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Mild and Efficient Functionalization at C6 of Purine 2′-Deoxynucleosides and Ribonucleosides[1]

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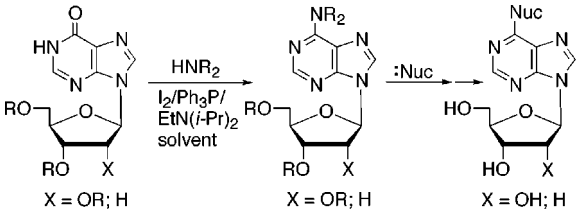
ABSTRACT



Treatment of sugar-protected inosine and 2′-deoxyinosine derivatives with a cyclic secondary amine or imidazole and I_2/Ph_3P/EtN(*i*-Pr)$_2$/(CH_2Cl_2 or toluene) gave quantitative conversions into 6-*N*-(substituted)purine nucleosides. S_NAr reactions with 6-(imidazol-1-yl) derivatives gave 6-(*N*, *O*, or *S*)-substituted products. The 6-(benzylsulfonyl) group underwent S_NAr displacement with an arylamine at ambient temperature.

We report mild and efficient transformations of sugar-protected derivatives of 2′-deoxyinosine and inosine into 6-substituted-purine ribonucleosides and 2′-deoxynucleosides via presumed 6-oxyphosphonium intermediates. For example, treatment of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine with a suspension of morpholine/I_2/Ph_3P/EtN(*i*-Pr)$_2$/toluene at ambient temperature for 45 min gave 9-(5-*O*-TBDMS-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)-6-(morpholin-4-yl)purine (99% after column chromatography), and analogous treatment with imidazole/I_2/Ph_3P/EtN(*i*-Pr)$_2$/toluene at 95 °C for 30 min gave the 6-(imidazol-1-yl) derivative (98%). These transformations also were successful with 2′,3′,5′-tri-*O*-acetylinosine and 3′,5′-di-*O*-acetyl-2′-deoxyinosine. The 6-(imidazol-1-yl) derivatives underwent nucleophilic aromatic substitution reactions to give 6-substituted-purine (2′-deoxy or ribo)nucleosides in high yields.

Currently, there is intense interest in the synthesis of "activated" purine (2′-deoxy or ribo)nucleosides and their transformation into substituted-purine derivatives[2−6] via S_NAr and palladium-promoted reactions. Lakshman et al. have described Pd-promoted coupling of arylamines with a 6-bromopurine analogue.[2a] They also reported syntheses of 6-substituted-purine deoxynucleosides[2b] via S_NAr displacements with 6-*O*-(arylsulfonyl)purine analogues developed by Reese[7] and Hata.[8] Johnson[3b,c] and Hopkins[4] and their coworkers have effected Pd-promoted coupling of aminopurine deoxynucleosides to prepare purine-linked products that were originally isolated from DNA treated with nitrous acid. Harris

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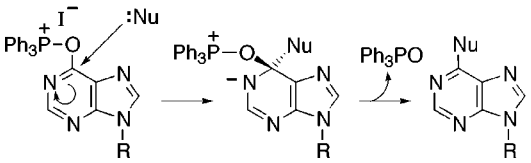
and co-workers have improved conversions of 6-chloropurine nucleosides into the more S_NAr-reactive 6-fluoro analogues.[5] Véliz and Beal have reported deoxygenative chlorination and bromination of 2′,3′,5′-tri-*O*-acetylinosine.[6]

Classical methods for C6 functionalization of purine nucleosides include deoxygenative chlorination of sugar-protected derivatives of inosine with phosphorus oxychloride ($POCl_3$) in the presence of a tertiary aromatic amine or with Vilsmeier−Haack reagent combinations [($POCl_3$ or $SOCl_2$)/DMF/$CHCl_3$].[9] These procedures give reasonable yields of 6-chloropurine ribonucleoside derivatives, but the acidic conditions (in situ generation of HCl) and temperatures normally employed result in cleavage of the glycosyl bond of the sensitive 2′-deoxynucleoside derivatives. Robins and Basom[10] developed the first practical transformation of 2′-deoxyinosine into 6-chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine and its 6-fluoro analogue, but careful attention to explicit experimental conditions[10b] ($SOCl_2$/DMF/CH_2Cl_2) is required to obtain the reported yields. Diazotization−bromodediazoniation has been applied with 2′-deoxyadenosine,[2a,3b,c,11] but modest yields (∼60%) were reported. Deoxygenative thiation with P_4S_{10} or Lawesson's reagent has been used to convert inosine derivatives into purine-6-thione nucleosides,[9] but these procedures cause major glycosyl bond cleavage with 2′-deoxy analogues. Elaboration of 2′-deoxyadenosine and related systems into their 6-(1,2,4-triazol-4-yl) derivatives, which undergo S_NAr, has been described.[12] However, no comparably mild and efficient procedures have been reported for conversion of 2′-deoxyinosine into nucleoside derivatives with a group at C6 that undergoes ready substitution. We now describe such methodology.

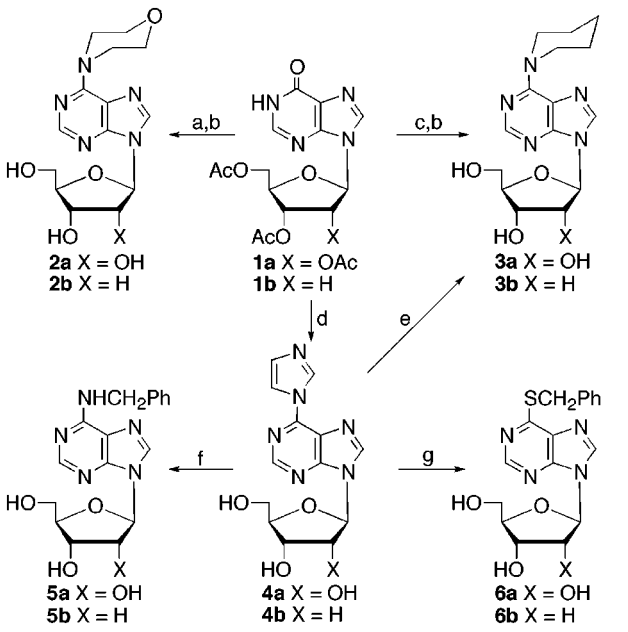
We chose a modified Appel combination[13] of elemental iodine and triphenylphosphine to generate a reactive phosphonium intermediate. Attack of O6 at phosphorus would



produce a purine 6-[(triphenylphosphonium)oxy] iodide complex (with absorption of hydrogen iodide by Hünig's base). It was recently noted[6] that sources of positive bromine or chlorine (NBS or CX_4) with $P(NMe_2)_3$ allowed S_NAr replacement of O6 [as $O{=}P(NMe_2)_3$] with halide to generate 6-halopurine ribonucleosides, but we had reasoned that analogous addition of the large and very weakly basic iodide and elimination of triphenylphosphine oxide should be significantly less favorable. The highly activated 6-[(phosphonium)oxy] intermediate should be susceptible to addition of external nitrogen nucleophiles followed by elimination of $Ph_3P{=}O$.

Treatment of 5′-*O*-TBDMS-2′,3′-*O*-isopropylideneinosine with I_2/Ph_3P/EtN(*i*-Pr)$_2$ in the presence of a secondary aliphatic amine (morpholine or piperidine) in toluene for ∼1 h at ambient temperature gave quantitative conversion (TLC) into the 6-(morpholin-4-yl or piperidin-1-yl) products, which were isolated as solid white foams (98−99%) by silica column chromatography. Other initial reactions and displacements were explored with this protecting group combination for convenience in manipulation and isolation (excellent yields in all cases). Similar treatment of 2′,3′,5′-tri-*O*-acetylinosine (**1a**) (Scheme 1) with (morpholine or piperidine)/I_2/Ph_3P/EtN(*i*-Pr)$_2$ in CH_2Cl_2 for ∼1 h at ambient temperature also gave quantitative conversions (TLC). The acetyl intermediates were deprotected (NaOMe/MeOH), and products were purified by anion-exchange chromatography to give 6-(morpholin-4-yl or piperidin-1-yl)-9-(β-D-ribofuranosyl)purine [**2a** (94%) or **3a** (96%), respectively]. Treatment of **1a** with imidazole/I_2/Ph_3P/EtN(*i*-Pr)$_2$ in toluene at 95 °C for 50 min gave the 6-(imidazol-1-yl) intermediate, which was deprotected (NH_3/MeOH) to give 6-(imidazol-1-yl)-9-(β-D-ribofuranosyl)purine (**4a**, 87%). S_NAr reactions were effected readily with **4a** and alkoxides or alkylthiolates at ambient temperature and primary or secondary amines at elevated temperatures. For example, **4a** in benzylamine at

Scheme 1[a]



[a] (a) Morpholine/I_2/Ph_3P/EtN(*i*-Pr)$_2$/CH_2Cl_2; (b) NaOMe/MeOH; (c) piperidine/I_2/Ph_3P/EtN(*i*-Pr)$_2$/CH_2Cl_2; (d) (i) imidazole/I_2/Ph_3P/EtN(*i*-Pr)$_2$/toluene/95 °C; (ii) NH_3/MeOH; (e) piperidine/60 °C; (f) $PhCH_2NH_2$/75−80 °C; (g) NaH/$PhCH_2SH$/DMF.

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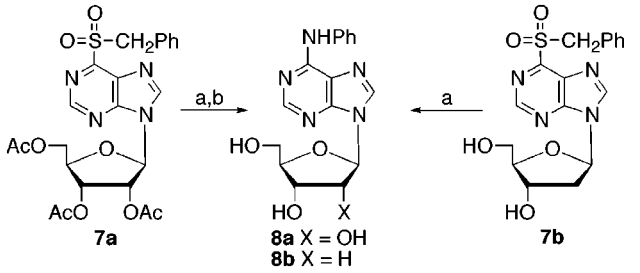
75 °C for 24 h gave 6-*N*-(benzyl)adenosine (**5a**, quantitative), and **4a** in piperidine at 60 °C for 4 days gave **3a** (90%).

Treatment of 3′,5′-di-*O*-acetyl-2′-deoxyinosine (**1b**) under the ambient temperature conditions followed by deprotection and chromatography gave the 6-(morpholin-4-yl or piperidin-1-yl)purine deoxynucleosides **2b** (95%) or **3b** (99%), respectively. Our conditions with imidazole at 95 °C, and deprotection, gave 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(imidazol-1-yl)purine (**4b**, 94%). A solution of **4b** in benzylamine was heated at 80 °C for 2 days to give 6-*N*-(benzyl)-2′-deoxyadenosine (**5b**, 82%). Treatment of **4b** with sodium benzylthiolate in DMF for 20 h at ambient temperature gave the 6-(benzylthio)purine deoxynucleoside **6b** (80%).

It has been reported that 6-chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine "does not react with arylamines".[2a] Because purine sulfones are good substrates for S_NAr displacements,[9] it was of interest to investigate such an example. Oxidation of **6b** with Oxone in buffered brine (pH ~5) gave the 6-(benzylsulfonyl)purine intermediate **7b** (93%) (Scheme 2). A solution of **7b** in aniline was stirred at ambient temperature for 6 h and chromatographed, and the residue was crystallized to give 2′-deoxy-6-*N*-(phenyl)adenosine (**8b**, 64%). Acetylation of **6a**, oxidation, and analogous treatment of **7a** was followed by deprotection and chromatography to give 6-*N*-(phenyl)adenosine (**8a**, 94%). Thus, the purine sulfones **7a**,**b** are excellent substrates for S_NAr displacements and react at ambient temperature, even with a much less basic arylamine.

Scheme 2[a]



[a] (a) Aniline; (b) NaOMe/MeOH.

In summary, we have developed mild and efficient procedures for transformation of protected inosine and 2′-deoxyinosine into C6-substituted purine derivatives. $I_2/Ph_3P/EtN(i\text{-}Pr)_2$ in the presence of secondary amines in CH_2Cl_2 or toluene effects quantitative conversion of the hypoxanthine nucleosides into their 6-(substituted-amino)purine analogues in ~1 h at ambient temperature. Analogous treatment with imidazole in toluene at 95 °C gives the 6-(imidazol-1-yl)-purine compounds, which undergo S_NAr reactions with a variety of nucleophiles under mild conditions. Displacement of imidazole with benzylthiolate and oxidation of the resulting benzyl sulfide provides 6-(benzylsulfonyl)purine intermediates. These heteroaryl sulfones are excellent substrates for S_NAr reactions and undergo substitution, even with an arylamine. Various examples with (2′-deoxy or)inosine derivatives and studies with the more challenging guanosine system will be reported in detail.

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Supporting Information Available: Experimental details for the synthesis and characterization of compounds **2**−**6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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