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S_NAr Iodination of 6-Chloropurine Nucleosides: Aromatic Finkelstein Reactions at Temperatures Below −40 °C[1]

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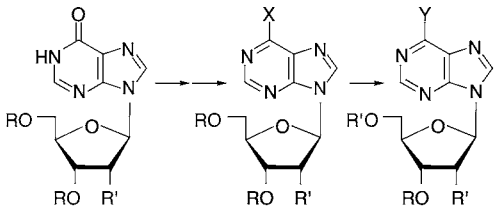
ABSTRACT



R = ArCO; R' = $ArCO_2$, H; X = Cl, I; Y = RC≡C, Ar, ArNH

Mesitoyl or toluoyl esters of inosine and 2′-deoxyinosine were deoxychlorinated at C6 to give the crystalline 6-chloropurine nucleoside derivatives, which underwent quantitative conversion to the 6-iodo analogues with NaI/TFA/butanone at −50 to −40 °C. The 6-iodo compounds were efficient substrates for S_NAr, Sonogashira, and Suzuki−Miyaura reactions, in contrast with the 6-chloro analogues, and gave good to high yields of C−N and C−C coupled products.

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,[2−5] and certain 6-aryl- and 6-alkynylpurine derivatives have been reported to possess cytostatic activity.[6] Advances in the synthesis of C6 modified purines have employed Sonogashira,[7,8] Suzuki−Miyaura,[9,10] and S_NAr[11] reactions, and the area of organometallic cross-coupling with purine and purine nucleoside derivatives has been reviewed.[12] Véliz and Beal[11] reported that 6-bromopurine nucleosides were more reactive than their 6-chloro analogues in S_NAr reactions with arylamines, whereas Lakshman and co-workers[10] found that the 6-chloro analogues usually provided better yields than 6-bromopurine

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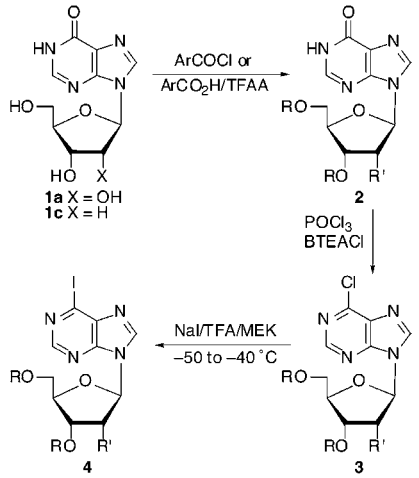
nucleosides for Suzuki−Miyaura couplings. Comparisons between 6-chloro- and 6-iodopurine nucleosides for Sonogashira, Suzuki−Miyaura, and S_NAr reactions have not been evaluated systematically. Aryl chlorides are usually much less reactive than the corresponding iodides for transition metal-catalyzed reactions with aromatic systems,[12,13] and Plenio and co-workers recently communicated a more efficient catalyst system for the Sonogashira coupling of aryl chlorides.[14]

Syntheses of 6-chloro- and bromopurine nucleoside derivatives are considerably less problematic[11,15,16] than preparation of their 6-iodo analogues. An earlier procedure for conversion of 6-chloro- to 6-iodopurines employed HI/H_2O at ice-bath temperature.[17] The large excess of aqueous HI at this temperature limits its utility with acid-labile compounds, especially with the important 2′-deoxynucleosides. Roberts and co-workers used ^{15}N NMR to identify protonation sites on purines and nucleosides with trifluoroacetic acid (TFA) in DMSO,[18] and applications of enhanced purine S_NAr reactivity with TFA have been noted.[19] Diazotive iododeamination of aminopurine nucleosides is an alternative methodology,[7,16,20] but this approach has limitations, including poor to moderate yields, byproduct formation, and expensive reagents.

Klapars and Buchwald[13] recently communicated a copper-catalyzed aromatic Finkelstein reaction, which converted aryl bromides into iodides at 110 °C. We now report highly efficient transformations of 6-chloropurine nucleoside and 2′-deoxynucleoside derivatives into their 6-iodo analogues via an acid-catalyzed aromatic Finkelstein reaction at temperatures below −40 °C. We also report the first direct comparisons of the utility of the corresponding chloro- and iodopurine nucleoside derivatives in C−C and C−N bond-forming reactions at C6 via Sonogashira, Suzuki−Miyaura, and S_NAr processes.

Sugar hydroxyl groups on the inosine nucleosides were protected[21,22] as mesitoyl (2,4,6-trimethylbenzoic acid and trifluoroacetic anhydride in CH_2Cl_2) or *p*-toluoyl (4-methylbenzoyl chloride/pyridine) esters because they crystallize much more readily.[22] These protected inosine and 2′-deoxyinosine derivatives **2a**−**c** were treated with $POCl_3$ under our previously developed conditions[15,23] to give the 6-chloropurine nucleosides **3a** and **3b** and the 2′-deoxynucleoside **3c** in good to high yields (Scheme 1). It is noteworthy that these new 6-chloropurine nucleoside derivatives are crystalline, in contrast with the amorphous esters obtained with acetyl or benzoyl protection.

Scheme 1[a]



[a] **2**−**4**: **a**, R = Mst, R′ = OMst; **b**, R = Tol, R′ = OTol; **c**, R = Tol, R′ = H.

Minimal iodo product formation was observed upon treatment of solutions of **3a** or **3b** with excess sodium iodide in acetone, acetonitrile, 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 (TLC). 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.[18]

We were gratified to observe quantitative conversions (>98% by ^1H NMR[24]) of the 6-chloropurine nucleosides into their iodo analogues upon treatment of **3a** and **3b** with 5 equiv of TFA and 20 equiv of NaI in butanone at −50 to −40 °C for 5 h. 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 ^1H NMR, 66% crystalline). This represents the first synthesis of a 6-iodopurine 2′-deoxynucleoside by an aromatic Finkelstein process.

The Sonogashira reaction is valuable for the synthesis of 6-alkynylpurine nucleosides, which serve as intermediates

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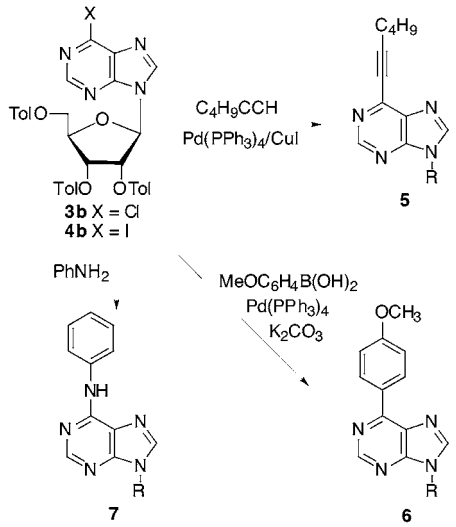
for the preparation of highly substituted 6-arylpurine nucleosides that are not readily accessible by standard coupling reactions.[25] No cross-coupling product was detected upon treatment of the 6-chloro analogue **3b** (Scheme 2) with

Scheme 2[a]



[a] R = 2′,3′,5′-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl.

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.

The Suzuki−Miyaura procedure has been used to prepare 6-phenylpurine nucleosides.[12] Treatment of **3b** with 4-methoxyphenylboronic acid/$Pd(PPh_3)_4$/K_2CO_3/toluene at 100 °C for 10 h gave the aryl substitution product **6** in 70% yield. By comparison, the 6-iodo analogue **4b** gave **6** in 83% after 5 h under identical conditions.

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. 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 Lakshman et al.[10,26] had resorted to palladium-catalyzed coupling of 6-chloropurine compounds with arylamines.

In summary, a remarkable aromatic Finkelstein reaction that proceeds readily at temperatures below −40 °C 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 certain transition metal-catalyzed cross-coupling reactions. In all of these processes, the 6-iodo compounds proved to be markedly superior to their 6-chloropurine analogues. Further systematic comparisons are in progress, which include S_NAr reactions of the corresponding 6-fluoro- and 6-bromopurine nucleoside analogues and different nitrogen, oxygen, and sulfur nucleophiles.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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