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Synthesis of Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridines[#]

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Summary. The synthesis of pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridines (**6a–6d**) is described. Substituted pyridones (**4a–4d**) were prepared by thermic cyclization of the corresponding acyl azides (**3a–3d**), available from substituted propenoic acids (**2a–2d**) *via* a one pot reaction with ethyl chloroformate and sodium azide. Upon treatment with phosphorus oxychloride the pyridones (**4a–4d**) gave substituted chloropyridines (**5a–5d**) which were reduced with zinc in acetic acid to yield the title compounds (**6a–6d**).

Keywords. 3-(Furo[3,2-*b*]pyrrol-2-yl)-propenoic acids; 3-(Furo[3,2-*b*]pyrrol-2-yl)-propenoyl azides; 8-Oxo-7,8-dihydropyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylates; 8-Chloropyrrolo[2′,3′:4,5]furo-[3,2-*c*]pyridine-2-carboxylates; Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridine-2-carboxylates.

Synthese von Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridinen

Zusammenfassung. Die Darstellung von Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridinen (**6a–6d**) wird beschrieben. Die substituierten Pyridone (**4a–4d**) entstehen durch thermische Cyclisierung der entsprechenden Acylazide (**3a–3d**), welche aus den Propensäuren (**2a–2d**) in einer Eintopfreaktion mit Chlorameisensäureethylester und Natriumazid zugänglich sind. Die Pyridone (**4a–4d**) liefern nach Behandlung mit Phosphoroxychlorid die Chlorpyridine (**5a–5d**), welche nach Reduktion mit Zink in siedender Essigsäure die Titelverbindungen (**6a–6d**) ergeben.

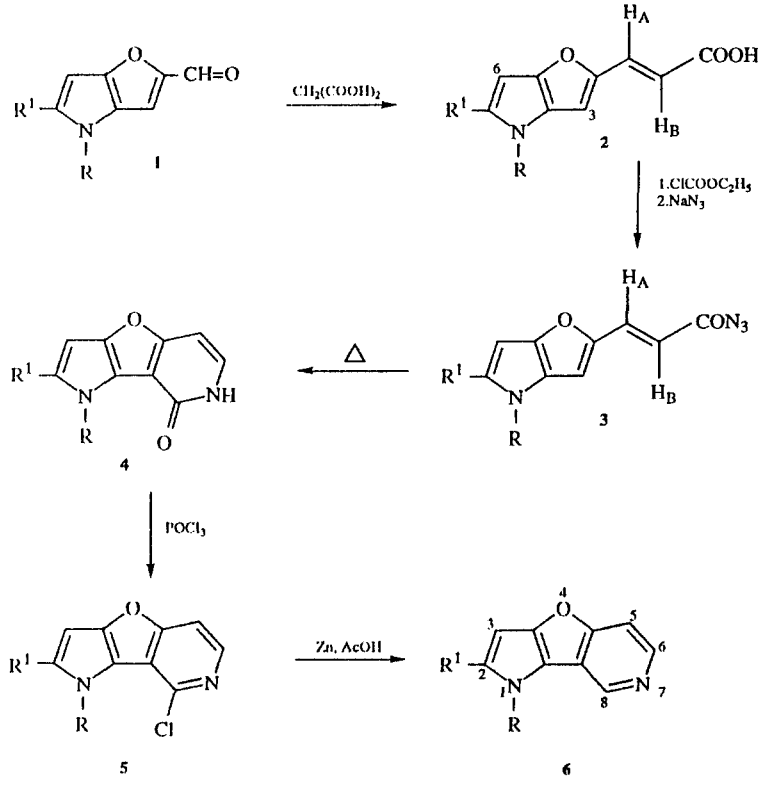
Introduction

The search for biologically active substances led us to the investigation of condensed O-,N-heterocycles. The biological activity of 4-substituted furo[3,2-*c*]pyridines has been studied [1]. Several methods have been used for the synthesis of the furo[3,2-*c*]pyridine system starting either from substituted pyridines [2–5] or furans [6–11]. Previously, we have reported the synthesis of furo[3,2-*c*]pyridines using the *aza Wittig* reaction of iminophosphoranes with heterocumulenes [12]. In this paper we describe the utilization of furo[3,2-*b*]pyrrole aldehydes [12, 13] for the preparation of the title compounds by thermic cyclization of acyl azides with further transformations in the pyridine ring [14, 15].

[#] Dedicated to Professor Dr. *Fritz Sauter* on the occasion of his 65[th] birthday

Results and Discussion

In continuation of our interest in the synthesis of compounds of the furo[3,2-*c*]-pyridine type, we report a method for the preparation of substituted pyrrolo[2′,3′:4,5]-furo[3,2-*c*]pyridines. Starting from furo[3,2-*b*]pyrrole **1a**–**1d** (Scheme 1) [12, 13] *via* the *Doebner* condensation, we synthesized the corresponding substituted propenoic acids **2a**–**2d**. The acyl azides **3a**–**3d** were prepared by treatment of the propenoic acids **2a**–**2d** with ethyl chloroformate and sodium azide in a one pot reaction in excellent yields [14]. Compounds **3a**–**3d** were transformed by thermic cyclization in the presence of tributylamine in diphenylether to substituted 8-oxo-7,8-dihydro-pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridines (**4a**–**4d**) [15]. Refluxing of **4a**–**4d** with phosphorus oxychloride afforded the chloroderivatives **5a**–**5d** which by reduction with zinc in boiling acetic acid led to the pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridines **6a**–**6d** substituted in the pyrrole ring.



1 - 6	R	R^1
a	$COOCH_3$	CH_3
b	$COOCH_3$	$CH_2C_6H_5$
c	$COOCH_2CH_3$	CH_3
d	$COOCH_2CH_3$	$CH_2C_6H_5$

Scheme 1

Experimental

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Tesla BS 487C (80 MHz) instrument (*DMSO*-d_6 as solvent with *HMDS* as internal standard, $CDCl_3$ as solvent with *TMS* as internal standard, δ in ppm, J in Hz). IR spectra were recorded on a FTIR PU 9802/25(Philips) spectrophotometer using KBr pellets (0.5 mg/300 mg KBr, ν in cm^{-1}). The following starting compounds were prepared according to known procedures: methyl 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (**1a**) [12], methyl 4-benzyl-2-formylfuro[3,2-*b*]pyrrole-5-carboxylate (**1b**) [12], ethyl 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (**1c**) [13], ethyl 4-benzyl-2-formylfuro[3,2-*b*]pyrrole-5-carboxylate (**1d**) [13], 3-(4-methyl-5-ethoxycarbonylfuro[3,2-*b*]pyrrol-2-yl)-propenoic acid (**2c**) [13], 3-(4-methyl-5-ethoxycarbonylfuro[3,2-*b*]pyrrol-2-yl)-propenoic acid (**2d**) [13]. Elemental analyses of the novel compounds gave satisfactory results (C, H, Cl, N).

3-(4-Methyl-5-methoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoic acid (**2a**; $C_{12}H_{11}NO_5$)

Compound **1a** (2.07 g, 0.01 mol) and malonic acid (1.04 g, 0.01 mol) dissolved in pyridine (5 ml) containing a few drops of piperidine were heated on a steam bath for 8 h. The reaction mixture was poured on crushed ice acidified with hydrochloric acid. The separated precipitate was filtered off. Yield 1.85 g (74%); m.p. 240–242 °C (ethanol); ^{1}H NMR (*DMSO*-d_6): 3.73 (s, 3H, O–CH_3), 3.87 (s, 3H, N–CH_3), 6.17 (d, 1H, J = 15.8; H–B), 6.75 (s, 1H, H-3), 7.12 (s, 1H, H-6), 7.37 (d, 1H, J = 15.8, H–A), 12.28 (bs, 1H, COOH); IR: 1659, 1705 (C=O).

3-(4-Benzyl-5-methoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoic acid (**2b**; $C_{18}H_{15}NO_5$)

Prepared according to the above procedure; yield 68%; m.p. 206–210 °C (ethanol); ^{1}H NMR (*DMSO*-d_6): 3.71 (s, 3H, O–CH_3), 5.61 (s, 2H, N–CH_2), 6.18 (d, 1H, J = 15.8, H–B), 6.86 (s, 1H, H-3), 7.04 (s, 1H, H-6), 7.34 (d, 1H, J = 15.8, H–A), 6.87–7.50 (m, 5H, H-arom), 12.39 (bs, 1H, COOH); IR: 1650, 1691 (C=O).

3-(4-Methyl-5-methoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoyl azide (**3a**; $C_{12}H_{10}N_4O_4$)

2a (2.00 g, 0.008 mol) dissolved in dry acetone (10 ml) was cooled to −10 °C. Triethylamine (0.94 g, 0.0093 mol) and ethyl chloroformate (1.13 g, 0.01 mol) in dry acetone (1 ml) were succesively added dropwise under stirring at a temperature lower than 0 °C. The reaction mixture was stirred for 30 min at the same temperature. A solution of sodium azide (0.8 g, 0.012 mol) in water (5 ml) was added. The temperature was not allowed to increase to 0 °C. The yellow suspension was stirred for an additional hour and allowed to warm to r.t. The mixture was poured on crushed ice, the yellow precipitate filtered off and washed with water. Yield 2.00 g (91%); m.p. 133–135 °C (toluene); ^{1}H NMR ($CDCl_3$): 3.82 (s, 3H, O–CH_3), 3.86 (s, 3H, N–CH_3), 6.37 (d, 1H, J = 15.4, H–B), 6.66 (s, 1H, H-3), 6.73 (s, 1H, H-6), 7.47 (d, 1H, J = 15.4, H–A); IR: 1684, 1707 (C=O), 2152 (azide).

3-(4-Benzyl-5-methoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoyl azide (**3b**; $C_{18}H_{14}N_4O_4$)

Prepared according to the above procedure; yield 92%; m.p. 137–140 °C (toluene); ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H, O–CH_3), 5.64 (s, 2H, N–CH_2), 6.24 (s, 1H, H-3), 6.34 (d, 1H, J = 15.4, H–B), 6.82 (s, 1H, H-6), 7.38 (d, 1H, J = 15.4, H–A), 7.06–7.44 (m, 5H, H-arom); IR: 1670, 1701 (C=O), 2143 (azide).

3-(4-Methyl-5-ethoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoyl azide (**3c**; $C_{13}H_{12}N_4O_4$)

Prepared according to the above procedure; yield 92%; m.p. 133–135 °C (benzene); ^{1}H NMR ($CDCl_3$): 1.38 (t, 3H, CH_3), 2.97 (s, 3H, N–CH_3), 4.33 (q, 2H, O–CH_2), 6.37 (d, 1H, J = 15.4, H–B), 6.66 (s, 1H, H-3), 6.74 (s, 1H, H-6), 7.47 (d, 1H, J = 15.4, H–A); IR: 1676, 1701 (C=O), 2139 (azide).

3-(4-Benzyl-5-ethoxycarbonylfuro[3,2-b]pyrrol-2-yl)-propenoyl azide (**3d**; $C_{19}H_{16}N_4O_4$)

Prepared according to the above procedure; yield 92%; m.p. 80–82 °C (benzene); ^{1}H NMR ($CDCl_3$): 1.36 (t, 3H, CH_3), 4.35 (q, 2H, O–CH_2), 5.64 (s, 2H, N–CH_2), 6.24 (s, 1H, H-3), 6.33 (d, 1H, $J = 15.1$, H–B), 6.83 (s, 1H, H-6), 7.37 (d, 1H, $J = 15.1$, H–A), 7.00–7.35 (m, 5H, H-arom); IR: 1666, 1699 (C=O), 2143 (azide).

Methyl-1-methyl-8-oxo-7,8-dihydropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**4a**; $C_{12}H_{10}N_2O_4$)

A solution of **2a** (1.20 g, 0.0044 mol) in dry toluene (200 ml) was added dropwise to a mixture of diphenylether (5 ml) and tributylamine (0.9 g, 0.0048 mol) heated to 230–240 °C at a rate that kept the lower boiling solvent continuously distilling. After toluene was removed, the mixture was cooled, the precipitate was filtered off, washed with ether and crystallized from dioxane. Yield 0.6 g (56%); m.p. 281 °C (dec); ^{1}H NMR (*DMSO*-d_6): 3.73 (s, 3H, O–CH_3), 4.27 (s, 3H, N–CH_3), 6.65 (d, 1H, $J = 7.3$, H-5), 6.87 (s, 1H, H-3), 7.35 (d, 1H, $J = 7.3$, H-6), 11.73 (bs, 1H, NH).

Methyl-1-benzyl-8-oxo-7,8-dihydropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**4b**; $C_{18}H_{14}N_2O_4$)

Prepared according to the above procedure; yield 50%; m.p. 264–268 °C; ^{1}H NMR (*DMSO*-d_6): 3.25 (s, 3H, O–CH_3), 5.41 (s, 2H, N–CH_2), 5.89 (s, 1H, H-3), 6.71 (d, 1H, $J = 8$, H-5), 7.42 (d, 1H, $J = 8$, H-6), 6.62–7.40 (m, 5H, H-arom), 11.80 (bs, 1H, NH).

Ethyl-1-methyl-8-oxo-7,8-dihydropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**4c**; $C_{13}H_{12}N_2O_4$)

Prepared according to the above procedure; yield 45%; m.p. 265–270 °C; ^{1}H NMR (*DMSO*-d_6): 1.25 (t, 1H, CH_3), 4.21 (q, 2H, O–CH_2), 4.33 (s, 3H, N–CH_3), 6.61 (d, 1H, $J = 7.3$, H-5), 6.86 (s, 1H, H-3), 7.33 (d, 1H, $J = 7.3$, H-6), 11.72 (bs, 1H, NH).

Ethyl-1-benzyl-8-oxo-7,8-dihydropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**4d**; $C_{19}H_{16}N_2O_4$)

Prepared according to the above procedure; yield 42%; m.p. 258–260 °C; ^{1}H NMR (*DMSO*-d_6): 0.94 (t, 3H, CH_3), 3.31 (q, 2H, O–CH_2), 4.53 (s, 2H, N–CH_2), 6.56–7.81 (m, 8H, H-arom, H-3, H-5, H-6), 11.78 (bs, 1H, NH).

Methyl-8-chloro-1-methylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**5a**; $C_{12}H_9ClN_2O_3$)

4a (0.25 g, 0.001 mol) was refluxed in phosphorus oxychloride for 4 h. The mixture was cooled, poured on crushed ice, the precipitate was filtered off and crystallized from toluene-isohexane. Yield 0.13 g (50%); m.p. 164–166 °C; ^{1}H NMR ($CDCl_3$): 3.89 (s, 3H, O–CH_3), 4.51 (s, 3H, N–CH_3), 6.92 (s, 1H, H-3), 7.41 (d, 1H, $J = 5.7$, H-5), 8.27 (d, 1H, $J = 5.7$, H-6).

Methyl-1-benzyl-8-chloropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**5b**; $C_{18}H_{13}ClN_2O_3$)

Prepared according to the above procedure; yield 40%; m.p. 168–170 °C; ^{1}H NMR ($CDCl_3$): 3.82 (s, 3H, O–CH_3), 6.31 (s, 2H, N–CH_2), 6.87–7.38 (m, 5H, H-arom), 7.09 (s, 1H, H-3), 7.43 (d, 1H, $J = 5.5$, H-5), 8.27 (d, 1H, $J = 5.5$, H-6).

Ethyl-8-chloro-1-methylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**5c**; $C_{13}H_{11}ClN_2O_3$)

Prepared according to the above procedure; yield 45%; m.p. 154–156 °C. ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, CH_3), 4.36 (q, 2H, O–CH_2), 4.51 (s, 3H, N–CH_3), 6.93 (s, 1H, H-3), 7.40 (d, 1H, $J = 5.5$, H-5), 8.27 (d, 1H, $J = 5.5$, H-6).

Ethyl-1-benzyl-8-chloropyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**5d**; $C_{19}H_{15}ClN_2O_3$)

Prepared according to the above procedure; yield 40%; m.p. 135–137 °C; ^{1}H NMR ($CDCl_3$): 1.32 (t, 3H, CH_3), 4.28 (q, 2H, O–CH_2), 6.32 (s, 2H, N–CH_2), 6.93–7.38 (m, 5H, H-arom), 7.04 (s, 1H, H-3), 7.44 (d, 1H, $J = 5.7$, H-5), 8.27 (d, 1H, $J = 5.7$, H-6).

Methyl-1-methylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**6a**; $C_{12}H_{10}N_2O_3$)

Zinc powder (0.5 g) was added to **5a** (0.26 g, 0.001 mol) dissolved in acetic acid and the mixture was refluxed for 8 h. The solvent was distilled off under reduced pressure, the residue alkalized with diluted sodium hydroxide solution and the precipitate filtered off. The product was extracted with chloroform and the solvent was evaporated. The crude product was crystallized from isohexane. Yield 0.12 g (55%); m.p. 175–177 °C; ^{1}H NMR ($CDCl_3$): 3.89 (s, 3H, O–CH_3), 4.28 (s, 3H, N–CH_3), 6.90 (s, 1H, H-3), 7.46 (d, 1H, $J = 5.7$, H-5), 8.52 (d, 1H, $J = 5.7$, H-6), 9.04 (s, 1H, H-8).

Methyl-1-benzylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**6b**; $C_{18}H_{14}N_2O_3$)

Prepared according to the above procedure; yield 48%; m.p. 146–148 °C; ^{1}H NMR ($CDCl_3$): 3.83 (s, 3H, O–CH_3), 5.95 (s, 2H, N–CH_2), 7.00 (s, 1H, H-3), 7.25 (bs, 5H, H-arom), 7.45 (d, 1H, $J = 6.1$, H-5), 8.49 (d, 1H, $J = 6.1$, H-6), 8.66 (s, 1H, H-8).

Ethyl-1-methylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**6c**; $C_{13}H_{12}N_2O_3$)

Prepared according to the above procedure; yield 50%; m.p. 125–127 °C; ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, CH_3), 4.28 (s, 3H, N–CH_3), 4.33 (q, 2H, O–CH_2), 6.91 (s, 1H, H-3), 7.45 (d, 1H, $J = 5.7$, H-5), 8.52 (d, 1H, $J = 5.7$, H-6), 9.03 (s, 1H, H-8).

Ethyl-1-benzylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**6d**; $C_{19}H_{16}N_2O_3$)

Prepared according to the above procedure; yield 45%; m.p. 107–108 °C; ^{1}H NMR ($CDCl_3$): 1.36 (t, 3H, CH_3), 4.36 (q, 2H, O–CH_2), 5.96 (s, 2H, N–CH_2), 7.00 (s, 1H, H-3), 7.26 (bs, 5H, H-arom), 7.43 (d, 1H, $J = 5.7$, H-5), 8.46 (d, 1H, $J = 5.7$, H-6), 8.59 (s, 1H, H-8).

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