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Kinetic Studies of 6-Halopurine Nucleoside in SNAr Reactions; 6-(Azolyl, Alkylthio and Fluoro)-purine Nucleosides as Substrates for Suzuki Reactions

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by

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GRADUATE COMMITTEE APPROVAL

of a dissertation submitted by

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This dissertation has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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_____ _____

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ABSTRACT

KINETIC STUDIES OF 6-HALOPURINE NUCLEOSIDES IN S_NAR REACTIONS; 6-(AZOLYL, ALKYLTHIO AND FLUORO)-PURINE NUCLEOSIDES AS SUBSTRATES FOR SUZUKI REACTIONS

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In chapter 1, we describe development of a mild and efficient method for S_NAr iodination of 6-chloropurine 2'-deoxynucleosides and nucleosides. Our studies demonstrate that 6-iodopurine nucleosides are excellent substrates for certain transition metal-catalyzed cross-coupling reactions.

In chapter 2, we describe synthesis of protected 6-fluoro, 6-chloro, 6-bromo and 6-sulfonylpurine nucleosides. Comparisons among 6-fluoro-, 6-chloro-, 6-bromo, 6-iodo and 6-sulfonylpurine nucleosides for S_NAr reactions with various N, O and S nucleophiles were investigated. Our results demonstrate that the 6-fluoropurine nucleoside is the best substrate for S_NAr reactions among the four 6-halopurine nucleosides with oxygen, sulfur and aliphatic amine nucleophiles, and also with an

aromatic amine plus TFA as a catalyst. However, the 6-iodopurine nucleoside is the best substrate for the aromatic amine without acid. With oxygen and sulfur nucleophiles, the 6-sulfonylpurine nucleoside reacted even faster than the 6-fluoropurine nucleoside.

In chapters 3 and 4, nickel- and palladium-based systems with imidazolium-carbene ligands can catalyze efficient Suzuki cross-couplings of arylboronic acids and 6-[(imidazol-1-yl)-, (1,2,4-trizaol-4-yl), fluoro, alkylsulfanyl and alkylsulfonyl]purine 2'-deoxynucleosides and nucleosides to give the corresponding 6-arylpurine products.

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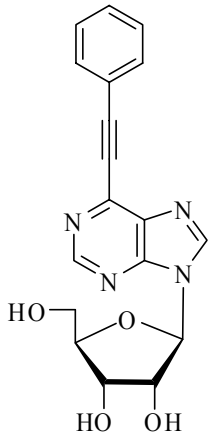
Chapter 1 S_NAr Iodination of 6-Chloropurine Nucleosides

1.1. Introduction

Natural purine bases play central roles in many biological processes. Purine derivatives with various substituents at C6 have received considerable recent attention due to their broad spectrum of biological activities.[1] Cytotoxic activity against a human chronic myelogenous leukemia cell line was observed for a 6-alkynylpurine nucleoside (Figure 1).[2]

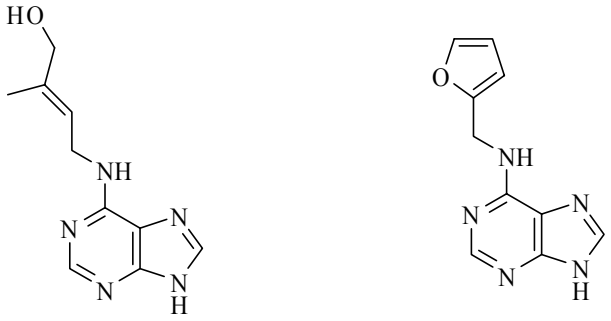
Figure 1. Structure of 6-(Phenylethynyl)purine Riboside



Cytokinins are plant hormones with a wide range of biological effects. They promote cell division and cell growth and they are involved in the retardation of senescence. *Trans*-Zeatin is a potent naturally occurring cytokinin growth hormone. Kinetin is plant growth stimulating (Figure 2).[3]

Significant cytostatic activity was found with 6-phenylpurine riboside (Figure 3).[4] The cytostatic activity was also observed with 2-amino-6-methoxypurine arabinoside (Figure 4),[5] and 6-ethylsulfanylpurine (Figure 5).[6]

Figure 2. Structures of *trans*-Zeatin and Kinetin



trans-Zeatin Kinetin

Figure 3. Structure of 6-Phenylpurine Riboside

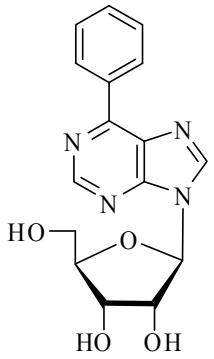


Figure 4. Structure of 2-Amino-6-methoxypurine Arabinoside

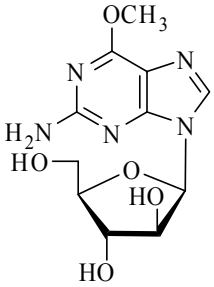
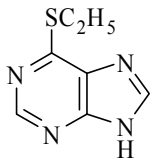


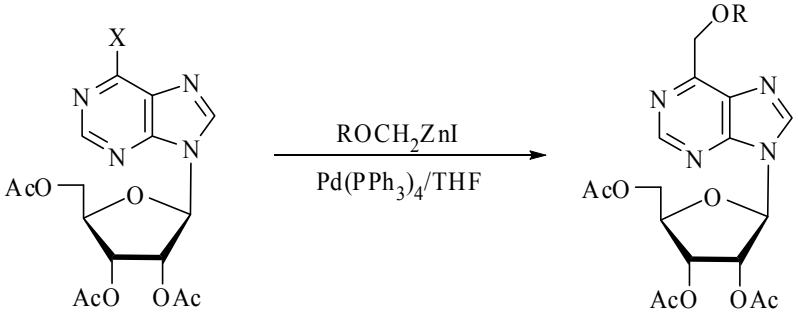
Figure 5. Structure of 6-Ethylsulfanylpurine



Advances in the synthesis of C6 modified purines have employed Sonogashira,[7] Suzuki-Miyaura,[8] and S_NAr reactions,[9] and the area of organometallic cross-coupling with purine and purine nucleoside derivatives has been reviewed.[10]

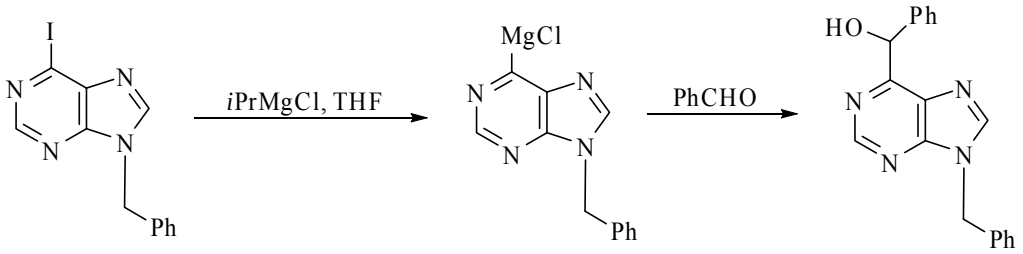
Véliz and Beal reported that 6-bromopurine nucleosides were more reactive than their 6-chloro analogues in S_NAr reactions with arylamines, whereas Lakshman and co-workers found that the 6-chloro analogues usually provided better yields than 6-bromopurine nucleosides for Suzuki-Miyaura couplings.[11] Hocek and coworkers reported that 6-iodopurines gave slightly better yields than their 6-chloro analogues for Negishi reactions of organozinic reagents with 6-halopurine nucleosides (Scheme 1).[12] However, Dvořák and coworkers reported that a purine-derived Grignard reagent was obtained only from 9-benzyl-6-iodopurine, and 9-benzyl-6-chloropurine was completely unreactive under these conditions (Scheme 2).[13] So, it was of interest to compare their reactivity for metal-catalyzed cross-coupling and S_NAr reactions. Prior to this work, comparisons between 6-chloro- and 6-iodopurine nucleosides for Sonogashira, Suzuki-Miyaura, and S_NAr reactions have not been evaluated systematically.

Scheme 1. Negishi Reaction of 6-Chloro- and 6-Iodopurine Nucleosides



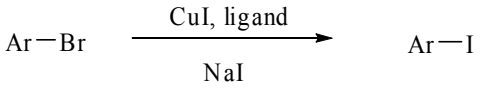
X = Cl, I

Scheme 2. Synthesis of a Grignard Reagent from 6-Iodopurine Derivatives



Aryl chlorides are usually much less reactive than the corresponding iodides for transition metal-catalyzed reactions with aromatic systems, and Plenio and co-workers communicated a more efficient system for Sonogashira coupling of aryl chlorides.[14] Klapars and Buchwald recently communicated a copper-catalyzed aromatic Finkelstein reaction, which converted aryl bromides into iodides at 110 ℃ (Scheme 3).[15]

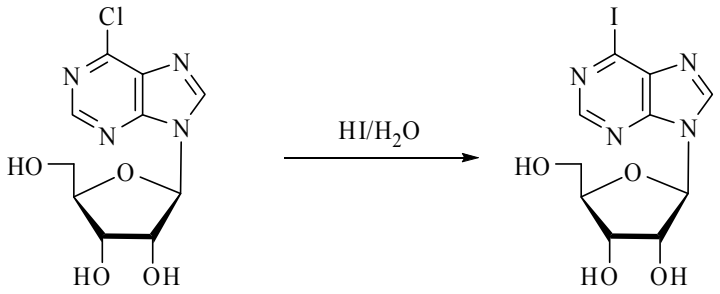
Scheme 3. Synthesis of Aryl Iodides from Aryl Bromides



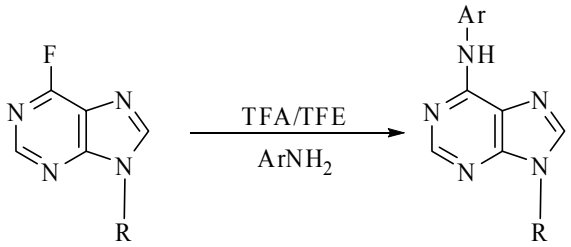
Syntheses of 6-chloropurine nucleoside derivatives are considerably less problematic than preparation of their 6-iodo analogues.[16] An earlier procedure for conversion of 6-chloro- to 6-iodopurines employed HI/H_2O at ice-bath temperature (Scheme 4).[17] The large excess of aqueous HI (even at this temperature) limits its utility with acid-labile compounds, especially with the important 2'-deoxynucleosides. No applications of this procedure to 2'-deoxynucleosides have been reported. Therefore, its general applicability is in doubt.

Roberts and co-workers used ^{15}N NMR to identify protonation sites on purines and nucleosides with trifluoroacetic acid in DMSO,[18] and an application of enhanced purine S_NAr reactivity with TFA has been noted (Scheme 5).[19]

Scheme 4. Synthesis of 6-Iodopurine Riboside from 6-Chloropurine Riboside

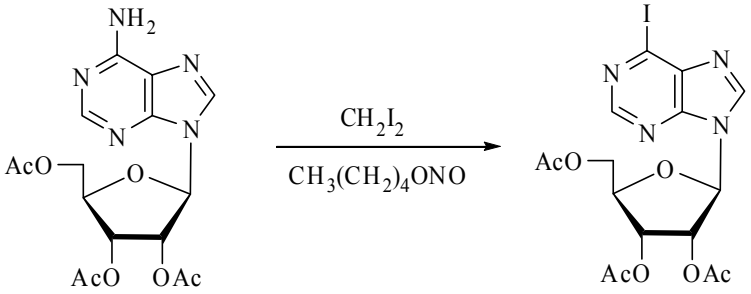


Scheme 5. Synthesis of 6-*N*-Arylpurine Derivatives from 6-Fluoropurine Compounds

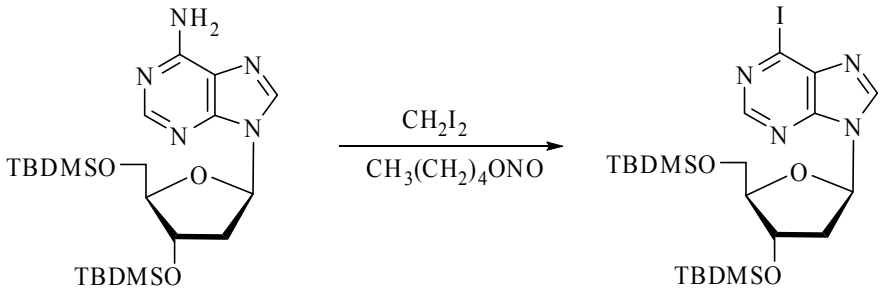


Diazotive iododeamination of aminopurine nucleosides is an alternative methodology. Conversion into the 6-iodopurine nucleosides by photoinduced diazotization with pentyl nitrite and diiodomethane was originally developed by Nair and Richardson (Scheme 6).[20] This procedure is also applicable for 6-iodopurine 2'-deoxynucleosides (Scheme 7).[21] However, this approach has limitations, including poor to moderate yields, byproduct formation, and expensive reagents.

Scheme 6. Synthesis of 6-Iodopurine Riboside by Diazotization



Scheme 7. Synthesis of a 6-Iodopurine 2'-Deoxynucleoside by Diazotization



1.2. Results and Discussion

1.2.1. Aromatic Finkelstein Reactions

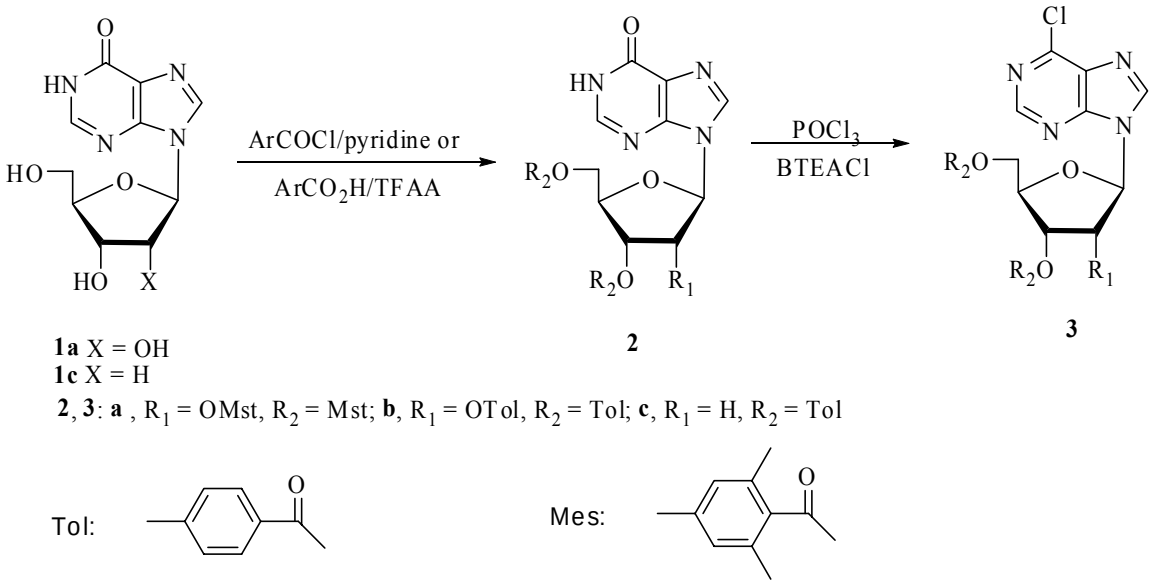
Sugar hydroxyl groups on inosine nucleosides were protected as mesitoyl (2,4,6-trimethylbenzoic acid and trifluoroacetic anhydride in CH_2Cl_2)[22] or *p*-toluoyl (4-methylbenzoyl chloride/pyridine)[23] esters because they crystallize much more readily.

The protected inosine and 2'-deoxyinosine derivatives **2a-c** were treated with $POCl_3$ under previously developed conditions[24] to give the 6-chloropurine nucleosides **3a** and **3b** and the 2'-deoxynucleoside **3c** in good to high yields (Scheme 8). It is noteworthy that these new 6-chloropurine nucleoside derivatives are crystalline, in contrast with the amorphous esters obtained with acetyl or benzoyl protection.

Minimal iodo product formation was observed upon treatment of solutions of **3a** or **3b** with excess sodium iodide in acetone or butanone at ambient temperature. Dark-colored solutions were formed upon heating. Addition of TFA at ambient temperature resulted in separation of a fine precipitate (NaCl), but these acid-catalyzed S_NAr reactions did not proceed beyond ~65% replacement of Cl by I. Reaction mixtures became darker upon standing, and heating resulted in further darkening and decomposition. We reasoned that the solubility of NaCl in butanone would be minimal at low temperatures but that the

addition-elimination of halides at C6 would proceed at reasonable rates with protonated purine cations in equilibrium with TFA.

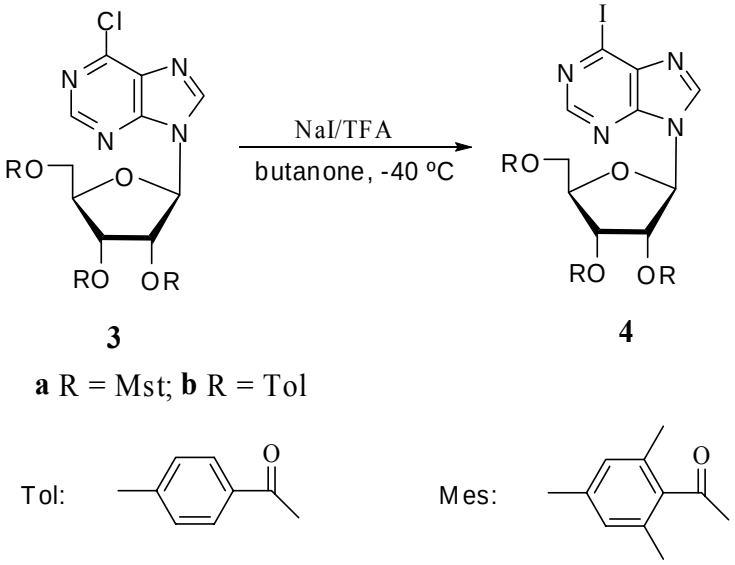
Scheme 8. Synthesis of 6-Chloropurine Nucleosides



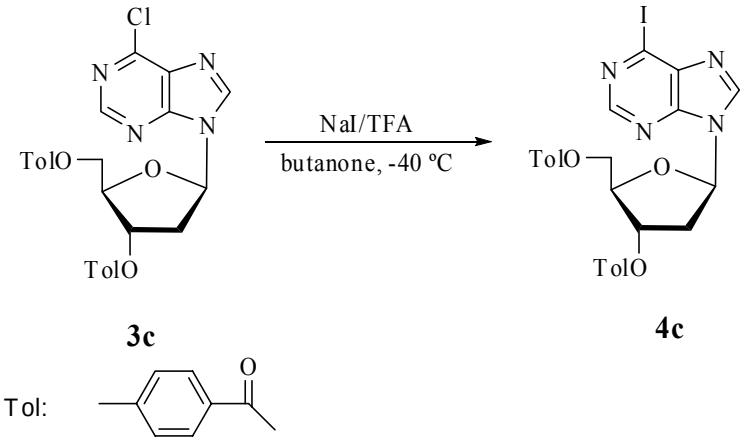
We were gratified to observe quantitative conversions (>98% by ^{1}H NMR[25]) of the 6-chloropurine nucleosides into their iodo analogues upon treatment of **3a** and **3b** with TFA and NaI in butanone at –50 to –40 ℃ for 5 h (Scheme 9). The iodo products were purified and isolated as crystalline solids [**4a** (80%) and **4b** (73%)].

These remarkably mild and convenient reaction conditions were then applied to iodide exchange with the 2'-deoxynucleoside **3c**, and **4c** was produced quantitatively (>98% by ^{1}H NMR, 66% crystalline, Scheme 10). The glycosyl bond in purine deoxynucleosides is known to be much more acid sensitive than in their ribosyl counterparts because of their lack of an electron-withdrawing 2'-hydroxyl group. This method represents the first synthesis of a 6-iodopurine 2'-deoxynucleoside by an aromatic Finkelstein process.

Scheme 9. Synthesis of 6-Iodopurine Nucleosides from 6-Chloro Compounds



Scheme 10. Synthesis of a 6-Iodopurine 2'-Deoxynucleosides from a 6-Chloro Compounds



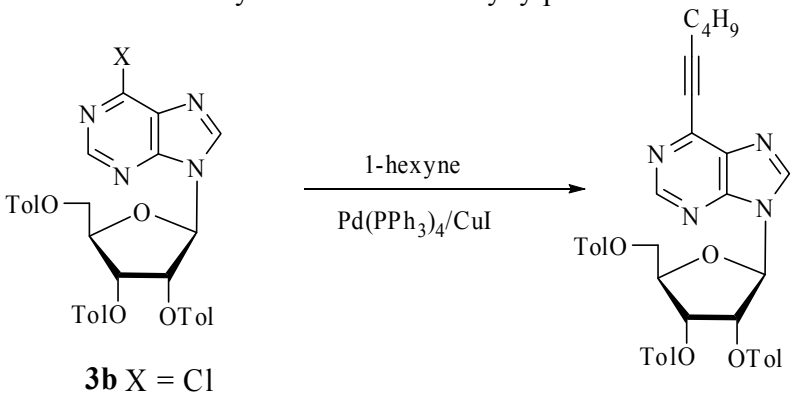
1.2.2. Reactivity Comparisons of 6-Chloro and 6-Iodopurine Nucleosides

1.2.2.1. Comparisons for the Sonogashira Reaction

The Sonogashira reaction is valuable for the synthesis of 6-alkynylpurine nucleosides, which serve as intermediates for the preparation of highly substituted 6-arylpurine nucleosides that are not readily accessible by standard coupling reactions.[26] No cross-coupling product was detected upon treatment of the 6-chloro analogue **3b** (Scheme

11) with 1-hexyne/$Pd(PPh_3)_4$/CuI/TEA for 10 h at ambient temperature. In contrast, parallel treatment of the 6-iodo compound **4b** gave the coupling product **5** in 92% yield after 20 min. Analogous treatment of **3b** with 1-hexyne at ambient temperature in DMF for 16 h gave 40% yield of **5**, whereas the conversion of **4b** to **5** was complete in 10 min under these conditions.

Scheme 11. Synthesis of a 6-Hexynylpurine Nucleoside



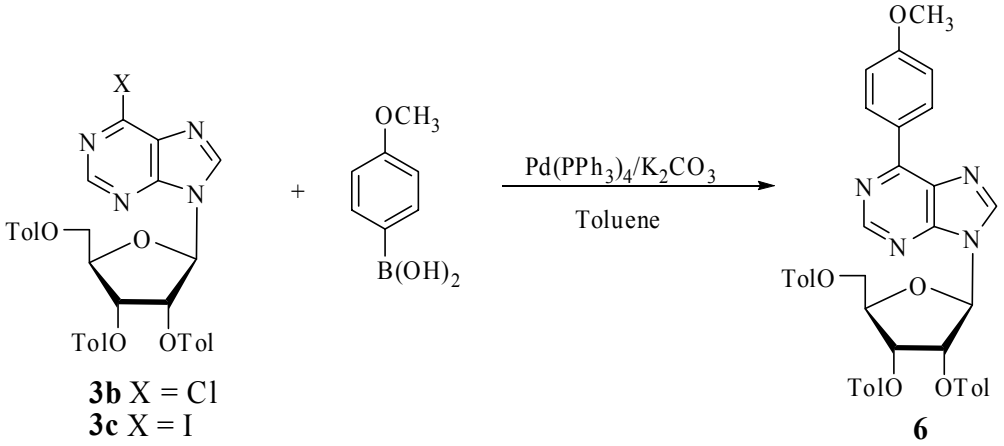
3b X = Cl
4b X = I

5

1.2.2.2. Comparisons for the Suzuki Reaction

The Suzuki-Miyaura procedure has been used to prepare 6-phenylpurine nucleosides. Our treatment of **3b** with 4-methoxyphenylboronic acid/$Pd(PPh_3)_4$/K_2CO_3/toluene at 100 ℃ for 10 h gave the aryl substitution product **6** in 70% yield (Scheme 12). By comparison, the 6-iodo analogue **4b** gave **6** in 83% after 5 h under identical conditions. Thus, 6-iodopurines also gave better yields than the 6-chloro analogues for Suzuki reactions.

Scheme 12. Suzuki Reactions of 6-Chloro and 6-Iodopurine Nucleosides



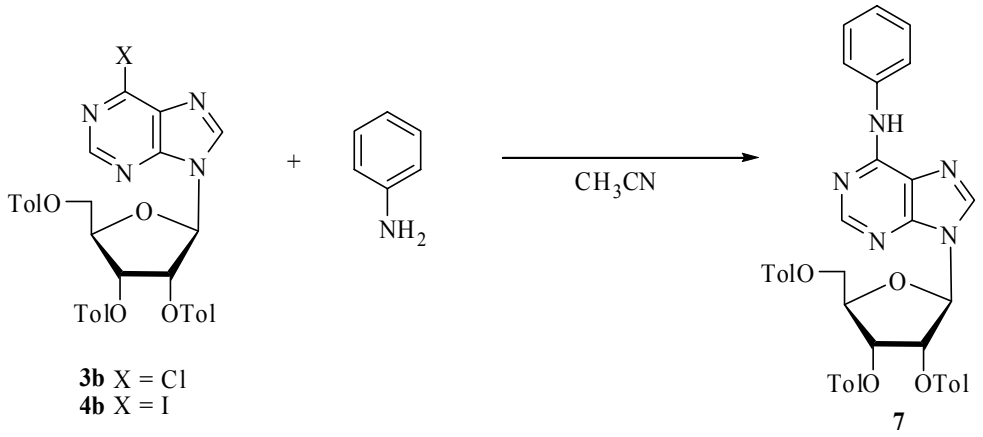
3b X = Cl
3c X = I

6

1.2.2.3. Comparison of S_NAr Reactions with the Weakly Nucleophilic Aniline

S_NAr displacement reactions provide convenient access to biologically important N-aryl-modified nucleosides. No product was observed upon treatment of the 6-chloro compound **3b** with aniline in CH_3CN at 70 ˚C for 3 h. In contrast, parallel treatment of the 6-iodo analogue **4b** gave the substitution product **7** in 80% yield (Scheme 13). Véliz and Beal[11] had noted that such substitution reactions did not proceed with 6-chloro- or 6-bromopurine nucleosides with arylamines in acetonitrile, and the desired product was obtained by the reaction 6-bromopurine nucleosides with aniline in methanol (Scheme 14). Further studies about S_NAr reaction with the weakly nucleophilic aniline are discussed in chapter 2. Lakshman and coworkers had resorted to palladium-catalyzed coupling of 6-chloropurine compounds with arylamines (Scheme 15).[27]

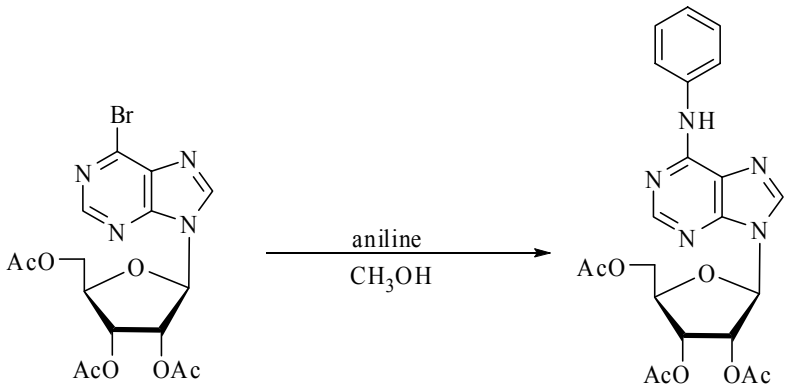
Scheme 13. Synthesis of a 6-*N*-Substituted Purine Nucleoside



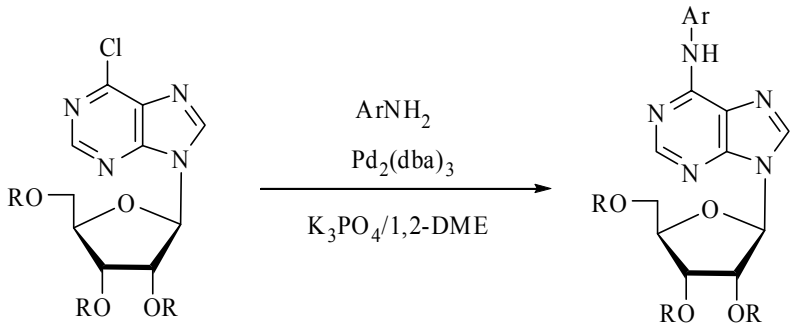
3b X = Cl
4b X = I

7

Scheme 14. Synthesis of a 6-*N*-Substituted Purine Nucleoside from a 6-Bromo Compound



Scheme 15. Synthesis of a 6-*N*-Substituted Purine Nucleoside by Palladium Catalysis



1.3. Conclusions

In summary, a remarkable aromatic Finkelstein reaction that proceeds readily at temperatures below –40 ℃ provides a simple, efficient, and cheap procedure for the preparation of synthetically important 6-iodopurine nucleosides and 2'-deoxynucleosides. Our examples demonstrate that these 6-iodopurine nucleosides are excellent substrates for S_NAr reactions with an arylamine as well as for certain transition metal-catalyzed cross-coupling reactions. In all of these processes, the 6-iodo compounds proved to be superior to their 6-chloropurine analogues.

1.4. Experimental Section

Uncorrected melting points were determined with a hot-stage apparatus. ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were determined with solutions in $CDCl_3$ unless otherwise indicated. High-resolution mass spectra (MS) were determined with FAB (glycerol, NaOAc). All chemicals and solvents were of reagent quality.

Method 1. Toluoyl chloride (4-methylbenzoyl chloride, 6 mmol) was added dropwise to a stirred suspension of inosine or 2'-deoxyinosine (1 mmol) in pyridine (7 mL) at 40 ℃. The mixture was heated for 2 h at 40 ℃ and then stirred overnight at ambient temperature. The solution was treated with saturated $NaHCO_3/H_2O$ and extracted with CH_2Cl_2 (50 mL). The organic layer was washed (cold 0.1 N HCl, $NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH, 50:1) and recrystallized from EtOH.

Method 2. $POCl_3$ (6 mmol) was added to a stirred solution of a protected inosine or deoxyinosine (1 mmol), benzyltriethylammonium chloride (2 mmol) and *N*,*N*-dimethylaniline (1.5 mmol) in CH_3CN (2 mL) at 80 ℃, and stirring was continued for 10 min. Volatiles were evaporated and the residue was partitioned (cold H_2O/CH_2Cl_2). The organic phase was washed ($NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated and the residue was recrystallized from EtOH.

Method 3. The 6-chloropurine nucleoside (1 mmol), TFA (5 mmol) and NaI (10 mmol) in butanone (8 mL) were stirred at –40 to –50 ℃ for 5 h. The reaction mixture was poured into saturated $NaHCO_3/H_2O$ and extracted (CH_2Cl_2, 50 mL). The organic layer was washed ($NaHSO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was recrystallized from EtOH.

2',3',5'-Tri-*O*-(2,4,6-trimethylbenzoyl)inosine (2a). Inosine (1.09 g, 4.1 mmol) was added to a stirred solution of 2,4,6-trimethylbenzoic acid (3.00 g, 18.3 mmol) and trifluoroacetic anhydride (2.58 mL, 3.84 g, 18.3 mmol) in CH_2Cl_2 (150 mL) at 0 ℃, and stirring was continued for 4 h. The reaction mixture was poured into saturated $NaHCO_3/H_2O$ (40 mL). The organic phase was washed (brine) and dried (Na_2SO_4). Volatiles were evaporated and the residue was chromatographed (CH_2Cl_2/MeOH 50:1) and recrystallized from EtOH to give **2a** (2.01 g, 70%): mp 244–246 ℃; ^{1}H NMR δ 2.19, 2.20, 2.30 (3 × s, 3 × 6H), 2.25, 2.29, 2.31 (3 × s, 3 × 3H), 4.71–4.80 (m, 3H), 6.08 (t, *J* = 5.0 Hz, 1H), 6.26 (t, *J* = 5.0 Hz, 1H), 6.30 (d, *J* = 5.0 Hz, 1H), 6.78, 6.83, 6.89 (3 × s, 3 × 2H), 7.89, 7.94 (2 × s, 2 × 1H), 12.20 (br, s, 1H); ^{13}C NMR δ 20.08, 20.15, 20.16, 21.37, 21.39, 21.45, 63.6, 71.5, 74.0, 81.1, 87.1, 125.7, 128.7, 128.88, 128.94, 129.3, 130.1, 135.5, 135.9, 136.2, 139.0 140.1, 140.4, 140.6, 145.0, 148.8, 158.7, 168.4, 168.8, 169.8; HRMS *m/z* 729.2889 [MNa^+ ($C_{40}H_{42}N_4O_8Na$) = 729.2900].

2',3',5'-Tri-*O*-(4-methylbenzoyl)inosine (2b). Treatment of inosine (0.53 g, 2.0 mmol) by method 1 gave **2b** (1.10 g, 89%): mp 210–213 ℃; ^{1}H NMR (DMSO-d_6) δ 2.35, 2.37, 2.39 (3 × s, 3 × 3H), 4.60–4.64 (m, 1H), 4.74–4.77 (m, 1H), 4.81–4.83 (m, 1H), 6.13 (t, *J* = 5.8 Hz, 1H), 6.34–6.36 (m, 1H), 6.52 (d, *J* = 4.9 Hz, 1H), 7.26–7.89 (m, 12H), 7.95, 8.35 (2 × s, 2 × 1H) 12.46 (br, s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.09, 21.10, 63.0, 70.4, 73.0, 79.3, 86.4, 124.9, 125.5, 125.7, 126.4, 129.19, 129.24, 129.26, 129.32, 139.7, 143.8, 144.3, 144.4, 146.1, 147.8, 156.3, 164.3, 164.5, 165.3; HRMS *m/z* 645.1978 [MNa^+ ($C_{34}H_{30}N_4O_8Na$) = 645.1961].

2'-Deoxy-3',5'-di-*O*-(4-methylbenzoyl)inosine (2c). Treatment of 2'-deoxyinosine (1.00g, 4.0 mmol) by method 1 gave **2c** (1.70g, 87%) as a colorless foam:

^{1}H NMR δ 2.40, 2.45 (2 × s, 2 × 3H), 2.81–2.86 (m, 1H), 3.05–3.11 (m, 1H), 4.64–4.77 (m, 3H), 5.80-5.82 (m, 1H), 6.50 (dd, *J* = 8.3, 5.8Hz, 1H), 7.27-8.02 (m, 8H), 8.02, 8.17 (2 × s, 2 × 1H); ^{13}C NMR δ 21.9, 22.0, 38.4, 64.2, 75.3, 83.4, 85.2, 125.6, 126.6, 126.9, 129.5, 129.6, 129.9, 130.1, 138.6, 144.5, 144.8, 145.4, 148.9, 159.5, 166.2, 166.4; HRMS *m/z* 511.1596 [MNa^+ ($C_{26}H_{24}N_4O_6Na$) = 511.1594].

6-Chloro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-*β*-D-ribofuranosyl]purine (3a). Treatment of **2a** (1.78 g, 2.50 mmol) by method 2 gave **3a** (1.60 g, 87%): mp 123–126 ℃; ^{1}H NMR δ 2.08, 2.19, 2.25 (3 × s, 3 × 6H), 2.26, 2.29, 2.32 (3 × s, 3 × 3H), 4.71–4.80 (m, 3H), 6.14 (t, *J* = 5.0 Hz, 1H), 6.36–6.40 (m, 2H), 6.79, 6.84, 6.87 (3 × s, 3 × 2H), 8.21, 8.65 (2 × s, 2 × 1H); ^{13}C NMR δ 20.07, 20.12, 20.2, 21.38, 21.40, 21.5, 63.4, 71.5, 73.9, 81.2, 87.6, 128.6, 128.86, 128.90, 129.0, 129.2, 129.9, 132.4, 135.4, 136.0, 136.1, 140.2, 140.5, 140.7, 144.1, 151.4, 151.8, 152.6, 168.6, 168.8, 169.7; HRMS *m/z* 747.2560 [MNa^+ ($C_{40}H_{41}N_4{}^{35}Cl\ O_7Na$) = 747.2561].

6-Chloro-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (3b). Treatment of **2b** (1.00 g, 1.6 mmol) by method 2 gave **3b** (0.87 g, 85%): mp 149–151 ℃; ^{1}H NMR δ 2.39, 2.43, 2.43 (3 × s, 3 × 3H), 4.67 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.82–4.86 (m, 1H), 4.92 (dd, *J* = 12.2, 2.9 Hz, 1H), 6.20 (t, *J* = 4.9 Hz, 1H), 6.38 (t, *J* = 4.6 Hz, 1H), 6.45 (d, *J* = 4.6 Hz, 1H), 7.16-7.98 (m, 12H), 8.28, 8.62 (2 × s, 2 × 1H); ^{13}C NMR δ 22.98, 22.02, 63.4, 71.6, 74.0, 81.5, 87.6, 125.8, 126.2, 126.7, 129.5, 129.56, 129.62, 129.98, 130.13, 130.14, 132.6, 144.1, 144.6, 144.9, 145.1, 151.6, 151.8, 152.6, 165.4, 165.6, 166.4; HRMS *m/z* 663.1625 [MNa^+ ($C_{34}H_{29}N_4{}^{35}Cl\ O_7Na$) = 663.1622].

6-Chloro-9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]purine (3c). Treatment of **2c** (0.50 g, 1.0 mmol) by method 2 gave **3c**

(0.31 g, 60%): mp 111–113 ℃ (lit.[28] 108–110 ℃); ^{1}H NMR δ 2.42, 2.46 (2 × s, 2 × 3H), 2.90–2.93 (m, 1H), 3.17–3.20 (m, 1H), 4.65–4.70 (m, 2H), 4.80–4.83 (m, 1H), 5.85–5.87 (m, 1H), 5.59 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.22–8.00 (m, 8H), 8.30, 8.69 (2 × s, 2 × 1H); ^{13}C NMR δ 21.96, 22.02, 38.2, 64.0, 75.2, 83.7, 85.6, 126.5, 126.7, 129.56, 129.59, 129.8, 130.1, 132.5, 143.7, 144.6, 144.9, 151.4, 151.6, 152.3, 166.2, 166.3; HRMS *m/z* 529.1263 [MNa^+ ($C_{26}H_{23}N_4{}^{35}Cl\ O_5Na$) = 529.1255].

6-Iodo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (4a). Treatment of **3a** (0.50 g, 0.7 mmol) by method 3 gave **4a** (0.41g, 73%): mp143–145 ℃; ^{1}H NMR δ 2.07, 2.19, 2.24 (3 × s, 3 × 6H), 2.25, 2.87, 2.33 (3 × s, 3 × 3H), 4.71–4.74 (m, 2H), 4.77–4.80 (m, 1H), 6.15 (t, *J* = 4.5 Hz, 1H), 6.32 (d, *J* = 4.5 Hz, 1H), 6.38 (t, *J* = 4.5 Hz, 1H), 6.79, 6.83, 6.86 (3 × s, 3 × 2H), 8.22, 8.52 (2 × s, 2 × 1H); ^{13}C NMR δ 20.09, 20.12, 20.2, 21.38, 21.39, 21.5, 63.4, 71.5, 73.9, 81.2, 87.8, 122.8, 128.6, 128.86, 128.88, 129.0, 129.2, 129.9, 135.4, 136.0, 136.1, 139.3, 140.2, 140.5, 140.7, 143.5, 147.6, 152.5, 168.6, 168.8, 169.8; HRMS *m/z* 839.1929 [MNa^+ ($C_{40}H_{41}N_4IO_7Na$) = 839.1918].

6-iodo-9-[2,3,5-Tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (4b). Treatment of **3b** (0.25 g, 0.4 mmol) by method 3 gave **4b** (0.23 g, 80%): mp 177–179 ℃; ^{1}H NMR δ 2.39 (s, 3H), 2.44 (s, 6H), 4.65 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.82–4.85 (m, 1H), 4.92 (dd, *J* = 12.0, 3.0 Hz, 1H), 6.20 (t, *J* = 5.2 Hz, 1H), 6.40 (t, *J* = 5.5 Hz, 1H), 6.43 (d, *J* = 5.0 Hz, 1H), 7.16–7.98 (m, 12H), 8.29, 8.50 (2 × s, 2 × 1H); ^{13}C NMR δ 21.98, 22.00, 22.02, 63.4, 71.6, 73.9, 81.5, 87.6, 122.9, 125.8, 126.2, 126.7, 129.5, 129.58, 129.63, 130.0, 130.13, 130.14, 139.5, 143.5, 144.6, 144.9, 145.1, 147.8, 152.5, 165.4, 165.6, 166.4; HRMS *m/z* 755.0969 [MNa^+ ($C_{34}H_{29}N_4IO_7Na$) = 755.0979].

9-(2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl)-6-iodopurine (4c). Treatment of **3c** (50 mg, 0.1 mmol) by method 3 gave **4c** (39 mg, 66%): mp 133–136 ℃; ^{1}H NMR δ 2.42, 2.46 (2 × s, 2 × 3H), 2.87–2.91 (m, 1H), 3.16–3.22 (m, 1H), 4.64–4.69 (m, 2H), 4.79–4.82 (m, 1H), 5.83–5.85 (m, 1H), 6.55 (dd, *J* = 8.2, 5.5 Hz, 1H), 7.22–8.00 (m, 8H), 8.31, 8.56 (2 × s, 2 × 1H); ^{13}C NMR δ 21.98, 22.02, 38.2, 64.0, 75.3, 83.7, 85.7, 122.7, 126.5, 126.7, 129.57, 129.58, 129.8, 130.1, 139.5, 143.0, 144.6, 144.9, 147.6, 152.2, 166.2, 166.3; HRMS *m/z* 621.0606 [MNa^+ ($C_{26}H_{23}N_4IO_5Na$) = 621.0611].

6-(Hexyn-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (5). To a solution of **4b** (50 mg, 0.068 mmol) in TEA (3 mL) were added $(Ph_3P)_4Pd$ (7 mg, 0.006 mmol) and CuI (2 mg, 0.011 mmol). 1-Hexyne (40 μL, 29 mg, 0.35 mmol) was added, and the mixture was stirred at room temperature for 20 min. Volatiles were removed in vacuo, and the residue was chromatographed (EtOAc/hexanes, 3:7) to give **5** (43 mg, 92%): ^{1}H NMR δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.49–1.54 (m, 2H), 1.67–1.71 (m, 2H), 2.38 (s, 3H), 2.42 (s, 6H), 2.59 (t, *J* = 7.3 Hz, 1H), 4.65 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.82–4.84 (m, 1H), 4.90 (dd, *J* = 12.2, 2.9 Hz, 1H), 6.22 (t, *J* = 5.3 Hz, 1H), 6.38 (t, *J* = 5.4 Hz, 1H), 6.47 (d, *J* = 5.4 Hz, 1H), 7.17–8.00 (m, 12H), 8.25, 8.79 (2 × s, 2 × 1H); ^{13}C NMR δ 13.8, 19.9, 21.96, 22.00, 22.4, 30.4, 63.6, 71.6, 73.9, 76.2, 81.3, 87.1, 102.3, 125.8, 126.2, 126.8, 129.48, 129.53, 129.6, 130.0, 130.1, 135.1, 143.2, 143.8, 144.5, 144.8, 145.0, 151.3, 153.1, 165.4, 165.6, 166.4; HRMS *m/z* 709.2632 [MNa^+ ($C_{40}H_{38}N_4O_7Na$) = 709.2638].

6-(4-Methoxyphenyl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (6). To a solution of **4b** (73 mg, 0.10 mmol) in toluene (3 mL)

were added $Pd(Ph_3P)_4$ (12 mg, 0.010 mmol) and K_2CO_3 (70 mg, 0.5 mmol). 4-Methoxyphenylboronic acid (30 mg, 0.20 mmol) was added and the mixture was stirred at 100 ℃ for 5 h. After cooling to ambient temperature, the mixture was filtered. Volatiles were evaporated in vacuo, and the residue was chromatographed (CH_2Cl_2/Me_2CO) to give **6** (63 mg, 83%): ^{1}H NMR δ 2.38, 2.40, 2.43 (3 × s, 3 × 3H), 3.90 (s, 3H), 4.69 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.85 (dd, *J* = 7.8, 4.4 Hz, 1H), 4.92 (dd, *J* = 12.2, 3.4 Hz, 1H), 6.27 (t, *J* = 5.3 Hz, 1H), 6.47 (t, *J* = 5.3 Hz, 1H), 6.54 (d, *J* = 5.4 Hz 1H), 7.06-8.01 (m, 14H), 8.27 (s, 1H), 8.77 (d, *J* = 8.8 Hz, 2H), 8.91 (s, 1H); ^{13}C NMR δ 21.9, 21.97, 22.00, 55.6, 63.7, 71.7, 74.0, 81.2, 87.1, 114.3, 126.0, 126.3, 126.8, 128.4, 129.48, 129.52, 129.6, 130.0, 130.1, 130.2, 131.3, 131.8, 142.6, 144.4, 144.8, 144.9, 152.2, 152.9, 155.3, 162.3, 165.5, 165.7, 166.5; HRMS *m/z* 735.2416 [MNa^+ ($C_{41}H_{36}N_4O_8Na$) = 735.2431].

2',3',5'-Tri-*O*-(4-methylbenzoyl)-6-*N*-phenyladenosine (7). Aniline (90 μL, 93 mg, 1.0 mmol) was added to a solution of **4b** (73 mg, 0.10 mmol) in acetonitrile (3 mL). The mixture was stirred at 82 ℃ for 5 h. Volatiles were removed in vacuo, and the residue was chromatographed (EtOAc/hexanes, 3:7) to give **7** (56 mg, 80%): ^{1}H NMR δ 2.38, 2.39, 2.42 (3 × s, 3 × 3H), 4.70 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.81–4.84 (m, 1H) 4.91 (dd, *J* = 12.2, 3.0 Hz, 1H) 6.25 (t, *J* = 5.0, 1H) 6.39 (t, *J* = 5.5 Hz, 1H), 6.48 (d, *J* = 5.4, 1H) 7.12 (t, *J* = 7.5 Hz, 1H), 7.16–7.26 (m, 6H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.87 (br, 1H), 7.91–8.01 (m, 4H), 8.04, 8.49 (2 ×s, 2 × 1H); ^{13}C NMR δ 21.8, 21.87, 21.89, 63.7, 71.6, 74.1, 81.1, 86.8, 120.7, 120.9, 123.9, 125.9, 126.2, 126.7, 129.2, 129.37, 129.40, 129.5, 129.9, 130.0, 130.1, 138.6, 139.4,

144.3, 144.7, 144.8, 149.6, 152.4, 153.2, 165.4, 165.6, 166.4; HRMS *m/z* 720.2431 [MNa^+ ($C_{40}H_{35}N_5O_7Na$) = 720.2434].

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Chapter 2 Kinetic Studies[1]

2.1. Introduction

Natural purine bases play a central role in many biological processes.[2] Recent advances in the synthesis of C6 modified purines have included the use of S_NAr,[3] Suzuki–Miyaura[4] and Sonogashira[5] coupling reactions. Many N, O and S substituents have been introduced at C6 by nucleophilic aromatic substitution of 6-halo purine nucleosides. For 1-halo-2,4-dinitrobenzenes, the order of reactivity for S_NAr is F>Cl>Br >I.[6] However, the order of reactivity for 6-halopurines is apparently different. Véliz and Beal reported that 6-bromopurine nucleosides are more reactive than 6-chloropurine nucleosides for S_NAr reactions using a weakly nucleophilic arylamine. Our previous studies showed that 6-iodopurine nucleosides are more reactive than 6-chloropurine nucleosides for S_NAr reactions using aniline.[7] Because 6-alkylsulfonyl purine derivatives are also good substrates for S_NAr displacement, it was of interest to compare the reactivity of a sulfone with that of the four 6-halopurine nucleosides.[8] To the best of our knowledge, comparisons among 6-fluoro-, 6-chloro-, 6-bromo, 6-iodo and 6-sulfonylpurine nucleosides for S_NAr reactions have not been systematically explored. Therefore, we initiated a detailed comparison of the S_NAr reactivity of a 6-sulfonylpurine and the four 6-halo nucleosides. Various N, O and S nucleophiles under different conditions were used in this study.

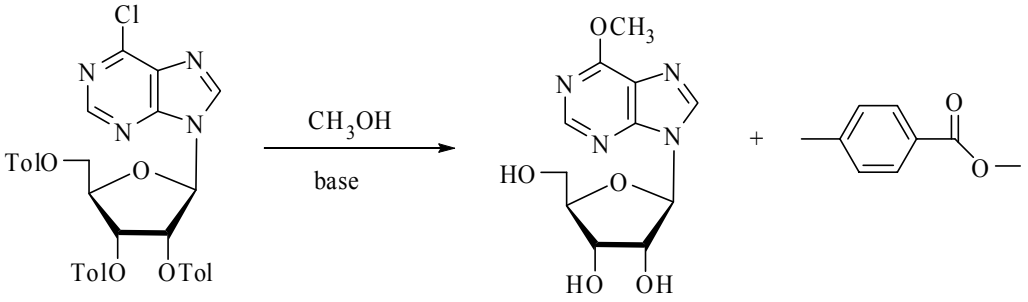
2.2. Results and Discussion

2.2.1. Preparation of 6-(Substituted)purine Nucleosides

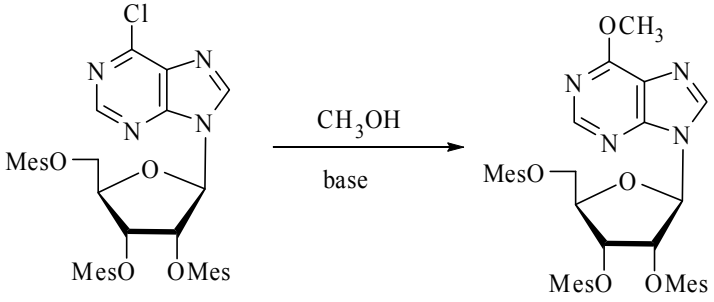
Initially, sugar hydroxyl groups on the precursor inosine nucleosides were protected as *p*-toluoyl (4-methylbenzoyl) esters because they crystallize much more

readily and are more stable to base than acetyl groups.[9] However, removal of the toluoyl groups from the sugar moiety of **1** was observed during the S_NAr reaction of **1** with methoxide (Scheme 1). Various bases, including DBU, Na_2CO_3 and K_2CO_3; and various reaction conditions were investigated. However, the S_NAr reaction did not go to completion without formation of deprotected analogs. Since a mesitoate ester is exceptionally stable to base, mesitoyl was tested for the sugar protecting group.[10] To our delight, no deprotection was detected during the S_NAr reaction of **2** and methoxide. When inosine was treated with 2,4,6-trimethylbenzoic acid and trifluoroacetic anhydride at room temperature,[11] some cleavage of the glycosyl linkage was detected. Once the reaction temperature was lowered to 0 ºC, no cleavage of the glycosyl linkage occurred and the sugar-protected inosine **3** was obtained in good yield (Scheme 2). The sugar protected adenosine **4** was obtained by a similar procedure.

Scheme 1. Synthesis of 6-Methoxypurine Nucleosides

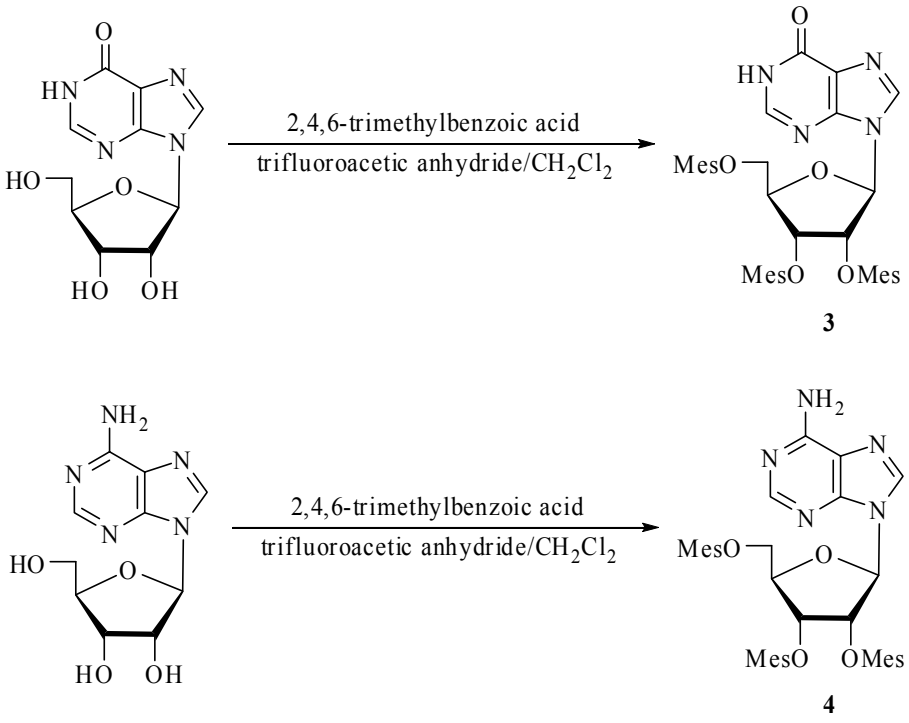


1



2

Scheme 2. Protection of Hydroxyl Group in Inosine and Adenosine



3

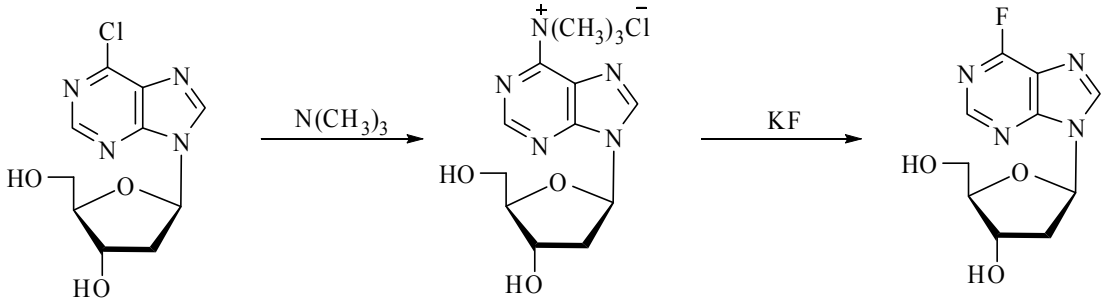
4

According to a previously reported method, a 6-fluoropurine compound could be obtained from its 6-chloropurine precursor. Lister and coworkers first reported treating 6-chloropurines and nucleosides with trimethylamine.[12] The resulting quaternary ammonium salt underwent displacement with KF to give both 6-fluoropurine riboside and 2-amino-6-fluoropurine riboside in moderate yields. Robins and coworkers improved this procedure to obtain 6-fluoropurine compounds in good yields and also applied it for the synthesis of the 6-fluoropurine 2′-deoxynucleoside (Scheme 3).[13] Harris and coworkers further modified the procedure by replacing the hygroscopic KF with a non-hygroscopic tetrabutylammonium triphenyldifluorosilicate ($Bu_4N^+Ph_3SiF_2^-$) salt.[14]

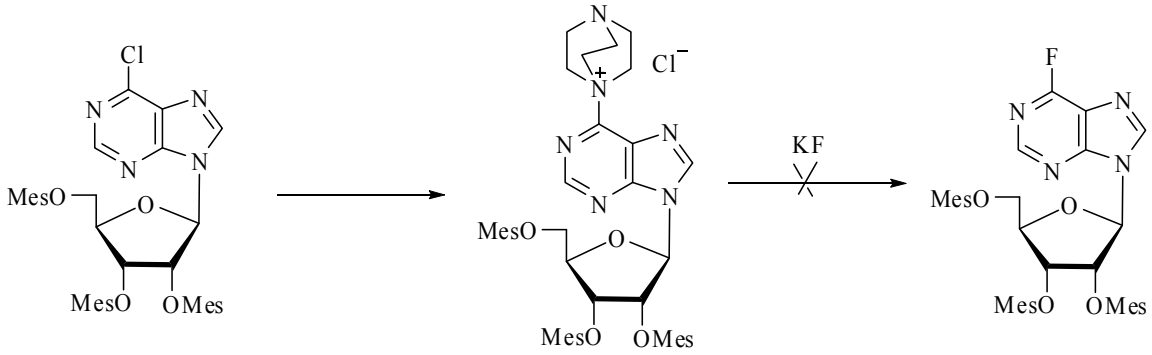
The method shown in Scheme 3 required working with the highly volatile compound trimethylamine. Initially, we used DABCO instead of trimethylamine to

replace chloride. However, no desired 6-fluoropurine nucleoside was formed when compound **5** was treated with KF.

Scheme 3. Synthesis of 6-Fluoropurine Nucleoside via a Quaternary Ammonium Salt



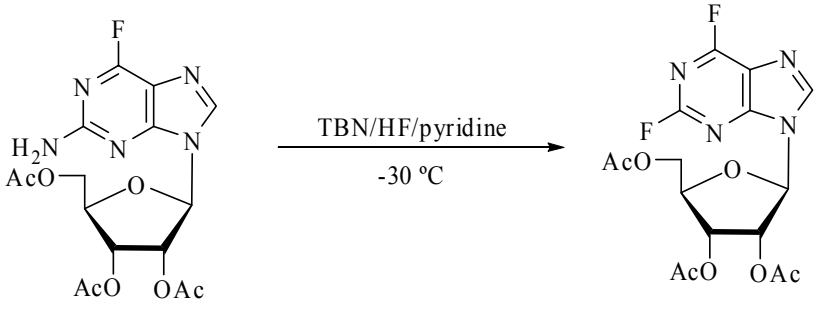
Scheme 4. Attempted Synthesis of a 6-Fluoropurine Nucleoside via a DABCO Salt



2 **5**

Such 6-fluoropurine compounds can also be made by diazotization reactions. Olah and coworkers[15] reported conversions of aromatic amines to aryl fluorides using HF-pyridine solutions and sodium nitrite. Robins[16] and Montgomery[17] and their coworkers have reported conversions of amino groups to fluoro substituents on purine rings using similar conditions. For example, the 2-aminopurine compound **6** was converted into the 2-fluoropurine compound **7** by treatment with HF-pyridine and *tert*-butyl nitrite (Scheme 5).

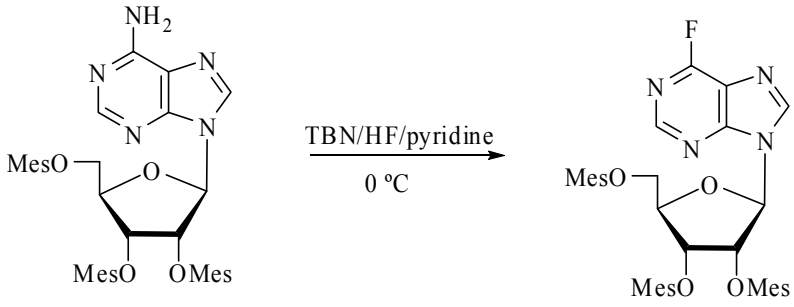
Scheme 5. Synthesis of a 2-Fluoropurine Nucleoside



6 **7**

We obtained compound **8** directly from its mesitoyl-protected adenosine precursor **4** via the fluorodeamination method with HF-pyridine and TBN (Scheme 6).

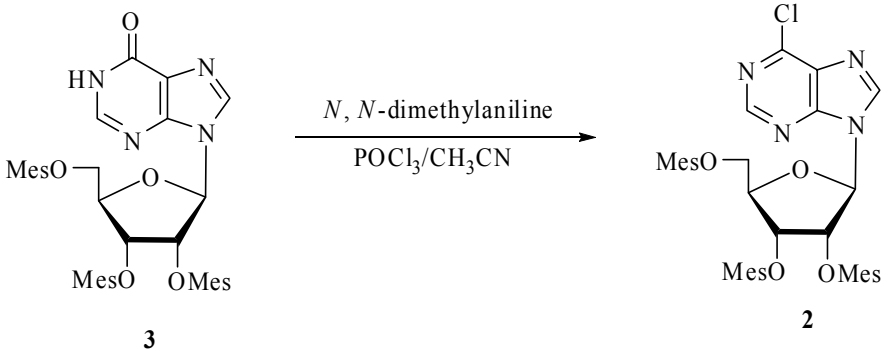
Scheme 6. Synthesis of a 6-Fluoropurine Nucleoside



4 **8**

Deoxygenative chlorination of the 6-oxo group of purine nucleosides has been a widely used method for syntheses of 6-chloropurine nucleosides. Gerster et al. reported the first synthesis of 6-chloropurine nucleosides from inosine.[18] Treatment of sugar-protected inosine with phosphorous oxychloride and *N*,*N*-dimethylaniline gave the corresponding 6-chloropurine nucleosides in moderate yields.[19] Our mesitoyl-protected inosine was treated with $POCl_3$ and *N*,*N*-dimethylaniline in CH_3CN to give the crystalline 6-chloropurine nucleoside **2** (Scheme 7).

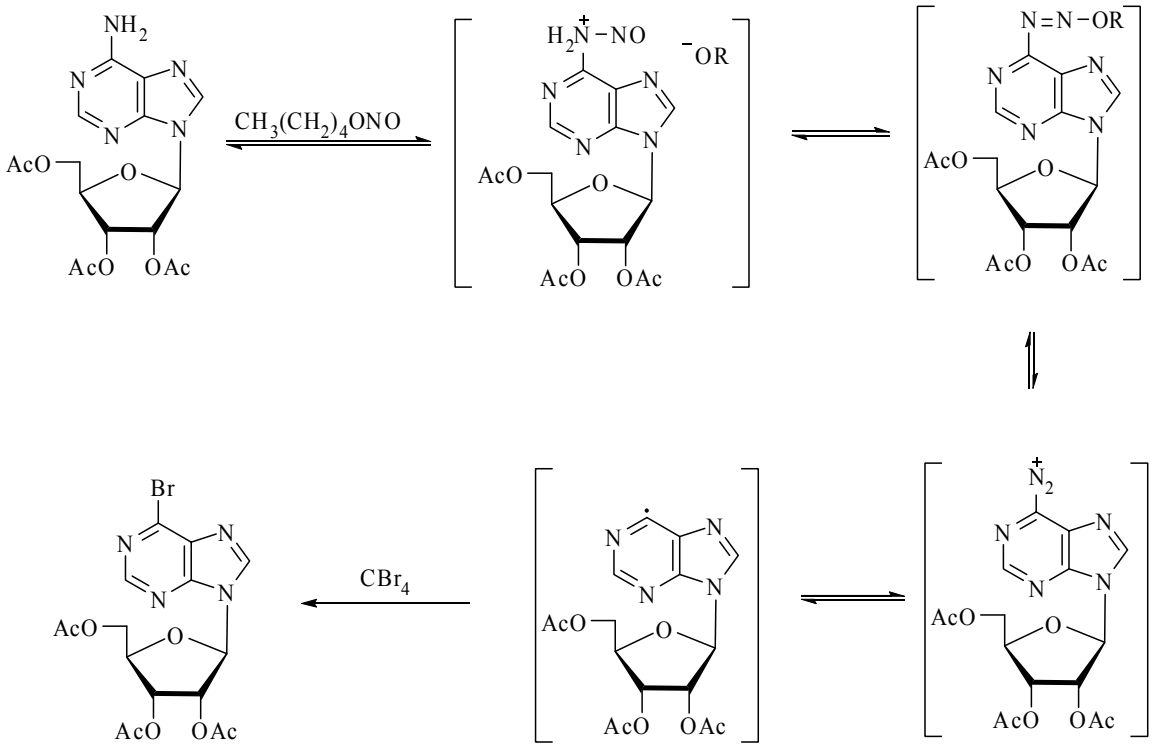
Scheme 7. Synthesis of a 6-Chloropurine Nucleoside



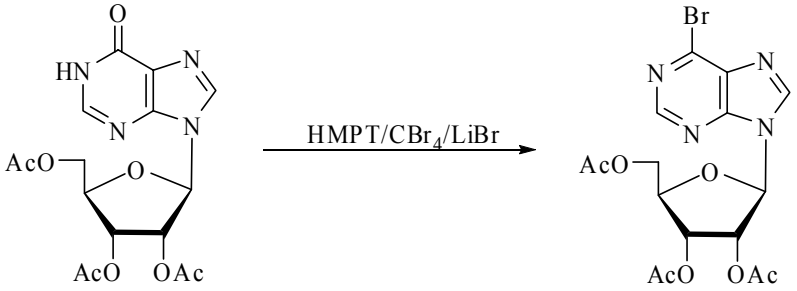
3 **2**

Nair and Richardson reported conversion of *O*-protected adenosine derivatives into 6-bromopurine analogs in good yields by diazotization (Scheme 8).[20] Beal and Véliz reported deoxygenative bromination of a protected inosine using a modified Appel protocol (Scheme 9).[3b] Treatment of a solution of a sugar-protected inosine with hexamethylphosphorous triamide (HMPT) and carbon tetrabromide in the presence of an external bromide source (LiBr) gave the 6-bromopurine derivative in good yield. However, one drawback of this procedure is that the carcinogenic reagents CBr_4 and HMPA (generated in the process) are involved.

Scheme 8. Mechanism of Synthesis of a 6-Bromopurine Nucleoside by Diazotization



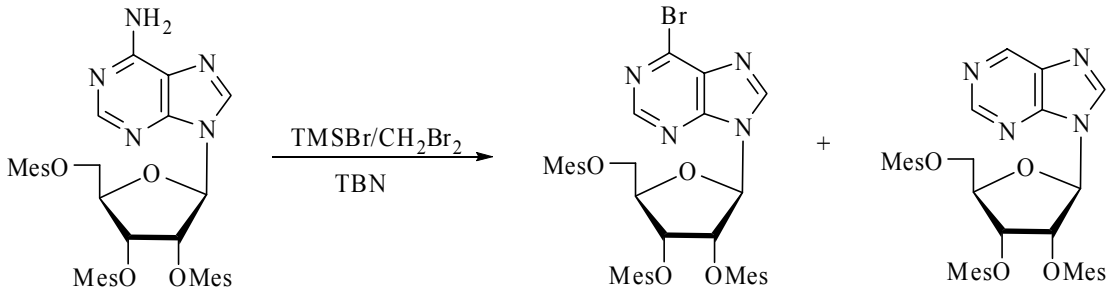
Scheme 9. Syntheis of a 6-Bromopurine Nucleoside from Inosine



Initially, our 6-bromopurine nucleoside was prepared by diazotization-bromodeamination. A small amount of the purine nucleoside byproduct **9** was detected, which was hard to remove by chromatography (Scheme 10). Then, we tried to prepare the 6-bromopurine nucleoside by a bromide/chloride displacement with NaBr/TFA. However, only 33% was converted to the desired product. A better conversion (67%) was obtained when LiBr/TFA was used instead of NaBr. Silyl-mediated halogen/halogen displacements with pyridines have been recently reported (Scheme 11).[21] A silicon-

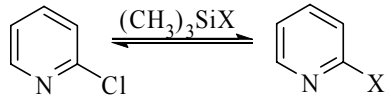
chloride bond is much stronger than a silicon-bromide bond, which drives this reaction. Then, we investigated silyl-mediated displacements in the purine system.

Scheme 10. Syntheis of a 6-Bromopurine Nucleoside by Diazotization



9

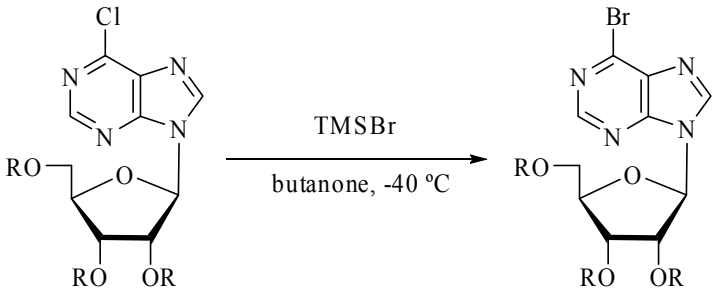
Scheme 11. Halo-chloro Exchangement on Pyridine with TMSX



X = Br, I

We observed high-yield conversions of 6-chloropurine nucleosides to their 6-bromo analogs via a bromide displacement reaction using TMSBr in butanone at ≤ –40 ºC (NMR conversion > 98%, isolated crystalline yield 80%) (Scheme 12). Syntheses of 6-bromopurine nucleosides from diazotative bromo-deamination demand considerable care to avoid formation of purine nucleoside byproducts. Our developed methodology gave analytically pure 6-bromopurine nucleoside **10** in good yields. No trace of the purine nucleoside was found. This method was extended to prepare compound **11**.

Scheme 12. Synthesis of 6-Bromopurine Nucleosides with TMSBr



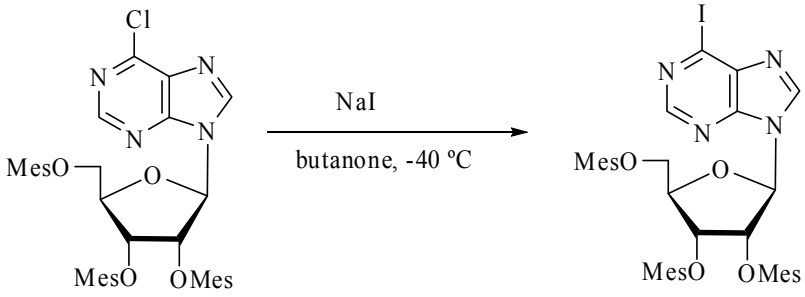
1, **2**

10, **11**

1, **11** R = Tol
2, 10 R = Mes

The 6-iodopurine nucleoside **12** was prepared from the 6-chloropurine nucleoside **2** by an aromatic Finkelstein reaction at ≤ –40 ºC (Scheme 13).

Scheme 13. Synthesis of a 6-Iodopurine Nucleoside

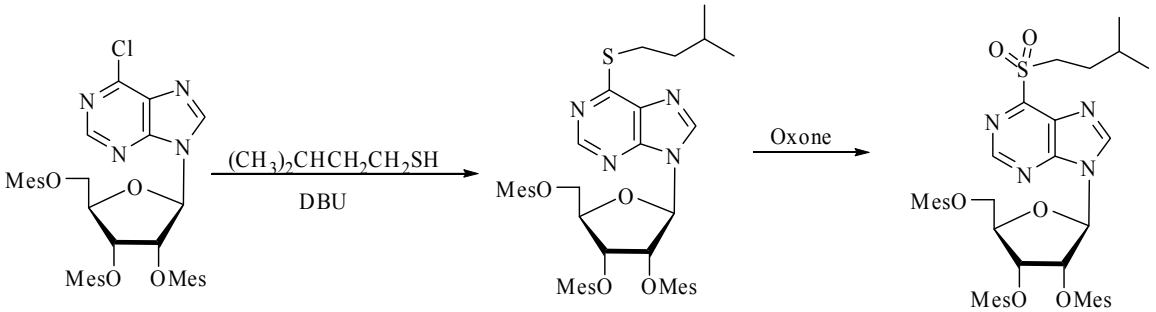


2

12

The 6-(isopentylsulfonyl)purine nucleoside **14** was synthesized by treatment of its 6-isopentylsulfanyl precursor **13** with Oxone/brine/pH 5 buffer in MeOH/H_2O (Scheme 14).[8]

Scheme 14. Synthesis of a 6-(Alkylsulfonyl)purine Nucleoside



2 **13** **14**

2.2.2. Kinetic Studies

All kinetic experiments were conducted under pseudo-first-order conditions.

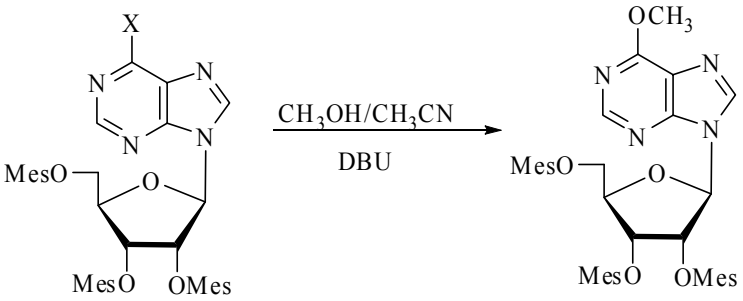
$k_1t = -2.303 \log(C/C_0) + a$ (equation 1)

where C/C_0 is the ratio of the concentration of 6-halopurine nucleoside in the mixture at time *t* to the initial concentration of 6-halopurine nucleoside. Values of the term $-\log(C/C_0)$ were plotted against *t* (min) k (sec^{-1}) = k_1 (min^{-1})/60

2.2.2.1. S_NAr Reactions of 6-Halopurine Nucleosides with Oxygen Nucleophiles.

To study the reactivity of 6-halopurine derivatives towards nucleophilic displacement with an oxygen nucleophile, methanol was allowed to react with the compounds **2**, **8**, **10** and **12** in the presence of DBU (5 eq) in acetonitrile/CH_3OH at 25 ºC. The rate constant for the reaction of fluoropurine nucleoside **8** was not determined because the reaction was immeasurably fast, even at 0 ºC. The reactivity order is F>>Cl≈Br>I (Table 1, Figure 1).

Scheme 15. S_NAr Reactions of **2**, **8**, **10**, and **12** with Methanol



2 X = Cl
8 X = F
10 X = Br
12 X = I

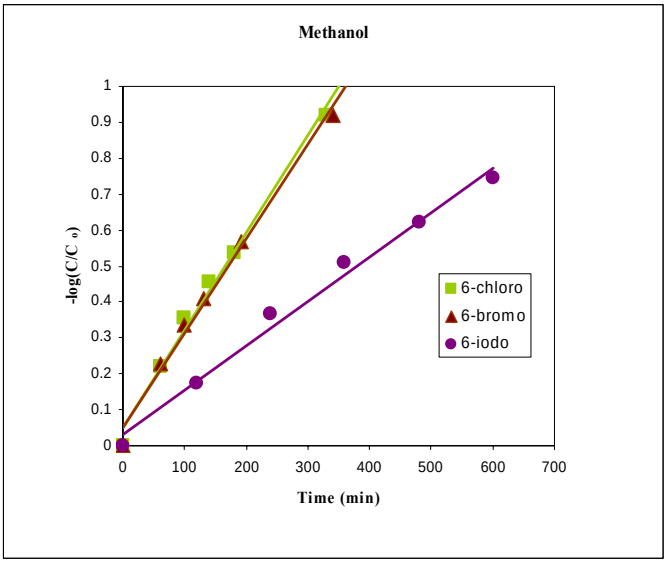
15

Table 1. Kinetic Data for Substitution with 6-Halopurine Nucleosides

Nucleophile		k (sec^{-1})	R^a	n^b
CH_3OH/DBU	Cl	1.0×10^{-4}	0.990	5
(MeCN)	Br	1.0×10^{-4}	0.991	5
(25 °C)	I	4.6×10^{-5}	0.989	5
$BuNH_2$	Cl	4.6×10^{-5}	0.997	5
(25 °C)	Br	7.3×10^{-5}	0.993	5
	I	2.3×10^{-5}	0.996	5
$K^{+-}SCOMe$	F	1.6×10^{-3}	0.999	5
(DMSO)	Cl	2.2×10^{-4}	0.999	9
(30 °C)	Br	5.2×10^{-4}	0.999	5
	I	5.2×10^{-4}	0.999	5
$PhNH_2$/TFA	F	2.5×10^{-3}	0.998	6
(MeCN)	Cl	3.8×10^{-4}	0.999	9
(50 °C)	Br	6.9×10^{-4}	0.999	10
	I	1.7×10^{-3}	0.999	7

[a] Correlation coefficient. [b] Number of points. [c] Experiments are repeated three times [differences among the three experiments were within $(k \pm 0.1) \times 10^{-n}$].

Figure 1. S_NAr Reactions of **2**, **10**, and **12** with Methanol



2.2.2.2. S_NAr Reactions of 6-Halopurine Nucleosides with Sulfur Nucleophiles.

To study the reactivity of 6-halo derivatives **2**, **8**, **10** and **12** towards nucleophilic displacement with sulfur nucleophiles, potassium thioacetate (5 eq) was allowed to react with the compounds in DMSO at 30 ºC. The reactivity order is F>Br≈I>Cl (Table 1, Figure 2). A comparative study using isopentyl thiol as the nucleophile in acetonitrile in the presence of DBU at ≤ –40 ºC gave the same reactivity order as did the reaction with potassium thioacetate (Scheme 16).

Scheme 16. S_NAr Reactions of **2**, **8**, **10**, and **12** with Thioacetate and Isopentylthiol

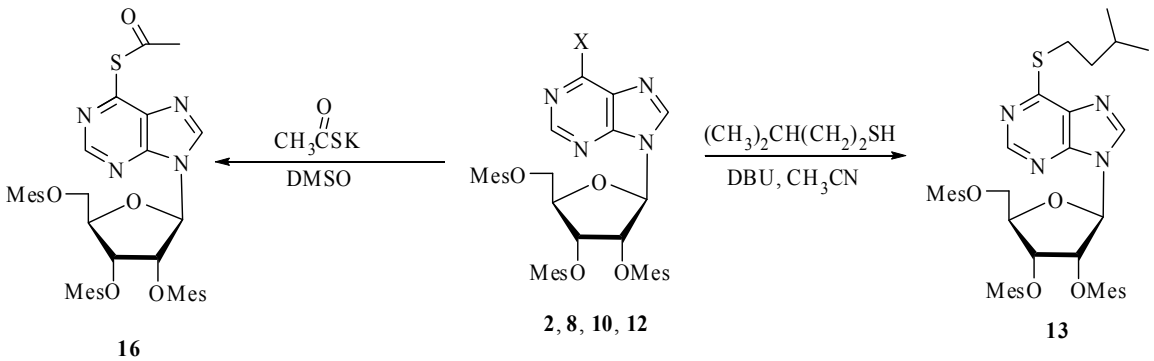
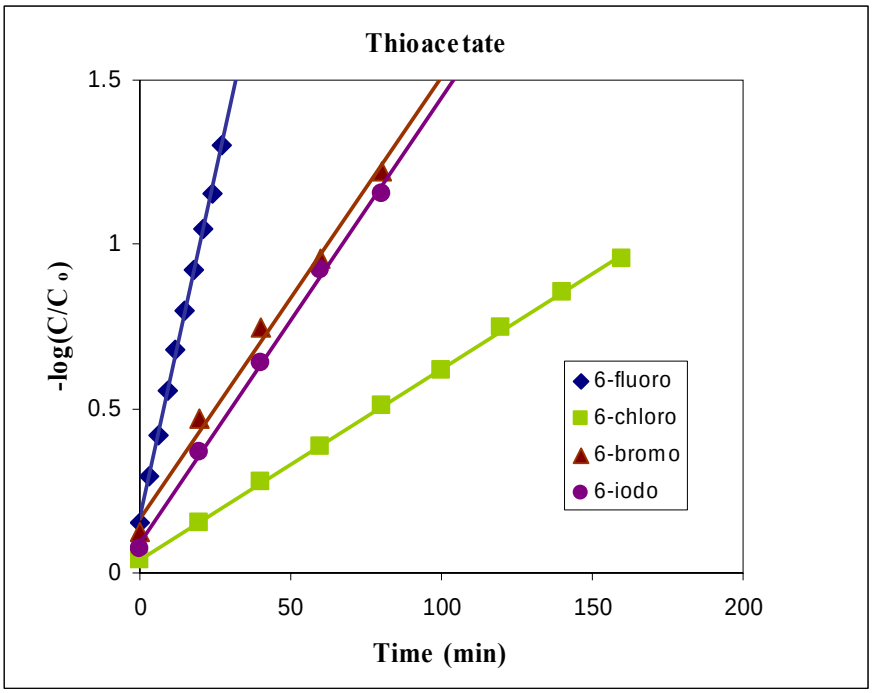


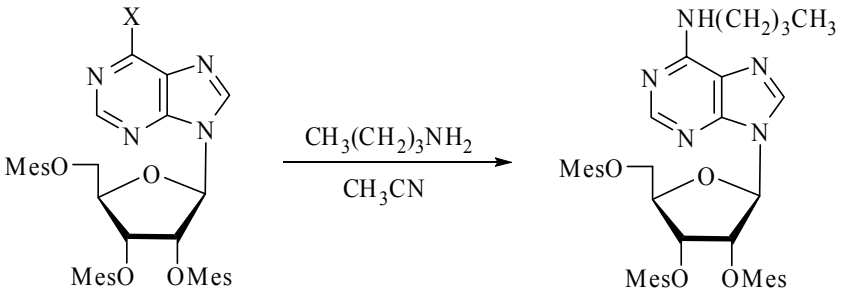
Figure 2. S_NAr Reactions of **2**, **8**, **10**, and **12** with Thioacetate



2.2.2.3. S_NAr Reactions of 6-Halopurine Nucleosides with a Primary Aliphatic Amine.

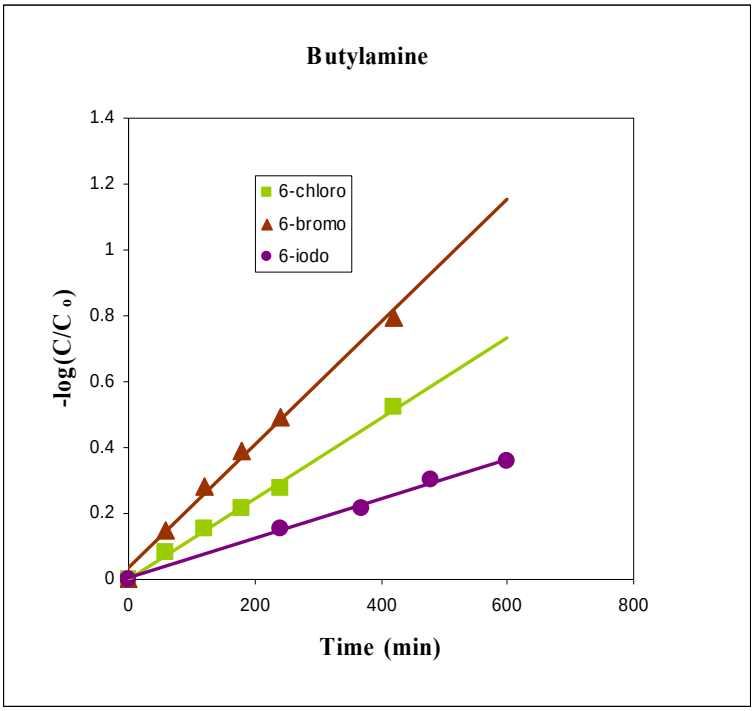
Butylamine (10 eq) reacts with the 6-halopurine ribonucleosides **2**, **8**, **10** and **12** in acetonitrile at 25 ºC (Scheme 17). The rate constant for the reaction of the fluoropurine nucleoside **8** was not measured because the reaction was too fast, even at 0 ºC. The reactivity order is F>>Br>Cl>I (Table 1, Figure 3).

Scheme 17. S_NAr Reactions of **2**, **8**, **10**, and **12** with Butylamine



2, **8**, **10**, **12** **17**

Figure 3. S_NAr Reactions of **2**, **10**, and **12** with Butylamine

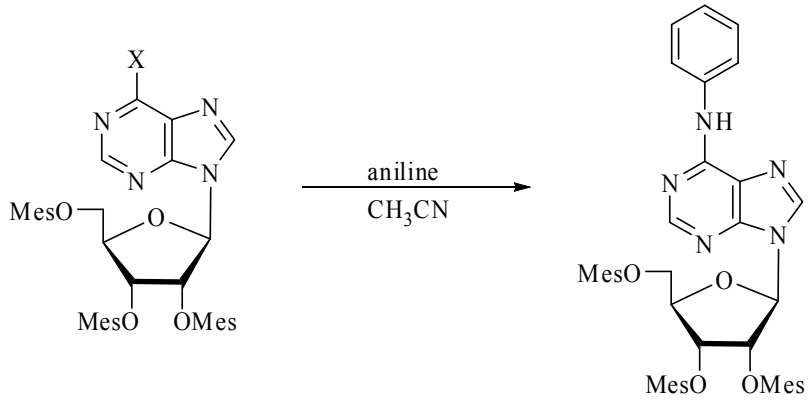


2.2.2.4. S_NAr Reactions of 6-Halopurine Nucleosides with Aromatic Amine Nucleophiles.

Lakshman and coworkers had resorted to palladium-catalyzed coupling of 6-chloropurine compounds with aryl amines,[22] wheras Véliz and Beal reported that 6-bromonucleosides react smoothly with aromatic amines in CH_3OH. However, we found that the 6-iodo derivative **4** was not very soluble in CH_3OH, so acetonitrile was used instead. The 6-halopurine ribonucleosides were treated with aniline (5 eq) in acetonitrile at 70 ºC. The reactivity order was I>Br>Cl>F. A lag period of approximately 50 min (iodo, **12**), 1 h (bromo, **10**), 2 h (chloro, **2**) and 6 h (fluoro, **8**) was observed before the S_NAr displacements began (Figure 4). Véliz and Beal had reported that acetonitrile did not support substitution reactions of 6-chloropurine or 6-bromopurine nucleosides with arylamines. The lag period appears to be an explanation for the observed reactivity

differences. We found that the rates of the 6-halopurine substitution reactions with aniline were accelerated at longer reaction times, which was ascribed to an autocatalytic effect of the hydrogen halide formed. Enhanced purine S_NAr reactivity with addition of TFA has been noted.[23] When TFA (2 eq) was used as catalyst, the lag period disappeared and the S_NAr reaction proceeded much faster at 50 ºC (rather than 70 ºC) (Figure 5). The reactivity order was F>I>Br>Cl with TFA catalysis.

Scheme 18. S_NAr Reactions of **2**, **8**, **10**, and **12** with Aniline



2, **8**, **10**, **12** **18**

This phenomenon prompted us to measure changes in the H2 and H8 ^{1}H NMR chemical shifts of the 6-halopurine nucleosides as a function of added TFA. The chemical shifts were measured by adding TFA to solutions of the 6-halopurine compounds (0.041 mmol) in $CDCl_3$ (0.6 mL) in NMR tubes. Figures 6 and 7 show the relationships between the chemical shifts of H8 and H2 with added TFA equivalents. The H8 signal shifts much more than that for H2 with each of the 6-halopurine nucleosides **2**, **8**, **10** and **12**.

Figure 4. S_NAr Reactions of **2**, **8**, **10**, and **12** with Aniline

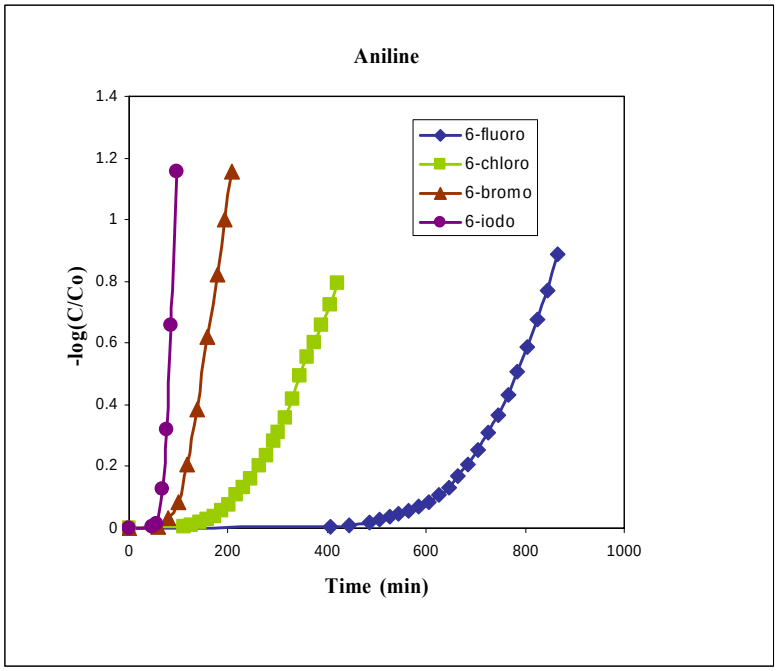


Figure 5. S_NAr Reactions of **2**, **8**, **10**, and **12** with Aniline/TFA

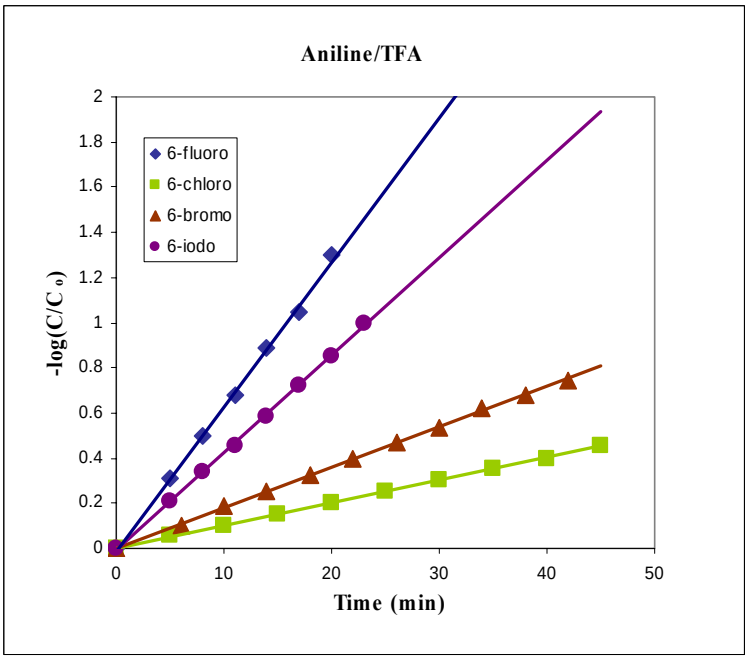


Figure 6. Dependence of the H8 ^{1}H NMR Chemical Shifts of **2**, **8**, **10** and **12** on the Trifluoroacetic Acid Concentration

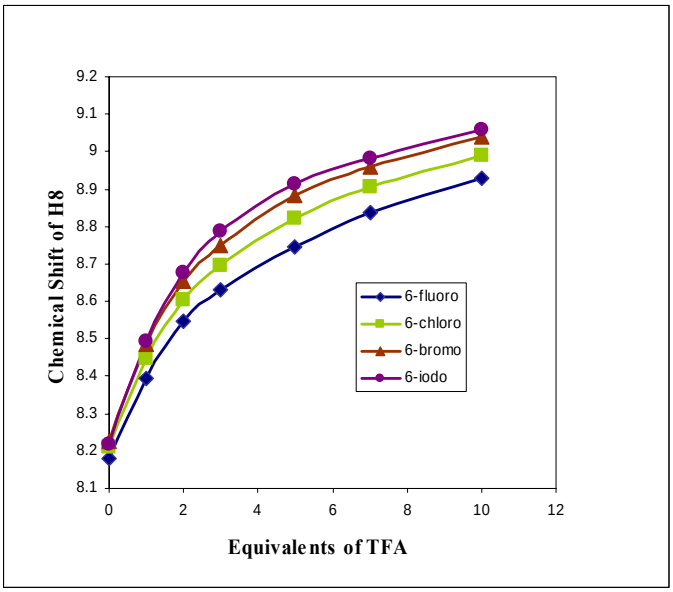
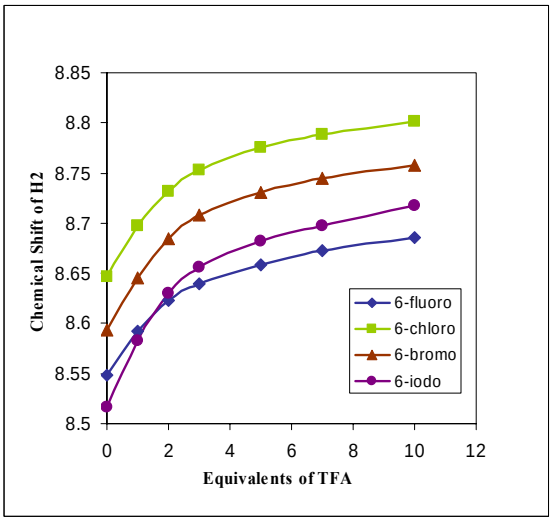


Figure 7. Dependence of the H2 ^{1}H NMR Chemical Shifts of **2**, **8**, **10** and **12** on the Trifluoroacetic Acid Concentration



The larger shifts observed for H8 relative to H2 motivated us to investigate the site of protonation on the 6-halopurine nucleosides. ^{15}N NMR is an ideal method to probe directly for protonation on nitrogen atoms, because the ^{15}N chemical shift is very sensitive to changes in the local environment.[24] TFA was used for identification of protonation sites on purines and nucleosides with ^{15}N NMR,[25] and ^{15}N NMR has been

used to evaluate metal binding to specific nitrogen atoms and for comparison of binding potentials of different sites in hammerhead ribozymes.[26] It seemed very worthwhile to investigate the behavior of the nitrogen resonances on protonation, because these should give direct information on the preferred site of protonation.

Assignments of resonances to the specific nitrogen atoms have been made on the basis of nitrogen-fluorine and nitrogen-hydrogen coupling constants, and ^{15}N studies of related compounds.[27] For the 6-fluoropurine nucleoside **8** (see Scheme 15), the $^{2}J_{(N1,\,F)}$ coupling constant at 139 ppm is 47.0 Hz, which is much larger than the 7.3 and 4.7 Hz couplings for N3–F and N7–F. The resonance of N7 at 145.9 ppm is identified by its proton coupling constant (12.1 Hz), which is smaller than the N3 (14.8 Hz) coupling at 134.6 ppm in the six-membered ring. The resonance at 217.7 ppm is assigned to N9 by analogy with adenosine (N9 at 205 ppm using HNO_3 as external standard, 223 ppm with CH_3NO_2 as standard). Assignments of resonances to specific nitrogen atoms of **10** (see Scheme 15) have been made on the basis of nitrogen-hydrogen coupling constants and ^{15}N studies of related compounds. The resonance of N7 is identified by its proton coupling constant (11.6 Hz), which is smaller than the N1 (15.9 Hz) and N3 (14.6 Hz) couplings in the six-membered ring. The reported coupling constant for N1–H of 1-[^{15}N]-6-bromo-9-(2′, 3′,5′-tri-O-acetyl-β-D-ribofuranosyl)purine is 15.9 Hz,[28] which is identical to that of N1 (15.9 Hz) of **10**. The ^{1}H–^{15}N HMQC spectrum of **8** and **10** confirmed the ^{15}N assignments.

The most basic nitrogen of adenosine is N1, while N7 is the most basic nitrogen of inosine and guanosine. Our results show that protonation of the 6-fluoropurine nucleoside **8** takes place mainly at N7 (upfield shift of 16 ppm), but do not exclude lesser

amounts of protonation at the other nitrogens. Protonation of the 6-bromopurine nucleoside **10** takes place mainly at N7 (upfield shift of 16 ppm) with significant protonation also at N1 (upfield 5.5 ppm). These results are consistent with our ^{1}H NMR data, which show larger H8 signal shifts than those for H2 when titrated with TFA.

Table 2. ^{15}N–^{1}H and ^{15}N–^{19}F Coupling Constants for **8** and **10**

Compound	$J_{(N1, H)}$ Hz	$J_{(N3, H)}$ Hz	$J_{(N7, H)}$ Hz	$J_{(N1, F)}$ Hz	$J_{(N3, F)}$ Hz	$J_{(N7, F)}$ Hz
8	15.4	14.8	12.1	47.0	7.3	4.7
10	15.9	14.6	11.6			

Table 3. Dependence of the ^{15}N NMR Chemical Shifts of 6-Fluoropurine Nucleoside **8** upon the Trifluoroacetic Acid Concentration (ppm upfield from external $CH_3{}^{15}NO_2$) in $CDCl_3$

Mol equiv of acid	N1	N3	N7	N9
0	139.0	134.6	145.9	217.7
0.2	138.9	134.6	147.0	216.9
0.6	138.9	134.4	152.8	
1.0	139.0	134.3	156.9	216.0
1.6	139.8	134.2	161.8	215.2

Table 4. Dependence of the ^{15}N NMR Chemical Shifts of 6-Bromopurine Nucleoside **10** upon the Trifluoroacetic Acid Concentration (ppm upfield from external $CH_3{}^{15}NO_2$) in $CDCl_3$

Mol equiv of acid	N1	N3	N7	N9
0	102.1	137.2	140.4	217.7
0.2	102.6	137.1	143.0	217.3
0.6	103.9	136.9	148.3	216.5
1.0	105.1	136.8	151.6	216.1
1.6	107.7	136.6	156.2	215.2

However, Roberts and coworkers reported that the ^{15}N NMR chemical shift change of N1 for adenosine is 71.7 ppm with 1.6 eq TFA, and 66.3 ppm for N7 of guanosine with 1.86 eq TFA in DMSO (Tables 5 and 6).[25a] Both chemical shift changes are much larger than our ^{15}N NMR chemical shift change of N7 for 6-bromopurine nucleoside **10** in DMSO, which is 1.2 ppm with 1.6 eq TFA (Table 7). Adenosine has pKa ≈ 3.4, guanosine has pKa ≈ 1.6 and DMSO has pka ≈ –1.8.[29] Because DMSO is a weak base, it can be protonated by TFA and compete with weakly basic nucleosides for protonation (Scheme 19). Adenosine and guanosine are much more basic than the 6-bromopurine nucleoside **10**. However, $CDCl_3$ is extremely nonbasic. From Tables 4 and 7, we can see that the ^{15}N NMR chemical shift change of N7 for 6-bromopurine nucleoside **10** is much larger in $CDCl_3$ than in DMSO (15.8 ppm campared to 1.2 ppm with 1.6 eq TFA). The 6-bromopurine nucleoside **10** is not in competition with a basic solvent (DMSO) for protonation because $CDCl_3$ is nonbasic. The protonation behavior of 6-bromopurine nucleoside **10** in CH_3CN should be similar to that in $CDCl_3$ because CH_3CN has pKa ≈ –10.

Scheme 19. Protonation of DMSO

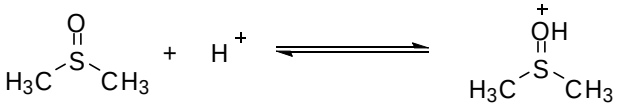


Table 5. Dependence of the ^{15}N NMR Chemical Shift Changes (ppm upfield from external $H^{15}NO_3$) of Adenosine upon the Trifluoroacetic Acid Concentration in DMSO[25a]

Mol equiv of acid	N1	N3	N7	N9
0.31	16.0	0.2	0.6	–1.2
1.6	71.7	–1.9	–3.3	–8.2

Table 6. Dependence of the ^{15}N NMR Chemical Shift Changes (ppm upfield from external $H^{15}NO_3$) of Guanosine upon the Trifluoroacetic Acid Concentration in DMSO[25a]

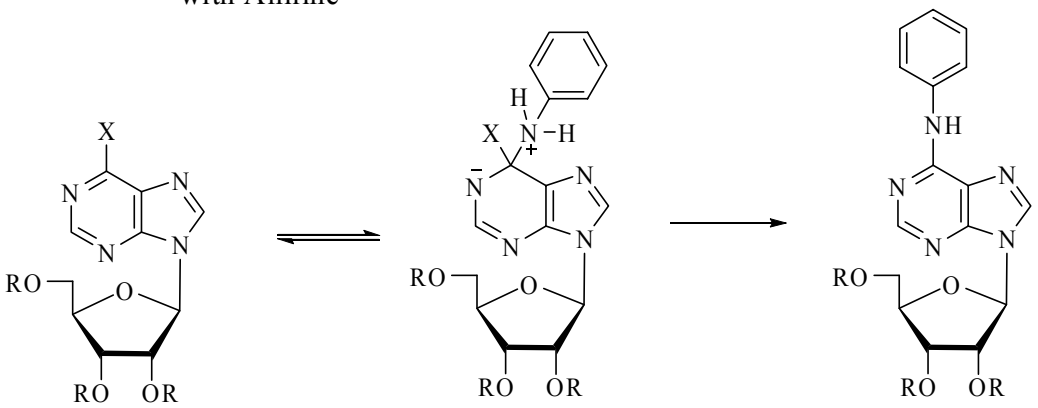
Mol equiv of acid	N1	N3	N7	N9
0.36	–0.8	0.4	21.9	–1.7
1.86	–2.0	1.5	66.3	–5.9

Table 7. Dependence of the ^{15}N NMR Chemical Shifts Changes (ppm upfield from external $CH_3{}^{15}NO_2$) of 6-Bromopurine Nucleoside **10** upon the Trifluoroacetic Acid Concentration in DMSO

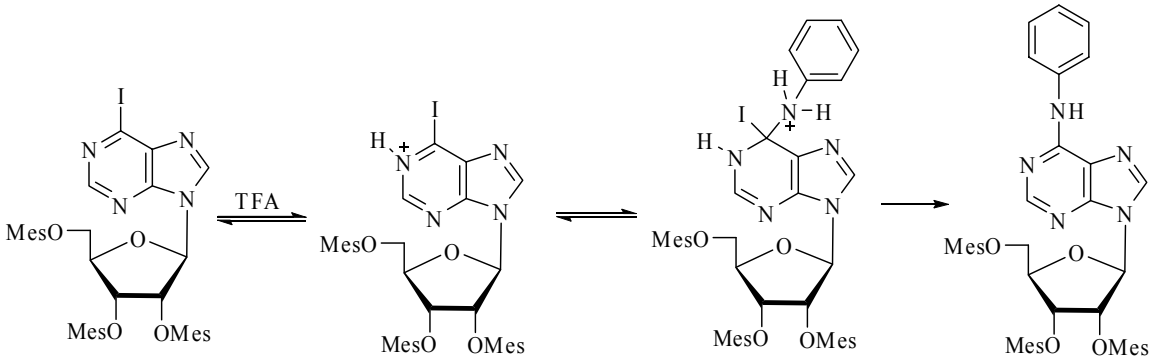
Mol equiv of acid	N1	N3	N7	N9
1.6	< 1	< 1	1.2	< 1

In conclusion, the kinetics for S_NAr reactions with an aromatic amine are consistent with the mechanism shown in Scheme 20. The first step, addition, is reversible and the second step, loss of halide, is rate-limiting. Hydrogen bonding of protons with the fluorine atom makes fluoride a better leaving group than iodide, so the rate with **8** is faster than with **12** when 2 eq of TFA is added (Schemes 21 and 22). This mechanism was proposed for S_NAr reactions of 1-fluoro-2,4-dinitrobenzene and weakly nucleophilic substituted-anilines.[30]

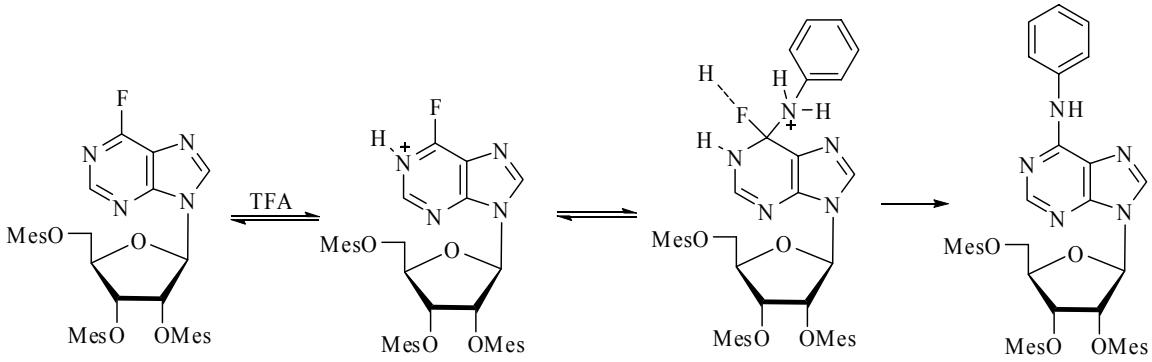
Scheme 20. Proposed Mechanism for the Reaction of 6-Halopurine Nucleosides with Aniline



Scheme 21. Mechanism for the Reaction of a 6-Iodopurine Nucleoside with Aniline and TFA



Scheme 22. Mechanism for the Reaction of a 6-Fluoropurine Nucleoside with Aniline and TFA



2.2.2.5. Comparisons of a 6-Sulfone with 6-Halopurine Nucleosides in S_NAr Reactions with O, N and S Nucleophiles

Oxidation of easily accessible 6-(alkylsulfanyl)purine derivatives provides the 6-(alkylsulfonyl)purine counterparts. Wetzel and Eckstein has noted that 6-(methysufonyl)-9-(β-D-ribofuranosyl)purine underwent S_NAr displacement reactions readily.[31] Reactivity competitions between quimolar quantities of 9-[(2,3,5-tri-O-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl)-6-(3-methylbutylsulfonyl)purine (**14**) and each of the four 6-halopurine analogues with butylamine, 3-methylbutane-1-thiol, and aniline (with and without 2 equiv. TFA) under the same condition described for the kinetic studies are summarized in Table 8.

The sulfone **14** was more reactive than the 6-fluoropurine analogue **1** with methanol/DBU and with 3-methylbutane-1-thiol/DBU (overall ordering: **14**>**8**>**10**≈**2**>**12** with MeOH/DBU, and **14**>**8**>**10**≈**12**>**2** with ^{i}PentSH/DBU). Sulfone **14** was second to **8** with both butylamine and aniline plus TFA (overall ordering: **8**>**14**>**10**>**2**>**12** with $BuNH_2$, and **8**>**14**>**12**>**10**>**2** with $PhNH_2$/TFA). The 6-iodopurine analogue **12** was most reactive with aniline in the absence of TFA; and **14** was third in reactivity, behind the bromopurine compound **10** (overall ordering: **12**>**10**>**14**>**2**>**8**). Combinations of C–X bond stability and autocatalysis by displaced HX appear to be operative in the latter series.

Table 8. Orders of Leaving Group Reactivities with Compounds **2**, **8**, **10**, **12**, and **14**

Nucleophile	reactivity
Methanol/DBU	RSO_2 > F > Br ≈ Cl > I
^{i}PentSH/DBU	RSO_2 > F > Br ≈ I > Cl
$BuNH_2$	F > RSO_2 > Br > Cl > I
$PhNH_2$	I > Br > RSO_2 > Cl > F
$PhNH_2$/TFA	F > RSO_2 > I > Br > Cl

2.3. Conclusions

In summary, our results demonstrate that the 6-fluoropurine nucleoside is the best substrate for S_NAr reactions among the four 6-halopurine nucleosides with oxygen, sulfur and aliphatic amine nucleophiles, and also with an aromatic amine plus TFA as a catalyst. However, the 6-iodopurine nucleoside is the best substrate for the aromatic amine without acid. With oxygen and sulfur nucleophiles, the 6-sulfonylpurine nucleoside reacted even faster than the 6-fluoropurine nucleoside. Our kinetic studies provide useful information for selection of suitable substrates for S_NAr reactions.

2.4. Experimental Section

Uncorrected melting points were determined with a hot-stage apparatus. ^{1}H (500 MHz), ^{13}C (125 MHz) and ^{15}N (50 Hz) spectra were determined with solutions in $CDCl_3$ unless otherwise indicated. All ^{15}N spectra were externally referenced to 45% formamide in DMSO-d_6 at –267.8 ppm on the nitromethane scale. High-resolution mass spectra (MS) were determined with FAB (glycerol, NaOAc) or 4-nitrobenzyl alcohol (NBA).

6-Chloro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (2). The title compound was prepared as reported. mp 123–126 ºC; Anal. Calcd for $C_{40}H_{41}N_4ClO_7$: C, 66.25; H, 5.70; N, 7.73. Found: C, 66.50; H, 5.70; N, 7.88.

6-Fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (8). 2',3',5'-Tri-*O*-(2,4,6-trimethylbenzoyl)adenosine (1.25 g, 1.77 mmol) was added to a solution of HF/pyridine (55%, 10 mL) at –15 ˚C, and *tert*-butyl nitrite (TBN) (2.5 mL, 2.2 g, 21 mmol) was added dropwise. The solution was stirred at –15 ˚C for 15 min, and cold H_2O and CH_2Cl_2 were added. The organic layer was washed ($NaHCO_3$/H_2O, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 3:7). The purified material was recrystallized from EtOH to give the title compound (1.02 g, 81%).[32] mp 117–120 ºC; ^{1}H NMR δ 2.07, 2.19 (2 × s, 2 × 6H), 2.25 (s, 9H), 2.28, 2.32 (2 × s, 2 × 3H), 4.71-4.81 (m, 3H), 6.12-6.15 (m, 1H), 6.37-6.40 (m, 2H), 6.78, 6.83, 6.87 (3 × s, 3 × 2H), 8.18, 8.55 (2 × s, 2 × 1H); ^{13}C NMR δ 20.0, 20.08, 20.09, 21.3, 21,4, 63.4, 71.5, 73.9, 81.1, 87.6, 121.1 (d, J(F,C) = 29 Hz), 128.6, 128.81, 128.86, 128.92, 129.2, 129.9, 135.4, 135.9, 136.1, 140.2, 140.4, 143.8, 152.5 (d, $J_{(F,C)}$ = 14 Hz), 155.0 (d, $J_{(F,C)}$ = 11 Hz), 160.0 (d, $J_{(F,C)}$ = 261 Hz),, 168.5 168.8, 169.7;

HRMS *m/z* 731.2856 [MNa^+ ($C_{40}H_{41}N_4FO_7Na$) = 731.2857]. Anal. Calcd for $C_{40}H_{41}N_4FO_7$: C, 67.78; H, 5.83; N, 7.90. Found: C, 67.68; H, 5.70; N, 7.83.

6-Bromo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (10). Compound **2** (0.20 g, 0.27 mmol) and TMSBr (0.4 mL, 0.3 g, 3 mmol) in butanone (5 mL) were stirred at –40 ºC for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed (brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was recrystallized from EtOH to give **3** (0.17 g, 80%): mp 121–124 ºC; ^{1}H NMR δ 2.07, 2.19, 2.24 (3 × s, 3 × 6H), 2.25, 2.28, 2.32 (3 × s, 3 × 3H), 4.70–4.81 (m, 3H), 6.14 (t, *J* = 5.0 Hz, 1H), 6.34 (d, *J* = 5.0 Hz, 1H), 6.38 (t, *J* = 5.5 Hz, 1H), 6.78, 6.83, 6.86 (3 × s, 3 × 2H) 8.22, 8.59 (2 × s, 2 × 1H); ^{13}C NMR δ 20.06, 20.10, 20.2, 21.4, 21.5, 63.4, 71.5, 73.9, 81.2, 87.7, 128.6, 128.85, 128.88, 128.94, 129.2, 129.9, 135.0, 135.4, 136.0, 136.1, 140.2, 140.5, 140.7, 143.88, 143.93, 150.1, 152.4, 168.5, 168.8, 169.7; HRMS *m/z* 791.2037 [MNa^+ ($C_{40}H_{41}N_4{}^{79}BrO_7Na$) = 791.2056]. Anal. Calcd for $C_{40}H_{41}N_4BrO_7$: C, 62.31; H, 5.21; N, 7.17. Found: C, 62.42; H, 5.37; N, 7.28.

6-Bromo-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (11). Treatmnet of 6-chloro-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-*β*-D-ribofuranosyl]purine **1** (50 mg, 0.078 mmol) by the same procedure used for compound **10** gave compound **11** (44 mg, 82%). ^{1}H NMR δ 2.38 (s, 3H), 2.43 (s, 6H), 4.65 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.84 (dd, *J* = 7.8, 3.9 Hz, 1H), 4.92 (dd, *J* = 12.2, 2.9 Hz, 1H), 6.20 (t, *J* = 5.4 Hz, 1H), 6.38 (t, *J* = 5.4 Hz, 1H), 6.45 (d, *J* = 5.4 Hz, 1H), 7.16–7.97(m, 12H), 8.29, 8.56 (2 × s, 2 × 1H); ^{13}C NMR δ 22.0, 63.4, 71.6, 74.0, 81.5, 87.6, 125.7, 126.2, 126.7, 129.5, 129.55, 129.62,

130.0, 130.1, 135.1, 143.9, 144.0, 144.6, 144.9, 145.1, 150.3, 152.4, 165.4, 165.6, 166.4; HRMS *m/z* 707.1121 [MNa^+ ($C_{34}H_{29}N_4BrO_7Na$) = 707.1117]

6-Iodo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (12). The title compound was prepared as reported. mp 143–145 ºC. Anal. Calcd for $C_{40}H_{41}N_4IO_7$: C, 58.83; H, 5.06; N, 6.86. Found: C, 58.60; H, 4.92; N, 6.72.

6-(3-Methylbutylsulfanyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (13). 3-Methylbutane-1-thiol (43 μL, 36 mg, 0.34 mmol) was added to a solution of **2** (50 mg, 0.069 mmol) and DBU (21 μL, 21 mg, 0.14 mmol) in CH_3CN (3 mL) at ambient temperature. The reaction mixture was stirred until the displacement was complete. The solution was treated with cold 0.01 N HCl/H_2O and extracted with CH_2Cl_2 (50 mL). The organic layer was washed ($NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes 3:7) to give a white foam (46 mg, 85%). ^{1}H NMR δ 0.98 (d, *J* = 6.4 Hz, 6H), 1.65–1.70 (m, 2H), 1.77–1.85 (m, 1H), 2.05, 2.18, 2.26 (3 × s, 3 × 6H), 2.24, 2.28, 2.30 (3 × s, 3 × 3H), 3.39–3.42 (m, 2H), 4.70–4.83 (m, 3H), 6.11 (t, *J* = 4.9 Hz, 1H), 6.33(d, *J* = 5.4 Hz, 1H), 6.37 (t, *J* = 5.2 Hz, 1H), 6.76, 6.82, 6.85 (3 × s, 3 × 2H), 8.01, 8.63 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 20.2, 21.38, 21.4, 22.6, 27.2, 27.8, 38.4, 63.8, 71.7, 73.7, 81.0, 87.0, 128.7, 128.81, 128.84, 128.9, 129.4, 130.1, 132.1, 135.5, 135.9, 136.2, 140.0, 140.4, 140.5, 141.3, 148.2, 152.5, 162.4, 168.5, 168.8, 169.8; HRMS *m/z* 815.3441 [MNa^+ ($C_{45}H_{52}N_4O_7SNa$) = 815.3454].

6-Isopentylsulfonyl-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (14). A solution of Oxone (0.78 g, 1.3 mmol) in NaOAc/HOAc (1M, 30 mL) buffer was added dropwise to a vigorously stirred solution of **13** (0.50 g,

0.63 mmol) in CH_3OH (30 mL). The suspension was stirred for 5 h, concentrated, and the resulting solution was extracted (CH_2Cl_2). The organic phase was dried (Na_2SO_4), and evaporated. The residue was chromatographed to give **14** (0.46 g, 89%). ^{1}H NMR δ 0.93 (d, *J* = 6.4 Hz, 6H), 1.73–1.77 (m, 3H), 2.08, 2.18 (2 × s, 2 × 6H), 2.26 (s, 9H), 2.28, 2.31 (2 × s, 2 × 3H), 3.65–3.69 (m, 2H), 4.72–4.83 (m, 3H), 6.11 (t, *J* = 5.4 Hz, 1H), 6.33 (t, *J* = 5.2 Hz, 1H), 6.43 (d, *J* = 4.9 Hz, 1H), 6.79, 6.83, 6.86 (3 × s, 3 × 2H), 8.41, 8.99 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 20.2, 21.36, 21.42, 22.3, 27.7, 30.4, 52.0, 63.3, 71.4, 74.0, 81.2, 87.8, 128.5, 128.9, 129.0, 129.1, 129.9, 130.4, 135.4, 136.0, 136.1, 140.2, 140.5, 140.7, 146.6, 152.3, 154.0, 154.5, 168.6, 168.8, 169.7; HRMS (NBA) *m/z* 825.3533 [MH^+ ($C_{45}H_{54}N_4O_9S$) = 825.3535]. Anal. Calcd for $C_{45}H_{52}N_4O_9S$: C, 65.51; H, 6.51; N, 6.79. Found: C, 65.70; H, 6.51; N, 6.89.

General Procedure for Reactions of the 6-Halopurine Derivatives with Methanol (Method 1). DBU (31 μL, 31 mg, 0.21 mmol) was added to a stirred solution of **2** (29.7 mg, 0.0410 mmol) in CH_3OH/CH_3CN (1/1 v/v, 3 mL) at 25 ºC. The reaction was quenched after certain times with a buffer (pHydrion buffer 6.00 ± 0.02) and extracted with CH_2Cl_2. The organic layer was evaporated and the residue was dissolved in $CDCl_3$ (0.55 mL). The ratio of C/C_0 was obtained by ^{1}H NMR. The same procedure was used for **8**, **10** and **12**.

6-Methoxy-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (15). Treatment of **2** (50 mg, 0.069 mmol) by method 1 gave **15** (44 mg, 88%): ^{1}H NMR δ 2.05, 2.19 (2 × s, 2 × 6H), 2.24, 2.30 (2 × s, 2 × 3H), 2.28 (s, 9H), 4.20 (s, 3H), 4.71–4.84 (m, 3H), 6.11–6.13 (m, 1H), 6.36–6.39 (m, 2H), 6.76, 6.82, 6.86 (3 × s, 3 × 2H), 8.00, 8.50 (2 × s, 2 × 1H); ^{13}C NMR δ 20.07, 20.11, 21.35, 21.37, 21.43, 54.6, 63.8, 71.8,

73.7, 81.1, 87.0, 122.2, 128.6, 128.82, 128.85, 128.88, 129.4, 130.1, 135.5, 135.9, 136.2, 140.0, 140.4, 140.5, 140.9, 151.8, 152.8, 161.4, 168.4, 168.9, 169.8; HRMS *m/z* 743.3060 [MNa^+ ($C_{41}H_{44}N_4O_8Na$) = 743.3057].

General Procedure for Reactions of the 6-Halopurine Derivatives with Potassium Thioacetate (Method 2). Potassium thioacetate (11.9 mg, 0.105 mmol) was added to a solution of **2** (14.8 mg, 0.0205 mmol) in DMSO-*d6* (0.6 mL) in a NMR tube. The reaction mixture was warmed to 30 ºC in the NMR spectrometer. The ratio of C/C_0 was obtained by ^1H NMR acquisition.

2′,3′,5′-Tri-O-(2,4,6-trimethylbenzoyl)-6-thioinosine. Due to S-deacetylation during workup, treatment of **2** (50 mg, 0.069 mmol) by method 2 (CH_3CN instead of DMSO) gave the title compound (43 mg, 87%). ^1H NMR δ 2.08, 2.18, 2.26 (3 × s, 3 × 6H), 2.24, 2.27, 2.30 (3 × s, 3 × 3H), 4.71–4.85 (m, 3H), 6.11 (t, *J* = 5.0 Hz, 1H), 6.26 (d, *J* = 5.0 Hz, 1H), 6.33 (t, *J* = 5.0 Hz, 1H), 6.77, 6.82, 6.87 (3 × s, 3 × 2H), 8.12, 8.23 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 20.2, 21.4, 21.5, 63.4, 71.5, 73.9, 81.2, 87.7, 128.6, 128.87, 128.93, 129.3, 130.1, 135.5, 136.0, 136.2, 136.5, 140.1, 140.4, 140.6, 141.8, 143.7, 144.8, 168.4, 168.8, 169.8, 176.9; HRMS *m/z* 745.2664 [MNa^+ ($C_{40}H_{42}N_4O_7SNa$) = 745.2672].

General Procedure for Reactions of the 6-Halopurine Derivatives with Butylamine (Method 3). Butylamine (40 μL, 30 mg, 0.41 mmol) was added to a stirred solution of **2** (29.7 mg, 0.0410 mmol) in CH_3CN (3 mL) at 25 ºC. The reaction was quenched after certain times with buffer (pH 6) and extracted with CH_2Cl_2. The organic layer was evaporated and the residue was dissolved in $CDCl_3$ (0.55 mL). The ratio of C/C_0 was obtained by NMR. The same procedure was used for **8**, **10** and **12**.

6-*N*-Butyl-2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl)adenosine (17). Treatment of **2** (50 mg, 0.069 mmol) by method 3 gave **17** (46 mg, 87%): ^{1}H NMR δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.44–1.49 (m, 2H), 1.65–1.70 (m, 2H), 2.05, 2.18, 2.29 (3 × s, 3 × 6H), 2.24, 2.27, 2.29 (3 × s, 3 × 3H), 3.66 (br, 2H), 4.68–4.71 (m, 1H), 4.73–4.77 (m, 1H), 4.80–4.84 (m, 1H), 5.70 (br, 1H), 6.09–6.11 (m, 1H), 6.30 (d, *J* = 5.4 Hz, 1H), 6.34–6.37 (m, 1H), 6.76, 6.81, 6.86 (3 × s, 3 × 2H), 7.82, 8.35 (2 × s, 2 × 1H); ^{13}C NMR δ 14.0, 20.1, 20.3, 21.3, 21.4, 32.0, 40.7, 64.0, 71.9, 73.7, 80.9, 86.6, 120.4, 128.78, 128.81, 128.84, 129.5, 130.2, 135.6, 135.9, 136.2, 136.3, 138.3, 139.9, 140.2, 140.4, 149.0, 153.8, 155.2, 168.5, 168.9, 169.8; HRMS *m/z* 762.3871 [MH^+ ($C_{44}H_{52}N_5O_7$) = 762.3867].

General Procedure for Reactions of the 6-Halopurine Derivatives with Aniline. Method 4: Aniline (9.5 μL, 9.7 mg, 0.10 mmol) was added to a solution of **2** (15 mg, 0.021 mmol) in CD_3CN (0.6 mL) in a NMR tube. The reaction mixture was heated at 70 ºC in the NMR spectrometer. The ratio of C/C_0 was obtained by ^{1}H NMR acquisition. The same procedure was used for **8**, **10** and **12**. **Method 5:** Aniline (9.5 μL, 9.7 mg, 0.10 mmol) and TFA (3.2 μL, 4.7 mg, 0.042 mmol) were added to a solution of **2** (15 mg, 0.021 mmol) in CD_3CN (0.6 mL) in a NMR tube. The reaction mixture was heated at 50 ºC in NMR spectrometer. The ratio of C/C_0 was obtained by ^{1}H NMR. The same procedure was used for **8**, **10** and **12**.

6-*N*-Phenyl-2',3',5'-tri-*O*-(2,4,6-trimethylbenzoyl)adenosine (18). Treatment of **2** (50 mg, 0.069 mmol) by method 4 (CH_3CN instead of CD_3CN) gave **18** (44 mg, 82%). ^{1}H NMR δ 2.09, 2.21, 2.31 (3 × s, 3 × 6H), 2.26, 2.29, 2.30 (3 × s, 3 × 3H), 4.73–4.86 (m, 3H), 6.16 (t, *J* = 4.9 Hz, 1H), 6.37 (d, *J* = 4.9 Hz, 1H), 6.42 (t, *J* = 5.3 Hz, 1H), 6.78, 6.84, 6.87 (3 × s, 3 × 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.81 (d,

J = 7.8 Hz, 2H), 7.85 (br, 1H), 7.97, 8.50 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 20.2, 21.38, 21.41, 21.44, 63.9, 71.8, 73.9, 81.0, 86.9, 120.8, 120.9, 124.0, 128.82, 128.86, 128.91, 129.3, 129.4 130.2, 135.5, 135.9, 136.2, 138.6, 139.5, 140.0, 140.4, 140.5, 149.6, 152.5, 153.4, 168.6, 168.9, 169.8; HRMS *m/z* 804.3368 [MNa^+ ($C_{46}H_{47}N_5O_7Na$) = 804.3373].

Procedure for Titration with TFA (^{15}N NMR). A solution of compound **8** (200 mg, 0.282 mmol) in $CDCl_3$ (0.5 mL) was added to a NMR tube. Then, measured quantities of TFA were added. ^{15}N NMR signal acquisition required 12 h for each set of data. The same procedure was used for **10** (217 mg, 0.282 mmol).

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Chapter 3 Azoles as Suzuki Cross-Coupling Leaving Groups

3.1. Introduction

Modified purines and purine nucleoside derivatives play a major role in biology, biochemistry, and pharmaceutics.[1] Recently, 6-arylpurine ribonucleosides have been shown to possess cytostatic activity.[2] Classic methodology for the synthesis of biaryls by the Suzuki-Miyaura protocol involves the Pd/Ni-mediated cross-coupling of haloaromatic or arylsulfonate derivatives with arylboronic acids (Schemes 1 and 2, Figure 1).[3] 6-Arylpurine ribonucleosides are accessible by Pd-mediated cross-coupling of 6-halo or 6-arylsulfonylpurine derivatives with arylboronic acids (Schemes 3 and 4).[2,4]

Scheme 1. Suzuki Reaction with an Aryl Sulfonate

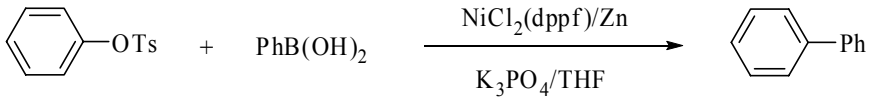
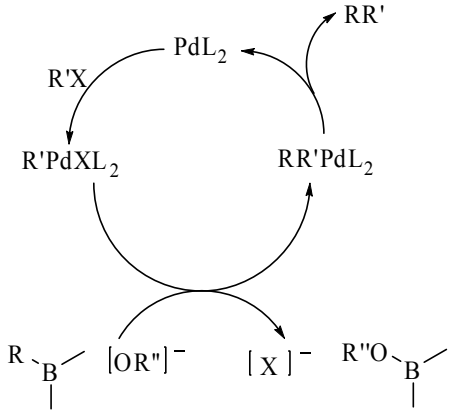
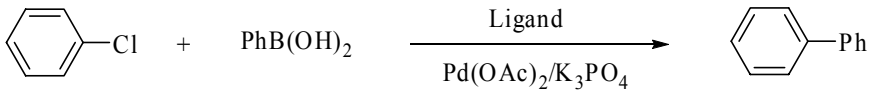


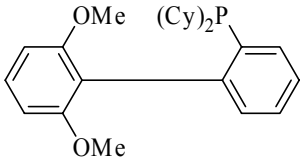
Figure 1. Suzuki Reaction Catalytic Cycle



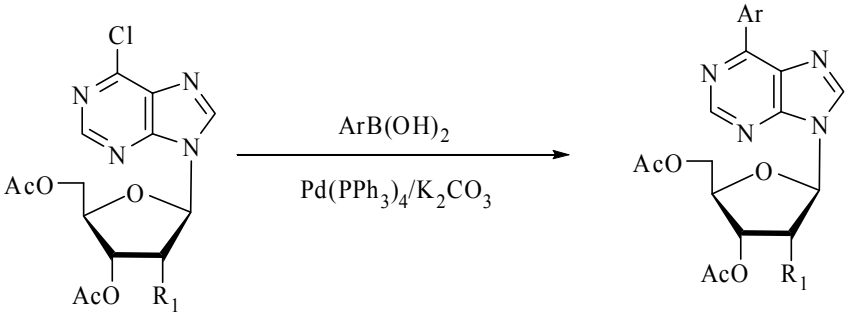
Scheme 2. Suzuki Reaction with an Aryl Chloride



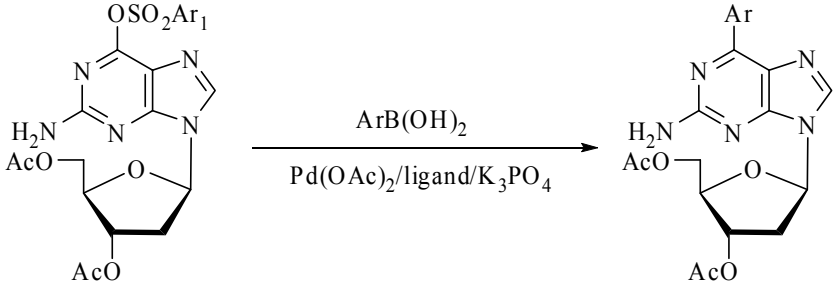
Ligand:



Scheme 3. Suzuki Reaction with 6-Chloropurine Nucleosides



Scheme 4. Suzuki Reaction with Purine 6-Arylsulfonate Nucleosides

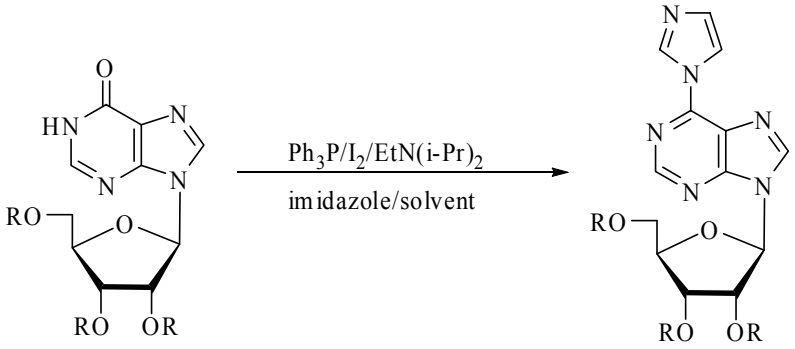


Ligand: 2-(dicyclohexylphosphino)biphenyl

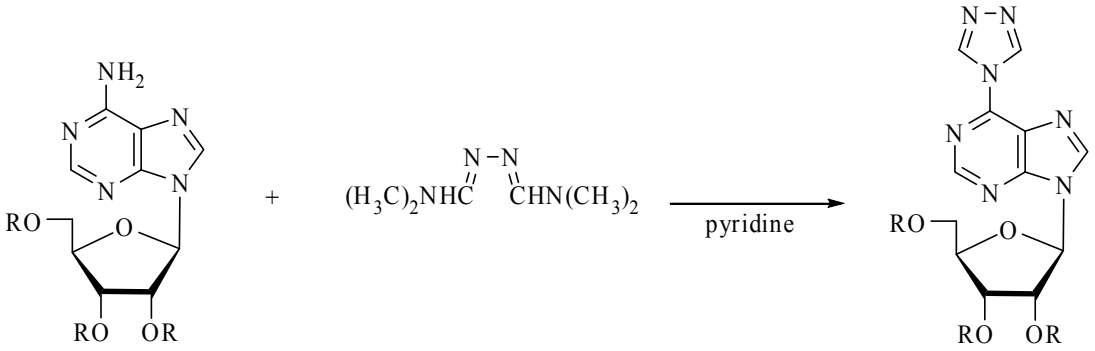
Our previous study demonstrated that 6-iodopurine nucleoside derivatives are superior to their 6-chloropurine analogues as substrates for the Suzuki-Miyaura and other cross-coupling procedures.[5] However, syntheses of such 6-halopurine 2'-deoxynucleosides from naturally occurring 2'-deoxy(inosine/adenosine) are problematic,

and high yields are obtained only with considerable care and persistence.[5,6] By contrast, 6-(imidazol-1-yl)purine (2'-deoxy)nucleoside derivatives can be prepared readily in excellent yields from (2'-deoxy)inosine (Scheme 5).[7] Robins and coworkers' modified-Appel approach for quantitative conversion of 6-oxopurine (2'-deoxy)nucleoside derivatives into the corresponding 6-(azolyl)purine analogues is also buttressed by the methodology for elaboration of the amino group of 6-aminopurine (2'-deoxy)nucleosides into their 6-(1,2,4-triazol-4-yl)purine counterparts (Scheme 6).[8] Thus, such 6-(azolyl)purine (2'-deoxy)nucleosides are readily available by convenient transformations of the natural products (2'-deoxy)adenosine and (2'-deoxy)inosine, as well as for other naturally occurring and synthetic analogues. The 1,2,4-triazol-4-yl substituent lowered the pKa of the leaving group (pKa ≈10 for the triazolyl group versus pKa ≈ 36 for NH_2) and enhanced nucleophilic attack at C6 because of attachment of the π-deficient heterocyclic ring. However, the 6-(1,2,4-triazol-4-yl) ring as a leaving group for Suzuki coupling reactions had never been investigated. So, we decided to explore the utility of 6-(imidazol-1-yl)- and 6-(1,2,4-triazol-4-yl)purine nucleosides as substrates for cross-coupling with arylboronic acids. Such couplings would provide a new avenue for modifications at C6 of purine nucleosides from readily accessible 6-azolyl precursors.

Scheme 5. Synthesis of 6-(Imidazol-1-yl)purine Nucleosides

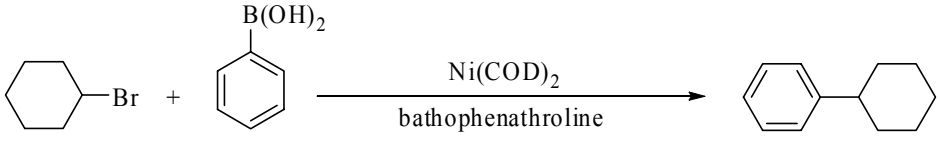


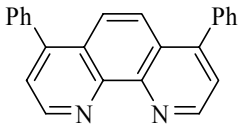
Scheme 6. Synthesis of 6-(1,2,4-Triazol-4-yl)purine Nucleosides



Nickel catalysts have been used successfully in a wide variety of Suzuki reactions, which provide ample precedent for transmetalations with arylboronic acids.[9] Zhou and Fu communicated a $Ni(COD)_2$/bathophenathroline catalyst system that achieved the first Suzuki reactions of unactivated secondary alkyl bromides and iodides (Scheme 7).[10] Hu and Tang reported arylsulfonates as coupling partners for room-temperature Suzuki cross-couplings. The catalyst system, derived from $Ni(COD)_2$ and PCy_3, represents the first general palladium or nickel catalyst system that can catalyze the Suzuki couplings of arylsulfonates at room temperature (Scheme 8).[11]

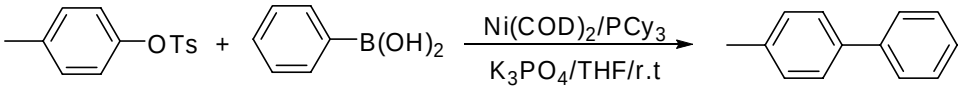
Scheme 7. Suzuki Reaction with an Alkyl Bromide Catalyzed by $Ni(COD)_2$





bathophenathroline

Scheme 8. Suzuki Reaction with an Aryl Sulfonate Catalyzed by $Ni(COD)_2$



3.2. Results and Discussion

Our initial attempts to couple 4-methoxyphenylboronic acid and 6-(imidazol-1-yl)purine nucleoside derivatives with palladium-based catalyst systems were not successful. Yanishita and Hartwig recently prepared three-coordinate arylpalladium amido complexes, which were subjected to reductive elimination to give *N*-coupled arylamines (Scheme 9).[12] However, the precursor three-coordinate arylpalladium amido complexes were prepared by treatment of an arylpalladium bromide complex with the potassium salt of a diarylamine. This is drastically different from palladium insertion into the C-N bond of a 6-(imidazol-1-yl)purine. Our challenge was to identify a catalytic complex that could insert readily into the purine-imidazole (C6-N) bond.

Imidazolium carbene ligands (Figure 2) have been used successfully in various cross-coupling reactions, and they are easy-to-make ligands with great potential in homogeneous catalysis. They tolerate functional groups, and work at mild condition.[13] Andrus and coworkers have investigated imidazolium carbene ligands for unusual Suzuki coupling reactions.[14] Blakey and MacMillan recently reported activating aryl-ammonium bonds for Suzuki cross-coupling reactions using a novel IMes·HCl catalyst complex (Scheme 10).[15] We examined $Ni(COD)_2$ as a catalyst with addition of IPr·HCl for the cross-coupling of 6-(imidazol-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (**3**) and 4-methoxyphenylboronic acid (**4**) (Scheme 11). However, none of the coupling product, 6-(4-methoxyphenyl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (**5**), was detected (Table 1, entry 9). Next, we investigated the catalyst complex resulting from $Ni(COD)_2$ and SIPr·HCl in the presence of K_3PO_4. We were delighted that the cross-coupled adduct **5** was produced in high yield (83% isolated)

(entry 7). Heating (60 ºC) was required to achieve reasonable reaction rates (entry 8). Replacement of $Ni(COD)_2$ by palladium catalysts in analogous coupling reaction mixtures did not give coupling products in meaningful yields (Table 1, entries 1–3).

Scheme 9. Coupling of an Aryl Bromide with a Potassium Diarylamide

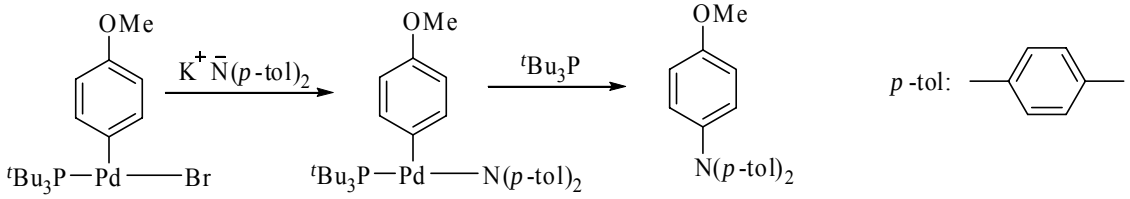
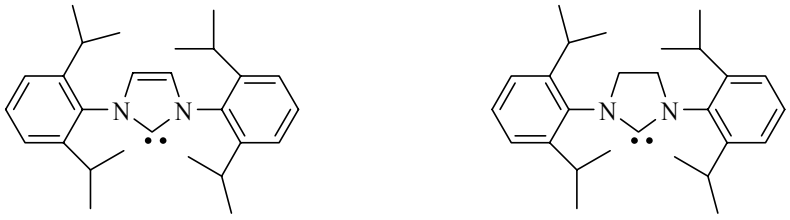


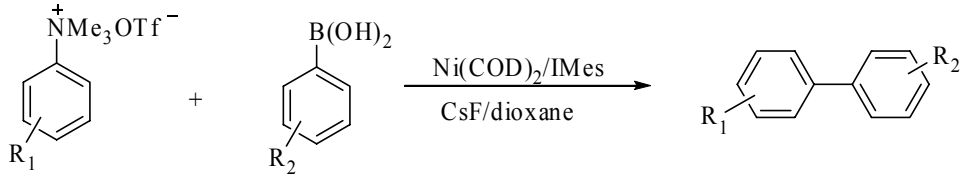
Figure 2. Structures of Ligands **1** and **2**



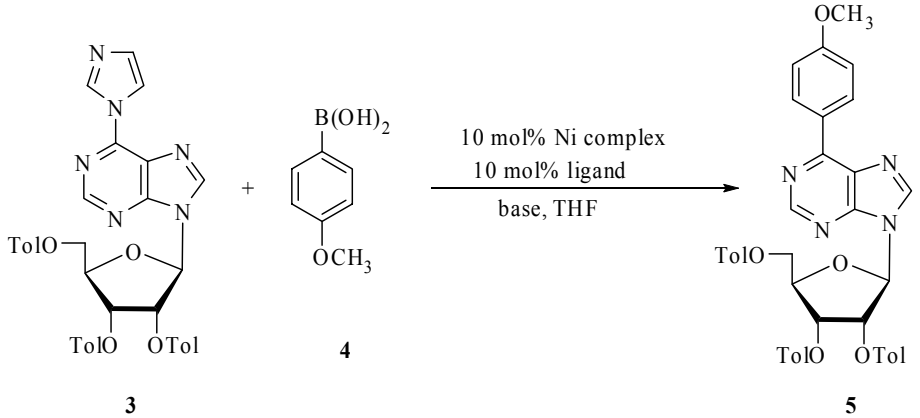
1
IPr

2
SIPr

Scheme 10. Suzuki Reaction of an Aryl Quaternary Ammonium Salt



Scheme 11. Suzuki Reaction of a 6-(imidazol-1-yl)purine Nucleoside with a Phenyl Boronic Acid



3 **4** **5**

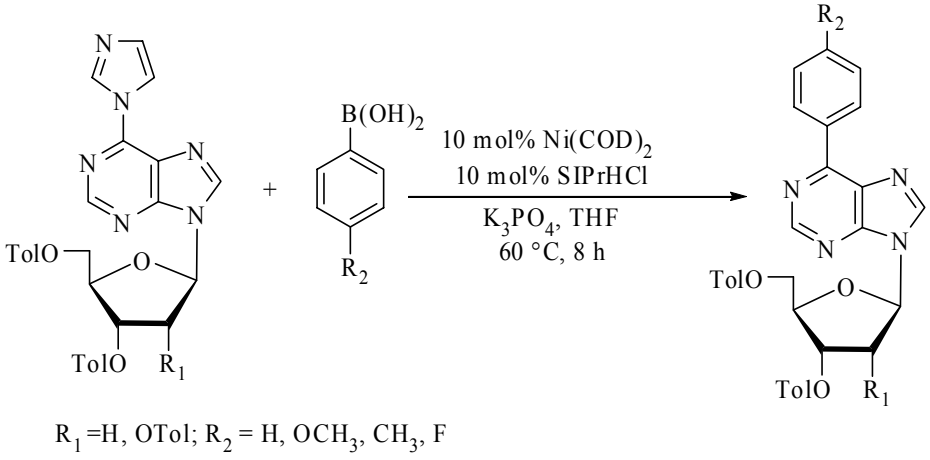
Table 1. Cross-coupling Reaction Conditions and Yields

entry	catalyst	ligand	base	% yield
1	$Pd(PPh_3)_4$		K_2CO_3	<5
2	$Pd(PPh_3)_4$	SIPr	K_3PO_4	<5
3	$Pd(OAc)_2$	SIPr	K_3PO_4	<5
4[b]	$Ni(dppp)Cl_2$	SIPr	K_3PO_4	30
5	$Ni(COD)_2$	SIPr	KF	<5
6	$Ni(COD)_2$	SIPr	CsF	64
7	$Ni(COD)_2$	SIPr	K_3PO_4	83
8[c]	$Ni(COD)_2$	SIPr	K_3PO_4	<5
9	$Ni(COD)_2$	IPr	K_3PO_4	<5

[a] Reaction conditions: 1.0 equiv of 3, 2.0 equiv of 4, 10 mol % of catalyst, 10 mol % of ligand, 3.0 equiv of base, 60 °C, 8 h. [b] 0.4 equiv of nBuLi was used to reduce Ni(II) to Ni(0). [c] Ambient temperature instead of 60 °C

The superior reaction efficiency observed with the Ni(0)·SIPr system and K_3PO_4 as base prompted additional evaluation with this catalytic combination. Potential electronic effects on the coupling of 6-(imidazol-1-yl)purine nucleosides by the aryl substituent of the boronic acids was then investigated. Both electron-rich and electron-poor arylboronic acids underwent coupling with **3** in good yields (Schemes 11 and 12) (Table 1, entry 7; Table 2, entries 1-3)

Scheme 12. Coupling Reactions with Varied Substrates

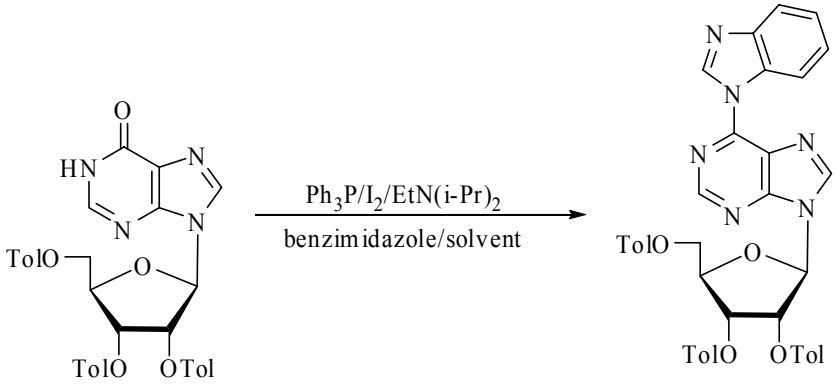


R_1 =H, OTol; R_2 = H, OCH_3, CH_3, F

Table 2. Yields of Coupling Products with Varied Substrates

entry	R_1	R_2	%yield
1	OTol	CH_3	81
2	OTol	F	78
3	OTol	H	73
4	H	OCH_3	75
5	H	F	65
6	H	CH_3	61
7	H	H	68

Scheme 13. Synthesis of a 6-(Benzimidazol-1-yl)purine Nucleoside



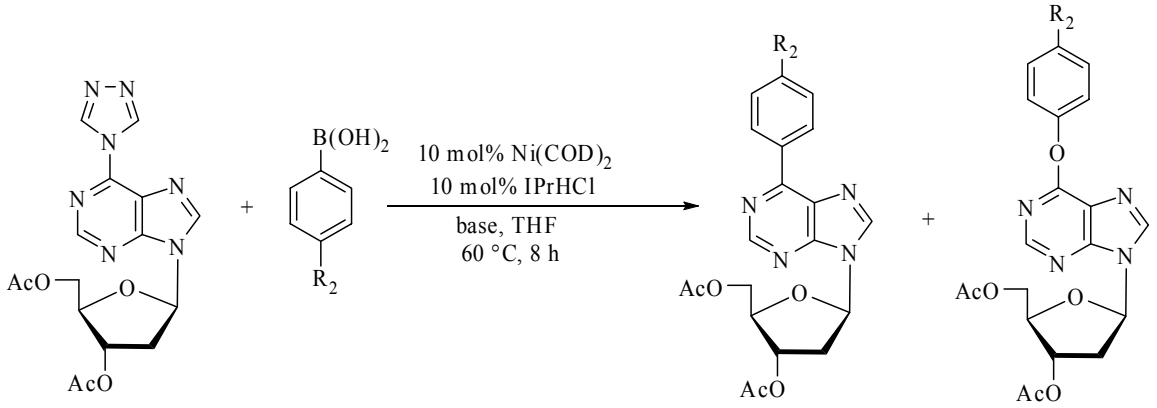
6

This methodology is efficient for conversions of inosine into various 6-arylpurine ribonucleosides, but alternative cross-coupling reactions with 6-halopurine nucleosides provide comparatively convenient approaches. However, syntheses of 6-halopurine 2'-deoxynucleosides are more challenging because of the markedly less stable glycosyl linkage of the 2'-deoxy analogues, which can result in cleavage under even mildly acidic conditions.[1,5] The modified Appel methodology provides convenient conversions of 2'-deoxyinosine derivatives into 6-(imidazol-1-yl)purine 2'-deoxynucleoside analogues in excellent yields (>90%) with virtually no glycosyl bond cleavage. Application of the present coupling protocol to such protected 2'-deoxynucleosides gave the corresponding 6-arylpurine products in good isolated yields (Table 2, entries 4-7).

Sensitivity to the azole substituent was probed with the 6-(benzimidazol-1-yl)purine nucleoside derivative **6** (also prepared in excellent yield by modified Appel procedure, Scheme 13). Coupling of **6** (under the noted conditions) gave **5** (80% isolated yield), which demonstrated that azoles other than imidazole could be used.

A brief investigation of the 6-(1,2,4-triazol-4-yl)purine system was then undertaken (Scheme 14, Table 3). No desired product was detected with $Pd(PPh_3)_4$ as catalyst. The noted reaction conditions were applied to cross-coupling of 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**7**) and 4-methoxyphenylboronic acid (**4**). Two products, **8c**/**9c** (45:55), were obtained. Fortunately, the use of IPr·HCl as ligand and CsF as base gave the desired cross-coupling product **8c** in high yield (85%), with the oxygen-insertion byproduct **9c** detected as a minor impurity (~5%). This coupling also was found to be tolerant with respect to substituents on the arylboronic acid component [with trace oxygen-insertion byproduct formation (≤5%)].

Scheme 14. Couplings with a 6-(1,2,4-triazol-4-yl)purine Nucleoside



R_2 = (a) H, (b) CH_3, (c) OCH_3, (d) F

Table 3. Yields of Coupling Products **8** with Varied Substrates

entry	R_2	**8** (%)
1	H	80
2	CH_3	78
3	OCH_3	85
4	F	75

3.3. Conclusions

In summary, nickel-based catalyst systems with imidazolium carbene ligands catalyze efficient Suzuki cross-coupling of arylboronic acids and 6-(imidazol-1-yl)-, 6-(benzimidazol-1-yl)-, and 6-(1,2,4-triazol-4-yl)purine (2'-deoxy)nucleoside derivatives to provide the corresponding 6-arylpurine (2'-deoxy)nucleosides. Different ligand/base combinations give better results with imidazole versus triazole substrates. Novel 6-(aryloxy)purine 2'-deoxynucleosides, oxygen-insertion byproducts, were observed with the 6-(1,2,4-triazol-1-yl)purine derivatives.

3.4. Experimental Section

Method 1. Under a flushing atmosphere of argon in a glove bag, 6-(imidazol-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (100 mg, 0.149 mmol), $Ni(COD)_2$ (4.1 mg, 0.015 mmol), SIPr·HCl (6.4 mg, 0.015 mmol) a boronic acid (2 equiv.) and K_3PO_4 (95 mg, 0.446 mmol) were combined in a Schlenk flask containing a magnetic stirrer bar under argon flushing atmosphere. The flask was evacuated and refilled with argon three times and then charged with THF. The mixture was heated with stirring at 60 ºC and allowed to cool to ambient temperature. The mixture was filtered, and the filter was washed with ethyl acetate. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica gel; EtOAc/Hexanes, 1:4) to give the isolated coupling products.

Method 2. Under a flushing atmosphere of argon in a glove bag, 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (50 mg, 0.129 mmol), $Ni(COD)_2$ (4 mg, 0.013 mmol), IPr·HCl (6 mg, 0.013 mmol) a boronic acid (2 equivalents) and CsF (59 mg, 0.39 mmol) were combined in a Schlenk flask containing a magnetic stirrer bar under argon flushing atmosphere. The flask was evacuated and refilled with argon three times and then charged with THF. The mixture was heated with stirring at 60 ºC and allowed to cool to ambient temperature. The mixture was filtered, and the filter was washed with ethyl acetate. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica gel; CH_2Cl_2/acetone 15:1) to give the isolated coupling products.

6-(Imidazol-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (3). ^{1}H NMR δ 2.39, 2.40, 2.44 (3 × s, 3 × 3H), 4.67 (dd, J = 12.5, 4.4 Hz, 1H), 4.84–4.87

(m, 1H), 4.93 (dd, *J* = 12.5, 3.5 Hz, 1H), 6.22 (t, *J* = 5.0 Hz, 1H), 6.43 (t, *J* = 5.4 Hz, 1H), 6.49 (d, *J* = 4.9 Hz, 1H), 7.16–7.97 (m, 13H), 8.27, 8.69, 9.14 (3 × s, 3 × 1H), 8.357–8.363 (m, 1H); ^{13}C NMR δ 21.96, 21.99, 22.02, 63.5, 71.6, 74.0, 81.4, 87.6, 117.6, 123.3, 125.8, 126.2, 126.7, 129.5, 129.6, 130.0, 130.1, 131.0, 137.9, 143.4, 144.6, 144.9, 145.1, 146.1, 152.8, 153.4, 165.5, 165.7, 166.4; HRMS *m/z* 695.2230 [MNa^+ ($C_{37}H_{32}N_6O_7Na$) = 695.2230].

6-(Benzimidazol-1-yl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (6). ^{1}H NMR δ 2.36, 2.39, 2.44 (3 × s, 3 × 3H), 4.68 (dd, *J* = 12.5, 4.2 Hz, 1H), 4.86–4.88 (m, 1H), 4.95 (dd, *J* = 12.2, 3.4 Hz, 1H), 6.25 (t, *J* = 5.1 Hz, 1H), 6.43 (t, *J* = 5.4 Hz, 1H), 6.47 (t, *J* = 5.4 Hz, 1H), 6.53 (d, *J* = 4.9 Hz, 1H), 7.17–7.25 (m, 6H), 7.41–7.48 (m, 2H), 7.83–7.97 (m, 7H), 8.29, 9.88 (2 × s, 2 × 1H), 8.83–8.84 (m, 2H); ^{13}C NMR δ 21.9, 22.0, 63.5, 71.6, 74.1, 81.4, 87.5, 116.8, 120.7, 123.5, 124.7, 125.2, 125.8, 126.2, 126.7, 129.5, 129.6, 130.0, 130.1, 132.2, 142.6, 144.3, 144.6, 144.9, 145.0, 148.1, 152.8, 152.9, 165.5, 165.7, 166.4; HRMS *m/z* 745.2402[MNa^+ ($C_{41}H_{34}N_6O_7Na$) = 745.2387].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(Imidazol-1-yl)purine. ^{1}H NMR δ 2.36, 2.45 (2 × s, 2 × 3H), 2.90–2.95 (m, 1H), 3.19–3.25 (m, 1H), 4.64–4.70 (m, 2H), 4.82 (dd, *J* = 11.7, 3.4 Hz, 1H), 5.84–5.87 (m, 1H), 6.60–6.62 (m, 1H), 7.16–7.99 (m, 9H), 8.28, 8.35, 8.72, 9.12 (4 × s, 4 × 1H); ^{13}C NMR δ 21.9, 22.0, 38.2, 64.0, 75.2, 83.6, 85.6, 117.6, 123.2, 126.5, 126.7, 129.4, 129.6, 129.8, 130.1, 131.0, 137.9, 142.9, 144.5, 144.9, 146.0, 152.5, 153.2, 166.2, 166.3; HRMS *m/z* 561.1874 [MNa^+ ($C_{29}H_{26}N_6O_5Na$) = 561.1862].

6-Phenyl-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine.

Treatment of 3 (100 mg, 0.15 mmol) with phenylboronic acid (36 mg, 0.30 mmol) by method 1 gave the title compound (74 mg, 73%): ^{1}H NMR δ 2.39, 2.40, 2.43, 4.68 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.84–4.86 (m, 1H), 4.92 (dd, *J* = 12.2, 3.4 Hz, 1H), 6.26 (t, *J* = 5.5 Hz, 1H), 6.47 (t, *J* = 5.3 Hz, 1H), 6.53 (d, *J* =5.4 Hz, 1H), 7.16–8.00 (m, 15H), 8.28, 8.95 (2 × s, 2 × 1H), 8.71–8.73 (m, 2H); ^{13}C NMR δ 21.98, 22.01, 63.7, 71.7, 73.9, 81.2, 87.1, 125.9, 126.3, 126.8, 128.9, 129.5, 129.6, 130.01, 130.04, 130.1, 131.3, 131.9, 135.7, 143.1, 144.5, 144.8, 144.9, 152.3, 153.0, 155.7, 165.4, 165.7, 166.5; HRMS *m/z* 705.2324 [MNa^+ ($C_{40}H_{33}N_4O_7Na$) = 705.2305].

9-[2,3,5-Tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-(4-methylphenyl)purine. Treatment of **3** (100 mg, 0.15 mmol) with 4-methylphenylboronic acid (40 mg, 0.30 mmol) by method 1 gave the title compound (84 mg, 81%): ^{1}H NMR δ 2.38, 2.40, 2.43, 2.45 (4 × s, 4 × 3H), 4.68 (dd, *J* = 12.2, 3.9 Hz, 1H), 4.83–4.85 (m, 1H), 4.91(dd, *J* = 12.2, 3.0 Hz, 1H), 6.26 (t, *J* = 5.2 Hz, 1H), 6.46 (t, *J* = 5.3 Hz, 1H), 6.53 (t, *J* = 5.4 Hz, 1H), 7.16–8.00 (m, 14H), 8.27, 8.93 (2 × s, 2 × 1H), 8.64 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 21.87, 21.95, 22.01, 63.7, 71.7, 73.9, 81.2, 87.0, 125.9, 126.3, 126.8, 129.47, 129.52, 129.6, 129.7, 130.0, 130.1, 131.7, 132.9, 141.8, 142.8, 144.4, 144.8, 144.9, 152.2, 152.9, 155.7, 165.4, 165.7, 166.5; HRMS *m/z* 719.2483 [MNa^+ ($C_{41}H_{36}N_4O_7Na$) = 719.2482].

9-[2,3,5-Tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-(4-methoxyphenyl)purine (5). Treatment of **3** (100 mg, 0.15 mmol) with 4-methoxyphenylboronic acid (**4**) (45 mg, 0.30 mmol) by method 1 gave **5** (88 mg, 83%): ^{1}HNMR δ 2.38, 2.40, 2.43 (3 × s, 3 × 3H), 3.90 (s, 3H), 4.69 (dd, *J* = 12.2, 3.9 Hz, 1H),

4.85 (dd, J = 7.8, 4.4 Hz, 1H), 4.92 (dd, J = 12.2, 3.4 Hz, 1H), 6.27 (t, J = 5.3 Hz, 1H), 6.47 (t, J = 5.3 Hz, 1H), 6.54 (d, J = 5.4 Hz 1H), 7.06–8.01 (m, 14H), 8.27 (s, 1H), 8.77 (d, J = 8.8 Hz, 2H), 8.91 (s, 1H); ^{13}C NMR δ 21.9, 21.97, 22.00, 55.6, 63.7, 71.7, 74.0, 81.2, 87.1, 114.3, 126.0, 126.3, 126.8, 128.4, 129.48, 129.52, 129.6, 130.0, 130.1, 130.2, 131.3, 131.8, 142.6, 144.4, 144.8, 144.9, 152.2, 152.9, 155.3, 162.3, 165.5, 165.7, 166.5; HRMS *m/z* 735.2416 [MNa^+ ($C_{41}H_{36}N_4O_8Na$) = 735.2431].

6-(4-Fluorophenyl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine. Treatment of **3** (100 mg, 0.15 mmol) with 4-fluorophenylboronic acid (42 mg, 0.30 mmol) by method 1 gave the title compound (81 mg, 78%): ^{1}H NMR δ 2.38, 2.40, 2.43 (3 × s, 3 × 3H), 4.68 (dd, J = 12.2, 3.9 Hz, 1H), 4.84–4.86 (m, 1H), 4.92 (dd, J = 12.2, 3.0 Hz, 1H), 6.25 (t, J = 5.0 Hz, 1H), 6.46 (t, J = 5.5 Hz, 1H), 6.52 (d, J =5.4 Hz, 1H), 7.16–8.00 (m, 14H), 8.28, 8.92 (2 × s, 2 × 1H), 8.78–8.81 (m, 2H); ^{13}C NMR δ 21.97, 22.01, 63.7, 71.6, 73.9, 81.2, 87.2, 116.0 (d, $J_{(F,C)}$ = 21 Hz), 125.9, 126.2, 126.8, 129.5, 129.6, 130.0, 130.1, 131.6, 131.9, 132.3 (d, $J_{(F,C)}$ = 8 Hz), 143.1, 144.5, 144.8, 144.9, 152.4, 152.9, 154.4, 164.9 (d, $J_{(F,C)}$ = 251 Hz), 165.5, 165.7, 166.5; HRMS *m/z* 723.2225 [MNa^+ ($C_{40}H_{33}N_4O_7Na$) = 723.2231].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-phenylpurine. Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(imidazil-1-yl)purine (50 mg, 0.093 mmol) with phenylboronic acid (23 mg, 0.19 mmol) by method 1 gave the title compound (35 mg, 68%): ^{1}H NMR δ 2.37, 2.46 (2 × s, 2 × 3H), 2.89–2.94 (m, 1H), 3.20–3.26 (m, 1H), 4.67–4.71 (m, 2H), 4.79–4.82 (m, 1H), 5.85–5.87 (m, 1H), 6.64–6.67 (m, 1H), 7.19–8.00 (m, 11H), 8.31, 8.99 (2 × s, 2 × 1H), 8.74–8.75 (m, 2H); ^{13}C NMR δ 21.9, 22.0, 38.2, 64.2, 75.4, 83.4, 85.2, 126.6,

126.9, 128.9, 129.5, 129.6, 129.8, 130.0, 130.1, 131.3, 131.9, 135.7, 142.6, 144.4, 144.8, 152.2, 152.7, 155.5, 166.2, 166.4; HRMS *m/z* 571.1949 [MNa^+ ($C_{32}H_{28}N_4O_5Na$) = 571.1957].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(4-methylphenyl)purine. Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(imidazol-1-yl)purine (50 mg, 0.093 mmol) with 4-methylphenylboronic acid (25 mg, 0.19 mmol) by method 1 gave the title compound (32 mg, 61%): ^{1}H NMR δ 2.38, 2.46 (2 × s, 2 × 3H), 2.89–2.93 (m, 1H), 3.20–3.25 (m, 1H), 4.67–4.71 (m, 2H), 4.79–4.82 (m, 1H), 5.85–5.86 (m, 1H), 6.64–6.67 (m, 1H), 7.20–8.00 (m, 10H), 8.23, 8.96 (2 × s, 2 × 1H), 8.65 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 21.88, 21.92, 22.0, 38.2, 64.2, 75.4, 83.4, 85.2, 126.6, 126.8, 129.5, 129.6, 129.7, 129.9, 130.0, 130.1, 131.7, 133.0, 141.8, 142.4, 144.4, 144.8, 152.1, 152.7, 155.5, 166.2, 166.4; HRMS *m/z* 585.2122 [MNa^+ ($C_{33}H_{30}N_4O_5Na$) = 585.2114].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(4-methoxyphenyl)purine. Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(imidazol-1-yl)purine (100 mg, 0.186 mmol) with 4-methoxyphenylboronic acid (**4**) (56 mg, 0.37 mmol) by method 1 gave the title compound (80 mg, 75%): ^{1}H NMR δ 2.38, 2.46 (2 × s, 2 × 3H), 2.88–2.92 (m, 1H), 3.18–3.23 (m, 1H), 3.91 (s, 3H), 4.68–4.71 (m, 2H), 4.78–4.82 (m, 1H), 5.58–5.86 (m, 1H),, 6.64–6.66 (m, 1H),7.07–8.00 (m, 10H), 8.27, 8.93 (2 × s, 2 × 1H), 8.77 (d, *J* = 8.5 Hz, 2H), ^{13}C NMR δ 21.9, 22.0, 38.2, 55.6, 64.2, 75.4, 83.4, 85.2, 114.3, 126.7, 126.9, 128.4, 129.5, 129.9, 130.1, 131.3, 131.8, 142.1, 144.4, 144.8, 152.0, 152.6, 155.1, 162.3, 166.2, 166.4; HRMS *m/z* 601.2061 [MNa^+ ($C_{33}H_{30}N_4O_6Na$) = 601.2063].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(4-fluorophenyl)purine. Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(imidazol-1-yl)purine (50 mg, 0.093 mmol) with 4-fluorophenylboronic acid (26 mg, 0.19 mmol) by method 1 gave the title compound (34 mg, 65%): ^{1}H NMR δ 2.37, 2.46 (2 × s, 2 × 3H), 2.89–2.94 (m, 1H), 3.20–3.25 (m, 1H), 4.67–4.71 (m, 2H), 4.79–4.82 (m, 1H), 5.85–5.87 (m, 1H), 6.63–6.66 (m, 1H), 7.20–8.00 (m, 10H), 8.30, 8.95 (2 × s, 2 × 1H), 8.81–8.84(m, 2H); ^{13}C NMR δ 21.9, 22.0, 38.2, 64.2, 75.4, 83.4, 85.3, 116.0 (d, $J_{(F,C)}$ = 22 Hz), 126.6, 126.8, 129.5, 129.6, 129.8, 130.1, 131.6, 131.9, 132.3 (d, $J_{(F,C)}$ = 8 Hz), 142.6, 144.4, 144.8, 152.2, 152.6, 154.2, 164.9 (d, $J_{(F,C)}$ = 252 Hz), 166.2, 166.4; HRMS *m/z* 589.1865 [MNa^+ ($C_{32}H_{27}N_4O_5FNa$) = 589.1863].

9-[3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-phenylpurine (8a). Treatment of **7** (50 mg, 0.13 mmol) with phenylboronic acid (32 mg, 0.26 mmol) by method 2 gave **8a** (41 mg, 80%): ^{1}H NMR δ 2.11, 2.16 (2 × s, 2 × 3H), 2.68–2.73 (m, 1H), 3.00–3.06 (m, 1H), 4.38–4.47 (m, 3H), 5.47–5.49 (m, 1H), 6.56–6.59 (m, 1H), 7.54–7.60 (m, 3H), 8.32, 9.03 (2 × S, 2 × 1H), 8.76–8.78 (m, 2H); ^{13}C NMR δ 21.0, 21.2, 37.8, 64.0, 74.8, 82.9, 84.9, 128.9, 130.0, 131.4, 131.9, 135.7, 142.5, 152.2, 152.7, 155.6, 170.5, 170.6; HRMS *m/z* 419.1337 [MNa^+ ($C_{20}H_{20}N_4O_5Na$) = 419.1331].

9-[3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(4-methylphenyl)purine (8b). Treatment of **7** (50 mg, 0.13 mmol) with 4-methylphenylboronic acid (35 mg, 0.26 mmol) by method 2 gave **8b** (41 mg, 78%): ^{1}H NMR δ 2.11, 2.16, 2.46 (3 × s, 3 × 3H), 2.67–2.72 (m, 1H), 3.00–3.05 (m, 1H), 4.37–4.47 (m, 3H), 5.47–5.49 (m, 1H), 6.55–6.58 (m, 1H), 7.38, 8.69 (2 × d, 2 × 2H), 8.30, 9.00 (2 × S, 2 × 1H); ^{13}C NMR δ 21.0, 21.2, 21.8, 37.8, 64.0, 74.8, 82.9, 84.9, 129.7, 130.0,

131.7, 133.0, 141.9, 142.2, 152.0, 152.7, 155.6, 170.5, 170.6; HRMS *m/z* 433.1489 [MNa^+ ($C_{21}H_{22}N_4O_5Na$) = 443.1488].

9-[3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(4-methoxyphenyl)purine (8c). Treatment of 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**7**) (50 mg, 0.13 mmol) with 4-methoxyphenylboronic acid (**4**) (39 mg, 0.26 mmol) by method 2 gave **8c** (47 mg, 85%): ^{1}H NMR δ 2.10, 2.16 (2 × s, 2 × 3H), 3.91 (s, 3H), 2.66–2.71 (m, 1H), 2.98–3.04 (m, 1H), 4.37–4.46 (m, 3H), 5.46–5.48 (m, 1H), 6.54–6.57 (m, 1H), 7.08, 8.80 (2 × d, 2 × 2H), 8.28, 8.96 (2 × s, 2 × 1H); ^{13}C NMR δ 21.0, 21.2, 37.8, 55.6, 64.0, 74.8, 82.9, 84.9, 114.4, 128.4, 131.3, 131.8, 142.0, 151.9, 152.7, 155.2, 162.4, 170.5, 170.6; HRMS *m/z* 427.1621 [MH^+ ($C_{21}H_{23}N_4O_6$) = 427.1618].

9-[3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(4-fluorophenyl)purine (8d). Treatment of **7** (50 mg, 0.13 mmol) with 4-fluorophenylboronic acid (39 mg, 0.26 mmol) by method 2 gave **8d** (40 mg, 75%): ^{1}H NMR δ 2.11, 2.16 (2 × s, 2 × 3H), 2.68–2.72 (m, 1H), 3.00–3.05 (m, 1H), 4.36–4.46 (m, 1H), 5.47–5.49 (m, 1H), 6.55–6.58 (m, 1H), 7.23–7.26 (m, 2H), 8.31–9.00 (2 × s, 2 × 1H), 8.83–8.86 (m, 2H); ^{13}C NMR δ 21.0, 21.2, 37.8, 64.0, 74.7, 83.0, 85.0, 116.0 (d, $J_{(F,C)}$ = 21 Hz), 131.6, 131.9, 132.2 (d, $J_{(F,C)}$ = 8 Hz), 142.5, 152.1, 152.7, 154.3, 165.0 (d, $J_{(F,C)}$ = 252 Hz), 170.5, 170.6; HRMS *m/z* 415.1421 [MH^+ ($C_{20}H_{20}N_4O_5F$) = 415.1418].

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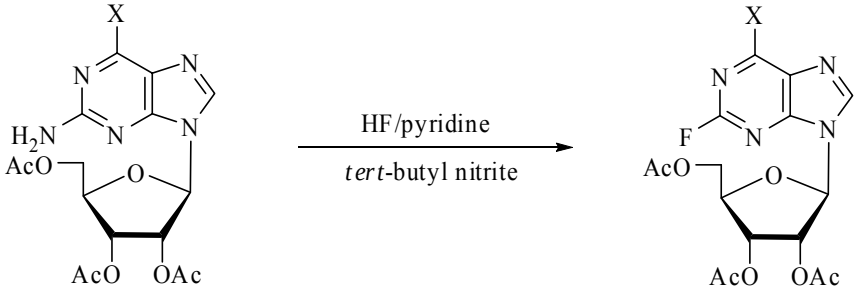
Chapter 4

Fluoro, Alkylsulfanyl and Alkylsulfonyl Leaving Groups in Suzuki Cross-Coupling Reactions of Purine 2'-Deoxynucleosides and Nucleosides

4.1. Introduction

Aryl fluorides have rarely been used in organometallic cross-coupling reactions because of their diminished reactivity. In 1981, Robins and coworkers reported efficient methodology for the synthesis of 2-fluoropurine nucleosides by nonaqueous diazotization fluoro-dediazoniation of the 2-amino group of protected purine nucleosides (Scheme 1).[1] Secrist and coworkers have applied this protocol for the conversion of 6-amino- to 6-fluoropurine nucleoside derivatives.[2]

Scheme 1. Synthesis of 2-Fluoropurine Nucleosides



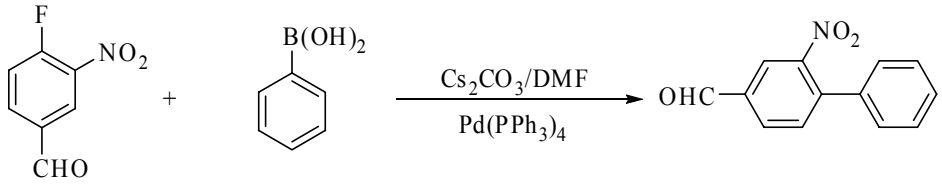
X = F, Cl

Our previous studies have shown that 6-fluoropurine nucleosides are good substrates for S_NAr reactions. However, 6-fluoropurine nucleosides as substrates in Suzuki cross-coupling reaction have never been reported. We then began an investigation of the utility of 6-fluoropurine nucleoside derivatives as cross-coupling partners with

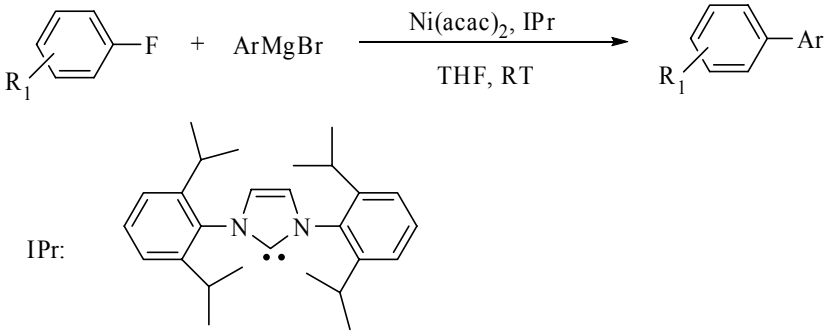
arylboronic acids. This study would open an effective new avenue for modifications at C6 of purine nucleosides.

Our first challenge was to identify a catalytic complex that would insert readily into the purine C6-F bond. Several methods involving different transition metal centers have been described for activation of aromatic carbon-fluorine bonds.[3] Palladium-catalyzed Suzuki coupling of electron-deficient aryl fluorides have been reported (Scheme 2).[4] Cross-couplings of phenylmagnesium halides and fluorobenzenes have been performed at ambient temperature with nitrogen-heterocyclic carbene ligands and nickel catalysts (Scheme 3).[5]

Scheme 2. Suzuki Reaction with an Aryl Fluoride



Scheme 3. Coupling of Aryl Fluorides with Grignard Reagents

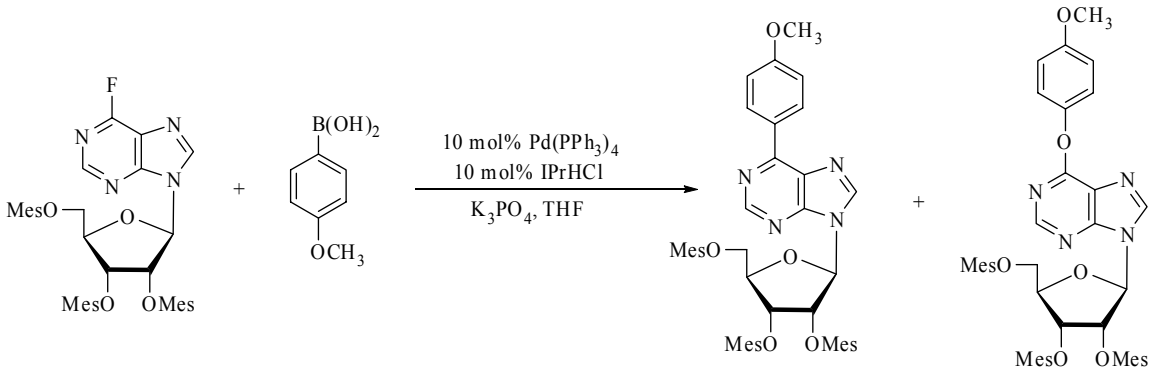


4.2. Results and Discussion

We first tried palladium complexes for cross-coupling of 4-methoxyphenyl boronic acid and 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-

ribofuranosyl]purine. However, major formation of an oxygen-insertion product, **2**, was detected (Scheme 4).

Scheme 4. Palladium-Catalyzed Suzuki Reaction of a 6-Fluoropurine Nucleoside



We then tried $Ni(COD)_2$ with addition of 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene (IPr) for cross-coupling of 4-methoxyphenylboronic acid and 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine. At ambient temperature, none of the coupling product was detected. However, we were delighted to find that the desired 6-(4-methoxyphenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (**1c**) was produced in high yield (84% isolated) in THF at 60 ˚C (Scheme 5; Table 1, entry 3). Different boronic acids were employed to evaluate the scope of this coupling reaction. Both electron-rich and electron-poor arylboronic acids underwent coupling in good yields with 6-fluoropurine nucleoside derivatives (Table 1, entries 1–4).

Scheme 5. Coupling Reactions with Varied Substrates

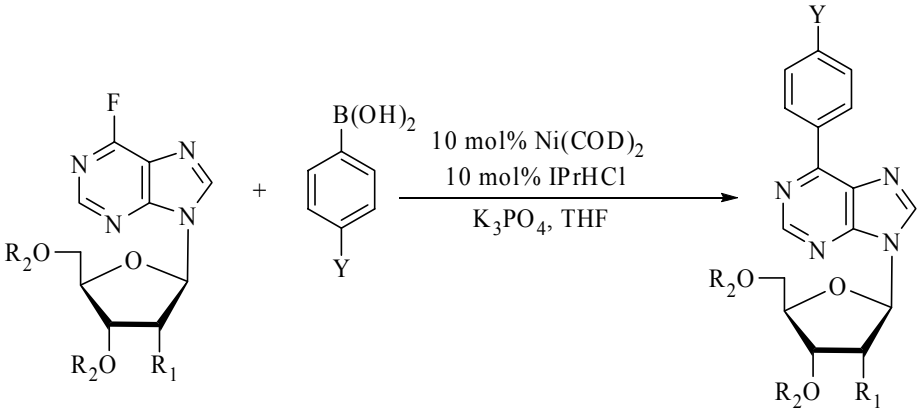
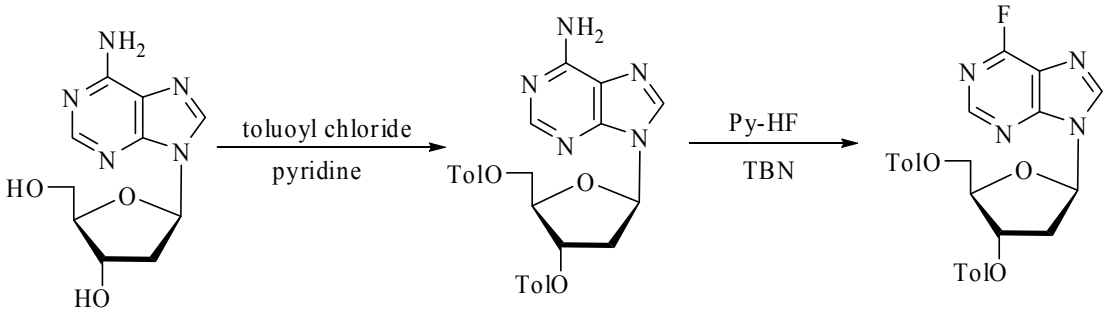


Table 1. Yields of Coupling Products with Varied Substrates

entry	R_2	R_1	Y	product (% yield)
1	Mes	OMes	H	**1a** (84)
2	Mes	OMes	CH_3	**1b** (82)
3	Mes	OMes	OCH_3	**1c** (84)
4	Mes	OMes	F	**1d** (73)
5	Tol	H	CH_3	**1e** (60)
6	Tol	H	F	**1f** (67)

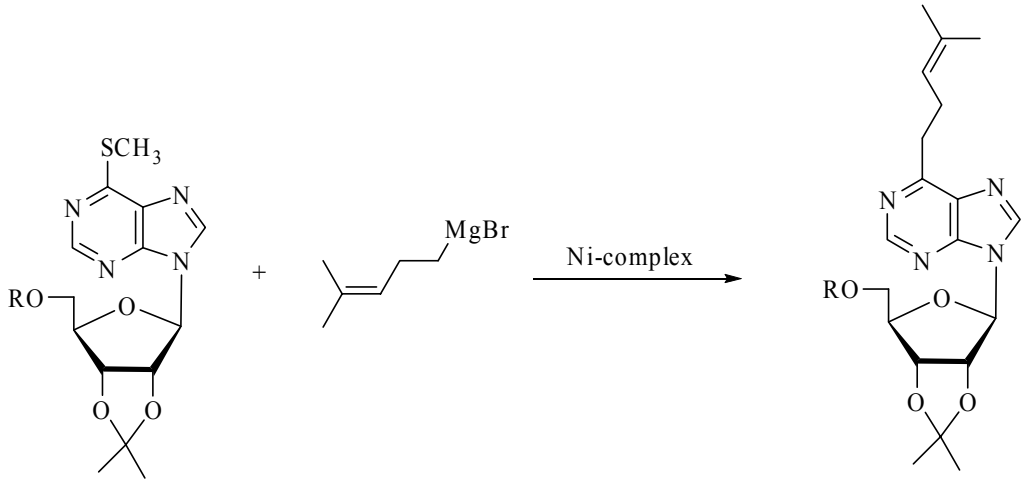
We recently found that the diazotative fluoro-deamination of protected 2'-deoxyadenosine analogues gives the 6-fluoropurine compounds in good yields (Scheme 6). Application of our coupling protocol with a protected 6-fluoropurine 2'-deoxynucleoside also gave 6-arylpurine products in good isolated yields (Table 1, entries 5, 6).

Scheme 6. Synthesis of a 6-Fluoropurine 2'-Deoxynucleoside



We next focused our attention on cross-couplings of 6-alkylsulfanylpurine nucleoside derivatives, which are readily accessible by S_NAr displacements with 6-(imidazol-1-yl)-,[6] 6-(1,2,4-triazol-4-yl)-,[7] and 6-halopurine[8] precursors. They also are easily prepared by alkylation of thioinosine derivatives,[8,9] which can be obtained by deoxygenative thiation of inosine or deaminative sulfhydrolysis of 6-N-substituted adenosine intermediates. Cross-coupling of Grignard reagents and 6-(methylsulfanyl)purine derivatives with a nickel-phosphine complex had been reported (Scheme 7).[10]

Scheme 7. Coupling of a 6-Methysulfanylpurine Nucleoside with a Grignard Reagent



R = *p*-$CH_3OC_6H_4(C_5H_5)_2C$, *t*-$C_4H_9(CH_3)_2Si$

Our first cross-coupling of 6-[(3-methylbutyl)sulfanyl]-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine and 4-methoxyphenylboronic acid was incomplete after 8 h with $Pd(OAc)_2$/IPr/K_2CO_3/THF at 60 ºC. However, when the solvent was changed from THF to toluene and the temperature was increased to 90 ºC, the coupling reaction was complete in 8 h. Electron-rich and electron-poor arylboronic acids were also well tolerated with the alkylsulfanylpurine substrates (Scheme 8; Table 2).

Scheme 8. Suzuki Reactions with a 6-Isopentylsulfanylpurine Nucleoside

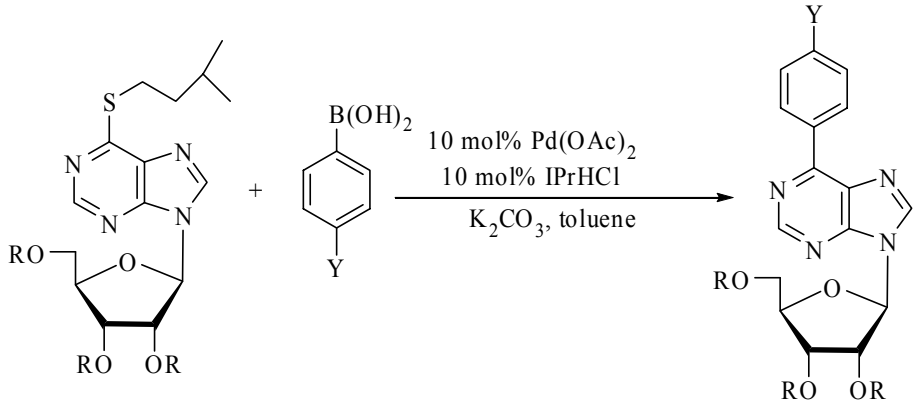


Table 2. Yields of Coupling Products of a 6-Isopentylsulfanylpurine Nucleoside with Varied Substrates

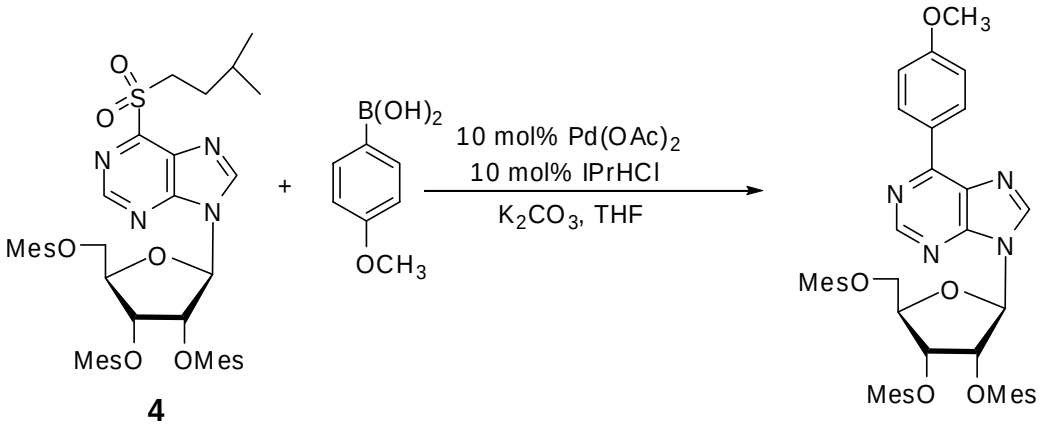
entry	R	Y	product (% yield)
1	Tol	CH_3	**3a** (69)
2	Ac	OCH_3	**3b** (78)
3	Tol	F	**3c** (71)

The oxidation state of the sulfur substituent at C6 was then briefly probed. Oxidation of 6-benzylsulfanylpurine nucleoside derivatives with Oxone in buffered brine had given 6-benzylsulfonyl compounds in high yields. Oxidation of a protected 6-(isopentylsulfanyl)purine nucleoside gave 6-[(3-methylbutyl)sulfonyl]-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (**4**). The sulfone **4** and 4-

methoxyphenylboronic acid underwent coupling at 60 ºC in 8 h [$Pd(OAc)_2$/IPr/K_2CO_3/THF] to give **1c** (81%, isolated yield) (Scheme 9)

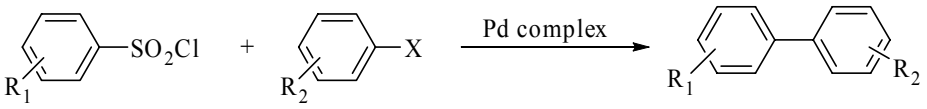
This coupling with the sulfone **4** occurred more readily (60 ºC, THF) than with the corresponding thioether (90 ºC, toluene). It was known that arylsulfonyl chlorides function as substrates for Suzuki and Stille couplings (Scheme 10), but we did not find prior examples of Suzuki couplings with sulfones.[11] Cross-couplings of phenylmagnesium halides and aryl sulfonamides have been performed with nickel catalysts (Scheme 11).[12]

Scheme 9. Suzuki Reaction of a 6-Isopentylsulfonylpurine Nucleoside



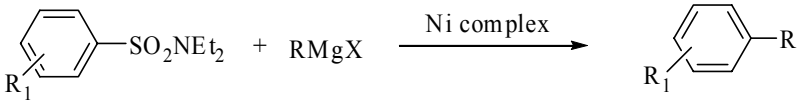
4

Scheme 10. Suzuki and Stille Reactions of Arylsulfonyl Chlorides



X = $B(OH)_2$, $SnBu_3$

Scheme 11. Coupling Reactions of Aryl Sulfonamides



4.3. Conclusions

In summary, we have developed nickel- and palladium-based systems with imidazolium-carbene ligands that catalyze efficient Suzuki cross-couplings of arylboronic acids and 6-fluoro-, 6-[(3-methylbutyl)sulfanyl]-, and 6-[(3-methylbutyl)sulfonyl]purine nucleoside derivatives to give the corresponding 6-arylpurine products. These reactions enlarge the scope of our complementary Suzuki couplings of arylboronic acids and 6-(azolyl)purine derivatives and expand possibilities for new medicinal applications.

4.4. Experimental Section

Spectral Methods: ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were determined with solutions in $CDCl_3$. High-resolution mass spectra (HRMS) were determined with FAB (glycerol, NaOAc) unless otherwise indicated.

6-Phenyl-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1a). Treatment of 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (30 mg, 0.042 mmol) and phenylboronic acid by general method 1 (see **1c**) gave **1a** (30 mg, 84%) as a solid glass: ^{1}H NMR δ 2.07, 2.20, 2.26 (3 × s, 3 × 6H), 2.25, 2.27, 2.29 (3 × s, 3 × 3H), 4.73–4.84 (m, 3H), 6.18 (t, *J* = 5.0 Hz, 1H), 6.41 (d, *J* = 5.0 Hz, 1H), 6.48 (d, *J* = 5.5 Hz, 1H), 6.77 (s, 2H), 6.83 (s, 4H), 7.55–7.61 (m, 3H), 8.76–8.78 (m, 2H), 8.21, 8.96 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 21.4, 63.7, 71.7, 73.7, 81.0, 87.2, 128.81, 128.85, 128.89, 128.93, 129.4, 130.1, 131.4, 131.8, 135.5, 135.7, 135.9, 136.1, 140.0, 140.4, 140.5, 143.1, 152.2, 152.9, 155.6, 168.6, 168.9, 169.8; HRMS *m/z* 789.3273 [MNa^+ ($C_{46}H_{46}N_4O_7Na$) = 789.3264].

6-(4-Methylphenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1b). Treatment of 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (30 mg, 0.042 mmol) and 4-methylphenylboronic acid by general method 1 (see **1c**)gave **1b** (27 mg, 82%) as a solid glass: ^{1}H NMR δ 2.06, 2.20, 2.25 (3 × s, 3 × 6H), 2.24, 2.27, 2.28, 2.47 (4 × s, 4 × 3H), 4.72–4.83 (m, 3H), 6.17 (t, *J* = 5.4 Hz, 1H), 6.41 (d, *J* = 4.9 Hz, 1H), 6.46 (t, *J* = 5.3 Hz, 1H), 6.77 (s, 2H), 6.83 (s, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 8.68 (d, *J* = 8.0 Hz, 2H), 8.19, 8.93 (2 × s, 2 × 1H); ^{13}C NMR δ 20.08, 20.11, 21.4, 21.9, 63.7, 71.7, 73.7, 81.0, 87.1, 128.80, 128.85, 128.9, 129.4, 129.7, 130.0, 131.6, 132.9, 135.5, 135.9, 136.1, 140.0,

140.4, 140.5, 141.9, 142.8, 152.1, 152.9, 155.6, 168.6, 168.9, 169.8; HRMS *m/z* 803.3428 [MNa^+ ($C_{47}H_{48}N_4O_7Na$) = 803.3421].

6-(4-Methoxyphenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1c). ***General Method 1.*** Under a flushing atmosphere of argon in a glove bag, 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (50 mg, 0.070 mmol), $Ni(COD)_2$ (2 mg, 0.007 mmol; 0.1 equiv.), IPr•HCl (3.0 mg, 0.007 mmol; 0.1 equiv.), 4-methoxyphenylboronic acid (21.3 mg, 0.14 mmol; 2 equiv.), and K_3PO_4 (45 mg, 0.21 mmol; 3 equiv.) were added to a Schlenk flask containing a magnetic stir bar. The flask was evacuated and refilled with Ar (3×). The flask was then charged with dried THF, and the mixture was heated at 60 ˚C with stirring for 3 h. The mixture was allowed to cool to ambient temperature, filtered, and the filter cake was washed with EtOAc. Volatiles were removed in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:4) to give **1c** (47 mg, 84%) as a solid glass: ^{1}H NMR δ 2.06, 2.20, 2.26 (3 × s, 3 × 6H), 2.24, 2.27, 2.28 (3 × s, 3 × 3H), 3.92 (s, 3H), 4.73–4.84 (m, 3H), 6.17 (t, *J* = 5.0 Hz, 1H), 6.41 (d, *J* = 5.4 Hz, 1H), 6.46 (t, *J* = 5.4 Hz, 1H), 6.77 (s, 2H), 6.83 (s, 4H), 7.09 (d, *J* = 9.0 Hz, 2H), 8.80 (d, *J* = 9.5 Hz, 2H), 8.18, 8.90 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 21.4, 55.6, 63.7, 71.7, 73.7, 81.0, 87.0, 114.3, 128.4, 128.8, 128.9, 129.4, 130.1, 131.2, 131.9, 135.5, 135.9, 136.2, 140.0, 140.3, 140.5, 142.5, 152.0, 152.9, 155.2, 162.4, 168.5, 168.9, 169.8; HRMS *m/z* 819.3361 [MNa^+ ($C_{47}H_{48}N_4O_8Na$) = 819.3370].

6-(4-Fluorophenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1d). Treatment of 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (30 mg, 0.042 mmol) and 4-

fluorophenylboronic acid by general method 1 gave **1d** (24 mg, 73%) as a solid glass: ^{1}H NMR δ 2.07, 2.19, 2.25 (3 × s, 3 × 6H), 2.25, 2.27, 2.28 (3 × s, 3 × 3H), 4.73–4.84 (m, 3H), 6.17 (t, J = 5.0 Hz, 1H), 6.41 (d, J = 5.0 Hz, 1H), 6.46 (t, J = 5.5 Hz, 1H), 6.77 (s, 2H), 6.83 (s, 4H), 7.24–7.28 (m, 2H), 8.83–8.86 (m, 2H), 8.20, 8.92 (2 × s, 2 × 1H); ^{13}C NMR δ 20.1, 21.4, 63.7, 71.6, 73.7, 81.0, 87.2, 116.0 (d, $J_{C,F}$ = 21 Hz), 128.8, 128.86, 128.90, 129.3, 130.0, 131.5, 131.9, 132.3 (d, $J_{C,F}$ = 9 Hz), 135.5, 135.9, 136.1, 140.0, 140.4, 140.6, 143.1, 152.2, 152.9, 154.3, 165.0 (d, $J_{C,F}$ = 251 Hz), 168.6, 168.9, 169.8; HRMS *m/z* 807.3185 [MNa^+ ($C_{46}H_{45}N_4O_7Na$) = 807.3170].

2'-deoxy-3',5'-di-*O*-(4-methylbenzoyl)adenosine.[13] Toluoyl chloride (4-methylbenzoyl chloride, 2.0 mL, 2.3 g, 15 mmol) was added dropwise to a stirred suspension of 2'-deoxyadenosine (2.0 g, 7.4 mmol) in pyridine (75 mL) at –10 ℃. The mixture was stirred for 2 h at –10 ℃ and then stirred overnight at ambient temperature. The solution was treated with saturated $NaHCO_3/H_2O$ and extracted with CH_2Cl_2 (50 mL). The organic layer was washed (cold 0.1 N HCl, $NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH, 50:1) and recrystallized from EtOH to give the title compound 1.5 g (42%). ^{1}H NMR (DMSO) δ 2.36, 2.39 (2 × s, 2 × 3H), 2.71–2.75 (m, 1H), 3.33–3.39 (m, 1H), 4.52–4.55 (m, 2H), 4.61–4.65 (m, 1H), 5.79–5.80 (m, 1H), 6.51 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 2H), 7.32 (s, 2H), 7.36, 7.86, 7.94 (3× d, J = 7.5 Hz, 3 × 2H), 8.11, 8.33 (2 × s, 2 × 1H); ^{13}C NMR (DMSO) δ 21.88, 21.92, 36.1, 64.7, 75.7, 82.3, 84.5, 120.0, 127.2, 127.3, 130.00, 130.04, 130.2, 140.4, 144.5, 144.8, 149.9, 153.3, 156.8, 166.0, 166.2; HRMS *m/z* 510.1741 [MNa^+ ($C_{26}H_{25}N_5O_5Na$) = 510.1753].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-fluoropurine. 2'-Deoxy-3',5'-di-*O*-(4-methylbenzoyl)adenosine (0.50 g, 1.0 mmol) was added to a solution of HF/pyridine (55%, 6 mL) at –15 ˚C, and *tert*-butyl nitrite (TBN) (1.4 mL, 1.2 g, 12 mmol) was added dropwise. The solution was stirred at –15 ˚C for 15 min, and cold H_2O and CH_2Cl_2 were added. The organic layer was washed ($NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 3:7) to give the title compound (0.36 g, 71%) as a solid foam after chromatography: ^{1}H NMR δ 2.39, 2.43 (2 × s, 2 × 3H), 2.87–2.91 (m, 1H), 3.15–3.20 (m, 1H), 4.64–4.68 (m, 2H), 4.78 (dd, J = 13.7, 5.4 Hz, 1H), 5.83–5.85 (m, 1H), 6.59 (dd, J = 7.8, 5.9 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 7.5 Hz, 2H), 8.28, 8.56 (2 × s, 2 × 1H); ^{13}C NMR δ 21.9, 22.0, 38.2, 64.0, 75.2, 83.6, 85.7, 121.2 (d, $J_{C,F}$ = 29 Hz), 126.5, 126.8, 129.5, 129.6, 129.8, 130.0, 143.5, 144.5, 144.8, 152.2 (d, $J_{C,F}$ = 14 Hz), 155.0 (d, $J_{C,F}$ = 10 Hz), 160.0 (d, $J_{C,F}$ = 260 Hz), 166.1, 166.3; HRMS *m/z* 513.1560 [MNa^+ ($C_{26}H_{23}N_4FO_5Na$) = 513.1550].

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(4-methylphenyl)purine (1e). Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-fluoropurine (50 mg, 0.10 mmol) and 4-methylphenylboronic acid by general method 1 gave **1e** (34 mg, 60%) as a solid glass with ^{1}H and ^{13}C NMR spectra identical to those of an authentic sample[14] of **1e**.

9-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-(4-fluorophenyl)purine (1f). Treatment of 9-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-6-fluoropurine (50 mg, 0.10 mmol) and 4-fluorophenylboronic

acid by general method 1 gave **1f** (39 mg, 67%) as a solid glass with ^{1}H and ^{13}C NMR spectral data the same as reported[15] for **1f**.

9-[2,3,5-Tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-[(3-methylbutyl)sulfanyl]purine. ***General Method 2.*** 3-Methyl-1-butanethiol (0.38 mL, 320 mg, 3.0 mmol) was added to a solution of 6-chloro-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (500 mg, 0.761 mmol) and DBU (0.14 mL, 140 mg, 0.94 mmol) in MeCN (4 mL) at ambient temperature. The solution was stirred until the displacement was complete (~30 min, TLC). Cold 0.01 M HCl/H_2O was added, and the solution was extracted with CH_2Cl_2 (50 mL). The organic layer was washed ($NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 3:7) to give the title compound (440 mg, 82%) as a solid foam: ^{1}H NMR δ 0.96, 0.97 (2 × s, 2 × 3H), 1.64–1.68 (m, 2H), 1.78 (sept, *J* = 6.8 Hz, 1H), 2.38 (s, 3H), 2.42 (s, 6H), 3.37–3.40 (m, 2H), 4.67 (dd, *J* = 12.2, 4.4 Hz, 1H), 4.80–4.82 (m, 1H), 4.88 (dd, *J* = 12.0, 3.4 Hz, 1H), 6.20 (dd, *J* = 5.6, 4.8 Hz, 1H), 6.38 (t, *J* = 5.8 Hz, 1H), 6.45 (d, *J* = 5.8 Hz, 1H), 7.16–7.25 (m, 6H), 7.81–8.00 (m, 6H), 8.10, 8.64 (2 × s, 2 × 1H); ^{13}C NMR δ 21.9, 22.5, 27.1, 27.7, 38.3, 63.7, 71.7, 73.9, 81.2, 86.9, 125.9, 126.2, 126.8, 129.4, 129.5, 129.6, 130.0, 130.09, 130.11, 132.1, 141.3, 144.4, 144.8, 148.3, 152.4, 162.4, 165.3, 165.6, 166.4; HRMS *m/z* 735.2517 [MNa^+ ($C_{39}H_{40}N_4O_7SNa$) = 731.2515]. This material was used for coupling reactions without further purification.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-[(3-methylbutyl)sulfanyl]purine. Treatment of 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (1.0 g, 2.4 mmol) by general method 2 gave the title compound (0.87 g, 75%) as a solid glass: ^{1}H NMR δ 0.95, 0.97 (2 × s, 2 × 3H), 1.64–1.68 (m, 2H), 1.79 (sept, *J* = 6.8 Hz, 1H), 2.07, 2.12, 2.14

(3 × s, 3 × 3H), 3.39 (t, *J* = 7.3 Hz, 2H), 4.36 (dd, *J* = 12.9, 5.0 Hz, 1H), 4.43–4.45 (m, 2H), 5.66 (t, *J* = 4.9 Hz, 1H), 5.95 (t, *J* = 5.4 Hz, 1H), 6.20 (d, *J* = 4.9 Hz, 1H), 8.11, 8.70 (2 × s, 2 × 1H); ^{13}C NMR δ 20.6, 20.8, 21.0, 22.5, 27.2, 27.7, 38.4, 63.2, 70.8, 73.3, 80.6, 86.6, 132.1, 141.1, 148.1, 152.3, 162.5, 169.5, 169.8, 170.5; HRMS *m/z* 481.1743 [MH^+ ($C_{21}H_{29}N_4O_7S$) = 481.1757].

9-[2,3,5-Tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-(4-methylphenyl)purine (3a). Treatment of 9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-[(3-methylbutyl)sulfanyl]purine (50 mg, 0.07 mmol) and 4-methylphenylboronic acid by general method 3 (see **3b**) gave **3a** (34 mg, 69%) as a solid glass with ^{1}H and ^{13}C NMR spectra identical to those of an authentic sample of **3a**.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-(4-methoxyphenyl)purine (3b). ***General Method 3.*** 9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-[(3-methylbutyl)sulfanyl]purine (50 mg, 0.10 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol; 0.11 equiv.), IPr•HCl (4.5 mg, 0.011 mmol; 0.11 equiv.), 4-methoxyphenylboronic acid (30.4 mg, 0.20 mmol; 2.0 equiv.), and K_2CO_3 (43 mg, 0.31 mmol; 3.1 equiv.) were added to a Schlenk flask containing a magnetic stir bar. The flask was evacuated and refilled with argon (3×). The flask was then charged with dried toluene, and the mixture was heated at 90 ˚C with stirring for 8 h. The mixture was allowed to cool to ambient temperature, filtered, and the filter cake was washed with EtOAc. Volatiles were removed in vacuo, and the residue was chromatographed (EtOAc/hexanes 1:4) to give **3b** (39 mg, 78%) as a solid glass: ^{1}H NMR spectral data were the same as reported;[16] ^{13}C NMR δ 20.6, 20.7, 55.6, 63.3, 70.9, 73.3, 80.6, 86.5, 114.3, 128.3, 131.3, 131.8, 142.1, 152.1, 152.9, 155.3, 162.5, 169.5, 169.7, 170.5; HRMS *m/z* 507.1484 [MNa^+ ($C_{23}H_{24}N_4O_8Na$) = 507.1492].

6-(4-Fluorophenyl)-9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]purine (3c). Treatment of 9-[2,3,5-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl]-6-[(3-methylbutyl)sulfanyl]purine (50 mg, 0.07 mmol) and 4-fluorophenylboronic acid by general method 3 gave **3c** (35 mg, 71%) as a solid glass with ^{1}H and ^{13}C NMR spectra identical to those of an authentic sample of **3c**.

6-(4-Methoxyphenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1c). (From **4).** Treatment of 6-Isopentylsulfonyl-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (**4**) (50 mg, 0.061 mmol) and 4-methoxyphenylboronic acid (18 mg, 0.12 mmol) by a modification of general method 3 [dried THF was used as solvent (rather than toluene) and heating for 8 h was at 60 ˚C (rather than 90 ˚C)] gave **1c** (39 mg, 81%) as a solid glass with ^{1}H and ^{13}C NMR spectra identical to those of **1c** from general method 1.

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