ELECTROPHILIC SUBSTITUTION OF INDOLES : PART XI[1]. LEWIS ACID INDUCED REACTION OF SKATOLE WITH BEZIL

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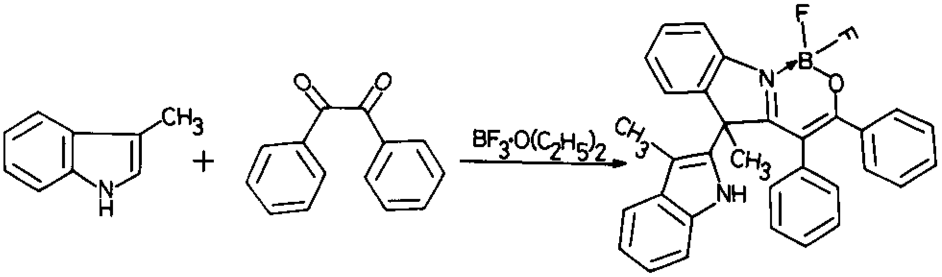
Abstract - The electrophilic substitution of 3-methylindole with benzil in the presence of $BF_3.Et_2O$ resulted in a novel heterocyclic system incorporating a stable boron difluoride chelate. The structure was established from spectral analysis (^{1}H-, ^{13}C-, ^{11}B-, ^{19}F-nmr) and X-ray crystallographic analysis.

In continuation of our studies[2] on the aspects of the Lewis acid induced electrophilic substitution reactions of indoles with carbonyl compounds we investigated the reaction of skatole (3-methylindole) with benzil in the presence of boron trifluoride etherate. A bright yellow crystalline compound (1) (M^+ 502 and 501 with an intensity ratio of 4:1 corresponding to ^{11}B and ^{10}B; exact mass measurement gave 502.2025; calcd for $C_{32}H_{25}N_2OBF_2$ 502.2028), mp 256°C (benzene), was isolated in 60% yield. The 300 MHz ^{1}H-nmr spectrum in DMSO-d_6 revealed the presence of one indole >NH at δ 11.11 (s), sixteen aromatic protons in the region δ 8.36-7.66 (m), two isolated aromatic protons at δ 6.98 (1H, t, J=8.0 Hz) and 6.48 (1H, d, J=8.0 Hz) and two methyls at δ 2.23 (6H, s). Hence it could be concluded that two skatole units and one benzil moiety were involved in the reaction. The ^{13}C-nmr signals of 1 in DMSO-d_6 (Table 1) notably at δ 177.57, 55.21 and 21.53 ppm suggested that one skatole unit possibly existed in the indolenine form. The

235.36 MHz ^{19}F-nmr spectrum indicated the presence of two non-equivalent fluorine atoms which shifted to -136.35 and -135.15 ppm (ill resolved dq each) with respect to $CFCl_3$. The 80.25 MHz ^{11}B-nmr spectrum revealed the presence of one boron atom which shifted to 1.12 ppm (dd), with respect to $BF_3.Et_2O$. These data confirmed that a BF_2 residue (a reminiscent part of the Lewis acid used in the preparation of the compound) had been entangled within the molecule. The mass spectrum exhibited a significant elimination of 20 mu (HF) to give the characteristic pair of signals at m/z 481/482 (exact mass 482.1990, calcd for $C_{32}H_{24}N_2OBF$ 482.1970) followed by the loss of 105 mu (C_6H_5CO) from the benzil part of the molecule (m/z 376/377; exact mass 377.1629, calcd for $C_{26}H_{19}N_2BF$ 377.1630). All the spectral data are in accord with the proposed structure (1) for the isolated product.

Table 1 : 75 MHz ^{13}C-nmr signals of 1 in DMSO-d_6 ppm

C	CH	CH_3
177.57	132.92	21.53
172.04	131.85	7.41
141.78	130.75	
141.51	129.16(x2)	
135.18	128.95	
134.74	127.91(x2)	
131.31(x2)	127.80(x2)	
128.77	127.35	
128.63	127.10	
109.20	122.85	
55.21	121.23	
	118.68	
	117.85	
	116.07	
	111.40	



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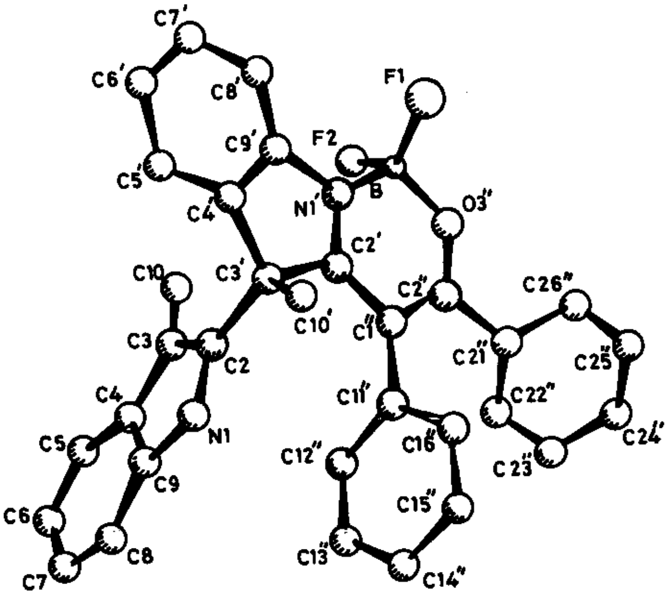
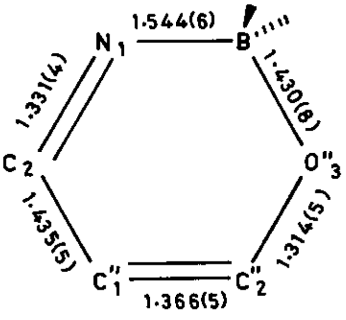


Figure 1 X-Ray structure of compound **1**

The structure of **1** was unambiguously settled from X-ray crystallographic analysis. The crystals of the complex were grown as bright yellow prisms from a toluene solution at room temperature. The molecular structure and atom labelling scheme are presented as a stereoscopic view in Figure 1.

The characteristic feature of **1** is the presence of a stable boron difluoride chelate[3]



formed by the participation of a BF_2 residue from the Lewis acid used. The BF_2 residue is linked to both oxygen of the carbonyl and the nitrogen of one skatole unit, with the conjugation retained in the right part of the structure. The double bond localisation given in Figure 1 was deduced from bond lengths measurements in the hetero six-membered ring around the BF_2 residue.

The chelate resisted hydrolysis with 0.5 N-HCl. The stability of this interesting and unusual chelate is due to the formation of six-membered ring.

EXPERIMENTAL

Melting points were recorded in a Kofler block and are uncorrected. The uv spectra (95% aldehyde free ethanol) were recorded in a Varian 634 spectrophotometer, the ir spectra (KBr) in a Perkin-Elmer 782 spectrophotometer, the nmr spectra in a Bruker AM-300L spectrometer and the mass spectra in Finnigan-MAT HSQ-30 instrument. X-Ray diffraction experiments were performed on a Philips PW 1000 automatic four-circle diffractometer operating with the Cu-Kα radiation (λ= 1.5418Å) monochromated by graphite. The system is monoclinic, $P2_1/c$ with a = 8.650 (4); b = 8.571 (3); c = 35.850 (6) Å; β= 97.6 (1)° and Z = 8. Final R value 6.9% for 2327 structure factors. Tables of positional parameters, bond distances and angles have been deposited within the Cambridge Crystallographic Data Centre, Laboratory of Chemistry, Lensfield Road, CBI 2EW Cambridge, UK. The structure was solved by means of direct methods and refined with isotropic and then anisotropic thermal factors, for the non-hydrogen atoms, by fullmatrix least squares procedures.

Isolation of Complex 1

To a solution of skatole (1.5g, 11.45 mmol) in dry methylene chloride (20 ml) and benzil (1 g, 4.76 mmol) in dry methylene chloride (20 ml) at 0°C boron trifluoride etherate (1 ml) was added dropwise cautiously with constant stirring (10 h). The reaction mixtures was decomposed over ice chips and extracted with methylene chloride (3 x 100 ml). The organic layer was washed with 2% aqueous $NaHCO_3$ (3 x 50 ml), water (3 x 50 ml) and dried over anhydrous sodium sulphate. The concentrate was chromatographed over Brockmann alumina (grade basic) with solvents (petrol, petrol-benzene mixture, benzene, benzene-ethyl acetate mixture and ethyl acetate) of increasing polarity. The fractions of the benzene eluate afforded bright yellow complex (1), (0.9 g, 60%) mp 256°C (benzene), λ_{max} : 283, 227 and 208 nm ($\log\epsilon$ = 4.13, 4.59 and 4.77 respectively), λ_{max} (EtOH + 50% $HClO_4$) : 263, 225 and 214 nm ($\log\epsilon$ = 4.41, 4.58 and 4.57 respectively), ν_{max} : 3420, 1600, 1580, 1550, 1490, 1280, 740 cm^{-1}; m/z : 502, 501, 482, 481, 454, 377, 376, 217, 216, 130, 105 and 77; Found : C, 76.75%; H, 5.01%; N, 5.13%. $C_{32}H_{25}N_2OBF_2$ requires C, 76.53%; H, 5.01%; N, 5.57%.

Attempted hydrolysis of complex 1

Complex (1) (2 mg, 0.004 mmol) was added to 0.5 N aqueous HCl (2 ml) and the mixture was refluxed for 2 h. After usual work up the compound isolated (2 mg, 100%) was found to be identical to 1 from the superimposable ir spectra and co-tlc experiment.

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