Reactions of furo[3,2-*b*]pyrroles and their benzo[*b*] analogues

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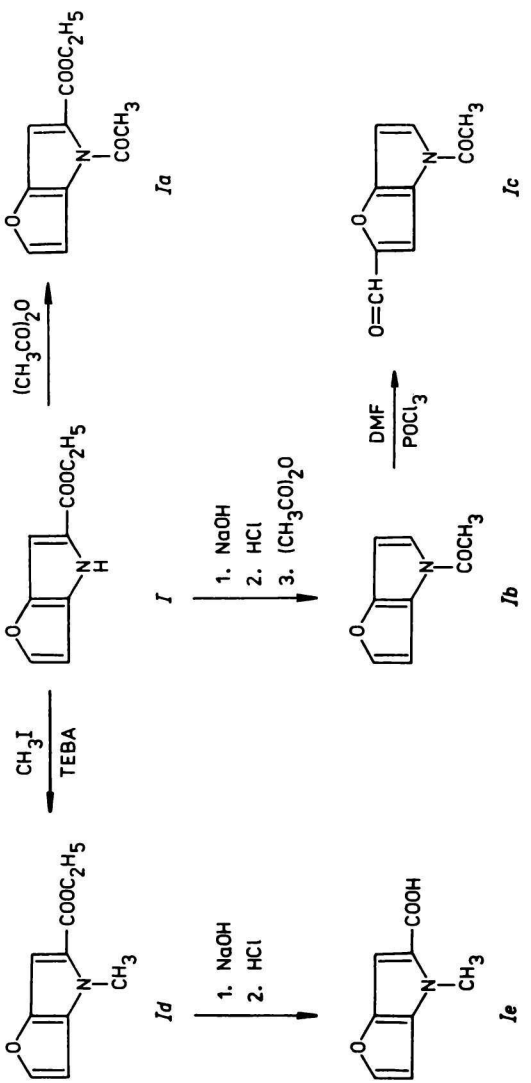
Dedicated to Professor Ing. J. Kováč, DrSc., in honour of his 60th birthday

Reaction of 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid and 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid with acetic anhydride is described. Results of a study of formylation, alkylation, and acetylation reactions of furo[3,2-*b*]pyrroles and their benzo[*b*] analogues are presented.

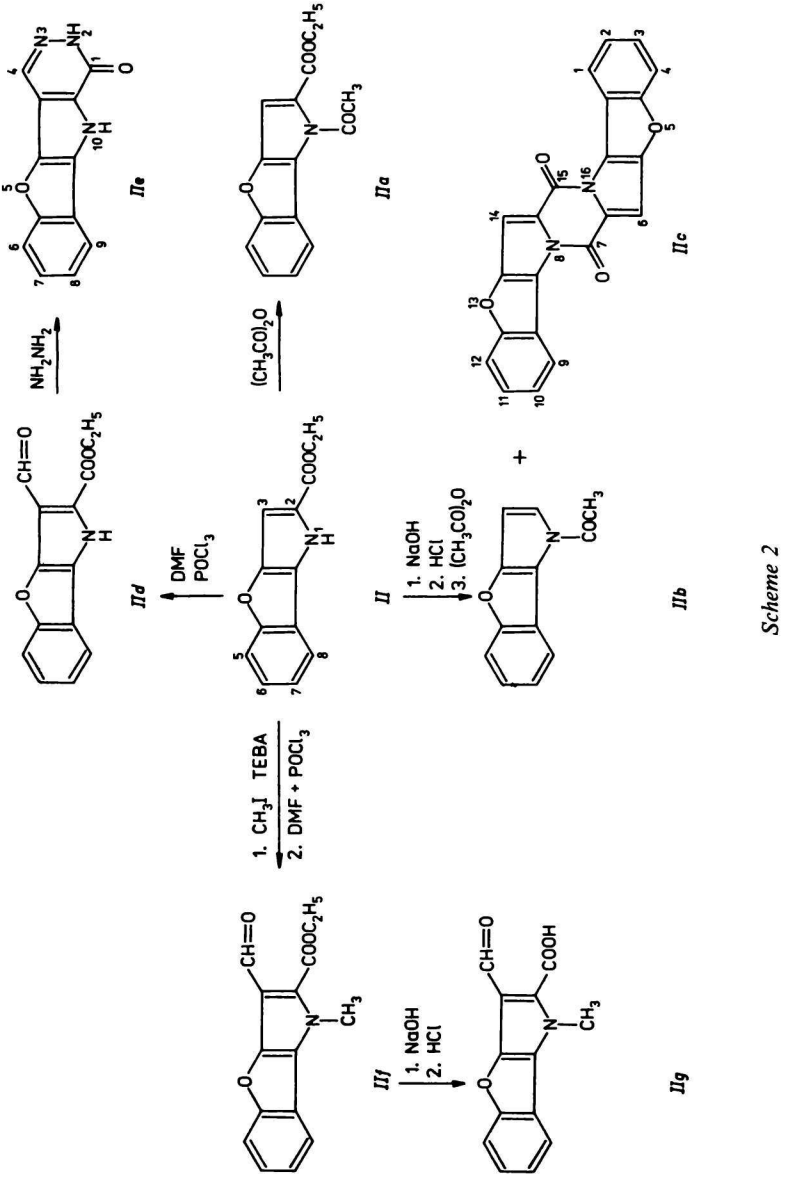
Описана реакция 4*H*-фуро[3,2-*b*]пиррол-5-карбоновой и 1*H*-бензо[*b*]фуро[3,2-*b*]пиррол-2-карбоновой кислот с уксусным ангидридом. Приводятся результаты исследования реакций формилирования, алкилирования и ацетилирования фуро[3,2-*b*]пирролов и их бензо[*b*] аналогов.

Although a great attention was paid to electrophilic substitution reactions in pyrrole and furan series, the reactions of furo[3,2-*b*]pyrroles have little been mentioned [1, 2]. As a continuation of our preceding investigation [1, 3] this paper concerns the reaction of 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid and 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid with acetic anhydride and the study of formylation, alkylation, and acetylation of some furo[3,2-*b*]pyrrole derivatives and benzo[*b*] analogues.

During heating in a boiling acetic anhydride 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid undergoes an acetylative decarboxylation to yield 4-acetylfuro[3,2-*b*]pyrrole (*Ib*) (Scheme 1); it behaves in this reaction similarly as 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid [4]. 1*H*-Benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid in the same conditions gives beside 1-acetylbenzo[*b*]furo[3,2-*b*]-pyrrole (*IIb*) the product of an intermolecular dehydration, a little soluble 6,7,14,15-tetrahydrodibenzo[*b*]furo[3,2-*b*]pyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-7,15-dione (*IIc*) (Scheme 2). A formation of dimer product in furo[3,2-*b*]pyrrole series was observed under condition of flash vacuum pyrolysis of 1*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid and its ethyl ester, respectively [5]. The formation of compounds *Ib* and *IIb* is significant from a preparative point of view, because during decarboxylation of these acids the acetylation takes place, and in simple conditions the stable derivatives of furo[3,2-*b*]pyrrole and its benzo[*b*] analogue


COOC2H5
COCH3
Ia
(CH3CO)2O
I
1. NaOH
2. HCl
3. (CH3CO)2O
Ib
DMF
POCl3
O=CH
Ic
CH3I
TEBA
Id
1. NaOH
2. HCl
COOH
Ie

Scheme 1


NH2NH2
(CH3CO)2O
DMF
POCl3
1. CH3I TEBA
2. DMF + POCl3
1. NaOH
2. HCl
3. (CH3CO)2O
1. NaOH
2. HCl
IIe
IIa
IIc
IId
II
IIb
IIf
IIg

Scheme 2

are obtained, which are useful for the further synthesis [6]. In the same conditions the corresponding acetylated esters *Ia* and *IIa* were prepared.

Furo[3,2-*b*]pyrrole derivatives and their benzo[*b*] analogues were formylated under conditions of Vilsmeier reaction. Ethyl 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2--carboxylate and ethyl 1-methylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate gave 3-formylated products *IId*, *IIf* which were the suitable starting compounds for the preparation of new fused heterocycles. Starting from ethyl 3-formylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (*IId*) 1,2-dihydrobenzo[*b*]furo[2′,3′:4,5]-pyrrolo[2,3-*d*]pyridazin-1-one (*IIe*) was obtained and from ethyl 1-methyl-3--formylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (*IIf*) the corresponding acid as a possible precursor of the β-substituted benzo[*b*]furo[3,2-*b*]pyrrole derivatives was prepared. The studied furo[3,2-*b*]pyrrole derivatives were formylated at C-2 (α-position of the furan ring). From 4-acetylfuro[3,2-*b*]pyrrole 4-acetylfuro[3,2--*b*]pyrrole-2-carbaldehyde (*Ic*) was prepared. Methylation of ethylfuro[3,2-*b*]-pyrrole-5-carboxylate under the phase-transfer catalysis conditions yielded the product *Id*, which on hydrolysis gave an acid (*Ie*).

Experimental

Compounds *I*, *II* were prepared according to [7, 8].

The IR spectra were measured with Specord 71 IR (Zeiss, Jena) using KBr technique (1 mg of the substance in 100 mg KBr). The electronic spectra were measured with a Specord UV VIS (Zeiss, Jena) spectrometer. Measuring range 200—800 nm, concentrations 5×10^{-5} mol dm^{-3} in methanol at room temperature. The ^{1}H NMR spectra were recorded with Tesla BS 487 C apparatus operating at 80 MHz. Chemical shifts in hexadeuteriodimethyl sulfoxide were related to hexadimethyldisiloxane as an internal reference, those in deuteriochloroform to tetramethylsilane.

Ethyl 4-acetylfuro[3,2-b]pyrrole-5-carboxylate (Ia)

The compound *I* (1.79 g; 0.01 mol) was refluxed in acetic anhydride (30 cm^3) for 4 h. Acetic anhydride was distilled off *in vacuo* and an oily residue was crystallized. Yield = = 2.1 g (94.9 %), m.p. = 32 °C (ethanol). For $C_{11}H_{11}NO_4$ (M_r = 221.2) w_i(calc.): 59.72 % C, 5.01 % H, 6.33 % N; w_i(found): 59.86 % C, 4.99 % H, 6.32 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d$_6$): 7.55 (1H, d, C-2—H), 6.80 (1H, dd, C-3—H), 6.84 (1H, d, C-6—H), $J_{2,3}$ = 2.2 Hz, $J_{3,6}$ = 0.8 Hz. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1702 (C=O).

Similarly from *II* was prepared ethyl 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (*IIa*). Yield = 95 %, m.p. = 64—65 °C (ethanol). For $C_{15}H_{13}NO_4$ (M_r = 271.2) w_i(calc.): 66.42 % C, 4.83 % H, 5.16 % N; w_i(found): 66.38 % C, 4.78 % H, 5.12 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d$_6$): 7.30—8.17 (4H, m, H$_{ar}$), 7.33 (1H, s, C-3—H), 4.28 (2H, q, CH$_2$), 2.68 (3H, s, COCH$_3$), 1.31 (3H, CH$_3$, t). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1706 (C=O).

4-Acetylfuro[3,2-b]pyrrole (Ib)

4*H*-Furo[3,2-*b*]pyrrole-5-carboxylic acid (3.5 g; 0.025 mol) was refluxed under stirring in acetic anhydride (3.5 g; 0.025 mol) for 4 h. Acetic anhydride was distilled off *in vacuo* and an oily product was distilled *in vacuo* as well. Yield = 1.6 g (35 %), b.p. (0.266 kPa) = 94 °C, m.p. = 34 °C (diethyl ether—n-hexane, volume ratio = 1 : 1). For $C_8H_7NO_2$ (M_r = 149.1) w_i(calc.): 80.55 % C, 4.73 % H, 9.39 % N; w_i(found): 80.59 % C, 4.69 % H, 9.35 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 7.66 (1H, dd, C-2—H), 7.37 (1H, dd, C-5—H), 6.84 (1H, dd, C-3—H), 6.49 (1H, dd, C-6—H), $J_{5,6}$ = 3.4 Hz, $J_{2,3}$ = 2 Hz, $J_{3,6}$ = 0.8 Hz, $J_{2,5}$ = 0.6 Hz. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1728 (C=O). UV spectrum (methanol), λ_{max}/nm (log {ε}): 289 (3.30).

In the same conditions 1*H*-benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid gave two products: 7,8,15,16-tetrahydrodibenzo[*b*]furo[3,2-*b*]pyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-7,15--dione (*IIc*) — the light yellow compound precipitated already during reaction. After cooling of the reaction mixture *IIc* was filtered off. Yield = 0.3 g (23 %), m.p. over 340 °C (acetic anhydride). For $C_{22}H_{10}N_2O_4$ (M_r = 366.3) w_i(calc.): 72.13 % C, 2.75 % H, 7.64 % N; w_i(found): 72.10 % C, 2.70 % H, 7.60 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 6.48 (2H, s, C-6—H, C-14—H), 7.1—8.1 (8H, m, H_{ar}). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1692 (C=O).

The second product — 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole (*IIb*) was obtained after concentration of filtrate. Yield = 0.5 g (33 %), m.p. = 101 °C (ethanol). For $C_{12}H_9NO_2$ (M_r = 199.2) w_i(calc.): 72.35 % C, 4.55 % H, 7.03 % N; w_i(found): 72.30 % C, 4.58 % H, 7.12 % N. ^{1}H NMR spectrum, δ/ppm ($CDCl_3$): 6.93 (1H, dd, C-2—H), 6.27 (1H, d, C-3—H), 2.45 (3H, s, CH_3), 7.1—8.1 (4H, m, H_{ar}). IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1716 (C=O). UV spectrum (methanol), λ_{max}/nm (log {ε}): 253 (3.40), 307 (3.17).

4-Acetylfuro[3,2-b]pyrrole-2-carbaldehyde (Ic)

Dimethylformamide (6 g; 0.08 mol) and phosphorus oxychloride (3.4 g; 0.2 mol) were stirred at 0 °C for 20 min. To this mixture 4-acetylfuro[3,2-*b*]pyrrole (2 g; 0.013 mol) dissolved in dimethylformamide (6 g) was added at temperature up to 10 °C, stirring was continued at an ambient temperature for 1 h and then at 50—60 °C for 2 h. The mixture was poured in an ice-cold water, neutralized with sodium hydrogen carbonate and left in a fridge for a night. The precipitate was filtered off and the filtrate was extracted by ether. The ethereal solution was distilled off and residues were collected. Yield of *Ic* = = 0.8 g (34.7 %), m.p. = 113 °C (ethanol). For $C_9H_7NO_2$ (M_r = 177.1) w_i(calc.): 60.99 % C, 3.98 % H, 7.90 % N; w_i(found): 61.01 % C, 4.00 % H, 8.01 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 9.49 (1H, s, CH=O), 7.84 (2H, m, C-3—H, C-5—H), 6.60 (1H, dd, C-6—H), 2.58 (3H, s, CH_3), $J_{5,6}$ = 3.6 Hz, $J_{3,6}$ = 0.9 Hz. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1722 (C=O), 1643 (CH=O).

The next compounds were prepared analogically:

Ethyl 3-formylbenzo[b]furo[3,2-b]pyrrole-2-carboxylate (IId): the reaction time 40 h, yield = 1.3 g (59 %), m.p. = 252 °C (ethanol). For $C_{14}H_{11}NO_4$ (M_r = 257.2)

w_i(calc.): 65.37 % C, 4.31 % H, 5.44 % N; w_i(found): 65.40 % C, 4.32 % H, 5.52 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 10.35 (1H, s, CH═O), 7.26—7.81 (4H, m, H_{ar}), 4.35 (2H, q, CH_2), 2.46 (1H, s, NH), 1.32 (3H, t, CH_3). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1695 (C═O), 1640 (CH═O).

Ethyl 1-methyl-3-formylbenzo[b]furo[3,2-b]pyrrole-2-carboxylate (IIf): the reaction time 20 h, yield = 1.5 g (70.9 %), m.p. = 168 °C (ethanol). For $C_{15}H_{13}NO_4$ (M_r = 271.3) w_i(calc.): 66.40 % C, 4.83 % H, 5.16 % N; w_i(found): 66.35 % C, 4.76 % H, 5.27 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 10.23 (1H, s, CH═O), 7.25—7.95 (4H, m, H_{ar}), 4.32 (2H, q, CH_2), 4.11 (3H, s, N—CH_3), 1.31 (3H, t, CH_3). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1705 (C═O), 1655 (CH═O).

Ethyl 4-methylfuro[3,2-b]pyrrole-5-carboxylate (Id)

A 50 % aqueous solution of sodium hydroxide (90 cm^3) was poured into ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (3 g; 0.017 mol) in benzene (300 cm^3) and while stirred, methyl iodide (3 g) and triethylbenzylammonium bromide (1.2 g) were added. The solution was kept stirred at 60 °C for 4 h. The mixture was cooled, the organic layer separated and the aqueous one extracted with ether. The combined organic solutions were washed with water, dried with anhydrous sodium sulfate. The solvent was distilled off *in vacuo* and a raw product was crystallized. Yield = 2.9 g (89 %), m.p. = 67 °C (diethyl ether). For $C_{10}H_{11}NO_3$ (M_r = 193.2) w_i(calc.): 62.12 % C, 5.73 % H, 7.25 % N; w_i(found): 62.15 % C, 5.70 % H, 7.37 % N. ^{1}H NMR spectrum, δ/ppm ($CDCl_3$): 7.46 (1H, d, C-2—H), 6.77 (1H, d, C-6—H), 6.39 (1H, dd, C-9—H), 4.28 (2H, q, —CH_2—), 3.93 (3H, s, N—CH_3), 1.34 (3H, t, CH_3). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1690 (C═O).

4-Methylfuro[3,2-b]pyrrole-5-carboxylic acid (Ie)

Compound *Id* (1.94 g; 0.01 mol) was dissolved in ethanol (20 cm^3) and 10 % sodium hydroxide (20 cm^3) was added. The mixture was heated on a steam bath for 3 h and concentrated to a half of its original volume. The precipitate was dissolved in dilute ethanol, acidified with hydrochloric acid (volume ratio = 1 : 1) and poured onto ice. The work up gave *Ie*. Yield = 1.7 g (87 %), m.p. = 161 °C (ethanol). For $C_8H_7NO_3$ (M_r = = 165.1) w_i(calc.): 58.19 % C, 4.27 % H, 8.48 % N; w_i(found): 58.24 % C, 4.25 % H, 8.42 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 7.72 (1H, d, C-2—H), 6.72 (1H, d, C-6—H), 6.72 (1H, d, C-3—H), 3.89 (3H, s, N—CH_3), $J_{3,6}$ = 0.7 Hz, $J_{2,3}$ = 1.9 Hz. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1650 (C═O).

1,2-Dihydrobenzo[b]furo[2',3':4,5]pyrrolo[2,3-d]pyridazin-1-one (IIe)

Ethyl 3-formylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (1 g; 0.004 mol) was dissolved in ethanol (50 cm^3) and 64 % aqueous solution of hydrazine hydrate (0.45 g). The

reaction mixture was refluxed for 6 days. The crystalline precipitate was filtered off and crystallized from dimethylformamide. Yield = 0.6 g (58 %), m.p. = 305 °C (subl.). For $C_{12}H_7N_3O_2$ (M_r = 225.2) w_i(calc.): 63.99 % C, 3.13 % H, 18.66 % N; w_i(found): 63.96 % C, 3.18 % H, 18.67 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 8.38 (1H, s, C-4—H), 7.33—7.85 (4H, m, H_{ar}). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1650 (C=O).

3-Formyl-1-methylbenzo[b]furo[3,2-b]pyrrole-2-carboxylic acid (IIg)

Ethyl 3-formyl-1-methylbenzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (1 g; 0.004 mol) was dissolved in ethanol (50 cm^3) and 5 % sodium hydroxide (30 cm^3). The reaction mixture was refluxed for 2 h. The solvent was distilled off and sodium salt of the acid *IIg* was dissolved in 50 % ethanol, and the hot solution was acidified with hydrochloric acid (volume ratio = 1 : 1). The residue was filtered off. Yield = 0.6 g (61.7 %), m.p. = 261 °C (ethanol). For $C_{13}H_9NO_4$ (M_r = 243.2) w_i(calc.): 64.19 % C, 3.73 % H, 5.75 % N; w_i(found): 64.10 % C, 3.70 % H, 5.71 % N. ^{1}H NMR spectrum, δ/ppm (DMSO-d_6): 10.32 (1H, s, CH=O), 7.24—7.89 (4H, m, H_{ar}), 4.15 (3H, s, N—CH_3). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1663 (C=O), 1617 (CH=O).

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