ELECTROPHILIC SUBSTITUTION REACTIONS OF FURO[3,2-*b*]PYRROLE DERIVATIVES

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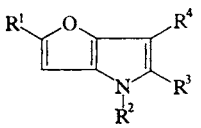
Formylation of ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its N-methyl analogue afforded the 2-formyl products *Ia, b* which on nitration yielded 2-nitro derivatives *IIc, d*. Formylation, nitration, Mannich reaction, and copulation of the starting products, having position 2 occupied by an aryl, took place at the pyrrole ring.

Although electrophilic substitution reactions of substances related to pyrrole[1-6] and furan[7] are well reported, those of furo[3,2-*b*]pyrrole system have little been mentioned[8].

This paper presents the formylation, nitration, Mannich reaction, and copulation of variously substituted furo[3,2-*b*]pyrrole derivatives under formation of compounds *I*–*IV*.



Compound	R^1	R^2	R^3	R^4
Ia	CH=O	H	$COOC_2H_5$	H
Ib	CH=O	CH_3	$COOC_2H_5$	H
Ic	C_6H_5	CH=O	$COOC_2H_5$	H
Id	4-CH_3—C_6H_4	CH=O	$COOC_2H_5$	H
Ie	C_6H_5	H	$COOC_2H_5$	CH=O
If	C_6H_5	CH_3	$COOC_2H_5$	CH=O
Ig	4-CH_3—C_6H_4	CH_3	$COOC_2H_5$	CH=O
Ih	C_6H_5	H	CH=O	H
Ii	4-CH_3—C_6H_4	H	CH=O	H
IIa	C_6H_5	H	$COOC_2H_5$	NO_2
IIb	4-CH_3—C_6H_4	H	$COOC_2H_5$	NO_2
IIc	NO_2	H	$COOC_2H_5$	H
IId	NO_2	CH_3	$COOC_2H_5$	H
III	C_6H_5	H	$COOC_2H_5$	$CH_2N(CH_3)_2$
IVa	C_6H_5	H	N=N—C_6H_5	H
IVb	4-CH_3—C_6H_4	H	N=N—C_6H_5	H

Furo[3,2-*b*]pyrrole derivatives were formylated under conditions of Vilsmeier reaction. Ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its N-methyl analogue gave the 2-formylated products *Ia,b*. In such a system, where positions 2 and 5 are occupied, the 8 h-lasting reaction afforded products of N-formylation *Ic, d*. Several times extended reaction time leads to product formylated in β position of the pyrrole ring *Ie*. The same position was also formylated when starting from the N-methylated analogue giving *If, g*. 4-Acetyl-2-arylfuro[3,2-*b*]pyrrole yielded a 5-formylated product. Introduction of the formyl group in this position gave rise to products undergoing a spontaneous decomposition. Heating in polar and nonpolar solvents resulted in cleavage of the acetyl group from nitrogen, furnishing 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carbaldehyde (*Ih, i*) and therefore, the acetyl derivative failed to be obtained in a pure form required for identification.

Formylation of furo[3,2-*b*]pyrrole derivatives shows that the preferred positions for this reactions are 2 and 5, *i.e.* α-positions of the furan and pyrrole rings followed by position 4 and finally by position 6 (β-position of the pyrrole).

Nitration of furo[3,2-*b*]pyrrole system was investigated with the mixture consisting of fuming nitric acid and acetic anhydride. Nitration was successful when positions 2 and 5 were occupied by at least one electron-accepting substituent. Whereas nitration of ethyl 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate was directed to position 6 (*IIa, b*), that of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its N-methyl analogue is accompanied by substitution of the formyl group by the nitro group (*IIc, d*).

The Mannich reaction was investigated employing ethyl 2-phenyl-4*H*-furo[3,2-*b*]-pyrrole-5-carboxylate; the electrophilic displacement occured in position 6 (*III*).

2-Aryl-4*H*-furo[3,2-*b*]pyrrole easily undergoes a copulation reaction with benzenediazonium chloride. The reaction occured in position 5 (*IVa,b*).

Products of formylation (*Ic,d*) displayed absorption bands at 1 712–1 725 cm^{-1} associated with vibration ν(C=O) of the formyl group bound to the nitrogen. Attachment of formyl group to carbon of the furo[3,2-*b*]pyrrole system (*Ia, b, e, f, g, h, i*) was manifested by a considerable lowering of the wavenumber ν(CH=O) down to 1 635–1 675 cm^{-1}. Nitro derivatives *IIa–IId* are characteristic of absorption bands at 1 512–1 536 cm^{-1} ($\nu_{as}(NO_2)$) and 1 321–1 349 ($\nu_s(NO_2)$). Electronic spectra of all formylation products *Ia–Ii*, nitration products *IIc–IId* and especially copulation products *IVa,b* revealed a noticeable bathochromic shift λ_{max} of the most intense band in relation to that of the starting compounds[9–11] associated with an extension of the conjugated system. Introduction of a nitro group into position 6 did not affect the λ_{max} value of the most intense band. The ^{1}H NMR spectra of formyl derivatives *Ia—Ii* are indicative of the formyl group proton at δ = 9·45 to 10·54 ppm. The ^{1}H NMR spectra of nitro derivatives displayed a significant downfield shift of the $C_{(3)}$—H proton by more than 1 ppm due to an electron-accepting effect of the adjacent nitro group.

EXPERIMENTAL

Ethyl 2-Formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*Ia*)

A mixture of dimethylformamide (6 g, 80 mmol) and phosphorus oxychloride (3·4 g, 20 mmol) was stirred at 0°C for 20 min. Ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate[9] (1·79 g, 10 mmol) dissolved in dimethylformamide (6 g) was added at a temperature not exceeding 10°C. The mixture was stirred at 60°C for 2 h, poured into ice-cold water, neutralized with sodium hydrogen carbonate, allowed to stand in the cold and the separated substance was filtered off. Yield 58%, m.p. 138°C (ethanol). For $C_{10}H_9NO_4$ (207·2) calculated: 57·97% C, 4·38% H, 6·76% N; found: 57·14% C, 4·21% H, 6·69% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 669 (C=O), 1 638 (C=O). UV spectrum, λ_{max}, nm (log ε): 343 (3·55). ^{1}H NMR spectrum, δ, ppm (hexadeuteriodimethyl sulfoxide): 9·51 (1 H, s, CH=O), 7·53 (1 H, dd, $C_{(3)}$—H), 6·77 (1 H, dd, $C_{(6)}$—H), 4·25 (2 H, q, CH_2), 1·25 (3 H, t, CH_3, $J_{3,6}$ = 0·8). Compounds *Ib*—*Ig* (Table I) were synthesized employing the same procedure.

Ib: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 706 (C=O), 1 662 (C=O). UV spectrum λ_{max}, nm (log ε): 344 (3·55). ^{1}H NMR spectrum, δ, ppm (hexadeuteriodimethyl sulfoxide): 9·56 (1 H, s, CH=O), 7·75 (1 H, dd, $C_{(3)}$—H), 6·82 (1 H, dd, $C_{(6)}$—H), 4·20 (2 H, q, CH_2), 3·92 (3 H, s, N—CH_3), 1·25 (3 H, t, CH_3, $J_{3,6}$ = 0·8).

Ic: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 715 (C=O), 1 685 (C=O). UV spectrum λ_{max}, nm (log ε): 377 (3·75), 353 (3·70). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 9·85 (1 H,

TABLE I

Compounds *Ib*—*Ig*

Compound	Formula (M_r)	M.p., °C[a] (yield, %)	Calculated/Found			°C[b] (h[c])
			% C	% H	% N	
Ib	$C_{11}H_{11}NO_4$	159	59·72	5·01	6·33	60
	(221·2)	(71)	58·19	4·92	6·21	(2)
Ic	$C_{16}H_{13}NO_4$	151	67·84	4·63	4·94	80
	(283·3)	(44)	67·13	4·48	4·87	(8)
Id	$C_{17}H_{15}NO_4$	167	68·68	5·09	4·71	80
	(297·3)	(54)	68·92	5·31	4·94	(8)
Ie	$C_{16}H_{13}NO_4$	148	67·84	4·63	4·94	80
	(283·3)	(43)	66·93	4·48	4·63	(60)
If	$C_{17}H_{15}NOa$	177	68·68	5·09	4·71	80
	(297·3)	(67)	68·42	5·01	4·46	(60)
Ig	$C_{18}H_{17}NO_4$	153	69·44	5·50	4·49	80
	(311·3)	(62)	68·71	5·32	4·23	(60)

[a] Crystallized from ethanol, [b] reaction temperature, [c] reaction time.

s, CH=O), 7·49 (1 H, dd, $C_{(6)}$—H), 7·26 (1 H, dd, $C_{(3)}$—H), 7·81–7·32 (5 H, m, H_{arom}), 4·26 (2 H, q, CH_2), 1·26 (3 H, t, CH_3).

Id: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 712 (C=O), 1 675 (C=O). UV spectrum λ_{max}, nm (log ε): 340 (3·73), 355 (3·68). ^1H NMR spectrum, δ, ppm (C^2HCl_3): 10·06 (1 H, s, CH=O), 7·60, 7·23 (4 H, dd, H_{arom}), 7·12 (1 H, dd, $C_{(3)}$—H), 7·06 (1 H, dd, $C_{(6)}$—H), 4·35 (2 H, q, CH_2), 2·37 (3 H, s, CH_3), 1·38 (3 H, t, CH_3).

Ie: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 685 (C=O), 1 662 (C=O). UV spectrum λ_{max}, nm (log ε): 360 (3·36). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 10·33 (1 H, s, CH=O), 7·90–7·30 (5 H, m, H_{arom}), 7·28 (1 H, s, $C_{(3)}$—H), 4·30 (2 H, q, CH_2), 1·30 (3 H, t, CH_3).

If: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 687 (C=O), 1 655 (C=O). UV spectrum λ_{max}, nm (log ε): 367 (3·27), 302 (3·45). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 10·24 (1 H, s, CH=O), 7·82–7·35 (5 H, m, H_{arom}), 7·35 (1 H, s, $C_{(3)}$—H), 4·30 (2 H, q, CH_2), 3·93 (3 H, s, CH_3), 1·29 (3 H, t, CH_3).

Ig: IR spectrum (KBr) ν_{max}, cm^{-1}: 1 689 (C=O), 1 651 (C=O). UV spectrum λ_{max}, nm (log ε): 371 (3·29), 302 (3·44). ^1H NMR spectrum δ, ppm (C^2HCl_3): 10·43 (1 H, s, CH=O), 7·67, 7·17 (4 H, dd, H_{arom}), 6·60 (1 H, s, $C_{(3)}$—H), 4·37 (2 H, q, CH_2), 3·97 (3 H, s, CH_3), 2·35 (3 H, s, CH_3), 1·40 (3 H, t, CH_3).

2-Phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carbaldehyde (*Ih*)

Dimethylformamide (6 g, 80 mmol) and phosphorus oxychloride (3·4 g, 20 mmol) were stirred at 0°C for 20 min. To this mixture 4-acetyl-2-phenyl-furo[3,2-*b*]pyrrole (2·11 g, 10 mmol) dissolved in dimethylformamide (6 g)was added at a temperature up to 10°C; stirring was continued at an ambient temperature for 1 h. The mixture was poured in an ice-cold water, neutralized with sodium hydrogen carbonate, and the orange 4-acetyl-2-phenylfuro[3,2-*b*]pyrrole-5-carbaldehyde was filtered off (IR spectrum (KBr) ν_{max}, cm^{-1}: 1 712 (C=O), 1 635 (C=O)). The compound was dried and refluxed in ethanol (120 ml) for 30 min, the solution was cooled and the title product was filtered off. Yield 76%, m.p. 226°C (ethanol). For $C_{13}H_9NO_2$ (211·2) calculated: 73·92% C, 4·43% H, 6·63% N; found: 72·65% C, 4·22% H, 6·12% N. IR spectrum ($CHCl_3$) ν_{max}, cm^{-1}: 1 640 (C=O). UV spectrum λ_{max}, nm (log ε): 368 (3·73), 358 (3·72). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 9·45 (1 H, s, CH=O), 7·92–7·37 (5 H, m, H_{arom}), 7·18 (1 H, dd, $C_{(6)}$—H), 6·97 (1 H, dd, $C_{(3)}$—H).

2-(4-*Tolyl*)-4*H*-*furo*[3,2-*b*]*pyrrole*-5-*carbaldehyde* (Ii) was prepared in an analogous way as *Ih*. Yield 72%, m.p. 266°C (ethanol). For $C_{14}H_{11}NO_2$ (225·2) calculated: 74·69% C, 4·92% H, 6·22% N; found: 72·94% C, 4·67% H, 6·07% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 620 (C=O). UV spectrum λ_{max}, nm (log ε): 371 (3·76), 361 (3·75). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 9·36 (1 H, s, CH=O), 7·67, 7·20 (4 H, dd, H_{arom}), 7·07 (1 H, dd, $C_{(6)}$—H), 6·91 (1 H, dd, $C_{(3)}$—H).

Ethyl 2-Phenyl-6-nitro-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*IIa*)

Mixture of fuming nitric acid (1·26 g, 20 mmol) and acetic anhydride (3 ml) was added to a stirred solution of ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate[10] (2·25 g, 10 mmol) in acetic anhydride (7 ml) at 0°C during 20 min, and stirring was continued at 5°C for 10 min. The mixture was poured into ice-cold water and an addition of ether have the compound precipitated: yield 28%, m.p. 265°C (ethanol). For $C_{15}H_{12}N_2O_5$ (300·3) calculated: 60·00% C, 4·03% H, 9·33% N; found: 58·92% C, 3·94% H, 9·21% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 670 (C=O), 1 536

$(NO_2)_{as}$, 1 349 $(NO_2)_s$. UV spectrum λ_{max}, nm (log ε): 311 (3·52). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·87—7·31 (5 H, m, H_{arom}), 7·26 (1 H, s, $C_{(3)}$—H), 4·29 (2 H, q, CH_2), 1·25 (3 H, t, CH_3).

Ethyl 6-nitro-2-(4-tolyl)-4H-furo[3,2-*b*]*pyrrole-5-carboxylate* (IIb) was prepared analogously as *IIa*. Yield 24%, m.p. 236°C (ethanol). For $C_{16}H_{14}N_2O_5$ (314·3) calculated: 61·09% C, 4·49% H, 8·91% N; found: 59·93% C, 4·27% H, 8·76% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 691 (C=O), 1 549 $(NO_2)_{as}$, 1 352 $(NO_2)_s$. UV spectrum λ_{max}, nm (log ε): 302 (3·46). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·66, 7·33 (4 H, dd, H_{arom}), 6·90 (1 H, s, $C_{(3)}$—H), 4·25 (2 H, q, CH_2), 1·26 (3 H, t, CH_3).

Ethyl 2-Nitro-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*IIc*)

Mixture of fuming nitric acid (1·26 g, 20 mmol) and acetic anhydride (7 ml) was added to a stirred solution of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate *Ia* (2·07 g, 10 mmol) in acetic anhydride (7 ml) at 0°C. The temperature of the mixture was then raised to 10°C for additional 2 h. The precipitate (0·56 g, 26%) was filtered off and the mother liquor was poured into water and extracted with ether. The organic layer was washed with water, dried with sodium sulfate and the solvent was removed. The residue was treated with a small amount of ethanol and filtered off. The yield of the second crop was 0·2 g (9%), total yield 34%, m.p. 225°C (ethanol). For $C_9H_8N_2O_5$ (224·2) calculated: 48·22% C, 3·60% H, 12·50% N; found: 47·62% C, 3·51% H, 12·23% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 321 $(NO_2)_s$, 1 512 $(NO_2)_{as}$. UV spectrum λ_{max}, nm (log ε): 384 (3·55). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·81 (1 H, dd, $C_{(3)}$—H), 6·84 (1 H, dd, $C_{(6)}$—H), 4·25 (2 H, q, CH_2), 1·25 (3 H, t, CH_3).

Ethyl 4-methyl-2-nitrofuro[3,2-*b*]*pyrrole-5-carboxylate* (IId) was obtained as *IIc*. Yield 38%, m.p. 205°C (ethanol). For $C_{10}H_{10}N_2O_5$ (238·2) calculated: 50·42% C, 4·23% H, 11·76% N; found: 49·23% C, 4·09% H, 11·53% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 700 (C=O), 1 532 $(NO_2)_{as}$, 1 330 $(NO_2)_s$. UV spectrum λ_{max}, nm (log ε): 382 (3·56). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 8·03 (1 H, dd, $C_{(3)}$—H), 6·85 (1 H, dd, $C_{(6)}$—H), 4·25 (2 H, q, CH_2), 1·25 (3 H, t, CH_3).

Ethyl 6-(N,N-Dimethylaminomethyl)-2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*III*)

Mixture consisting of dimethylamine (1·35 g of a 40%-solution, 10 mmol) acetic acid (1·4 g) and formaldehyde (0·76 g of a 40%-solution, 10 mmol) was added to ethyl 2-phenyl-4*H*-furo-[3,2-*b*]pyrrole-5-carboxylate[10] (2·25 g, 10 mmol) in acetic acid (100 ml). This mixture was refluxed for 7 days, then 50%-NaOH (50 ml) was added and the precipitate was filtered off. Yield 39%, m.p. 178°C (ethanol). For $C_{18}H_{20}N_2O_3$ (312·4) calculated: 69·21% C, 6·45% H, 8·97% N; found: 67·92% C, 6·12% H, 8·83% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 681 (C=O). UV spectrum λ_{max}, nm (log ε): 336 (3·68), 351 (3·63). ^{1}H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·81—7·20 (5 H, m, H_{arom}), 6·97 (1 H, s, $C_{(3)}$—H), 4·21 (2 H, q, CH_2), 3·79 (2 H, s, CH_2—N), 2·18 (6 H, s, $N(CH_3)_2$), 1·27 (3 H, t, CH_3).

2-Phenyl-5-phenylazo-4*H*-furo[3,2-*b*]pyrrole (*IVa*)

A solution of benzenediazonium chloride prepared from aniline (0·5 g) in dilute hydrochloric acid (1 : 1, 3·2 ml) and sodium nitrite (0·2 g) in water (2 ml) was added to a stirred solution of sodium salt of 2-phenylfuro[3,2-*b*]pyrrole[11] (1 g, 5 mmol) in water (50 ml), to which sodium acetate (1·8 g) was added. The red precipitate immediately separating was stirred at room temperature for 30 min and the raw product was filtered off. Yield 74%, m.p. 222°C (ethanol). For

$C_{18}H_{13}N_3O$ (287·3) calculated: 75·24% C, 4·50% H, 14·64% N; found: 73·86% C, 4·41% H, 14·35% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 352 (N=N). UV spectrum λ_{max}, nm (log ε): 475 (3·67). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·88—7·32 (10 H, m, H_{arom}), 7·15 (1 H, dd, $C_{(3)}$—H), 6·88 (1 H, dd, $C_{(6)}$—H).

5-*Phenylazo*-2-(4-*tolyl*)-4*H*-*furo*[3,2-*b*]*pyrrole* (IVb) was obtained as *IVa*. Yield 66%, m.p. 224°C (ethanol). For $C_{19}H_{15}N_3O$ (301·4) calculated: 75·73% C, 5·02% H, 13·95% N; found: 74·91% C, 4·89% H, 13·83% N. IR spectrum (KBr) ν_{max}, cm^{-1}: 1 344 (N=N). UV spectrum λ_{max}, nm (log ε): 475 (3·72). ^1H NMR spectrum δ, ppm (hexadeuteriodimethyl sulfoxide): 7·75—7·62 (5 H, m, H_{arom}), 7·41—7·21 (4 H, dd, H_{arom}), 7·07 (1 H, dd, $C_{(3)}$—H), 6·86 (1 H, dd, $C_{(6)}$—H).

Spectral Measurements

The IR spectra were measured with a Specord, model 71 IR, (Zeiss, Jena) spectrophotometer, the UV spectra of methanolic solutions were taken with a Specord UV VIS (Zeiss, Jena) apparatus at an ambient temperature; the concentration of compounds varied within $1 \cdot 10^{-5}$—$5 \cdot 10^{-5}$ mol l^{-1}. The ^1H NMR spectra were recorded with a Tesla BS 487 C instrument operating at 80 MHz. Internal reference substances were tetramethylsilane and hexamethyldisiloxane for deuteriochloroform and hexadeuteriodimethyl sulfoxide, respectively.

REFERENCES

1. Martin G., Povignant S.: J. Chem. Soc., Perkin Trans. 2, *1964*, 1802.
2. Anderson H. J.: Can. J. Chem. *35*, 21 (1957).
3. Rinkes I. J.: Rec. Trav. Chim. Pays-Bas *53*, 1167 (1934).
4. Bachman W., Heisey L.: J. Amer. Chem. Soc. *69*, 1969 (1964).
5. Herz W., Dittmer K., Cristol S.: J. Amer. Chem. Soc. *69*, 1968 (1947).
6. Triebs A., Fritz G.: Justus Liebigs Ann. Chem. *611*, 162 (1958).
7. Traynelis V. J., Mickel J. J., Sowa J. A.: J. Org. Chem. *22*, 1269 (1957).
8. Krutošíková A., Kováč J., Dandárová M., Veverka M.: This Journal *44*, 1805 (1979).
9. Hemetsberger H., Knittel D.: Monatsh. Chem. *103*, 194 (1972).
10. Krutošíková A., Kováč J., Krištofčák J.: This Journal *44*, 1799 (1979).
11. Krutošíková A., Kováč J., Kráľovičová E.: This Journal *48*, 772 (1983).

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