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Synthesis of benzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-ones, derivatives of a novel heterocyclic system

<https://doi.org/10.1515/hc-2017-0143>

Received August 1, 2017; accepted April 2, 2018; previously published online July 19, 2018

Abstract: Methyl 2-[(cyanophenoxy)methyl]-3-furoates obtained from methyl 2-(chloromethyl)-3-furoate and salicylonitriles undergo tandem cyclization in the presence of excess *t*-BuOK in *N,N*-dimethylformamide (DMF) solution at 65°C to give substituted benzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-ones, derivatives of a novel heterocyclic system.

Keywords: alkylation; benzofuro[3,2-*b*]furo[2,3-*d*]pyridines; methyl 2-(chloromethyl)-3-furoates; salicylonitriles; tandem cyclization.

Introduction

Benzofuro[3,2-*b*]pyridines are biomedically attractive compounds. For instance, some 2-oxo-3-carboxylic acids derived from them act as endothelin receptor antagonists [1, 2], and the esters are P₂X₄ receptor modulators [3]. A number of analogous heterocyclic systems with the benzo[*d*]-annelated pyridine ring, such as benzofuro[3,2-*c*]isoquinolines [4–6], inhibit hepatitis C viral infection [7] and are used to treat erectile dysfunction [8], inflammation and cardiovascular diseases [9]. At the same time, heteroannelated benzofuopyridines are much less studied and the reported compounds are restricted to a few quinolino [10, 11] and coumarino derivatives [12, 13] with anti-inflammatory and antimicrobial activities. Their analogues with a fused furan ring are hitherto unknown. These structures can be regarded as polycyclic systems originated from superposition of benzofuro[3,2-*b*]pyridine

and furo[3,2-*c*]pyridine moieties. It is worth noting, that among furo[3,2-*c*]pyridine derivatives used for reversible control of protein transport [14], melanin-concentrating hormone receptor 1 antagonists [15] and protein kinase inhibitors [16] have been found.

Most of the benzo and heteroannelated benzofuopyridines described in the literature have been synthesized starting with salicylonitriles [4–6, 11–13] under the conditions of the Pictet-Spengler reaction. One approach used in this paper, provides a convenient way to obtain benzofuro[3,2-*b*]furo[2,3-*d*]pyridine, a novel heterocyclic system. More specifically, easily accessible methyl 2-(chloromethyl)-3-furoate [17] has been used as a bis-electrophilic component in the condensation with a salicylonitrile.

Results and discussion

Methyl 2-(chloromethyl)-3-furoate (**1**) is an effective reagent for the alkylation of salicylonitriles **2a–i**. The reaction conducted in the presence of K₂CO₃ in DMF solution at 60°C produces methyl 2-[(cyanophenoxy)methyl]-3-furoates **3a–i** in 69–80% yields (Scheme 1). When heated with *t*-BuOK in DMF solution at 65°C, compounds **3a–i** are converted in 67–83% yields to derivatives **5a–h** of benzofuro[3,2-*b*]furo[2,3-*d*]pyridine, a hitherto unknown heterocyclic system (Scheme 1). This reaction is a variation of tandem cyclization, with its first step proceeding by the Thorpe-Ziegler scheme and leading to intermediate aminobenzofurans **4** that undergo intramolecular condensation between the amino and methoxycarbonyl groups to form the pyridone ring.

For compound **3i** containing a fluorine atom at position 3 of the benzene ring, it was found using liquid chromatography-mass spectrometry (LC-MS) analysis that the reaction mixture after 3 h at 65°C contained not only 54% of 6-fluorinated product **5i** but also 40% of 6-methoxy derivative **5j**. Heating of **3i** at 90°C led to the formation of the product **5j** exclusively, which was isolated in 68% yield. This transformation is caused by a nucleophilic substitution of compound **5i** with MeOK which is generated under the reaction conditions as a side product of the cyclocondensation (Scheme 2).

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2–5a: $R^1 = H$; $R^2 = H$

2b: $R^1 = 5\text{-Br}$; $R^2 = H$

2c: $R^1 = 4\text{-Cl}$; $R^2 = H$

2d: $R^1 = 4\text{-Br}$; $R^2 = H$

2e: $R^1 = 5\text{-CF}_3$; $R^2 = H$

2f: $R^1 = 3\text{-Me}$; $R^2 = 5\text{-Cl}$

2g: $R^1 = 3\text{-Br}$; $R^2 = 5\text{-Br}$

2h: $R^1 = 3\text{-COMe}$; $R^2 = H$

2i: $R^1 = 2\text{-F}$; $R^2 = H$

3b: $R^1 = 4\text{-Br}$; $R^2 = H$

3c: $R^1 = 5\text{-Cl}$; $R^2 = H$

3d: $R^1 = 5\text{-Br}$; $R^2 = H$

3e: $R^1 = 4\text{-CF}_3$; $R^2 = H$

3f: $R^1 = 6\text{-Me}$; $R^2 = 4\text{-Cl}$

3g: $R^1 = 2\text{-Br}$; $R^2 = 4\text{-Br}$

3h: $R^1 = 2\text{-COMe}$; $R^2 = H$

3i: $R^1 = 3\text{-F}$; $R^2 = H$

5b: $R^1 = 7\text{-Br}$; $R^2 = H$

5c: $R^1 = 8\text{-Cl}$; $R^2 = H$

5d: $R^1 = 8\text{-Br}$; $R^2 = H$

5e: $R^1 = 8\text{-CF}_3$; $R^2 = H$

5f: $R^1 = 9\text{-Me}$; $R^2 = 7\text{-Cl}$

5g: $R^1 = 7\text{-Br}$; $R^2 = 9\text{-Br}$

5h: $R^1 = 9\text{-COMe}$; $R^2 = H$

Scheme 1

Scheme 2

The possibility of the synthesis of compound **5a** without isolation of the intermediate product **3a** was studied using salicylonitrile **2a**. It was found that the addition of *t*-BuOK after the first step and heating of the reaction mixture at 65°C also leads to the formation of **5a**, albeit in a low yield of 24%.

Structural determination of the synthesized compounds was performed using analytical and spectral methods. In particular, the infrared (IR) spectra of compounds **5a–j** feature characteristic N–H ($\nu_{\max}$ 3154–5170 cm^{-1}) and C=O ($\nu_{\max}$ 1665–1671 cm^{-1}) absorption peaks. Typical downfield signals of the C=O carbon of the pyridone moiety (δ 158–164) are observed in carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra.

Conclusion

An efficient construction of the previously unknown benzofuro[3,2-*b*]furo[2,3-*d*]pyridine system based on tandem heterocyclization of 2-[(2-cyanophenoxy) methyl]-

3-furoates was developed. The products, due to the presence of a lactam fragment can be considered as promising scaffolds for further modifications aiming at the identification of bioactive derivatives.

Experimental

All commercially available chemicals were purchased from Sigma-Aldrich Chemicals (Steinheim, Germany). Methyl 2-(chloromethyl)-3-furoate **1** and salicylic nitriles **2a–i** were purchased from Enamine Ltd (Kyiv, Ukraine). The reactions were monitored by thin-layer chromatography (TLC) using commercial silica gel plates Silufol UV-254. Melting points were taken on a hot-stage apparatus. IR spectra were obtained on a Bruker Vertex 70 spectrometer in KBr pellets. Proton nuclear magnetic resonance (^1H NMR) (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian VXR-400 spectrometer using deuterated dimethyl sulfoxide- d_6 (DMSO- d_6) as a solvent. Elemental analyses were conducted at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Science of Ukraine. Electrospray ionization mass spectra (ESI-MS) were recorded on an Agilent 1100/DAD/HSD/VLG119562 instrument.

General procedure for preparation of compounds 3a–i

To a solution of methyl 2-(chloromethyl)-3-furoate (**1**, 0.52 g, 3 mmol) in dry DMF (10 mL) was added salicylic nitrile **2a–i** (3 mmol) and anhydrous K_2CO_3 (0.83 g, 6 mmol). The mixture was stirred for 2 h at 60°C. After removal of the solvent under reduced pressure, the residue was washed with water (10 mL) and crystallized from ethanol.

Methyl 2-[(2-cyanophenoxy)methyl]-3-furoate (3a) Brown solid; yield 80%; mp 73–74°C; IR: $\nu_{\max}$ 2231 (CN), 1721 cm^{-1} (C=O); 1H NMR: δ 3.79 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 6.83 (s, 1H, CH), 7.15 (t, 1H, $J=7.6$ Hz, CH), 7.40 (d, 1H, $J=8.4$ Hz, CH), 7.71 (m, 2H), 7.88 (s, 1H, CH); ^{13}C NMR: δ 52.3, 62.0, 101.4, 111.2, 113.9, 116.6, 117.3, 122.3, 134.3, 135.6, 144.9, 154.35, 159.8, 163.2; ESI-MS: m/z 258 (M+H) $^+$. Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.30; H, 4.38; N, 5.39.

Methyl 2-[(4-bromo-2-cyanophenoxy)methyl]-3-furoate (3b) Brown solid; yield 78%; mp 142–143°C; IR: $\nu_{\max}$ 2230 (CN), 1714 cm^{-1} (C=O); 1H NMR: δ 3.79 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 6.82 (s, 1H, CH), 7.38 (d, 1H, $J=9.6$ Hz, CH), 7.88 (m, 2H), 8.02 (s, 1H, CH); ^{13}C NMR: δ 52.2, 62.4, 103.5, 111.1, 113.1, 115.2, 116.1, 117.4, 136.2, 138.3, 145.0, 154.0, 159.3, 163.2; ESI-MS: m/z 336 and 338 (M+H) $^+$. Anal. Calcd for $C_{14}H_{10}BrNO_4$: C, 50.03; H, 3.00; N, 4.17. Found: C, 50.20; H, 3.08; N, 4.05.

Methyl 2-[(5-chloro-2-cyanophenoxy)methyl]-3-furoate (3c) Brown solid; yield 75%; mp 138–139°C; IR: $\nu_{\max}$ 2233 (CN), 1718 cm^{-1} (C=O); 1H NMR: δ 3.80 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 6.83 (s, 1H, CH), 7.22 (d, 1H, $J=8.4$ Hz, CH), 7.59 (s, 1H, CH), 7.79 (d, 1H, $J=8.4$ Hz, CH), 7.89 (s, 1H, CH); ^{13}C NMR: δ 52.4, 62.4, 100.4, 111.3, 114.7, 115.9, 117.6, 122.6, 135.6, 140.6, 145.2, 153.7, 160.5, 163.2; ESI-MS: m/z 292 and 294 (M+H) $^+$. Anal. Calcd for $C_{14}H_{10}ClNO_4$: C, 57.65; H, 3.46; N, 4.80. Found: C, 57.88; H, 3.32; N, 4.64.

Methyl 2-[(5-bromo-2-cyanophenoxy)methyl]-3-furoate (3d) Brown solid; yield 74%; mp 147–148°C; IR: $\nu_{\max}$ 2234 (CN), 1715 cm^{-1} (C=O); 1H NMR: δ 3.80 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 6.83 (s, 1H, CH), 7.36 (d, 1H, $J=8.4$ Hz, CH), 7.69–7.72 (m, 2H), 7.88 (s, 1H, CH); ^{13}C NMR: δ 52.4, 62.4, 100.8, 111.3, 116.0, 117.5, 117.6, 125.5, 129.0, 135.6, 145.1, 153.8, 160.2, 163.2; ESI-MS: m/z 336 and 338 (M+H) $^+$. Anal. Calcd for $C_{14}H_{10}BrNO_4$: C, 50.03; H, 3.00; N, 4.17. Found: C, 50.23; H, 3.10; N, 4.02.

Methyl 2-[(2-cyano-4-(trifluoromethyl)phenoxy)methyl]-3-furoate (3e) Beige solid; yield 69%; mp 102–104°C; IR: $\nu_{\max}$ 2231 (CN), 1720 cm^{-1} (C=O); 1H NMR: δ 3.80 (s, 3H, CH_3), 5.65 (s, 2H, CH_2), 6.84 (s, 1H, CH), 7.62 (d, 1H, $J=8.8$ Hz, CH), 7.90 (s, 1H, CH), 8.08 (d, 1H, $J=8.8$ Hz, CH), 8.25 (s, 1H, CH); ^{13}C NMR: δ 52.4, 62.6, 102.2, 111.3, 114.7, 115.3, 117.6, 122.9 (q, $J=33.5$ Hz), 123.8 (q, $J=271.5$ Hz), 132.0, 132.7, 145.1, 153.7, 162.4, 163.2; ESI-MS: m/z 326 (M+H) $^+$. Anal. Calcd for $C_{15}H_{10}F_3NO_4$: C, 55.39; H, 3.10; N, 4.31. Found: C, 55.58; H, 3.07; N, 4.22.

Methyl 2-[(4-chloro-2-cyano-6-methylphenoxy)methyl]-3-furoate (3f) Brown solid; yield 73%; mp 141–144°C; IR: $\nu_{\max}$ 2233 (CN), 1722 cm^{-1} (C=O); 1H NMR: δ 2.14 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 6.78 (s, 1H, CH), 7.67 (s, 1H, CH), 7.78 (s, 1H, CH), 7.89 (s, 1H, CH); ^{13}C NMR: δ 15.2, 51.6, 65.4, 108.3, 111.0, 114.8, 117.4, 128.6, 130.3, 135.1, 135.9, 144.6, 153.4, 156.8, 162.4; ESI-MS: m/z 306 and 308 (M+H) $^+$. Anal. Calcd for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; Cl, 11.60; N, 4.58. Found: C, 58.99; H, 3.90; Cl, 11.54; N, 4.51.

Methyl 2-[(2,4-dibromo-6-cyanophenoxy)methyl]-3-furoate (3g) Beige solid, yield 70%; mp 163–165°C; IR: $\nu_{\max}$ 2231 (CN), 1720 cm^{-1} (C=O); 1H NMR: δ 3.62 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 6.77 (s, 1H, CH), 7.86 (s, 1H, CH), 8.10 (s, 1H, CH), 8.27 (s, 1H, CH); ^{13}C NMR: δ 51.7, 65.8, 110.4, 111.1, 113.5, 117.4, 118.0, 119.1, 135.2, 140.4, 144.8, 152.5, 155.8, 162.4; ESI-MS: m/z 414, 416 and 418 (M+H) $^+$. Anal. Calcd for $C_{14}H_9Br_2NO_4$: C, 40.52; H, 2.19; Br, 38.50; N 3.37. Found: C, 40.59; H, 2.25; Br, 38.59; N, 3.31.

Methyl 2-[(2-acetyl-6-cyanophenoxy)methyl]-3-furoate (3h) Brown solid; yield 69%; mp 103–104°C; IR: $\nu_{\max}$ 2233 (CN), 1721 cm^{-1} (C=O); 1H NMR: δ 2.50 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 6.75 (s, 1H, CH), 7.41 (t, 1H, $J=7.8$ Hz, CH), 7.87 (m, 2H), 7.99 (d, 1H, $J=7.8$ Hz, CH); ^{13}C NMR: δ 30.1, 51.6, 67.3, 108.0, 111.0, 115.4, 117.7, 125.2, 134.1, 134.6, 137.1, 144.6, 152.8, 158.0, 162.3, 197.8; ESI-MS: m/z 300 (M+H) $^+$. Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.29; H, 4.44; N, 4.59.

Methyl 2-[(2-cyano-3-fluorophenoxy)methyl]-3-furoate (3i) Brown solid; yield 69%; mp 103–104°C; IR: $\nu_{\max}$ 2232 (CN), 1721 cm^{-1} (C=O); 1H NMR: δ 3.80 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 6.83 (s, 1H, CH), 7.10 (m, 1H, CH), 7.27 (m, 1H, CH), 7.75 (q, 1H, $J=7.2$ Hz, CH), 7.88 (s, 1H, CH); ^{13}C NMR: δ 52.4, 62.6, 91.1 (d, $J^2=19$ Hz), 109.3 (d, $J^2=19$ Hz), 110.0, 111.3, 111.9, 117.5, 137.0 (d, $J^2=11$ Hz), 145.1, 153.9, 160.9 (d, $J^2=4$ Hz), 163.2, 164.7 (d, $J^2=255$ Hz); ESI-MS: m/z 276 (M+H) $^+$. Anal. Calcd for $C_{14}H_{10}FNO_4$: C, 61.09; H, 3.66; N, 5.09. Found: C, 61.31; H, 3.54; N, 5.01.

General procedure for the preparation of compounds 5a–h

To a solution of methyl 2-[(cyanophenyl)methyl]-3-furoate **3a–h** (3 mmol) in dry DMF (10 mL) was added *t*-BuOK (0.34 g, 3 mmol). The mixture was stirred for 3 h at 65°C. After removal of the solvent under reduced pressure, water (5 mL) was added to the residue followed by acidification with hydrochloric acid to pH 6. The resulting precipitate was filtered off and crystallized from DMF.

Benzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5a) Yellow solid; yield 83%; mp > 250°C; IR: $\nu_{\max}$ 3154 (NH), 1670 cm^{-1} (C=O); 1H NMR: δ 7.12 (s, 1H, CH), 7.42 (t, 1H, $J=7.2$ Hz, CH), 7.51 (t, 1H, $J=7.2$ Hz, CH), 7.75 (d, 1H, $J=8$ Hz, CH), 8.09 (m, 2H), 12.65 (s, 1H, NH); ^{13}C NMR: δ 109.2, 112.4, 115.3, 121.0, 123.1, 123.3, 126.6, 128.9, 133.4, 143.3, 146.4, 155.5, 164.1; ESI-MS: m/z 226 (M+H) $^+$. Anal. Calcd for $C_{13}H_7NO_3$: C, 69.33; H, 3.13; N, 6.22. Found: C, 69.49; H, 3.01; N, 6.09.

7-Bromobenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5b) Yellow solid; yield 69%; mp > 250°C; IR: $\nu_{\max}$ 3162 (NH), 1665 cm^{-1} (C=O); 1H NMR: δ 7.13 (s, 1H, CH), 7.64 (d, 1H, $J=8.4$ Hz, CH), 7.74 (d, 1H, $J=8.4$ Hz, CH), 8.08 (s, 1H, CH), 8.24 (s, 1H, CH), 12.53 (s, 1H, NH); ^{13}C NMR: δ 108.5, 116.1, 116.4, 120.4, 120.7, 124.7, 128.5, 134.9, 135.1, 150.0, 152.1, 157.8, 158.3; ESI-MS: m/z 304 and 306 (M+H) $^+$. Anal. Calcd for $C_{13}H_6BrNO_3$: C, 51.35; H, 1.99; N, 4.61. Found: C, 51.59; H, 1.85; N, 4.68.

8-Chlorobenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5c) Beige solid; yield 70%; mp > 250°C; IR: $\nu_{\max}$ 3168 (NH), 1669 cm^{-1} (C=O); 1H NMR: δ 7.09 (s, 1H, CH), 7.43 (d, 1H, $J=8$ Hz, CH), 7.85 (s, 1H, CH), 7.96 (m, 2H), 12.61 (s, 1H, NH); ^{13}C NMR: δ 108.7, 112.4, 115.5, 120.9, 121.4, 123.6, 129.2, 130.2, 130.4, 143.6, 146.2, 155.1, 162.0;

ESI-MS: m/z 260 and 262 ($M+H$)⁺. Anal. Calcd for C₁₃H₆ClNO₃: C, 60.14; H, 2.33; N, 5.39. Found: C, 60.36; H, 2.21; N, 5.50.

8-Bromobenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5d) Yellow solid; yield 68%; mp > 250°C; IR: $\nu_{\max}$ 3170 (NH), 1671 cm⁻¹ (C=O); ¹H NMR: δ 7.09 (s, 1H, CH), 7.59 (d, 1H, $J=8.4$ Hz, CH), 7.91 (m, 3H), 12.61 (s, 1H, NH); ¹³C NMR: δ 108.1, 115.5, 117.8, 118.3, 122.5, 126.3, 129.1, 130.8, 134.1, 149.6, 151.8, 157.9, 158.8; ESI-MS: m/z 304 and 306 ($M+H$)⁺. Anal. Calcd for C₁₃H₆BrNO₃: C, 51.35; H, 1.99; N, 4.61. Found: C, 51.17; H, 2.08; N, 4.75.

8-(Trifluoromethyl)benzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5e) Beige solid; yield 68%; mp > 250°C; IR: $\nu_{\max}$ 3165 (NH), 1669 cm⁻¹ (C=O); ¹H NMR: δ 7.17 (s, 1H, CH), 7.85 (d, 1H, $J=8.4$ Hz, CH), 8.02 (d, $J=8.4$ Hz, CH), 8.12 (s, 1H, CH), 8.53 (s, 1H, CH), 12.64 (s, 1H, NH); ¹³C NMR: δ 108.5, 115.7, 116.5, 122.5, 120.2, 125.8 (q, $J=270$ Hz), 129.1, 129.2, 130.9 (q, $J=34$ Hz), 135.3, 150.3, 152.1, 158.7, 160.2; ESI-MS: m/z 294 ($M+H$)⁺. Anal. Calcd for C₁₄H₆F₃NO₃: C, 57.35; H, 2.06; N, 4.78. Found: C, 57.47; H, 1.98; N, 4.69.

7-Chloro-9-methylbenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5f) Beige solid; yield 68%; mp > 250°C; IR: $\nu_{\max}$ 3169 (NH), 1663 cm⁻¹ (C=O); ¹H NMR: δ 2.68 (s, 1H, CH₃), 7.47 (s, 1H, CH), 7.51 (s, 1H, CH), 7.88 (s, 1H, CH), 8.04 (s, 1H, CH); ¹³C NMR: δ 14.9, 108.2, 118.9, 119.4, 127.1, 128.0, 129.2, 133.3, 133.6, 134.8, 150.1, 152.1, 156.4, 157.2; ESI-MS: m/z 274 and 276 ($M+H$)⁺. Anal. Calcd for C₁₄H₈ClNO₃: C, 61.44; H, 2.95; Cl, 12.95; N, 5.12. Found: C, 61.49; H, 2.97; Cl, 12.90; N, 5.17.

7,9-Dibromobenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5g) Beige solid; yield 71%; mp > 250°C; IR: $\nu_{\max}$ 3166 (NH), 1670 cm⁻¹ (C=O); ¹H NMR: δ 7.12 (s, 1H, CH), 7.88 (s, 1H, CH), 8.07 (s, 1H, CH), 8.29 (s, 1H, CH), 12.33 (s, 1H, NH); ¹³C NMR: δ 105.4, 108.6, 116.1, 117.0, 120.2, 121.5, 122.2, 129.6, 131.3, 134.5, 145.8, 150.5, 158.2; ESI-MS: m/z 382, 384 and 386 ($M+H$)⁺. Anal. Calcd for C₁₃H₅Br₂NO₃: C, 40.77; H, 1.32; Br, 41.73; N, 3.66. Found: C, 40.71; H, 1.37; Br, 41.64; N, 3.62.

9-Acetylbenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5h) Brown solid, yield 68%; mp > 250°C; IR: $\nu_{\max}$ 3167 (NH), 1668 cm⁻¹ (C=O); ¹H NMR: δ 2.88 (s, 1H, CH₃), 7.11 (s, 1H, CH), 7.48 (m, 1H, CH), 7.93 (m, 1H, CH), 8.05 (s, 1H, CH), 8.32 (m, 1H, CH), 12.44 (s, 1H, NH); ¹³C NMR: δ 30.38, 108.6, 116.1, 120.3, 123.8, 125.0, 125.4, 127.6, 145.3, 146.5, 152.6, 158.4, 162.3, 194.9; ESI-MS: m/z 268 ($M+H$)⁺. Anal. Calcd for C₁₄H₉NO₄: C, 67.42; H, 3.39; N, 5.24. Found: C, 67.47; H, 3.30; N, 5.28.

Preparation of 6-methoxybenzofuro[3,2-*b*]furo[2,3-*d*]pyridin-4(5*H*)-one (5j)

To a solution of methyl 2-[(cyano-3-fluorophenoxy)methyl]-3-furoate (**3i**, 0.3 g, 1.1 mmol) in dry DMF (7 mL) was added *t*-BuOK (0.25 g, 2.2 mmol). The mixture was stirred for 4 h at 90°C. Then the solvent was removed under reduced pressure, water (5 mL) was added to the residue, and the mixture was acidified with hydrochloric acid to pH 6. The resulting precipitate was filtered off and crystallized from DMF: yield 68% of a brown solid; mp > 250°C; IR: $\nu_{\max}$ 3167 (NH), 1674 cm⁻¹ (C=O); ¹H NMR: δ 3.96 (s, 3H, CH₃), 6.91 (d, 1H, $J=8$ Hz, CH), 7.12 (s, 1H, CH), 7.32 (d, 1H, $J=8$, CH), 7.43 (m, 1H, CH), 8.04 (s, 1H, CH),

11.59 (s, 1H, NH); ¹³C NMR: δ 56.1, 105.2, 105.3, 108.9, 110.2, 114.6, 127.8, 128.7, 144.1, 144.6, 146.7, 154.5, 156.1, 160.0; ESI-MS: m/z 256 ($M+H$)⁺. Anal. Calcd for C₁₄H₉NO₄: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.74; H, 3.59; N, 5.52.

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