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An Improved Synthesis of 2′-fluoro-2′-deoxyarabinofuranosyl Pyrimidine Nucleosides

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Abstract □ Several potent anti-herpes virus nucleosides, 2′-fluoro-2′-deoxyarabinofuranosyl pyrimidine nucleosides, were prepared in good yields by a new condensation method using sodium iodide and a new solvent system, and FMAU could be also prepared directly from thymine by this method.

Keywords □ Anti-herpes virus nucleoside,
2-Fluoroarabino sugar,
Pyrimidine nucleoside synthesis.

Fischer and Helferich first reported the synthesis of certain purine nucleosides by glycosylation of suitable purines with acetobromoglucose. After that time a tremendous number of nucleosides have been prepared with purines, pyrimidines and related heterocycles as the aglycon.[1]

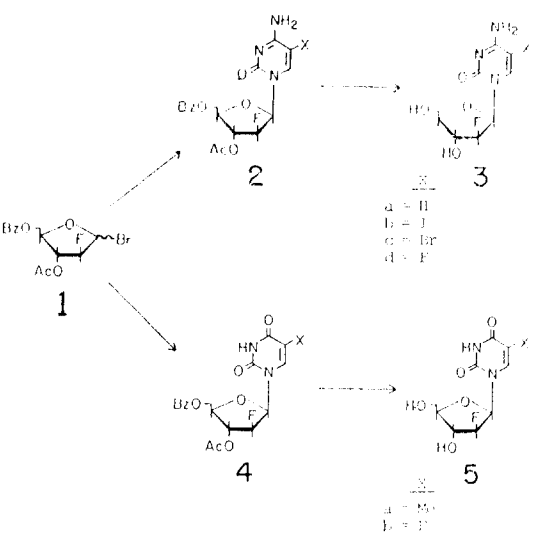
While early efforts have been geared to the synthesis of nucleosides of the nucleic acids, later efforts were directed toward the preparation of unnatural nucleosides as potential antimetabolites for biochemical and chemotherapeutic purposes including anti-cancer and anti-viral agents[2] and to mimic the relatively recently discovered nucleoside antibiotics.[3]

A detailed examination of reported syntheses of nucleosides by glycosylation shows that essentially three basic approaches have been employed, namely, the Koenigs-Knorr, the Hilbert-Johnson, and the Helferich type reactions.[1]

Among several methods available for the synthesis of pyrimidine nucleosides[1], the condensation of 1-O-acetylsugars with the trimethylsilylated base in the presence of a Friedel-Crafts catalyst such as tin (IV) chloride[4] is currently used most frequently.

Recently Fox and co-workers[5~7] reported the synthesis of several potent anti-herpes virus pyrimidine nucleosides containing the 2′-fluoroarabinofuranosyl moiety but condensation of the 2-fluoroarabino sugar with 5-substituted pyrimidine was a difficult step since the reaction required two weeks to complete, so that the overall-yield was very low.

Especially 2′-fluoro-5-methyl-ara-U(FMAU) (5a) was originally prepared in three steps by condensation of the fluorosugar with 5-methyl-



cytosine, followed by saponification and hydrative deamination[5].

This report describes the improved synthetic method of those nucleosides. A new method was introduced by which the bromosugar was spontaneously converted into the much more reactive iodosugar using sodium iodide and a new solvent system (4:1 mixture of $ClCH_2CH_2Cl$ and CH_3CN)[8], so that the reaction could be completed within three days in good yield. And FMAU could be prepared directly from thymine by the new condensation methodology of this paper.

It seems that this new method can be applied to the preparation of other related nucleosides.

Table I: Yield of compound 2, 3, 4, and 5.

Compd.	Yield(%)	Compd.	Yield(%)
2a	72	3a	87
2b	76	3b	83
2c	82	3c	88
2d	64	3d	76
4a	51	5a	77
4b	48	5b	83

EXPERIMENTAL METHODS

1-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-substituted Cytosines and Uracils

To a solution of trimethylsilylated base (prepared from 0.015mol of cytosine, 5-iodocytosine, 5-bromocytosine, 5-fluorocytosine, 5-methyluracil, and 5-fluorouracil, respectively) in $ClCH_2CH_2Cl$ (30ml) were added a solution of 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (1) (3.6g, 0.01mol) in $ClCH_2CH_2Cl$ (30ml) and a solution of NaI (1.5g, 0.01mol) in CH_3CN (15ml), and the mixture was stirred for 3 days at room temperature. MeOH (7ml) was added and the suspension was filtered through a Celite pad which was thoroughly washed with CH_2Cl_2. The combined filtrate and washings were evaporated to dryness in vacuo, and the residue was partitioned between CH_2Cl_2 (100 ml) and H_2O (100 ml). The organic layer was washed with 5% $Na_2S_2O_3$ solution and H_2O, dried over Na_2SO_4, and evaporated to dryness in vacuo. The residue was crystallized from EtOH to give a pretected nucleoside (2 and 4) which were identified by a direct comparison (mixed melting point determination and NMR spectra) with authentic samples (Yield: see Table I).

1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-substituted Cytosines (3) *and Uracils* (5).

Compound (2 and 4) (1.1g) was dissolved in saturated NH_3-MeOH (30ml). After 24hr. the solvent was removed in vacuo and the residue was triturated with acetone. Crystalline was filtered and recrystallized to give pure nucleoside (3 and 5) which were identified by mixed melting point determination and comparison of NMR spectra with authentic samples (Yield: see Table I).

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