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6-(2-Alkylimidazol-1-yl)purines Undergo Regiospecific Glycosylation at N9†

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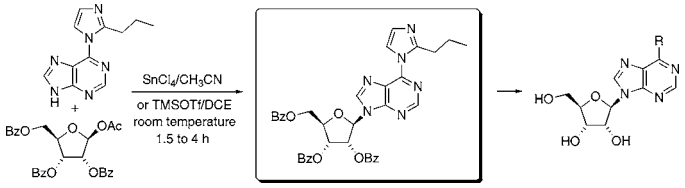
ABSTRACT



Regioselective control of glycosylation of purines at N9 (versus N7) has been a continuing challenge. We now report Lewis acid catalyzed regiospecific glycosylations of 6-(2-alkylimidazol-1-yl)purines at N9. The 6-(2-alkyl)imidazole moiety also functions as a versatile leaving group that can be replaced by nucleophiles (S_NAr) and aryl groups (Suzuki cross-coupling).

The most challenging aspects of nucleoside synthesis by glycosylation involve the achievement of concomitant regio- and stereocontrol. Alkylation or glycosylation of purines is rarely regiospecific, and both usually produce mixtures of N9 and N7 (and even N3 and/or N1[1]) products. Factors known to influence N9/N7 ratios include the composition of the alkylating reagent or glycosyl donor, the purine, and the reaction conditions.[2,3] Numerous studies have pursued ways to maximize N9 glycosylation, but few have resulted in systematic improvements. Regioselective coupling of adenine, 6-chloropurine, and 2,6-dichloropurine with ribofuranose donors under catalysis by $SnCl_4$ was reported by Saneyoshi and Satoh,[4] who did not detect N1, N3, or N7 isomers by TLC. However, reaction times were lengthy, and emulsion formation during workup was problematic. Bulky protecting groups on C6 substituents have been used to improve selectivity for N9 glycosylation. Geen et al. reported that N9/N7 ratios were increased significantly by expansion from an O6-methyl to an O6-isopropyl group.[5] Benner and co-workers have employed 2-*N*-isobutyryl-6-*O*-[*p*-nitrophenyl)ethyl]guanine for regioselective alkylation and glycosylation at N9.[6] Robins et al.[7] and Timar et al.[8] have achieved highly regioselective N9 glycosylations and alkylations with the 6-*O*-diphenylcarbamoyl (6-*O*-DPC) group. However, the sensitive 6-*O*-DPC group was less effective for smaller electrophiles and for acidic glycosyl donors under Lewis acid conditions.[9] Therefore, a serious need for methods to exclude N7 alkylation and glycosylation remained.

Five-membered heteroaryl rings have been introduced at C6 of purines for temporary protection of the N6 amino group, for leaving groups, and for biological studies.[10] Imidazole and 1,2,4-triazole rings have been used as replaceable substituents at C6 of purines and C4 of pyrimidines.

† Nucleic Acid Related Compounds. 128. For part 127, see: Nowak, I.; Conda-Sheridan, M.; Robins, M. J. *J. Org. Chem.* **2005**, *70*, 7455−7458.

(1) For a recent example, see: Guillarme, S.; Legoupy, S.; Bourgougnon, N.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 9635−9639.

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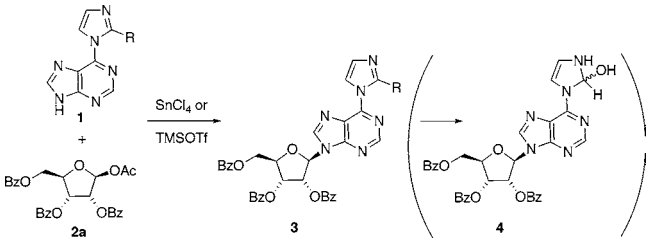
Recently, we have elaborated the 6-amino group of adenine-type nucleosides into 6-(1,2,4-triazol-4-yl)[11] and 6-(2,5-dimethylpyrrol-1-yl) moieties[12] and employed a modified Appel reaction for introduction of an (imidazol-1-yl) ring at C6 of purine nucleosides.[13] Both theoretical calculations and X-ray crystal structures indicate that the two heteroaromatic rings of 6-(imidazol-1-yl)purines are essentially coplanar. This causes apparent shielding of N7 by H5′ of the imidazole ring, which should result in highly regioselective N9 glycosylation.

The purine sodium salt glycosylation procedure[14] is an important nucleoside-forming methodology, but N7 isomer formation is problematic. Our attempts to couple sodium salts of certain substituted 6-(imidazol-1-yl)purines with either 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride or 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide were not promising. We then examined Vorbrüggen-type glycosylations of 6-(imidazol-1-yl)purine (**1a**) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (**2a**) with $SnCl_4$ in acetonitrile[4] or pretrimethylsilylated **1a** (BSA/DCE) with TMSOTf in toluene (Scheme 1). The $SnCl_4$-catalyzed glycosylation went to

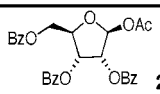
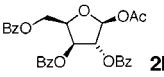
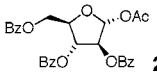
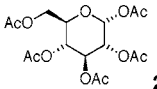
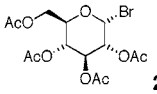
Scheme 1. Glycosylation of 6-(Imidazol-1-yl)purines **1** with **2a**



completion, and the coupling product **3** (R = H) was formed in high yield as single regioisomer. However, addition of water to the imidazole ring occurred to give **4** (diastereomeric mixture). Chromatography of a TMSOTf-catalyzed reaction mixture gave a salt of **3** (R = H) that produced the hydrate **4** (81%) upon neutralization with $NaHCO_3/H_2O$.

We reasoned that replacement of imidazole per se by a 2-alkylimidazole at C6 of the purine ring might prevent hydration of the 6-(2-alkylimidazol-1-yl)purine nucleoside intermediates **3**. Thus, 6-(2-propylimidazol-1-yl)purine (**1b**) and **2a** in acetonitrile with $SnCl_4$ as catalyst gave **3a** (R = Pr) in 79% isolated yield (Table 1, entry 1). The xylosyl, **2b**, and arabinosyl, **2c**, donors coupled equally well under these conditions to give nucleosides **3b** (78%) (entry 3) and **3c** (81%) (entry 5). In contrast, 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (**2d**) did not undergo coupling under the same conditions (entry 7), which is likely attributable to the less favorable formation of an oxocarbenium ion with pyranosides and different activation energy barriers.[15] Conversion of the anomeric acetate of **2d** to the pyranosyl bromide[16] of **2e**, and use of $SnCl_4$ as catalyst, resulted in successful coupling to give the desired product **3d** (83%) in good yield upon extension of the reaction time to 9 h (entry 9).

Table 1. Glycosylations of 6-(2-Propylimidazol-1-yl)purine[a]

entry	donor	catalyst	time[b]	yield[c]
1	 **2a**	$SnCl_4$	4	79
2		TMSOTf	1.5	83
3	 **2b**	$SnCl_4$	4	81
4		TMSOTf	1.5	84
5	 **2c**	$SnCl_4$	4	78
6		TMSOTf	1.5	76
7	 **2d**	$SnCl_4$	4	*d*
8		TMSOTf	1.5	*d*
9	 **2e**	$SnCl_4$	9	83
10		TMSOTf	1.5	*d*

[a] Reactions were performed by the general procedure (Supporting Information). [b] Hours. [c] Percent isolated. [d] No reaction.

We also subjected the reactants to coupling with TMSOTf as catalyst. This one-step, one-pot procedure employed TMSOTf (in DCE) both for trimethylsilylation of 6-(2-propylimidazol-1-yl)purine (**1b**) and for catalytic activation of the glycosyl donors. Couplings were complete within 1.5 h at ambient temperature with furanosyl donors **2a**−**c** (entries 2, 4, and 6). The isolated yields in these cases (∼80%) were comparable to those under catalysis with $SnCl_4$ and were completed in less than half the time. However, TMSOTf-catalyzed coupling was not observed with the pyranosyl donors **3d** (entry 8) and **3e** (entry 10).

It is noteworthy that glycosylations of silylated purines under Vorbrüggen conditions typically give lower (60−70%) yields and mixtures of regioisomers,[17] whereas the Vorbrüggen methodology usually gives high yields of the desired N1 isomer with silylated pyrimidines.[3] Our present procedures combine ambient temperature conditions, good yields, and versatility with regiospecific coupling of purines. Additionally, we have developed a modified workup of reactions that employ $SnCl_4$ to avoid formation of the troublesome

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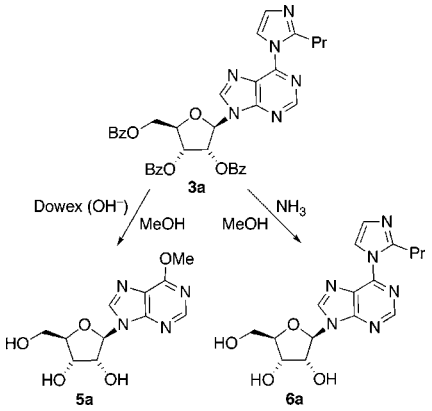
emulsions.[18] A 10-fold excess of solid $NaHCO_3$ and a tiny amount of H_2O was stirred with the concentrated reaction mixture containing $SnCl_4$. The resulting suspension was filtered using Celite, and the filter cake was washed thoroughly. The combined filtrate was flash evaporated, and the residue was purified by chromatography.

The imidazole moiety in 6-(2-alkylimidazol-1-yl)purines can function as a leaving group for S_NAr reactions with nitrogen, oxygen, and sulfur nucleophiles[13a] and as a cross-coupling partner with arylboronic acids for Suzuki reactions.[19] Our present methodology expands the generality of these substitution/cross-coupling applications from examples derived from naturally occurring purine nucleosides and 2′-deoxynucleosides[13,19] to the unlimited variety of purine and sugar combinations available through sugar-base coupling.

Selective O-deacylation without displacement of the imidazole moiety (Scheme 2) was achieved readily in methanolic

Scheme 2. Methanolysis or Deprotection of **3a**[a]



[a] Reactions were performed at ambient temperature as described in the Supporting Information.

ammonia at ambient temperature. Heating **3a** in the same solution at 80 °C produced mixtures of **5a** and adenosine (adenosine can be obtained exclusively at higher temperatures) (Table 2). Clean formation of the 6-methoxypurine nucleoside **5a** was effected by stirring **3a** with Dowex 1 × 2 (OH^-) resin in MeOH at ambient temperature.[11] Analogous substitution with other alkoxy groups can be effected with Dowex 1 × 2 (OH^-) in a solution of a 6-(2-alkylimidazol-1-yl)purine intermediate in a different primary alcohol.

In conclusion, we have employed a (2-alkylimidazol-1yl) substituent at C6 of the purine ring to direct glycosylation to N9. Vorbrüggen procedures provide the N9 isomers regiospecifically with $SnCl_4$/acetonitrile or TMSOTf/DCE. Either Lewis acid catalyst works well with the furanosyl donors, and reactions with TMSOTf/DCE were completed in less than half the time (1.5 h). Coupling with the pyranosyl donors was not observed with TMSOTf/DCE under these conditions, but the $SnCl_4$/acetonitrile system works well for

(18) For other workup applications that avoid emulsions, see ref 13.
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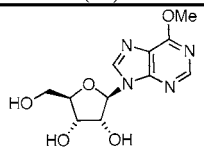
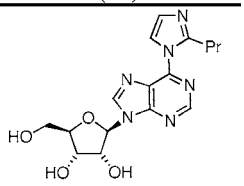
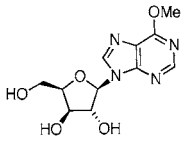
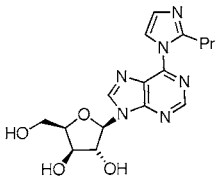
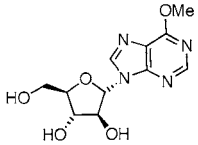
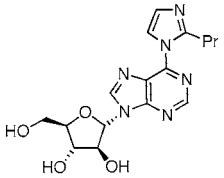
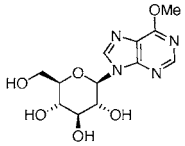
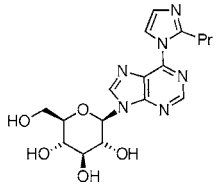
Table 2. Methanolysis or Deprotection of **3**[a]

entry	**5** (%)[b]	entry	**6** (%)[b]
1	 **5a** (85)	5	 **6a** (88)
2	 **5b** (82)	6	 **6b** (73)
3	 **5c** (90)	7	 **6c** (78)
4	 **5d** (89)	8	 **6d** (91)

[a] Reactions were performed at ambient temperature as described in the Supporting Information. [b] Isolated yields.

both the furanosyl donors (4 h) and the pyranosyl bromide (9 h). A modified workup procedure avoids formation of emulsions usually encountered with $SnCl_4$, which markedly enhances the convenience of reactions with this catalyst. Both procedures are mild (ambient temperature) and provide ∼80% isolated yields of only the N9 isomer, whereas the sodium salt and Vorbrüggen glycosylation methods with halopurines give both N9 and N7 regioisomers. The 6-(2-alkylimidazol-1-yl)purine nucleoside derivatives undergo selective deacylation readily, and the imidazole moiety can be displaced by nucleophiles (S_NAr) or aryl groups (Suzuki cross-coupling). Biological evaluations of these new compounds are in progress.

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Supporting Information Available: Experimental procedures and spectral data and ^{13}C NMR spectra of compounds **3a**−**d**, **5a**−**d**, and **6a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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