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Synthesis of 1-(hydroxyaryl)furo[3,4-*c*]pyridines from 1-amino(alkoxy)furo[3,4-*c*]pyridines and (poly)phenols

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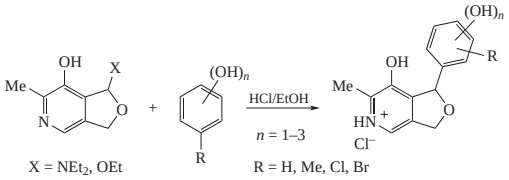
The herein obtained 1-diethylamino-6-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-7-ol or its 1-ethoxy analogue in their reactions with phenols or polyphenols undergo replacement of Et_2N/OEt groups with (poly)hydroxyaryl moieties.



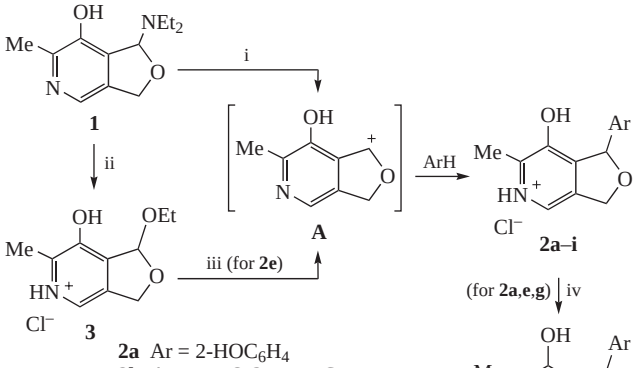
Vitamin B_6 represents a group of compounds (pyridoxal, pyridoxine, pyridoxamine), among which extremely valuable pyridoxal[1–8] is investigated to a lesser extent. On the other hand, aromatic compounds, for example, phenols, are widely known for their biological activity. To date, a large number of reports have been devoted to the synthesis of new phenolic compounds and study of their biological activity.[9–12]

Cyclic derivatives of pyridoxal, furo[3.4-*c*]pyridines, in which furan ring is linked to aryl substituent, are of certain interest from the viewpoint of biological activity. Among them 3-aryl-substituted furopyridines are exemplified by cycletanine, which exhibits diuretic action and is used in hypertension therapy,[13] as well as its numerous derivatives.[14] Data on furo[3,4-*c*]pyridines bearing aryl or heteroaryl fragment in the 1-position are scarce. Such a furopyridine bearing *p*-chlorophenyl substituent affects potassium ion transport through the cell membrane of erythrocytes,[15] however, the synthesis of this compound was not described. Another compound of this series was patented as a remedy for neurophysiological consequences, which are related to the accumulation of the products of glycosylation in organism, such as Parkinson and Alzheimer's diseases.[16] Taking these facts into account, the development of methods for the synthesis of 1-aryl-substituted furo[3,4-*c*]pyridines seems to be a topical problem.

We have previously shown that nitrogen-containing acetals (such as methylaminoacetaldehyde dimethyl acetal) can participate in electrophilic aromatic substitution in acidic media.[17] Since pyridoxal exists in equilibrium with cyclic furopyridine acetal,[18] its reactions with phenols and polyphenols in ethanol in the presence of hydrochloric acid afford 1-(hydroxyaryl)furo[3,4-*c*]-pyridines.[19]

We reasoned that the synthesis of 1-(hydroxyaryl)furo[3,4-*c*]-pyridines can also be carried out based on cyclic hemiaminal, such as 1-diethylaminofuro[3,4-*c*]pyridine **1**. Compound **1** can be prepared *via* several routes, namely, by long-term exposure of pyridoxal–diethylamine mixture in benzene in the presence of calcium hydride,[20] by the reaction of pyridoxal with *N*,*N*-diethyl-*N*-trimethylsilylamine,[21] and by treatment of pyridoxal hydrochloride with excess diethylamine.

The heating of 1-diethylaminofuro[3,4-*c*]pyridine **1** with phenols and polyphenols in ethanol in the presence of hydrochloric acid resulted in 1-(hydroxyaryl)furo[3,4-*c*]pyridines **2a–i** (Scheme 1).†



2a Ar = 2-HOC_6H_4
2b Ar = 2-HO-3,4-$Me_2C_6H_2$
2c Ar = 2-HO-3,4,6-Me_3C_6H
2d Ar = 2-HO-4-$MeOC_6H_3$
2e Ar = 2,4-$(HO)_2C_6H_3$
2f Ar = 2,4-$(HO)_2$-3-MeC_6H_2
2g Ar = 2,3,4-$(HO)_3C_6H_2$
2h Ar = 2,4-$(HO)_2$-5-ClC_6H_2
2i Ar = 2,4-$(HO)_2$-5-BrC_6H_2

4a Ar = 2-HOC_6H_4
4b Ar = 2,4-$(HO)_2C_6H_3$
4c Ar = 2,3,4-$(HO)_3C_6H_2$

Scheme 1 *Reagents and conditions:* i, ArH, HCl, EtOH, Δ; ii, EtOH, HCl, Δ; iii, ArH, EtOH, HCl; iv, EtONa/EtOH.

† *Synthesis of furopyridines* **2a–i** (*general procedure*). The equimolar mixture of aminofuropyridine **1** (2.25 mmol), appropriate phenol and concentrated hydrochloric acid (1 ml) in anhydrous ethanol (10 ml) was refluxed for 3–5 h. The mixture was cooled, the precipitate was separated, washed with ethanol and diethyl ether and dried *in vacuo*. In the case of compound **2e**, the reactant was either aminal **1** or acetal **3**.

7-Hydroxy-1-(2-hydroxy-3,4-dimethylphenyl)-6-methyl-1,3-dihydrofuro[3,4-c]pyridin-5-ium chloride **2b**. Yield 25%, mp 221 °C. IR (ν/cm^{-1}): 1059, 1553, 3396. ^{1}H NMR (400 MHz, DMSO–d_6) δ: 2.10 (s, 3H, Me), 2.18 (s, 3H, Me), 2.60 (s, 3H, Me), 5.16 (d, 1H^a, CH_2O, J 13.3 Hz), 5.24 (dd, 1H^b, CH_2O, J 13.3 Hz, J 1.9 Hz), 6.64 (q, 2H, CH_{arom}, J 7.9 Hz), 6.73 (d, 1H, CH, J 1.6 Hz), 8.33 (s, 1H, CH_{arom}). ^{13}C NMR (DMSO-d_6) δ: 12.76 (C^{15}), 14.86 (C^8), 20.43 (C^{16}), 70.87 (C^3), 80.73 (C^1), 121.87 (C^{11}), 124.34 (C^{13}), 125.09 (C^{14}), 125.48 (C^9), 125.60 (C^{12}), 138.47 (C^4), 139.34 (C^{3c}), 142.37 (C^6), 145.25 (C^{4c}), 148.91 (C^{10}), 152.94 (C^7). MS, *m*/*z*: 271 [M – HCl]$^+$. Found (%): C, 62.04; H, 5.97; Cl, 11.63; N, 4.76. Calc. for $C_{16}H_{18}ClNO_3$ (%): C, 62.43; H, 5.84; Cl, 11.54; N, 4.55.

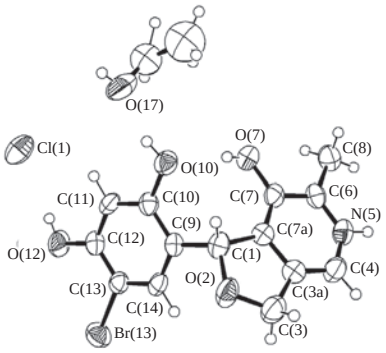


Figure 1 Molecular structure of compound **2i**. Selected bond lengths (Å): Br(13)–C(13) 1.894(4), O(2)–C(1) 1.433(6), O(2)–C(3) 1.412(6), O(7)–C(7) 1.347(5), O(10)–C(10) 1.376(5), O(12)–C(12) 1.357(6), N(5)–C(4) 1.337(6), N(5)–C(6) 1.338(7), C(1)–C(7a) 1.515(6), C(1)–C(9) 1.521(6), C(3)–C(3a) 1.488(6); selected bond angles (°): C(4)–N(5)–C(6) 124.9(4), O(2)–C(1)–C(9) 110.2(3), O(2)–C(1)–C(7a) 104.3(4), O(2)–C(3)–C(3a) 105.9(4), N(5)–C(4)–C(3a) 118.5(4), N(5)–C(6)–C(7) 118.4(4), N(5)–C(6)–C(8) 119.5(4), O(7)–C(7)–C(6) 116.5(4), O(7)–C(7)–C(7a) 125.4(4).

Relying on published data[22] one may hypothesize that under the reaction conditions, the formation of ethoxyfuropyridine **3** is initially occurs (see Scheme 1), which is followed by its further addition at (poly)phenols. In fact, ethoxy derivative **3** was generated from aminal **1** upon treatment with HCl in EtOH in the absence of phenols. Independent reaction of acetal **3** with resorcinol afforded the same product **2e** which was formed from aminal **1** as well (see Scheme 1). Obviously, the reaction follows the mechanism involving protonation of amino or alkoxy group and formation of stabilized carbocation **A**.

The structure of the products was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, as well as MALDI mass spectrometry. X-ray analysis was performed for the bromoresorcinol derivative **2i**.‡ This compound crystallized in monoclinic space group $P2_1/n$. There are two disordered ethanol solvent molecules, as well as counterion Cl^- in the independent part of unit cell along with the main compound. Substituted benzene, pyridine and furan heterocycles are planar, while the planes of benzene and pyridine cycles form the angle of 68.2°. Bilayer structure is formed due to hydrogen bonds of O–H···O, N–H···O, and O–H···Cl types, as well as molecular interactions of C–H···Cl type.

Treatment of salts **2a**,**e**,**g** with sodium hydride gives neutral compounds **4a**–**c** (see Scheme 1). Some changes in the appearance and position of the signals of protons in ^{1}H NMR spectra upon comparison of salts **2** and neutral molecules **4** should be noted. On transition **2a** → **4a**, upfield shifts of the methyl signal from 2.59 to 2.35 ppm and pyridine singlet from 8.31 to 7.89 ppm are observed.

In summary, we have carried out the synthesis of furo[3,4-*c*]-pyridines containing hydroxyaryl substituent in the 1-position starting from 1-diethylamino-6-methyl-1,3-dihydrofuro[3,4-*c*]-pyridin-7-ol. The obtained compounds can be of interest for biological tests and as the substrates for further functionalization. The X-ray data of 1-arylfuropyridine containing pyridoxal fragment have been obtained for the first time.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.035.

‡ *X-ray diffraction data for* **2i**. Crystals of $C_{14}H_{13}BrNO_4^+Cl^-\cdot 2\,C_2H_6O$, M = 466.74, monoclinic, at 296 K, space group $P2_1/n$, a = 12.076(3), b = 8.222(2) and c = 21.399(5) Å, β = 97.630(3)°, V = 2105.9(9) Å^3, Z = 4, d_{calc} = 1.472 g cm^{-3}, μ = 2.111 mm^{-1}, $F(000)$ = 960. The cell parameters and the experimental data were obtained on an automatic Bruker Smart APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scanning], $2\theta < 54°$, R_{int} = 0.068. Total of 15694 reflections were collected, from which 4595 were independent; the number of the observed reflections with $I > 2\sigma(I)$ was 2406. The absorption correction was applied using the SADABS program.[23] The structure was solved by the direct method using the SIR program[24] and refined by the full-matrix least-squares method using the SHELXL97 program package.[25] The hydrogen atoms of the hydroxyl groups were revealed by means of the difference electron density maps and refined in the isotropic approximation. The coordinates of the other hydrogen atoms were calculated geometrically and refined in a riding model. All the calculations were carried out using the WinGX[26] and APEX2[27] programs; the final values of the divergence factors were R = 0.0502, wR_2 = 0.1471, GOF = 1.02; the number of parameters to be refined was 300.

CCDC 1845109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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