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COPPER MEDIATED REACTIONS IN NUCLEOSIDE SYNTHESIS

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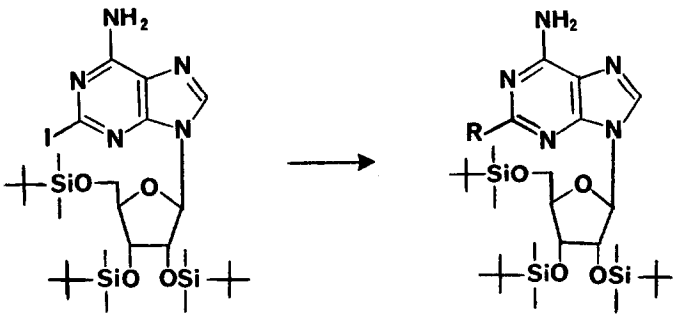
Summary: The regiospecific functionalization of the base moiety of purine nucleosides through copper-mediated nucleophilic reactions is described.

Although copper mediated reactions have played a significant role in aromatic nucleophilic displacements,[1] such transformations are nearly non-existent in synthesis involving nucleosides. Cuprous iodide has been used to prepare alkynyl copper reagents[2] and these have been used in palladium-catalyzed cross-coupling reactions to furnish alkyn-1-yl pyrimidine and purine nucleosides.[3,4] However, due to the limited availability of useful Cu(I) organocopper reagents, transformations involving these have been of limited scope.[5] The reaction of a halogenated nucleoside with Cu(I)X and an appropriate nucleophile potentially allows for the introduction of a wide range of interesting functional groups or synthons into specific positions of nucleosides. This communication reports on the development of copper-mediated reactions leading to interesting functionalized analogues of adenosine. The work complements our previous reports on palladium-catalyzed cross-coupling with organostannanes.[6,7]

The requisite precursor, the silylated 2-iodoadenosine, **1**, was prepared as described previously by us.[8] Treatment of **1** with sodium cyanide and cuprous bromide in DMF at 120° C for 1 h gave the 2-cyano compound **2** in 64% yield after work-up and purification (Table 1, Entry 1). Similar results were obtained with cuprous cyanide (Entry 2). In order to circumvent complexation of the nucleoside with copper ions,[9] the work-up included neutralization of the basic reaction mixture and subsequent treatment with gaseous hydrogen sulfide. Line broadening of the H-8 resonance in the high-field ^{1}H NMR spectrum was evidence of copper complexation.[10] Although 2-halogenated adenine nucleosides are

susceptible to nucleophilic displacements, the reactions proceed in low yields and for a very limited number of nucleophiles.[11,12] Thus, for example, the conversion of **1** to **2** did not proceed with sodium cyanide in the absence of CuBr.



1

2 R = CN
3 R = SCN
4 R = NH_2
5 R = N_3
6 R = NHOH,
7 R = $C{\equiv}CC_4H_9$
8 R = $CH(CO_2Et)_2$

When the reaction was carried out with copper thiocyanide, clean conversion to 2-thiocyanoadenosine **3** occurred (Entry 3). In contrast, when compound **1** was treated with NaSCN and CuBr, much longer reaction times were required, and the reaction proceeded less cleanly and a mixture of 2-thiocyanide **3** and the corresponding 2-bromide was produced (Entry 4). The latter compound, the product of a copper-mediated halogen exchange reaction,[13] is of interest, because, in the absence of nucleophiles, **1** can be converted easily to the corresponding chloro and bromo compounds with appropriate cuprous salts. Copper mediated reactions involving other nucleophiles may also be affected. For example, exposure of **1** to ammonia in the presence of CuBr gave a 75% yield of **4** which could be readily deprotected to 2,6-diaminoadenosine (Entry 5). This new synthesis of 2,6-diaminoadenosine avoids the use of the high temperatures and pressures of previous preparations.[14]

2-Azidoadenosine, a biologically active nucleoside,[12,15,16] can be easily prepared in its protected form (**5**) through the reaction of **1** with CuBr and NaN_3 at room temperature (Entry 6). A side product of this transformation was the 2-N-hydroxyaminoadenosine derivative **6** which apparently results from the copper catalyzed decomposition of the 2-azido compound (Entry 6). The yield of this side product can be maximized to about 72% by

raising the reaction temperature (Entry 7). Other N-hydroxyamino nucleosides have been evaluated for anticancer activity and for use as biological probes,[17] and have been found to be mutagenic through covalent modification of guanine residues in DNA.[18] Monosubstituted alkynes may also be introduced at the 2-position of adenosine (Entry 8). The copper salt of diethylmalonate reacts cleanly with **1** to furnish **8**, a potential precursor to a number of other 2-substituted adenosines.

Table 1. Copper Catalyzed Functionalization of Purine Nucleosides

Entry	Reagents	Conditions[a]	Product[b]	Functionality (R)	% Yield
1	NaCN, CuBr	120 °C, 1 h	**2**	CN	64
2	CuCN	120 °C, 1 h	**2**	CN	68
3	CuSCN	120 °C, 8 h	**3**	SCN	64
4	NaSCN, CuBr	120 °C, 18 h	**3**	SCN	55[c]
5	NH_3, CuBr	R.T., 24 h	**4**	NH_2	75
6	NaN_3, CuBr	R.T., 24 h	**5** **6**	N_3 NHOH	66 27
7	NaN_3, CuBr	120 °C, 1 h	**6**	NHOH	72
8	$C_4H_9C{\equiv}CH$, NaH, CuI	120 °C, 1 h	**7**	$C{\equiv}CC_4H_9$	61 [72][d]
9	$CH_2(CO_2Et)_2$, NaH, CuI	120 °C, 1 h	**8**	$CH(CO_2Et)_2$	71 [85][d]

a. DMF was the solvent of choice.

b. These products were purified by preparative TLC on silica gel. They were converted to the deprotected nucleosides by reaction with tetraethylammonium fluoride. The deprotected functionalized nucleosides were purified by reversed-phase HPLC on Amberlite XAD-4 resin with ethanol/water as the eluting solvent. The yields of purified deprotected compounds were in the range of 65-70%. The silylated and deprotected products were characterized by high-field ^1H and ^{13}C NMR, UV, FTIR, and mass spectral (including FAB HRMS) data.

c. 2-Bromo-9-(2,3,5-tri-O-t-butyldimethylsilyl-β-D-ribofuranosyl)adenine was produced in 24% yield.

d. % Conversion.

In summary, cuprous ion mediated reactions provide a facile approach to the regiospecific functionalization of the base moiety of purine nucleosides. This methodology, although known in aromatic chemistry, has seen little utilization previously

in nucleoside systems. In addition to the examples presented, a wide variety of other nucleophiles may potentially be used in these reactions.

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