SYNTHESIS AND REACTIONS OF FURO[3,2-*b*]PYRROLE TYPE ALDEHYDES

Alžbeta KRUTOŠÍKOVÁ[a], Miloslava DANDÁROVÁ[a] and Juraj ALFÖLDI[b]

[a] *Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava, The Slovak Republic*

[b] *Institute of Chemistry, Slovak Academy of Sciences, 842 38 Bratislava, The Slovak Republic*

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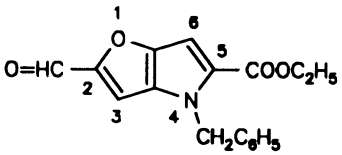
The synthesis of ethyl 2-formyl-4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (*I*) is described. A series of furo[3,2-*b*]pyrrole-2-carbaldehyde 2,6-dialkylphenylhydrazones (*IIa – IIg*) and dimethylhydrazones (*IIIa – IIId*) were prepared. By reaction of title compounds with hydroxylammonium chloride in acetic anhydride in the presence of pyridine corresponding cyano-substituted compounds (*IVa – IVd*) were obtained. Alkaline hydrolysis of *IVa – IVd* gave *Va – Vb* and the reaction with sodium azide and ammonium chloride in dimethylformamide led to *VIa – VId*. The structure of the compounds have been proved by UV, IR, ^{1}H and ^{13}C NMR spectra.

The several reaction centers of ethyl 2*H* or 2-substituted furo[3,2-*b*]pyrrole-5-carboxylates were studied and utilized for synthesis of many new heterocyclic compounds[1–4]. The papers[5,6] present the formylation, nitration, Mannich reaction and copulation of variously substituted furo[3,2-*b*]pyrroles or their benzo[*b*]derivatives.

This paper presents the formylation of ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate under conditions of Vilsmeier reaction. In this reaction analogously as in the case of ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its 4-methyl derivative[5] was obtained 2-formylated product *I*.

By the reaction of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its 4-methyl or 4-benzyl derivative (*I*) with 2,6-dialkylphenylhydrazines in refluxing toluene, with catalytic amount of 4-methylbenzenesulfonic acid were obtained hydrazones *IIa – IIg*. Analogously *N,N*-dimethylhydrazones *IIIa – IIId* were made starting from *unsym*-dimethylhydrazine and aldehydes or 4-acetylfuro[3,2-*b*]pyrrole-2-carbaldehyde[6].

The reaction of title compounds with hydroxylammonium chloride in acetic anhydride in the presence of pyridine at 90 °C gave corresponding cyano substituted compounds (*IVa – IVd*). Alkaline hydrolysis of *IVa – IVd* gave *Va – Vb* and the reaction *IVa – IVd* with sodium azide and ammonium chloride in dimethylformamide led to *VIa – VId*.



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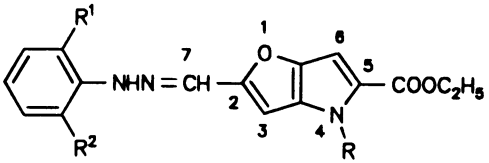
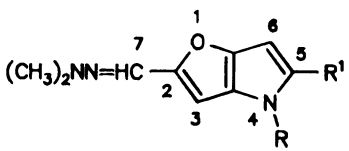
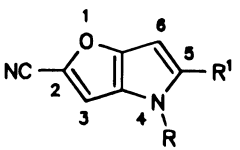


II

	R	R^1	R^2
a	H	CH_3	CH_3
b	H	CH_3	C_2H_5
c	H	C_2H_5	C_2H_5
d	CH_3	CH_3	CH_3
e	CH_3	CH_3	C_2H_5
f	CH_3	C_2H_5	C_2H_5
g	$CH_2C_6H_5$	CH_3	CH_3



III



IV

	R	R^1
a	H	$COOC_2H_5$
b	CH_3	$COOC_2H_5$
c	$CH_2C_6H_5$	$COOC_2H_5$
d	$COCH_3$	H

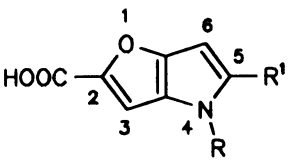
	R	R^1
a	H	$COOC_2H_5$
b	CH_3	$COOC_2H_5$
c	$CH_2C_6H_5$	$COOC_2H_5$
d	$COCH_3$	H

Characteristic data, IR and UV spectra of synthesized compounds are listed in Tables I and II.

The structure of the studied compounds has been confirmed by ^{1}H NMR spectra (Tables III and IV) and for some studied compounds the ^{13}C NMR spectra are reported (Table V).

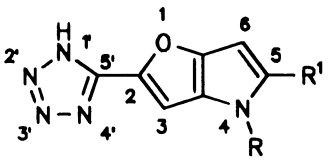
The ^{1}H NMR spectra of furo[3,2-*b*]pyrroles substituted at position 2,4 and 5 display doublets of H-3 and H-6 protons resulting from a long-range coupling $^5J(3,6)$ = 0.8 Hz or broad signals with unresolved coupling constants. For compounds *IIId*, *IVd* and *VId* signal H-6 appears as doublet of doublet due to interaction with H-5, $^3J(5,6)$ = 3.5 Hz. For compounds, where R = H, H-6 signal is split by the NH proton, $^4J(4,6)$ = 1.2 – 1.4 Hz.

For the assignment of carbon atoms the selective heteronuclear decoupling in semiselective INEPT experiment were applied as well as the comparison with the values of ^{13}C chemical shifts of some substituted furo[3,2-*b*]pyrroles[7].



V

	R	R^1
a	H	COOH
b	CH_3	COOH
c	$CH_2C_6H_5$	COOH



VI

	R	R^1
a	H	$COOC_2H_5$
b	CH_3	$COOC_2H_5$
c	$CH_2C_6H_5$	$COOC_2H_5$
d	$COCH_3$	H

Fungicidal activity of prepared compounds was examined according to the previously published methods[8]. In laboratory conditions by the diffusive method in vitro on the model micromycetes, the atifungal activity of *IIa*, *IIc*, *IId* was revealed. All active compounds were advanced to further screening. None of the prepared compounds in standard test methods[9] on herbicidal activity reached the value of the used standards.

TABLE I
Characteristic data of synthesized compounds

Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found		
			% C	% H	% N
I	$C_{17}H_{15}NO_4$	118 – 120	68.68	5.08	4.71
	(297.3)	74	68.48	4.92	4.80
IIa	$C_{18}H_{19}N_3O_3$	166 – 167	66.45	5.89	12.91
	(325.4)	78	66.24	5.82	12.89
IIb	$C_{19}H_{21}N_3O_3$	128 – 129	67.24	6.24	12.38
	(339.4)	74	67.20	6.26	12.40
IIc	$C_{20}H_{23}N_3O_3$	145 – 147	67.97	6.56	11.89
	(353.4)	76	67.95	6.50	11.80
IId	$C_{19}H_{21}N_3O_3$	175 – 176	67.24	6.24	12.38
	(339.4)	82	67.30	6.36	12.48
IIe	$C_{20}H_{23}N_3O_3$	119 – 122	67.97	6.56	11.89
	(353.4)	68	67.91	6.54	12.92
IIf	$C_{21}H_{25}N_3O_3$	150 – 154	68.64	6.86	11.44
	(367.4)	72	68.70	6.84	11.40
IIg	$C_{25}H_{25}N_3O_3$	80 – 82	72.27	6.06	10.11
	(415.5)	76	72.30	6.10	10.12
IIIa	$C_{12}H_{15}N_3O_3$	122 – 124	57.82	6.07	16.86
	(249.3)	74	57.62	6.16	16.80
IIIb	$C_{13}H_{17}N_3O_3$	67 – 68	59.30	6.51	15.96
	(263.3)	72	59.30	6.20	15.76
IIIc	$C_{19}H_{21}N_3O_3$	124 – 127	67.24	6.24	12.38
	(339.4)	70	67.40	6.32	12.48
IIId	$C_{11}H_{13}N_3O_2$	102 – 104	60.26	5.98	19.17
	(219.2)	65	60.16	5.82	19.36
IVa	$C_{10}H_8N_2O_3$	194 – 196	58.82	3.95	13.72
	(204.2)	78	58.68	3.90	13.66
IVb	$C_{11}H_{10}N_2O_3$	129 – 131	60.55	4.62	12.84
	(218.21)	80	60.28	4.58	12.78
IVc	$C_{17}H_{14}N_2O_3$	102 – 104	69.38	4.79	9.52
	(294.3)	74	69.34	4.62	9.48
IVd	$C_9H_6N_2O_2$	154 – 157	62.07	3.47	16.08
	(174.1)	68	61.99	3.37	16.12

TABLE I
(*Continued*)

Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found		
			% C	% H	% N
Va	$C_8H_5NO_5$	>340	49.24	2.58	7.18
	(195.1)	62	49.45	2.56	7.28
Vb	$C_9H_7NO_5$	>340	51.68	3.37	6.70
	(209.1)	76	51.69	3.42	6.62
Vc	$C_{15}H_{11}NO_5$	>340	63.16	3.89	4.91
	(285.3)	62	63.08	3.82	4.82
VIa	$C_{10}H_9N_5O_3$	258 – 262	48.59	3.69	28.33
	(247.2)	68	48.34	3.54	28.36
VIb	$C_{11}H_{11}N_5O_3$	238 – 240	50.57	4.24	26.81
	(261.2)	72	50.42	4.34	26.74
VIc	$C_{17}H_{15}N_5O_2$	200 – 203	60.53	4.48	20.76
	(337.3)	82	60.64	4.64	20.66
VId	$C_7H_8N_5O$	244 – 247	49.77	3.25	32.25
	(178.2)	72	49.66	3.34	32.34

EXPERIMENTAL

Melting points were determined on Kofler hot plate apparatus and were uncorrected. All NMR experiments were performed on a Bruker AM-300 FT NMR spectrometer at 298 K. ^{1}H NMR spectra were recorded at 300 MHz in $(CD_3)_2SO$. The following measurement conditions were used for ^{13}C NMR spectra: 75.43 MHz, tube size 10 mm, standard internal TMS, pulse width 12 ms, flip angle 50°, acquisition time 0.4 s, pulse delay 2 s, spectral width 5 kHz. For the signal assignment the selective SF decoupling and semiselective INEPT experiment was carried out, with the optimalization for *J*(long-range) = 7 Hz. The UV spectra were measured on a M-40 (Zeiss, Jena) spectrophotometer in methanol (λ_{max}/log ε; λ_{max} in nm, ε in m^2 mol^{-1}. The IR spectra were recorded on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr technique (0.5 mg/300 mg KBr) (ν_{max} in cm^{-1}).

The starting compounds were prepared: 2,6-dialkylphenylhydrazinium chlorides[10,11]; (the corresponding hydrazines were liberated with sodium hydroxide); ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, its 4-methyl derivative[5] and 4-acetylfuro[3,2-*b*]pyrrole-2-carbaldehyde[6].

Ethyl 2-Formyl-4-benzylfuro[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-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (4.14 g, 20 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 and separated substance was filtered off and crystallized from ethanol.

5-Ethoxycarbonyl-4*H*-furo[3,2-*b*]pyrrole-2-carbaldehyde 2,6-Dimethylphenylhydrazone (*IIa*)

2,6-Dimethylphenylhydrazine (1.35 g, 10 mmol) in toluene (5 ml) was added to the solution of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (2.07 g, 20 mmol) in toluene (30 ml) and a catalytic amount of acetic acid (0.5 ml). The mixture was refluxed for 2 h, the solvent was distilled off under reduced pressure and the residue was crystallized from ethanol.

This procedure was also applied for the preparation of the compounds *IIb* – *IIg*.

TABLE II
UV and IR spectral data of synthesized compounds

Compound	λ_{max}	log ε	ν(C=O)	Compound	λ_{max}	log ε	ν(C=O)
I	342	3.56	1 661	*IVc*[a]	319	3.61	1 720
			1 701		310	3.58	
IIa	362	3.67	1 686	*IVd*[a]	296	3.41	1 700
IIb	362	3.68	1 684	*Va*	314	3.32	1 684
IIc	362	3.67	1 684	*Vb*	321	3.52	1 688
IId	364	3.67	1 700	*Vc*	322	3.58	1 684
IIe	364	3.71	1 701	*VIa*	353	3.64	1 690
IIf	362	3.55	1 701		337	3.70	
IIg	359	3.65	1 692	*VIb*	333	3.58	1 700
IIIa	351	3.72	1 692		321	3.61	
IIIb	354	3.70	1 698	*VIc*	333	3.57	1 695
IIIc	358	3.70	1 698		320	3.61	
IIId	336	3.37	1 703	*VId*	305	3.28	
IVa[a]	317	3.63	1 680		251	2.96	
	309	3.62					
IVb[a]	317	3.63	1 700				
	310	3.62					

[a] Compounds *IVa* – *IVd* displayed at 2 220 cm^{-1} ν(CN).

5-Ethoxycarbonyl-4*H*-furo[3,2-*b*]pyrrole-2-carbaldehyde Dimethylhydrazone (*IIIa*)

A stirred solution of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (2.07 g, 10 mmol) in toluene (10 ml) containing a catalytic amount of 4-methylbenzenesulfonic acid (5 mg) was treated carefully with *N*,*N*-dimethylhydrazine (0.60 g, 10 mmol). The solution was then refluxed for 2 h and water formed during the reaction was removed in Dean–Stark trap. The solvent was removed under reduced pressure and the residue was crystallized from ethanol. Compounds *IIIb* – *IIId* were prepared in the same manner and were crystallized from ethanol.

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

To the mixture of ethyl 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (2.07 g, 10 mmol), pyridine (8 ml), hydroxyammonium chloride (1.2 g, 17 mmol) and acetic anhydride (5.5 ml) was added under stirring

TABLE III
^{1}H NMR spectra (δ in ppm, *J* in Hz) of compounds *I*, *IIa* – *IIg* and *IIIa* – *IIId*

Compound[a]	H-3	H-6[e]	H-7	NH	R^1	R^2	R
I	6.88	6.76	9.53[f]	–	–	–	5.67 (CH_2)
							7.15 – 7.37 (C_6H_5)
IIa[b]	6.56	6.71	7.45	8.50	2.30	2.30	10.30 (NH)
IIb[b]	6.56	6.71	7.46	8.54	2.30	2.70	10.20 (NH)
						1.19	
IIc[b]	6.54	6.70	7.44	8.51	2.70	2.70	10.20 (NH)
					1.19	1.19	
IId[b]	6.68	6.71	7.50	8.55	2.32	2.32	3.93 (CH_3)
IIe[b]	6.66	6.71	7.47	8.57	2.30	2.73	3.94 (CH_3)
						1.19	
IIf[b]	6.64	6.71	7.46	8.54	2.70	2.70	3.94 (CH_3)
					1.19	1.19	
IIg[b]	6.52	6.80	7.41	8.52	2.29	2.29	5.67 (CH_2)
							7.15 – 7.37 (C_6H_5)
IIIa[c,d]	6.48	6.70	7.15	–	–	–	10.40 (NH)
IIIb[c,d]	6.58	6.74	7.13	–	–	–	3.94 (CH_3)
IIIc[c,d]	6.43	6.80	7.09	–	–	–	5.70 (CH_2)
							7.15 – 7.30 (C_6H_5)
IIId[d,g]	6.77	6.38	7.18	–	–	–	2.59 ($COCH_3$)

[a] *I* in $CDCl_3$, *IIa* –*IIId* in $(CD_3)_2CO$; [b] 7.00 – 7.15 (H-3′,4′,5′), R^1: 4.26 (CH_2), 1.30 (CH_3); [c] 4.30 (CH_2), 1.30 (CH_3); [d] 2.96 ($N(CH_3)_2$); [e] *J*(3,6) = 0.8; [f] CH=O; [g] 7.35 (H-5), *J*(5,6) = 3.5.

at 95 °C. The reaction mixture was kept at 85 – 95 °C for 2 h, cooled and poured on ice. The separated precipitate was filtered off and crystallized from ethanol. Similarly procedures were used for the preparation of compounds *IVb* – *IVd*.

4*H*-Furo[3,2-*b*]pyrrole-2,5-dicarboxylic Acid (*Va*)

Sodium hydroxide (5%, 25 ml) was added to solution of ethyl 2-cyano-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (2.04 g, 10 mmol) in ethanol (50 ml). The mixture was refluxed for 10 h, evaporated and a residue was dissolved in 50% ethanol. The hot solution was acidified with hydrochloric acid (17%) to a weakly acidic reaction, poured on ice, the precipitate was filtered off and washed with water. The product was recrystallized from ethanol–ethyl acetate 1 : 1. Compounds *Vb* – *Vd* were prepared analogously.

Ethyl 2-(5'-Tetrazolyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*VIa*)

A stirred mixture of *Va* (1.8 g, 10 mmol), sodium azide (0.72 g, 12 mmol) ammonium chloride (0.64 g, 12 mmol) and dimethylformamide (13 ml) was heated at 100 °C for 4 h. The solvent was distilled off in vacuo, the residue was dissolved in water, the solution was acidified with hydrochloric acid and the precipitate was filtered off and crystallized from ethanol. Compounds *VIb* – *VId* were prepared analogously.

TABLE IV
^{1}H NMR spectra (δ in ppm, *J* in Hz) of compounds *IVa* – *IVd*, *Va* – *Vc* and *VIa* – *VId* [a]

Compound	H-3[b]	H-6	R	Other signals
IVa	7.11	6.81	9.07 (NH)	4.39 (CH_2), 1.40 (CH_3)
IVb	7.09	6.78	3.99 (CH_3)	4.35 (CH_2), 1.39 (CH_3)
IVc	6.85	6.53	5.63 (CH_2)	4.33 (CH_2), 1.36 (CH_3)
			7.15 – 7.30 (C_6H_5)	
IVd	7.41	6.40	2.60 ($COCH_3$)	7.48 (H-5)
Va	7.27	6.80	11.80 (NH)	7.55, 7.95 (COOH)
Vb	7.45	6.75	3.89 (CH_3)	4.10 (COOH)
Vc	7.32	6.90	5.68 (CH_2)	4.40 (COOH)
			7.15 – 7.30 (C_6H_5)	
VIa	7.31	6.86	11.90 (NH)	4.24 (CH_2), 1.26 (CH_3)
VIb	7.56	6.86	3.94 (CH_3)	4.25 (CH_2), 1.27 (CH_3)
VIc	7.41	6.97	5.61 (CH_2)	4.23 (CH_2), 1.26 (CH_3)
			7.15 – 7.30 (C_6H_5)	
VId	7.63	6.63	2.58 ($COCH_3$)	7.55 (H-5)[c]

[a] *IVa* – *IVd* in $CDCl_3$, *Va* – *Vc* and *VIa* – *VId* in $(CD_3)_2SO$; [b] *J*(3,6) = 0.8; [c] *J*(5,6) = 3.5.

TABLE V
^{13}C NMR chemical shifts (δ, ppm) of some studied compounds (for solvents see Tables III and IV)

Compound	C-2	C-3	C-3a	C-5	C-6	C-6a	C-7	Other signals
I	156.18	108.02	131.79	129.86	98.34	149.61	178.04[a]	R^1: 161.05 (CO), 60.73 (CH_2), 14.18 (CH_3); R: 50.92 (CH_2), 136.51 (C-1), 127.49 (C-2′, 6′), 128.70 (C-3′, 5′), 127.96 (C-4′)
IIc	158.79	96.23	131.39	125.09	96.56	148.27	126.12	Ar[b]: 25.55 (CH_2), 15.59 (CH_3), 138.79 (C-1′), 140.36 (C-2′, 5′), 127.84 (C-3′,5′), 126.91 (C-4′); R^1: 162.03 (CO), 60.62 (CH_2), 14.77 (CH_3)
IIe	158.69	95.23	133.47	124.71	97.94	145.85	126.20	Ar[b]: 18.85 (CH_3), 25.62 (CH_2), 15.63 (CH_3), 139.66 (C-1′), 139.31 (C-6′), 135.58 (C-2′), 129.42 (C-3′,5′), 121.99 (C-4′); R^1: 162.02 (CO), 60.11 (CH_2), 14.71 (CH_3); R: 34.88 (CH_3)
IIIb	159.79	93.96	135.75	124.16	97.96	145.36	122.59	R^1: 162.02 (CO), 60.11 (CH_2), 14.72 (CH_3); R: 34.84 (CH_3), 42.57 ($N(CH_3)_2$)
IVb	130.43	108.57	129.80	129.46	97.68	147.84	112.30[c]	R^1: 161.37 (CO), 60.67 (CH_2), 14.33 (CH_3); R: 35.02 (CH_3)
IVc	129.72	109.56	129.47	129.27	98.37	148.09	112.21[c]	R^1: 161.24 (CO), 60.75 (CH_2), 14.25 (CH_3); R: 51.13 (CH_2), 136.27 (C-1′), 127.69 (C-2′,6′), 128.82 (C-3′,5′), 128.16 (C-4′)

TABLE V
(*Continued*)

Compound	C-2	C-3	C-3a	C-5	C-6	C-6a	C-7	Other signals
Va	152.05	101.86	128.36	127.37	95.43	147.72	–	159.85 (COOH), 162.20 (COOH)
Vb	148.69	105.15	132.16	128.11	97.23	146.47	–	159.81 (COOH), 162.30 (COOH); R: 34.63 (CH_3)
Vc	148.62	105.61	131.69	127.81	98.33	147.07	–	159.81 (COOH), 162.30 (COOH); R: 49.74 (CH_2), 137.94 (C-1′), 127.20 (C-2′,6′), 128.50 (C-3′,5′), 127.48 (C-4′)
VIa	148.46	101.25	129.02	126.31	95.81	144.46	–	148.9 (C-5′); R^1: 160.82 (CO), 60.24 (CH_2), 14.36 (CH_3);
VIb	145.94	100.80	133.07	125.79	97.30	144.47	–	149.00 (C-5′); R^1: 160.74 (CO), 59.99 (CH_2), 14.23 (CH_3); R: 34.79 (CH_3)
VIc	146.39	101.15	132.70	125.36	98.42	144.76	–	149.11 (C-5′); R^1: 160.71 (CO), 60.16 (CH_2), 14.70 (CH_3); R: 49.99 (CH_2), 137.80 (C-1′), 127.11 (C-2′,6′), 128.58 (C-3′,5′), 127.53 (C-4′)

[a] CH=O; [b] 2,6-dialkylphenyl; [c] C≡N.

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