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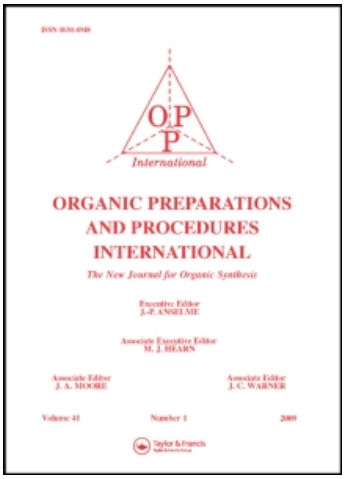

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AN EFFICIENT SYNTHESIS OF 2,3-DICYANOINDOLE

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AN EFFICIENT SYNTHESIS OF 2,3-DICYANOINDOLE

Submitted by Tomasz Janosik, Adam C. Lipson, and Gordon W. Gribble*
(03/02/04)

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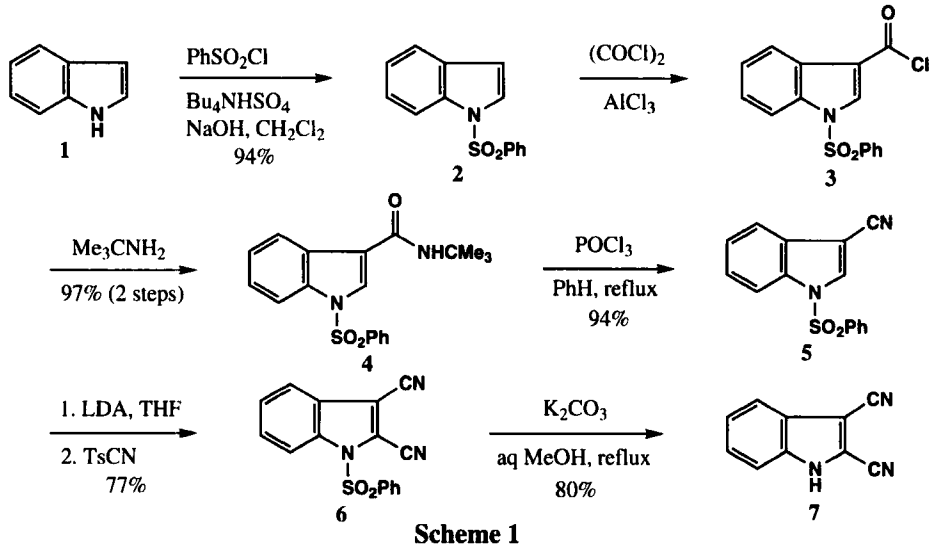
In continuation of our studies of indoles substituted with electron-withdrawing groups at the C-2 and C-3 positions (i. e., nitro, phenylsulfonyl),[1] we became interested in 2- and 3-cyano- and 2,3-dicyanoindole. Due to its strong electron-withdrawing ability and small size, the cyano group could prove useful in activating the indole double bond to the chemistry we have been exploring.[1] Despite a simple structure, no practical syntheses of 2,3-dicyanoindoles exist, as the only two reports of these compounds originate from studies of the reaction of 2-chloro- and 2-(phenylsulfonyl)indoles with sodium azide (26–32%),[2a] the electrolytic oxidation of 1-

methylindole in the presence of sodium cyanide (59%),[2b] and the cyanation of 3-bromo-2-cyano-1-methylindole with cuprous cyanide (74%).[2b] In contrast, numerous syntheses of both 2-[3] and 3-cyanoindole[4] are known. We now describe an efficient route to 2,3-dicyano-1-(phenylsulfonyl)indole (**6**) and 2,3-dicyanoindole (**7**), neither compound of which has been characterized in the literature.

Our synthesis (*Scheme 1*) utilizes regiospecific C-2 lithiation of 3-cyano-1-(phenylsulfonyl)indole (**5**), which we had previously synthesized in excellent yield from indole (**1**),[4e] and quenching with *p*-toluenesulfonyl cyanide to give **6** in 77% yield. Base cleavage of **6** affords 2,3-dicyanoindole (**7**) in 80% yield. Both compounds were fully characterized. The overall yield of **7** from indole is 53%, which is superior to those of the existing methods.[2]



Scheme 1

It should be noted that an earlier approach to **6** in our laboratory was unsuccessful. Thus, attempts to effect C-2 lithiation of both **4** and **5** followed by quenching with *tert*-butylisocyanate gave the expected 2-(1,1-dimethylethyl)carboxamides in poor yield at best.

EXPERIMENTAL SECTION

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded at 300 MHz or 75.4 MHz, respectively. Elemental analyses were performed by Atlantic Microlab, Inc, Norcross, GA. THF was distilled from sodium and benzophenone. LDA was purchased from Acros Organics. All other solvents (analytical grade) and reagents were used as received.

2,3-Dicyano-1-(phenylsulfonyl)indole (6).- To a solution of 3-cyano-1-(phenylsulfonyl)-indole[4e] (**5**) (385 mg, 1.36 mmol) in dry THF (12 mL), was added a solution of LDA in THF/heptane (2 M, 0.83 mL, 1.66 mmol) at –78°C under N_2. After stirring at –78°C for 1 h, a

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suspension of *p*-toluenesulfonyl cyanide (330 mg, 1.82 mmol) in dry THF (1.5 mL) was added. The resulting mixture was allowed to slowly reach rt overnight, was thereafter quenched by addition of aqueous saturated NH_4Cl (50 mL), and was then stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a solid brownish residue, which was subjected to flash column chromatography on silica [hexanes-CH_2Cl_2 (1:1)], to give **6** (301 mg, 77%) as a colorless solid, mp 167-169°C (*i*-PrOH); IR (neat): 2234, 1399, 1263, 1191, 966, 780, 757, 745, 723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.30-8.27 (m, 1H), 8.13-8.09 (m, 2H), 7.85-7.67 (m, 3H), 7.63-7.50 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 136.7, 136.1, 135.6, 130.5, 130.4, 127.7, 126.6, 126.4, 121.3, 115.0, 114.3, 110.9, 109.4, 105.8. MS (EI, 70 eV) *m/z:* 308 ([M+1]$^+$, 3), 307 ([M$^+$], 14), 167 (8), 141 (54), 77 (100); HRMS (EI) *m/z*: Calcd for $C_{16}H_9N_3O_2S$ 307.0415; Found 307.0421.

Anal. Calcd for $C_{16}H_9N_3O_2S$: C, 62.53; H, 2.95; N, 13.67. Found: C, 62.55; H, 2.95, N, 13.70

2,3-Dicyanoindole (7).- A mixture of 2,3-dicyano-1-(phenylsulfonyl)indole (**6**) (60 mg, 0.20 mmol), and K_2CO_3 (106 mg, 0.77 mmol) in MeOH (4 mL) and water (1 mL), was heated at reflux under N_2 for 2 h. After cooling, the solution was concentrated *in vacuo*, diluted with water (~5 mL), and acidified to pH 4-5 by addition of AcOH. The precipitate was collected, washed with several portions of water, and dried to give **7** (26 mg, 80%) as a colorless solid, mp 248-250°C (EtOH). IR (neat): 3282, 2231, 1435, 1236, 1151, 746 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.72 (br s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.52 (app. t, J = 7.5 Hz, 1H), 7.40 (app. t, J = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 135.9, 127.3, 125.6, 123.9, 119.6, 113.8, 113.2, 112.7, 111.5, 94.0. MS (EI, 70 eV) *m/z:* 168 ([M+1]$^+$, 16), 167 ([M$^+$], 100), 142 (11), 140 (10), 115 (27), 77 (11); HRMS (EI) *m/z*: Calcd for $C_{10}H_5N_3$ 167.0483; Found 167.0484.

Anal. Calcd for $C_{10}H_5N_3 \cdot 1/16\ H_2O$: C, 71.37; H, 3.18; N, 24.97

Found: C, 71.43; H, 3.05; N, 24.87

This sample was crystallized from 95% EtOH and dried at 60°C overnight under high vacuum, but water remained in the sample.

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SYNTHESIS OF 6-(2,2-DIMETHYL-3,4-DIHYDRO-3-OXO-1,4(2*H*)-BENZOXAZIN-7-YL)PYRIDAZIN-3-ONES

Submitted by (03/09/04)

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In recent years, a number of highly potent positive inotropes which increase the force of contraction of heart muscle, have been described in the literature.[1-3] These compounds incorporate a 4,5-dihydro-2*H*-pyridazin-3-one ring bearing aromatic nuclei, *e. g.* indolinan (**1**)[4] and