Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine Derivatives Reactions in the Pyridine and Pyrrole Ring

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Methyl 1-methylpyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate was oxidized with *m*-chloroperbenzoic acid in dichloromethane to 2-methoxycarbonyl-1-methylpyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-7-oxide. Treatment of this compound with benzoyl chloride and cyanide anion (Reissert—Henze reaction) was shown to produce the corresponding methyl 8-cyano-1-methylpyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate. Methyl 1*H*-pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate was prepared by reduction of methyl 8-chloro-1*H*-pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate with hydrazine and palladium on carbon. Both esters with hydrazine hydrate yielded the corresponding carbohydrazides, which by reaction with orthoesters afforded 4-substituted 2*H*-pyrido[3″,4″:4′,5′]furo[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-1-ones.

The search for biologically active substances led us to the investigation of condensed oxygen- and nitrogen-containing heterocycles. Furopyridines are very similar to such skeletons as quinoline, isoquinoline, and benzofuran which are present in many compounds possessing biological activity. Also substances containing 1,2,4-triazine moiety are used in pharmacy and agriculture. Therefore the chemists are concentrated to the synthesis of condensed 1,2,4-triazines possessing potentially biological properties [1, 2].

For a number of years we have been interested in studying the synthesis and reactivity of various furo[3,2-*c*]pyridines [3—6]. In our other paper [6] we were interested in transformations in the pyridine ring of some furo[3,2-*c*]pyridines. The Reissert—Henze reaction serves to introduce a cyano group into an α (or occasionally γ) position to the heteronitrogen atom of an azine ring [7—9]. To provide this reaction it is necessary to prepare the corresponding pyridine *N*-oxides by oxidation with hydrogen peroxide [10] or *m*-chloroperbenzoic acid [11]. The synthesis of 1,2,4-triazines fused with furo[3,2-*b*]pyrrole on [*d*]-bond has been object of our preceding studies [12—19].

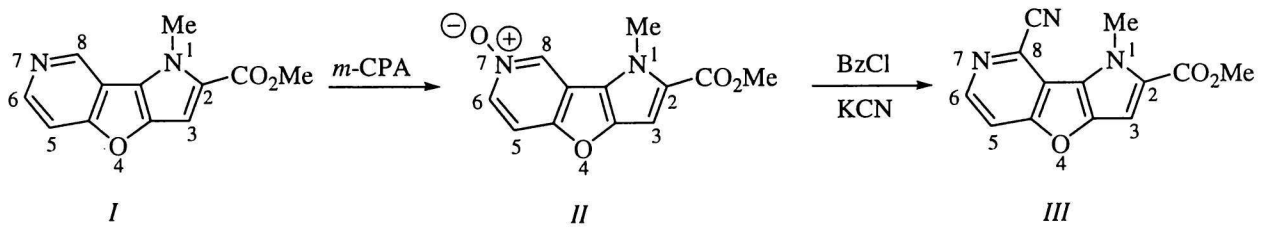
In continuation of our previous efforts towards the study of the reactivity of various furo[3,2-*c*]pyridines we here present some simple transformations in the pyridine ring of methyl 1-methylpyrrolo[2′,3′:4,5]-furo[3,2-*c*]pyridine-2-carboxylate (*N*-oxidation and Reissert—Henze reaction) and the utilization of suitable substituted pyrrolo-furopyridine derivatives in the synthesis of fused 1,2,4-triazinones.

Methyl 1-methylpyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate (*I*) [4] was oxidized by addition of *m*-chloroperbenzoic acid in dichloromethane to the corresponding *N*-oxide *II*. Then, the synthesized *N*-oxide *II* was treated with benzoyl chloride and cyanide anion in a two-phase mixture of water and dichloromethane for 48 h (Scheme 1).

Under these conditions *N*-oxide *II* reacted simultaneously to effect *N*-deoxygenation and α-cyanation. These transformations resulting in the formation of the product – methyl 8-cyano-1-methylpyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate (*III*) were easily verified by IR, ^{1}H, ^{13}C NMR, and mass spectra. In the IR spectra the loss of the *N*-oxide band at 1296 cm^{-1} and the appearance of the nitrile absorption at 2224 cm^{-1} were observed. The location of the cyano substituent was followed by the disappearance of the most downfield signal of proton H—C-8 in the ^{1}H NMR spectrum.

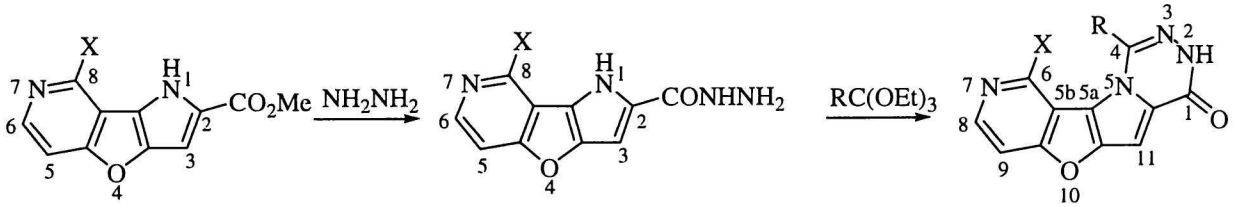
In continuation of our program aimed at developing efficient syntheses of fused 1,2,4-triazines we here report on the utilization of methyl 8-X-1*H*-pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylates *IVa* (X = Cl) and *IVb* (X = H) in the synthesis of fused 1,2,4-triazinones *VIa*—*VIf*.

Methyl 8-chloro-1*H*-pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylate (*IVa*) [5] was prepared starting from methyl 2-formyl-1*H*-furo[3,2-*b*]pyrrole-5-carboxylate [20]. Dehalogenation of *IVa* with zinc in acetic acid [5] gave a low yield of *IVb*, therefore another method [21] was tried. The reduction of *IVa* with hy-



I *II* *III*

Scheme 1



IVa X = Cl
IVb X = H

Va X = Cl
Vb X = H

VIa X = Cl, R = H
VIb X = Cl, R = Me
VIc X = Cl, R = Et
VId X = H, R = H
VIe X = H, R = Me
VIf X = H, R = Et

Scheme 2

Table 1. Characterization of the Synthesized Compounds

Compound	Formula	w_i(calc.)/% w_i(found)/%			Yield	M.p.
	M_r	C	H	N	%	°C
II	$C_{12}H_{10}N_2O_4$	58.54	4.09	11.38	60	288—289[a]
	246.22	58.32	3.95	11.15		
III	$C_{13}H_9N_3O_3$	61.18	3.55	16.46	78	198—199[a]
	255.23	60.95	3.40	16.28		
Va	$C_{10}H_7ClN_4O_2$	47.92	2.81	22.35	95	> 350[b]
	250.64	47.78	2.65	22.15		
Vb	$C_{10}H_8N_4O_2$	55.56	3.73	25.91	90	> 350[b]
	216.20	55.35	3.65	25.75		
VIa	$C_{11}H_5ClN_4O_2$	50.69	1.93	21.50	85	> 350[c]
	260.64	50.47	1.80	21.35		
VIb	$C_{12}H_7ClN_4O_2$	52.48	2.57	20.40	50	292—293[c]
	274.67	52.35	2.45	20.25		
VIc	$C_{13}H_9ClN_4O_2$	54.09	3.14	19.41	65	209—211[b]
	288.69	53.95	3.00	19.28		
VId	$C_{11}H_6N_4O_2$	58.41	2.67	24.77	72	325—330[c]
	226.19	58.32	2.55	24.55		
VIe	$C_{12}H_8N_4O_2$	60.00	3.36	23.32	35	345 dec.[c]
	240.22	59.85	3.20	23.20		
VIf	$C_{13}H_{10}N_4O_2$	61.41	3.96	22.04	68	350 dec.[c]
	254.25	61.30	3.72	21.85		

Crystallized from *a*) methanol, *b*) ethanol, *c*) *N*,*N*-dimethylformamide.

drazine as a source of hydrogen in absolute ethanol on the palladium on carbon catalyst gave satisfactory results. Compounds *IVa* and *IVb* on treatment with an excess of hydrazine hydrate in boiling ethanol afforded carbohydrazides *Va* and *Vb* which were further transformed in good yields to 1,2,4-triazinones *VIa*—*VIf* by heating with triethyl orthoformate or -acetate and -propionate in *N*,*N*-dimethylformamide (Scheme 2). Attempts to aromatize the triazine ring by chlorination with phosphorus oxychloride or phosphorus pentachloride failed probably due to a low stability of this system under such vigorous conditions.

Characteristic data of the synthesized compounds are given in Table 1. The structures of synthesized

Table 2. ^{1}H NMR Data of the Prepared Compounds *Va*, *Vb* in DMSO-d_6

Compound	δ_i					
	H-3	H-5	H-6[a]	H-8	NH	NH_2
Va	6.96 s	7.66 d[a]	8.10 d	–	12.10 bs 9.55 bs	4.43 bs
Vb	6.92 s	7.59 d[a]	8.37 d	8.87 s	12.10 bs 9.54 bs	4.41 bs

a) $J_{5,6}$ = 5.7 Hz.

Table 3. ^{1}H NMR Data of the Prepared Compounds *VIa*—*VIf* in DMSO-d_6

Compound	δ_i							
	H-4	H-6	H-8[a]	H-9[a]	H-11	CH_3	CH_2	NH
VIa	8.84 s	–	8.33 d	7.80 d	7.29 s	–	–	12.14 bs
VIb	–	–	8.23 d	7.75 d	7.01 s	2.54 s	–	13.19 bs
VIc	–	–	8.23 d	7.69 d	7.01 s	1.30 t	2.90 q	13.96 bs
VId	9.45 s	9.13 s	8.55 d	7.77 d	7.28 s	–	–	12.06 bs
VIe	–	9.20 s	8.53 d	7.76 d	7.27 s	2.93 s	–	11.84 bs
VIf	–	9.17 s	8.54 d	7.79 d	7.28 s	1.34 t	3.32 q	11.99 bs

a) $J_{8,9}$ = 5.7 Hz.

Table 4. ^{13}C NMR Data of the Compounds *VIa*—*VIf* in DMSO-d_6

Compound	δ_i										
	C-1	C-4	C-5a	C-5b	C-6	C-8	C-9	C-9a	C-10a	C-11	C-11a
VIa	154.53	127.04	127.81	114.25	139.47	145.27	108.52	164.79	150.82	92.95	114.76
VIb	162.92	158.93	120.98	115.00	139.79	143.95	108.21	164.38	149.81	94.03	119.59
VIc	166.87	158.91	121.07	115.05	139.85	144.01	108.26	164.44	149.88	94.12	119.65
VId	163.69	127.52	126.51	114.60	141.50	145.46	108.03	154.38	150.12	92.38	115.89
VIe	163.91	134.96	127.42	115.27	142.00	145.55	108.55	154.19	150.49	92.87	116.01
VIf	163.90	138.05	127.54	115.29	141.86	145.52	108.50	154.17	150.49	92.73	115.50

a) Other signals: *VIb*: 10.61 (CH_3); *VIc*: 10.55 (CH_3), 18.48 (CH_2); *VIe*: 19.61 (CH_3); *VIf*: 9.76 (CH_3), 25.43 (CH_2).

compounds *V* and *VI* were confirmed by their IR, ^{1}H and ^{13}C NMR spectra (Tables 2—4). The assignment of the carbon atoms was based on the analysis of H,C-COSY spectra and semiselective INEPT experiments were applied.

EXPERIMENTAL

Melting points were determined on a Kofler hot-plate apparatus. The IR spectra were taken on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr technique (0.5 mg in 300 mg of KBr). ^{1}H NMR (300 MHz) and ^{13}C NMR (75.43 MHz) spectra of compounds *III*, *IVb*, and *VIa*—*VIf* were recorded on a Varian VXR-300 spectrometer. ^{1}H NMR spectra of compounds *II*, *Va*, *Vb* were recorded on a Tesla BS 587 spectrometer (80 MHz). Mass spectra were taken on an MS 902-S instrument (AEI Manchester), direct inlet, ionizing electron energy 70 eV, trap current 100 μA, ion source temperature 160—180 °C.

2-Methoxycarbonyl-1-methylpyrrolo[2′,3′:4,5]-furo[3,2-*c*]pyridine-7-oxide (*II*)

A mixture of methyl 1-methylpyrrolo[2′,3′:4,5]furo-[3,2-*c*]pyridine-2-carboxylate (1.93 g; 8.4 mmol) and *m*-chloroperbenzoic acid (9.75 g; 14.6 mmol) in dichloromethane (50 cm^3) was stirred at room temperature for 2 d. The mixture was filtered slowly through an alumina column (chloroform as eluent), the filtrate was evaporated.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1296 ν(N$^+$—O$^-$). ^{1}H NMR spectrum ($CDCl_3$), δ: 3.90 (s, 3H, O—CH_3), 4.19 (s, 3H, N—CH_3), 6.89 (s, 1H, H-3), 7.40 (d, 1H, $J_{5,6}$ = 7.3 Hz, H-5), 8.19 (dd, 1H, $J_{5,6}$ = 7.3 Hz, $J_{6,8}$ = 1.8 Hz, H-6), 8.69 (d, 1H, $J_{6,8}$ = 1.8 Hz, H-8).

Methyl 8-Cyano-1-methylpyrrolo[2′,3′:4,5]furo-[3,2-*c*]pyridine-2-carboxylate (*III*)

To a solution of potassium cyanide (2.5 g; 38 mmol) in water (3.5 cm^3) were added a solution of *II* (3.7 mmol) in dichloromethane (20 cm^3) and then dropwise a solution of benzoyl chloride (0.6 cm^3, 4.3 mmol) in dichloromethane (20 cm^3). After vigorous stirring at room temperature for 2 d, the organic layer was separated and the aqueous layer was extracted with chloroform. After drying over magnesium sulfate, the combined organic layers were evaporated. The residue was purified by column chromatography on silica gel (isohexane—ethyl acetate ($\varphi_r = 2.5 : 1$) as eluent) and crystallization.

IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 2224 ν(CN). ^{1}H NMR spectrum ($CDCl_3$), δ: 3.92 (s, 3H, O—CH_3), 4.54 (s, 3H, N—CH_3), 6.94 (s, 1H, H-3), 7.64 (d, 1H, $J_{5,6}$ = 5.5 Hz, H-5), 8.59 (d, 1H, $J_{5,6}$ = 5.5 Hz, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ: 36.34 (N—CH_3), 51.90 (O—CH_3), 97.96 (C-3), 111.06 (C-5), 118.06 (CN), 119.97, 122.39, 122.55 (C-2, C-8, C-8a), 128.32 (C-8b), 145.51 (C-6), 149.28 (C-3a), 161.31 (C-4a), 164.61 (C=O). Mass spectrum, m/z (I_r/%): 255 (100, $[M]^+$), 224 (78), 210 (17), 197 (28), 169 (28), 155 (11), 141 (17), 100 (11), 87 (17), 75 (28), 53 (28), 39 (17), 31 (5), 28 (10), 27 (5).

Methyl 1*H*-Pyrrolo[2′,3′:4,5]furo[3,2-*c*]-pyridine-2-carboxylate (*IVb*)

A mixture of compound *IVa* (1.0 g; 3.8 mmol) and palladium on carbon (10 %, 0.4 g) was boiled in absolute ethanol (130 cm^3) and hydrazine hydrate (94 %, 4 cm^3) for 30 min. The hot reaction mixture was filtered off and the solvent was removed to a minimum. The precipitate was filtered off and crystallized from toluene. Yield 0.66 g (80 %), m.p. = 275—276 °C. ^{1}H NMR data were in agreement with those published [5]. ^{13}C NMR spectrum (DMSO-d_6), δ: 51.70 (OCH_3), 96.38 (C-3), 108.48 (C-5), 115.42 (C-8a), 121.78 (C-2), 124.94 (C-8b), 140.90 (C-8), 145.25 (C-6), 148.53 (C-3a), 161.14 (C-4a), 164.24 (C=O).

1*H*-Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carbohydrazide (*Vb*) and its 8-Chloro Derivative *Va*

Hydrazine hydrate (94 %, 5 cm^3) was added to a solution of *IVa* (0.5 g; 2 mmol) or *IVb* (0.45 g; 2.08 mmol) in ethanol (150 cm^3), the mixture was refluxed for 30 h. After evaporation of 3/4 of the solvent and cooling the separated *Va* or *Vb* were filtered off, washed with ethanol and crystallized.

6-Chloro-4-R-2*H*-pyrido[3″,4″:4′,5′]furo[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-1-ones (*VIa*—*VIc*)

Compound *Va* (0.5 g; 2 mmol) and corresponding triethyl orthoester (2.6 mmol) were refluxed in *N*,*N*-dimethylformamide (5 cm^3) for 12 h. After cooling the precipitate was filtered off and crystallized.

IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$ for *VIa*: 1673 (C=O); for *VIb*: 1614 (C=O); for *VIc*: 1673 (C=O).

4-R-2*H*-Pyrido[3″,4″:4′,5′]furo[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-1-ones (*VId*—*VIf*)

Compound *Vb* (0.5 g; 2.3 mmol) and corresponding triethyl orthoester (3.1 mmol) were refluxed in *N*,*N*-dimethylformamide (11 cm^3) for 8 h. After cooling the precipitate was filtered off and crystallized.

IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$ for *VId*: 1691 (C=O); for *VIe*: 1673 (C=O); for *VIf*: 1665 (C=O).

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