Molecules **1996**, *1*, 163 – 165

Synthesis of Pyrrolo[2',3':4,5]Furo[3,2-*c*]Pyridine-2-Carboxylic Acids

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Received: 22 October 1996 / Accepted: 7 November 1996 / Published: 4 February 1997

Abstract

1*H*-Pyrrolo[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylic acid (**6a**) and its 1-methyl (**6b**) and 1-benzyl (**6c**) derivatives were synthesized. 3-(5-Methoxycarbonyl-4*H*-furo[3,2-*b*]-pyrrole-2-yl)propenoic acid (**1**) was converted to the corresponding azide **2**, which in turn was cyclized to give **3** by heating in diphenylether. The pyridone **3** obtained was aromatized with phosphorus oxychloride, then reduced with zinc in acetic acid to give methyl 1*H*-pyrrolo[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylate (**5**), which by hydrolysis gave the corresponding carboxylic acid **6a**.

Keywords: Methyl 2-formyl-1*H*-furo[3,2-*b*]pyrrole-5-carboxylate; 3-(5-Methoxycarbonyl-4*H*-furo[3,2-*b*]pyrrole-2-yl)-propenoic acid; 1*H*-Pyrrolo[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylic acid.

Introduction

The fusion of a π-excessive furan ring to a π-deficient pyridine nucleus gives rise to six isomeric furopyridines; the members of all types are known [1]. Synthetic approaches to furo[3,2-*c*]pyridines are based on the furan ring formation starting from substituted pyridines or the pyridine ring formation starting from suitable substituted furans [1]. Previously, we have reported the synthesis and reactions of 2-nitrophenylfuro[3,2-*c*]pyridine [2], recently 2,3-dimethylfuro-[3,2-*c*]pyridine [3], pyrrolo[2',3':4,5]-furo[3,2-*c*]pyridines [4–7] and 2-arylfuro[3,2-*c*]pyridines [8].

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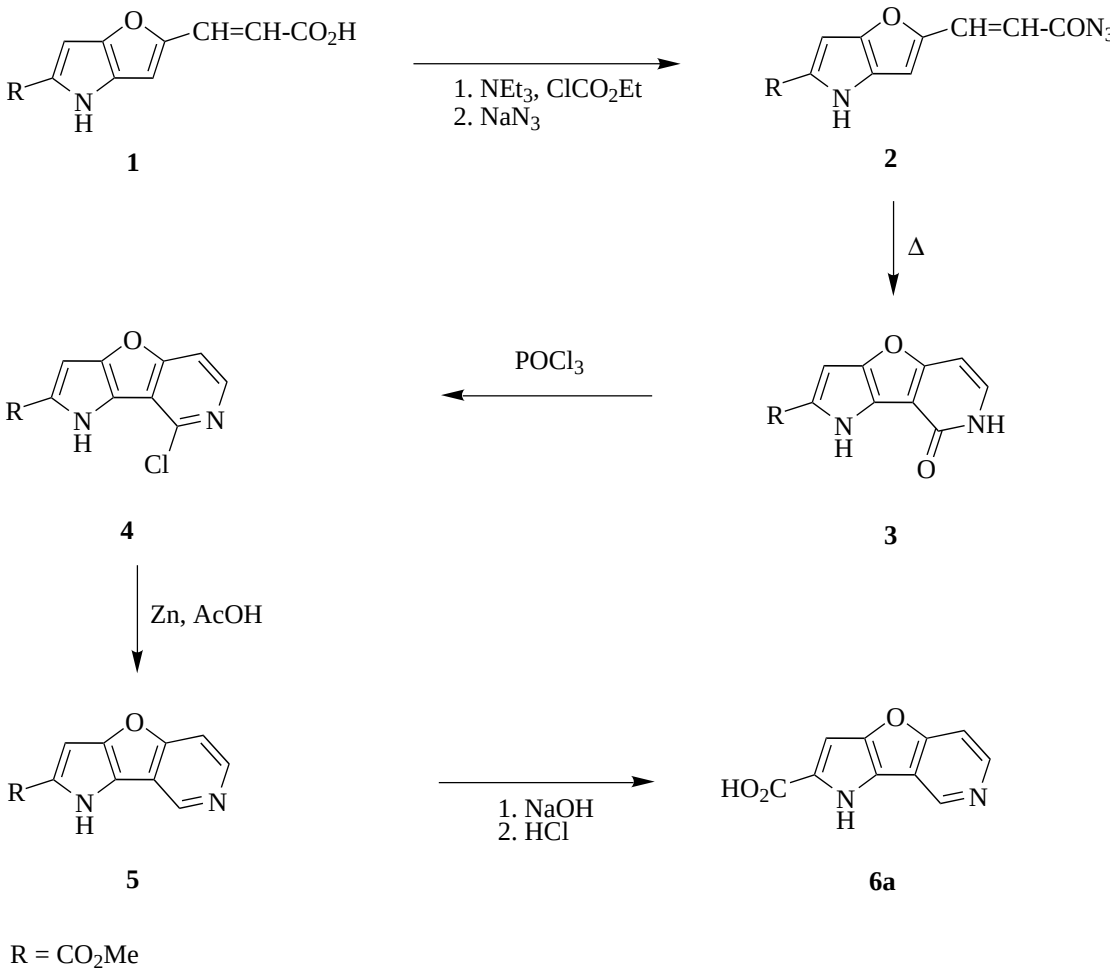
† *Presented at the Joint 12th Symposium on the Chemistry of Heterocyclic Compounds (SCHHC) and the 6th Blue Danube Symposium on Heterocyclic Chemistry (BDSHC), Brno, Czech Republic, September 1–4, 1996.*

Results

Recently in our paper [7] we presented the synthesis of methyl 1-methyl and 1-benzyl-pyrrolo[2',3':4,5]furo-[3,2-*c*]pyridine-2-carboxylate (**5b**, **5c**). In this paper we describe the synthesis of 1*H*-pyrrolo[2',3':4,5]furo-[3,2-*c*]pyridine-2-carboxylic acid (**6a**), which was prepared starting from methyl 2-formyl-1*H*-furo[3,2-*b*]-pyrrole-5-carboxylate [5] (Scheme 1). 3-(5-Methoxycarbonyl-4*H*-furo[3,2-*b*]pyrrole-2-yl)propenoic acid (**1a**) was synthesized via the Doebner condensation. Its corresponding azide **2** was prepared by treatment of **1** with ethyl chloroformate and sodium azide in a one pot reaction. The compound **2** was transformed by the thermic cyclization in the presence of tributylamine in diphenylether to methyl 8-oxo-7,8-dihydro-1*H*-pyrrolo[2',3':4,5]furo[3,2-*c*]-pyridine-2-carboxylate (**3**). By refluxing of **3** with phosphorus oxychloride compound **4** was obtained. Reduction



Scheme 1

of **4** with zinc in acetic acid afforded methyl-1*H*-pyrrolo-[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylate (**5**), which underwent hydrolysis giving **5**. Analogously by hydrolysis of 1-methyl and 1-benzyl derivatives of **6a** the corresponding carboxylic acids **6b**, **6c** were prepared.

Experimental Part

Melting points were determined on a Kofler hot plate apparatus. ^{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). IR spectra were recorded on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr pellets (0.5 mg/300 mg KBr).

*3-(5-Methoxycarbonyl-4H-furo[3,2-b]pyrrole-2-yl)-propenoic acid (**1**)*

Methyl 2-formyl-1*H*-furo[3, 2-*b*]pyrrole-5-carboxylate (10.0 g; 51 mmol) and malonic acid (5.9 g; 56 mmol) were dissolved in pyridine (30 ml) containing a few drops of piperidine and heated on a steam bath for 8 h. The reaction mixture was poured onto crushed ice, acidified with hydrochloric acid (40 ml; 35%). The separated precipitate was filtered off and crystallized from ethanol. Yield: 6.5 g (54%); m.p. 234–236 °C. IR: 1680, 1713 (C = O). ^{1}H-NMR (DMSO-d_6): 3.76 (s, 3H, OCH_3); 6.16 (d, 1H, H-B); 6.71 (s, 1H, H-3); 6.99 (s, 1H, H-6); 7.39 (d, 1H, H-A); 11.85 (bs, 1H, NH); 12.32 (bs, 1H, COOH); $J_{A,B}$ = 15.8 Hz.

*3-(5-Methoxycarbonyl-4H-furo[3,2-b]pyrrole-2-yl)-propenoyl azide (**2**)*

Compound **1** (5.8 g; 24.9 mmol) was dissolved in dry acetone (125 ml) and cooled to –10 °C and under stirring. Triethylamine (4.1 ml, 28.9 mmol) and ethyl chloroformate

(3.1 ml; 32.4 mmol) were successively added dropwise at a temperature lower than 0 °C. The reaction mixture was stirred for 30 min at the same temperature. A solution of sodium azide (2.5 g; 38 mmol) in water (8 ml) was added. The yellow suspension was stirred for 1 h longer and allowed to warm to room temperature. The mixture was poured onto crushed ice, the yellow precipitate filtered off and washed with water. Yield: 4.9 g (76%); m.p. 155–157 °C. IR: 1682, 1699 (C = O); 2158 (azide). ^{1}H-NMR (DMSO-d_6): 3.76 (s, 3H, OCH_3); 6.21 (d, 1H, H-B); 6.73 (s, 1H, H-3); 7.16 (s, 1H, H-6); 7.55 (d, 1H, H-A); 11.96 (bs, 1H, NH); $J_{A,B}$ = 15.6 Hz.

*Methyl 8-oxo-7,8-dihydro-1H pyrrolo[2',3':4,5]furo-[3,2-c]pyridine-2-carboxylate (**3**)*

Compound **2** (2.0 g; 7.7 mmol) and toluene (60 ml) were added to a mixture of diphenylether (60 ml) and tributylamine (9.0 ml; 7.7 mmol). The reaction mixture was succesively heated to 230–240 °C. The solvent was continuously distilled off. After toluene was removed the mixture was cooled, the precipitate was filtered off, washed with ether and crystallized from dioxane. Yield: 0.9 g (55%); m.p. 237 °C (dec.). IR: 1666, 1711 (C = O). ^{1}H-NMR (DMSO-d_6): 3.73 (s, 3H, OCH_3); 6.65 (d, 1H, H-5); 6.84 (s, 1H, H-3); 7.33 (d, 1H, H-6); 11.63 (bs, 1H, NH); 12.44 (bs, 1H, NH); $J_{5,6}$ = 7.3 Hz.

*Methyl 8-chloro-1H-pyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**4**)*

Compound **3** (1.0 g; 4.3 mmol) was refluxed in phosphorus oxychloride (15 ml) for 4 h. The mixture was cooled and the solvent removed. The residue was poured onto crushed ice, the precipitate was filtered off and crystallized from toluene-isohexane. Yield: 0.4 g (54%); m.p. 237 °C. IR: 1705 (C = O). ^{1}H-NMR ($CDCl_3$): 3.96 (s, 3H, OCH_3); 6.94 (d, 1H, H-3); 7.43 (d, 1H, H-5); 8.30 (d, 1H, H-6); 9.46 (bs, 1H, NH); $J_{1,3}$ = 1.8 Hz; $J_{5,6}$ = 5.7 Hz.

*Methyl 1H-pyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylate (**5**)*

Zinc pulver (4.4 g) was added to compound **4** (0.6 g; 2.4 mmol) dissolved in acetic acid (40 ml) and the mixture was refluxed for 18 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. Yield: 140 mg (30%); m.p. 260–262 °C. ^{1}H-NMR (DMSO-d_6): 3.80 (s, 3H, OCH_3); 6.91 (s, 1H, H-3); 7.64 (d, 1H, H-5); 8.44 (d, 1H, H-6); 8.91 (s, 1H, H-8); 11.41 (bs, 1H, NH); $J_{5,6}$ = 5.7 Hz.

*1H-Pyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylic acid (**6a**)*

Compound **5** (0.4 g, 1.9 mmol) in ethanol (150 ml) and 5% sodium hydroxide (7 ml) was heated on a steam bath for 2 h and concentrated to a half of its original volume. The precipitate was dissolved in dilute ethanol, acidified with hydrochloric acid 1:1 and poured onto ice. Yield: 80 mg (21%); m.p. 275–280 °C. ^{1}H-NMR (DMSO-d_6): 6.90 (s, 1H, H-3); 7.65 (d, 1H, H-5); 8.43 (d, 1H, H-6); 8.90 (s, 1H, H-8); 11.40 (bs, 1H, NH); $J_{5,6}$ = 5.7 Hz.

*1-Methylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylic acid (**6b**)*

Prepared analogously to the above procedure from compound methyl 1-methylpyrrolo-[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylate [7]. Yield: 78%; m.p. 195–199 °C. ^{1}H-NMR (DMSO-d_6): 4.19 (s, 3H, N-CH_3); 6.89 (s, 1H, H-3); 7.65 (d, 1H, H-5); 8.46 (d, 1H, H-6); 9.18 (s, 1H, H-8); $J_{5,6}$ = 5.7 Hz

*1-Benzylpyrrolo[2',3':4,5]furo[3,2-c]pyridine-2-carboxylic acid (**6c**)*

Prepared analogously to the above procedure from compound methyl 1-benzylpyrrolo-[2',3':4,5]furo[3,2-*c*]pyridine-2-carboxylate [7]. Yield: 75%; m.p. 215–220 °C. ^{1}H-NMR (DMSO-d_6): 5.99 (s, 2H, N-CH_2); 6.88–7.50 (m, 5H, H-arom); 7.60 (s, 1H, H-3); 7.64 (d, 1H, H-5); 8.41 (d, 1H, H-6); 8.81 (s, 1H, H-8); $J_{5,6}$ = 5.9 Hz

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