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S_NAr Displacements with 6-(Fluoro, Chloro, Bromo, Iodo, and Alkylsulfonyl)purine Nucleosides: Synthesis, Kinetics, and Mechanism[1]

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Abstract: S_NAr reactions with 6-(fluoro, chloro, bromo, iodo, and alkylsulfonyl)purine nucleosides and nitrogen, oxygen, and sulfur nucleophiles were studied. Pseudo-first-order kinetics were measured with 6-halopurine compounds, and comparative reactivities were determined versus a 6-(alkylsulfonyl)purine nucleoside. The displacement reactivity order was: F > Br > Cl > I (with $BuNH_2$/MeCN), F > Cl ≈ Br > I (with MeOH/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/MeCN), and F > Br > I > Cl [with $K^+ {}^-SCOCH_3$/dimethyl sulfoxide (DMSO)]. The order of reactivity with a weakly basic arylamine (aniline) was: I > Br > Cl ≫ F (with 5 equiv of aniline in MeCN at 70 °C). However, those reactions with aniline were autocatalytic and had significant induction periods (∼50 min for the iodo compound and ∼6 h for the fluoro analogue). Addition of trifluoroacetic acid (TFA) eliminated the induction period, and the order then was F > I > Br > Cl (with 5 equiv of aniline and 2 equiv of TFA in MeCN at 50 °C). The 6-(alkylsulfonyl)purine nucleoside analogue was more reactive than the 6-fluoropurine compound with both MeOH/DBU/MeCN and ^{i}PentSH/DBU/MeCN and was more reactive than the Cl, Br, and I compounds with $BuNH_2$ and aniline/TFA. Titration of the 6-halopurine nucleosides in $CDCl_3$ with TFA showed progressive *downfield* ^{1}H NMR chemical shifts for H8 (larger) and H2 (smaller). The major site of protonation as N7 for both the 6-fluoro and 6-bromo analogues was confirmed by large *upfield* shifts (∼16 ppm) of the ^{15}N NMR signal for N7 upon addition of TFA (1.6 equiv). Mechanistic considerations and resolution of prior conflicting results are presented.

Introduction

Purine bases play central roles in a wide variety of biological processes.[2] Advances in the synthesis of purines that are modified at C6 include the use of S_NAr,[3] Suzuki−Miyaura,[4] and Sonogashira[5] reactions. Many nitrogen-, oxygen-, and sulfur-linked substituents have been introduced at C6 by nucleophilic aromatic substitution with 6-halopurine nucleosides. It is well-known[6] that the order of reactivity for S_NAr reactions with 1-halo-2,4-dinitrobenzenes is F > Cl ≥ Br > I. However, conflicting orders of reactivity have been noted with 6-halopurine derivatives. Véliz and Beal[3b] reported that 6-bromopurine nucleosides were more reactive than the corresponding 6-chloropurine compounds in S_NAr reactions with a weakly nucleophilic arylamine, and our studies[7] had shown that 6-iodopurine nucleosides were more reactive than 6-chloro analogues in S_NAr reactions with aniline. Because 6-(alkylsulfonyl)purine derivatives are known to be highly reactive substrates for S_NAr displacements,[8] it was of interest to compare the reactivity of such a sulfone with those of the four 6-halopurine nucleosides.

(1) Nucleic Acid Related Compounds. 144. For paper 143, see: Nowak, I.; Robins, M. J. *J. Org. Chem.*, published online Mar 27, 2007 http://dx.doi.org/10.1021/jo062614d.

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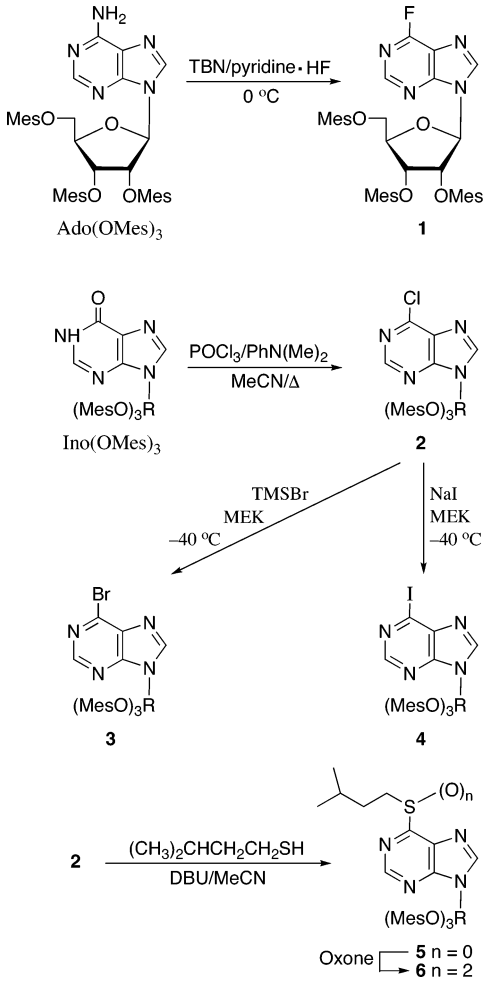
Scheme 1

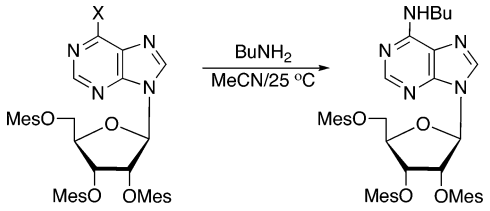


A systematic comparison of 6-(fluoro-, chloro-, bromo, iodo, and alkylsulfonyl)purine nucleosides in S_NAr reactions was lacking.

Results and Discussion

Synthesis of Suitable 6-(Substituted)purine Nucleoside Substrates. Nucleoside derivatives with the sugar hydroxyl groups protected with stable, lipophilic entities are much easier to manipulate. We first examined 2′,3′,5′-tri-*O*-(4-methylbenzoyl) derivatives, which are easily prepared and readily crystallized.[9] However, minor quantities of partially deprotected byproducts were observed in the more basic nucleophilic systems upon extended exposure with the *p*-toluyl esters. Therefore, 2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl) (mesitoyl, Mes) analogues were prepared[7,10] and found to be stable[11] in all of our systems. Our fluorodeamination method[12] [pyridine·HF/*tert*-butyl nitrite (TBN)] with 2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl)-adenosine[13] [Ado(OMes)$_3$] (Scheme 1) gave the 6-fluoropurine nucleoside **1**. Chlorodeoxygenation[14] ($POCl_3$/*N*,*N*-dimethylaniline/acetonitrile/Δ) of 2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl)-inosine [Ino(OMes)$_3$] gave the crystalline 6-chloropurine nucleoside **2**.

Scheme 2



We first employed conversion of adenosine derivatives into 6-bromopurine analogues by diazotive bromodeamination,[15,16] but the 6-bromopurine nucleoside was contaminated with traces of a reductively deaminated purine nucleoside that was hard to remove. S_NAr displacements of chloride from **2** with metal bromides were not effective (<35% of **3** with NaBr/trifluoroacetic acid (TFA) and <70% with LiBr/TFA). Silicon-mediated chloride/bromide exchange with chloropyridines showed that the much stronger silicon−chlorine bond favors replacement by bromide.[17] That approach was successful, and conversion of **2** to **3** proceeded cleanly with trimethylsilyl bromide (TMSBr) in butanone (methyl ethyl ketone, MEK) at ≤−40 °C [>98% conversion with no detected purine nucleoside byproduct (^{1}H NMR), 80% crystalline **3** isolated].

A Finkelstein−S_NAr reaction (NaI/MEK at ≤−40 °C)[7] efficiently converted **2** into the 6-iodopurine analogue **4**. Treatment of **2** with 3-methylbutane-1-thiol/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) gave the 6-(isopentylsulfanyl)purine nucleoside **5**, which was oxidized (oxone/pH 5 buffer/brine/MeOH/H_2O)[8] to give the sulfone **6**.

Kinetic Studies. All kinetic determinations (in triplicate) were conducted under pseudo-first-order conditions:

$$k_1 t = -2.303 \log(C/C_0) + a \qquad (1)$$

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 (s^{-1}) = k_1 (min^{-1})/60].

S_NAr Reactions of 6-Halopurine Nucleosides with a Primary Aliphatic Amine. The 6-halopurine nucleosides **1**−**4** (Scheme 2) were treated with butylamine (10 equiv) in acetonitrile at 25 °C to give the 6-(butylamino)purine compound **7**. The rate constant for the reaction with the fluoropurine nucleoside **1** was too fast to measure, even at 0 °C. The reactivity order was F ≫ Br > Cl > I (Figure 1, Table 1).

S_NAr Reactions of 6-Halopurine Nucleosides with an Aliphatic Alcohol/Base. Compounds **1**−**4** (Scheme 3) were treated with DBU (∼5 equiv) in methanol/acetonitrile (1:1 v/v) at 25 °C to give the 6-methoxypurine nucleoside **8**. Again, the rate constant for the reaction with the 6-fluoropurine nucleoside **1** was too fast to measure, even at 0 °C. The reactivity order

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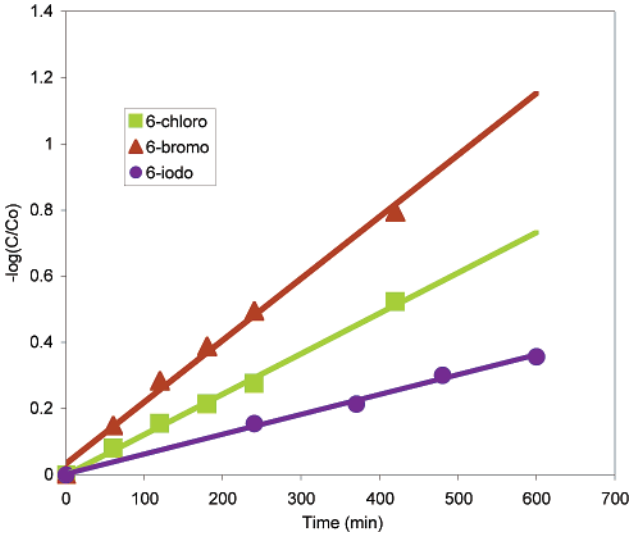


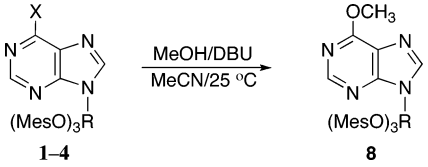
Figure 1. S_NAr reactions of **2**−**4** with butylamine.

Table 1. Kinetic Data and S_NAr Rate Constants[a]

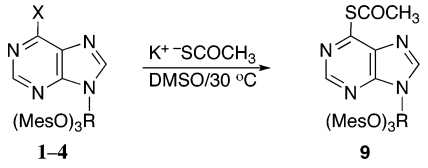
nucleophile	solvent	temp (°C)	entry	X	k (s^{-1})	R[b]	n[c]
$BuNH_2$	MeCN	25	1	Cl	4.6×10^{-5}	0.997	5
$BuNH_2$	MeCN	25	2	Br	7.3×10^{-5}	0.993	5
$BuNH_2$	MeCN	25	3	I	2.3×10^{-5}	0.996	5
MeOH/DBU	MeCN	25	4	Cl	1.0×10^{-4}	0.990	5
MeOH/DBU	MeCN	25	5	Br	1.0×10^{-4}	0.991	5
MeOH/DBU	MeCN	25	6	I	4.6×10^{-5}	0.989	5
$K^+ {}^-SCOMe$	DMSO	30	7	F	1.6×10^{-3}	0.999	5
$K^+ {}^-SCOMe$	DMSO	30	8	Cl	2.2×10^{-4}	0.999	9
$K^+ {}^-SCOMe$	DMSO	30	9	Br	5.2×10^{-4}	0.999	5
$K^+ {}^-SCOMe$	DMSO	30	10	I	5.2×10^{-4}	0.999	5
$PhNH_2$/TFA	MeCN	50	11	F	2.5×10^{-3}	0.998	6
$PhNH_2$/TFA	MeCN	50	12	Cl	3.8×10^{-4}	0.999	9
$PhNH_2$/TFA	MeCN	50	13	Br	6.9×10^{-4}	0.999	10
$PhNH_2$/TFA	MeCN	50	14	I	1.7×10^{-3}	0.999	7

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

Scheme 3



Scheme 4



was F ≫ Cl ≈ Br > I (kinetic plots are in the Supporting Information, Table 1).

S_NAr Reactions of 6-Halopurine Nucleosides with Thiolate Nucleophiles. Compounds **1**−**4** were treated with potassium thioacetate (5 equiv) in dimethyl sulfoxide (DMSO) at 30 °C to give the 6-(acetylthio)purine nucleoside **9** (Scheme 4). The reactivity order was F > Br ≈ I > Cl (kinetic plots are in the Supporting Information, Table 1) [the same reactivity order (F > Br ≈ I > Cl) was observed with 3-methylbutane-1-thiol/DBU in acetonitrile at ≤−40 °C].

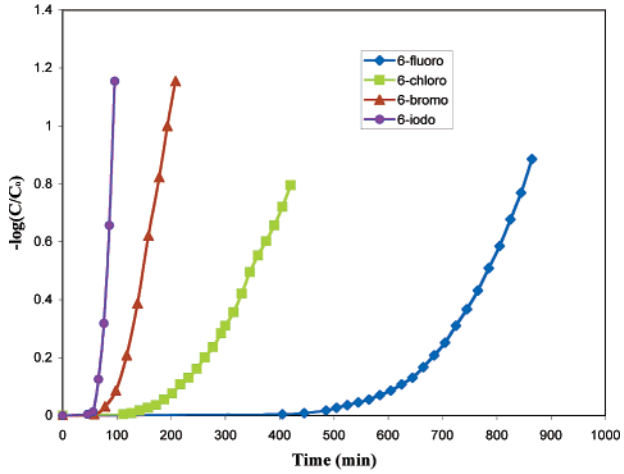
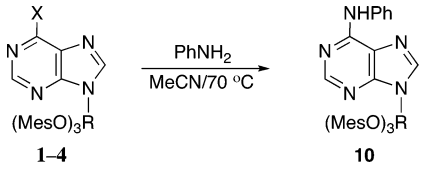


Figure 2. S_NAr reactions of **1**−**4** with aniline.

Scheme 5



S_NAr Reactions of 6-Halopurine Nucleosides with an Aromatic Amine. Véliz and Beal[3b] reported that 6-bromopurine nucleosides reacted smoothly with aromatic amines in methanol, in contrast to the lack of reactivity they found with acetonitrile as solvent. They also noted that the 6-bromo compounds were more reactive than 6-chloro analogues, whereas Lakshman et al.[18] had resorted to palladium-catalyzed coupling of 6-chloropurine compounds with arylamines. Because the 6-iodopurine compound **4** was not very soluble in methanol, we used acetonitrile. Treatment of **1**−**4** with aniline (5 equiv) in acetonitrile at 70 °C (Scheme 5) resulted in S_NAr displacements—but with significant lag times. The reactivity order was I > Br > Cl > F with lag periods of ∼50 min (**4**), ∼1 h (**3**), ∼2 h (**2**), and ∼6 h (**1**) (Figure 2).

Our observation of such lag times rationalizes the apparent differences between our results and those of Véliz and Beal.[3b] Accelerating rates of displacement of halide from 6-halopurine compounds with aniline at longer reaction times is consistent with autocatalysis by the generated hydrogen halides. Trifluoroacetic acid (TFA) had been used for identification of protonation sites on purines in the ^{15}N NMR studies of Roberts and co-workers,[19] and addition of TFA enhanced the reactivity of purine derivatives in S_NAr reactions.[20] Our addition of TFA (2 equiv) to the reaction mixtures of Scheme 5 resulted in disappearance of lag times, and the S_NAr reactions proceeded at accelerated rates (and at 50 °C, rather than 70 °C). The

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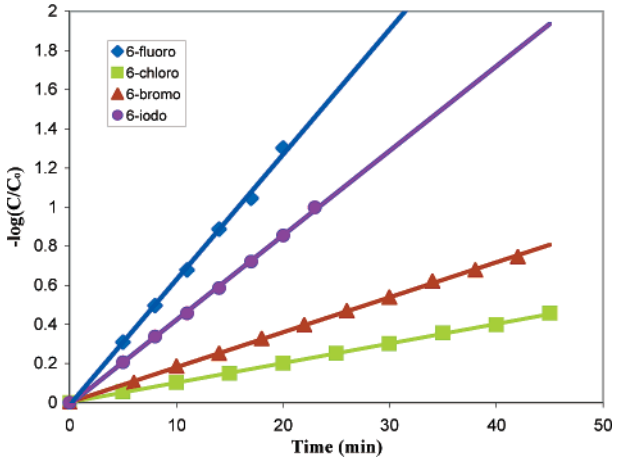

Figure 3. S_NAr reactions of **1**−**4** with TFA/aniline.

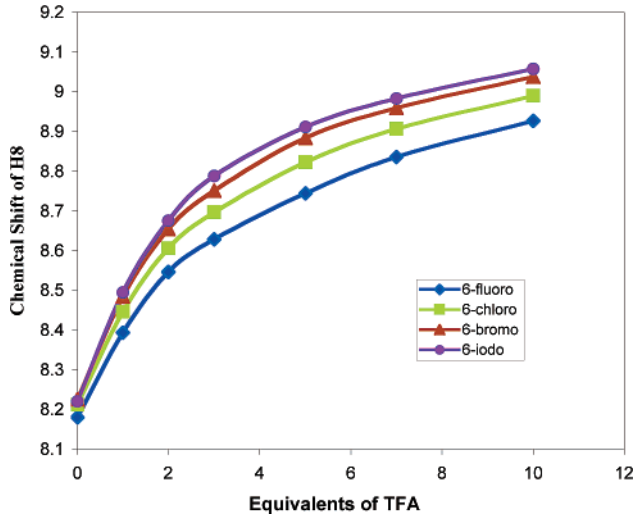

Figure 4. Effects of addition of TFA on H8 of **1**−**4**.

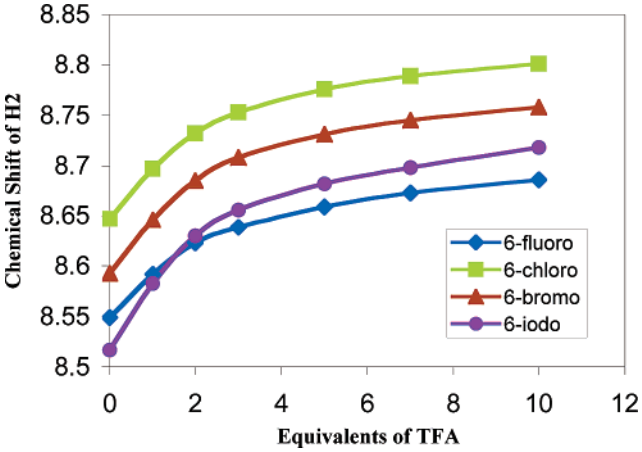

Figure 5. Effects of addition of TFA on H2 of **1**−**4**.

reactivity order with aniline (5 equiv) plus TFA (2 equiv) was F > I > Br > Cl (Figure 3). The kinetic data from Schemes 2−4 and from Scheme 5 ($PhNH_2$ + TFA at 50 °C) are collected in Table 1.

The dramatic effect of adding TFA to S_NAr reactions with aniline prompted our investigation of the site(s) of protonation on the purine bases. Changes in the ^1H NMR chemical shifts of H2 and H8 of **1**−**4** [0.041 mmol in $CDCl_3$ (0.6 mL) in standard NMR tubes] were measured as a function of added

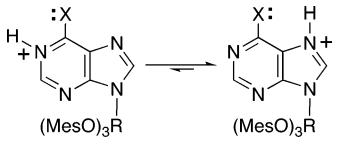

Figure 6. Thermodynamic protonation of N7.

Table 2. Changes of ^{15}N NMR Chemical Shifts[a] of **3** in $CDCl_3$ with Addition of TFA

TFA (equiv)	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

[a] Shifts are given in parts per million (ppm) upfield from external $CH_3{}^{15}NO_2$.

TFA. The relative changes ($\Delta\delta$) for H8 (Figure 4) are greater than those for H2 (Figure 5) with added TFA.

The $\Delta\delta$ changes of both the H2 and H8 signals for these compounds are in the order **4** > **3** > **2** > **1**. The larger relative shifts for the H8 signals indicate that thermodynamic protonation occurs at N7 > N1 (Figure 6). Greater stabilization of positive charge at protonated N7 might result from peri interactions with electrons on X [the largest effect observed with H8 of **4**] rather than from resonance delocalization of electron density directly from X to protonated N1.

Although the larger $\Delta\delta$ shifts for H8 relative to H2 suggested preferential protonation at N7, ^{15}N NMR is a superior method to probe for protonation on nitrogen because ^{15}N chemical shifts are very sensitive to changes in the local environment.[21] TFA was used for identification of protonation sites on purines and nucleosides with ^{15}N NMR,[19] 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.[21]

Roberts and co-workers[19a] had observed upfield ^{15}N NMR $\Delta\delta$ shifts of ~72 ppm for N1 of adenosine (1.6 equiv of TFA) and ~66 ppm for N7 of guanosine (1.86 equiv of TFA) in DMSO. In contrast, we found an upfield $\Delta\delta$ shift of 1.2 ppm for N7 of **3** in DMSO (1.6 equiv of TFA). The $\Delta\delta$ shifts for N1, N3, and N9 were all <1 ppm. Adenosine (pK_a 3.4) and guanosine (pK_a 1.6) are considerably more basic than DMSO (pK_a −1.8) and compete effectively for protons in TFA/DMSO. The much less basic **3** was protonated to only a small extent in TFA/DMSO [i.e., the $\Delta\delta$ shifts for adenosine (N1) and guanosine (N7) were much larger than that for N7 of the weakly basic **3**]. $CDCl_3$ is essentially nonbasic, and the ^{15}N NMR $\Delta\delta$ shift for N7 of **3** upon addition of TFA (1.6 equiv) is much larger in $CDCl_3$ (~16 ppm) (Table 2) than in DMSO (1.2 ppm). Extensive protonation at N7 of **1** (Table 3) and **3** (Table 2) by TFA should occur in nonbasic solvents such as CH_3CN (pK_a −10) as well as in $CDCl_3$. Our ^{15}N NMR data show that 6-fluoropurine nucleoside **1** undergoes protonation at N7 (~16 ppm upfield shift) (Table 3). Preferential protonation at N7 of the 6-bromopurine nucleoside **3** is apparent (~16 ppm upfield shift), but protonation at N1 of **3** (~5.5 ppm upfield shift) also is significant (Table 2) in comparison with protonation at N1 of **1** (Table 3).

(21) Wang, G.; Gaffney, B. L.; Jones, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 8908−8909.

Table 3. Changes of ^{15}N NMR Chemical Shifts[a] of **1** in $CDCl_3$ with Addition of TFA

TFA (equiv)	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

[a] Shifts are given in parts per million (ppm) upfield from external $CH_3{}^{15}NO_2$.

Our ^1H and ^{15}N NMR data are consistent in that larger downfield ^1H NMR $\Delta\delta$ shifts for the H8 signals relative to those for H2 coincide with preferential N7 protonation apparent in ^{15}N NMR spectra with additions of TFA. Although ^1H NMR $\Delta\delta$ shift trends are parallel in spectra of **1**−**4**, differences are apparent (Figures 4 and 5). Protonation at N1 of **3** (Table 2) relative to the $\Delta\delta$ shifts for N1 in ^{15}N NMR spectra of **1** (Table 3) suggest that different mechanistic combinations might be operative in acid-catalyzed S_NAr reactions with such purine derivatives that have several basic sites. A mechanism proposed for S_NAr reactions of 1-fluoro-2,4-dinitrobenzene with weakly nucleophilic anilines invoked reversible addition in the first step followed by rate-limiting loss of fluoride.[22] Our reactions of aniline with **1**−**4** (Figure 2) are consistent with this hypothesis. Loss of halide (and a proton) from the addition complex generates HX for autocatalysis, and the order of reactivity is **4** > **3** > **2** ≫ **1**. Addition of TFA results in thermodynamic protonation at N7 (and likely kinetic protonation at N1—and possibly at N3), which assists the addition of aniline at C6 of the C═N double bond. However, TFA also could protonate (hydrogen bond) with fluoride (H—F−C6), which would activate the F−C bond for departure of HF. Hydrogen bonding would be much less significant with chloride and absent with bromide and iodide. Halide−C6 bond breaking must be involved because the ordering is **1** > **4** > **3** > **2** (Figure 3) with TFA added. Multiple mechanistic effects include (1) thermodynamic and kinetic protonation of the 6-halopurine substrates, as well as the aniline nucleophile; (2) hydrogen bonding with halide leaving groups; and (3) carbon−halogen bond strengths. Our studies have clarified some parameters involved in choices of synthetic approaches with 6-halopurine nucleosides as S_NAr substrates.

Comparisons of a 6-(Alkylsulfonyl)purine Nucleoside with 6-Halopurine Analogues. Oxidation of easily accessible 6-(alkylsulfanyl)purine derivatives provides the 6-(alkylsulfonyl)purine counterparts. Wetzel and Eckstein[23] had noted that 6-(methylsulfonyl)-9-(β-D-ribofuranosyl)purine underwent S_NAr displacements readily. Reactivity competitions between equimolar quantities of 9-[(2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]-6-(3-methylbutylsulfonyl)purine[13] (**6**) and each of the four 6-halopurine analogues with butylamine, methanol, 3-methylbutane-1-thiol, and aniline (with and without 2 equiv of TFA) under the same conditions described for the kinetic studies are summarized in Table 4. Because sulfone **6** was more reactive than the fluoride **1** with MeOH/DBU and ^{i}PentSH/DBU, and the reactivity with $BuNH_2$ also was too fast under comparable conditions (as noted above for the 6-fluoro analogue **1**), kinetic plots with sulfone **6** are not included.

(22) (a) Forlani, L.; Tortelli, V. *J. Chem. Res., Synop.* **1982**, 62−63. (b) Forlani, L. *J. Chem. Res., Synop.* **1984**, 260−261.
(23) Wetzel, R.; Eckstein, F. *J. Org. Chem.* **1975**, *40*, 658−660.

Table 4. Orders of Leaving Group Reactivities with Compounds **1**−**4** and **6**

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

Sulfone **6** was more reactive than the 6-fluoropurine analogue **1** with methanol/DBU and with 3-methylbutane-1-thiol/DBU (overall ordering: **6** > **1** > **3** ≈ **2** > **4** with MeOH/DBU and **6** > **1** > **3** ≈ **4** > **2** with ^{i}PentSH/DBU). Sulfone **6** was second to **1** with both butylamine and aniline plus TFA (overall ordering: **1** > **6** > **3** > **2** > **4** with $BuNH_2$ and **1** > **6** > **4** > **3** > **2** with $PhNH_2$/TFA). The 6-iodopurine analogue **4** was most reactive with aniline in the absence of TFA; and **6** was third in reactivity, behind the bromopurine compound **3** (overall ordering: **4** > **3** > **6** > **2** > **1**). Combinations of C−X bond stability and autocatalysis by displaced HX might be operative in the latter series.

Conclusions

Our results demonstrate that the 6-fluoropurine nucleoside **1** is the most reactive substrate for S_NAr reactions among the four 6-halopurine analogues with an aliphatic amine, an arylamine plus TFA, and with oxygen and sulfur nucleophiles. However, the 6-iodopurine analogue **4** is the best substrate for the aromatic amine (autocatalysis by generated HI) in the absence of an external acid catalyst. The 6-(alkylsulfonyl)purine nucleoside **6** is even more reactive than **1** with oxygen and sulfur nucleophiles. An array of substrates and quantitative as well as qualitative comparisons are now available to guide choices for syntheses of 6-(substituted)purine derivatives that are readily accessible by S_NAr processes.

Experimental Section[24]

6-Fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (1). This compound[13] was prepared as reported: mp 117−120 °C. Anal. Calcd for $C_{40}H_{41}FN_4O_7$: C, 67.78; H, 5.83; N, 7.90. Found: C, 67.68; H, 5.70; N, 7.83.

6-Chloro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (2). This compound[7] was prepared as reported: mp 123−126 °C. Anal. Calcd for $C_{40}H_{41}ClN_4O_7$: C, 66.25; H, 5.70; N, 7.73. Found: C, 66.50; H, 5.70; N, 7.88.

6-Bromo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (3). A solution of **2** (200 mg, 0.27 mmol) and TMSBr (0.4 mL, 0.3 g, 3 mmol) in butanone (5 mL) was stirred at −40 °C for 2 h. The reaction mixture was poured into saturated $NaHCO_3/H_2O$ and extracted (CH_2Cl_2). The organic layer was washed (brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was recrystallized (EtOH) to give **3** (170 mg, 80%): mp 121−124 °C; ^1H 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 [M + Na^+ ($C_{40}H_{41}{}^{79}BrN_4O_7Na$) = 791.2056]. Anal. Calcd for $C_{40}H_{41}BrN_4O_7$: C, 62.31; H, 5.21; N, 7.17. Found: C, 62.42; H, 5.37; N, 7.28.

(24) Experimental details are in the Supporting Information.

6-Iodo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]-purine (4). This compound[7] was prepared as reported: mp 143−145 °C. Anal. Calcd for $C_{40}H_{41}IN_4O_7$: 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 (5). This compound[13] was prepared and characterized as reported.

6-(3-Methylbutylsulfonyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (6). This compound[13] was prepared and characterized as reported.

General Procedure A: Reactions of 1−4 with Butylamine. $BuNH_2$ (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 °C. Aliquots were removed after specified times and quenched into aqueous buffer (pHydrion buffer 6.00 ± 0.02). The mixtures were extracted (CH_2Cl_2), and volatiles were evaporated from the organic layers. The residues were dissolved ($CDCl_3$, 0.55 mL), and C/C_0 ratios were measured by integration of ^{1}H NMR acquisitions. The same procedure was used for **3** and **4** (the reaction with **1** was too fast to measure).

6-*N*-Butyl-2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl)adenosine (7). Treatment of **2** (50 mg, 0.069 mmol) by general procedure A gave **7** (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 s, 2H), 4.68−4.71 (m, 1H), 4.73−4.77 (m, 1H), 4.80−4.84 (m, 1H), 5.70 (br s, 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 [M + H^+ ($C_{44}H_{52}N_5O_7$) = 762.3867].

General Procedure B: Reactions of 1−4 with Methanol/DBU. 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 °C. Aliquots were removed after specified times and quenched into aqueous buffer (pHydrion buffer 6.00 ± 0.02). The mixtures were extracted (CH_2Cl_2), and volatiles were evaporated from the organic layers. The residues were dissolved ($CDCl_3$, 0.55 mL), and C/C_0 ratios were measured by integration of ^{1}H NMR acquisitions. The same procedure was used for **3** and **4** (the reaction with **1** was too fast to measure).

6-Methoxy-9-[2,3,5-tri-O-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (8). Treatment of **2** (50 mg, 0.069 mmol) by general procedure B gave **8** (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 [M + Na^+ ($C_{41}H_{44}N_4O_8Na$) = 743.3057].

General Procedure C: Reactions of 1−4 with Potassium Thioacetate. KSAc (11.9 mg, 0.105 mmol) was added to a solution of **2** (14.8 mg, 0.0205 mmol) in DMSO-d_6 (0.6 mL) in an NMR tube. The reaction mixture was warmed at 30 °C in the NMR spectrometer, and C/C_0 ratios were measured by integration of ^{1}H NMR acquisitions. The same procedure was used for **1**, **3**, and **4**. [A similar procedure was used with ^{i}PentSH/DBU and **1**−**4** with cooling to ∼−40 °C in the NMR spectrometer, and the same order of reactivity was observed.]

2′,3′,5′-Tri-*O*-(2,4,6-trimethylbenzoyl)-6-thioinosine. Treatment of **2** (50 mg, 0.069 mmol) by general procedure C (with CH_3CN as solvent instead of DMSO, and workup as in general procedure B) resulted in S-deacetylation during workup to give the title compound (43 mg, 87%): ^{1}H 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 [M + Na^+ ($C_{40}H_{42}N_4O_7SNa$) = 745.2672].

Table 5. ^{15}N−^{1}H and ^{15}N−^{19}F Coupling Constants for **1** and **3**

compd	$J_{(N1-H2)}$, Hz	$J_{(N3-H2)}$, Hz	$J_{(N7-H8)}$, Hz	$J_{(N1-F)}$, Hz	$J_{(N3-F)}$, Hz	$J_{(N7-F)}$, Hz
1	15.4	14.8	12.1	47.0	7.3	4.7
3	15.9	14.6	11.6			

General Procedure D: Reactions of 1−4 with Aniline. $PhNH_2$ (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 an NMR tube. The reaction mixture was heated at 70 °C in the NMR spectrometer, and C/C_0 ratios were measured by integration of ^{1}H NMR acquisition data. The same procedure was used for **1**, **3**, and **4**.

General Procedure E: Reactions of 1−4 with Aniline/TFA. $PhNH_2$ (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 an NMR tube. The reaction mixture was heated at 50 °C in the NMR spectrometer, and C/C_0 ratios were measured by integration of ^{1}H NMR adquisition data. The same procedure was used for **1**, **3**, and **4**.

6-*N*-Phenyl-2′,3′,5′-tri-*O*-(2,4,6-trimethylbenzoyl)adenosine (10). Treatment of **2** (50 mg, 0.069 mmol) by general procedure D (with CH_3CN instead of CD_3CN) gave **10** (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 s, 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 [M + Na^+ ($C_{46}H_{47}N_5O_7Na$) = 804.3373].

Relative Reactivity Comparisons with 1−4 and 6. Solutions of equimolar quantities of (**1** and **6**), (**2** and **6**), (**3** and **6**), and (**4** and **6**) in five series of four separate NMR tubes were subjected to treatment under the same conditions with the same molar ratios of $BuNH_2$, MeOD/DBU, ^{i}PentSH/DBU, $PhNH_2$, and $PhNH_2$/TFA used in the kinetic experiments. Integration of ^{1}H NMR acquisition data allowed measurement of the relative quantities of products formed.

Procedure for Titration with TFA (^{1}H NMR). A solution of **1** (29.4 mg, 0.0410 mmol) in $CDCl_3$ (0.6 mL) was added to an NMR tube. Precise quantities of TFA were added, and the ^{1}H NMR chemical shifts of H2 and H8 were measured accurately. The same procedure was used with equimolar quantities of **2**, **3**, and **4**.

Procedure for Titration with TFA (^{15}N NMR). A solution of **1** (200 mg, 0.282 mmol) in $CDCl_3$ (0.5 mL) was added to an NMR tube. Precise quantities of TFA were added, and ^{15}N NMR chemical shifts were measured. The ^{15}N NMR acquisitions required 12 h for each set of data (the signal/noise ratio precluded measurement of the shift for N9 after addition of 0.6 equiv of TFA). The same procedure was used for **3** (217 mg, 0.282 mmol).

^{15}N Signal Assignments. The ^{15}N−^{1}H and ^{15}N−^{19}F coupling constants (Table 5), as well as reported ^{15}N NMR studies of related compounds,[25] were used to make resonance peak assignments for specific nitrogen atoms. The $^2J_{(N1-F)}$ = 47.0 Hz coupling constant for the signal centered at 139 ppm in the spectrum of **1** is much larger than the N3−F and N7−F couplings of 7.3 and 4.7 Hz. The resonance peak for N7 at 145.9 ppm was identified by its N7−H8 coupling constant (12.1 Hz), which is smaller than the N3−H2 coupling (14.8 Hz) at 134.6 ppm in the six-membered ring. The peak at 217.7 ppm was assigned to N9 by analogy with adenosine (N9 at 205 ppm with

(25) Sibi, M. P.; Lichter, R. L. *Org. Magn. Reson.* **1980**, *14*, 494−496.

HNO_3 as external standard, 223 ppm with CH_3NO_2). Assignments of resonance peaks to the nitrogen atoms in **3** were made on the basis of $^{15}N-^{1}H$ coupling constants and ^{15}N studies of related compounds. The N7 resonance was identified by its N7−H8 coupling constant (11.6 Hz), which is smaller than the N1−H2 (15.9 Hz) and N3−H2 (14.6 Hz) couplings in the six-membered ring. The reported coupling constant for N1−H (15.9 Hz)[26] of [1-^{15}N]-6-bromo-9-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)purine is identical to that for N1−H (15.9 Hz) of **3**. $^{1}H-^{15}N$ HMQC spectra of **1** and **3** confirmed the ^{15}N assignments.

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Supporting Information Available: General experimental details, enlarged pseudo-first-order plots (containing all data points) for S_NAr reactions of **1**−**4** with nitrogen, oxygen, and sulfur nucleophiles, and enlarged titration plots of H8 and H2 resonance shifts with additions of TFA. This material is available free of charge via the Internet at http://pubs.acs.org.

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