First Electrophilic Substitutions of 3-Substituted Indoles with Diethoxycarbenium Tetrafluoroborate: Functionalized Indole Derivatives

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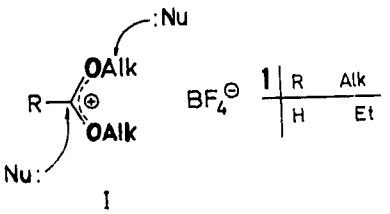
The indoles **2a-2c** react with diethoxycarbenium tetrafluoroborate (**1**) to furnish the indolecarbaldehydes **3a-3d**. In the thermodynamically controlled reaction of 3-methylindole (**2a**) with **1** the tris(indolyl)methane **4** and diskatole (**5**), are formed in addition. The limitations of these reactions are discussed and evidence is presented for a C-3-*ipso*-attack and a *Wagner-Meerwein* rearrangement, respectively, leading to the formation of **3b** or **3d**.

Erste elektrophile Substitution von 3-substituierten Indolen mit Diethoxycarbenium-Tetrafluoroborat: Funktionalisierte Indol-Derivate

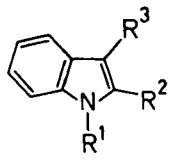
Die Indole **2a-2c** reagieren mit dem *per se* synthetisierten Diethoxycarbenium-Tetrafluoroborat (**1**) zu den Indolcarbaldehyden **3a-3d**. In einer thermodynamisch kontrollierten Reaktion von 3-Methylindol (**2a**) mit **1** werden weitere Produkte, nämlich das Trisindolylmethan **4** und Diskatol (**5**) gebildet. Die Grenzen der Reaktionen werden aufgezeigt, und es werden Hinweise gefunden, die für die Bildung von **3b** und **3d** einen C-3-*ipso*-Angriff und eine *Wagner-Meerwein*-Umlagerung wahrscheinlich machen.

The dialkoxycarbenium tetrafluoroborates **I**, first discovered by *Meerwein* and coworkers[1] and made preparatively accessible by the heterolysis of ortho esters, represent an interesting class of highly stabilised carbenium ions. Their ambident reactivity is now well known[2-6]. However, the synthetic potential of these electrophiles **I** towards electron-rich compounds (e.g., hetarenes[6]) has still not yet been investigated sufficiently. Thus, in continuation of our ongoing investigations[6], we now report on the first reactions of the 3-substituted indoles **2a-2e** with the sufficiently electrophilic diethoxycarbenium tetrafluoroborate (**1**) which can, in principle, function both as a formylium and as an ethylium synthetic equivalent[1,7].



I

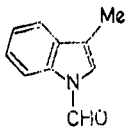
1	R	Alk
	H	Et



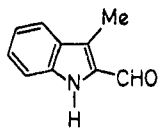
2	R^1	R^2	R^3
a	H	H	Me
b	H	Me	Me
c	Me	H	Me
d	Me	Me	Me
e	SO_2Ph	H	Me
f	SO_2Ph	H	H

Under kinetic control, the reactions of the indoles **2a**, **2b**, and **2c** proceed by way of the indolyl-stabilised ethoxycarbenium tetrafluoroborate stage[2,3,4,7] to furnish the indolecarbaldehydes **3a**, **3b** (as by-product), **3c**, and **3d**.

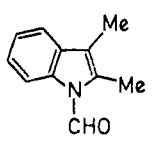
Under thermodynamic control of the reaction, in contrast, the indole-2-carbaldehyde **3b** and, through the intermediacy of the cyanine **II**, its subsequent product, the C-3-symmetrical tris(indolyl)methane **4**[8], are formed from **2a** and **1**. The yields of the indole derivatives obtained from the reactions of **2a** are always reduced on account of its known proton-catalysed dimerisation to form diskatole (**5**)[9].



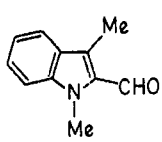
3a (31%)



3b (3-8%)



3c (23%)



3d (67%)

In spite of numerous variations of the reaction conditions, the indoles **2d** and **2e** could not be induced to react with **1**. Substitution at the phenyl nucleus of the indole was the expected result of the reaction of **2d** with **1**. This lack of reaction is certainly attributable to the lower nucleophilicities of these indole derivatives[10]. The inability of the cation **1** to react with 3-methyl-1-phenylsulfonylindole (**2e**) can, in general, be considered as evidence for an *ipso*-mechanism (*Jackson's* hypothesis)[10] in the electrophilic substitution of 3-substituted indoles since the 1,3-dimethylindole (**2c**) tested by us was indeed formylated at C-2 in good yield by the electrophile **1**. As observed in numerous experiments in support of *Jackson's* hypothesis, attack of an electrophile on 3-substituted indoles occurs initially at the 3-position (see Fig. 1, frontier orbitals[11]) of **2a** and **1**, based on MNDO calculations[12]. The indoleninium ion[10] resulting from such an

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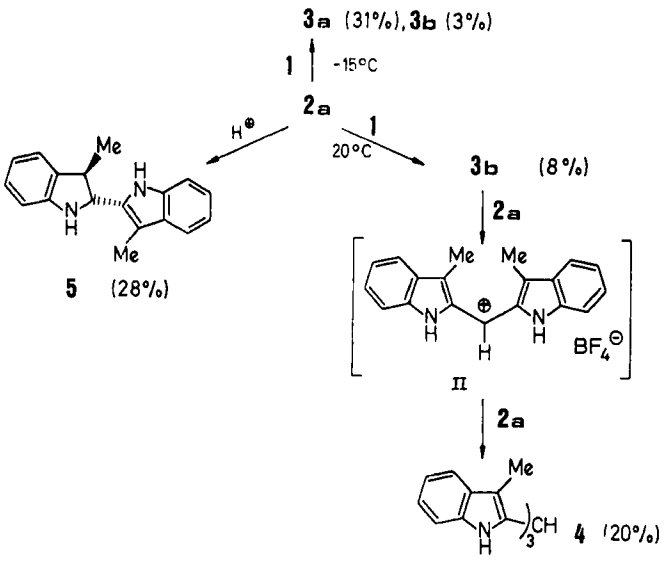


attack undergoes subsequent stabilisation via a classic *Wagner-Meerwein* rearrangement with formation of a 2,3-disubstituted indole. In the case of **2e**, the nucleophilicity at C-3 is apparently reduced (lowering of the HOMO energy and reduction of the HOMO coefficients at C-3)[11] as a result of the -I effect of the phenylsulfonyl group. These considerations are further validated by an additional experimental observation: 1-phenylsulfonylindole (**2f**) also does not react with **1** (subject to a sufficient nucleophilicity, 3-unsubstituted indoles also react preferentially at C-3)[10].

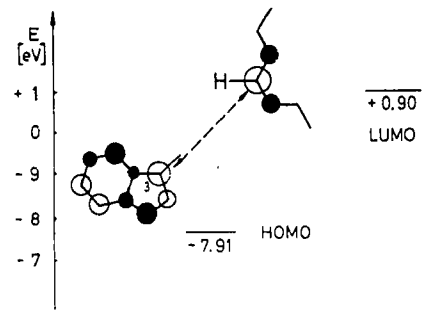
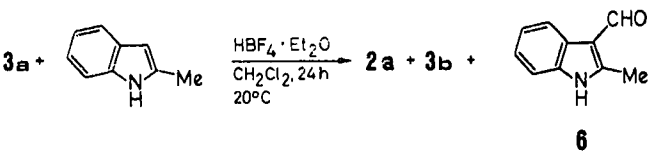
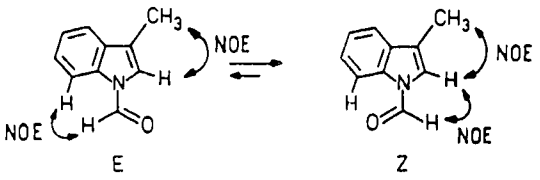


Fig. 1: HOMO-LUMO interaction of 3-methylindole (**2a**) and the cation of diethoxycarbenium tetrafluoroborate (**1**), on the basis of MNDO calculations (see also Rf.[11]) with optimised geometries.

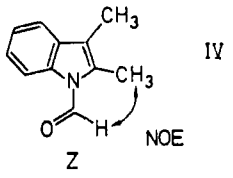
The indole-2-carbaldehydes **3b** and **3d** are extremely stable towards protic acids. In contrast, the *N*-formyl derivatives **3a** and **3c**, for example, even under strictly anhydrous conditions in a tetrafluoroboric acid/diethyl ether/dichloromethane medium are cleaved slowly and **2a** and **2b** can be detected by tlc. In the case of the proton-catalysed cleavage of **3a**, **3b** is formed in addition to **2a**. By means of a cross experiment, it was shown that, in the presence of the highly nucleophilic 2-methylindole[10] and in the presence of tetrafluoroboric acid, the rearrangement reaction of **3a** is an intermolecular process. After 24 h at 20°C, one obtains, in addition to **2a** and **3b**, also the indole-3-carbaldehyde **6** (ratio 1:2:10). From the results of the reaction of **2a** with **1**, we have deduced that the attack of the electrophile at N-1 proceeds under kinetic control and that the attack of the electrophile at C-2 proceeds under thermodynamic control by primary C-3-*ipso* attack.



The constitutions of the indole derivatives obtained in these investigations, which were all known[7], were unequivocally confirmed by comparison of their physical data with those of authentic samples available in our laboratory. It was attempted by means of differential $^1H,^1H$-NOE measurements of **3a** and **3c** to determine the preferential conformation in solution. The NOE spectrum of **3a** recorded at -40°C in CD_2Cl_2 (slow exchange) indicated that two rotamers (*E*/*Z*) were present in a ratio of 4:6 (formula **III**)[13]. This ratio does not change significantly at either -20° or 0°C. The temp. dependent ^1H-NMR spectra and NOE measurements of **3c** demonstrated the existence of a conformational equilibrium at -60°C (slow exchange) in which the (*Z*)-rotamer **IV** participates to an extent of about 90%[13]. At -20° and 0°C, *Z*-IV prevails to an extent of about 70 and 55%, respectively.



III



IV

Experimental Part

Melting points: Büchi SMP-20 capillary m.p. apparatus, uncorrected.- CHN-microanalyses: Perkin-Elmer Model 240 B elemental analyser.- ^1H-NMR spectra: JEOL JNMC 60 HL, Bruker WH 90, and Bruker WM 400 spectrometers (δ scale).- ^{13}C-NMR spectra: Varian XL 100A spectrometer (25 MHz).- Prep. tlc: Merck PF60 silica gel.- Flash chromatography: Merck 60 silica gel (grain size: 0.040-0.063 mm, volume of column: 60 cm^3).- Mass spectra: Varian CH 7A spectrometer (70 eV).

All reactions with the dialkoxycarbenium salt **1** must be performed in highly pure and strictly anhydrous solvents under argon. Diethoxycarbenium tetrafluoroborate (**1**) was prepared from triethyl orthoformate and tetrafluoroboric acid in a special apparatus described by us[3].

General Procedure for the Synthesis of Indolecarbaldehydes

To an excess of freshly prepared diethoxycarbenium tetrafluoroborate (**1**)[3] was slowly added dropwise from a syringe at -70°C a solution of the indole **2** (18-20 mmol) in 75 ml CH_2Cl_2. The reaction mixture was stirred at -70 to +20°C for several h (see under the individual compounds for exact details). The reaction mixtures or the precipitated crystals, if not otherwise stated, were hydrolysed in a two phase system comprised of CH_2Cl_2/water at 20°C for about 1 h and the resultant mixture was then neutralised with 3% NaOH. The org. phase was separated, dried with Na_2SO_4, and the solvent evaporated under mild conditions using a rotary evaporator. The products were separated and purified by crystallisation and/or chromatographic methods.

3-Methylindole-1-carbaldehyde (**3a**) and 3-Methylindole-2-carbaldehyde (**3b**)

The reaction was performed as described in the general procedure using 3-methylindole (**2a**) (2.62 g, 20 mmol) and **1** [prepared from triethyl orthoformate (4.44 g, 30 mmol) and tetrafluoroboric acid (6.50 g, 40 mmol, as a 54% solution of HBF_4 in diethyl ether)]. The reaction time was 1.5 h, the reaction temp. -15°C. **3a** and **3b** were separated by flash chromatography (CH_2Cl_2/*n*-hexane, 1/1).

Yield of **3a**: 1 g (31%); colourless crystals; bp. 98-100°C/0.03 torr[14].- ^{1}H-NMR (400 MHz, CD_2Cl_2): δ (ppm) = 2.22 (d, $^4J_{Me}$,C-2-H = 1.22 Hz, 3H, CH_3); 7.10 (s, 1H, C-2-H [*Z*]; 7.25-7.40 and 7.45-7.60 (2m, 4H, C-4-H, C-5-H, C-6-H [*E* and *Z*], C-2-H [*E*]; 8.34 (d, ^3J = 6.7 Hz, 1H, C-7-H [*Z*]; 9.03 (s, 1H, CHO [*Z*]; 9.37 (br s, 1H, CHO [*E*]).- MS (70 eV) m/z: 159 (M^+, 51%), 130 (100).- $C_{10}H_9NO$ (159.2) Calcd. C 75.5 H 5.70 N 8.8 Found C 75.1 H 5.82 N 8.78.

Yield of **3b**: 100 mg (3%); colourless crystals; mp 139°C (CH_2Cl_2/*n*-hexane); Ref.[14], mp 138-140°C.- ^{1}H-NMR (90 MHz, acetone-d_6): δ (ppm) = 2.60 (s, 3H, CH_3); 7.10 (dd, ^3J = 7 Hz, ^4J = 1.9 Hz, 1H, aromat. H); 7.20 (mc, 2H, aromat. H); 7.70 (d, ^3J = 7.8 Hz, 1H, aromat. H); 10.10 (s, 1H, CHO); 10.50 (s, 1H, NH).- MS (70 eV) m/z: 159 (M^+, 100%), 130 (84).- $C_{10}H_9NO$ (159.2) Calcd. C 75.5 H 5.70 N 8.8 Found C 75.5 H 5.74 N 8.7.

Reaction of **2a** *with* **1** *under Thermodynamic Control: Preparation of 3-Methyl-2-(3-methylindol-2-yl)indoline* (**5**) *and Tris(3-methylindol-2-yl)methane* (**4**)

The reaction was performed as described for the preparation of **3a** and **3b** using 18 mmol of **2a** but with a reaction time of 12 h and a reaction temp. of 20°C. The residue was separated by prep. tlc (mobile phase: *n*-hexane/diisopropyl ether, 85/15).

Yield of **4**: 100 mg (20%); pale green crystals; mp. 310°C (decomp. and sublimation).- The physical data of **4** are in complete accord with those reported[8].

Yield of **5**: 120 mg (28%); colourless crystals; mp 127-128°C.- ^{1}H-NMR (60 MHz, $CDCl_3$): δ (ppm) = 1.27 (d, 3H, ^3J = 7.5 Hz, indoline-CH_3; 2.26 (s, 3H, indole-CH_3); 2.80-3.40 (m, 1H, indoline C-3-H); 3.78 (s, 1H, indoline NH); 4.55 (d, 1H, ^3J = 10 Hz, indoline C-2-H); 6.42-7.60 (m, 8H, aromat. H); 8.15 (br s, 1H, indole NH); the resonances at 4.55 and 8.15 ppm disappear on addition of NaOD.- MS (70 eV) m/z: 262 (M^+, 100%); 130 (42).- $C_{18}H_{18}N_2$ (262.4) Calcd. C 82.4 H 6.92 N 10.7 Found C 82.4 H 7.12 N 10.4.

2,3-Dimethylindole-1-carbaldehyde (**3c**)

The reaction was performed with 2,3-dimethylindole (**2b**) (2.61 g, 18 mmol) and diethoxycarbenium tetrafluoroborate (**1**) [prepared from triethyl orthoformate (3.70 g, 25 mmol) and tetrafluoroboric acid diethyl etherate (4.88 g, 30 mmol)]. The reaction time was 5.5 h, the reaction temp. 0°C. The residue obtained was recrystallised from cyclohexane. Yield 0.60 g (23%); colourless crystals; mp 88°C (Ref.[14], mp. 87-88°C).- ^{1}H-NMR (400 MHz, CD_2Cl_2): δ (ppm) = 2.18 (d, 3H, ^4J = 0.82 Hz, C-3-CH_3); 2.46 (s, 3H, C-2-CH_3); 7.28 (mc, 2H, aromat. H); 7.43 (mc, 1H, aromat. H); 8.34 (s, 1H, C-7-H); 9.18 (s, 1H, CHO).- ^{13}C-NMR (25 MHz, J-modulated spin-echo experiment, CD_2Cl_2): δ (ppm) = 8.52 (C_p, C-3-$\underline{C}H_3$); 10.47 (C_p, C-2-$\underline{C}H_3$); 115.01 (C_q,); 115.93 (C_q); 118.50 (C_t); 124.32 (C_t); 124.66 (C_t); 130.86 (C_q); 131.92 (C_t); 135.02 (C_q); 158.82 (C=O).- MS (70 eV) m/z: 173 (M^+, 74%); 144 (100).- $C_{11}H_{11}NO$ (173.2) Calcd. C 76.3 H 6.40 N 8.1 Found C 76.2 H 6.41 N 7.9.

1,3-Dimethylindole-2-carbaldehyde (**3d**)

The reaction was performed as described above for **3c**. The oil obtained after hydrolysis of the reaction mixture was crystallised from petroleum ether (40-60°C) at -30°C. Yield 1.8 g (67%); light yellow crystals; mp. 36°C (Ref.[15], mp. 36°C).- ^{1}H-NMR (60 MHz, $CDCl_3$): δ (ppm) = 2.60 (s, 3H, C-3-CH_3); 4.0 (s, 3H, NCH_3); 6.87-7.87 (m, 4H, aromat. H); 10.12 (s, 1H, CHO).- MS (70 eV) m/z: 173 (M^+, 100%); 130 (20).- $C_{11}H_{11}NO$ (173.2) Calcd. C 76.3 H 6.40 N 8.1 Found C 76.2 H 6.45 N 8.1.

Cross Experiment of the Reaction of **3a** *and 2-Methylindole with* **1**

A mixture of **3a** (10 mmol) and 2-methylindole (10 mmol) dissolved in 100 ml CH_2Cl_2 was treated with 5 ml of a 54% solution tetrafluoroboric acid in diethyl ether and the reaction mixture was stirred at 20°C for 24 h. The residue was separated by flash chromatography (CH_2Cl_2/*n*-hexane, 1/9). **2a**, **3b**, and 2-methylindole-3-carbaldehyde (**6**) were obtained in a ratio 1:2:10. The physical data of **6** were in complete agreement with those reportet[16].

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