Monatshefte für Chemie 121, 77–80 (1990)

Monatshefte für Chemie
Chemical Monthly
© by Springer-Verlag 1990

Short Communication

First Electrophilic Substitution of 4-Methoxyindole with Triethyl Orthoformate as an a^1-Synthon

Ulf Pindur* and **Helmut Witzel**

Institut für Pharmazie, Fachbereich Chemie und Pharmazie, Universität Mainz, D-6500 Mainz 1, Federal Republic of Germany

Summary. 4-Methoxyindole (**2**) reacts with triethyl orthoformate (**1 a**) under proton catalysis to yield the functionalized indoles **3 a**–**3 e** in dependence on the reaction conditions. The attack of the electrophile takes place regiospecifically at the 3-position of the indole **2**

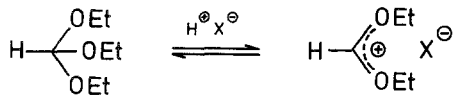
Keywords. Electrophilic substitution; 4-Methoxyindole; Triethyl orthoformate.

Erste elektrophile Substitution von 4-Methoxyindol mit Orthoameisensäuretriethylester als a^1-Synthon (Kurze Mitt.)

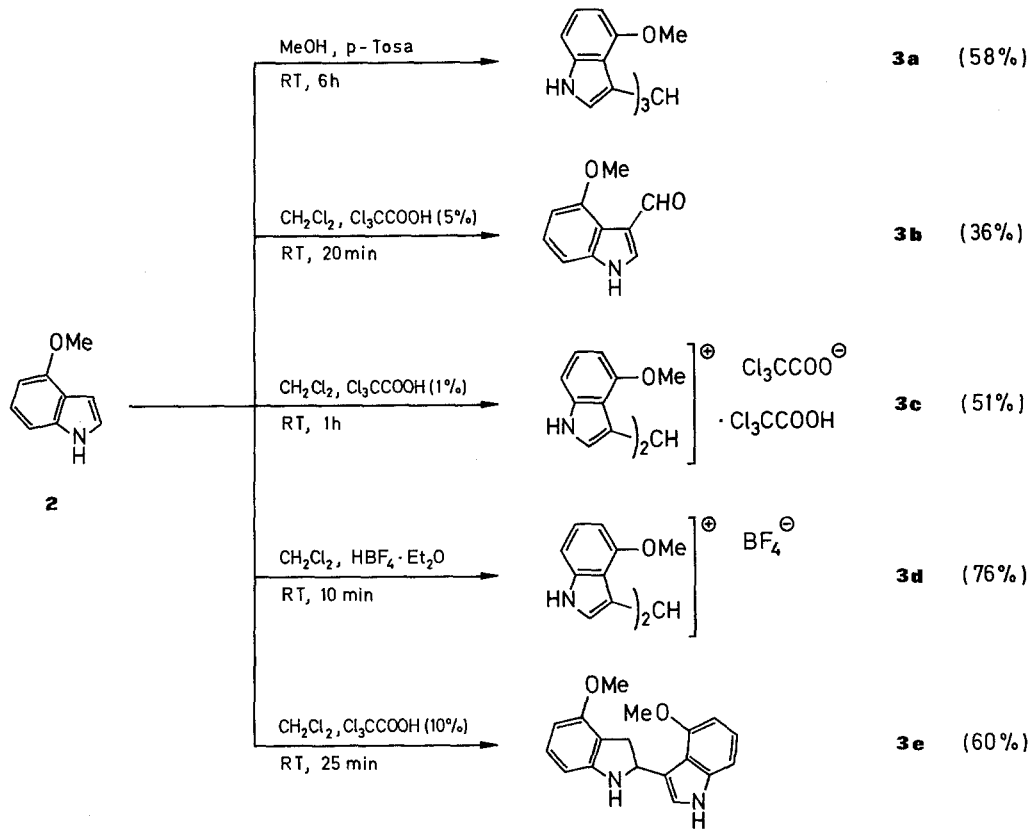
Zusammenfassung. In Abhängigkeit von den Reaktionsbedingungen reagiert 4-Methoxyindol (**2**) mit Orthoameisensäuretriethylester (**1 a**) zu funktionalisierten Indolderivaten **3 a**–**3 e**. Der Angriff des Elektrophils erfolgt regiospezifisch an der 3-Position von **2**.

The highly selective electrophilic reactivity of triethyl orthoformate (**1 a**) via the *in situ* generated diethoxycarbenium ion (**1 b**) has now been firmly established by others and by our group [1, 2] (Scheme 1). However, the synthetic potential of the reactivity of **1 a** as an a^1-synthon for the functionalization of electron-rich heterocyclic systems has not yet been investigated sufficiently [2]. Therefore, in continuation of our studies in this field [5], we now report on the first reactions of **1 a** with 4-methoxyindole (**2**) which we performed with the objectives of establishing the regiochemistry of attack of the electrophile and of elaborating further synthetic routes to functionalized indoles by way of the orthoester reaction [2].

Thus, we have found that 4-methoxyindole (**2**) reacts with **1 a** under Brönsted acid-catalysis to furnish a variety of indole derivatives **3** by regiospecific electrophilic



1 a **1 b** **Scheme 1**



Scheme 2

attack of **1b** at the 3-position of **2**. The products **3a–3e** formulated in Scheme 2 each represent the major product obtained under the specified reaction conditions. Hence, catalysis of the reaction by *p*-toluenesulphonic acid results preferentially in the formation of the novel, three-bladed propeller **3a**, whereas catalysis by trichloroactic acid gives rise to either the indole-3-carbaldehyde **3b**, the dinuclear cyanine **3c**, or solely the dimerisation product **3e**. In the presence of tetrafluoroboric acid, the cyanine tetrafluoroborate **3d** was isolated from the reaction mixture.

In summary, the present results demonstrate a similar reactivity pattern to that already described by us for the reaction of 4-methoxycarbazole with **1** [5]. For a comparison with the reactions of **1** with other simple indoles, see also Ref. [2].

Experimental

Melting points (not corrected): Linström apparatus; mass spectra: Varian MAT 7 (70 eV) spectrometer; field desorption mass spectra: Varian MAT 711 spectrometer; ^{1}H NMR spectra (at 400 MHz): Bruker WM 400 spectrometer; elemental analyses: Carlo Erba Strumentazione Model 1064 apparatus; centrifugal thin layer chromatography (CLC): Chromatotron Model 7924 apparatus (Harrison Research), silica gel 60 PF_{254} (Merck), layer thickness: 2 mm. All reactions were performed in highly pure solvents; the petroleum ether used had the boiling range 40–60°C.

3,3',3"-Methylidynetris(4-methoxyindole) (**3a**)

4-Methoxyindole (**2**; 147 mg, 1 mmol) together with *p*-toluenesulphonic acid monohydrate (19 mg, 0.1 mmol) and triethyl orthoformate (**1a**; 296 mg, 2 mmol) were dissolved in 2.2 ml of methanol. The reaction mixture rapidly turned violet and within 20 min a light-coloured precipitate began to form. After 6 h, the formed precipitate was separated and washed several times with methanol to furnish a light violet-coloured amorphous powder. Yield: 87 mg (58%), m.p. 325°C (dec.).

EI-MS (70 eV): m/z (%) = 451 ($M^{+\cdot}$, 100), 450 (11), 436 (4), 420 (9), 305 (7), 304 (19), 303 (9), 290 (7), 289 (14), 273 (11), 225 (8), 160 (4). ^{1}H NMR (400 MHz, *DMSO-d*$_6$): δ (ppm) 3.59 (s, 9 H, OCH_3), 6.32 (mc, 3 H, indole C 5-H), 6.44 (d, J = 1.2 Hz, 3 H, indole C 2-H), 6.85–6.90 (m, 6 H, indole C 6-H, indole C 7-H), 7.28 (s, 1 H, methine H), 10.48 (d, J = 1 Hz, 3 H, indole NH). $C_{28}H_{25}N_3O_3$ (451.53); calcd. 74.48, H 5.58, N 9.31; found C 74.40, H 5.59, N 8.81.

4-Methoxyindole-3-carbaldehyde (**3b**)

A) Preparation using triethyl orthoformate. 4-Methoxyindole (**2**; 74 mg, 0.5 mmol) was mixed with triethyl orthoformate (**1a**; 148 mg, 1 mmol) and 7.5 ml of a 5% solution of trichloroacetic acid (2.3 mmol of acid) in anhydrous dichloromethane were added. The mixture immediately turned violet-red. After 20 min the reaction mixture was neutralized with dilute aqueous ammonia solution and extracted by shaking with three 20 ml portions of dichloromethane. The organic phase was dried with $CaCl_2$, concentrated, the resultant crude product was taken up in a small volume of ethyl acetate, and separated by CLC [eluent: petroleum ether/ethyl acetate (1/1)] to give pale yellow crystals that were recrystallized from methanol. Yield: 31 mg (36%); the yield could be increased considerably by increasing the *ortho* ester and acid concentrations.

B) Vilsmeier-Haack formylation [4]. 4-Methoxyindole (**2**; 147 mg, 1 mmol) was dissolved in dimethylformamide, the solution was cooled, and phosphoryl chloride (0.11 ml, 1.18 mmol) was slowly added dropwise. The reaction mixture was then warmed to 40°C. After a total reaction time of 1 h, 5 ml of ice/water were added whereupon the formed precipitate dissolved. As soon as the solution became clear it was made basic by addition of 5% aqueous NaOH solution and warmed again for a short time on a water bath. The precipitate formed on basification was separated and washed several times with water. The product thus obtained was almost pure according to TLC and was recrystallized from methanol. Yield: 142 mg (82%), m.p. 156°C (methanol); Ref. [4] m.p. 162–163°C.

EI-MS (70 eV): m/z (%) = 175 ($M^{+\cdot}$, 100), 174 (19), 160 (34), 159 (17), 157 (12), 146 (38), 144 (43), 104 (89). ^{1}H NMR (400 MHz), *DMSO-d*$_6$): δ (ppm) = 3.94 (s, 3 H, OCH_3), 6.74 (br. d, J = 7 Hz, 1 H, indole C 5-H), 7.09–7.18 (m, 2 H, indole C 6–H, indole C 7-H, 8.05 (s, 1 H, indole C 2-H), 10.33 (s, 1 H, CHO), 12.22 (s, 1 H, indole NH). $C_{10}H_9NO_2$ (175.19); calcd. C 68.56, H 5.18, N 8.01; found C 68.38, H 5.28, N 7.99.

Bis (4-methoxyindol-3-yl)methylium Trichloroacetate (**3c**)

4-Methoxyindole (**2**; 74 mg, 0.5 mmol) and triethyl orthoformate (**1a**; 148 mg, 1 mmol) were dissolved together in 5 ml of anhydrous dichloromethane. On addition of trichloroacetic acid (50 mg, 0.31 mmol) the solution showed an intense violet colour. Within the following 15 min the reaction mixture was swirled several times. After 1 h, the precipitate was filtered off and washed several times with dichloromethane. The remaining red-violet, metallic-shining needles were the pure product according to TLC analysis. Yield: 81 mg (51%), m.p. 240–245°C (dec., discolouration above about 130°C).

EI-MS (70 eV): m/z (%) = 306 (13), 147 (100), 132 (73). UV/VIS (0.5% H_2SO_4 in methanol): λ_{max} (nm) (log ε) = 560 (4.47). $C_{21}H_{17}Cl_3N_2O_4$ (631.13); calcd. C 43.77, H 2.87, N 4.43, Cl 33.70; found C 44.00, H 2.79, N 4.31, Cl 33.69.

Bis(4-methoxyindol-3-yl)methylium Tetrafluoroborate (**3d**)

4-Methoxyindole (**2**; 147 mg, 1 mmol) together with triethyl orthoformate (**1a**; 74 mg, 0.5 mmol) was dissolved in 4 ml of anhydrous dichloromethane and HBF_4 diethyl etherate (0.5 mmol, 0.7 ml of 54%

HBF_4 in diethyl ether) was added dropwise. The reaction mixture was swirled several times at room temperature and a dark precipitate formed. After 10 min, the dark precipitate may be filtered off; it consisted of practically pure product according to TLC and was recrystallized from methanol to furnish fine, dark green, highly matted needles. Yield: 148 mg (76%), m.p. 220–223°C (dec., methanol).

EI-MS (70 eV): m/z (%) = 306 (3), 148 (30), 147 (100), 132 (4), 104 (87). FD-MS: m/z (%) = 305 (M^+·–BF_4, 100), 304 (16). ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 4.15 (s, 6 H, OCH_3), 7.06 (d, J = 8.1 Hz, 2 H, indole C 5-H or indole C 7-H), 7.25 (d, J = 8 Hz, 2 H, indole C 7-H or C 5-H), 7.42 (t, J = 8 Hz, 2 H, indole C 6-H), 8.98 (s, 2 H, indole C 2-H), 10.13 (s, 1 H, methine H). UV/VIS (0.5% H_2SO_4 in methanol): λ_{max} (nm) (log ε) = 560 (4.41). $C_{19}H_{17}N_2O_2 \cdot BF_4$ (392.16); calcd. C 58.19, H 4.37, N 7.14; found C 57.30, H 4.41, N 6.98.

3-(4-Methoxyindolin-2-yl)-4-methoxyindole (**3e**)

4-Methoxyindole (**2**; 74 mg, 0.5 mmol) together with triethyl orthoformate (**1a**; 148 mg, 1 mmol) and trichloroacetic acid (300 mg, 1.84 mmol) were dissolved in 3 ml of dichloromethane and the mixture was stirred at room temperature. After a reaction time of 25 min, the mixture was made basic by addition of dilute aqueous ammonia solution and then extracted three times with dichloromethane. The combined organic phases were dried with $CaCl_2$ and evaporated almost to dryness under reduced pressure. Excess petroleum ether was added to the residue and the pure (according to TLC) product precipitated as white crystals which turned dark green on storage. Yield: 44 mg (60%), m.p. 156°C (petroleum ether).

EI-MS (70 eV): m/z (%) = 294 (M^+·, 100), 293 (20), 264 (15), 263 (18), 158 (8), 147 (50), 132 (34), 104 (23). ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 3.04 (dd, ^2J = 15.4 Hz, J = 8.2 Hz, 1 H, indoline C 3-H), 3.37 (dd, ^2J = 15.4 Hz, J = 8.8 Hz, 1 H, indoline C 3-H), 3.81 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 5.42 (t, J = 8.5 Hz, 1 H, indoline C 2-H), 6.30 (dd or 2 d, J = approx. 8 Hz, 2 H), 6.53 (d, J = 7.8 Hz, 1 H), 6.95–7.01 (m, 3 H), 7.09 (t, J = 8 Hz, 1 H), 8.16 (br. s, 1 H, indole NH), indoline NH, broad. $C_{18}H_{18}N_2O_2$ (294.35); calcd. C 73.45, H 6.16, N 9.52; found C 73.51, H 5.65, N 9.51.

References

[1] Perst H. (1971) Oxonium Ions in Organic Chemistry. Verlag Chemie, Weinheim (and references cited therein); De Wolfe R. H. (1970) Carboxylic Ortho Acid Derivatives. Academic Press, New York (and references cited therein)

[2] Pindur U., Müller J., Flo C., Witzel H. (1987) Chem. Soc. Rev. **16**: 75 (and references cited therein)

[3] Witzel H., Pindur U. (1988) J. Heterocycl. Chem. **25**: 907

[4] Somei M., Yamada F., Kunimoto M., Kaneka C. (1984) Heterocycles **22**: 797

Received August 15, 1989. Accepted September 22, 1989