5-AMINOFURO[3,2-*c*]PYRIDINIUM TOSYLATES AND SUBSTITUTED FURO[3,2-*c*]PYRIDINE *N*-OXIDES: SYNTHESIS AND REACTIONS

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5-Aminofuro[3,2-*c*]pyridinium tosylates **2a**–**2c** were synthesized by direct *N*-amination of furo[3,2-*c*]pyridines **1a**–**1c** with *O*-(4-methylbenzenesulfonyl)hydroxylamine in dichloromethane. Zwitterionic furo[3,2-*c*]pyridinium *N*-imides **3a**–**3c** generated from **2a**-**2c** and anhydrous potassium carbonate in *N*,*N*-dimethylformamide afforded by 1,3-dipolar cycloaddition reactions with dimethyl butynedioate or ethyl propiolate the corresponding furo[3,2-*c*]pyrazolo[1,5-*a*]pyridinecarboxylic esters **4a**–**4c** and **5a**–**5c**. Furo[3,2-*c*]pyridine *N*-oxides **6a**–**6c** and their benzo derivative **6d** were synthesized by reaction of **1** with 3-chloroperbenzoic acid in dichloromethane. Treatment of *N*-oxides **6** with benzoyl chloride and cyanide anion (Reissert–Henze reaction) was shown to produce the corresponding furo[3,2-*c*]pyridine-4-carbonitriles **7**. In further transformations (acid and alkaline hydrolysis), the cyano group was converted successively to amide and carboxylic acid.

Key words: 1,3-Dipolar cycloadditions; Furo[3,2-*c*]pyridines; Furo[3,2-*c*]pyrazolo[1,5-*a*]pyridines; *N*-Oxides; Fused heterocycles.

Furopyridines are of chemical interest due to their similarity to quinoline, isoquinoline, and benzofuran which are important ring systems present in many biologically active compounds.

As a continuation of our previous efforts towards the synthesis of fused oxygen and nitrogen heterocycles, we report utilization of substituted furo[3,2-*c*]pyridines[1,2] in the synthesis of new bridgehead nitrogen-containing fused heterocyclic furo[3,2-*c*]pyrazolo[1,5-*a*]pyridines.

Much of the work on pyrazolo[1,5-*a*]pyridines has been stimulated by a variety of physiological activities, such as antiallergic, antiasthmatic and others[3]. Earlier reviews[4,5] described a number of synthetic approaches to this system. The most generally useful, however, were those starting with *N*-aminopyridinium derivatives and constructing the five-membered ring.

A synthetically important method for the preparation of the *N*-aminoazonium salts is direct N-amination of heteroaromatic bases[4]. The

most general preparations are based on the reaction of heteroaromatic bases with O-substituted hydroxylamines, most commonly with hydroxylamine-*O*-sulfonic acid (HSA) and *O*-(2,4,6-trimethylbenzenesulfonyl)hydroxylamine (MSH). Other hydroxylamine derivatives that can be used for the N-amination include slightly less reactive *O*-(2,4,6-triisopropylbenzenesulfonyl)hydroxylamine and less stable *O*-(4-methylbenzenesulfonyl)hydroxylamine[6].

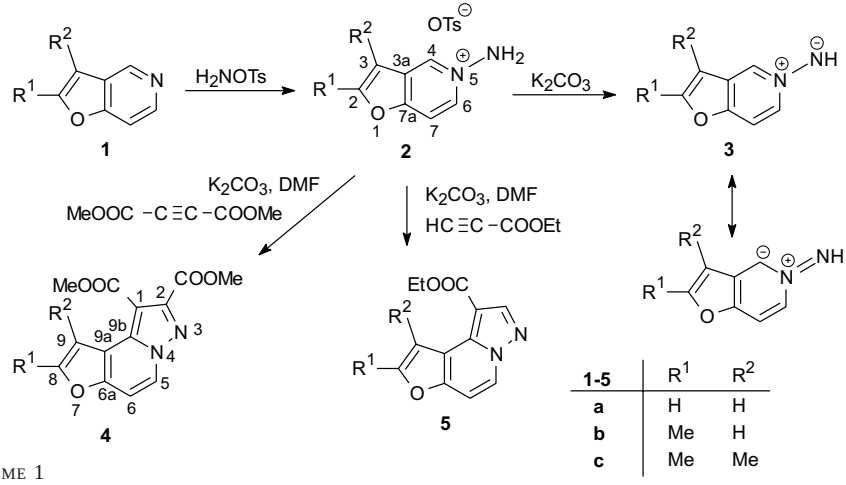
N-Aminopyridinium salts represent precursors of very reactive 1,3-dipoles which undergo intermolecular cycloadditions with a variety of activated alkynic dipolarophiles in the presence of base[4,5,7–9].

N-Oxidation of pyridines with several peroxy acids has been used[10,11]. The Reissert–Henze[12,13] reaction introduces a cyano group into an azine ring in the α (or occasionally γ) position to the ring nitrogen.

Recently, we presented[1] the synthesis of 2,3-dimethylfuro[3,2-*c*]-pyridine (**1c**). In this paper, we describe the synthesis of 5-aminofuro[3,2-*c*]pyridinium tosylates **2** by a procedure typical of the N-amination[9]. A mixture of compounds **1** and TSH in dichloromethane was allowed to stand at room temperature for a few hours. After addition of diethyl ether, the precipitated crystals of 5-aminofuro[3,2-*c*]pyridinium tosylates **2** were isolated in good yields. The furo[3,2-*c*]pyridinium salts **2a**–**2c** thus obtained are stable crystalline solids soluble in water. We supposed that by their treatment with anhydrous potassium carbonate in *N*,*N*-dimethylformamide the ylides **3a**–**3c** are formed *in situ*, analogously, as it was described in pyridine series by Huisgen and coworkers[7]. Further reactions of **3a**–**3c** with dienophiles confirmed our assumption. They gave with dimethyl butynedioate the corresponding dimethyl furo[3,2-*c*]pyrazolo[1,5-*a*]pyridine-1,2-dicarboxylates **4a**–**4c**. Similarly, cycloaddition of ethyl propiolate to **3** resulted in desired ethyl furo[3,2-*c*]pyrazolo[1,5-*a*]pyridine-1-carboxylates **5** (Scheme 1). As shown by ^{1}H NMR spectra of the crude products, the reaction under given conditions gives only products without any side products other than bituminous unidentified material. The yields are unfortunately low, but they are better than were observed in the pyridine series[7].

The structures of compounds **2**, **4**, and **5** were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectra, IR, UV and mass spectra. The ^{1}H NMR spectra of compounds **2** show doublets of H-7 protons with coupling constant $^3J(6,7)$ = 7.08 Hz. Signal H-6 appears as a doublet doublet due to the interaction with H-7 and a long-range coupling, $^4J(4,6)$ = 1.8 Hz. Coupling between H-4 and H-6 led to splitting of the H-4 signal in doublet. Protons of NH_2 are shown as a broad signal at 8.11–8.25 ppm. The assignment of aromatic protons was made on the basis of characteristic splitting patterns and

substituent chemical shifts for substituted benzenes. Signals of protons H-4 and H-6 are shifted to higher δ values in comparison with the starting furo[3,2-*c*]pyridines **1** due to the presence of the positively charged nitrogen atom of the pyridine ring. Structure elucidation of 1,3-dipolar cycloadducts **4** and **5** was accomplished by ^{1}H NMR spectral analysis. The transformation was verified by disappearance of the most downfield signal H-4 of each starting heterocycle **2** and appearance of signals of ester groups. Formation of pyrazolo derivatives **5** was supported by appearance of H-5 proton signals. For the assignment of carbon signals in compounds **2**, **4**, and **5**, selective heteronuclear decoupling, semiselective INEPT experiments and ^{1}H-^{13}C HETCOR spectra were used.

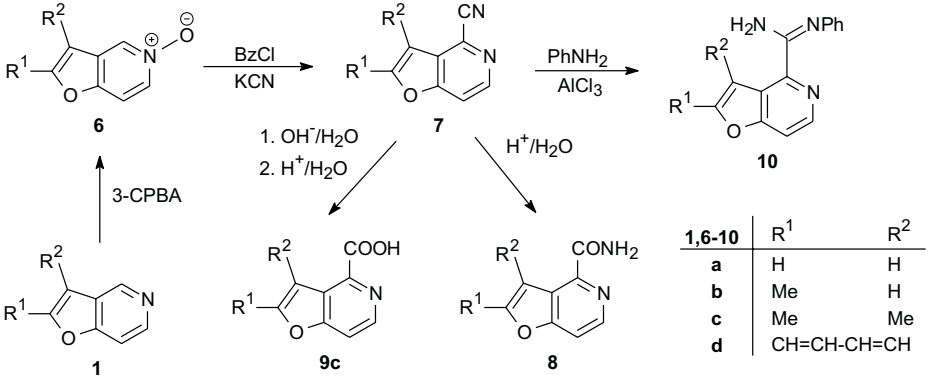


SCHEME 1

In the same manner, we intended to utilize furo[3,2-*c*]pyridine *N*-oxides **6** in the cycloaddition reactions. At first we prepared the corresponding *N*-oxides **6** by a simple procedure – treatment of compounds **1** with 3-chloroperoxybenzoic acid in dichloromethane. An alternative oxidation with hydrogen peroxide in acetic acid did not give satisfactory results. However, our attempts to realize the above mentioned cycloaddition reactions failed.

To accomplish the Reissert–Henze reaction[10,11], the nucleophilic substitution with cyanide anion, the synthesized furo[3,2-*c*]pyridine *N*-oxides, including the benzo derivative **6d**, were treated with benzoyl chloride and cyanide anion in a two-phase mixture of water and dichloromethane for 48 h. Under these conditions, substrates **6** were N-deoxygenated and cyanated (Scheme 2).

These transformations were easily verified by means of infrared spectra, loss of *N*-oxide band at *ca* 1 250 cm^{-1} in the spectra of **7** and appearance of nitrile absorption at *ca* 2 226–2 230 cm^{-1}. Disappearance of the most downfield signal in the ^1H NMR spectrum of each starting compound **6** also supported the structure of compounds **7**. Carbonitriles **7b** and **7c** were hydrolyzed to the respective carboxamides **8b** and **8c** with warm dilute sulfuric acid. The synthesized carboxamides **8b** and **8c** were characterized by amide NH and NH_2 bands in the region 3 200–3 416 cm^{-1} and carbonyl absorptions in the region 1 690–1 709 cm^{-1}. Two-hour alkaline hydrolysis of the nitrile **7c** gave only the corresponding carboxamide **8c**, whereas two-day alkaline hydrolysis of **8c** resulted in 66% yield of 2,3-dimethylfuro[3,2-*c*]pyridine-4-carboxylic acid (**9c**). Carbonitriles are starting materials for the preparation of amidines which are useful starting materials with wide utilization in organic synthesis[14]. Furo[3,2-*c*]pyridine-4-carbonitrile (**7a**) is such a suitable substrate; its transformation to amidine **10** was achieved by reaction with aniline in the presence of aluminum chloride in dichloromethane at room temperature. The structure of compounds **6**–**10** was confirmed by IR and ^1H NMR spectra.



SCHEME 2

EXPERIMENTAL

Melting points were determined on a Kofler hot-plate apparatus and are uncorrected. UV spectra of methanolic solutions [λ_{max} (log ε); λ_{max} in nm, ε in m^2 mol^{-1}] were recorded on a Specord UV-VIS M-40 (Zeiss, Jena) instrument. IR spectra were recorded on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr pellets (0.5 mg/300 mg KBr). ^1H NMR (300 MHz) and ^{13}C NMR (75.43 MHz) spectra of compounds **2**, **4**, **5**, and **6d** were recorded on a Varian VXR-300 spectrometer in $CDCl_3$ and $(CD_3)_2SO$. ^1H and ^{13}C chemical shifts were referred to internal TMS (δ 0.00). The ^1H NMR (80 MHz) spectra of other compounds were

recorded on a Tesla BS 587 spectrometer in $CDCl_3$ and $(CD_3)_2SO$. ^1H chemical shifts were referred to internal TMS (δ 0.00). Mass spectra were taken on a MS 902-S instrument (AEI, Manchester), with direct inlet, ionizing electron energy 70 eV, trap current 100 μA, and ion source temperature 160–180 °C. The starting furo[3,2-*c*]pyridines were prepared by methods described in the literature[1,2].

5-Aminofuro[3,2-*c*]pyridinium Tosylates **2a**–**2c**. General Procedure

A solution of TSH (1.87 g, 10 mmol) in dichloromethane (15 ml) was added to a stirred solution of furo[3,2-*c*]pyridine **1a**–**1c** (10 mmol) in dichloromethane (10 ml) at room temperature. Stirring was continued for 5 h, then the product was precipitated by addition of ether (50 ml) and filtered off. The crude product was recrystallized.

5-Aminofuro[3,2-c]pyridinium tosylate (**2a**). Yield: 82%, m.p. 165–173 °C (methanol–ether). For $C_{14}H_{14}N_2O_4S$ (306.3) calculated: 54.89% C, 4.61% H, 9.14% N; found: 54.55% C, 4.45% H, 8.98% N. ^1H NMR ($(CD_3)_2SO$): 2.27 s, 3 H (CH_3); 7.10 d, 2 H, *J*(2′,3′) = 8.05 (H-3′, H-5′); 7.43 d, 1 H, *J*(2,3) = 2.28 (H-3); 7.50 d, 2 H, *J*(2′,3′) = 8.05 (H-2′, H-6′); 8.25 bs, 2 H (NH_2); 8.36 d, 1 H, *J*(6,7) = 7.08 (H-7); 8.56 d, 1 H, *J*(2,3) = 2.28 (H-2); 8.75 dd, 1 H, *J*(6,7) = 7.08, *J*(4,6) = 1.8 (H-6); 9.35 d, 1 H, *J*(4,6) = 1.8 (H-4). ^{13}C NMR ($(CD_3)_2SO$): 20.81 (C-4′-CH_3); 106.70 (C-3); 110.94 (C-7); 125.48 (C-2′, C-6′); 126.94 (C-3a); 128.14 (C-3′, C-5′); 136.68 (C-4); 136.86 (C-6); 137.83 (C-4′); 145.45 (C-1′); 152.43 (C-2); 158.26 (C-7a). IR: 3 125, 3 252 (NH). UV: 244 (3.68), 255 (3.03), 285 (2.63).

5-Amino-2-methylfuro[3,2-c]pyridinium tosylate (**2b**). Yield: 80%, m.p. 114–119 °C (methanol–ether). For $C_{15}H_{16}N_2O_4S$ (320.4) calculated: 56.24% C, 5.03% H, 8.74% N; found: 56.00% C, 4.90% H, 8.53% N. ^1H NMR ($(CD_3)_2SO$): 2.27 s, 3 H (C-4′-CH_3); 2.58 s, 3 H (C-2-CH_3); 7.04 s, 1 H (H-3); 7.10 d, 2 H, *J*(2′,3′) = 7.97 (H-3′, H-5′); 7.48 d, 2 H, *J*(2′,3′) = 7.97 (H-2′, H-6′); 8.18 bs, 2 H (NH_2); 8.22 d, 1 H, *J*(6,7) = 7.0 (H-7); 8.66 dd, 1 H, *J*(6,7) = 7.0, *J*(4,6) = 1.87 (H-6); 9.19 d, 1 H, *J*(4,6) = 1.87 (H-4). ^{13}C NMR ($(CD_3)_2SO$): 13.77 (C-2-CH_3); 20.78 (C-4′-CH_3); 102.32 (C-3); 109.95 (C-7); 125.45 (C-2′, C-6′); 128.10 (C-3′, C-5′); 128.39 (C-3a); 135.22 (C-4); 136.26 (C-6); 137.79 (C-4′); 145.44 (C-1′); 158.12 (C-7a); 163.03 (C-2). IR: 3 121, 3 240 (NH). UV: 223 (3.46), 256 (2.94), 290 (2.44).

5-Amino-2,3-dimethylfuro[3,2-c]pyridinium tosylate (**2c**). Yield: 77%, m.p. 153–156 °C (methanol–ether). For $C_{16}H_{18}N_2O_4S$ (334.4) calculated: 57.47% C, 5.43% H, 8.38% N; found: 57.20% C, 5.25% H, 8.20% N. ^1H NMR ($(CD_3)_2SO$): 2.22 s, 3 H (C-3-CH_3); 2.27 s, 3 H (C-4′-CH_3); 2.51 s, 3 H (C-2-CH_3); 7.10 d, 2 H, *J*(2′,3′) = 8.06 (H-3′, H-5′); 7.47 d, 2 H, *J*(2′,3′) = 8.06 (H-2′, H-6′); 8.11 bs, 2 H (NH_2); 8.18 d, 1 H, *J*(6,7) = 7.0 (H-7); 8.65 dd, 1 H, *J*(6,7) = 7.0, *J*(4,6) = 1.35 (H-6); 9.24 d, 1 H, *J*(4,6) = 1.35 (H-4). ^{13}C NMR ($(CD_3)_2SO$): 7.11 (C-3-CH_3); 11.59 (C-2-CH_3); 20.63 (C-4′-CH_3); 109.60 (C-7); 109.87 (C-3); 125.30 (C-2′, C-6′); 127.93 (C-3′, C-5′); 129.19 (C-3a); 134.44 (C-4); 136.24 (C-6); 137.58 (C-4′); 145.37 (C-1′); 157.25 (C-2); 158.09 (C-7a). IR: 3 125, 3 240 (NH). UV: 223 (3.41), 256 (2.93), 290 (2.40).

1,3-Dipolar Cycloaddition Reactions of 5-Aminofuro[3,2-*c*]pyridinium Tosylates **2a**–**2c**. General Procedure

Potassium carbonate (0.52 g, 3.75 mmol) and dimethyl butynedioate (5 mmol) or ethyl propiolate (5 mmol) were added to a stirred solution of 5-aminofuro[3,2-*c*]pyridinium tosylate **2** (2.5 mmol) in *N*,*N*-dimethylformamide (25 ml) at 0 °C. The mixture was stirred vigorously for 24 h at room temperature. The solvent was evaporated *in vacuo*, the residue

was dissolved in ether and the insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the product recrystallized.

Dimethyl furo[3,2-c]pyrazolo[1,5-a]pyridine-1,2-dicarboxylate (**4a**). Yield: 30%, m.p. 145–148 °C (toluene–isohexane). For $C_{13}H_{10}N_2O_5$ (274.2) calculated: 56.94% C, 3.68% H, 10.22% N; found: 56.71% C, 3.50% H, 10.03% N. ^{1}H NMR ($CDCl_3$): 3.96 s, 3 H (OCH_3); 4.04 s, 3 H (OCH_3); 7.30 d, 1 H, *J*(5,6) = 7.45 (H-6); 7.67 d, 1 H, *J*(8,9) = 2.04 (H-9); 7.78 d, 1 H, *J*(8,9) = 2.04 (H-8); 8.41 d, 1 H, *J*(5,6) = 7.45 (H-5). ^{13}C NMR ($CDCl_3$): 51.73 (OCH_3); 53.02 (OCH_3); 102.96 (C-1); 103.34 (C-6); 108.85 (C-9); 116.42 (C-9a); 126.24 (C-5); 137.90 (C-9b); 145.29 (C-8); 147.57 (C-2); 152.18 (C-6a); 162.69 (C-2-**C**O); 163.40 (C-1-**C**O). IR: 1 713, 1 740 (C=O). UV: 229 (3.41), 292 (3.22). Mass spectrum: 274 ($M^{+\bullet}$, 98), 258 (6), 243 (100), 213 (30), 185 (11), 184 (12), 171 (11), 158 (11), 157 (19), 156 (9), 132 (4), 130 (7), 128 (9), 118 (6), 102 (6), 101 (10), 92 (8), 91 (12), 86 (5), 75 (6), 63 (6), 59 (12), 44 (12).

Dimethyl 8-methylfuro[3,2-c]pyrazolo[1,5-a]pyridine-1,2-dicarboxylate (**4b**). Yield: 30%, m.p. 166–168 °C (toluene–isohexane). For $C_{14}H_{12}N_2O_5$ (288.3) calculated: 58.33% C, 4.20% H, 9.72% N; found: 58.08% C, 4.02% H, 9.55% N. ^{1}H NMR ($CDCl_3$): 2.53 s, 3 H (C-8-CH_3); 3.95 s, 3 H (OCH_3); 4.04 s, 3 H (OCH_3); 7.21 d, 1 H, *J*(5,6) = 7.45 (H-6); 7.25 s, 1 H (H-9); 8.33 d, 1 H, *J*(5,6) = 7.45 (H-5). ^{13}C NMR ($CDCl_3$): 13.89 (C-8-CH_3); 51.61 (OCH_3); 52.92 (OCH_3); 102.44 (C-1); 102.98 (C-6); 104.69 (C-9); 117.68 (C-9a); 125.03 (C-5); 137.49 (C-9b); 147.38 (C-2); 151.39 (C-6a); 156.21 (C-8); 162.75 (C-2-**C**O); 163.46 (C-1-**C**O). IR: 1 709, 1 726 (C=O). UV: 225 (3.40), 300 (3.26). Mass spectrum: 288 ($M^{+\bullet}$, 100), 257 (98), 227 (20), 199 (9), 198 (13), 185 (18), 171 (11), 144 (7), 132 (5), 128 (4), 115 (8), 91 (3), 89 (4), 81 (3), 77 (3), 59 (10), 44 (8), 43 (9).

Dimethyl 8,9-dimethylfuro[3,2-c]pyrazolo[1,5-a]pyridine-1,2-dicarboxylate (**4c**). Yield: 30%, m.p. 207–208 °C (toluene–isohexane). For $C_{15}H_{14}N_2O_5$ (302.3) calculated: 59.60% C, 4.67% H, 9.27% N; found: 59.40% C, 4.50% H, 9.02% N. ^{1}H NMR ($CDCl_3$): 2.21 s, 3 H (C-9-CH_3); 2.43 s, 3 H (C-8-CH_3); 3.99 s, 3 H (OCH_3); 4.01 s, 3 H (OCH_3); 7.14 d, 1 H, *J*(5,6) = 7.45 (H-6); 8.32 d, 1 H, *J*(5,6) = (H-5). ^{13}C NMR spectrum ($CDCl_3$): 10.02, 11.77 (C-8-CH_3 and C-9-CH_3); 52.68 (OCH_3); 52.82 (OCH_3); 102.10 (C-1); 103.34 (C-6); 111.46 (C-9); 117.57 (C-9a); 124.71 (C-5); 135.33 (C-9b); 149.20 (C-2); 150.82 (C-8); 152.09 (C-6a); 162.22 (C-2-**C**O); 165.74 (C-1-**C**O). IR: 1 709, 1 726 (C=O). UV: 225 (3.52), 295 (2.95). Mass spectrum: 302 ($M^{+\bullet}$, 2), 292 (1), 271 (60), 270 (100), 242 (6), 241 (8), 227 (7), 203 (12), 201 (14), 197 (14), 195 (7), 183 (16), 135 (10), 120 (6), 92 (5), 91 (7), 77 (6), 59 (12), 44 (8), 43 (22).

Ethyl furo[3,2-c]pyrazolo[1,5-a]pyridine-1-carboxylate (**5a**). Yield: 39%, m.p. 101–102 °C (isohexane). For $C_{12}H_{10}N_2O_3$ (230.2) calculated: 62.61% C, 4.38% H, 12.17% N; found: 62.45% C, 4.19% H, 11.99% N. ^{1}H NMR ($CDCl_3$): 1.45 t, 3 H (CH_3); 4.42 q, 2 H (OCH_2); 7.21 d, 1 H, *J*(5,6) = 7.45 (H-6); 7.75 d, 1 H, *J*(8,9) = 2.04 (H-9); 7.75 d, 1 H, *J*(8,9) = 2.04 (H-8); 8.41 s, 1 H (H-2); 8.41 d, 1 H, *J*(5,6) = 7.45 (H-5). ^{13}C NMR ($CDCl_3$): 14.61 (CH_2-**C**H_3); 60.10 (OCH_2); 101.76 (C-6); 104.55 (C-1); 109.06 (C-9); 116.29 (C-9a); 126.36 (C-5); 137.33 (C-9b); 144.82, 145.13 (C-8 and C-2); 152.13 (C-6a); 163.35 (C-1-**C**O). IR: 1 697 (C=O), 1 639 (C=N). UV: 222 (3.34), 293 (3.26). Mass spectrum: 230 ($M^{+\bullet}$, 67), 202 (27), 186 (14), 185 (100), 172 (2), 158 (31), 157 (16), 120 (12), 118 (2), 102 (8), 92.5 (7), 78.5 (3), 75 (12), 63 (5), 51 (9), 44 (8), 43 (4), 28 (16).

Ethyl 8-methylfuro[3,2-c]pyrazolo[1,5-a]pyridine-1-carboxylate (**5b**). Yield: 36%, m.p. 107–109 °C (isohexane). For $C_{13}H_{12}N_2O_3$ (244.3) calculated: 63.93% C, 4.95% H, 11.47% N; found: 63.70% C, 4.75% H, 11.35% N. ^{1}H NMR ($CDCl_3$): 1.44 t, 3 H (CH_3); 2.52 s, 3 H (C-8-CH_3); 4.41 q, 2 H (OCH_2); 7.11 d, 1 H, *J*(5,6) = 7.45 (H-6); 7.37 s, 1 H (H-9); 8.33 d, 1 H, *J*(5,6) = 7.45 (H-5); 8.37 s, 1 H (H-2). ^{13}C NMR ($CDCl_3$): 13.94 (C-8-**C**H_3); 14.61 (CH_2-**C**H_3);

59.98 (OCH_2); 101.46 (C-6); 104.01 (C-1); 104.96 (C-9); 117.59 (C-9a); 125.22 (C-5); 136.99 (C-9b); 144.99 (C-2); 151.40 (C-6a); 155.66 (C-8); 163.42 (C-1-**C**O). IR: 1 684 (C=O), 1 638 (C=N). UV: 222 (3.36), 302 (3.29). Mass spectrum: 244 ($M^{+\bullet}$, 96), 216 (39), 199 (100), 172 (39), 171 (21), 144 (8), 132 (3), 116 (10), 115 (6), 99 (11), 89 (10), 80 (4), 77 (4), 63 (7), 51 (3), 44 (9), 43 (10), 28 (3).

Ethyl 8,9-dimethylfuro[3,2-c]pyrazolo[1,5-a]pyridine-1-carboxylate (**5c**). Yield: 33%, m.p. 146–148 °C (isohexane). For $C_{14}H_{14}N_2O_3$ (258.3) calculated: 65.11% C, 5.46% H, 10.85% N; found: 64.98% C, 5.32% H, 10.70% N. ^{1}H NMR ($CDCl_3$): 1.41 t, 3 H (CH_2-CH_3); 2.43 s, 6 H (C-8-CH_3 and C-9-CH_3); 4.37 q, 2 H (OCH_2); 7.07 d, 1 H, *J*(5,6) = 7.45 (H-6); 8.33 d, 1 H, *J*(5,6) = 7.45 (H-5); 8.36 s, 1 H (H-2). ^{13}C NMR ($CDCl_3$): 11.79, 11.98 (C-8-**C**H_3 and C-9-**C**H_3); 14.55 (CH_2-**C**H_3); 60.09 (OCH_2); 101.55 (C-6); 104.55 (C-1); 112.60 (C-9); 117.90 (C-9a); 125.39 (C-5); 136.37 (C-9b); 145.76 (C-2); 151.00 (C-6a); 151.77 (C-8); 163.30 (C-1-**C**O). IR: 1 707 (C=O), 1 629 (C=N). UV: 219 (3.37), 305 (3.30). Mass spectrum: 258 ($M^{+\bullet}$, 100), 230 (9), 213 (77), 201 (4), 197 (8), 186 (37), 158 (7), 130 (7), 116 (3), 106 (6), 99 (14), 77 (7), 63 (4), 51 (5), 44 (8), 43 (14), 28 (28).

Furo[3,2-*c*]pyridine *N*-Oxides **6a**–**6d**. General Procedure

A mixture of furo[3,2-*c*]pyridine **1a**–**1d** (8.4 mmol) and 3-chloroperoxybenzoic acid (9.75 g, 14.6 mmol) in dichloromethane (50 ml) was stirred at room temperature for 2 days. The mixture was filtered slowly through an alumina column (chloroform) and the filtrate was evaporated.

Furo[3,2-c]pyridine 5-oxide (**6a**) prepared by this method was identified by comparison of its IR and ^{1}H NMR spectra with the literature data[10,11].

2-Methylfuro[3,2-c]pyridine 5-oxide (**6b**). Yield: 60%, m.p. 178–180 °C (toluene). For $C_8H_7NO_2$ (149.1) calculated: 64.42% C, 4.73% H, 9.39% N; found: 64.22% C, 4.52% H, 9.20% N. ^{1}H NMR ($CDCl_3$): 2.49 s, 3 H (CH_3); 6.40 s, 1 H (H-3); 7.30 d, 1 H, *J*(6,7) = 7.0 (H-7); 8.13 d, 1 H, *J*(6,7) = 7.0 (H-6); 8.45 s, 1 H (H-4).

2,3-Dimethylfuro[3,2-c]pyridine 5-oxide (**6c**). Yield: 60%, m.p. 222–225 °C (toluene). For $C_9H_9NO_2$ (163.2) calculated: 66.25% C, 5.56% H, 8.58% N; found: 66.05% C, 5.48% H, 8.45% N. ^{1}H NMR ($CDCl_3$): 2.13 s, 3 H (C-3-CH_3); 2.40 s, 3 H (C-2-CH_3); 7.24 d, 1 H, *J*(6,7) = 7.0 (H-7); 8.11 dd, 1 H, *J*(6,7) = 7.0, *J*(4,6) = 1.5 (H-6); 8.39 d, 1 H, *J*(4,6) = 1.5 (H-4).

[1]Benzofuro[3,2-c]pyridine 2-oxide (**6d**). Yield: 70%, m.p. 206–207 °C (toluene). For $C_{11}H_7NO_2$ (185.2) calculated: 71.35% C, 3.81% H, 7.56% N; found: 71.20% C, 3.63% H, 7.45% N. ^{1}H NMR ($CDCl_3$): 7.40–7.47 m, 1 H (H-8); 7.50 d, 1 H, *J*(3,4) = 6.6 (H-4); 7.55–7.70 m, 2 H (H-6, H-7); 7.94 d, 1 H, *J*(8,9) = 7.2 (H-9); 8.35 d, 1 H, *J*(3,4) = 6.6 (H-3); 8.91 s, 1 H (H-1). ^{13}C NMR ($CDCl_3$): 109.34 (C-4); 112.40 (C-8); 120.21 (C-9a); 121.67 (C-9); 123.76 (C-9b); 124.39 (C-6); 129.90 (C-7); 132.69 (C-1); 138.28 (C-3); 152.81 (C-4a); 157.65 (C-5a).

Furo[3,2-*c*]pyridine-4-carbonitriles **7a**–**7d**. General Procedure

To a solution of potassium cyanide (2.5 g, 38 mmol) in water (3.5 ml) a solution of *N*-oxide **6a**–**6d** (3.7 mmol) in dichloromethane (20 ml) was added and then dropwise a solution of benzoyl chloride (0.6 ml, 4.3 mmol) in dichloromethane (20 ml). After vigorous stirring at room temperature for 2 days, the organic layer of the reaction mixture was separated and the aqueous layer was extracted with chloroform. After drying over magnesium sulfate, the combined organic layers were evaporated and the residue was purified by column chromato-

graphy on silica gel (isohexane–ethyl acetate 2.5 : 1) and following sublimation or crystallization.

Furo[3,2-c]pyridine-4-carbonitrile (**7a**) prepared by this method was identified by comparison of its IR and ^{1}H NMR spectra with the literature data[15].

2-Methylfuro[3,2-c]pyridine-4-carbonitrile (**7b**). Yield: 60%, m.p. 120–122 °C (subl.). For $C_9H_6N_2O$ (158.2) calculated: 68.35% C, 3.82% H, 17.71% N; found: 68.15% C, 3.70% H, 17.63% N. ^{1}H NMR ($CDCl_3$): 2.56 s, 3 H (CH_3); 6.67 d, 1 H, *J*(3,7) = 1.0 (H-3); 7.53 dd, 1 H, *J*(6,7) = 5.7, *J*(3,7) = 1.0 (H-7); 8.52 d, 1 H, *J*(6,7) = 5.7 (H-6). IR: 2 230 (CN).

2,3-Dimethylfuro[3,2-c]pyridine-4-carbonitrile (**7c**). Yield: 70%, m.p. 98–102 °C (toluene–isohexane). For $C_{10}H_8N_2O$ (172.2) calculated: 69.76% C, 4.68% H, 16.27% N; found: 69.63% C, 4.50% H, 16.10% N. ^{1}H NMR ($CDCl_3$): 2.41 s, 3 H (C-3-CH_3); 2.46 s, 3 H (C-2-CH_3); 7.48 d, 1 H, *J*(6,7) = 5.5 (H-7); 8.48 d, 1 H, *J*(6,7) = 5.5 (H-6). IR: 2 230 (CN).

[1]Benzofuro[3,2-c]pyridine-1-carbonitrile (**7d**). Yield: 85%, m.p. 139–141 °C (toluene–isohexane). For $C_{12}H_6N_2O$ (194.2) calculated: 74.22% C, 3.11% H, 14.43% N; found: 74.12% C, 2.98% H, 14.24% N. ^{1}H NMR ($CDCl_3$): 7.47–7.75 m, 4 H (H-arom); 8.41 m, 1 H (H-4); 8.73 d, 1 H, *J*(3,4) = 5.7 (H-3). IR: 2 226 (CN).

Furo[3,2-*c*]pyridine-4-carboxamides **8a**–**8c**. General Procedure

Compound **7a**–**7c** (1.82 mmol) was heated with a mixture of concentrated sulfuric acid (2.8 ml) and water (0.5 ml) on a water bath for 30 min. The cooled reaction mixture was diluted with water (15 ml), alkalinized with sodium hydrogencarbonate and extracted with chloroform. After drying over magnesium sulfate, the combined extract was evaporated and the residue was purified by crystallization.

Furo[3,2-c]pyridine-4-carboxamide (**8a**) prepared by this method was identified by comparison of its IR and ^{1}H NMR spectra with the literature data[15].

2-Methylfuro[3,2-c]pyridine-4-carboxamide (**8b**). Yield: 10%, m.p. 229–230 °C (methanol). For $C_9H_8N_2O_2$ (176.2) calculated: 61.36% C, 4.58% H, 15.90% N; found: 61.15% C, 4.35% H, 15.70% N. ^{1}H NMR ($CDCl_3$): 2.52 s, 3 H (CH_3); 7.24 s, 1 H (H-3); 7.46 d, 1 H, *J*(6,7) = 5.5 (H-7); 8.37 d, 1 H, *J*(6,7) = 5.5 (H-6). IR: 1 702 (C=O), 3 415 (NH).

2,3-Dimethylfuro[3,2-c]pyridine-4-carboxamide (**8c**). Yield: 83%, m.p. 189–190 °C (methanol). For $C_{10}H_{10}N_2O_2$ (190.2) calculated: 63.15% C, 5.30% H, 14.73% N; found: 63.07% C, 5.20% H, 14.63% N. ^{1}H NMR ($CDCl_3$): 2.45 s, 6 H (C-2-CH_3 and C-3-CH_3); 7.42 d, 1 H, *J*(6,7) = 5.4 (H-7); 8.32 d, 1 H, *J*(6,7) = 5.4 (H-6). IR: 1 690 (C=O), 3 415 (NH).

2,3-Dimethylfuro[3,2-*c*]pyridine-4-carboxylic Acid (**9c**)

Compound **8c** (0.32 g, 1.7 mmol) was refluxed with a solution of potassium hydroxide (1.6 g, 29 mmol) in 80% ethanol (25 ml) for 3 days. After evaporation of the solvent *in vacuo*, the residue was dissolved in water (10 ml), acidified with hydrochloric acid and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated to give crude **9c**, which was purified by recrystallization. Yield: 66%, m.p. >300 °C (methanol). For $C_{10}H_9NO_3$ (191.2) calculated: 62.82% C, 4.74% H, 7.33% N; found: 62.70% C, 4.65% H, 7.25% N. ^{1}H NMR ($(CD_3)_2SO$): 2.18 s, 3 H (C-3-CH_3); 2.38 s, 3 H (C-2-CH_3); 7.67 d, 1 H, *J*(6,7) = 5.5 (H-7); 8.36 d, 1 H, *J*(6,7) = 5.5 (H-6). IR: 1 630 (C=O).

Furo[3,2-*c*]pyridine-4-carboximidamide (**10**)

To a mixture of compound **7a** (0.22 g, 1.5 mmol) and aniline (0.14 g, 1.5 mmol) in dichloromethane (4 ml) powdered aluminum chloride (0.21 g, 1.55 mmol) was added in portions with constant swirling. The reaction mixture was stirred at room temperature for 48 h. After evaporation of the solvent, the thick mixture was added to warm water and alkalinized with 30% aqueous NaOH to pH 14. The formed solid was extracted with chloroform and the extract was dried over magnesium sulfate and evaporated to give crude **10**, which was purified by recrystallization from toluene–isohexane. Yield: 50%, m.p. 80–82 °C (toluene–isohexane). For $C_{14}H_{11}N_3O$ (237.3) calculated: 70.87% C, 4.67% H, 17.71% N; found: 70.57% C, 4.50% H, 17.51% N. ^{1}H NMR ($CDCl_3$): 5.84 bs, 2 H (NH); 7.01–7.55 m, 6 H (H-3, H-arom.); 7.67–7.81 m, 2 H (H-2, H-7); 8.43 d, 1 H, J(6,7) = 5.5 (H-6). IR: 3 386, 3 547 (NH).

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REFERENCES

1. Bobošík V., Krutošíková A., Jordis U.: *Monatsh. Chem.* **1995**, *126*, 747.
2. Eloy F., Deryckere A.: *Bull. Soc. Chim. Fr.* **1971**, 1442.
3. Howard A. S. in: *Comprehensive Heterocyclic Chemistry II* (G. Jones, Ed.), Vol. 8, p. 258. Pergamon, Oxford 1996.
4. Tamura Y., Ikeda M.: *Adv. Heterocycl. Chem.* **1981**, *29*, 71.
5. Potts K. T. in: *Comprehensive Hetrocyclic Chemistry* (K. T. Potts, Ed.), Vol. 5, p. 147. Pergamon, Oxford 1984.
6. Bátori S., Hajós G., Sándor P., Messmer A.: *J. Org. Chem.* **1989**, *54*, 3062.
7. Krischke R., Grashey R., Huisgen R.: *Liebigs Ann. Chem.* **1977**, 498.
8. Boekelheide V., Fedoruk N. A.: *J. Org. Chem.* **1968**, *33*, 2062.
9. Tamura Y., Sumida Y., Miki Y., Ikeda M.: *J. Chem. Soc., Perkin Trans. 1* **1975**, 406.
10. McFarland J. W., Essary W. A., Cilenti L., Cozart W., McFarland P. E.: *J. Heterocycl. Chem.* **1975**, *12*, 705.
11. Shiotani S., Taniguchi K., Ishida T., In Y.: *J. Heterocycl. Chem.* **1996**, *33*, 647.
12. Reissert A.: *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1610, 3415.
13. Henze M.: *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1566.
14. Gautier J.-A., Miocque M., Farnoux C. C. in: *The Chemistry of Amidines and Imidates* (S. Patai, Ed.), Vol. 1, p. 283. Wiley, London 1975.
15. Shiotani S., Taniguchi K.: *J. Heterocycl. Chem.* **1997**, *34*, 493.