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Structure and Synthesis of 6-(Substituted-imidazol-1-yl)purines: Versatile Substrates for Regiospecific Alkylation and Glycosylation at N9[1]

Minghong Zhong, Ireneusz Nowak, John F. Cannon, and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

morris_robins@byu.edu

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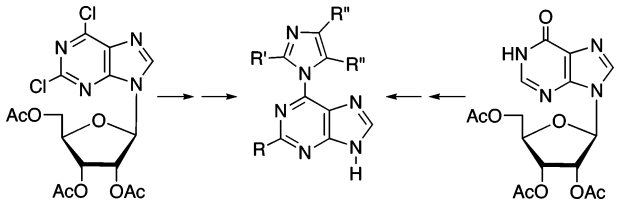

X-ray crystal structures of several 6-(azolyl)purine base and nucleoside derivatives show essentially coplanar conformations of the purine and appended 6-(azolyl) rings. However, the planes of the purine and imidazole rings are twisted ~57° in a 2-chloro-6-(4,5-diphenylimidazol-1-yl)purine nucleoside, and a twist angle of ~61° was measured between the planes of the purine and pyrrole rings in the structure of a 6-(2,5-dimethylpyrrol-1-yl)purine nucleoside derivative. Shielding "above" N7 of the purine ring by a proximal C−H on the 6-azolyl moiety is apparent with the coplanar compounds, but this effect is diminished in those without coplanarity. Syntheses of 6-(azolyl)purines from both base and nucleoside starting materials are described. Treatment of 2,6-dichloropurine with imidazole gave 2-chloro-6-(imidazol-1-yl)purine. Modified Appel reactions at C6 of trityl-protected hypoxanthine and guanine derivatives followed by detritylation gave 6-(imidazol-1-yl)- and 2-amino-6-(imidazol-1-yl)purines. Imidazole was introduced at C6 of 2′,3′,5′-tri-*O*-acetylinosine by a modified Appel reaction, and solvolysis of the glycosyl linkage gave 6-(imidazol-1-yl)purine. Guanosine triacetate was transformed into the protected 2,6-dichloropurine nucleoside, which was subjected to S_NAr displacement with imidazoles at C6 followed by glycosyl solvolysis to provide 2-chloro-6-(substituted-imidazol-1-yl)purines. Potential applications of these purine derivatives are outlined.

Introduction

Alkylation of purines usually results in formation of regioisomeric mixtures.[2] Treatment of 6-substituted- and 2,6-disubstituted-purines with a base such as sodium hydride followed by addition of an alkylating agent normally produces both 7- and 9-alkylpurines. Glycosylation of purines suffers from the regioselectivity problem,[3] and additionally complex diastereomeric mixtures can be encountered when no anchimeric participating group is present at C2 of the glycosylating sugar.[4] Purine derivatives with appropriate substituents can direct alkylation/glycosylation exclusively (or highly preferentially) to N9. For example, we had shown that 2-acetamido-6-(diphenylcarbamoyloxy)purine underwent regiospecific glycosylation at N9 under rigorously anhydrous conditions.[5] This provided a successful route to guanine N9 nucleosides, but the sensitivity of the diphenylcarbamoyloxy group to moisture, Brønsted acids, and heat limits its applicability and convenience.[6]

* Corresponding author. Phone: (801) 422-6272. Fax: (801) 422-0153.

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We have developed convenient methodologies for synthesis of 6-(heteroaryl)purine compounds and demonstrated the utility of the 6-azolyl substituents as leaving groups for Suzuki-type cross-coupling reactions[7] as well as S_NAr displacements.[8] It had been observed that unsubstituted heteroaryl rings appended at C6 of purines adopt essentially coplanar ring alignments.[9] Our analysis of X-ray crystal structures of several compounds revealed that space "above" N7 of the purine ring can be shielded by a proximal C−H of an appended heteroaryl moiety. A possible nonclassical hydrogen-bonding interaction (C−H···N7) might also decrease the nucleophilicity of N7. This prompted our systematic investigation of the use of such purine analogues as substrates for regiocontrolled N9 alkylations and glycosylations.

Purine derivatives with an azole ring nitrogen bonded to C6 of the purine ring can be prepared by two common approaches: (1) an existing N-linked substituent at C6 of a purine (or purine precursor) can be elaborated into an azole ring; (2) a leaving group at C6 can be displaced by a nucleophilic azole ring nitrogen (S_NAr). Examples of the first type include treatment of adenine derivatives with 2,5-dimethoxyfuran or 2,5-hexanedione under appropriate conditions to produce the respective 6-(pyrrol-1-yl)purine or 6-(2,5-dimethylpyrrol-1-yl)-purine compounds.[2c,10] Likewise, treatment of adenine derivatives with 1,2-bis-(dimethylaminomethylene)hydrazine affords 6-(1,2,4-triazol-4-yl)purines.[11] Examples of the second type include S_NAr displacement of bromide or chloride from 6-(bromo or chloro)purines with imidazole to give the 6-(imidazol-1-yl)purine analogues.[2c,12] Also, the mechanistically related S_NAr replacement of a leaving group generated by in situ treatment of the 6-oxo group of inosine and guanosine derivatives with imidazole/I_2/Ph_3P/EtN(^{i}Pr)$_2$ produces 6-(imidazol-1-yl)- and 2-amino-6-(imidazol-1-yl)purine nucleosides.[8] Such 6-(imidazol-1-yl)purine derivatives are quite robust and can be manipulated and purified without difficulty. However, S_NAr displacement of the azole moiety at C6 can be effected readily,[8] and Suzuki-type cross-coupling reactions are successful with both electron-poor and electron-rich arylboronic acids.[7]

Our initial investigations on S_NAr and cross-coupling reactions of 6-(azolyl)purines were performed with compounds derived from naturally occurring nucleosides.[7,8] However, we recently have found that glycosylation reactions with 6-(azolyl)-purines catalyzed by Lewis acids produce the desired N9 isomers exclusively.[13] This expands the scope of S_NAr and cross-coupling reactions that were available with natural products to an unlimited variety of readily accessible 9-glycosyl derivatives. The reactivity and solubility of 6-(azolyl)purine derivatives can be altered by the choice of substituents on the appended azole ring, and a number of biological effects have been observed with such substituted purine derivatives.[2c,9a,b,d,14]

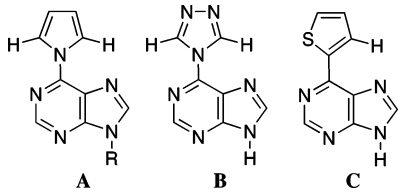

FIGURE 1. Coplanar rings have C−H above N7.

Results and Discussion

Structure and Reactions. Mintas and co-workers prepared various 6-(pyrrol-1-yl)purine derivatives **A** (Figure 1) and determined X-ray crystal structures of several compounds.[9] The purine and appended pyrrole rings are close to coplanar in most of their structures. However, these authors noted that alkylation of the sodium salt of 6-(pyrrol-1-yl)purine (**A**, R = H) with propylene carbonate in DMF at elevated temperatures gave a minor amount of the N7 isomer in addition to the N9 product.[9b] Rotation about the C6−N1′ bond toward a more nearly perpendicular orientation is not sterically restricted, but calculations indicate that a coplanar conformation is more stable in (pyrazol-1-yl)phenyl ring systems because of π-electron delocalization.[15] The "protection" of N7 afforded by the proximal pyrrole hydrogen at lower temperatures might be compromised at higher temperatures.

Our X-ray structure of 6-(1,2,4-triazol-1-yl)purine[11] (**B**) (see the Supporting Information) has a projection angle of 1.4° between the planes of the triazole and purine rings. Alkylation of the sodium salt of 2-amino-6-(1,2,4-triazol-1-yl)purine with methyl iodide and 1-bromopropane in DMF at ambient temperature had been reported to give the N9 isomers.[16] Regiospecific arylation of 6-(thien-2-yl)purine (**C**) at N9 with arylboronic acids in the presence of copper(II) acetate and phenanthroline also had been noted.[17] However, cross-couplings occur by entirely different mechanisms, and related cross-couplings with chloro and methylsulfanyl substituents at C6 of the purine ring also gave N9 isomers[17] (which might be influenced by the size and/or nature of the attacking organometallic complex). It is noteworthy that alkylation of **C** with an epoxide in DMSO (or its sodium salt in DMF) gave N9 and N3 isomers.[2c]

We reasoned that alkylation and glycosylation reactions with 6-(azolyl)purines that have favored coplanar conformation populations should give high regioselectivity for the N9 isomers at ambient temperature. Imidazol-1-yl substituents at C6 of purine rings are stable under quite robust conditions but can be substituted readily by cross-coupling[7] and S_NAr[8] processes. Low solubility is a major problem with most purines, and incorporation of a lipophilic group at C2′ of the appended imidazole ring

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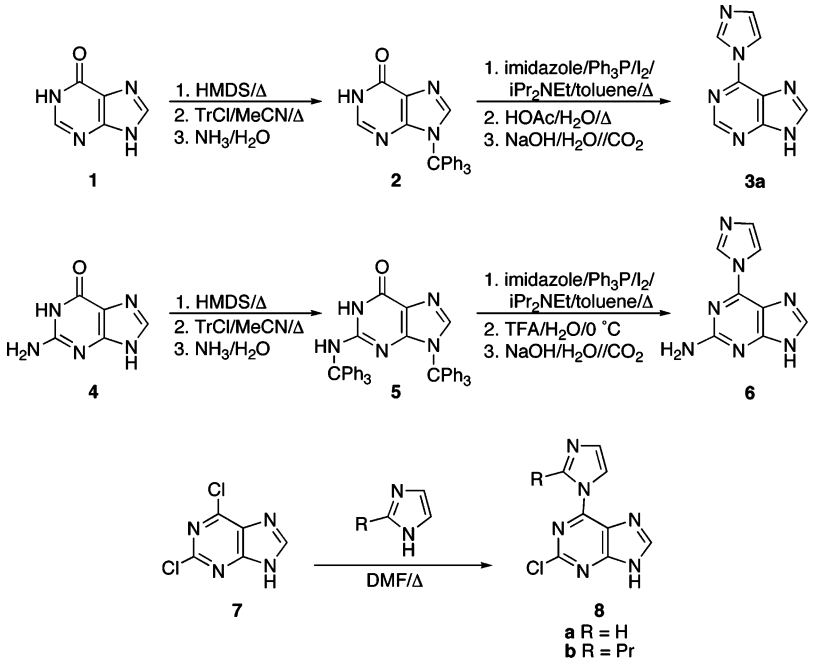
SCHEME 1. Preparation of 6-(Azolyl)purines from Purine Bases



can promote solubility in less polar solvents. Therefore, we began a structure versus N7/N9 isomer preference investigation of alkylation and glycosylation[13] of 6-(azolyl)purines.

As noted, the projection angle between the planes of the triazole and purine rings in **B** is 1.4°. The corresponding angles of 3.4° for 6-(2-butylimidazol-1-yl)-2-chloropurine (**8c**) (Scheme 2) and 6.5° for 9-(5-*O*-acetyl-*β*-D-ribofuranosyl)-6-(imidazol-1-yl)purine (**D**) (Figure 2) also indicate small deviations from

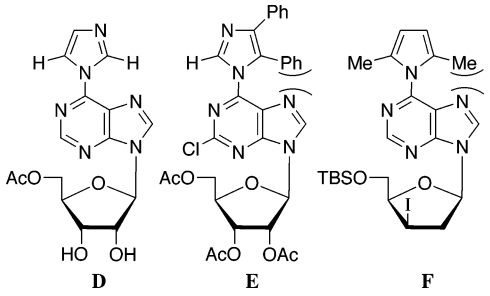


FIGURE 2. Structures of compounds **D**−**F**.

coplanarity. In marked contrast, the projection angles of 56.5° between the planes of the imidazole and purine rings in 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-(4,5-diphenylimidazol-1-yl)-purine (**E**) and 60.6° between the pyrrole and purine rings in 9-(5-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-3-iodo-*β*-D-*threo*-pentofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine[18] (**F**) are more than halfway toward perpendicular orientations. We recognize that crystal-packing forces affect projection angles with base and nucleoside derivatives. However, we anticipate that these major differences between the two sets of projection angles will be reflected in changes in regioselectivity for alkylation and/or glycosylation with the two types of 6-(azolyl)purine substrates (especially with smaller electrophiles and more reactive glycosyl entities). Our preliminary results demonstrate that N9 glycosylations of 6-(2-propylimidazol-1-yl)purine can be effected with tin(IV) chloride in acetonitrile or trimethylsilyl triflate in 1,2-dichloroethane at ambient temperature.[13]

Synthesis. Trimethylsilylation/tritylation[19] of hypoxanthine (**1**) (Scheme 1) and treatment of the product 9-tritylhypoxanthine (**2**) with imidazole/I_2/Ph_3P/Et$N(^iPr)_2$ in hot toluene[8a] followed by detritylation (HOAc/H_2O/60 °C or TFA/H_2O/0 °C) gives 6-(imidazol-1-yl)purine (**3a**). Trimethylsilylation/bis-tritylation of guanine (**4**) and analogous introduction of imidazole[8b] at C6 of the 2-*N*,9-dityrityl derivative **5** followed by detritylation gives 2-amino-6-(imidazol-1-yl)purine (**6**). Treatment of 2,6-dichloropurine (**7**) with imidazole/DMF at 65 °C[12] results in selective replacement of chloride from the more reactive C6 position[20] to give 2-chloro-6-(imidazol-1-yl)purine (**8a**).

Such treatment of 6-halopurines with imidazole/DMF/Δ gives the 6-(imidazol-1-yl)purines in moderate to good yields, but 6-chloropurine, 2-amino-6-chloropurine, and 2,6-dichloropurine (**7**) are costly.[21] Hypoxanthine (**1**) and guanine (**4**) are less expensive, but they are insoluble in most solvents. The tedious trimethylsilylation/tritylation sequence[19] produces isomeric mixtures of mono- and bis-trityl derivatives under different reaction conditions. Therefore, we investigated alternative routes for the preparation of 6-(imidazol-1-yl)purines from inosine and guanosine. Inosine was acetylated (95%), and the 2′,3′,5′-tri-*O*-acetylinosine (**9**) (Scheme 2) was subjected to our modified Appel conditions to give 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-6-(imidazol-1-yl)purine[8a] (**10a**). Treatment of the crude product with acetyl chloride in acetic acid at 65 °C resulted in clean solvolysis of the glycosyl linkage[20] of **10a** to give the hydrochloride salt of 6-(imidazol-1-yl)purine (**3a**) (80% overall yield from commercially available **9**).

Acetylation (86%) and deoxychlorination of guanosine gave 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-chloropu-

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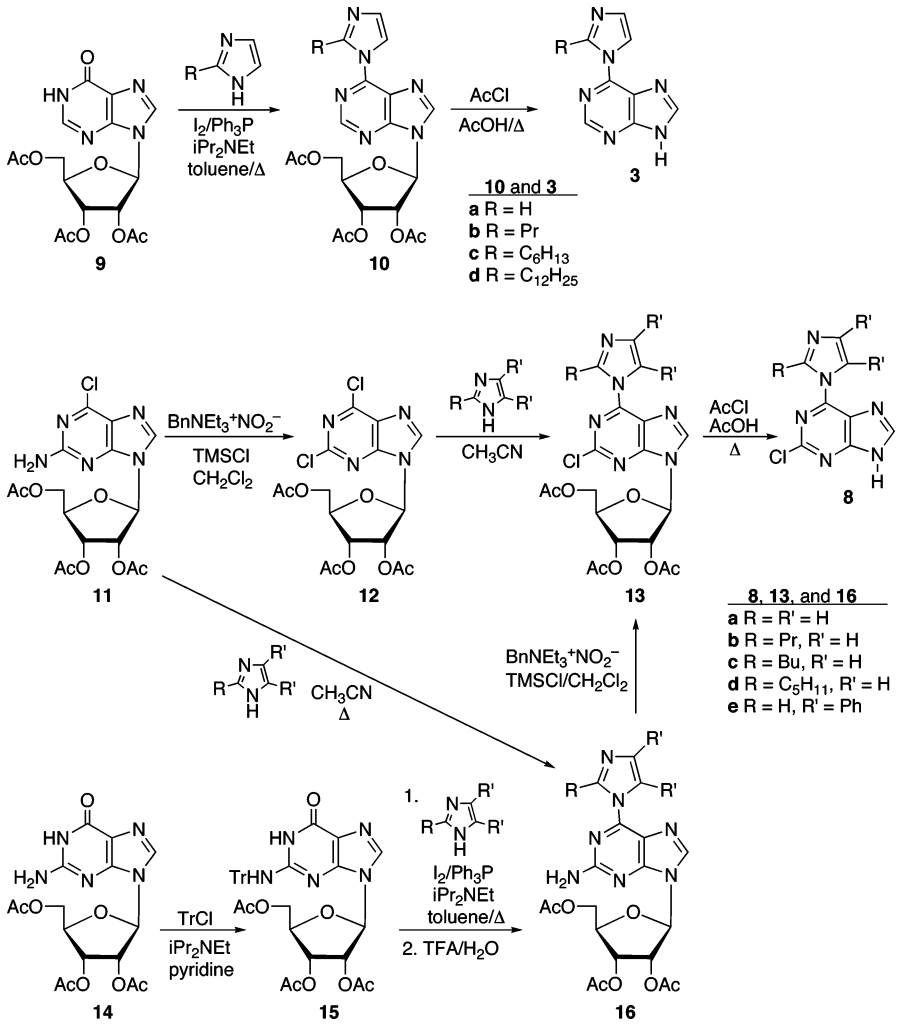
SCHEME 2. Synthesis of 6-(Imidazol-1-yl)purines from Inosine and Guanosine



rine[22] (**11**) (87%). Diazotization/chloro-dediazoniation[23] of **11** gave 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-dichloropurine (**12**) (99% from commercially available **11**). A solution of **12** and imidazole in acetonitrile was stirred at ambient temperature. The resulting 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-chloro-6-(imidazol-1-yl)purine (**13a**) was heated with acetyl chloride in acetic acid to give 2-chloro-6-(imidazol-1-yl)purine (**8a**) (72% after neutralization and purification). Treatment of **12** with substituted imidazoles in acetonitrile followed by solvolysis with acetyl chloride/acetic acid provided convenient access to the 2-chloro-6-(substituted-imidazol-1-yl)purines **8**. The corresponding S_NAr reaction of **12** in DMF was incomplete, and heating resulted in partial bis substitution (also at C2).

An alternative route beginning with 2′,3′,5′-tri-*O*-acetylguanosine (**14**) was less successful. Tritylation of **14** (98%) and treatment of the 2-*N*-trityl derivative **15** by our modified Appel conditions[8b] followed by detritylation gave 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-(imidazol-1-yl)purine (**16a**). Diazotization/chloro-dediazoniation[23] of **16a** gave **13a** (33% overall resulting from difficulty with separation of **16a** and **13a** from triphenylphosphine oxide).

Cladribine (2-chloro-2′-deoxyadenosine) is a clinical anticancer drug of choice for the treatment of hairy-cell leukemia and a number of other disease states. It has been prepared via the purine sodium salt procedure[3] by coupling a 2,6-disubstituted-purine with 2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl chloride. Use of that sugar α-anomer in a nonpolar solvent allows good S_N2 stereoselectivity for the 2′-deoxynucleoside *β*-anomer, but both 7- and 9-glycosyl regioisomers are formed. Our present synthesis of the 2-chloro-6-(substituted-imidazol-1-yl)purine analogues **8** provides substrates with tunable reactivity and solubility for studies on the regioselectivity of alkylation and glycosylation reactions relevant to improved syntheses of cladribine.

Summary and Conclusions

As noted, X-ray crystal structures of a number of 6-(azolyl)-purine bases and nucleoside derivatives show an essentially coplanar alignment of the appended unsubstituted azole and purine rings. This results in protrusion of an α C−H bond of the azole into the region of space "above" N7 of the purine. However, structures of certain derivatives that contain azole rings with substituents exhibit major conformational shifts toward a perpendicular orientation of the linked azole and purine rings. Few studies on alkylation of such compounds have been reported. Selective formation of N9 isomers has been noted, but other reports indicate formation of N3/N9 and N7/N9 mixtures. Our preliminary results demonstrate that glycosylations of 6-(2-propylimidazol-1-yl)purine with catalytic $SnCl_4$

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in acetonitrile or TMSOTf in DCE at ambient temperature can produce the desired N9 isomers exclusively,[13] and more recent results have confirmed the applicability of this approach for regiospecific alkylation at N9. Substrates with 6-(1,2,4-triazol-1-yl)- and 6-(substituted-imidazol-1-yl)purines can be prepared from both purine base and nucleoside precursors. We have prepared two types of substrates with small (1.4−6.5°) and moderate (∼60°) projection angles between the planes of the linked azole and purine rings. Studies on alkylation and glycosylation reactions as well as biological evaluations are presently under investigation.

Experimental Section

The starting materials 6-(1,2,4-triazol-4-yl)purine[11] (**B**), 2′,3′,5′-tri-*O*-acetylinosine[24] (**9**), 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-(imidazol-1-yl)purine[8a] (**10a**), 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine[22] (**11**), 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloropurine[23] (**12**), and 2′,3′,5′-tri-*O*-acetylguanosine[22] (**14**) were prepared as described, and their purities were confirmed by ^{1}H and ^{13}C NMR.

I. 9-Tritylhypoxanthine (2). A suspension of hypoxanthine (**1**) (2.0 g, 14.7 mmol) and $(NH_4)_2SO_4$ (0.46 g) was stirred in HMDS (300 mL) for 15 h at reflux. Volatiles were evaporated in vacuo from the clear solution, and the residue was dissolved in dried CH_3CN (150 mL). Trityl chloride (8.81 g, 30 mmol) was added, and the clear solution was stirred for 48 h at reflux. Volatiles were evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (50 mL). NH_3/H_2O (28−30% w/w, 80 mL) was added, and precipitation occurred immediately. The mixture was stirred overnight at ambient temperature, and volatiles were evaporated in vacuo. The residue was washed (H_2O, CH_2Cl_2) to give solid **2** (3.02 g). Volatiles were evaporated from the combined organic layers, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:60 → 1:30). The solid was washed (CH_2Cl_2) to give additional **2** (0.59 g) (65% total yield): ^{1}H NMR (DMSO-d_6) δ 12.23, 7.72, 7.65 (3 × s, 3 × 1H), 7.30−7.37 (m, 9H), 7.13 (d, J = 7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 157.5, 150.2, 145.0, 141.9, 140.7, 130.0, 128.8, 128.4, 126.6, 75.8; HRMS m/z 401.1390 (MNa^+ [$C_{24}H_{18}N_4ONa$] = 401.1378).

Other mono- and ditritylated [MS (FAB) m/z 643 (MNa^+ [$C_{43}H_{32}N_4ONa$] = 643)] byproducts were formed. Treatment of a mixture of two monotritylated regioisomers by the following Appel conditions followed by detritylation gave **3a** as the only product.

II. 6-(Imidazol-1-yl)purine (3a). II.1. Method 1. A suspension of **2** (3.0 g, 8 mmol), Ph_3P (11.9 g, 45 mmol), I_2 (11.3 g, 44 mmol), and imidazole (2.9 g, 43 mmol) in EtN(^{i}Pr)$_2$ (7.1 mL, 5.27 g, 41 mmol) and toluene (240 mL) was stirred overnight at 95 °C. Volatiles were evaporated, and the residue was extracted with boiling EtOAc (2 × 100 mL). The combined EtOAc extracts were evaporated to dryness. The original residue and the solid obtained from the EtOAc extracts were treated independently with HOAc/H_2O (9:1, 150 mL) and stirred for 20 h at 60 °C. Volatiles were evaporated in vacuo from the two solutions, and the residues were dissolved in 0.1 M NaOH/H_2O and washed (CH_2Cl_2). Precipitation (CO_2 was bubbled into the solution) and filtration gave **3a** (350 mg and 550 mg, respectively). Volatiles were evaporated from the combined mother liquors, and the residue was extracted (NaOH/H_2O). Neutralization of the extract (CO_2) caused precipitation of additional **3a** (30 mg) (63% total yield).

II.2. Method 2. A suspension of **9**[24] (4.0 g, 10 mmol), Ph_3P (6.4 g, 24 mmol), I_2 (5.3 g, 20.9 mmol), and imidazole (2.5 g, 37 mmol) in EtN(^{i}Pr)$_2$ (8.8 mL, 6.53 g, 50.5 mmol) and toluene (100 mL) was stirred overnight at 95 °C.[8a] Volatiles were evaporated in vacuo, and the residue was extracted with boiling EtOAc. The combined EtOAc extracts were evaporated to dryness. The residue was dissolved in HOAc (400 mL), and AcCl [4.2 mL, 4.64 g, 58 mmol (5.8 equiv)] was added. The mixture was stirred overnight at 65 °C (reaction complete, TLC). The solution was concentrated to 100 mL and cooled. The solid precipitate was filtered, and the filter cake was washed with HOAc and then CH_2Cl_2 to give **3a**·HCl (1.78 g, 80%).

(A) Recrystallization of this material (MeOH) gave **3a**·HCl: mp 296−297 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.01 (d, J = 1.8 Hz, 1H), 8.96, 8.88, 8.73, 7.85 (4 × s, 4 × 1H); ^{13}C NMR (DMSO-d_6) δ 156.0, 152.3, 147.5, 143.3, 137.1, 124.1, 122.7, 119.8; HRMS m/z 186.0673 (M^+ [$C_8H_6N_6$] = 186.0654).

(B) The precipitated **3a**·HCl was dissolved in 0.5 M NaOH/H_2O, and needlelike crystals precipitated from the solution upon standing at ambient temperature. This material was filtered and recrystallized (MeOH/Et_2O) to give the sodium salt of **3a** as a white solid: ^{1}H NMR (DMSO-d_6) δ 9.15 (t, J = 1.1 Hz, 1H), 8.44 (t, J = 1.3 Hz, 1H), 8.40, 8.04 (2 × s, 2 × 1H), 7.13−7.14 (m, 1H).

(C) The white solid from (B) was washed with CO_2/H_2O (saturated) to give **3a**: UV max 281, 290 nm (ϵ 15 100, 11 900), min 234, 288 nm (ϵ 3300, 11 800); ^{1}H NMR (DMSO-d_6) δ 13.90 (br s, 1H), 9.09−9.10 (m, 1H), 8.82, 8.72 (2 × s, 2 × 1H), 8.42−8.44 (m, 1H), 7.26−7.27 (m, 1H).

See the Supporting Information for analogous preparations of **3b**−**3d**.

III. 2-*N*,9-Ditritylguanine (5). Guanine (**4**) (450 mg, 3 mmol) [freshly activated by dissolving in 0.5 M NaOH/H_2O, precipitating by neutralization (HCl/H_2O) to pH ∼10, drying, grinding to a fine powder, and redrying] and $(NH_4)_2SO_4$ (60 mg) were heated at reflux with stirring for 24 h in HMDS (50 mL). Volatiles were evaporated in vacuo from the clear solution, and the residue was dissolved in dried CH_3CN (50 mL). Trityl chloride (3.5 g, 12.6 mmol) was added, and the solution was stirred for 48 h at reflux. Volatiles were evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). NH_3/H_2O (28−30%, 30 mL) was added, and precipitation occurred immediately. The mixture was stirred at ambient temperature overnight, and volatiles were evaporated in vacuo. The residue was washed (H_2O, CH_2Cl_2) to give a solid (1.37 g, 72%). This material was stirred with MeOH/CH_2Cl_2 (1:15), and the cloudy solution was filtered. Volatiles were evaporated to give purified **5**: ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 7.35 (s, 1H), 7.08−7.19 (m, 19H), 6.87 (d, J = 7.4 Hz, 6H), 6.81 (d, J = 7.3 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 157.3, 151.8, 151.0, 145.3, 142.4, 139.6, 129.6, 128.8, 128.5, 128.3, 127.6, 126.9, 120.3, 75.4, 71.1; HRMS m/z 635.2675 (M^+ [$C_{43}H_{33}N_5O$] = 635.2685).

IV. 2-Amino-6-(imidazol-1-yl)purine (6). A mixture of **5** (1.90 g, 3 mmol), I_2 (3.88 g, 15 mmol), Ph_3P (3.99 g, 15 mmol), and imidazole (1.10 g, 15 mmol) in toluene (150 mL) was stirred for 15 min at 95 °C, and EtN(^{i}Pr)$_2$ (2.9 mL, 2.15 g, 16.6 mmol) was added. The reaction mixture was stirred overnight at 95 °C, volatiles were evaporated, and the residue was extracted with boiling EtOAc (3×). The combined extracts were filtered (hot), and volatiles were evaporated from the filtrate. The residue was dissolved in TFA/H_2O (9:1, 60 mL), and the solution was stirred for 4 h at 0 °C. Volatiles were evaporated in vacuo, and the residue was partitioned between 0.1 M NaOH/H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic layer was extracted with 0.1 M NaOH/H_2O (50 mL × 2), and the combined aqueous layers were washed [CH_2Cl_2 (2 × 50 mL)]. Neutralization (CO_2 was bubbled into the basic solution) and evaporation of volatiles in vacuo gave a residue that was washed (H_2O, CH_2Cl_2) to give **6** (400 mg, 66%): UV (MeOH) max 222, 320 nm (ϵ 29 800, 8700), min 280 nm (ϵ 1500); ^{1}H NMR (DMSO-d_6) δ 12.89, 8.94, 8.25, 8.16, 7.18 (5 × s, 5 × 1H), 6.67 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 160.7, 157.5, 145.4, 141.9, 137.2, 130.5, 117.7, 115.4; HRMS m/z 201.0753 (M^+ [$C_8H_7N_7$] = 201.0763).

V. 2-Chloro-6-(imidazol-1-yl)purine (8a). V.1. Method 1 (via 7). Imidazole (820 mg, 12.1 mmol) and 2,6-dichloropurine (**7**) (380 mg, 2 mmol) were dissolved in freshly distilled DMF (36 mL). The solution was stirred for 20 h at 65 °C, and volatiles were evaporated. The residue was washed with a large volume of CH_2Cl_2 to give **8a** (290 mg, 66%).

(24) Bredereck, H.; Martini, A. *Chem. Ber.* **1947**, *80*, 401−405.

V.2. Method 2a (via 12 and 13a). A solution of imidazole (4.71 g, 68.9 mmol) and **12**[23] (1.71 g, 3.83 mmol) in CH_3CN (75 mL) was stirred for 36 h at ambient temperature under N_2 (reaction complete, TLC). Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:95 → 1:90) to give 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-chloro-6-(imidazol-1-yl)purine (**13a**) (1.54 g, 84%): ^{1}H NMR ($CDCl_3$) δ 9.14, 8.34, 8.28, 7.26 (4 × s, 4 × 1H), 6.27 (d, J = 5.8 Hz, 1H), 5.83 (t, J = 5.7 Hz, 1H), 5.61 (dd, J = 4.3, 5.5 Hz, 1H), 4.44−4.52 (m, 3H), 2.19, 2.18, 2.11 (3 × s, 3 × 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.9, 169.7, 154.8, 154.4, 146.9, 143.0, 138.0, 131.4, 122.1, 117.6, 86.5, 81.0, 73.5, 70.9, 63.2, 21.1, 20.8, 20.6; HRMS (EI) *m*/*z* 501.0908 (MNa^+ [$C_{19}H_{19}ClN_6O_7Na$] = 501.0901), 478.0987 (M^+ [$C_{19}H_{19}ClN_6O_7$] = 478.1003).

Compound **13a** (1.32 g, 2.75 mmol) was dissolved in HOAc (114 mL), and AcCl (1.14 mL, 1.26 g, 16.0 mmol) was added. The mixture was stirred for 11 h at 65 °C in a sealed flask, and volatiles were evaporated in vacuo. The residue was washed (CH_2Cl_2) and dissolved in 0.1 M NaOH/H_2O. Neutralization (CO_2 was bubbled into the solution) resulted in precipitation of a solid (510 mg, 83%) that was recrystallized (MeOH) to give **8a** (350 mg, 58%): UV (MeOH) max 218, 288, 298 nm (*ϵ* 27 300, 14 100, 13 300), min 241, 262, 295 nm (*ϵ* 5800, 6400, 12 000); ^{1}H NMR (DMSO-d_6) δ 14.09 (br s, 1H), 9.03, 8.72, 8.34, 7.26 (4 × s, 4 × 1H); ^{13}C NMR (DMSO-d_6) δ 157.0, 152.4, 146.8, 145.7, 137.7, 131.4, 121.4, 118.1; HRMS *m*/*z* 220.0275 (M^+ [$C_8H_5ClN_6$] = 220.0264).

V.3. Method 2b (via 11 and 16a). A stirred mixture of imidazole (615 mg, 9 mmol) and **11**[22] (213 mg, 0.5 mmol) in CH_3CN (10 mL) was heated for 12 h at reflux under N_2 (reaction complete, TLC). Volatiles were evaporated in vacuo, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:60) to give 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-amino-6-(imidazol-1-yl)purine (**16a**) as a solid (193 mg, 88%).

TMSCl (1.5 mL × 2, 2.57 g, 23.6 mmol) was added dropwise to a stirred solution of crude **16a** (570 mg, 1.24 mmol) and $BnNEt_3^+NO_2^-$ (890 mg, 3.7 mmol) in dry CH_2Cl_2 (40 mL) under N_2.[23] Stirring was continued overnight at ambient temperature, and $CHCl_3$ (200 mL) was added. The solution was washed ($NaHCO_3$/H_2O) and dried (Na_2SO_4), and volatiles were evaporated in vacuo. The residue was chromatographed (EtOAc/hexanes, 7:3) to give **13a** (480 mg, 81%).

V.4. Method 2c (via 15 and 16a). A mixture of **14**[22] (1.0 g, 2.45 mmol) and trityl chloride (2.32 g, 8.3 mmol) in EtN(^{i}Pr)$_2$ (1.45 mL, 1.08 g, 8.3 mmol) and pyridine (40 mL) was stirred for 20 h at ambient temperature under N_2 (a trace of **14** remained unreacted, TLC). Volatiles were evaporated in vacuo, and toluene was added and evaporated. The residue was dissolved (CH_2Cl_2), and the solution was washed (H_2O, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:30) to give 2′,3′,5′-tri-*O*-acetyl-2-*N*-tritylguanosine (**15**) as a white solid (1.55 g, 98%): ^{1}H NMR (DMSO-d_6) δ 10.72, 7.86, 7.70 (3 × s, 3 × 1H), 7.21−7.30 (m, 15H), 5.28−5.32 (m, 2 H), 5.03 (t, J = 5.0 Hz, 1H), 4.00−4.14 (m, 3H), 2.08, 2.04, 1.95 (3 × s, 3 × 3H); ^{13}C NMR (DMSO-d_6) δ 170.2, 169.4, 169.0, 156.5, 151.5, 149.9, 144.7, 136.0, 128.7, 127.9, 126.9, 117.4, 84.1, 79.0, 71.8, 70.5, 69.9, 63.2, 20.7, 20.5, 20.3; HRMS *m*/*z* 696.2062 (MNa_2 − H [$C_{35}H_{32}N_5O_8Na_2$] = 696.2046).

A mixture of **15** (1.46 g, 2.24 mmol), I_2 (2.84 g, 11.2 mmol), Ph_3P (2.94 g, 11.2 mmol), and imidazole (0.76 g, 11.2 mmol) was stirred in toluene (60 mL) for 15 min at 95 °C. EtN(^{i}Pr)$_2$ (3.9 mL, 2.89 g, 22.4 mmol) was added, and the mixture was stirred overnight at 95 °C. Volatiles were evaporated, and the residue was extracted with boiling EtOAc (100 mL + 10 mL × 3). The combined EtOAc extracts were evaporated to dryness, and the residue was dried under vacuum. This material was stirred with TFA/H_2O (9:1, 60 mL) for 1.5 h at 0 °C. Volatiles were evaporated in vacuo, and the residue was chromatographed (CH_2Cl_2 → MeOH/CH_2Cl_2, 1:30) to give a colored solid. This material was dissolved in MeOH, charcoal was added, and the mixture was heated and filtered. Volatiles were evaporated from the filtrate, and the residue was dissolved (CH_2Cl_2). The solution was washed ($NaHCO_3$/H_2O, brine) and dried (Na_2SO_4). Volatiles were evaporated in vacuo, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:20) to give **16a** as a slightly colored solid (570 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 9.06, 8.29, 7.88, 7.22 (4 × s, 4 × 1H), 6.06 (d, J = 4.9 Hz, 1H), 6.00−6.02 (m, 1H), 5.80−5.82 (m, 1H), 5.16 (s, 2H), 4.41−4.50 (m, 3H), 2.17 (s, 3H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 169.9, 169.8, 159.6, 155.2, 146.5, 140.3, 137.6, 130.5, 117.6, 117.2, 86.7, 80.06, 73.09, 70.7, 63.2, 20.9, 20.8, 20.7; HRMS *m*/*z* 482.1387 (MNa^+ [$C_{19}H_{21}N_7O_7Na$] = 482.1400).

See the Supporting Information for analogous preparations of **8b**−**8e**.

VI. 2-Chloro-6-(2-propylimidazol-1-yl)purine (8b). VI.1. Method 1 (via 7). 2-Propylimidazole (1.32 g, 12 mmol) and **7** (0.38 g, 2 mmol) were dissolved in freshly distilled DMF (10 mL). The solution was stirred for 20 h at 65 °C, and volatiles were evaporated. The residue was dissolved in 0.1 M NaOH/H_2O (100 mL) and CH_2Cl_2 (50 mL), and the organic phase was extracted with 0.1 M NaOH/H_2O (3 × 50 mL). The combined aqueous phase was washed (CH_2Cl_2, 2 × 50 mL) and then neutralized (CO_2 bubbled into the solution). The solid precipitate was filtered and washed (H_2O) to give **8b** (380 mg, 72%).

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Supporting Information Available: X-ray crystal structures and data in CIF format for compounds **B**, **D**−**F**, and **8c**; experimental details and synthetic procedures for compounds **3b**−**3d** and **8b**−**8e**; ^{13}C NMR spectra of new compounds for which elemental analyses were not obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

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