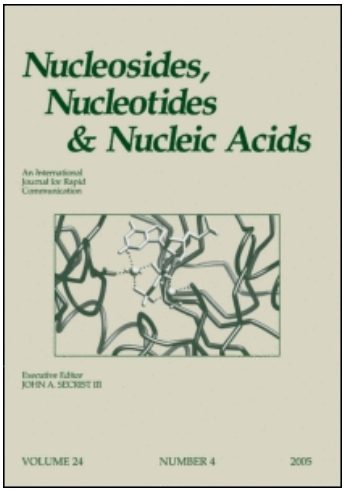

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Recent Advances in Palladium-Mediated Reactions of Nucleosides

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Recent Advances in Palladium-Mediated Reactions of Nucleosides

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Abstract

Synthetic methodology for generating a thioether linkage at C-5 of pyrimidine nucleosides via a palladium-mediated reaction of mercurated nucleosides with organic disulfides was recently reported by our laboratory. We have continued to explore the scope of the reaction with respect to both the nucleoside component and the disulfide. In particular, the reaction of N,N'-bis(trifluoroacetyl)cystamine with mercurated nucleosides has been explored in more detail.

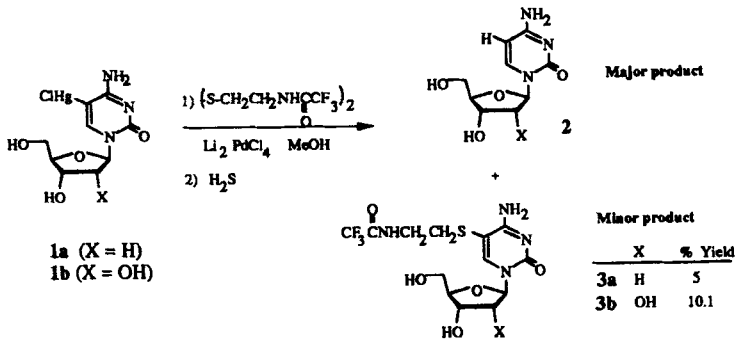
Results and Discussion

Previously we reported only the reaction of 5-chloromercuri-2'-deoxyuridine with disulfides.[1] We have more recently investigated the scope of this reaction by examining the mercurinucleosides, 5-chloromercuri-2'-deoxycytidine (**1a**), 5-chloromercuricytidine (**1b**), and 5-chloromercuritubercidin (**5**). In addition, we have tried to at least partially determine the mechanism of the reaction. Finally, since the chloromercuri compounds are very insoluble in either organic or aqueous solution we have attempted to find a derivative of 5-mercuri-2'-deoxyuridine which would be soluble in methanol or water.

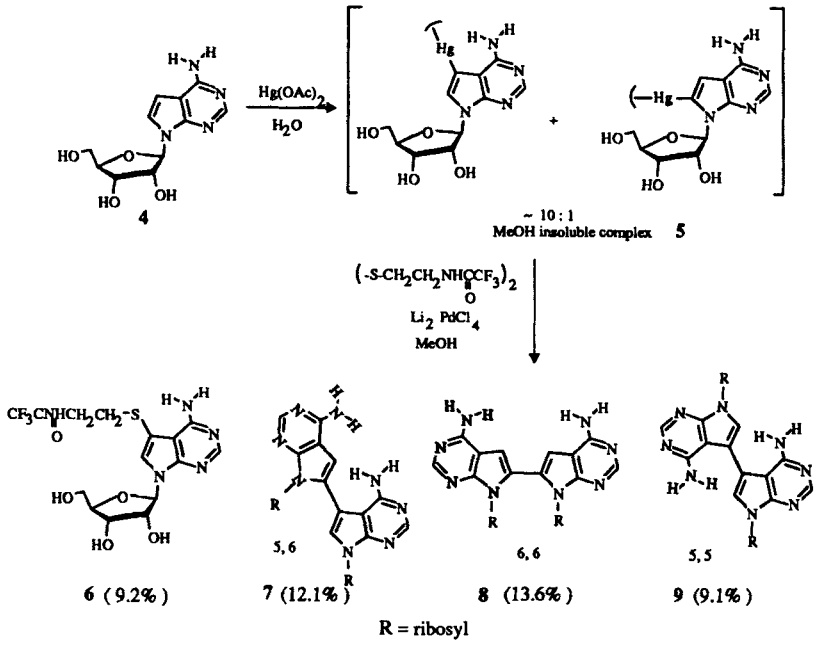
The reaction of mercurated cytosine nucleosides and disulfides has so far been examined only for N,N'-bis(trifluoroacetyl)cystamine and n-butyl disulfide. The results of the study with N,N'-bis(trifluoroacetyl)cystamine are shown in scheme I. The yields of thioether substituted nucleoside are very low (5-10%) and the principal product in each instance appears to be the parent nucleoside, cytidine (**2**, X = OH) and 2'-deoxycytidine (**2**, X= H). We had previously noted that the palladium-mediated reaction of 5-chloromercuricytidine and 5-chloromercuri-2'-deoxycytidine with alkenes was slower than the corresponding reaction with 5-chloromercuri-2'-deoxyuridine. Since the palladium-mediated decomposition of disulfides is relatively fast, the slower reaction between the mercurated cytidines and palladium may not compete effectively with the Pd-disulfide decomposition.

The palladium-mediated reaction of chloromercuritubercidin with alkenes yields C-5 substituted tubercidin derivatives,[2] but the yields are typically lower than for the equivalent palladium-mediated reactions of 5-chloromercuri-2'-deoxyuridine. This also seems to be the case for the reaction of chloromercuritubercidin with N,N'-bis(trifluoroacetyl)cystamine (scheme II). The major products are the dimers **7**, **8**, and **9**. Reaction of chloromercuritubercidin with methanolic lithium palladium chloride in the absence of disulfide gives these dimers as the only isolated products.

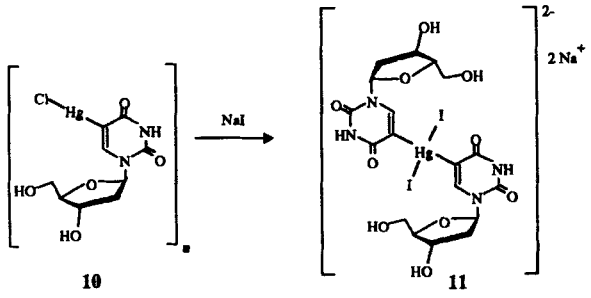
One can speculate from the above studies that the palladium-mediated disulfide coupling reaction is not likely to be useful for C-5 modification of cytidine or tubercidin



Scheme I



Scheme II



Scheme III

unless the rate of the reaction can be increased in order to compete with the disulfide decomposition. A major limitation may be the lack of solubility of the mercurinucleosides which would limit the rate of the Pd-Hg exchange reaction.

The reaction of organic disulfides with Pd^{2+} is not at all understood. It appears that the final product is a polymer in which palladium atoms are bridged by η_2-thiol ligands. At least one polymer (synthesized from thiol and Pd^{2+}) of this type has been characterized by x-ray crystallography.[3] These polymers are typically insoluble in organic solvents, and we found that disulfides which rapidly yield polymer (e.g. 1,2-dithiane) do not couple to 5-chloromercuri-2'-deoxyuridine. The single literature report[4] on the characterization of an adduct between an organic disulfide and Pd^{2+} has been shown to be incorrect.[5]

We have been studying the reaction between N,N'-bis(trifluoroacetyl)cystamine and Li_2PdCl_4 in methanol and have noted the appearance of a transitory species with λmax in the visible spectrum at 418 nm. Within one hour this species is almost completely transformed to a product with λmax at 385 nm. Reactions between N,N'-bis(trifluoroacetyl)cystamine, chloromercuri-2'-deoxyuridine, and Li_2PdCl_4 in which the nucleoside was added following (20 min) the decrease in absorbance at 418 nm gave lower yields of coupled product (28-36%) than when the nucleoside was present from the outset (50%). Yet typically because of its insolubility in methanol, the mercurinucleoside is still evident as a precipitate in the reaction mixture for hours following combination of the reagents.

Since it appeared that the insolubility of the mercurinucleosides may contribute to the low yields observed in the coupling reaction, an attempt was made to obtain new soluble derivatives. Iodide ion is known to form water soluble complexes with organomercurials. When sodium iodide and 5-chloromercuri-2'-deoxyuridine were combined, a water (or methanol with a few percent water added) soluble product was obtained. This product has been characterized as dimer **11** shown in scheme III. In the process of iodide complexation symmetrization has also occurred. The same product can also be obtained by treating the reaction mixture between 2'-deoxyuridine and mercuric acetate (after 3 hr at 60°)with sodium iodide. Reaction of this complex with N,N'-bis(trifluoroacetyl)cystamine and lithium palladium chloride in aqueous methanol did not improve the yield of the reaction.

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