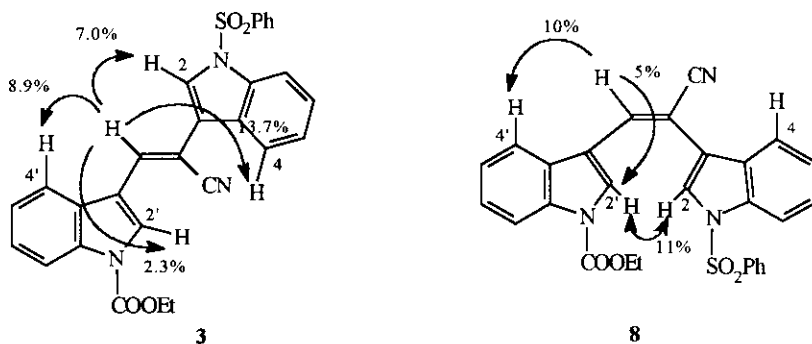
Besides, the photocyclization of the two isomers (**3**) and (**8**) gave the same compound (**4**) (Scheme 6).

Scheme 6



The reported stereochemistry, *E* for compound (**8**) and *Z* for compound (**3**), was assigned on the basis of the $^1\text{H-NMR}$ spectra and NOE experiment. The $^1\text{H-NMR}$ spectrum of compound (**3**) shows the ethyl group at δ 1.45 and 4.55, whereas for compound (**8**) a significant upfield shift (δ 1.14 and 4.25) of the same hydrogens was observed. For compound (**3**) significant NOE interactions, as depicted in Figure 1, were observed between the olefin proton and the H-2, H-2', H-4 and H-4'. For compound (**8**), significant NOE interactions were observed between the olefin proton and the H-2' and H-4' only and between H-2 and H-2'. No NOE effect was observed between the olefin proton and the H-2 indole proton which indicates the structure (**8**) is *cis*.

Figure 1



In consideration of the good results of the coupling reaction to prepare 1,2-bis(3-indolyl)ethylidene, this synthetic path is an easy route to obtain indolocarbazoles.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in nujol mull for solids and as liquid film for oils. ¹H-NMR were recorded on a Varian Gemini 200 spectrometer. NOE experiments were recorded on a Bruker AC 300 spectrometer. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator. Irradiations were carried out with an HPK-125W Philips high pressure mercury vapor lamp in a preparative photochemical reactor equipped with a pyrex double-walled immersion well for water cooling of lamp. Sodium sulfate was used as drying agent.

2-(1-Benzenesulfonyl-1*H*-indol-3-yl)-3-(1*H*-indol-3-yl)acrylonitrile (2).

To an ice cold solution of 1-benzenesulfonyl-3-cyanomethylindole² (1.18 g, 4 mmol) in anhydrous THF (20 mL), under nitrogen, 2M LDA was added (4 mL, 8 mmol). The reaction mixture was stirred at 0°C for 20 min, diluted with 8% HCl (100 mL) (HCN evolution) and extracted with CH₂Cl₂ (2 x 50 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent CH₂Cl₂) to give pure compound (2) (670 mg, 79%); mp 198 °C from CH₂Cl₂-Et₂O; IR : ν_{max} 3280 br, 2200 cm⁻¹; ¹H-NMR (DMSO-d₆): δ 12.06 (1H, br s, exch. D₂O), 8.40 (1H, br s), 8.32 (1H, s), 8.26 (1H, s), 8.10 (5H, m), 7.40-7.80 (6H, m), 7.25 (2H, m); MS m/z : 423 (M⁺), 282 (100%). Anal. Calcd for C₂₅H₁₇N₃O₂S : C, 70.91; H, 4.05; N, 9.92. Found : C, 70.88; H, 3.99; N, 9.86.

Ethyl (Z)-3-[2(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-cyanovinyl]indole-1-carboxylate (3).

Compound (2) (847 mg, 2 mmol) was dissolved in CH₂Cl₂ (60 mL) and then Et₃N (0.56 mL, 4 mmol) was added. The reaction mixture was cooled at 0-5°C and ethyl chlorocarbonate (0.29 mL, 3 mmol) was added under stirring. After 5 min the reaction mixture was washed with H₂O (2 x 50 mL). The organic layer was dried, filtered and evaporated. The residue was crystallized from CH₂Cl₂ to give pure compound (3) (932 mg, 94%); mp 199-200°C (CH₂Cl₂); IR : ν_{max} 2190, 1722 cm⁻¹; ¹H-NMR (DMSO-d₆): δ 8.65 (1H, s), 8.46 (1H, s), 8.26 (1H, s), 8.15 (6H, m), 7.65 (3H, m), 7.46 (4H, m), 4.55 (2H, q, J = 7.1 Hz), 1.45 (3H, t, J = 7.1 Hz); ¹H-NMR (C₆D₆): δ 8.86 (1H, s), 8.56 (1H, d, J = 8.3 Hz), 8.22 (1H, m), 7.97 (1H, s), 7.82 (1H, d, J = 7.4 Hz), 7.66 (2H, m), 7.41 (1H, s), 7.32 (1H, m), 7.28 (1H, m), 7.16 (2H, m), 7.05

(1H, m), 6.68 (3H, m), 3.93 (2H, q, $J = 7.1$ Hz), 0.89 (3H, t, $J = 7.1$ Hz). Anal. Calcd for $C_{28}H_{21}N_3O_4S$: C, 67.87; H, 4.27; N, 8.48. Found: C, 67.81; H, 4.08; N, 8.36.

Photocyclization of Compound (3). Compound (4) Prepared.

Compound (3) (496 mg, 1 mmol) was dissolved in a 1 : 1 mixture of MeCN and CH_2Cl_2 (100 mL), the solution placed in the photochemical reactor and nitrogen bubbled through the solution for 3 min before irradiation. After irradiation for 3 h, the solution was evaporated and the residue purified by column chromatography (eluent 1 : 1, hexane- CH_2Cl_2) to give pure compound (4) (206 mg, 58%); mp 239-240°C from CH_2Cl_2 - Et_2O ; IR: ν_{max} 3350, 2190, 1710 cm^{-1} ; 1H -NMR (DMSO- d_6): δ 11.41 (1H, s, exch. D_2O), 8.62 (1H, s), 8.50 (1H, d, $J = 7.9$ Hz), 8.36 (1H, d, $J = 7.0$ Hz), 8.23 (1H, d, $J = 8.1$ Hz), 7.97 (1H, d, $J = 8.3$ Hz), 7.58 (3H, m), 7.37 (1H, m), 4.71 (2H, q, $J = 7.1$ Hz), 1.57 (3H, t, $J = 7.1$ Hz). Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.69; H, 4.22; N, 11.78.

2-(1-Benzenesulfonyl-1H-indol-3-yl)-3-hydroxyacrylonitrile (5).

To a solution of 1-benzenesulfonyl-3-cyanomethylindole (1) (1.48 g, 5 mmol) in anhydrous THF (30 mL), at $-50^\circ C$ under nitrogen, 2M LDA was added (2.5 mL, 5 mmol). After 5 min at $-50^\circ C$, ethyl formate (0.55 mL, 7 mmol) was added. After being warmed at rt, the reaction mixture was diluted with 4.5 % HCl (150 mL) and extracted with Et_2O (2 x 70 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent 20 : 1, CH_2Cl_2 - Et_2O) to give: unreacted 1 (614 mg) and pure compound (5) (730 mg, 45%, 77% on the reacted material); mp 198-199°C from CH_2Cl_2 - Et_2O ; IR: ν_{max} 3100 br, 2200, 1620 cm^{-1} ; 1H -NMR (DMSO- d_6): δ 12.40 (1H, br s, exch. D_2O), 7.38 (2H, m), 7.55-7.80 (4H, m), 8.02 (5H, m). Anal. Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.87; H, 3.69; N, 8.59.

2-(1-Benzenesulfonyl-1H-indol-3-yl)-2-cyanovinyltrifluoromethanesulfonate (6).

Compound (5) (649 mg, 2 mmol) was dissolved in CH_2Cl_2 (20 ml) and then *N,N*-diisopropylethylamine (0.7 mL, 4 mmol) was added. The reaction mixture was cooled at $0-5^\circ C$ and trifluoromethanesulfonic anhydride (0.5 mL, 3 mmol) was added. After 5 min the reaction mixture was washed with water (2 x 20 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent 1 : 1, hexane- CH_2Cl_2) to give pure compound (6) (603 mg, 66%); mp 151-152°C from Et_2O ; IR: ν_{max} 1600, 1526 cm^{-1} ; 1H -NMR ($CDCl_3$): δ 7.30-7.65 (6H, m), 7.94 (4H, m), 8.06 (1H, m). Anal. Calcd for $C_{18}H_{11}F_3N_2O_5S_2$: C, 47.37; H, 2.43; N, 6.14. Found: C, 47.19; H, 2.40; N, 6.01.

Ethyl (*E*)-3-[2(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-cyanovinyl]indole-1-carboxylate (8).

To a solution of compound (6) (456 mg, 1 mmol) in anhydrous THF (40 mL) were added 3-tributylstannyl-indole-1-carboxylic acid ethyl ester (7) ⁶ (956 mg, 2 mmol), LiCl (170 mg, 4 mmol), CuI (95 mg, 0.5 mmol) and Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was heated to reflux for 1 h. After cooling, the mixture was evaporated, diluted with CH₂Cl₂ (50 mL), filtered and washed with water (40 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent 2 : 1, hexane-CH₂Cl₂) to give pure compound (8) (381 mg, 77%); mp 148°C from Et₂O-hexane; IR : ν_{\max} 2190, 1720, 1712 cm⁻¹; ¹H-NMR (DMSO-d₆): δ 8.26 (1H, s), 8.15 (1H, s), 8.05 (4H, m), 7.76 (1H, m), 7.64 (3H, m), 7.10-7.50 (6H, m), 4.25 (2H, q, *J* = 7.2 Hz), 1.14 (3H, t, *J* = 7.2 Hz); ¹H-NMR (C₆D₆): δ 8.34 (1H, d, *J* = 8.3 Hz), 8.08 (1H, d, *J* = 8.4 Hz), 7.73 (1H, s), 7.58 (2H, m), 7.34 (1H, s), 7.27 (1H, d, *J* = 8.1 Hz), 7.15 (1H, m), 7.05 (3H, m), 6.95 (1H, m), 6.82 (1H, m), 6.68 (3H, m), 3.69 (2H, q, *J* = 7.2 Hz), 0.75 (3H, t, *J* = 7.2 Hz). Anal. Calcd for C₂₈H₂₁N₃O₄S : C, 67.87; H, 4.27; N, 8.48. Found : C, 67.82; H, 4.05; N, 8.31.

Photocyclization of Compound (8). Compound (4) Prepared.

Compound (8) (248 mg, 0.5 mmol) was dissolved in a mixture of MeCN and CH₂Cl₂ 1:1 (60 mL), the solution placed in a photochemical reactor and nitrogen bubbled through the solution for 3 min before irradiation. After irradiation for 3 h, the solution was evaporated and the residue purified by column chromatography (eluent hexane-CH₂Cl₂ 1:1) to give pure compound (4) (112 mg, 63%).

REFERENCES

1. C.A. Merlic and D.M. McInnes, *Tetrahedron Lett.*, 1997, **38**, 7661 and references therein.
2. a) W. Steglich, B. Steffan, L. Kopanski and G. Eckhardt, *Angew. Chem. Int. Ed.*, 1980, **19**, 459; b) E. Winterfeldt and B. Sarstedt, *Heterocycles*, 1983, **20**, 469; c) E.M. Beccalli, A. Marchesini and T. Pilati, *Tetrahedron*, 1993, **49**, 4741.
3. E.M. Beccalli and A. Marchesini, *Synth. Commun.*, 1997, **27**, 4215.
4. D. Nagarathnam, *J. Heterocycl. Chem.*, 1992, **29**, 953.
5. D. Nagarathnam and M.E. Johnson, *Tetrahedron Lett.*, 1993, **34**, 3215.
6. F. Clerici, E. Erba, M.L. Gelmi and M. Valle, *Tetrahedron*, 1997, **53**, 15859.
7. W.J. Scott and J.K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033.