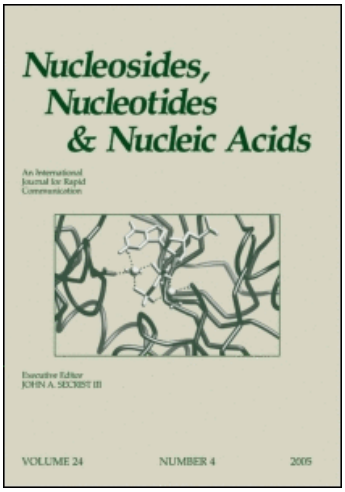

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Metal Mediated Reactions in Nucleside Synthesis

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METAL MEDIATED REACTIONS IN NUCLEOSIDE SYNTHESIS

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Abstract. The reaction of a halogenated nucleoside with cuprous ions and appropriate nucleophiles allows for the introduction of a wide range of functional groups or synthons into specific positions of the base moiety of nucleosides.

The use of metal-mediated reactions as key steps in the synthesis of biologically-active nucleosides is part of a developing program in our laboratory. For example, we have shown recently that palladium-catalyzed cross-coupling reactions with synthon bearing organostannanes provide efficient approaches to the synthesis of novel modified nucleosides.[1-3] Although copper mediated reactions have played a significant role in aromatic nucleophilic displacements,[4] such transformations have not received much attention in synthesis involving nucleosides.[5-7] This paper reports on the development of copper-mediated reactions leading to functionalized analogues of nucleosides.[8]

The results presented are for copper mediated reactions at the 2-position of the purine ring where normal thermal substitution reactions are usually the most difficult. For example, protected 2-iodoadenosine does not react with sodium cyanide in DMF at 120 °C. However, when this same reaction was carried out in the presence of CuBr, very good yields of the 2-cyano product were obtained. Similar results were obtained with azide ions except that the copper mediated reaction to the azido compound

proceeded at room temperature. When the azide reaction was heated, the major product was the 2-hydroxylamino compound. General classes of nucleophiles studied include carbon, nitrogen, oxygen, halogen, sulfur and their combinations. The structures of the products were confirmed by high-field ^{1}H and ^{13}C NMR, UV, FTIR and mass spectral data.

The general synthetic methodology can be represented as follows:

$$\text{Pur-Y} \xrightarrow[\text{Nucleophile}]{\text{Cu(1)}} \text{Pur-X}$$

Pur-Y = Silyl Protected Purine Nucleoside, Y = Halogen or Displaceable Group at the 2-position, X = Functional Group or Synthon, e.g. CN, SCN, NH_2, N_3, NHOH, Halogen, Functionalized Alkyl Groups, and others.

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