Efficient Conversion of 6-Aminopurines and Nucleosides into 6-Substituted Analogues via Novel 6-(1,2,4-Triazol-4-yl)purine Derivatives[1]

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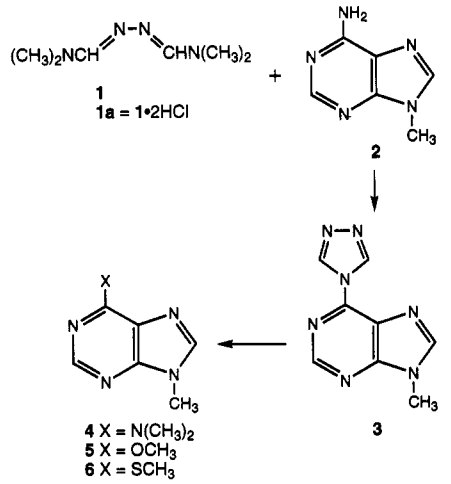
Functional group transformations with nucleic acid bases are important synthetic manipulations in the chemistry of nucleosides and nucleotides.[2] Diazotization–hydrolytic dediazoniations of adenine (6-amino) to hypoxanthine (6-oxo) and guanine (2-amino-6-oxo) to xanthine (2,6-dioxo) compounds have been known for over a century.[2b] More recently, diazotization–halodediazoniations have been developed with aqueous[3,4] and nonaqueous[5,6] systems. Sulfhydrolysis of an amino group with liquid hydrogen sulfide/pyridine in a pressure vessel had been employed to obtain thione products.[7] However, a convenient general procedure for nucleophilic replacement of amino groups on nucleic acid bases is lacking.

Bartlett and Humphrey prepared azine **1** and its dihydrochloride **1a** from *N,N'*-diformylhydrazine and thionyl chloride in *N,N*-dimethylformamide (DMF) and reported cyclizations with amines to provide 4-*N*-substituted-1,2,4-triazoles.[8] The pK_a of

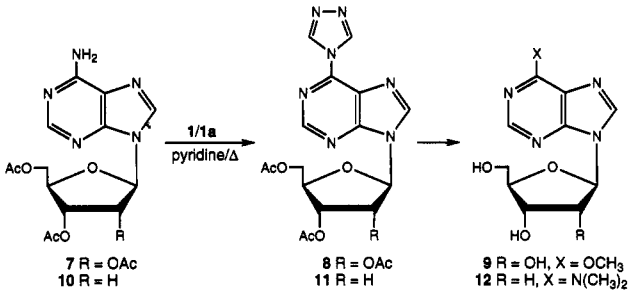


1,2,4-triazole (~10)[9] makes this ring a suitable candidate for nucleophilic addition–elimination displacements. Divakar and Reese had developed conversions of uracil to cytosine nucleosides via formation of 4-(1,2,4-triazol-1-yl)pyrimidin-2-one intermediates generated by treatment of uracil compounds with $POCl_3$/1,2,4-triazole.[10] We now report methodology for elaboration of the exocyclic 6-amino group of adenine compounds into a 6-(1,2,4-triazol-4-yl)purine functionality which can be displaced by nucleophiles to give 6-substituted-purine analogues in good to excellent yields.

Thus, 9-methyladenine (**2**; 1.33 g, 8.9 mmol) was mixed with dried 1,2-bis[(dimethylamino)methylene]hydrazine dihydrochloride[8] (**1a**; 2.54 g, 11.8 mmol) in DMF (250 mL) and heated at reflux for 18 h. Additional **1a** (1.47 g, 6.8 mmol) was added, and heating was continued for 2 days. Volatiles were evaporated, MeOH was added and evaporated (4×), and the residue was suspended in MeOH, filtered, and dried to give 9-methyl-6-(1,2,4-triazol-4-yl)purine (**3**, 85%). A sample was recrystallized (MeOH) to give **3**: mp 292.5–294 °C; UV (MeOH) max 276 nm (ε 13 300), min 235 nm (ε 2200); MS *m/z* 201, $M^+[C_8H_7N_7]$ = 201; ^1H NMR (Me_4Si/Me_2SO-d_6) δ 3.92 (s, 3H), 8.78 (s, 1H), 8.94 (s, 1H), and 9.66 (s, 2H).[11]

Treatment of **3** with 40% aqueous dimethylamine at ambient temperature for 1 h gave 6-(dimethylamino)-9-methylpurine[12,13] (**4**, 99% after chromatography). Sodium methoxide in MeOH/DMF effected rapid replacement of triazole to give 6-methoxy-9-methylpurine[12,14] (**5**, 97%). Displacement of triazole by sodium thiomethoxide in DMF gave 6-(methylthio)-9-methylpurine[12,14] (**6**, 84% recrystallized).

Having demonstrated the viability of this approach with 9-methyladenine as a stable model, its application to nucleosides was evaluated with 2',3',5'-tri-*O*-acetyladenosine (**7**). Treatment of **7** with excess **1a** in anhydrous pyridine at 100 °C for 20 h gave 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**8**, 88% after chromatography).[11] The UV spectrum of **8** (in



MeOH) had maxima at 274 and 256 nm (ε 12 700 and 8200) and minima at 259 and 231 nm (ε 8100 and 2000). NMR and MS data also were in harmony with structure **8**. A solution of **8** in MeOH was applied to a column of Dowex 1 × 2 (OH^-) resin that had been washed with H_2O, H_2O/MeOH (1:1), and MeOH. The column was allowed to stand overnight and then was eluted with MeOH. Evaporation of appropriate fractions and recrystallization of the residue gave 6-methoxy-9-(β-D-ribofuranosyl)-purine[15,16] (**9**, 89%).

Application to an acid- and heat-sensitive deoxynucleoside was then pursued. A mixture of dried 3',5'-di-*O*-acetyl-2'-deoxyadenosine (**10**; 139 mg, 0.41 mmol), **1** (267 mg, 1.88 mmol), and **1a** (45 mg, 0.21 mmol) was suspended in anhydrous pyridine and evaporated. Anhydrous pyridine (1 mL) and trimethylsilyl chloride (TMS-Cl; 0.21 mL, 180 mg, 1.65 mmol) were added, and the mixture was heated at 100 °C under N_2 for 48 h (an

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additional "drop" of TMS-Cl was added at 45 h). Volatiles were evaporated, and the residue was dissolved in ice-cold CH_2Cl_2 (20 mL) and washed with a cold mixture of brine (10 mL) and 2 M HCl/H_2O (7 mL). The organic layer was filtered through Na_2SO_4 and evaporated to half the volume. An equal portion of EtOAc was added, and the solution was evaporated. Drying in vacuo (5 h) gave a white solid (149 mg, 93%), which was recrystallized (EtOAc) to give 9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(1,2,4-triazol-4-yl)purine (**11**; 132 mg, 82%, 2 crops)[11] with mp 179–179.5 °C; UV (MeOH) max 275 nm (ε 13 900), shoulder 258 nm (ε 9100), min 232 nm (ε 3000). NMR and MS data also were in harmony with structure **11**.

To a suspension of **11** (50 mg, 0.13 mmol) in pyridine (1 mL) was added 40% aqueous dimethylamine (1 mL), and stirring was continued for 4 h. The mixture was evaporated, and the residue was applied to a column of Dowex 1 × 2 (OH^-) resin (cooled at 5 °C to enhance retention of the product). The cold column was washed with H_2O (14 mL), and the product was eluted with $MeOH/H_2O$ (1:1, 2 mL) and MeOH (8 mL). The combined eluate was evaporated, acetonitrile was added and coevaporated (2×), and the resulting white solid was dried in vacuo (100 °C, 4 days) to give 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(dimethylamino)purine (**12**; 35 mg, 97%): mp 171.5–173 °C (lit.[17] mp 177.5–179 °C); ^{1}H NMR (Me_2SO-d_6) δ 2.28 (ddd, $J_{2''-2'}$ = 13.2 Hz, $J_{2''-1'}$ = 6.1 Hz, $J_{2''-3'}$ = 3.0 Hz, 1, H2″), 2.71 (ddd, $J_{2'-1'}$ = 7.6 Hz, $J_{2'-3'}$ = 5.7 Hz, 1, H2′), 3.41 [m (br s after D_2O shift of H_2O peak), 6, NMe_2], 3.52 [m (dd, $J_{5''-5'}$ = 12.1 Hz, $J_{5''-4'}$ = 4.3 Hz, after D_2O), 1, H5″], 3.62 [m (dd, $J_{5'-4'}$ = 3.9 Hz, after D_2O), 1, H5′], 3.90 ("q", 1, H4′), 4.42 (m, 1, H3′), 5.23 (t, 1, OH5′), 5.34 (d, $J_{OH-3'}$ = 4.0 Hz, 1, OH3′), 6.38 (dd, 1, H1′), 8.22 (s, 1, H2), 8.37 (s, 1, H8).

In summary, treatment of 9-methyladenine, 2′,3′,5′-tri-*O*-acetyladenosine, or the acid- and heat-sensitive 3′,5′-di-*O*-acetyl-2′-deoxyadenosine with azine **1** and/or **1a** under appropriate conditions gave high yields of the corresponding 6-(1,2,4-triazol-4-yl) derivatives which were obtained in pure crystalline form. Treatment of these derivatives with nucleophiles resulted in displacement of 1,2,4-triazole and formation of the 6-substituted-purine analogues in good to excellent yields. This represents the first general procedure for direct functionalization/displacement of an amino group on nucleic acid bases, and applications to other systems are in progress. Careful manipulation of these triazole derivatives should provide access to a new class of building blocks for incorporation into nucleic acid fragments which should be subject to postsynthetic modification[18] to give altered nucleotide units.

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