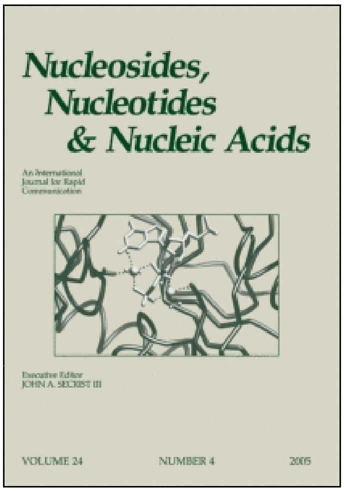

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Organometallic Intermediates in the Synthesis of Nucleoside Analogs

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ORGANOMETALLIC INTERMEDIATES IN THE SYNTHESIS OF NUCLEOSIDE ANALOGS

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1. Introduction

The common nucleosides, modified or derivatized in some way at the heterocyclic ring carbons, include examples of structures which are useful as biological probes and chemotherapeutic agents. Like previous authors, we will use the term "nucleoside analog" for structures related to one of the common naturally occurring nucleosides. Nucleoside analogs can be derivatives which differ by such minor modification as replacement of hydrogen by a single atom or derivatives which are grossly modified at both the carbohydrate and the base. Examples of the former include 5-fluoro-2'-deoxyuridine, an inhibitor of thymidylate synthetase as its

5'-phosphate, and 5'-iodo-2'-deoxyuridine, a clinically useful antiviral agent. Larger groups have frequently been linked to nucleoside as probes for enzymatic processes. Side chains in "nonrestricted positions" may be used to carry spectroscopic or chemically reactive probes, or provide the means to attach a molecule to an affinity column. Ultimately with positions of bulk tolerance defined, it may be possible to design "active site directed irreversible enzyme inhibitors" as defined by B.R. Baker.[1] Nucleoside structures in which a side chain is attached at a pyrimidine or purine carbon will undoubtedly, in some instances be the most appropriate structure. Yet, these have typically been more difficult to synthesize than analogs with side chains attached to heteroatoms.

Ideally the repertoire of the organic chemist would include reactions to link carbon chains directly to virtually every position of the base at the nucleoside level.

The present review was prompted by new developments in synthetic methodology, especially in the area of organotransition metal chemistry. The introduction of side chains into the C-5 position of pyrimidine nucleosides[2] has been greatly simplified by the use of organopalladium intermediates. Similarly the C-6 and C-8 positions of purine nucleosides and the C-5 position of pyrrolo[2,3-d]pyrimidine nucleosides have been modified via organopalladium and organonickel intermediates. The organopalladium route to substituted nucleosides is exceptionally selective. Coupling via organolithium intermediates is a useful alternative in some instances. Purines have been selectively alkylated at C-6 and C-8 and pyrimidine nucleosides at C-6.

The primary emphasis of this review is a discussion of the reactions of organometallic intermediates generated from nucleosides, protected nucleosides, or analogs of the common nucleosides where a sugar equivalent is attached at N-1 or N-9. Where appropriate, reactions at the heterocyclic base level will be discussed, but no attempt has been made to comprehensively review the literature in this area. The synthesis of C-nucleosides has been reviewed extensively elsewhere during the past few years, and with few exceptions is not included here. Finally since the emphasis of this review is on nucleoside derived organometallic intermediates we have omitted discussion of methods for C-substitution via leaving group displacement of the heterocycle.[3-16]

Classically many nucleoside analogs in which the base is hypermodified have been synthesized by coupling a suitably protected and activated sugar to a suitably protected modified heterocyclic base. For example, 5-alkyl-2'-deoxyuridines can be obtained by the reaction of 1-

chloro-2-deoxy-3,5-di-O-p-chlorobenzoylribofuranose with 2,5-bis-O-(trimethylsilyl)-5-alkyluracils.[17]

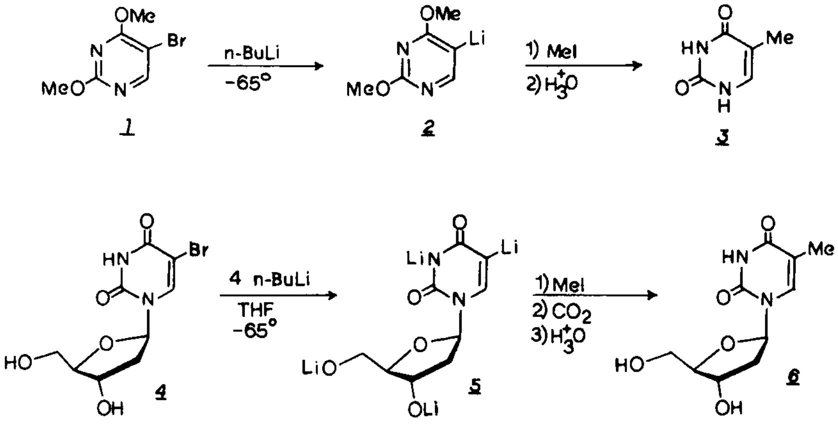
Particularly where a series of similar molecules are to be synthesized, the closer towards the end of the synthesis that it becomes divergent, the more efficient. Hence modification at the nucleoside level is in many cases preferable to modification at the heterocyclic level followed by coupling to a sugar.

2. Nucleoside Analogs via Organolithium Intermediates

Most modern methods of carbon-carbon bond formation should be applicable to nucleoside modification. However, especially in the case of organolithium intermediates, functional groups having active hydrogen (-OH, NH) generally must be protected.

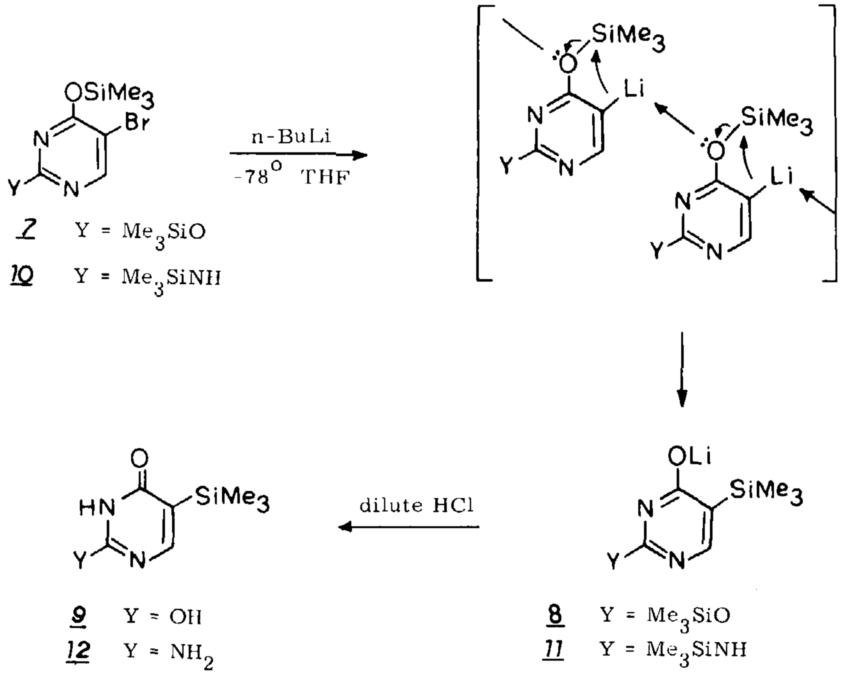
Initial studies on the preparation and reactions of organolithium derivatives of a pyrimidine and a pyrimidine nucleoside were reported by Ulbricht in 1959.[18] As shown in Scheme 1, 5-bromo-2,4-dimethoxypyrimidine (1) reacts with n-butyllithium at -65° in THF to give 5-litho-2,4-dimethoxypyrimidine (2). Pyrimidine 2 is relatively unstable even at -65°, but if treated immediately with methyl iodide, gives a respectable yield (40%) of thymine (3). This provided a rapid convenient route to thymine -$^{14}CH_3$.

A similar series of steps starting with unprotected 5-bromo-2'-deoxyuridine (4) gave thymidine (6) in yields up to 10%. Ulbricht reasonably suggested that the low yield could be attributed to the insolubility of intermediate 5 and its precursors in tetrahydrofuran. Other solvents were examined but gave no better results.

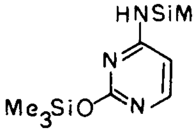


Scheme 1.

Pichat and coworkers[19] later attempted to improve the reaction by preparing lithium derivatives from 5-bromo-2,4-bis-O-trimethylsilyluracil and tetrakis-trimethylsilyl-5-bromouridine. Neither methyl iodide nor CO_2 gave the desired coupling reactions. The problem lies in the trimethylsilyl group at O-4. Arai and Daves examined the reaction of n-butyllithium with 5-bromo-2,4-bis-O-trimethylsilyluracil (7) at -78° in THF and discovered a rearrangement occurring at this temperature (Scheme 2).[20] A 1,3-anionic shift of silicon from O-4 to C-5 was proposed to account for the formation of intermediate 8. Hydrolysis of 8 in dilute HCl at room temperature gave 5-trimethylsilyluracil (9). A similar rearrangement occurred with the presumed intermediate, 5-lithio-2,4-bis-N,O-trimethylsilylisocytosine obtained from 5-bromo-2,4-bis-N,O-trimethylsilylisocytosine (10). Rearrangement to 11 and aqueous acid workup gave 5-trimethylsilylisocytosine (12). This rearrangement was not observed with the lithium salt derived from 5-bromo-2,4-bis-N,O-trimethylsilylcytosine (13). Transfer of the trimethylsilyl group from N-4 and C-5 is apparently not so facile as transfer from oxygen. Consequently the latter intermediate may be used successfully in coupling reactions. David and Lubineau were able to prepare C-nucleosides by coupling 5-lithio-bis-N,O-trimethylsilylcytosine with an aldehydo-D-ribose.[21]



Scheme 2.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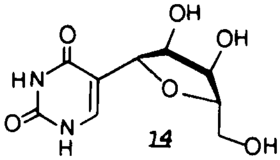
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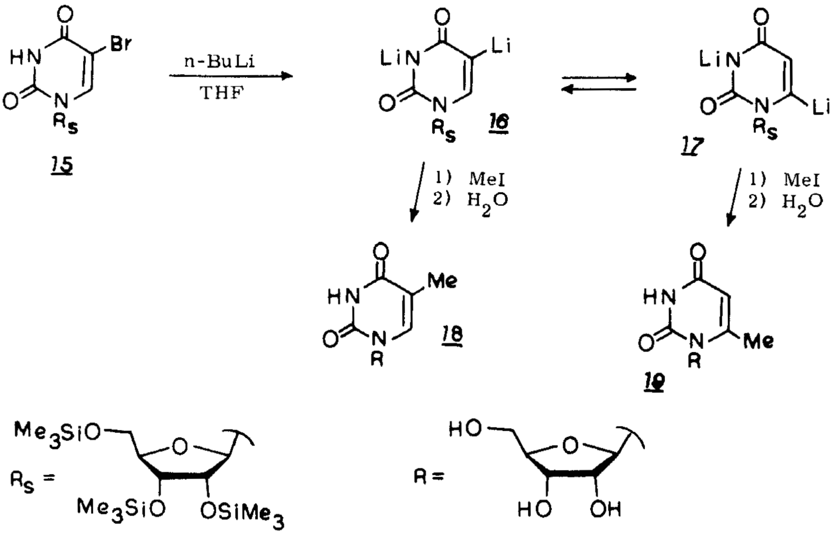
The C-nucleoside, psuedouridine (14) had been prepared earlier in very low yield by the coupling reactions between 5-lithio-2,4-dimethoxypyrimidine and 1-chloro-2,3,4-tri-O-benzoylribofuranose,[22] and in somewhat higher yield from 5-lithio-2,4-di-t-butoxypyrimidine and 2,4:3,5-di-O-benzylideneribose.[23,24] 1,5-Bis-(β-D-ribofuranosyl)uracil was prepared from the 5-lithio derivative of 2',3'-O-isopropylideneuridine by reaction with the same protected ribose.[23] Deblocking and cyclization of the acyclic sugar was achieved by treatment with warm methanolic HCl. Other analogues of pseudouridine have been constructed from 5-lithio-2,4-dibenzyloxypyrimidine and various protected sugars, including 2,3: 5,6-di-O-isopropylidene 1,4-D-manno- and gulonolactones,[25] and the 2,3: 4,5-di-O-isopropylidenealdehydo derivatives of D-xylose, D-arabinose and D-ribose.[26]

The protecting group at O-4 is not absolutely necessary. Pichat and coworkers treated 2',3', 5'-tris-O-(trimethylsilyl)-5-bromouridine (15) with n-BuLi in a solution of THF-HMPA at -60°C to obtain the intermediate dianion (16), which gave 5-methyluridine (18) on treatment with methyl iodide followed by deprotection (Scheme 3).[27] ^{14}C-5-methyluridine was obtained in 51% yield by this procedure. Optimum yields were obtained in 8% HMPA-THF. Under these conditions 6-methyluridine (19) was formed in yields of 7-8% of that of 5-methyluridine. 6-Methyluridine is probably a result of proton transfer to give the 6-lithio intermediate 17 which would react with methyl iodide to give 19. At low concentration in the absence of HMPA the yield of 18 was much lower, and 3-methyluridine was formed as a side product.

The silylated derivatives of uridine and deoxyuridine are metalated by n-BuLi in HMPA-THF to give a mixture of the C-5 and C-6 lithio derivatives.[28] These lithiated derivatives, on methylation (methyl iodide) and subsequent deprotection, gave respectively, a 4:1 mixture of 5-methyluridine and 6-methyluridine, and a 4:3 mixture of deoxythymidine and 6-methyl-2'-deoxyuridine. Deuterium is introduced into the C-5 and C-6 positions in similar relative yields by quenching with D_2O. In contrast Miyasaha and coworkers found that regiospecific alkylation of uridine at C-6 could be achieved by treating 2',3'-O-isopropylideneuridine (20)

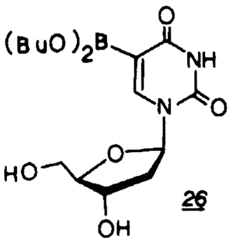


Scheme 3.

with lithium diisopropylamide in THF at -78° followed by reaction with a primary halide (Scheme 4)[29] to give 6-alkyl-2',3'-*O*-isopropylideneuridines 22 - 25 (46-60% isolated yields). These authors propose stabilization of the 6-lithio derivative 21 through chelation by the 5' oxyanion. Chelation with a lithium cation at C-5 is not possible. Pichat's results could be interpreted by assuming either that the C-5 anion is formed more rapidly or is more stable than the C-6 anion. The preparation of C-6 lithiopyrimidines via halogen-metal exchange with n-butyllithium has been described by others, but not in connection with modified nucleoside syntheses.[30,31]

5-Dihydroxyboryl-2'-deoxyuridine (26) and 5-trimethylsilyl-2'-deoxyuridine (27) have been prepared from 5-bromo-3',5'-bis-*O*-trimethylsilyl-2'-deoxyuridine following a procedure[32] similar to Pichat's. An intermediate 5-lithio derivative was allowed to react with tri-*n*-butylborate to give 26 and with trimethylsilyl chloride to give nucleoside 27. No C-6 substitution was observed.

Modification of purine nucleosides at C-8 via organolithium inter-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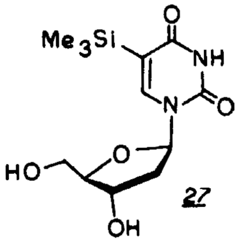
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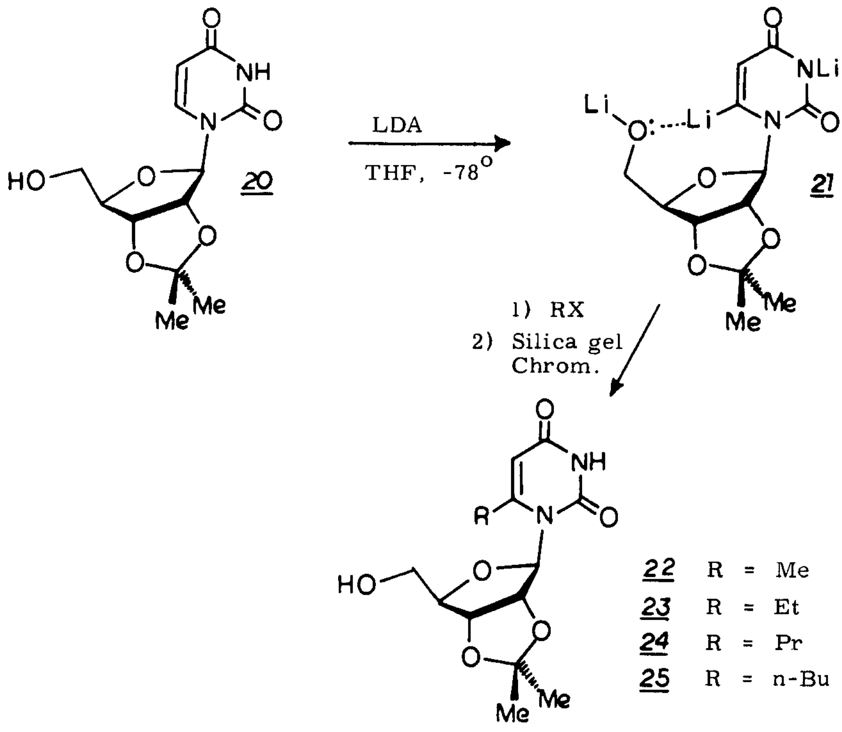
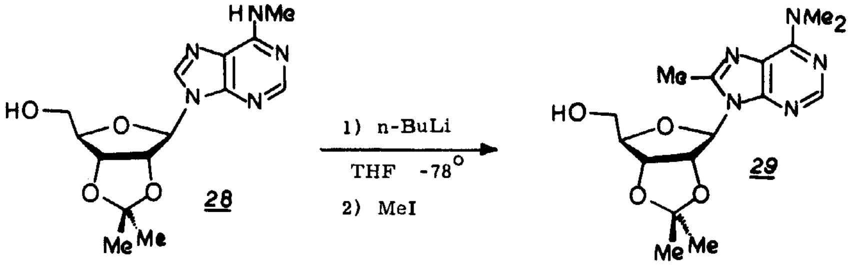


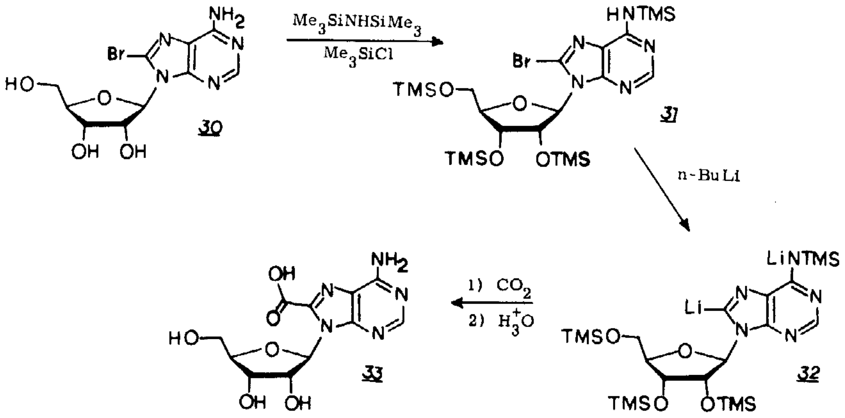
Scheme 4.

mediates has been described by two groups. Barton and coworkers treated N^6-methyl-2',3'-O-isopropylideneadenosine (28) with 3 equivalents of n-BuLi in THF at -78°C and then reacted the intermediate with excess methyl iodide to obtain (29) in 35% yield (Scheme 5).[33] Methylation at the unprotected 5' ribosyl hydroxyl was not observed, however, a higher yield of C-8 methylated product was obtained when the starting nucleoside was protected at 0-5' and the C-6 substituent was dimethylamine.

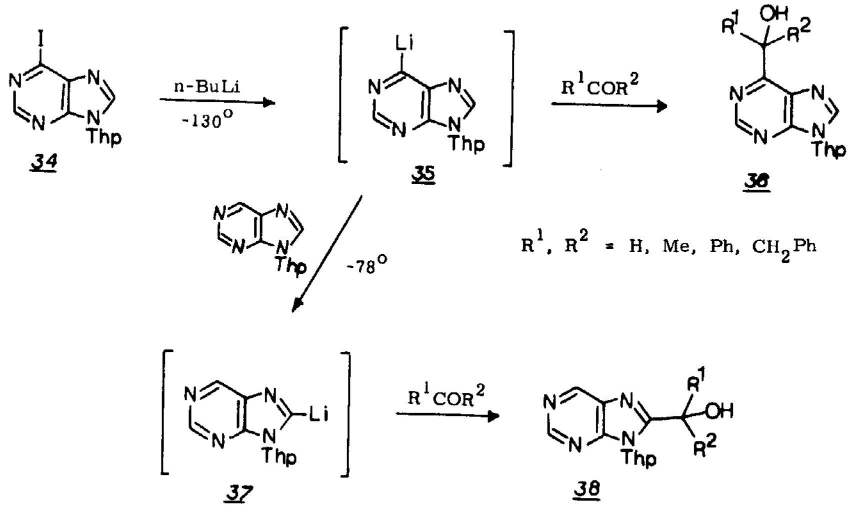
Inosine, adenosine, and guanosine were modified at C-8 via reaction of the trimethylsilylated 8-bromoderivatives with n-BuLi followed by a reactive organic halide, carbonyl compound, or carbon dioxide.[34] Organic halides gave the lowest yields (10-12%) and carbon dioxide the highest. For example, 5-bromoadenosine was converted to 8-carboxyadenosine in 50% yield as outlined in Scheme 6. Leonard and Bryant investigated the preparation and reactions of 6-lithio-9-(tetrahydropyran-2-yl)purine (35) as a model for preparation of 6-alkylpurine nucleosides.[35] They found that 6-iodo-9-(tetrahydropyran-2-yl)purine (34) reacts with n-butyllithium in THF at -130° to give intermediate 35 which attacks aldehydes or ketones to give derivatives of structure 36 (Scheme 7). If the THF



Scheme 5.



Scheme 6.



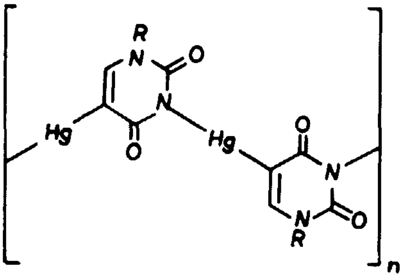
Scheme 7.

solution of the 6-lithio intermediate 35 was allowed to warm to -78° prior to addition of the carbonyl compound, substitution occurred at C-8. The C-8 carbanion is thermodynamically more stable, and a pathway involving proton abstraction by the C-6 carbanion to give the C-8 lithio derivative 37 (Scheme 7) was proposed. When 6-chloro-9-(tetrahydropyran-2-yl)purine was treated with n-butyllithium the 6-chloro substituent remained intact while the proton at C-8 was lost to give 6-chloro-8-lithio-9-(tetrahydropyran-2-yl)purine. This intermediate coupled with ketones to give C-8 substituted 6-chloro-9-(tetrahydropyran-2-yl) purines. Since the C-6 chloro is easily replaced by amino, hydroxy, or mercapto groups, this sequence opens a general route to C-8 substituted derivatives of adenine, hypoxanthine, and 6-mercaptopurine. These reactions should be applicable to the silyl protected nucleosides.

3. Mercurinucleosides

Of all nucleoside derived organometallic intermediates, the mercurinucleosides may be the most versatile. They function as tools for biochemical research in their own right in addition to serving as valuable synthetic intermediates. Mercuri complexes of pyrimidines and their nucleosides have been known for decades. Indeed, one of the principal means for glycosidic bond formation is the coupling reaction between a mercuri -pyrimidine or -purine and a 1-halofuranose or pyranose. Intermediates in which mercury is bound to N or O of the heterocycle are likely.[36] Since the condensation reactions typically involve mercuric ion bound by ligands with high affinity for mercury (Cl^-, Br^-, CN^-) the concentration of the species $XHg^{\oplus}$ is probably insufficient to give a measurable rate of electrophilic mercuration at carbon. The conventional electrophilic mercurating agent is mercuric acetate which dissociates in polar solvents to $Hg^{\oplus}OAc$. Mercuric acetate rapidly mercurates pyrimidine nucleosides and nucleotides at the C-5 position in aqueous solution. Dale and coworkers first reported the mercuration of the 5'-triphosphates of uridine, cytidine, and tubercidin (7-deazaadenosine) in 1973.[37] Stable water soluble compounds were obtained which when derivatized as a mercurialkylthiol were substrates for a number of polynucleotide polymerases. Polyribonucleotides can be mercurated selectively at the C-5 position of cytidine and uridine.[38] Details for the preparation of mercurinucleosides have appeared more recently.[39-41]

Unlike the mercurinucleotides, the mercurinucleosides are relatively water insoluble. It is likely that the mercurinucleosides are complex polymeric species with mercury bound at both C-5 and N-3 in uracil derived nucleosides (39) and N-4, C-5 on mercuration of tubercidin. Addition of chloride ion to 39 converts it to a derivative which though largely water insoluble should have the monomeric structure 40. Mercuration of cytidine proceeds in a similar fashion where again the absolute



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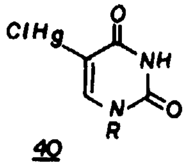

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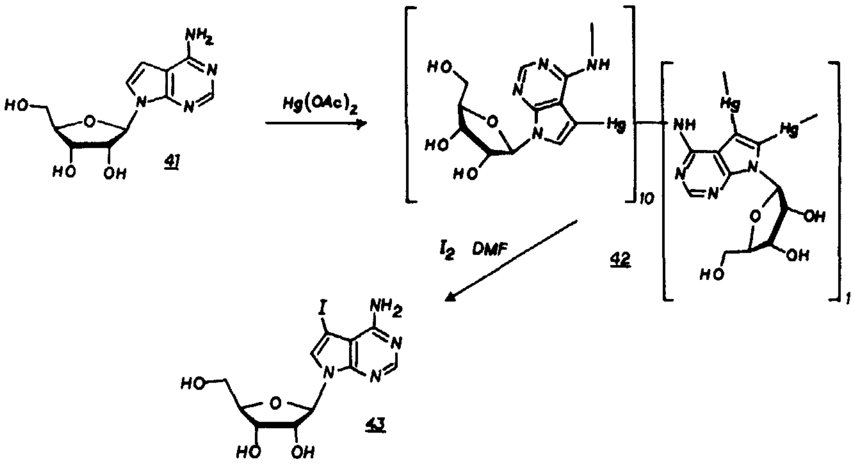
R = β-D-ribofuranosyl or
β-D-2'-deoxyribofuranosyl

structure of the complex has not been determined. For use as synthetic intermediates, the structural uncertainty is not nearly as important as when such derivatives are to be used as biochemical probes. For example, 5-mercuritubercidin (42) is an ill defined complex which includes 8% or more 5,6-dimercuritubercidin, yet it serves well as an intermediate in a convenient synthesis of 5-iodotubercidin (43) (Scheme 8).[42] Of 116 purine nucleoside analogs studied, twelve were potent adenosine kinase inhibitors, and of these 5-iodotubercidin was the most potent.[43] The 5-mercurinucleosides triphosphates have been converted to C-5 halogenated compounds by reaction with iodine or N-bromosuccinimide and to the C-5 tritiated compounds with sodium borotritiide.[44]



Scheme 8.

Mercury in the +2 oxidation state bound to sp^2 hybridized carbon exchanges via halide bridging with less electropositive metals.[45] The reactions of organopalladium intermediates derived from the exchange reaction between $PdCl_2$ and 5-mercurinucleosides, which is described in the following section, is one of the most effective means for creating carbon-carbon bonds to nucleosides.

Initial studies to establish the potential of mercurinucleotides and mercuripolynucleotides as biochemical tools have given mixed results.

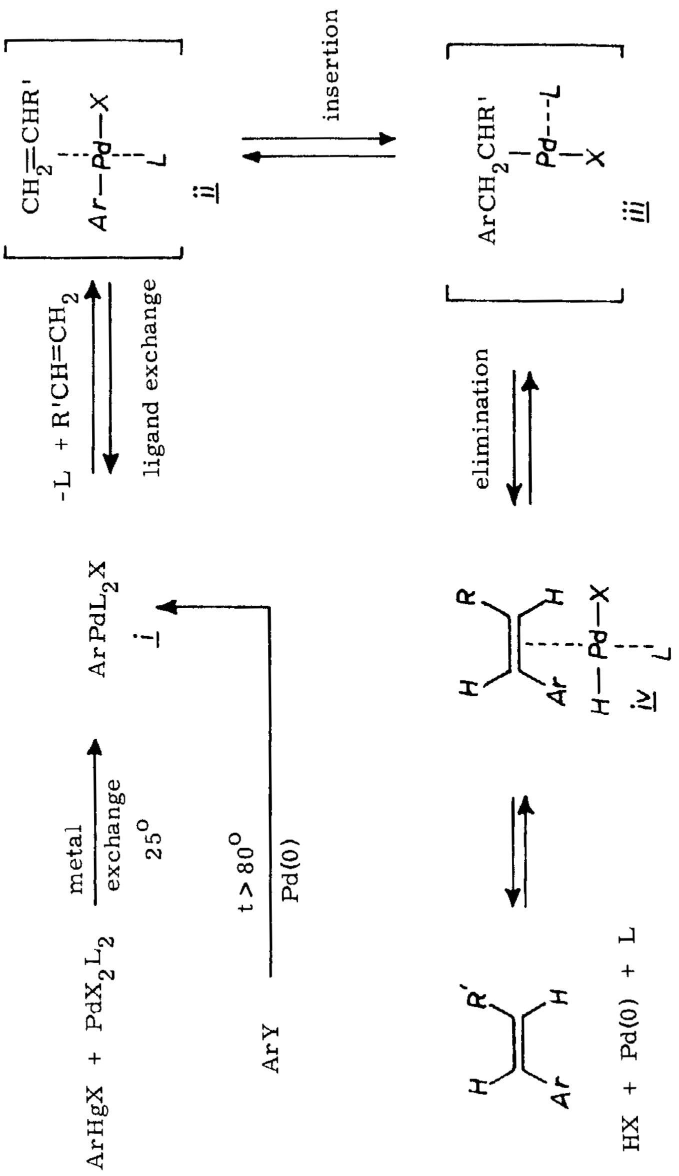
The instability of the 5-alkylthiolmercuripyrimidine nucleotide derivatives limits their use in studies of DNA replication or transcription.[46] They are apparently demercurated via thiol catalysed symmetrization.[45,46] Partially mercurated nucleic acids are easily purified because they are retained on sulfhydryl-agarose. Dale and Ward[38] demonstrated this to be a useful method for isolation of specific in vitro transcription products. The method has been applied to the isolation of mRMA sequences for immunoglobulin kappa light chain.[47]

4. C-5 Substituted Pyrimidine Nucleosides via Organopalladium Intermediates.

Few reactive intermediates capable of effecting carbon-carbon bond formation show the selectivity that is characteristic of the reaction of organopalladium intermediates with olefins.

Organopalladium intermediates, in which palladium is attached by a σ bond to sp^2 hybridized carbon are normally stable to aliphatic fluorides and chlorides, esters, amides, ethers, hydroxyl, and dialkylamino groups. Aryl halides and alkyl halides are stable at lower temperatures. Arylamines, phenols, aldehydes, ketones and carboxylic acids are also unreactive under some conditions that give high yields of olefin coupling. The functional groups towards which palladium is most reactive includes alkenes, carbon monoxide and alkynes.

The organopalladium intermediates are easily generated in situ from aryl iodides and arylmercurials, and react with olefins by the route shown in Scheme 9.[48,49] The reaction of an arylmercurial with a soluble form of palladium(II) ($LiPdCl_3$ in acetonitrile or Li_2PdCl_4 in methanol) initially gives the organopalladium intermediate i which generally can not be isolated (Scheme 9). The structure of the ligands and the aryl group σ bonded to palladium are major factors in the stability of i. A weakly bound ligand can exchange for olefin to give π complex ii. The key step in the overall process is the organometallic insertion reaction in which the π bonded olefin inserts into the Ar-Pd σ bond to give iii.



X = Cl, OAc Y = Br, I L = ligand

Scheme 9.

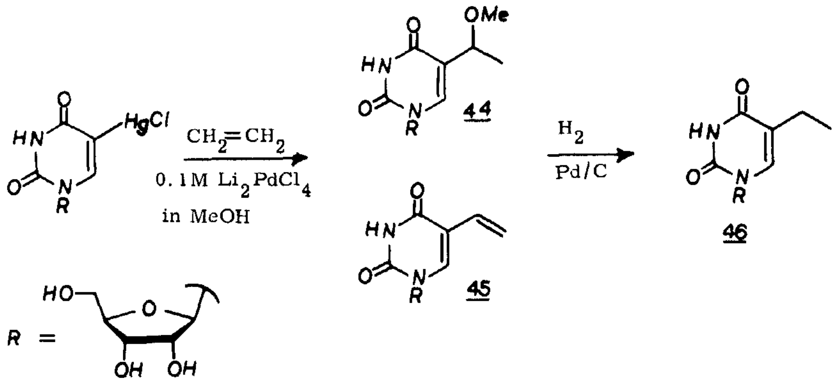
Elimination of Pd-H regenerates the double bond to give iv which dissociates to the free olefin, Pd(0) and HX. The regioselectivity and stereoselectivity of the reaction depends on the structure of the olefin. A significant number of olefins couple only at the terminal carbon and give specifically the E isomer. Since aryl bromides and iodides are more readily available than the mercurials, far more studies have been conducted on the reaction in which the first step (Scheme 9) is oxidative addition of Pd(0) to the aryl halide. This scheme also offers the advantage that it is catalytic overall in palladium. Palladium(0) is regenerated in the last step in the reaction. In contrast the arylmercurials require Pd(II) for the metal-metal exchange reaction, which is reduced to Pd(0) by the overall reaction. Although not always successful, this latter problem can often be surmounted by incorporating an *in situ* reoxidant, such as cupric chloride, to transform Pd(0) to Pd(II).

The synthesis of C-5 substituted pyrimidine nucleosides via the organopalladium coupling procedure has been most frequently accomplished from the 5-mercuri-derivatives. Mercurinucleosides are easily synthesized, stable intermediates. The metal-metal exchange reaction with Pd(II) goes at room temperature, whereas the oxidative addition of Pd(0) to aryl halides generally requires temperatures in excess of 80° for extended periods of time.

The initial report of a coupling reaction between an olefin and a nucleoside derived organopalladium intermediate[50] revealed one important difference from those reactions described initially by Heck,[51] which gave only aryl substituted alkenes (Scheme 9).

When 5-chloromercuriuridine[40] was combined with ethylene (0-30 psi) and Li_2PdCl_4 in a closed system in methanol, the coupling reaction was complete in less than one hour at room temperature.[50,52] The major product, obtained in 39% yield after purification was 5-(1-methoxyethyl)-uridine (44) (Scheme 10). The expected product, 5-vinyluridine constituted no more than 6% of the total nucleoside product. Since both side chains, vinyl and α-methoxyethyl can be reduced catalytically, the method provides a very clean route to 5-ethyl derivatives. In this way 5-ethyl-2'-deoxyuridine was obtained in an overall yield of 58% from 2'-deoxyuridine.

The type of product that may be expected from the coupling reaction depends largely on the structure of the olefin. However, they fall roughly into four categories (Scheme 11): 1) Terminal alkenes couple at both vinyl carbons, to give alkenyl and methoxyalkyl side chains.



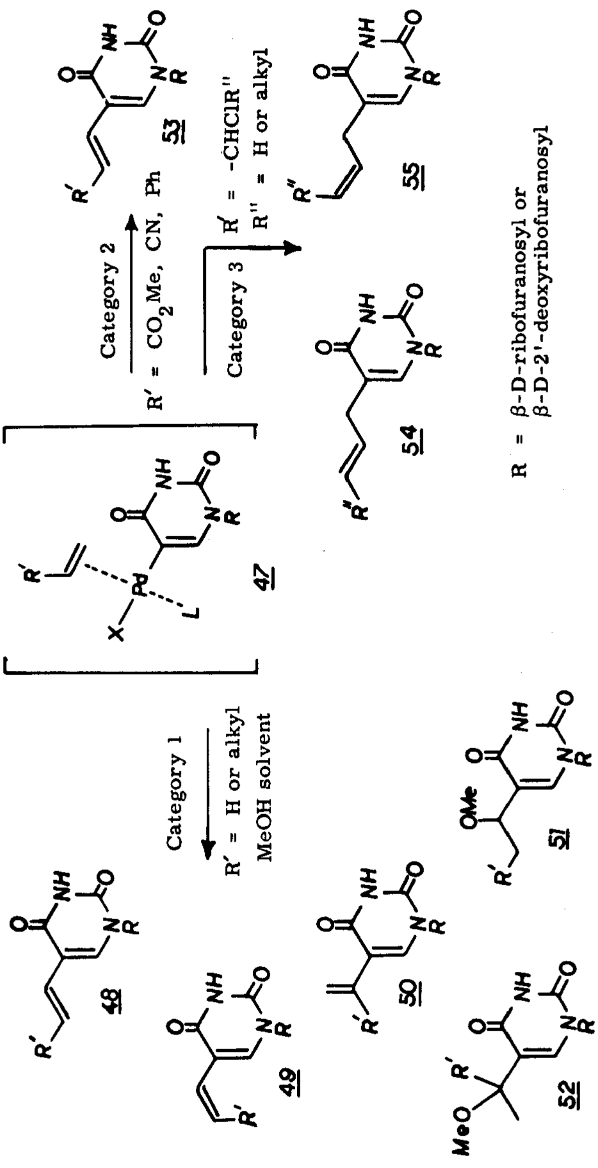
Scheme 10.

2) Conjugated olefins couple regioselectively at the terminal alkenyl carbon to give trans olefins. 3) Allylic chlorides couple at the terminal alkenyl carbon and eliminate $PdCl_2$ to give E and Z 5-alkenylpyrimidine nucleosides. 4) Olefins with functional groups that complex with or react with palladium at some intermediate stage in the reaction may provide unusual and unpredictable results.

Reactions in category 1, with the exception of ethylene (R'= H, Scheme 11) are not synthetically useful.[52] For example the reaction with propylene (47, R' = CH_3, R = 2'-deoxyribosyl) gives five products, 48-52 (R' = CH_3), with the major component (E)-5-(1-propenyl)-2'-deoxyuridine (48) isolated in a maximum yield of 11%.

Reactions in category 2 are useful because a single major product is obtained. The only product isolated from the reaction between methyl acrylate (R' = CO_2Me) and 47 was (E)-5-(2-methoxycarbonylethenyl)uridine (53, R' = CO_2Me, R = ribosyl). Alternatively 53 (R' = CO_2Me, R = ribosyl) was obtained in 53% yield by the reaction of 5-iodouridine with methyl acrylate as catalyzed by palladium acetate (0.05 molar equivalents) in the presence of triethylamine and triphenylphosphine. Mechanistically this reaction is similar, if not identical to the mercurinucleoside procedure, with the exception of the first step, oxidative addition of Pd(0) to 5-iodouridine. The Pd(0) is initially formed by reduction of the palladium acetate-phosphine complex to a Pd(0)-phosphine complex by the olefin.

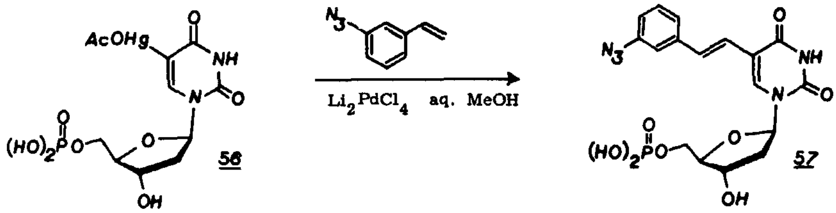
Styrene in complex 47 (R' = C_6H_5) reacts to give the fluorescent nucleoside derivative 53 (R' = C_6H_5, R = ribosyl).[52] The reaction of styrene derivatives with uridine, 2'-deoxyuridine and their 5-monophosphates have been more extensively studied by Mertes.[53,54] The versa-



R = β-D-ribofuranosyl or
β-D-2′-deoxyribofuranosyl

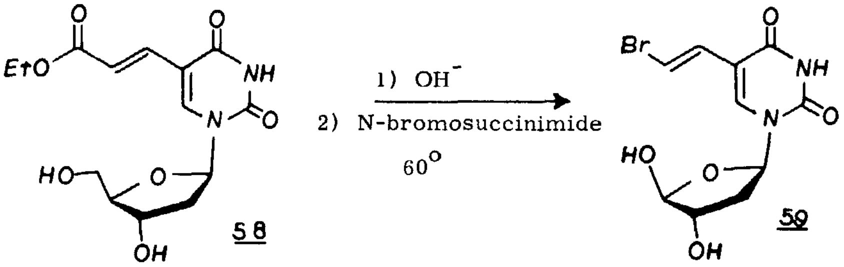
Scheme 11.

tility of the coupling reaction is illustrated by the synthesis of a photoactivated probe for thymidylate synthetase,[55] (E)-5-(3-azidostyryl)-2'-deoxyuridine 5'-phosphate (56) by the coupling reaction between 3-azidostyrene and the 5-mercurinucleotide 56.



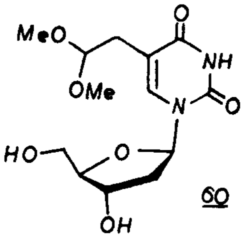
Illustrative of the synthetic power of the organopalladium coupling method is its application at the polynucleotide level. Mercurated polyuridylic acid[39] treated with styrene and Li$_2$PdCl$_4$ in aqueous-methanol at 50° (36 hr) gave modified polyuridylic acid in which up to 20% of the uridine residues were covalently linked at C-5 to styrene.[56] Such modified polynucleotides may eventually prove useful for the study of the nature and specificity of interactions between polynucleotides and the molecules to which they bind in biological systems.

The acrylate ester 58 obtained via the organopalladium coupling reaction was the key intermediate in the synthesis of (E)-5-(2-haloethenyl)-2'-deoxyuridines.[57] (E)-5-(2-Bromoethenyl)-2'-deoxyuridine (59), one of the most potent antiherpes agents known,[58] was obtained from nucleoside 58 by basic hydrolysis followed by decarboxylation and bromination at 60° with N-bromosuccinimide.



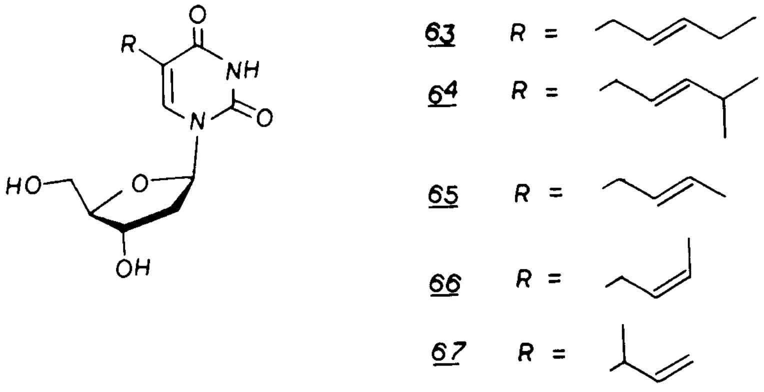
Nucleoside 59 cannot be obtained directly by the coupling reaction with vinyl bromide (47, R = Br). This reaction in methanol gave a low yield of a number of side chain methoxylated products, of which 5-(2,2-dimethoxyethyl)-2'-deoxyuridine (60) was the predominant.[59]

The third category of olefins, allylic chlorides, react regioselectively by a mechanism that is catalytic in Pd(II). 5-Allyl-2'-deoxyuridine (61) produced in high yield from allyl chloride and 5-chloromercuri-2'-deoxyuridine via complex 47 (R = 2'-deoxyribosyl) (Scheme 12).[60]



60

(E)-5-(1-propenyl)-2'-deoxyuridine (62) obtained by the rhodium catalyzed isomerization of 61 is a potent inhibitor of *Herpes simplex* virus type I. Cheng has recently demonstrated that the inhibition of human KB cell growth shown by 62 can be completely reversed when 2'-deoxythymidine is included without affecting its antiviral activity.[61] On the basis of these results the concept of selective protection in antivirus chemotherapy has been proposed.



63 R =

64 R =

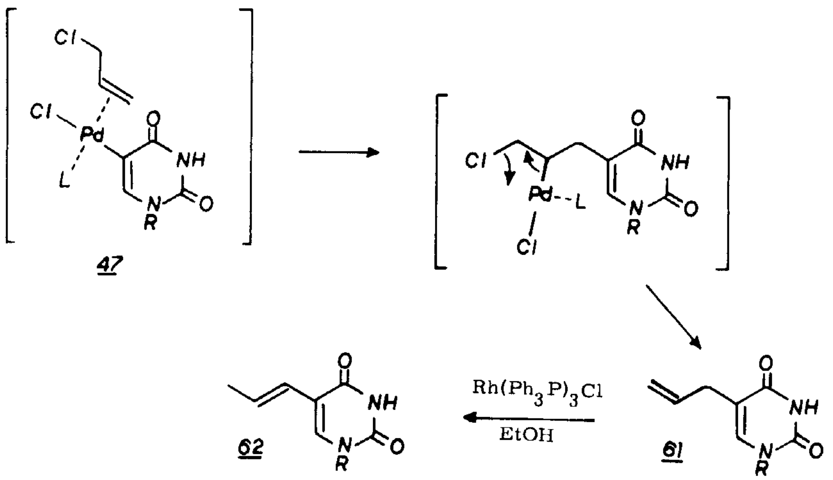
65 R =

66 R =

67 R =

A comprehensive study of the coupling reaction with allylic halides has revealed that it is possible to add long aliphatic side chains regioselectively and stereoselectively.[62] 3-Chloro-1-pentene gives exclusively the trans isomer 63, and 3-chloro-4-methyl-1-pentene gives only 64. The importance of steric effects in controlling the outcome of the coupling reaction is dramatically illustrated by the contrast to 3-chloro-1-butene. 3-Chloro-1-butene gave three products, 65-67, of which the E and Z isomer 65 and 66 predominated.

The forth category includes olefins which for the most part react by unknown mechanisms. For example 4-penten-2-ol adds regioselectively (unlike other 1-alkenes) at the terminal olefinic carbon to



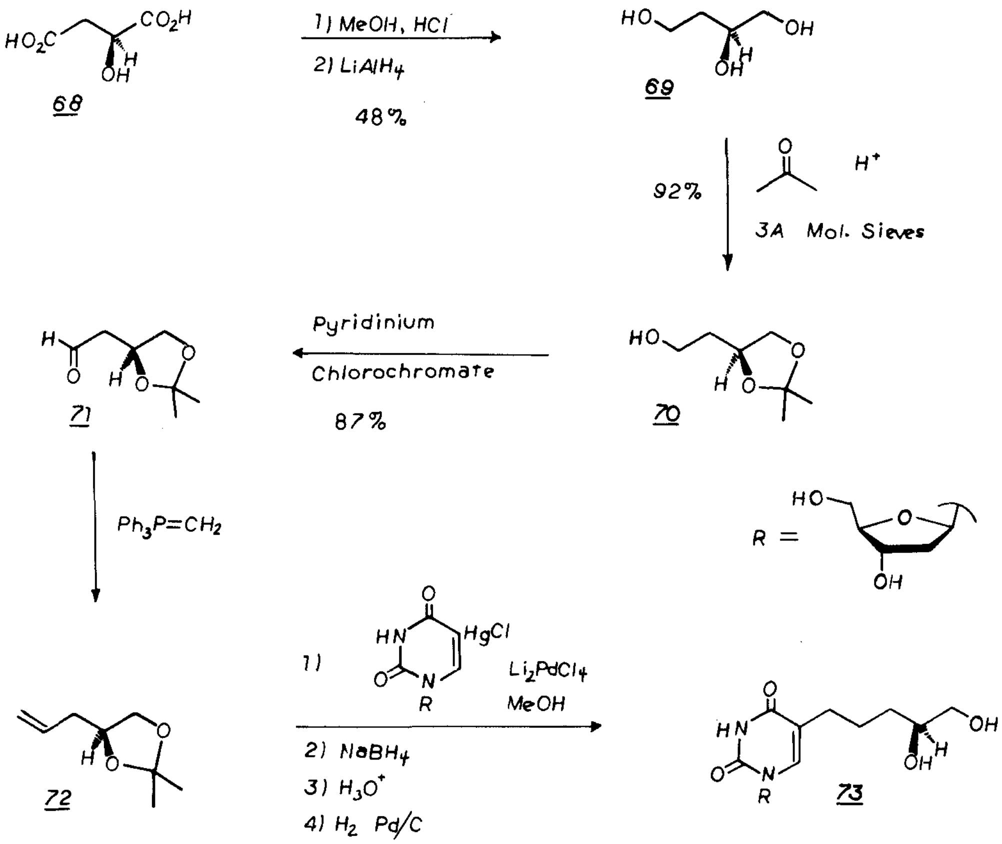
R = β-D-2'-deoxyribofuranosyl

Scheme 12.

give, after catalytic hydrogenation (which would reduce both the carbon-carbon double bond and the α-methoxy function), 5-(4-hydroxypentyl)uridine and 5-pentyluridine.[52]

The regioselectivity thus gained by an oxygen function on C-4 of a terminal alkene has been used effectively in a synthesis of (S)-5-(4',5'-dihydroxypentyl)-2'-deoxyuridine (73)[63] (Scheme 13), a nucleoside which occurs naturally in the DNA of the bacteriophage SP-15.[64] Acetonide 70 was synthesized from (S)-(-)-malic acid (68) following the procedure of Hayashi and Nakanishi.[65] Oxidation of 70 by pyridinium chlorochromate gave aldehyde 71 which was condensed with methylenetriphenylphosphorane to give alkene 72. Li_2PdCl_4 mediated coupling of 72 with 5-chloromercuri-2'-deoxyuridine, followed by reduction of side chains containing either a carbon-carbon double bond or an α-methoxy group gave nucleoside 73. A stereospecific synthesis of the free base utilized the reaction of 5-lithio-2,4-di-tert-butoxypyrimidine with a five carbon aldehyde.[50]

The palladium catalyzed coupling reactions of mercurinucleosides with vinyl halides, ethers and acetate (CH_2=CHX, X = F, Cl, Br, OMe, OEt, OAc) give complex mixtures of products including the following C-5 side chains: 2,2-dimethoxyethyl, 1-methoxyethyl, 1,2-dimethoxyethyl and vinyl.[59] Cyclic enol ethers have been shown to couple regiospecifically to the organopalladium intermediate derived from 1,3-dimethyl-2,4-pyrimidinedion-5-yl-mercuric acetate (74). In developing a new route to

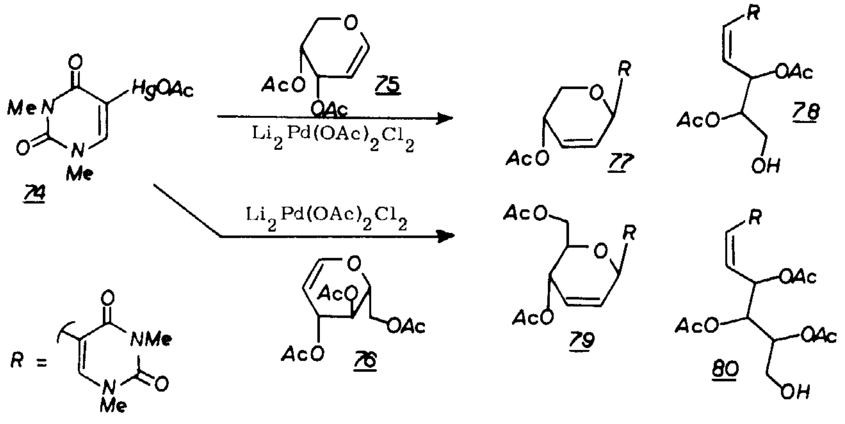


Scheme 13.

C-nucleosides Arai and Daves[66] coupled 74 to the unsaturated pyranose derivatives 75 and 76. Both reactions gave a mixture of two products, one an acyclic sugar linked at C-5 of the pyrimidine and the other a cyclic sugar linked β at C-5 (77-80, Scheme 14). The acylic products predominated in each instance.

Although never applied to a nucleoside, Daves and Arai showed that vinyl acetate can be coupled to C-5 of 1,3-dimethyl-5-iodouracil and 2,4-dimethoxy-5-iodopyrimidine to give the 5-vinyl derivatives in high yield.[67] The solvent (vinyl acetate rather than methanol) and reaction conditions are clearly critical factors in determining the outcome of the reaction.

Comparison of the coupling reaction between the mercuripyrimidine 74 and 3,4-dihydro-2H-pyran and between 1,3-dimethyl-5-iodouracil (75) and 3,4-dihydro-2H-pyran demonstrated further that the method by which the pyrimidine derived organopalladium intermediate is generated, effects

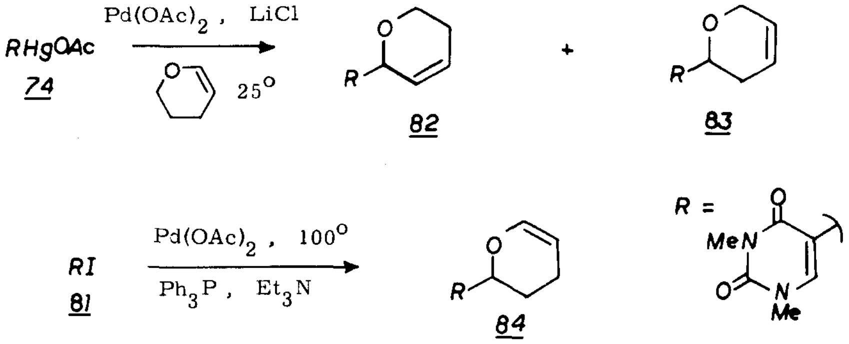


Scheme 14.

the outcome of the overall reaction (Scheme 15).[68] The difference in reaction temperature is probably the greatest single factor effecting product structure. Because of conjugation of the double bond with the oxygen, enol ether 84 should be thermodynamically more stable than either 82 or 83. The absence of an isomer with the double bond in conjugation with the pyrimidine may be a result of the mechanism by which the double bond migrates.[69]

The coupling reaction initially leads to an intermediate in which the palladium is on C-3' trans to the hydrogen on C-2'. Cis elimination of HPd can occur only in the opposite direction leading initially to the palladium π complex of 82. Dissociation of the π complex would give 82, H^+, and Pd(0). However, if instead of dissociation, the hydridopalladium species readds to the olefin with the opposite regiochemistry, palladium will become bonded at C-4 cis to the pyrimidine ring. Cis elimination can lead to the HPd π complexes of either 82 or 83. Assuming that the cis addition of HPd in the π-olefin complex is reversible, this process may repeat itself many times, in each case removing a hydrogen which is cis to the attached pyrimidine. Only dissociation of the intermediate π-complexes with production of Pd(0) breaks the cycle and leads to the products (82-84).

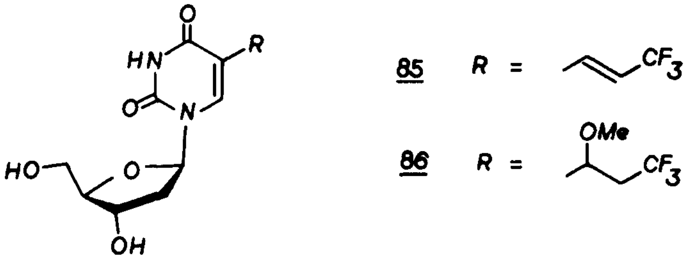
A few olefins give results characteristic of more than one category. 3,3,3-Trifluoropropene couples regioselectively in methanol to give (E)-5-(3,3,3-trifluoropropenyl)-2'-deoxyuridine (85) (21% yield) and 5-(1-methoxy-3,3,3-trifluoropropyl)-2'-deoxyuridine (86) (41%).[70] Thus, the regioselectivity characteristic of conjugated olefins prevails but the



Scheme 15.

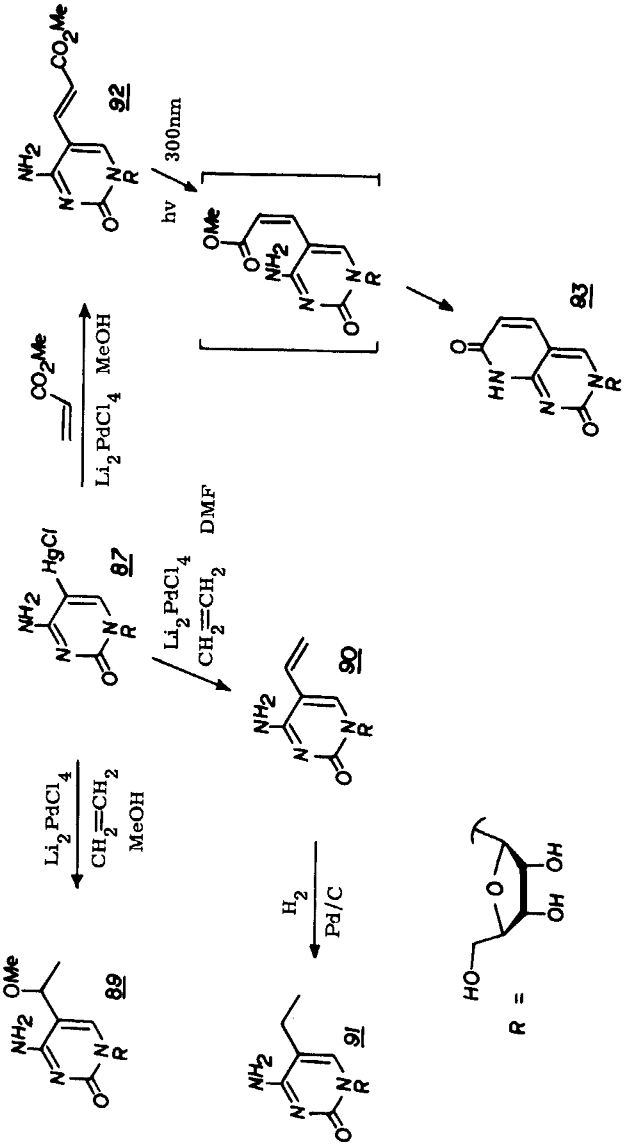
methoxy group is incorporated into the side chain as with category 1 olefins.

The 5'-monophosphate of 85 is apparently an irreversible or pseudo-irreversible mechanism-based inhibitor of dTMP synthetase. Nucleoside 85 is a potent antiviral agent against *Herpes simples* Type I, and shows greater selectivity in that respect than other drugs.[71]



5-Chloromercuricytidine (87) and 5-chloromercuri-2'-deoxycytidine (88) react with Pd(II) and olefins as readily as 5-chloromercuriuridine. Fewer reactions have been reported, although examples of each of the reaction categories shown in Scheme 11 are known.[60,62,72]

The major product from the reaction between 5-chloromercuricytidine, Li$_2$PdCl$_4$ in methanol and ethylene is 5-(1-methoxyethyl)cytidine (89) (Scheme 16) in analogy to the reaction of complex 47 (R = H) in methanol. However, unlike 5-chloromercuriuridine, which gives only low yields of 5-vinyluridine, 5-chloromercuricytidine reacts with ethylene in 0.1 M Li$_2$PdCl$_4$ in N,N-dimethylformamide to give 5-vinylcytidine (90) in substantial yield.[72] This material as well as 5-vinyl-2'-deoxycytidine are prone to polymerize on standing. 5-(1-Methoxyethyl)cytidine (89) unlike its uridine counterpart cannot be reduced by catalytic hydrogen-


NH2
HgCl
N
O
R
87
CO2Me
Li2PdCl4 MeOH
92
hν
300nm
OMe
93
Li2PdCl4
CH2=CH2
DMF
90
Li2PdCl4
CH2=CH2
MeOH
89
H2
Pd/C
91
R =
HO
OH
HN

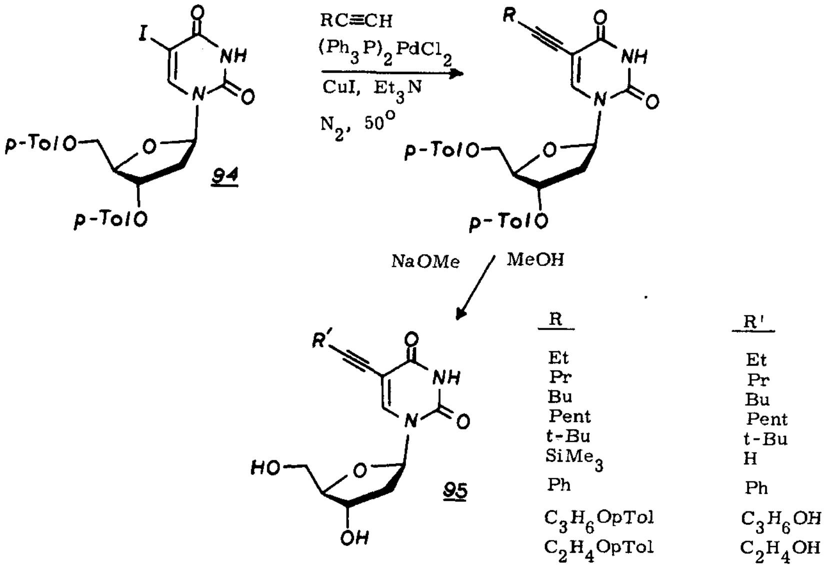
Scheme 16.

olysis to the 5-ethyl derivative. However, reduction of 90 by hydrogen over Pd/C gives 5-ethylcytidine (91) in good yield.

The product from coupling methyl acrylate to cytidine, nucleoside 92, is transformed on irradiation at 300 nm to the fluorescent pyrido-[2,3-d]pyrimidine nucleoside 93, the first example of a 3-β-D-ribofuranosyl pyrido[2,3-d]pyrimidine.[73]

A modification of the palladium coupling reaction that employs catalytic quantities of $(Ph_3P)_2PdCl_2$ and CuI gives C-5 substituted uracil nucleosides (72-91% yield) from alkynes and O-acyl protected 5-iodouracil nucleosides (Scheme 17).[74] 5-Ethynyl-2'-deoxyuridine (95) (R' = $C\equiv CH$) was obtained from the coupling reaction of 5-iodo-3',5'-di-O-p-toluyl-2'-deoxyuridine (94) with trimethylsilylacetylene followed by deblocking with sodium methoxide in methanol. Two longer syntheses of 5-ethynyl-2'-deoxyuridine involved condensation of protected sugars with trimethylsilyl derivatives of the modified pyrimidines.[75,76] Nucleoside 95 (R' = $C\equiv CH$) is active against both *Herpes simplex* Type I and vaccinia viruses but is also cytotoxic and appears to be an inhibitor of thymidylate synthestase as its 5'phosphate.[77]

A mechanism for the coupling reaction has been proposed that proceeds by way of a bis(triphenylphosphine)aryl alkynyl palladium(II) complex that is generated by oxidative addition of $(Ph_3P)_2Pd°$ to the aryl halide



R	R'
Et	Et
Pr	Pr
Bu	Bu
Pent	Pent
t-Bu	t-Bu
$SiMe_3$	H
Ph	Ph
C_3H_6OpTol	C_3H_6OH
C_2H_4OpTol	C_2H_4OH

Scheme 17

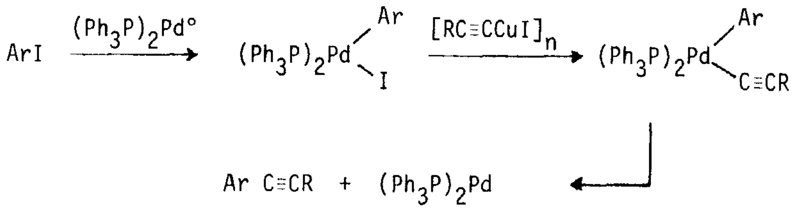
followed by copper catalyzed linkage of the alkyne to the palladium (Scheme 18).[78,79]

A somewhat more complex variation of this reaction appeared five weeks after the article by Robins and Barr. 3',5'-Bis-O-(trimethylsilyl)-2'-deoxy-5-iodouridine when combined with the zinc salt of terminal alkynes and a catalytic quantity of $(Ph_3P)_2PdCl_2$ in dry THF gave products of structure 95 (some R' were different and more complex than those in Scheme 17) in yields ranging from 10 to 35%.[80] Dichloro-[1,3-bis(diphenylphosphino)ethane]nickel(II) was also found to function as a catalyst in the one instance it was tried.

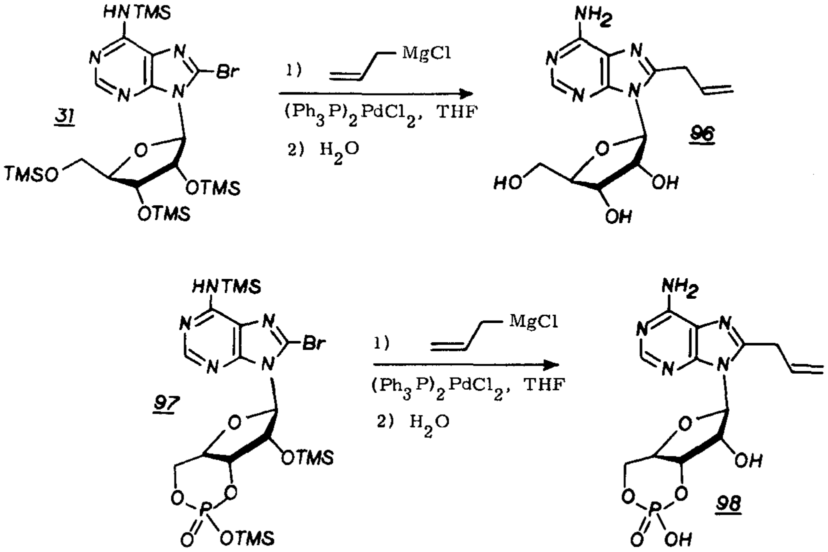
5. Substitution of Purine Nucleosides via Organometallic Intermediates Generated from Group VIII Transition Metals.

Only a single report of substitution of the purine nucleus catalyzed by palladium has appeared.[81] The trimethylsilyl protected derivative of 8-bromoadenosine (31) reacts with alkyl Grignard reagents and $Pd(PPh_3)_4$ to give 8-alkyladenosines. The reaction can be applied to trimethylsilylated 8-bromoadenosine 3',5'-cyclic-monophosphate (97). The highest yields were obtained with allylmagnesium chloride. 8-Allyladenosine (96) was isolated in 35% yield and 8-allyladenosine 3',5'-cyclicmonophosphate (98) in 30% yield (Scheme 19). Bistriphenylphosphine nickel(II) chloride was also an effective catalyst. The reaction may proceed by a somewhat different mechanism than that outlined for the organopalladium intermediates in Scheme 10.[82,83]

Of various palladium and nickel catalysts examined for the cross coupling of alkyl Grignard reagents with aryl and vinyl halides the most effective is dichloro-[1,3-bis(diphenylphosphino)propane]nickel(II).[84-86] Preliminary studies have shown that this catalyst with 2',3',5'-tris-O-(t-butyldimethylsilyl)-8-β-D-ribofuranosyl-6-chloropurine and ethylmagnesium bromide in THF gives the t-butyldimethysilyl protected derivative of 6-ethylpurine ribonucleoside .[87]



Scheme 18.



Scheme 19.

6. Organopalladium Intermediates in the Synthesis of C-5 Substituted Pyrrolo[2,3-*d*]pyrimidine Ribonucleosides.

Examples of biologically important C-5 substituted pyrrolo[2,3-*d*]-pyrimidine ribonucleosides include nucleoside Q[88] and Q*,[89] biosynthetic precursors of nucleoside Q,[90] and the nucleoside antibiotics toyocamycin and sangivamycin.[91] Most syntheses of nucleoside Q and nucleoside Q precursors and the nucleoside antibiotics are of a *de novo* type in which the carbon at C-5 is introduced prior to glycosidic bond formation. Alternatively starting from one of the naturally occurring C-5 substituted pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics it is possible to chemically transform the heterocycle. For example, Townsend and coworkers have described a synthesis of 2-amino-5-cyano-7-(β-*D*-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine-4-one, a potential precursor of nucleoside Q starting from toyocamycin.[92] T. Uematsu and R.J. Suhadolnik developed a sequence from sangivamycin to 5-hydroxymethyltubercidin via $LiAlH_4$ reduction of the 2',3'-*O*-isopropylidine derivative of 5-methoxycarbonyltubercidin.[93]

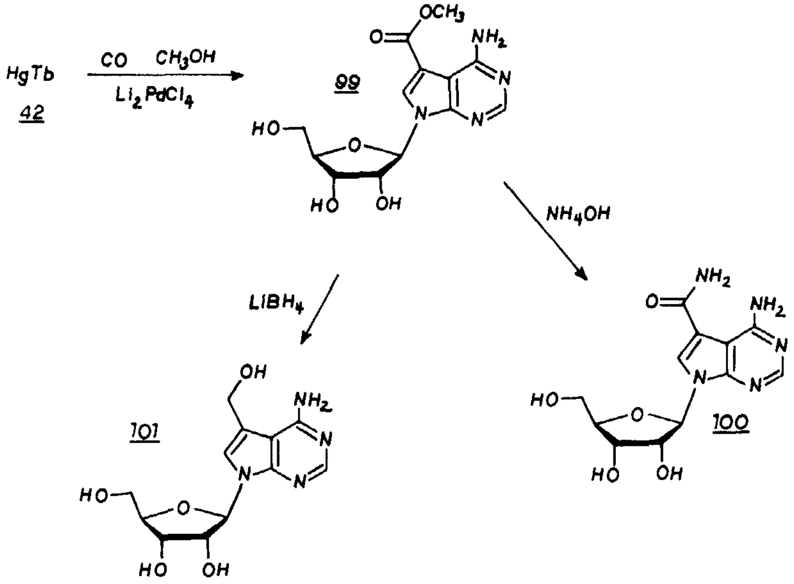
A carbon unit may be introduced into the 5-position of tubercidin by reaction with paraformaldehyde and morpholine in DMF.[94] The transformation of the intermediate 5-morpholinomethyltubercidin to 5-formyltubercidin, 5-hydroxymethyltubercidin and 5-cyanotubercidin (toyocamycin) has been described.

The introduction of side chains ranging from one to four carbons can be easily achieved by the reaction of 5-mercuritubercidin 42 with Pd(II) and carbon monoxide or olefins.[42] 5-Mercuritubercidin reacts at room temperature with carbon monoxide in methanol to give 5-methoxycarbonyltubercidin (99), whereupon the methoxycarbonyl group can be transformed to other C-5 one-carbon functional groups (Scheme 20). Reaction of 99 with ammonium hydroxide gives sangivamycin (100) whereas lithium borohydride in THF gives the cytotoxic derivative 5-hydroxymethyltubercidin (101).

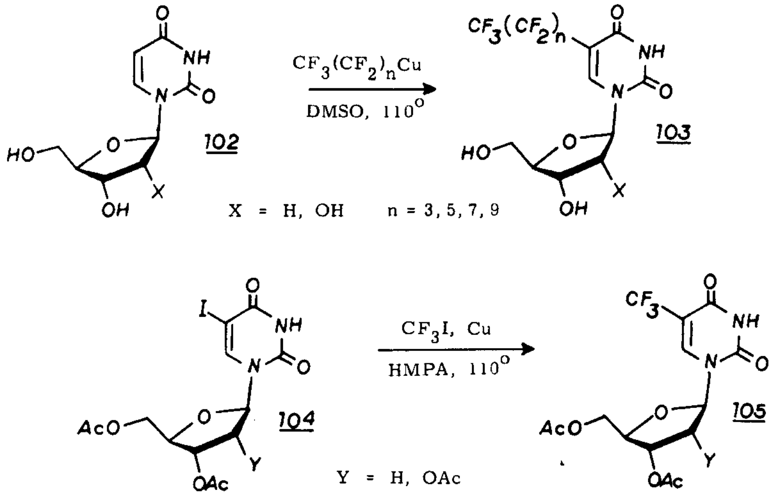
Olefins which have been successfully coupled to tubercidin, following the pattern established for the pyrimidine nucleosides, include, ethylene, methyl acrylate, acrylonitrile, 3-chloro-1-butene, and styrene.[42]

7. Nucleoside Analogs via Organocopper Intermediates.

There are no reports in the literature of preparation of pyrimidine or purine derived organocopper complexes. However, a number of modified nucleosides have been synthesized by reactions which many involve organocopper intermediates. 5-Perfluoroalkylpyrimidine nucleosides have been obtained in low yield by coupling preformed fluoroalkylcopper compounds with uridine and 2'-deoxyuridine (Scheme 21).[95] The same authors have applied the reaction to the synthesis of perfluoroalkylated derivatives



Scheme 20



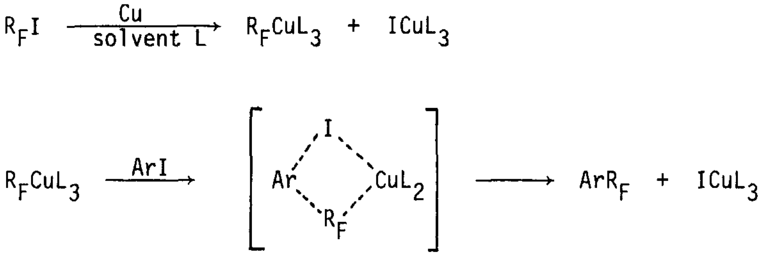
Scheme 21

of 5'-deoxy-5'-fluorouridine and 2',5'-dideoxy-5'-fluorouridine.[96] These results were somewhat unexpected because the original studies on the reaction by McLoughlin and Thrower[97] clearly established that the fluoroalkylcopper compounds coupled only at aryl carbons bearing a iodine or bromine (Scheme 22).

When the reaction was attempted with 5-iodouracil only uracil and unreacted starting material were obtained. Also in contrast to these results Kobayashi and coworkers found that 2',3',5'-tri-O-acetyl-5-trifluoromethyluridine (105, Y = OAc) could be prepared by heating 2',3',5'-tri-O-acetyl-5-iodouridine (104, Y = OAc) with CF$_3$I and copper powder in hexamethylphosphoric triamide at 110°.[98] However, unhalogenated nucleoside, 2',3',5'-tri-O-acetyluridine gave very little product. 2',5'-Di-O-acetyl-5-trifluoromethyl-2'-deoxyuridine (105, Y = H) was obtained in 54% yield starting from 2',5'-di-O-acetyl-5-iodo-2'-deoxyuridine (104, Y = H).

More recently the same authors have described the syntheses of the 5-trifluoromethyl analogs of cytidine, deoxycytidine, and arabinosylcytosine via the coupling reaction with O-acetyl and O-trityl protected 5-iodonucleosides.[99] The 8-trifluoromethyl derivatives of adenosine, deoxyadenosine, and inosine were prepared from the 8-iodonucleosides, and 6-trifluoromethyl-7-β-D-ribofuranously purine was obtained from the 6-chloropurine ribonucleoside.

The mechanism of the trifluoromethylation is probably similar to the general mechanism proposed by McLoughlin and Thrower (Scheme 22). An advantage of the reaction is its insensitivity to functional groups which

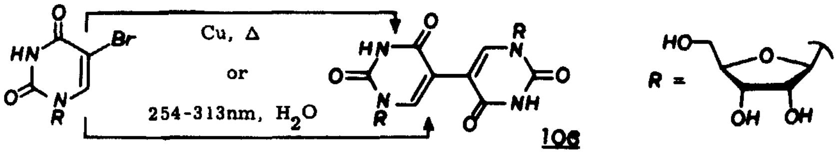


Scheme 22

are reactive toward organolithium and organomagnesium intermediates. Alkoxy, fluoro, chloro, alkoxycarbonyl, nitro, carboxyl, amino, and hydroxyl groups do not apparently interfere with the reaction. Direct comparisons between protected and unprotected nucleosides will be necessary to establish the extent of the reagents tolerance.

Suprisingly, there have been no reports of reactions of lithium dialkyl- or diarylcuprates with protected halogenated pyrimidine or purine nucleosides. Lithium dialkyl- and diarylcuprates (R_2CuLi) have been shown to react in high yield with aryl iodides to give Ar-R.[100] Conceivably C-5 bromo pyrimidine nucleosides could couple at C-6 as has been demonstrated for the reaction of cyanide with protected uracil and cytosine nucleosides.[3,4]

Finally 5-5'-diuridinyl (106) can be prepared in low yield by reacting 5-bromouridine with copper powder in refluxing DMF.[101] Much higher yields of 106 are obtained on irradiation of 5-bromouridine in frozen aqueous solution.[101]



9. Conclusion

The reactions described here represent only a portion of the pathways investigated for modifying carbon of the heterocyclic bases of nucleosides. The primary purpose of this report has been to review recent accomplishments in the use of organometallic reagents, for the synthesis of modified nucleosides.

Modifications via leaving group displacement on the heterocyclic,[3-16] free radical reactions,[102] rearrangements,[15,16,103] photochemical additions,[104] carbene reactions,[105] and a Wittig reaction,[106] have led to unique nucleosides analogs, many of which are not readily available by other pathways. Yet among all methods of modification, the recent developments in the use of organometallic intermediates, especially those derived from the group VIII transition metals, indicate tremendous potential for synthesis of complex nucleoside analogs. Organopalladium intermediates can be used to derivatize unprotected nucleoside, and nucleotides, with side chains bearing a wide variety of functional groups. Even where protecting groups are required, such as in the nickel catalyzed coupling of Grignard reagents at C-6 and C-8 of purine nucleosides, the overall scheme offers significant advantages in simplicity.

Until very recently the majority of carbon modified nucleosides were synthesized by building modified bases and attaching them to the required protected C-1 activated sugar derivative. Such lengthy routes to modified nucleosides can in many cases now be circumvented. Further developments in the organotransition metal chemistry of nucleosides and nucleotides should provide researchers with a wide variety of biologically interesting nucleoside analogs in the years ahead.

ACKNOWLEDGMENTS

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