Synthesis of 6-Amino-2-bromo-4-hydroxynicotinaldehyde Derivatives

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Abstract: Acylation of (1,3-dimethylbenzimidazol-2-ylidene)-, (3-methylbenzothiazol-2-ylidene)-, and (3,4-dimethylthiazol-2-ylidene)-acetonitriles with 1-(cyanoacetyl)-3,5-dimethylpyrazole was found to proceed at the exocyclic carbon atom, yielding the appropriate 2-heterylidene-3-oxopentanedinitriles. Treatment of the prepared dinitriles with hydrobromic acid in refluxing acetic acid afforded 2-(6-amino-2-bromo-4-hydroxypyridin-3-yl)-substituted quaternary salts of benzimidazolium, benzothiazolium, and thiazolium. Their structures were confirmed unambiguously by X-ray crystallographic studies. Reduction of these quaternary salts with excess sodium borohydride yielded the corresponding dihydro (in the case of benzoazoles) or tetrahydro (in the case of thiazole) derivatives, which were shown to be synthetic equivalents of the title nicotinaldehyde.

Key words: aldehydes, heterocycles, hydrazones, nitriles, pyridines

2-Bromopyridine-3-carbaldehydes are known as versatile building blocks in modern chemistry.[1–3] Multifarious reactivity of the aldehyde group[1] combined with the possibility of various cross-coupling reactions of the bromine[2] offers great opportunities for chemical modifications including different rings annulations.[1a,d,2c–e,3] A number of efforts in this field have provided particularly useful results. Thus, potent melanocortin[1a] and endothelin receptor[2d,3d,e] antagonists have been obtained starting from suitable 2-bromonicotinaldehyde derivatives. Moreover, some of these substances were prepared in multi-kilogram scales for clinical studies[2d,3d] and, for this purpose, large-scale syntheses (tens of kilograms) of the appropriate bromonicotinaldehyde precursors were elaborated.[2d,3d] Thus, the search for new approaches to the 2-bromopyridine-3-carbaldehyde core that allows the introduction of additional functionalities seems to be an important task.

To date, four general methods for achieving the target nicotinaldehyde derivatives are known. The first and most popular approach includes lithiation of 2-bromopyridines, followed by the trapping of the metalated species with *N*,*N*-dimethylformamide.[1b–e,2c,e,3b,4] However, despite wide use, the lithiation conditions do not tolerate many functional groups, thus the reaction requires multiple protection, which reduces its value. The second approach is the reduction of 2-bromonicotinonitriles with diisobutylaluminum hydride.[1a,2b,d,3c] This is a mild and convenient procedure that is only limited by the availability of the corresponding bromonitriles. The third approach is based on aldehyde group formation from a methyl group through radical bromination or chlorination and further transformation of the halomethyl moiety.[5] However, this method is not practical because of the long stepwise sequences and harsh conditions.[5b,c] Finally, Vilsmeyer formylation of certain 2-bromo-6-dialkylamino-pyridines was reported.[3d,e] This approach seems to be promising but, thus far, the amount of published data does not allow its scope and limitations to be accurately assessed.

The *N*,*N*′-dimethylbenzimidazolium[6] and *N*-methylbenzothiazolium[7] moieties are well known as synthetic equivalents of aldehyde functionality. Their reduction into 2,3-dihydro derivatives yields the masked formyl group,[6,7] which can, if necessary, be liberated by hydrolytic cleavage.[6a,7] Recently, we successfully employed such an approach for the preparation of masked aldehydes of pyrrole **1**,[8a] furan **2**,[8b] and certain fused pyrrole **3**[8c] cores (Figure 1). The corresponding quaternary salt precursors of compounds **1**–**3** were obtained from the readily available nitriles **4a** and **4b**.[9] Continuing our research in the field, we examined the application of compounds **4** to the synthesis of aldehydes of pyridine series and report the results herein.

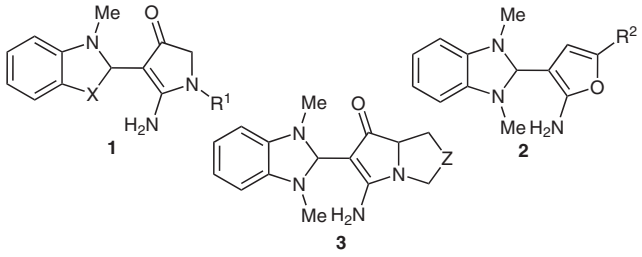

Figure 1 Previously prepared masked aldehydes. X = NMe or S; R^1 = alkyl or Ar; R^2 = CF_3 or Ar; Z = CH_2 or S.

The reaction of 1,5-dinitriles with HBr is known to give 2-bromopyridine derivatives,[10–12] and it has been well documented for aliphatic,[10] aromatic,[11] and heterocyclic[11c,12] dinitriles. Treatment of compounds **4a** and **4b** with cyanoacetic acid pyrazolide **5**[13] was found to yield 1,5-dinitriles **6a** and **6b**, respectively (Scheme 1). It should be noted that the pyrazolide **5** was widely used for the acyl-

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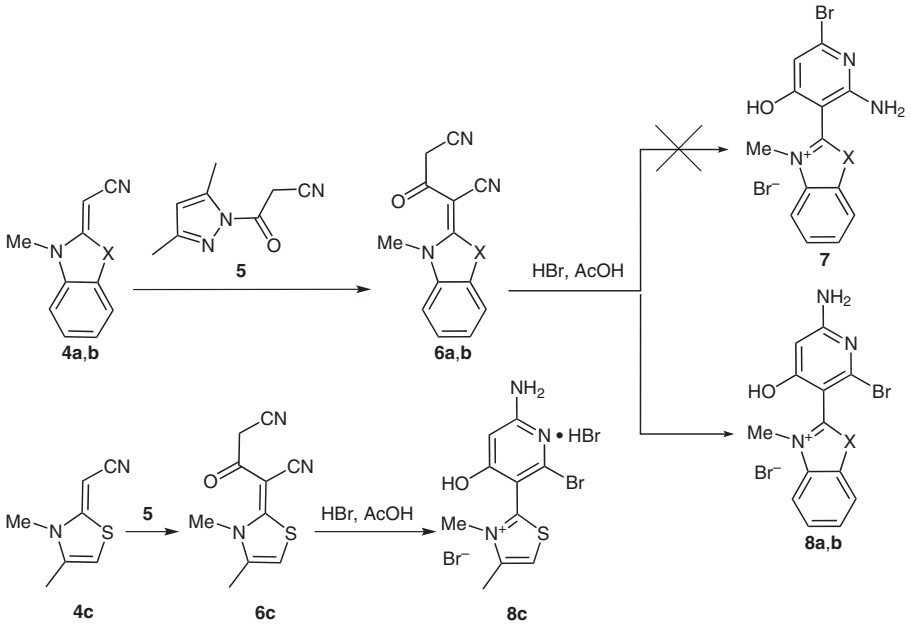


Scheme 1 Synthesis and reaction of 1,5-dinitriles with HBr. **a**: X = NMe, **b**: X = S.

ation of various amines and for the preparation of a range of cyanoacetamide derivatives.[14] To the best of our knowledge, the present synthesis of derivatives **6** is the first example of a C-acylation reaction with compound **5**. However, it was the predictable result, since nitriles **4a** and **4b** were previously shown to react with certain electrophiles at the exocyclic carbon atom.[8,9a,15]

With the dinitriles **6a** and **6b** in hand, their cyclization with hydrobromic acid was studied. Formally, it could afford two isomeric pyridines, **7** and **8**. In the literature, for unsymmetrical 1,5-dinitriles, both selective[10b,11,12d,f] and unselective[12a,b,e] cyclizations have been described. Nevertheless, in the present case, the reaction appeared to occur selectively, leading to the formation of a single compound. Since the spectral data did not allow the isomers **7** and **8** to be distinguished, an X-ray crystallographic study was carried out to assign the structure unambiguously (Figure 2). This study clearly revealed the products to be the 2-bromo-6-aminopyridine derivatives **8a** and **8b**.

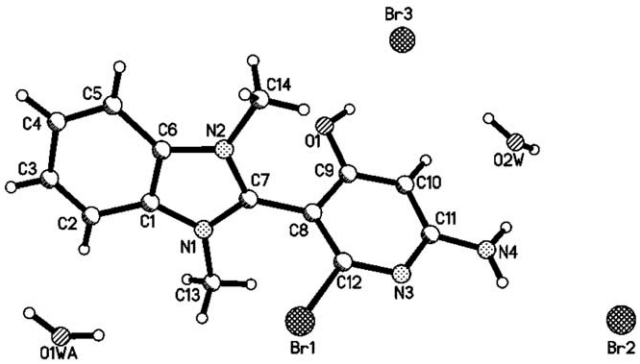


Figure 2 X-ray molecular structure of compound **8a**·H_2O with the atom numbering used in the crystallographic analysis. The asymmetric part of the crystal unit cell contains one organic cation and two bromide anions located in special positions on the symmetry elements (two-fold axis). The population of each bromide anion is 0.5, therefore the total charge is –1. The organic salt exists as the monohydrate in the crystal phase. The water molecule is disordered over two positions with equal populations and its one position coincides with the symmetry element (two-fold axis).

It was apparent that the reaction occurred through initial selective HBr addition to the appropriate nitrile (1-CN) and further ring closure at the expense of intramolecular addition of the formed imidoyl bromide salt moiety to the second nitrile group (5-CN). The latter was accompanied with a positive charge transfer to the benzoazole moiety. A higher reactivity towards HBr of 1-CN versus 5-CN is explained by the conjugation of 1-CN with the electron pair of the benzoazole nitrogen, which facilitates protonation of the nitrile, the primary act of HBr addition.

The sequence was extended to the new derivative **4c**, which was successfully converted into the corresponding dinitrile **6c** in the same manner (Scheme 1). Treatment of **6c** with hydrobromic acid furnished a product with ^{1}H and ^{13}C NMR spectra that were similar to those of derivatives **8a** and **8b**, and were consistent with the structure **8c**. However, elemental analysis indicated a significant excess of bromine, which approximately corresponded to the presence of an additional bromine atom. To clarify this point, an X-ray crystallographic study was performed (Figure 3), which revealed that the product did indeed have the quaternary salt structure **8c**, but that it was obtained with an additional hydrobromide salt at the pyridine moiety. Perhaps the better solubility in the reaction mixture of compound **8c** compared to its analogues **8a** and **8b** caused its precipitation as the hydrobromide salt during isolation.

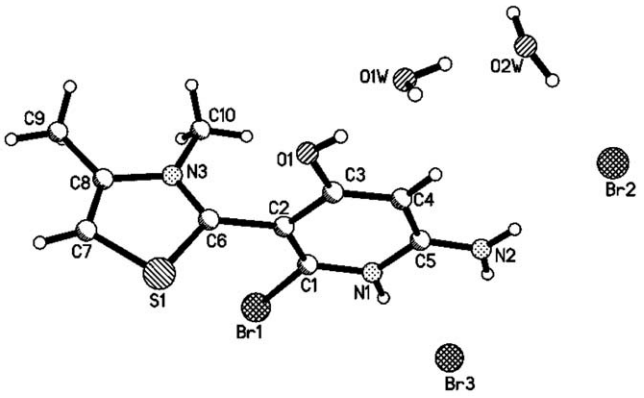


Figure 3 X-ray molecular structure of compound **8c**·HBr·2H_2O with the atom numbering used in the crystallographic analysis.

Reduction of the quaternary salts **8a** and **8b** with excess sodium borohydride afforded the target masked nicotinaldehyde derivatives **9a** and **9b**, respectively in 30–55% overall yield calculated from the nitriles **4** (Scheme 2). In the case of compound **8c**, the same reaction resulted in complete reduction of the thiazolium ring and formation of the thiazolidine analogue **9c**. It is noteworthy that similar reductions of other thiazolium salts were observed previously.[16] The structures of the prepared compounds **9a–c** were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. Their aldehyde nature was demonstrated by formation of the appropriate phenylhydrazone **10** and semicarbazone **11** upon treatment of derivatives **9a–c** with phenylhydrazine and semicarbazide, respectively. Preparation of the same compounds **10** and **11** starting from all the derivatives **9a–c** is good additional evidence for their structural assignments. It should be emphasized that better yields of compounds **10** and **11** were achieved by carrying out the reactions under an argon atmosphere because of a tendency of derivatives **9a–c** to oxidize. Indeed, benzimidazoline **9a** was found to be sensitive towards air, and oxidized significantly within several hours. Fortunately, the thiazole analogues **9b** and **9c** were found to be more stable and could be stored in air for several weeks without significant changes. Hence, since the yields of compounds **9a–c** were comparable, the thiazole derivatives **9b** and **9c** seem to be more convenient nicotinaldehyde equivalents for practical use.

To summarize, the present study has resulted in the synthesis of new polyfunctional nicotinaldehyde derivatives, namely the masked 2-bromo-6-amino-4-hydroxynicotinaldehydes **9a–c**. For the first time, aldehyde functionality has been brought into the pyridine core in the form of a quaternary benzoazolium salt. Furthermore, the thiazolium salt **8c** has been shown to be also applicable for this purpose. Generally, nitriles **4** were established to be suitable precursors for the synthesis of unique heterocyclic aldehydes **1–3** and **9**.[8] Their synthetic potential is believed not to be exhausted and, therefore, further investigations in the field are in progress.

Nitriles **4a**, **4b**,[9] and pyrazolide **5**[13] were prepared according to the described procedures. Other reagents were commercially available. All melting points were determined in open capillary tubes with a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal TMS; *J* values are in Hz. To obtain clear spectra, in the case of compounds **9a–c**, samples should be analyzed as soon as possible after sample preparation. In the spectral assignments, hydrogen and carbon atoms of the pyridine core are marked with subscript Py, while the atoms of other (hetero)aromatic moities are referred with subscript Ar. Elemental analyses were performed at the Microanalytical Department of the Institute of Organic Chemistry, NAS, Kiev, Ukraine. The purities of all compounds were checked by ^{1}H NMR spectroscopic analysis and by LC/MS analysis on an Agilent 1100 instrument.

(3,4-Dimethylthiazol-2-ylidene)acetonitrile (4c)

(4-Methylthiazol-2-yl)acetonitrile[17] (13.8 g, 0.10 mol) and dimethyl sulfate (16.4 g, 0.13 mol) were mixed without a solvent and heated on a water bath at 70–75 °C for 1.5–2 h, until the initially formed melt had solidified. Upon cooling, the solid was dissolved in H_2O (100 mL) and aq NaOH (10%, 50 mL) was added; this resulted in the separation of an oil, which quickly solidified. The solid was filtered and recrystallized from *i*-PrOH to give compound **4c**.

Yield: 10.8 g (71%); mp 116 °C.

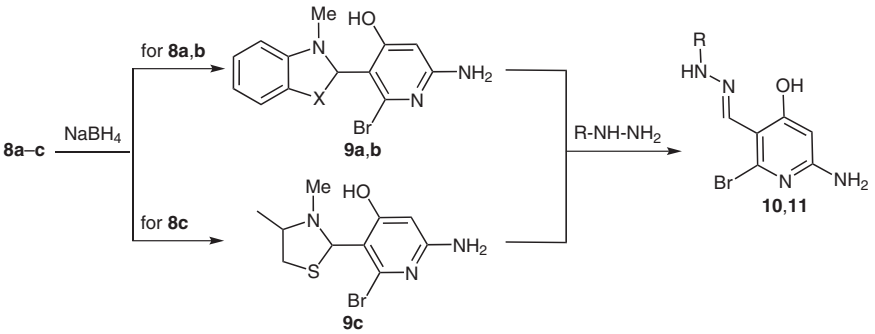
^{1}H NMR: δ = 2.10 (s, 3 H, CH_3), 3.12 (s, 3 H, NCH_3), 4.22 (s, 1 H, CHCN), 6.19 (s, 1 H, 5-H).

^{13}C NMR: δ = 14.3 (CH_3), 32.6 (NCH_3), 50.7 (*C*HCN), 97.0 (5-C), 122.7 (CN), 139.0 (4-C), 165.5 (2-C).

Anal. Calcd for $C_7H_8N_2S$: C, 55.23; H, 5.30; N, 18.40; S, 21.06. Found: C, 55.25; H, 5.18; N, 18.36; S, 21.10.

2-Heterylidene-3-oxopentanedinitriles 6a–c; General Procedure

A solution of compound **4a–c** (30 mmol) and the pyrazolide **5** (6.36



Scheme 2 Reduction of the quaternary salts. **a**: X = NMe, **b**: X = S. **10**: R = Ph, **11**: R = $CONH_2$.

g, 39 mmol) in anhydrous dioxane (40 mL) was heated at reflux for 3 h. After cooling, the solution was diluted with *i*-PrOH (80 mL) and the precipitate formed was filtered, washed with *i*-PrOH (15 mL) and recrystallized from an appropriate solvent yielding derivatives **6a–c**.

2-(1,3-Dimethyl-2,3-dihydrobenzimidazol-2-ylidene)-3-oxopentanedinitrile (6a)
Yield: 5.90 g (78%); mp 196 °C (EtOH).

^{1}H NMR: δ = 3.78 (s, 6 H, 2 × CH_3), 4.03 (s, 2 H, CH_2), 7.52 (m, 2 H, ArH), 7.80 (m, 2 H, ArH).

^{13}C NMR: δ = 29.3 (CH_2), 33.3 (2 × NCH_3), 59.0 (2-C), 112.4 (4,7-C_{Ar}), 117.2 (CN), 121.5 (CN), 125.5 (5,6-C_{Ar}), 132.2 (3a,7a-C_{Ar}), 151.4 (2-C_{Ar}), 177.7 (3-CO).

Anal. Cacld for $C_{14}H_{12}N_4O$: C, 66.66; H, 4.79; N, 22.21. Found: C, 66.60; H, 4.99; N, 22.34.

2-(3-Methylbenzothiazol-2(3*H*)-ylidene)-3-oxopentanedinitrile (6b)
Yield: 3.60 g (47%); mp 262 °C (EtOH).

^{1}H NMR: δ = 4.19 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 7.47 (t, *J* = 8.0 Hz, 1 H, ArH), 7.63 (t, *J* = 8.0 Hz, 1 H, ArH), 7.78 (d, *J* = 8.0 Hz, 1 H, ArH), 8.03 (d, *J* = 8.0 Hz, 1 H, ArH).

^{13}C NMR: δ = 30.3 (CH_2), 36.4 (CH_3), 75.9 (2-C), 113.8 (4-C_{Ar}), 116.3 (CN), 119.5 (CN), 123.2 (6-C_{Ar}), 125.5 (7-C_{Ar}), 126.6 (7a-C_{Ar}), 128.2 (5-C_{Ar}), 140.3 (3a-C_{Ar}), 165.8 (2-C_{Ar}), 182.0 (3-CO).

Anal. Calcd for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46; S, 12.56. Found: C, 61.21; H, 3.38; N, 16.31; S, 12.50.

2-(3,4-Dimethylthiazol-2(3*H*)-ylidene)-3-oxopentanedinitrile (6c)
Yield: 5.46 g (83%); mp 208 °C (MeOH).

^{1}H NMR: δ = 2.34 (s, 3 H, CH_3), 3.91 (s, 3 H, NCH_3), 4.16 (s, 2 H, CH_2), 7.10 (s, 1 H, ArH).

^{13}C NMR: δ = 14.4 (CH_3), 29.5 (CH_2), 36.9 (NCH_3), 74.2 (2-C), 109.3 (5-C_{Ar}), 116.6 (CN), 120.3 (CN), 140.7 (4-C_{Ar}), 164.7 (2-C_{Ar}), 180.0 (3-CO).

Anal. Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.85; H, 4.09; N, 19.20; S, 14.82.

Quaternary Salts 8a–c; General Procedure
Compounds **6a–c** (15 mmol) were dissolved in 40% HBr in acetic acid (30 mL, obtained by saturation of acetic acid with gaseous HBr) and the resulting solution was heated at reflux for 10 min. Upon cooling, the mixture was diluted with acetone (50 mL) and the solid precipitated was filtered, washed with cold acetone (10 mL) and recrystallized from a suitable solvent, affording derivatives **8a–c**.

2-(6-Amino-2-bromo-4-hydroxypyridin-3-yl)-1,3-dimethylbenzimidazolium Bromide (8a)
Yield: 6.03 g (97%); mp 300 °C (DMF).

^{1}H NMR: δ = 3.95 (s, 6 H, 2 × CH_3), 4.93 (br s, 2 H, NH_2, exch. D_2O), 6.23 (s, 1 H, 5-H_{Py}), 7.37 (br s, 1 H, OH, exch. D_2O), 7.79 (m, 2 H, ArH), 8.16 (m, 2 H, ArH).

^{13}C NMR: δ = 33.0 (2 × CH_3), 90.0 (5-C_{Py}), 97.0 (3-C_{Py}), 114.3 (4,7-C_{Ar}), 127.6 (5,6-C_{Ar}), 132.2 (3a,7a-C_{Ar}), 140.4 (2-C_{Py}), 146.5 (4-C_{Py}), 160.3 (6-C_{Py}), 162.0 (2-C_{Ar}).

Anal. Calcd for $C_{14}H_{14}Br_2N_4O$: C, 40.61; H, 3.41; N, 13.53; Br, 38.59. Found: C, 40.60; H, 3.42; N, 13.30; Br, 38.52.

2-(6-Amino-2-bromo-4-hydroxypyridin-3-yl)-3-methylbenzothiazolium Bromide (8b)
Yield: 5.94 g (95%); mp 260 °C (DMF).

^{1}H NMR: δ = 4.22 (s, 3 H, CH_3), 4.58 (br s, 2 H, NH_2, exch. D_2O), 6.19 (s, 1 H, 5-H_{Py}), 7.30 (br s., 1 H, OH, exch. D_2O), 7.94 (m, 1 H, ArH), 8.01 (m, 1 H, ArH), 8.45 (d, *J* = 8.5 Hz, 1 H, ArH), 8.64 (d, *J* = 8.0 Hz, 1 H, ArH).

^{13}C NMR: δ = 38.0 (CH_3), 90.1 (5-C_{Py}), 101.3 (3-C_{Py}), 118.6 (4-C_{Ar}), 125.5 (6-C_{Ar}), 129.6 (5-C_{Ar}), 130.5 (7-C_{Ar}), 131.9 (7a-C_{Ar}), 139.4 (2-C_{Py}), 141.6 (4a-C_{Ar}), 159.9 (4-C_{Py}), 161.4 (6-C_{Py}), 169.7 (2-C_{Ar}).

Anal. Calcd for $C_{13}H_{11}Br_2N_3OS$: C, 37.43; H, 2.66; N, 10.07; Br, 38.31; S, 7.69. Found: C, 37.32; H, 2.54; N, 10.10; Br, 38.40; S, 7.91.

2-(6-Amino-2-bromo-4-hydroxypyridin-3-yl)-3,4-dimethylthiazolium Bromide Hydrobromide (8c)
Yield: 5.75 g (83%); mp 232 °C (DMF–*i*-PrOH, 1:1).

^{1}H NMR: δ = 2.64 (s, 3 H, CH_3), 3.83 (s, 3 H, NCH_3), 4.62 (br s, 2 H, NH_2, exch. D_2O), 6.16 (s, 1 H, 5-H_{Py}), 7.27 (br s., 1 H, OH, exch. D_2O), 8.29 (s, 1 H, ArH), 10.47 (br s, detected by integration only, 1 H, N·HBr).

^{13}C NMR: δ = 14.5 (CH_3), 38.1 (NCH_3), 89.9 (5-C_{Py}), 101.7 (3-C_{Py}), 123.4 (5-C_{Ar}), 140.0 (2-C_{Py}), 147.2 (4-C_{Ar}), 159.5 (4-C_{Py}), 161.6 (6-C_{Py}), 164.7 (2-C_{Ar}).

Anal Calcd for $C_{10}H_{11}Br_2N_3OS$·HBr: C, 26.00; H, 2.62; N, 9.10; Br, 51.89; S, 6.94. Found: C, 26.14; H, 2.60; N, 9.11; Br, 51.64; S, 7.12.

Masked 6-Amino-2-bromo-4-hydroxynicotinaldehydes 9a–c; General Procedure
$NaBH_4$ (3.04 g, 70 mmol) was added cautiously in portions to an ice-cooled and stirred solution of the salt **8a–c** (7 mmol) in aqueous MeOH (20 mL; MeOH–H_2O, 7:3). After the addition was complete, the mixture was stirred at 0–5 °C for 1 h. The precipitate formed was filtered, washed with H_2O (10 mL) and recrystallized from an appropriate solvent to give derivatives **9a–c**.

6-Amino-2-bromo-3-(1,3-dimethyl-2,3-dihydrobenzimidazol-2-yl)pyridin-4-ol (9a)
Yield: 1.03 g (44%); mp 230 °C (*i*-PrOH).

^{1}H NMR: δ = 2.62 (s, 6 H, 2 × CH_3), 5.34 (s, 1 H, NCHN), 5.85 (s, 1 H, 5-H_{Py}), 6.40 (s, 2 H, NH_2), 6.59 (m, 2 H, ArH), 6.71 (m, 2 H, ArH), 10.49 (s, 1 H, OH).

^{13}C NMR: δ = 33.3 (2 × CH_3), 90.1 (NCHN), 93.1 (5-C_{Py}), 104.2 (4,7-C_{Ar}), 108.4 (3-C_{Py}), 117.2 (5,6-C_{Ar}), 141.6 (3a,7a-C_{Ar}), 141.7 (2-C_{Py}), 159.9 (4-C_{Py}), 164.8 (6-C_{Py}).

Anal. Calcd for $C_{14}H_{15}BrN_4O$: C, 50.17; H, 4.51; N, 16.71; Br, 23.84. Found: C, 50.24; H, 4.60; N, 16.54; Br, 23.76.

6-Amino-2-bromo-3-(3-methyl-2,3-dihydrobenzothiazol-2-yl)pyridin-4-ol (9b)
Yield: 2.04 g (86%); mp 218 °C (*i*-PrOH).

^{1}H NMR: δ = 2.62 (s, 3 H, CH_3), 5.85 (s, 1 H, SCHN), 6.31 (s, 2 H, NH_2), 6.39 (s, 1 H, 5-H_{Py}), 6.58 (m, 2 H, ArH), 6.92 (t, *J* = 6.5 Hz, 1 H, ArH), 6.97 (d, *J* = 6.5 Hz, 1 H, ArH, 10.60 (s, 1 H, OH).

^{13}C NMR: δ = 33.1 (CH_3), 73.3 (NCHS), 93.6 (5-C_{Py}), 108.8 (3-C_{Py}), 116.5 (4-C_{Ar}), 118.3 (7-C_{Ar}), 120.9 (5-C_{Ar}), 125.7 (6-C_{Ar}), 126.4 (7a-C_{Ar}), 141.8 (2-C_{Py}), 148.5 (3a-C_{Ar}), 160.5 (4-C_{Py}), 166.0 (6-C_{Py}).

Anal. Calcd for $C_{13}H_{12}BrN_3OS$: C, 46.17; H, 3.58; N, 12.42; Br, 23.62; S, 9.48. Found: C, 46.23; H, 3.60; N, 12.50; Br, 23.82; S, 9.41.

6-Amino-2-bromo-3-(3,4-dimethylthiazolidin-2-yl)pyridin-4-ol (9c)

Yield: 1.90 g (89%); mp 138 °C (MeCN).

^{1}H NMR: δ = 1.25 (d, *J* = 4.0 Hz, 3 H, CH_3), 2.30 (s, 3 H, NCH_3), 2.81 (m, 2 H, SCH_2), 3.15 (m, 1 H, NCH), 5.14 (s, 1 H, SCHN), 5.73 (s, 1 H, 5-H_{Py}), 6.20 (s, 2 H, NH_2), 12.80 (s, 1 H, OH).

^{13}C NMR: δ = 18.8 (CH_3), 36.8 (SCH_2), 37.2 (NCH_3), 64.0 (NCH), 73.9 (SCHN), 93.5 (5-C_{Py}), 107.7 (3-C_{Py}), 141.1 (2-C_{Py}), 160.6 (4-C_{Py}), 166.3 (6-C_{Py}).

Anal. Calcd for $C_{10}H_{14}BrN_3OS$: C, 39.48; H, 4.64; N, 13.81; Br, 26.27; S, 10.54. Found: C, 39.33; H, 4.57; N, 13.80; Br, 26.39; S, 10.52.

Phenylhydrazone 10 and Semicarbazone 11; General Procedure

A solution of compound **9a**–**c** (3.0 mmol) and phenylhydrazine hydrochloride (0.48 g, 3.3 mmol) or semicarbazide hydrochloride (0.37 g, 3.3 mmol) in *i*-PrOH (10 mL) was heated at reflux under argon atmosphere for 2 h. After cooling, the mixture was poured into H_2O (30 mL) and the solid that separated was filtered, washed with H_2O (5 mL) and recrystallized from a suitable solvent to yield derivatives **10** and **11**.

6-Amino-2-bromo-4-hydroxynicotinaldehyde Phenylhydrazone (10)

Yield: 0.67 g (73%); mp 231 °C (*i*-PrOH–H_2O, 2:1).

^{1}H NMR: δ = 5.92 (s, 1 H, 5-H_{Py}), 6.60 (s, 2 H, NH_2), 6.80 (t, *J* = 8.0 Hz, 1 H, ArH), 6.84 (d, *J* = 8.0 Hz, 2 H, ArH), 7.26 (t, *J* = 8.0 Hz, 2 H, ArH), 8.26 (s, 1 H, N=CH), 10.54 (s, 1 H, OH), 12.32 (s, 1 H, NH).

^{13}C NMR: δ = 92.7 (5-C_{Py}), 106.5 (3-C_{Py}), 111.9 (2,6-C_{Ar}), 119.8 (4-C_{Ar}), 129.9 (3,5-C_{Ar}), 140.4 (1-C_{Ar}), 141.7 (CH=N), 144.5 (2-C_{Py}), 159.9 (4-C_{Py}), 165.2 (6-C_{Py}).

Anal. Calcd for $C_{12}H_{11}BrN_4O$: C, 46.93; H, 3.61; N, 18.24; Br, 26.01. Found: C, 46.84; H, 3.63; N, 18.12; Br, 26.24.

6-Amino-2-bromo-4-hydroxynicotinaldehyde Semicarbazone (11)

Yield: 0.54 g (66%); mp 251 °C (MeOH).

^{1}H NMR: δ = 5.86 (s, 1 H, 5-H_{Py}), 6.30 (s, 2 H, NH_2), 6.62 (s, 2 H, $CONH_2$), 8.21 (s, 1 H, CH=N), 10.34 (s, 1 H, OH), 11.73 (br s, 1 H, CONH).

^{13}C NMR: δ = 93.3 (5-C_{Py}), 109.1 (3-C_{Py}), 140.2 (CH=N), 143.5 (2-C_{Py}), 158.2 (CO), 159.4 (4-C_{Py}), 165.6 (6-C_{Py}).

Anal. Calcd for $C_7H_8BrN_5O_2$: C, 30.68; H, 2.94; N, 25.55; Br, 29.15. Found: C, 30.65; H, 3.13; N, 25.54; Br, 29.05.

X-ray Crystal Structure Determination of Compound 8a

Intensities of 9696 reflections (2913 independent, R_{int} = 0.040) were measured with an Xcalibur-3 diffractometer in the ω-2Θ scan mode, $2\Theta_{max}$ = 50°, using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The absorption correction was performed using the multiscan method (T_{min} = 0.564, T_{max} = 0.615). Crystal data: $[C_{14}H_{14}N_4OBr]^+Br^-\cdot H_2O$; M_r = 1708.4; orthorhombic; *a* = 7.1595(4) Å, *b* = 20.634(1) Å, *c* = 22.631(1) Å; *V* = 3343.3(3) Å^3; *T* = 293 K; space group C222$_1$; Z = 2; μ(Mo-K_α) = 4.859 mm^{-1}. The structure was solved by direct method using the SHELXTL program package.[18] Positions of hydrogen atoms were located from electron density difference maps and refined by the riding model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for the methyl groups and water, n = 1.2 for the rest of hydrogens). The disordered water molecule was refined isotropically. During the refinement, a restraint was placed on the bond lengths in the benzene ring, C_{Ar}–C_{Ar} is 1.38 Å. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 2826 reflections converged to R_1 = 0.054, wR_2 = 0.134 [for 2141 reflections with $F > 4\sigma(F)$], *S* = 0.974. Full crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre under reference number CCDC 796000.

X-ray Crystal Structure Determination of Compound 8c

Intensities of 18303 reflections (4963 independent, R_{int} = 0.047) were measured with an Xcalibur-3 diffractometer in the ω-2Θ scan mode, $2\Theta_{max}$ = 60°, using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The absorption correction was performed using the multiscan method (T_{min} = 0.260, T_{max} = 0.699). Crystal data: $[C_{10}H_{12}N_3OBrS]^{2+}\cdot 2Br^-\cdot 2H_2O$; M_r = 498.05; monoclinic; *a* = 7.5513(3) Å, *b* = 11.0491(3) Å, *c* = 20.7868(7) Å, β = 97.941(3)°; *V* = 1717.7(1) Å^3; *T* = 293 K; space group P2$_1$/c; Z = 4; μ (Mo-K_α) = 7.175 mm^{-1}. The structure was solved by direct method using the SHELXTL program package.[18] Positions of hydrogen atoms were located from electron density difference maps and refined by the riding model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for the methyl groups and water, n = 1.2 for the rest of hydrogens). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 4938 reflections converged to R_1 = 0.036, wR_2 = 0.061 [for 2784 reflections with $F > 4\sigma(F)$], *S* = 0.857. Full crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre under reference number CCDC 796001.

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