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Synthesis and Reactions of 2,3-Dimethylfuro[3,2-*c*]pyridines#

V. Bobošík[1], **A. Krutošíková**[1], and **U. Jordis**[2]

[1] Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-81237 Bratislava, Slovakia
[2] Institute of Organic Chemistry, Technical University Vienna, A-1060 Wien, Austria

Summary. A number of substituted 2,3-dimethylfuro[3,2-*c*]pyridines was synthesized. 3-(4,5-Dimethyl-2-furyl)propenoic acid (**1**) was converted to the acid azide **2**, which in turn was cyclized to give 2,3-dimethyl-5*H*-furo[3,2-*c*]pyridine-4-one (**3**) by heating at 240°C in Dowtherm. The pyridone **3** was chlorinated with phosphorus oxychloride to give **4**, which was reduced with zinc and acetic acid to 2,3-dimethylfuro[3,2-*c*]pyridine (**5**). Treatment of **4** with several secondary heterocyclic amines led to compounds **6a–6c**. Reaction of pyridone **3** with phosphorus pentasulfide rendered the thione **7**, which was methylated to **8a**. The 4-methoxy derivative **8b** was obtained from **4** with sodium methoxide. 2,3,5-Trimethylfuro[3,2-*c*]pyridine-4-one (**9**) was obtained by reaction of **3** with methyl iodide.

Keywords. 5*H*-Furo[3,2-*c*]pyridine-4-ones; 5*H*-Furo[3,2-*c*]pyridine-4-thiones; Furo[3,2-*c*]pyridine.

Synthesen und Reaktionen von 2,3-Dimethylfuro[3,2-*c*]pyridinen

Zusammenfassung. Eine Anzahl von substituierten 2,3-Dimethylfuro[3,2-*c*]pyridinen wurde synthetisiert. 3-(4,5-Dimethyl-2-furyl)propensäure (**1**) wurde zum Acylazid **2** umgesetzt und durch Erhitzen auf 240 °C in Dowtherm zu 2,3-Dimethyl-5*H*-furo[3,2-*c*]pyridin-4-on (**3**) zyklisiert. Das Pyridon **3** lieferte nach der Chlorierung mit Phosphorylchlorid die Verbindung **4**, aus der durch Reduktion mit Zink in Essigsäure 2,3-Dimethylfuro[3,2-*c*]pyridin (**5**) erhalten wurde. Durch Behandlung von **4** mit einigen sekundären heterocyclischen Aminen entstanden die Verbindungen **6a–6c**. Die Reaktion von Pyridon **3** mit Phosphorpentasulfid lieferte das Thion **7**, welches zu **8a** methyliert wurde. Das 4-Methoxyderivat **8b** wurde durch Umsetzung von **4** mit Natriummethylat dargestellt. 2,3,5-Trimethylfuro[3,2-*c*]pyridin-4-on (**9**) entstand bei der Reaktion von **3** mit Methyljodid.

Introduction

The fusion of a furan nucleus to a pyridine ring gives rise to six isomeric furopyridines; the members of all types are known [1]. Synthetic approaches to furo[3,2-*c*]pyridines start either from substituted pyridines [2–5] or furans [6–11]. Previously, we have reported the synthesis and reactions of 2-nitrophenyl-

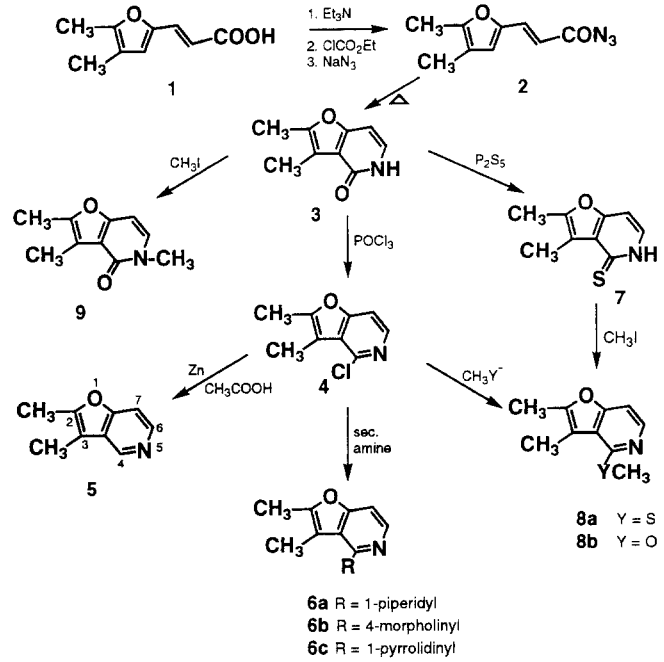
Dedicated to Professor Dr. *Fritz Sauter* on the occasion of his 65th birthday

substituted furo[3,2-*c*]pyridines [12]. Reactions [12–18], spectral [19], and biological [20] properties of furo[3,2-*c*]pyridines have been studied.

Results and Discussion

In continuation of our previous efforts towards the synthesis of fused O-, N-heterocycles we report an efficient synthesis of 2,3-dimethylfuro[3,2-*c*]pyridines (Scheme 1) starting from 4,5-dimethyl-2-furancarbaldehyde [21]. Condensation of 4,5-dimethyl-2-furancarbaldehyde with malonic acid afforded 3-(4,5-dimethyl-2-furyl)propenoic acid (**1**). The acid **1** was treated with ethyl chloroformate and triethylamine in acetone to give a mixed acid anhydride, which was converted to the acid azide **2** using sodium azide in a one pot synthesis. The azide **2** was heated in Dowtherm at 240 °C to give 2,3-dimethyl-4,5-dihydrofuro[3,2-*c*]pyridin-4-one (**3**). Isomerization from the *E* to the *Z*-isomer apparently occured during the cyclization of **2** to **3**.

Compound **3** was transformed to 4-chloro-2,3dimethylfuro[3,2-*c*]pyridine (**4**) by refluxing with phosphorus oxychloride. Reduction of **4** with zinc in acetic acid afforded 2,3-dimethyfuro[3,2-*c*]pyridine (**5**). Treatment of **4** with secondary amines gave **6a–6c**. Reaction of **3** with phosphorus pentasulfide led to the corresponding 2,3-dimethyl-4,5-dihydrofuro[3,2-*c*]pyridin-4-thione (**7**). 4-Methoxy-2,3-dimethyfuro[3,2-*c*]pyridine (**8a**) was obtained by treatment of the chloro derivative **4** with sodium methoxide in dimethylsulfoxide. Similarly, utilization of sodium methylthiolate gave **8b**, which was obtained alternatively by methylation of **7** with methyl iodide. Compound **9** resulted from the reaction of **3** with methyl iodide.



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 587 (80 MHz) instrument (*HMDS* as internal standard, *DMSO*-d_6 as solvent, δ values in ppm, J in Hz). The IR spectra were recorded on a FTIR 9802/25 (Philips) spectrophotometer using KBr (0.5 mg, 300 mg KBr, ν in cm^{-1}). UV spectra were measured on a M-40 (Carl Zeiss Jena) spectrophotometer in ethanol (λ_{max} (log ε); λ_{max} in nm, ε in $m^2 \cdot mol^{-1}$). The starting 4,5-dimethyl-2-furancarbaldehyde was prepared according to Ref. [21]. Elemental analyses of the novel componds gave satisfactory results (C, H, Cl, N, S).

E-3-(4,5-Dimethyl-2-furyl)propenoic azide (**2**; $C_9H_9N_3O_2$)

E-3-(4,5-dimethyl-2-furyl)propenoic acid (**1**) (5 g, 0.03 mol) was suspended in 35 ml of absolute acetone, cooled to 0 °C, and triethylamine (3.54 g, 0.035 mol) was added at 0 °C under stirring. Then the solution of ethyl chloroformate (4.2 g, 0.039 mol) in 5 ml acetone was added dropwise keeping the temperature below 0 °C. The mixture was stirred for 30 min at 0 °C; then sodium azide (3 g, 0.046 mol) in 12 ml of water was added. The mixture was stirred for an additional hour and then poured into ice water (140 ml). The yellow precipitate was filtered off, washed with water and dried on air. Yield 5.3 g (93%); m.p.: 71–72 °C (dec) (dichloromethane/hexane); ^{1}H NMR: 1.95 (s, 3H, C4′-CH_3), 2.26 (s, 3H, C5′-CH_3), 6.15 (d, 1H, J = 16, H3), 6.50 (s, 1H, H3′), 7.30 (d, 1H, J = 16, H2); IR: 1674 (C=O), 2143 (azide); UV: 356 (3.94).

2,3-Dimethyl-4,5-dihydrofuro[3,2-c]pyridin-4-one (**3**; $C_9H_9NO_2$)

Azide **2** (5 g, 0.026 mol) was dissolved in 50 ml of dry toluene and added dropwise to the mixture of tributylamine (4.8 g, 0.026 mol) and Dowtherm (20 ml) previously heated to 230 °C. The addition was effected at 230–240 °C by such a way that toluene distilled off continuously. After cooling, toluene (20 ml) was added to the mixture, the precipitate was filtered off, washed with toluene, dried and crystallized from ethanol. Yield 2.3 g (53.9%); m.p.: 196–197 °C; ^{1}H NMR: 2.32 (s, 6H, C2-CH_3, C3-CH_3), 6.48 (d, 1H, J = 7.1, H7), 7.19 (d, 1H, J = 7.1, H6), 12.24 (bs, 1H, NH); IR: 1652 (C=O); UV: 294 (2.90).

4-Chloro-2,3-dimethylfuro[3,2-c]pyridine (**4**; C_9H_8ClNO)

Pyridone **3** (3.26 g, 0.02 mol) was refluxed in phosphorus oxychloride (10 ml) for 4 h. $POCl_3$ was distilled off under reduced pressure and ice was added to the residue. The mixture was then alkalized by diluted aqueous ammonia. The precipitate was filtered off, washed with water and dried. The crude product was crystallized from hexane or from aqueous ethanol. Yield 3.0 g (82.9%); m.p.: 69–70°C; ^{1}H NMR: 2.32 (s, 3H, C3-CH_3), 2.37 (s, 3H, C2-CH_3), 7.21 (d, 1H, J = 5.5, H7), 8.12 (d, 1H, J = 5.5, H6); UV: 258 (3.12).

2,3-Dimethylfuro[3,2-c]pyridine (**5**; C_9H_9NO)

A mixture of 4-chloro-2,3-dimethylfuro[3,2-*c*]pyridine (**4**) (1 g, 0.0055 mol), Zn (pulverized, 2.2 g) and glacial acetic acid (10 ml) was refluxed for 8 h. After cooling, the solid was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. Diluted NaOH solution was added to the residue and the alkaline mixture was extracted with chloroform. The extract was dried with $CaCl_2$, chloroform was distilled off and the residual oil solidified after cooling. Crystallization from hexane afforded colorless needles. Yield 0.4 g (50%); m.p.: 45–46 °C; ^{1}H NMR: 2.20 (s, 3H, C3-CH_3), 2.40 (s, 3H, C2-CH_3), 7.31 (d, 1H, J = 5.6, H7), 8.43 (d, 1H, J = 5.6, H6), 8.77) (s, 1H, H4); UV: 251 (2.86).

2,3-Dimethyl-4-(1-piperidyl)furo[3,2-c]pyridine (**6a**; $C_{14}H_{11}N_2O$)

4-Chloro-2,3-dimethylfuro[3,2-*c*]pyridine (**4**) (0.54 g, 0.003 mol) was refluxed in piperidine (2 ml) for 48 h. The excess of the amine was distilled off under reduced pressure and the residue was purified on a silica gel column (25 g) eluting with chloroform. The oily product, which solidified after cooling, was crystallized from hexane. Yield 0.35 g (50.7%); m.p.: 55–56°C; ^{1}H NMR: 1.63 (m, 6H, piperidine), 2.31 (s, 3H, C3-CH_3), 2.35 (s, 3H, C2-CH_3), 3.22 (m, 4H, piperidine), 6.95 (d, 1H, $J = 5.8$, H7), 8.00 (d, 1H, $J = 5.8$, H6); UV: 279 (3.20).

Compounds **6b** and **6c** were prepared analogously:

2,3-Dimethyl-4-(4-morpholinyl)furo[3,2-c]pyridine (**6b**; $C_{13}H_{16}N_2O_2$)

Reaction time 100 h; yield 0.4 g (57.5%); m.p.: 84–85 °C; ^{1}H NMR: 2.30 (s, 3H, C3-CH_3), 2.36 (s, 3H, C2-CH_3), 3.27 (t, 4H, β-CH_2, morpholine), 3.91 (t, 4H, α-CH_2, morpholine), 7.00 (d, 1H, $J = 5.9$, H7), 8.02 (d, 1H, $J = 5.9$, H6); UV: 274 (3.16).

2,3-Dimethyl-4-(1-pyrrolidinyl)furo[3,2-c]pyridine (**6c**; $C_{13}H_{16}N_2O$)

Reaction time 48 h; yield 0.3 g (46.3%); m.p.: 53–54 °C; ^{1}H NMR: 1.93 (m, 4H, α-CH_2, pyrrolidine), 2.28 (s, 3H, C3-CH_3), 2.36 (s, 3H, C2-CH_3), 3.60 (m, 4H, β-CH_2, pyrrolidine), 6.80 (d, 1H, $J = 5.6$, H7), 7.92 (d, 1H, $J = 5.6$, H6); UV: 278 (3.18).

2,3-Dimethyl-4,5-dihydrofuro[3,2-c]pyridin-4-thione (**7**; C_9H_9NOS)

A mixture of pyridone **3** (1.6 g, 0.01 mol) and phosphorus pentasulfide (2.2 g, 0.01 mol) in dry pyridine (15 ml) was refluxed for 5 h. The hot reaction mixture was poured into hot water (150 ml). The mixture was allowed to settle overnight. The precipitate was collected by filtration, washed with water and crystallized from aqueous ethanol. Yield 1.0 g (55.8%); m.p.: 215–216 °C; ^{1}H NMR: 2.36 (s, 3H, C3-CH_3), 2.54 (s, 3H, C2-CH_3), 6.85 (d, 1H, $J = 7.0$, H7), 7.05 (d, 1H, $J = 7.0$, H6); IR: 1580 (C=S thioamide); UV: 333 (3.06).

2,3-Dimethyl-4-methylthiofuro[3,2-c]pyridine (**8a**; $C_{10}H_{11}NOS$)

Method A:

The chloro-derivative **4** (0.5 g, 0.00276 mol) was added to the solution of sodium methylthiolate (0.2 g, 0.00286 mol) in dimethylsulfoxide (2 ml). The mixture was heated at 100 °C for 15 min under stirring and then poured into cold water. The water solution was extracted with chloroform, the extract was dried and the solvent evaporated *in vacuo*. The residue was purified using a silica gel column (25 g) with chloroform as eluent. Crystallization from hexane afforded colorless needless. Yield 0.25 g (46.9%); m.p.: 59–60 °C; ^{1}H NMR: 2.35 (s, 6H, C2-CH_3 C3-CH_3), 2.65 (s, 2H, S-CH_3), 7.02 (d, 1H, $J = 5.5$, H7), 8.20 (d, 1H, $J = 5.5$, H6); UV: 276 (3.21).

Method B:

Thione **7** (0.36 g, 0.002 mol) was suspended in dichloromethane (10 ml) under vigorous stirring. Tetrabutylammonium bromide (0.1 g, 0.0003 mol) was added, followed by a solution of NaOH (0.4 g, 0.01 mol) in water (1 ml). The mixture was stirred for 15 min; then methyl iodide (0.7 g, 0.005 mol) was added dropwise. The stirring was continued for 20 min, the organic layer was separated, washed with

water, dried and evporated *in vacuo*. The residue was purified on a silica gel column (20 g) eluting with chloroform and then crystallized from hexane. The compound obtained was identical with that prepared according the method *A*. Yield 0.25 g (64.7%).

2,3-Dimethyl-4-methoxyfuro[3,2-c]pyridine (**8b**; $C_{10}H_{11}NO_2$)

The chloro derivative **4** (0.5 g, 0.00276 mol) was added to the solution of sodium methoxide (0.2 g, 0.0037 mol) in dimethylsulfoxide (2 ml). The mixture was heated at 100 °C for 15 min under stirring and then poured into cold water. The water solution was extracted with chloroform. After purification on a silica gel column (25 g), eluting with chloroform, 0.3 g (61.5%) of yellowish oil was obtained. ^{1}H NMR: 2.24 (s, 3H, C3-CH_3), 2.33 (s, 3H, C2-CH_3), 4.03 (s, 3H, O–CH_3), 6.93 (d, 1H, J = 5.8, H7), 7.87 (d, 1H, J = 5.8, H6); UV: 255 (3.06).

2,3,5-Trimethyl-4,5-dihydrofuro[3,2-c]pyridin-4-one (**9**; $C_{10}H_{11}NO_2$)

Pyridone **3** (0.8 g, 0.005 mol) was suspended in dry dimethylformamide (3 ml) and NaH (80% in mineral oil; 0.2 g, 0.0065 mol) was added under stirring. When the evolution of hydrogen was complete, methyl iodide (1 g, 0.007 mol) was added dropwise and the mixture stirred for 30 min. Then crushed ice was added and the mixture was extracted with chloroform. The extract was dried and evaporated *in vacuo*. The residue was triturated with ether and the solid was collected by filtration. The crude product was crystallized from toluene. Yield 0.5 g (65.5%); m.p.: 114–115 °C; ^{1}H NMR: 2.30 (s, 6H, C2-CH_3, C3-CH_3), 3.56 (s, 3H, N–CH_3) 6.38 (d, 1H, J = 7.3, H7), 7.06 (d, 1H, J = 7.3, H6); IR: 1660 (C=O); UV: 300 (2.95).

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