HALOGENATED (ACYLAMINO)IMIDAZOLES AND BENZIMIDAZOLES FOR DIRECTED HALOGEN-METAL EXCHANGE-BASED FUNCTIONALIZATION

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Abstract

Regioselective syntheses of 4- and 5-(acylamino)-1-alkylimidazoles bearing an *ortho*-halogen atom have been developed. Suitable for use in *ortho*-directed halogen-metal exchange-mediated ring functionalizations, these compounds are valuable precursors to *ortho*-functionalized versions of biologically active 4- and 5-aminoimidazoles. To widen the scope of this approach to cover similarly-substituted benzimidazoles and their potentially bioactive nucleosides, the synthesis of halogenated 5- and 6-(acylamino)-benzimidazoles and their ribosides was also explored.

Introduction

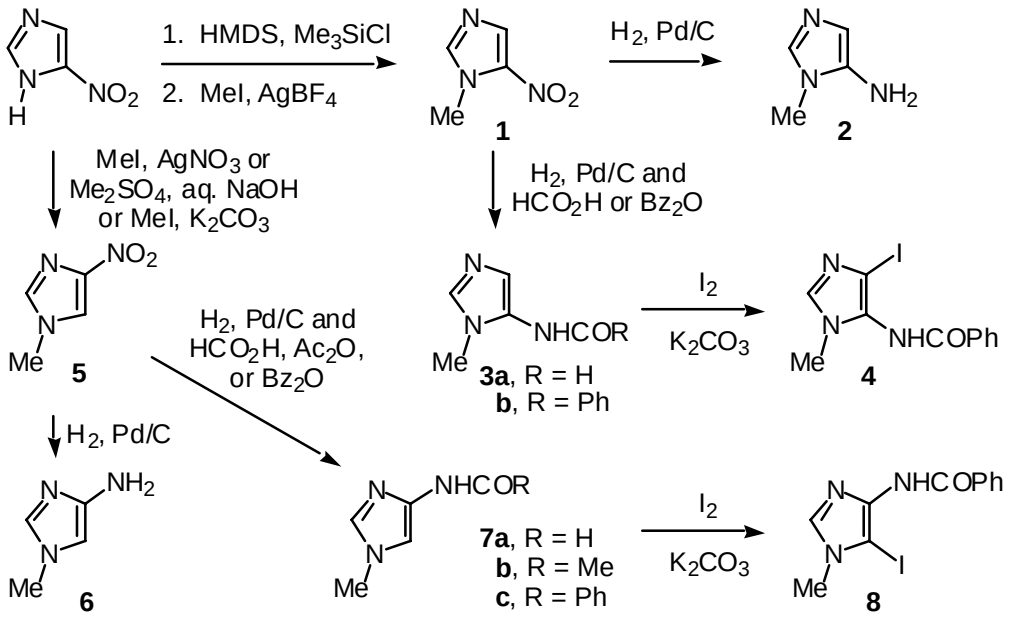
Imidazoles and their benzo derivatives are key components in a great many bioactive compounds of both natural and synthetic origin. In the imidazole class, nucleosides of amino derivatives are well known for their biological activity. Examples include 5-aminoimidazole ribonucleotide, a key intermediate on the *de novo* purine biosynthetic pathway [1] and 5-(formylamino)imidazole ribonucleoside, a competitive inhibitor of adenosine deaminase we have recently studied [2]. In the benzimidazole class, it is the nucleosides of halogeno derivatives that are becoming well known as bioactive compounds. For example, some of the (poly)halogenated benzimidazole nucleosides are potent antiviral agents [3-6], while others have been found to inhibit casein kinase [7]. One part of our program to develop new bioactive imidazole- and benzimidazole-based heterocycles and nucleosides focuses on 4(5)-aminoimidazoles and 5(6)-amino-

benzimidazoles equipped with a variable substituent *ortho* to the amino group. Although methodologies related to the preparation of the former [8-11] and the latter [12-15] do exist, we found there is clearly a need for wider regioselective access to both. To this end, *ortho*-halogenated 4- and 5-(acylamino)imidazoles and 5- and 6-(acylamino)benzimidazoles would be extremely useful, since these heterocycles could be used to prepare *ortho*-substituted aminoimidazoles and aminobenzimidazoles along a route like that developed by Sharp for the C-functionalization of aromatic tosyl-hydrazones [16]. In this approach, an amidate anion is generated (*e.g.*, with MeLi) and is used to direct a halogen-metal exchange (*e.g.*, with BuLi or EtMgBr), and then an *ortho* functionalization is effected by reacting the resulting dianion with an electrophile. By carefully controlling the reaction conditions, all of this can be accomplished even while the (benz)imidazole C2 position remains unprotected [17-20]. Simple deacylation would afford the desired *ortho*-substituted amino(benz)imidazoles. Herein, we report the synthesis of *ortho*-halogenated 4- and 5-(acylamino)imidazoles and 5- and 6-(acylamino)benzimidazoles suitable for use in just such a synthetic strategy.

Results and Discussion

The regioselective synthesis of *ortho*-halogenated 4- and 5-(acylamino)imidazoles is shown in Scheme 1. 1-Methyl-5-nitroimidazole (**1**) was prepared from 4(5)-nitro-imidazole by a new regioselective route we developed using a $AgBF_4$-assisted methyl-ation of 4-nitro-1-(trimethylsilyl)imidazole. This two-step, one-pot route gave **1** in a 68% overall yield—higher than other methods reported to date. We then used Ramsden's procedure [9] to reduce **1** to the air(oxidation)-sensitive amine **2** (97%). Attempts at *N*-acylating the enamine **2** did not proceed smoothly, and so instead we accessed the 5-(formylamino)- and 5-(benzoylamino)imidazoles **3a,b** directly from **1** via catalytic hydrogenation in the presence of the acylating agents HCO_2H and Bz_2O, respectively. Benzamide **3b** was then subjected to electrophilic iodination, which proceeded regioselectively to give the iodo-benzamide **4**.

Scheme 1



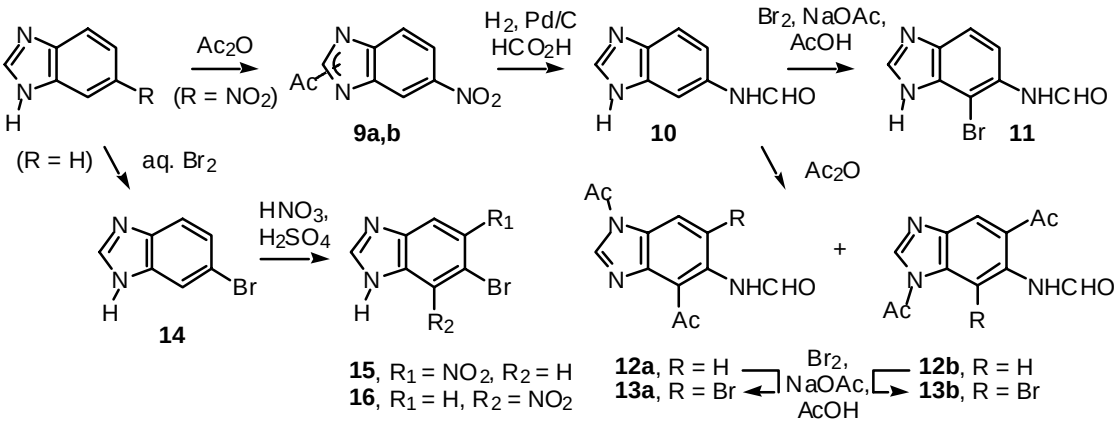
For the isomeric acylaminoimidazole, three methods for preparing the known 1-methyl-4-nitroimidazole (**5**) were examined. The first one employed the same silver 4(5)nitroimidazolide [21] that was reported to give a 1.6:1 mixture of 1-alkyl-5-nitro- and 1-alkyl-4-nitroimidazoles when condensed with 2,3,5-tri-*O*-acetylribofuranosyl bromide [22]. Using iodomethane in this procedure, we obtained **5** in a 41% yield. An alternative alkylation approach employing Me_2SO_4 and aq. NaOH [23] also gave predominantly **5**, in surprising contrast to a published report [24]. Finally, methylation with iodomethane using K_2CO_3 in dry DMF proceeded well, and gave **5** in a 70% yield. Catalytic hydrogenation of **5** gave the corresponding amine **6**, which like **2** could not be directly *N*-acylated in an efficient manner. Therefore, the formamide, acetamide, and benzamide derivatives **7a-c** were prepared by catalytic hydrogenation of **5** in the presence of the appropriate acylating agent (HCO_2H, Ac_2O, and Bz_2O, respectively). As with **3a**, electrophilic iodination proceeded regioselectively, giving iodo-benzamide **8**. The *ortho*-halogeno 4- and 5-(acylamino)imidazoles like **4** and **8** and their variants are ready for use in directed halogen-metal exchange-based functionalizations.

Similar regioselective access to *ortho*-halogeno 5- and 6-(acylamino)benzimidazoles is complicated by the fact that there is more than one *ortho* position activated for

electrophilic halogenation. Benzimidazoles are commonly synthesized from substituted benzenes by imidazole ring annelation. For instance, they can be prepared by oxidative cyclization of *N*-arylamidines [12,13] or from diaminobenzenes [15]. These routes, though, are not readily adapted to the preparation of acylamino-equipped compounds. Although 5(6)-formylamino-substituted benzimidazoles have been prepared by an annelation route [14,25-27] and some have even been converted to their corresponding nucleosides [28], none are suitable for halogen-metal exchange reactions because they are fluorinated.

We explored access to *ortho*-halogeno 5- and 6-(acylamino)benzimidazoles involving the manipulation of functional groups on preformed benzimidazoles. As shown in Scheme 2, 5(6)-nitrobenzimidazole was acetylated to a mixture of isomers **9a,b**, which was directly hydrogenated in HCO_2H to give 5(6)-(formylamino)benzimidazole (**10**, 70%). Formamide **10** underwent smooth regioselective electrophilic bromination to give 4(7)-bromo-5(6)-(formylamino)benzimidazole (**11**, 75%). After protection of the imidazole ring with, for instance, a trityl group, heterocycle **11** will be suitable for directed halogen-metal exchange-based functionalization.

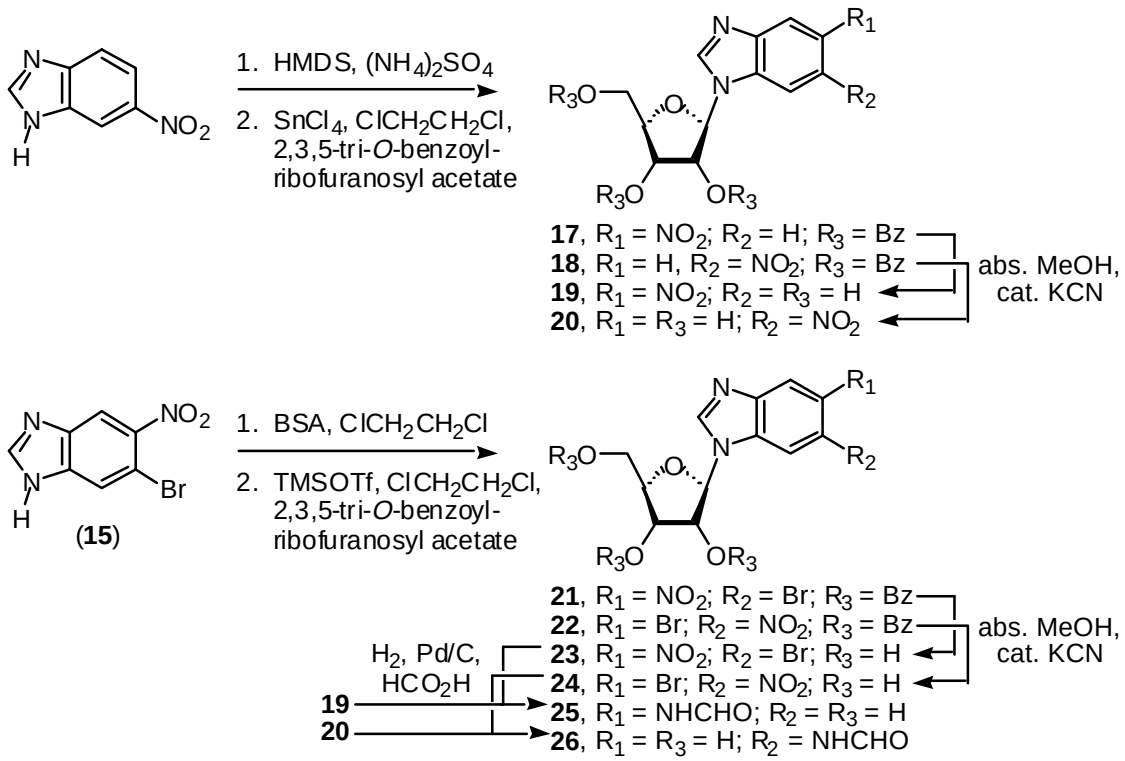
Scheme 2



Non-regioselective *ortho*-activation by the formylamino group was encountered next when we subjected **10** to acetylation. This gave a mixture of 1,4-diacetyl-5- and 1,5-diacetyl-6-(formylamino)benzimidazoles (**12a,b**). Even though benzimidazole itself is

known to undergo facile dinitration [29], the ease with which diacetylation occurred was somewhat surprising. Electrophilic bromination of the **12a,b** mixture in

Scheme 3



buffered AcOH gave the isomeric 6-bromo-1,4-diacetyl-5- and 7-bromo-1,5-diacetyl-6-(formylamino)benzimidazoles (**13a,b**), but the presence of the acetyl groups in these likely precludes their use in directed halogen-metal exchange reactions. Bromination of benzimidazole (60%) followed by nitration afforded a readily separated mixture of 5-bromo-6-nitro- and 5-bromo-4-nitrobenzimidazole (**15** and **16**, respectively). Since the former had an attractive substitution pattern, we chose it to for an exploration of nucleoside syntheses (Scheme 3).

In an initial effort, 5(6)-nitrobenzimidazole was silylated with HMDS and $(NH_4)_2SO_4$ and then was condensed with 2,3,5-tri-*O*-benzoylribofuranosyl acetate to give the protected nucleosides **17** and **18**. These were easily separated and deprotected (CH_3OH, cat. KCN) [30] to the corresponding ribosides **19** and **20**. Next, under slightly different conditions [6], BSA was used to trimethylsilylate **15** for condensation with the same ribofuranosyl acetate, this time in the presence of TMSOTf. The mixture of

isomers **21** and **22** obtained was not easily separated, and so it was deblocked to give a mixture of the ribosides **23** and **24**. Catalytic hydrogenation of these in formic acid gave only the halogen-less formamides **25** and **26**, also obtained from nucleosides **19** and **20** using the same procedure. Interestingly, the halogen atom in both 5-bromo-1-ethyl-6-nitrobenzimidazole and its 6-bromo-1-ethyl-5-nitro isomer is reportedly inert to metalation with BuLi or K metal [31]. As evidenced by the conversions of **23/24** to **25/26**, though, this type of halogen does not survive catalytic hydrogenation. Still, other non-Pd-based conditions for nitro group reductive-acylation can be applied to the task of converting **23/24** to their *ortho*-bromo (acylamino)-substituted counterparts, and then appropriate aglycon-protected versions of these can be used in the halogen-metal exchange-based ring functionalizations of interest.

Experimental

Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. Preparative (flash) column chromatography was performed using Merck silica gel-60 (200-430 ASTM), and radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA) using Merck silica gel-60 PF254 as adsorbent. Thin-layer chromatography (TLC) employed 250 micron silica gel-GF Analtech Uniplates illuminated by short-wave (254 nm) UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 or VXR-500 spectrometer using $(CH_3)_4Si$ (δ = 0.0 for ^{1}H), $CDCl_3$ (δ = 7.26 for ^{13}C), or $(CD_3)_2SO$ (δ = 39.5 for ^{13}C) as internal references. Moisture-sensitive reactions were conducted in flame-dried, argon-purged glassware. 5(6)-Nitrobenzimidazole, benzimidazole, *N,O*-bis(trimethylsilyl)acetamide (BSA), Bz_2O, $SnCl_4$, BH_3 in THF, trimethylsilyltriflate (TMSOTf), $AgBF_4$, and 10% Pd/C were purchased from Aldrich. Royer palladium catalyst beads (1% Pd on polyethyleneimine/SiO_2) were obtained from GFS Chemicals. 4(5)-Nitroimidazole was purchased from Acros, and 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-D-ribose was purchased from Pfanstiehl Laboratories. 1,4-Dioxane, Et_2O, and THF were each dried by distillation from Na(s) under argon using benzophenone ketyl as indicator. 1,2-Dichloroethane, CH_2Cl_2, and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were each

dried by distillation from CaH_2 under argon. CH_3OH was dried by distillation from $Mg(OCH_3)_2$ under argon, and both CH_3I and Ac_2O were freshly distilled from P_2O_5 under argon immediately before use. Anhydrous AcOH was prepared by distilling glacial AcOH from tetraacetoxydiborate prepared by heating $B(OH)_3$ in Ac_2O. Anhydrous HCO_2H was prepared by distilling 97% HCO_2H from B_2O_3. Some compounds were characterized solely on the basis of their NMR or mass spectral characteristics. Like the 5-(formylamino)imidazole ribonucleoside we studied earlier [2], many of the acylamino compounds reported herein were slowly interconverting *E* and *Z* amide rotamers in solution, determined by NMR.

1-Methyl-5-nitroimidazole (1). A suspension of 4(5)-nitroimidazole (1.13 g, 10 mmol) in 100 mL of HMDS containing 1 mL of $(CH_3)_3SiCl$ was heated at reflux under argon overnight. The volatiles were removed *in vacuo* to give 4-nitro-1-(trimethylsilyl)imidazole as a hygroscopic white solid: ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1H, H2), 7.49 (s, 1H, H4), 0.57 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 139.4 (C2), 121.4 (C4), 0.02 ($Si(CH_3)_3$). This was dissolved directly in 15 mL of anhyd. CH_3I, and $AgBF_4$ (1.95 g, 10 mmol) was added all at once to the solution. Although the reaction was likely complete earlier, the mixture was stirred at 23 °C for 10 h. The volatiles were removed by rotary evaporation, and the product was extracted from the residue with CH_2Cl_2. The extracts were combined and rotary evaporated to a yellow solid which was purified by column chromatography (15% CH_3OH/CH_2Cl_2 as eluent) to give 852 mg (68%) of **1** as yellow crystals: mp 48-53 °C (lit. [9,11] 53-55 °C). ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H, H2), 7.49 (s, 1H, H4), 3.94 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.5 (C2), 133.0 (C4), 35.1 (CH_3). Anal. Calcd. for $C_4H_5N_3O_2$•1/3H_2O: C, 36.09; H, 4.29; N, 31.57. Found: C, 36.19; H, 4.15; N, 31.53.

5-Amino-1-methylimidazole (2). [9,11] A solution of **1** (264 mg, 2 mmol) in 25 mL of anhyd. 1,4-dioxane was treated with 150 mg of 10% Pd/C and was stirred under 1 atm of H_2 for 6 h. The mixture was filtered through Celite and the filtrate was rotary evaporated to dryness to give 190 mg (97%) of **2** as a hygroscopic, air-sensitive grey powder with NMR spectral properties closely matching literature values: ^{1}H NMR

($(CD_3)_2SO$) δ 7.04 (s, 1H, H2), 6.01 (s, 1H, H4), 4.43 (bs, exchanges upon addition of D_2O, 2H, NH_2), 3.34 (s, 3H, CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ 138.3 (C2), 136.7 (C5), 110.4 (C4), 29.8 (CH_3).

5-(Formylamino)-1-methylimidazole (3a). A solution of **1** (700 mg, 5.51 mmol) in 25 mL of anhyd. HCO_2H was treated with 100 mg of 10% Pd/C and the mixture was stirred under 1 atm of H_2 overnight. The catalyst was removed by suction filtration and the solution was rotary evaporated to dryness under vacuum. The dark brown oil obtained was purified by column chromatography (10% CH_3OH/CH_2Cl_2 as eluent) to give 500 mg (70%) of **3a**, found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution: ^1H NMR ($(CD_3)_2SO$) δ 10.00 (bs, exchanges upon addition of D_2O, 1H, NH major), 9.65 (d, *J* = 10 Hz, exchanges upon addition of D_2O, 1H, NH minor), 8.24 (s, 1H, CHO major), 8.08 (d, *J* = 10 Hz, 1H, CHO minor), 7.45 (s, 1H, H2 major), 7.53 (s, 1H, H2 minor), 6.81 (s, 1H, H4 major), 6.79 (s, 1H, H4 minor), 3.46 (s, 3H, CH_3 major), 3.32 (s, 3H, CH_3 minor).

5-(Benzoylamino)-1-methylimidazole (3b). This was prepared from **1** by the procedure used to prepare **7c** from **5**: ^1H NMR ($(CD_3)_2SO$) δ 10.05 (bs, exchanges upon addition of D_2O, 1H, NH), 7.97 (d, *J* = 8 Hz, 2H, *o*-PhH), 7.61-7.47 (m, 4H, *m*-PhH, *p*-PhH, and H2), 7.00 (s, 1H, H4), 3.62 (s, 3H, CH_3). Low-resolution DCI mass spectrum, *m/z* 201 (MH^+), 219 (MNH_4^+).

5-(Benzoylamino)-4-iodo-1-methylimidazole (4). This was prepared from **3b** by the procedure used to prepare **8** from **7c**: ^1H NMR ($(CD_3)_2SO$) δ 10.0 (bs, exchanges upon addition of D_2O, 1H, NH), 7.97 (d, *J* = 8 Hz, 2H, *o*-PhH), 7.71 (s, 1H, H2), 7.58 (pseudo-q, 1H, *p*-PhH), 7.50 (pseudo-t, 2H, *m*-PhH), 3.62 (s, 3H, CH_3).

1-Methyl-4-nitroimidazole (5). Using $AgNO_3$ and CH_3I. In a modification of literature procedures [21,22], a stirred solution of 3.0 g (26.5 mmol) of 4(5)-nitroimidazole in a mixture of 40 mL of concd. aq. NH_4OH and 21 mL of EtOH was treated with a warm solution of 5.4 g (31.8 mmol, 1.2 equiv) of $AgNO_3$ in 75 mL of EtOH. After 15 min, the precipitated silver nitroimidazolide was collected by suction filtration and was washed with EtOH and dried overnight *in vacuo*. A suspension of this salt in 50 mL of

dry benzene was treated with 2 mL of freshly distilled CH_3I and the mixture was heated at reflux for 24 h, during which time two additional 2 mL portions of CH_3I were added at 8 h intervals. The benzene and the unreacted CH_3I were removed by distillation, and the residue was extracted with 200 mL of hot water. The aqueous solution was rotary evaporated to a solid, which was recrystallized from water and then purified by column chromatography (5% CH_3OH/CH_2Cl_2 as eluent) to afford 1.38 g (41%) of **5** as a yellow solid: mp 130-132 °C (lit. [21] 133-134 °C). ^{1}H NMR ($(CD_3)_2SO$) δ 8.40 (s, 1H, H2), 7.80 (s, 1H, H5), 3.79 (s, 3H, CH_3).

Using Me_2SO_4 and aq. NaOH. In a modification of another literature procedure [23,24], a solution of 4(5)-nitroimidazole (6.0 g, 53 mmol) and 60 mL of 10% aq. NaOH at 5 °C was treated dropwise with 0.56 mL (1.5 equiv.) of Me_2SO_4 and the mixture was stirred at 23 °C for 2 h. The pH of the solution was adjusted to 7 by the addition of cold dilute aq. HCl, and the solution was reduced to a small volume by rotary evaporation. The precipitate was collected by filtration and then purified by column chromatography (5% CH_3OH/CH_2Cl_2 as eluent) to give a 9:1 mixture of **5** and **1**, by ^{1}H NMR. This ratio is the exact opposite of that reported by Benjes and Grimmett [24].

Using MeI and K_2CO_3. A solution of dry 4(5)-nitroimidazole (5.23 g, 46.2 mmol) in 120 mL of dry DMF was treated with 65 g of powdered K_2CO_3 and then was stirred vigorously while 3.39 mL (54 mmol) of iodomethane was added dropwise via syringe. After 22 h of continued stirring at 23 °C, the mixture was suction filtered through 0.5 g of Celite and the filter cake was washed with additional dry DMF. The DMF solutions were combined and rotary evaporated *in vacuo* at 40 °C to a yellow-white solid which was purified by column chromatography (20% CH_3OH/CH_2Cl_2 as eluent to give a 4:1 mixture of **5** and **1** in a 92% yield. The latter was removed from the mixture by trituration with water, giving **5** in a 70% yield: mp 133-135 °C.

4-Amino-1-methylimidazole (6). The 9:1 mixture of **5**/**1** from above was reduced with 1 atm of H_2 overnight using 10% Pd/C in 1,4-dioxane to give **6** in a 60% yield. ^{1}H NMR ($(CD_3)_2SO$) δ 7.09 (s, 1H, H2), 6.10 (s, 1H, H5), 4.41 (bs, exchanges upon

addition of D_2O, 2H, NH_2), 3.49 (s, 3H, CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ 147.2 (C4), 133.3 (C2), 100.1 (C5), 32.9 (CH_3).

4-(Formylamino)-1-methylimidazole (7a). A solution of **5** (500 mg, 3.9 mmol) in 20 mL of 97% HCO_2H (20 mL) was treated with 250 mg of Pd/C and was stirred under 1 atm of H_2 overnight. The solution was rotary evaporated *in vacuo* to give **7a** as a dark brown oil, found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution. ^1H NMR ($(CD_3)_2SO$) δ 10.38 (s, exchanges with D_2O, 1H, NH major), 9.88 (s, exchanges with D_2O, 1H, NH minor), 8.50 (d, 1H, CHO minor), 8.09 (s, 1H, CHO major), 7.41 (s, 1H, H2 minor), 7.38 (s, 1H, H2 major), 7.19 (s, 1H, H5 major), 6.79 (s, 1H, H5 minor), 3.59 (s, 3H, CH_3 major), 3.40 (s, 3H, CH_3 minor).

4-(Acetylamino)-1-methylimidazole (7b). A solution of **5** (890 mg, 7.0 mmol) in 35 mL of Ac_2O was treated with 372 mg of 10% Pd/C and two drops of AcOH and was stirred under 1 atm of H_2 overnight. The catalyst was removed by filtration, washed with Ac_2O, and the filtrate and washing were combined and were rotary evaporated to give **7b**, found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution. ^1H NMR ($(CD_3)_2SO$) δ 10.2 (s, exchanges with D_2O, 1H, NH major), 9.66 (s, exchanges with D_2O, 1H, NH minor), 7.34 (s, 3H, H2 major, H2 minor, and H5 minor), 7.14 (s, 1H, H5 major), 3.59 (s, 3H, NCH_3 major), 3.40 (s, 3H, NCH_3 minor), 1.96 (s, 3H, $COCH_3$ minor), 1.89 (s, 3H, $COCH_3$ major). ^{13}C NMR ($(CD_3)_2SO$) δ 172.2 (C=O), 168.0 (C=O), 167.1, 166.4, 138.1, 133.6, 129.8, 122.3, 107.4 (C5), 33.1 (CH_3), 30.4 (CH_3), 21.3 (CH_3), 20.3 (CH_3).

4-(Benzoylamino)-1-methylimidazole (7c). A solution of **5** (2.0 g, 15.7 mmol) in 90 mL of dry 1,4-dioxane was treated with Bz_2O (5 g, 22.1 mmol) and 1.2 g 10% Pd/C, and the mixture was stirred under 1 atm of H_2 at 23 °C for 48 h. The catalyst was removed by suction filtration and the filtrate was rotary evaporated to a brown oil. A solution of this oil in CH_2Cl_2 was washed with satd. aq. $NaHCO_3$, and the organic soluble fraction was purified by column chromatography (4% CH_3OH/CH_2Cl_2 as eluent) to give 1.9 g (60%) of **7c**: mp 169-171 °C (EtOH). ^1H NMR ($CDCl_3$) δ 11.34 (bs, exchanges upon addition of D_2O, 1H, NH), 7.98-7.95 (m, 2H, *m*-PhH), 7.55-7.43 (m, 4H, *o*-PhH,

p-PhH, and H5), 6.78 (s, 1H, H2), 3.61 (s, 3H, CH_3); ($(CD_3)_2SO$) δ 10.71 (bs, exchanges upon addition of D_2O, 1H, NH), 8.01 (dd, *J* = 8.1, 1.8 Hz, 2H, *o*-PhH), 7.56-7.44 (m, 4H, *m*-PhH, *p*-PhH, and H2), 7.39 (s, 1H, H5), 3.66 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 165.2 (C=O), 138.8 (C2), 135.0 (*ipso*-PhC), 133.3 (C2), 131.2 (*p*-PhC), 128.2 (*o*-PhC), 127.7 (*m*-PhC), 108.7 (C5), 33.7 (CH_3). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.53; H, 5.52; N, 20.79.

4-(Benzoylamino)-5-iodo-1-methylimidazole (8). A solution of **7c** (503 mg, 2.5 mmol) in 25 mL of CH_2Cl_2 was treated with 3.5 g of K_2CO_3 and stirred vigorously at 23 °C while one equivalent of I_2 dissolved in Et_2O was added dropwise. The reaction mixture was stirred at 23 °C for 2 h, and then it was passed through a short pad of SiO_2 using 10% CH_3OH/CH_2Cl_2 as eluent. The solution collected was rotary evaporated to a dark brown oil that was separated by column chromatography to give **8** and of **7c** (200 mg). Recrystallization of the former from CH_2Cl_2 gave 245 mg (30%, 50% based upon unrecovered **7c**) of **8**: mp 176-177 °C. ^{1}H NMR ($(CD_3)_2SO$) δ 9.96 (bs, exchanges upon addition of D_2O, 1H, NH), 7.95-7.97 (m, 2H, *m*-PhH), 7.86 (s, 1H, H2), 7.50-7.56 (m, 3H, *o*-PhH, *p*-PhH), 3.59 (s, 3H, CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ 165.0 (C=O), 140.5 (C4), 138.0 (C2), 131.6 (*p*-PhC), 128.3 (*o*-PhC), 127.6 (*m*-PhC), 98.0 (C5), 35.2 (CH_3). Low-resolution DCI (direct chemical ionization) mass spectrum, m/z 328 (MH^+). Anal. Calcd. for $C_{11}H_{10}IN_3O$: C, 40.39; H, 3.08; N, 12.85. Found: C, 39.71; H, 3.00; N, 12.46.

1-Acetyl-5- and 6-nitrobenzimidazoles (9a,b). A solution of 5(6)-nitrobenzimidazole (16.3 g, 0.1 mol) in 200 mL of Ac_2O was stirred at 23 °C for 48 h. The white precipitate produced (10.8 g) and the pale yellow powder obtained by rotary evaporation of the filtrate (9.1 g) both proved to be a mixture of **9a,b** (97% combined) by TLC (5% CH_3OH/CH_2Cl_2) and NMR. **9a**: ^{1}H NMR ($(CD_3)_2SO$) δ 9.13 (s, 1H, H2), 8.54 (d, *J* = 1.2 Hz, 1H, H4), 8.22-8.29 (m, 1H, H6), 7.95 (d, *J* = 8.8 Hz, 1H, H7), 2.80 (s, 3H, CH_3). **9b**: ^{1}H NMR ($(CD_3)_2SO$) δ 9.20 (s, 1H, H2), 8.88 (d, *J* = 2.2 Hz, 1H, H7), 8.22-8.29 (m, 2H, H4, H5), 2.80 (s, 3H, CH_3).

5(6)-(Formylamino)-benzimidazole (10). A solution of the isomeric mixture of **9a,b** (19 g) in 200 mL of anhyd. HCO_2H was treated with 1.0 g of 10% Pd/C and the mixture was stirred under 1 atm of H_2 overnight. The catalyst was removed by suction filtration and the filtrate was rotary evaporated to a brown oil that was purified by a short column chromatography (15-20% CH_3OH/CH_2Cl_2 as eluent) to afford 10 g (70%) of pure **10**, found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution. ^1H NMR ($(CD_3)_2SO$) δ 10.25 (bs, exchanges upon addition of D_2O, 1H, NH major), 10.15 (d, *J* = 10 Hz, exchanges upon addition of D_2O, 1H, NH minor), 8.78 (d, *J* = 11 Hz, 1H, CHO minor), 8.25 (s, 1H, CHO major), 8.19 (s, 1H, H2), 8.11 (d, *J* = 1.8 Hz, H4 major), 7.58 (d, *J* = 8.7 Hz, H7), 7.45 (d, *J* = 1.8 Hz, H4 minor), 7.30 (dd, *J* = 8.6, 2.0 Hz, H6 major), 7.09 (dd, *J* = 8.6, 2.0 Hz, H6 minor). Low-resolution DCI mass spectrum, *m/z* 162 (MH^+).

4-Bromo-5-(formylamino)-benzimidazole (11). A solution of **10** (1.57 g, 10 mmol) and NaOAc (3 g, 36 mmol) in 20 mL of anhyd. AcOH was treated dropwise with Br_2 (0.51 mL, 10 mmol). The brown precipitate produced was collected by filtration and was dried *in vacuo* to afford 1.78 g (75%) of **11**, found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution: ^1H NMR ($(CD_3)_2SO$) δ 10.73 (bs, exchanges upon addition of D_2O, 1H, NH major), 10.22 (d, *J* = 11 Hz, exchanges upon addition of D_2O, 1H, NH minor), 9.57 (s, 1H, CHO major), 8.90 (d, *J* = 11 Hz, 1H, CHO minor), 8.39 (s, 1H, H2), 7.85 (d, *J* = 9 Hz, 1 H, H7), 7.60 (d, *J* = 8.9 Hz, 1H, H6).

1,4-Diacetyl-5- and 1,5-Diacetyl-6-(formylamino)-benzimidazoles (12a,b). A solution of **10** (3.2 g, 20 mmol) in 15 mL of Ac_2O was heated at reflux for 2 h, at which time **10** had been consumed, by TLC. The volatiles were removed by rotary evaporation to leave a mixture of **12a,b** as a brown solid. **12a**: ^1H NMR ($(CD_3)_2SO$) δ 9.45 (s, 1H, CHO), 8.97 (s, 1H, H2), 8.22 (d, *J* = 8.4 Hz, 1H, H7), 7.70 (s, 1H, H4), 7.28 (m, 2 H, H6), 2.26 (s, 3H, CH_3); **12b**: ^1H NMR ($(CD_3)_2SO$) δ 9.41 (s, 1H, CHO), 8.97 (s, 1H, H2), 8.05 (s, 1H, H4), 7.83 (d, *J* = 8.4 Hz, 1H, H7), 7.28 (m, 2 H, H6), 2.20 (s, 3H, CH_3). Low-resolution DCI mass spectrum, *m/z* 246 (MH^+).

6-Bromo-1,4-diacetyl-5- and 7-Bromo-1,5-diacetyl-6-(formylamino)-benzimidazoles (13a,b). A solution of **12a,b** (320 mg, 1.6 mmol) and NaOAc (394 mg, 4.8 mmol) in 3 mL of anhyd. AcOH was treated dropwise with Br_2 (82 μL, 1.6 mmol). The reaction mixture was stirred at 23 °C for 2 h. The volatiles were removed under vacuum, and the brown solid residue was purified by column chromatography (5-10% CH_3OH/CH_2Cl_2 as eluent) to afford **13a,b**: ^{1}H NMR ($(CD_3)_2SO$) δ 9.95 (s, 1H, CHO minor), 9.48 (s, 1H, CHO major), 8.36 (s, 2H, H2 major), 8.18 (s, 1H), 8.10 (s, 1H, H2 minor), 7.65 (d, 1H), 7.54 (d, 1H), 7.25 (dd, 1H), 7.05 (dd, 1H), 2.25-2.20 (four s, each 3H, each CH_3).

5(6)-Bromobenzimidazole (14). [25] A solution of Br_2 (260 μL) in 60 mL of water was added dropwise to a suspension of benzimidazole (600 mg, 5 mmol) in a solution of 2 g of KOAc in 50 mL of H_2O. The resulting white suspension was stirred at 23 °C overnight, and then was extracted with CH_2Cl_2. The combined organic layers were washed with satd. aq. NaCl and then were dried ($MgSO_4$). Rotary evaporation afforded 590 mg (60%) of **14** as a foam. ^{1}H NMR ($(CD_3)_2SO$) δ 8.28 (s, 1H, H2), 7.80 (s, 1H, H4), 7.55 (d, J = 8.6 Hz, 1H, H6), 7.31 (d, J = 8.5 Hz, 1H, H7). Low-resolution DCI mass spectrum, *m/z* 197 (MH^+).

5-Bromo-6-nitro- and 5-bromo-4-nitrobenzimidazole (15 and 16). [15] A solution of **14** (590 mg, 3 mmol) in 1 mL of 98% H_2SO_4 at 0 °C was treated dropwise with a solution of 0.1 mL of conc. HNO_3 in 1 mL of 98% H_2SO_4 [32]. The reaction mixture was stirred at 0-5 °C for 2 h, and then it was poured into an ice/water mixture. The pH of the mixture was adjusted to 8 by the addition of conc. NH_4OH, and the precipitate which formed was collected by suction filtration and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with satd. aq. NaCl and was dried ($MgSO_4$). The residue obtained by rotary evaporation of this was combined with the original precipitate, and the crude product mixture was purified by column chromatography (5-10% CH_3OH/CH_2Cl_2 as eluent) to afford **15** and **16** separately. **15**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.53 (s, 1H, H2), 8.35 (s, 1H, H4), 8.06 (s, 1H, H7). Low-resolu tion DCI mass spectrum, *m/z* 242/244 (MH^+); **16**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.47 (s, 1H, H2), 7.82

(d, *J* = 8.4 Hz, 1H, H6), 7.62 (d, *J* = 8.4 Hz, 1H, H7). Low-resolution DCI mass spectrum, *m/z* 242/244 (MH^+).

5- and 6-Nitro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-benzimidazoles (17 and 18). 5(6)-Nitrobenzimidazole (3.26 g, 20 mmol) was suspended in 60 mL of HMDS, 60 mg of $(NH_4)_2SO_4$ was added, and the reaction mixture was heated at reflux overnight, at which time most of the starting material had dissolved. The HMDS was removed by distillation, and white solid residue was dissolved in 100 mL of freshly distilled dichloroethane. This was treated with 1-acetyl-2,3,5-tribenzoylribofuranose (10.08 g, 20 mmol) and $SnCl_4$ (3-4 mL), and the reaction mixture was stirred at 23 °C overnight. The reaction mixture was treated with 250 mL of $CHCl_3$ and the organic phase was washed with satd. aq. $NaHCO_3$ solution thrice, and then with satd. aq. NaCl solution twice. The organic layer was dried (Na_2SO_4) and rotary evaporated *in vacuo* to a yellow foam. Column chromatography (0.5-0.75% CH_3OH/CH_2Cl_2) gave a mixture of **17** and **18**, which were separated by radial chromatography (1:1 EtOAc/hexanes as eluent). **17**: mp 88-93 °C. ^{1}H NMR ($(CD_3)_2SO$) δ 8.91 (s, 1H, H2), 8.59 (s, 1H, H4), 8.04-7.42 (m, 17H, H6, H7, and three Ph), 6.82 (d, 1H, H1'), 6.15 (m, 1H, H2'), 6.05 (m, 1H, H3'), 4.95 (m, 1H, H4'), 4.85 (m, 2H, 5'CH_2). Anal. Calcd. for $C_{33}H_{25}N_3O_9$: C, 65.24; H, 4.15; N, 6.92. Found: C, 65.05; H, 4.19; N, 6.66. **18**: mp 91-95 °C. ^{1}H NMR ($(CD_3)_2SO$) δ 9.00 (s, 1H, H2), 8.88 (s, 1H, H4), 8.20-7.46 (m, 17H, H6, H7, and three Ph), 6.95 (d, 1H, H1'), 6.20 (m, 1H, H2'), 6.05 (m, 1H, H3'), 4.95 (m, 1H, H4'), 4.83 (m, 2H, 5'CH_2). Anal. Calcd. for $C_{33}H_{25}N_3O_9$: C, 65.24; H, 4.15; N, 6.92. Found: C, 65.48; H, 4.19; N, 5.94.

5-Nitro-1-(β-D-ribofuranosyl)-benzimidazole (19). A suspension of **15** (300 mg) in 10 mL of CH3OH was treated with KCN (18 mg) [30] and the reaction mixture was stirred at 23 °C for 6 h, at which time no starting material remained, by TLC. The volatiles were removed by rotary evaporation, and the residue was purified by a column chromatography (15% CH_3OH/CH_2Cl_2 as eluent) to afford 138 mg (95%) of **19**: mp 191-192 °C. ^{1}H NMR ($(CD_3)_2SO$) δ 8.78 (s, 1H, H2), 8.55 (d, 1H, H4), 8.17 (dd, 1H, H7), 7.96 (d, 1H, H6), 5.98 (d, 1H, H1'), 5.55 (m, exchanges upon addition of D_2O, 1H,

OH), 5.27 (m, exchanges upon addition of D_2O, 1H, OH), 5.18 (m, exchanges upon addition of D_2O, 1H, OH), 4.37 (m, 1H, H2'), 4.14 (m, 1H, H3'), 4.02 (m, 1H, H4'), 3.66 (m, 2H, 5'CH_2). Low-resolution DCI mass spectrum, *m/z* 296 (MH^+). Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.23; H, 4.45; N, 13.88.

6-Nitro-1-(β-D-ribofuranosyl)-benzimidazole (20). This nucleoside was prepared from **18** by the method described above: mp 168-170 °C. ^{1}H NMR ($(CD_3)_2SO$) δ 8.85 (s, 1H, H2), 8.83 (d, 1H, H7), 8.15 (dd, 1H, H5), 7.86 (d, 1H, H7), 6.04 (d, 1H, H1'), 5.60 (m, exchanges upon addition of D_2O, 1H, OH), 5.26 (m, exchanges upon addition of D_2O, 2H, two OH), 4.40 (m, 1H, H2'), 4.15 (m, 1H, H3'), 4.05 (m, 1H, H4'), 3.70 (m, 2H, 5'CH_2). Low-resolution DCI mass spectrum, *m/z* 296 (MH^+). Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.69; H, 4.36; N, 14.00.

6-Bromo-5-nitro- and 5-Bromo-6-nitro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-benzimidazoles (21 and 22). Adapting a published procedure [6], a suspension of **15** (1.93 g, 8 mmol) in 40 mL of dichloroethane was treated dropwise with 2 mL of BSA, and the resulting yellow suspension was heated at 70-80 °C for 20 min, giving a clear solution. The reaction mixture was allowed to cool to 23 °C, and then was treated with 1-acetyl-2,3,5-tribenzoylribofuranose (4.43 g, 8.8 mmol) and TMSOTf (1.86 mL, 10.5 mmol). The reaction mixture was stirred at 23 °C overnight, at which point no starting material remained, by TLC. The reaction mixture was diluted with 100 mL of $CHCl_3$ and the organic solution was washed 3 times with satd. aq. $NaHCO_3$, 2 times with satd. aq. NaCl, and then was dried (Na_2SO_4). Rotary evaporation gave a yellow foam which was purified by column chromatography (1:1 EtOAc/hexanes as eluent) to give 1.4 g (26%) of a mixture of **21** and **22**. **21**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.92 (s, 1H, H2), 8.46 (s, 1H, H4), 8.43 (s, 1H, H7), 8.00-7.51 (m, 15H, three Ph), 6.82 (d, 1H, H1'), 6.16 (m, 1H, H2'), 6.05 (m, 1H, H3'), 4.92 (m, 1H, H4'), 4.80 (m, 2H, 5'CH_2). **22**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.99 (s, 1H, H2), 8.69 (s, 1H, H7), 8.23 (s, 1H, H4), 8.00-7.51 (m, 15H, three Ph), 6.82 (d, 1H, H1'), 6.16 (m H, H2'), 6.05 (m, 1H, H3'), 4.92 (m, 1H, H4'), 4.80 (m, 2H, 5'CH_2).

6-Bromo-5-nitro- and 5-Bromo-6-nitro-1-(β-D-ribofuranosyl)-benzimidazoles (23 and 24). The mixture of **21** and **22** from above (1.4 g, 2 mmol) was suspended in 20 mL of CH_3OH and 65 mg of KCN was added. The reaction mixture was stirred at 23 ˚C for 6 h, at which time the deprotection was complete, by TLC. The volatiles were removed *in vacuo*, and the residue purified by column chromatography (15% CH_3OH/CH_2Cl_2 as eluent) to give 700 mg (95%) of a mixture of **23** and **24**. **23**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.80 (s, 1H, H2), 8.46 (s, 1H, H4), 8.43 (s, 1H, H7), 6.00 (d, 1H, H1'), 5.60 (m, exchanges upon addition of D_2O, 1H, OH), 5.26 (m, exchanges upon addition of D_2O, 2H, two OH), 4.35 (m, 1H, H2'), 4.15 (m, 1H, H3'), 4.05 (m, 1H, H4'), 3.70 (m, 2H, 5'CH_2). **24**: ^{1}H NMR ($(CD_3)_2SO$) δ 8.76 (s, 1H, H2), 8.71 (s, 1H, H7), 8.21 (s, 1H, H4), 5.98 (d, 1H, H1'), 5.60 (m, exchanges upon addition of D_2O, 1H, OH), 5.26 (m, exchanges upon addition of D_2O, 2H, two OH), 4.35, 1H, H2'), 4.15 (m, 1H, H3'), 4.05 (m, 1H, H4'), 3.70 (m, 2H, 5'CH_2).

5- and 6-(Formylamino)-1-(β-D-ribofuranosyl)-benzimidazoles (25 and 26). [28] A solution of the above mixture of **23** and **24** (300 mg, 0.8 mmol) in 5 mL of anhyd. HCO_2H was treated with 50 mg of 10% Pd/C and then was stirred under 1 atm of H_2 at 23 ˚C overnight. The volatiles were removed *in vacuo*, and the residue was purified by radial chromatography to afford a mixture of **25** and **26**, each of which were found to exist as a mixture of *E* and *Z* amide rotamers in $(CD_3)_2SO$ solution: **25**: ^{1}H NMR ($(CD_3)_2SO$) δ 10.43 (bs, exchanges upon addition of D_2O, 1H, NH major), 10.12 (d, J = 11 Hz, exchanges upon addition of D_2O, 1H, NH minor), 8.75 (d, 1H, CHO minor), 8.40 (s, 1H, CHO major), 8.28 (s, 1H, H2), 8.10 (s, 1H, H7), 7.60 (d, 1H, H4), 7.32 (dd, 1H, H6), 5.78 (d, 1H, H1'), 5.48 (m, exchanges upon addition of D_2O, 1H, OH), 5.26-5.00 (m, exchanges upon addition of D_2O, 2H, two OH), 4.35 (m, 1H, H2'), 4.10 (m, 1H, H3'), 3.97 (m, 1H, H4'), 3.58 (m, 2H, 5'CH_2). **26**: ^{1}H NMR ($(CD_3)_2SO$) δ 10.32 (bs, exchanges upon addition of D_2O, 1H, NH major), 10.08 (d, J = 11 Hz, exchanges upon addition of D_2O, 1H, NH minor), 8.71 (d, 1H, CHO minor), 8.41 (s, 1H, CHO major), 8.26 (s, 1H, H2), 8.06 (s, 1H, H4), 7.67 (d, 1H, H4), 7.38 (dd, 1H, H6), 5.82 (d, 1H, H1'), 5.48 (m, exchanges upon addition of D_2O, 1H, OH), 5.26-5.00 (m, exchanges upon addition of D_2O, 2H, two OH), 4.35 (m, 1H, H2'), 4.10 (m, 1H, H3'), 3.97 (m, 1H, H4'),

3.58 (m, 2H, 5'CH_2). Low-resolution DCI mass spectrum, *m/z* 294 (MH^+). Nucleosides **19** and **20** also gave **25** and **26** when subjected to these conditions.

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Povzetek

Razvili smo regioselektivno sintezo 4- in 5-(acilamino)-1-alkilimidazolov s halogenom na orto mestu. Pripravljene spojine so primerni intermediati za pripravo derivatov bioaktivnih 4- in 5-aminoimidazolov z orto usmerjeno izmenjavo halogen-kovina in sledečo funkcionalizacijo. Pristop smo razširili tudi na derivate benzimidazola in njegove potencialno biološko aktivne nukleozide. Raziskali smo sinteze halogeniranih 5- in 6-(acilamino)-benzimidazolov.