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# Synthesis of Thymidine from 5-Iodo-2'-deoxyuridine

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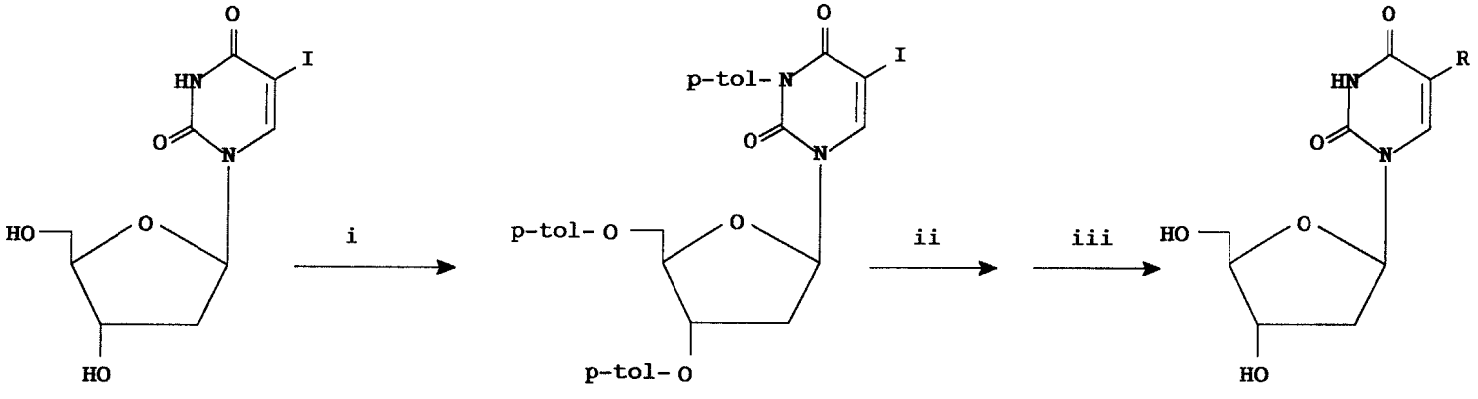
***Abstract***

A simple, high yield synthesis of thymidine from 5-iodo-2'-deoxyuridine is described, using tetramethyltin and tetrakis(triphenylphosphine)palladium(0) in hexamethylphoshoric triamide. Likewise, 5-phenyl- and 5-vinyl-2'-deoxyuridine can be obtained, and through reduction of the latter the 5-ethyl analogue is also at hand.

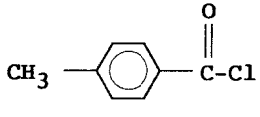
2'-Deoxynucleosides are the natural constituents of DNA. Therefore, the synthesis of analogues of these nucleosides has always attracted considerable attention. Analogues of 2'-deoxynucleosides have been synthesized with the aim of obtaining compounds with anti-tumour or antiviral activity. These molecules can be made either by modification of naturally occuring 2'-deoxynucleosides, or by a sugar-base condensation reaction after introduction of the modification in one of both moieties. The latter method has the advantage that once a modified sugar has been synthesized, different compounds can be obtained by condensation reaction with different bases. However, a limitation to this method is the low stereoselectivity of the sugar-base condensation reaction using 2'-deoxyribose derivatives as starting material. While considerable progress has been made in the condensation reactions with purine bases[1], condensation reactions with pyrimidine bases are never fully stereospecific[2-5] and separation of the α and β anomers is often a difficult and tedious task. Anomeric purity is an absolute requirement when compounds have to be evaluated for their biological activity. Moreover, the polarities of the α and β analogues are sometimes so equivalent to each other that one is unable to separate both isomers with regular laboratory equipment. This is often the case with nucleosides bearing an uracil or thymine base moiety.

Therefore, condensation of 2'-deoxyribose derivatives with a base moiety yielding an easily separable mixture of α and β nucleosides would be desirable. These nucleosides should then be easily convertible to the natural pyrimidine 2'-deoxynucleosides (2'-deoxyuridine, 2'-deoxycytidine and thymidine). This property can be fulfilled by 5-iodouracil. Condensation reactions of 2'-deoxy sugars with 5-iodouracil usually give a well separable mixture of α and β nucleosides. 5-Iodo-2'-deoxyuridine can be easily converted to 2'-deoxyuridine by catalytic hydrogenation, and further conversion to 2'-deoxycytidine likewise is well known[6]. However, a high yielding method to convert 5-iodo-2'-deoxyuridine to thymidine has not been described yet.

We now report this reaction can be carried out readily using organotin chemistry. The weakness of the Sn-C linkage allows easy cleavage of this bond with the accompanying formation of new carbon-carbon bonds via substitution reactions. These reactions are normally performed with asymmetric tetraorganotin compounds like allyl-, vinyl-, alkynyl- and aryltrialkyltin derivatives in the presence of transition metal catalysts (Pd,Rh,Ni). However, symmetric tetraorganotin compounds are also useful carbon-carbon bond forming reagents. They are commonly used as starting material for other organic tin derivatives and related metal organics[7]. Methyl-transfer reactions can be achieved using tetramethyltin and a Pd catalyst[8]. Likewise, this reagent has been used for the synthesis of methyl ketones from organic halides and carbon monoxide in the presence of transition metals (mainly



1 2 3a: R = $CH_3$ 3b: R = $CH{=}CH_2$ 3c: R = $C_6H_5$

i)  , $[(CH_3)_2CH]_2NC_2H_5$ , Pyridine

ii) $(R)_4Sn$ , $Pd(Ph_3P)_4$ , HMPA

iii) $CH_3ONa$ , $CH_3OH$

p-tol: p-toluoyl

Palladium complexes)[9].

Reaction of 3',5'-di-*O*-toluoyl-5-iodo-2'-deoxyuridine with tetramethyltin in the presence of $Pd(Ph_3P)_4$ in HMPA (60°C, overnight) yields a protected methylated thymidine derivative indicating that concomitant methylation of the $N^3$-function occurred. Therefore, we decided to protect the base moiety of 5-iodo-2'-deoxyuridine as well. Analogous to the synthesis of $N^3$-acylated uridine derivatives[10], reaction of 5-iodo-2'-deoxyuridine (1) with p-toluoyl chloride in the presence of diisopropylethylamine gives the pertoluoylated compound (2) in 90% yield. Substitution of the 5-iodo funtionality by a 5-methyl group can be performed with tetramethyltin in HMPA in the presence of $Pd(Ph_3P)_4$ at 60°C for 16 h. Removal of the protecting groups afforded thymidine (3a) in 76 % yield.

Likewise, the same reaction could be carried out using either tetravinyltin (60°C, overnight) yielding 5-vinyl-2'-deoxyuridine (3b, 80 % yield) or with tetraphenyltin (60°C, 3 days) affording 5-phenyl-2'-deoxyuridine (3c, 35 % yield). However, the reaction was unsuccessful, using tetraethyltin. This is consistent with the observation that cross-coupling reactions using tetraalkyltin compounds work at best when no β-elimination reaction can compete with the reductive elimination reaction of the intermediate $R^1PdL_2R^2$ complex. However, the 5-vinyl analogue can be used as precursor for the 5-ethyl analogue[11] making also 5-ethyl-2'-deoxyuridine (3d) easily available from 5-iodo-2'-deoxyuridine.

The direct introduction of a methyl group in the 5-position of pyrimidine nucleosides has been described previously by methylation with methyl iodide of the C-5 lithio derivative (obtained with n-BuLi in HMPA-THF at -60°C)[12,13,14]. However, this reaction gives a mixture of thymidine and 6-methyl-2'-deoxyuridine. Moreover, the yields are lower than with tetramethyltin and $Pd(Ph_3P)_4$.

## Experimental

To a solution of 354 mg (1 mmol) of 5-iodo-2'-deoxyuridine (1) in 10 mL anhydrous pyridine containing 260 mg (2 mmol) of N-ethyldiisopropylamine was added 930 mg (0.8 mL, 6 mmol) of p-toluoyl chloride at 0°C. The reaction mixture was stirred for 3 h at room temperature, $H_2O$ (1 mL) was added and the mixture was evaporated. The residue was diluted with $CHCl_3$ (30 mL), washed with $H_2O$ (2x20 mL), dried and evaporated. Following flash chromatography 3'-*O*,5'-*O*,$N^3$-tritoluoyl-5-iodo-2'-deoxyuridine (2) was obtained in 89 % yield (630 mg, 0.89 mmol) as crystalline material from EtOAc. A solution of 354 mg (0.5 mmol) of tritoluoyl-5-iodo-2'-deoxyuridine, 179 mg (1 mmol) of tetramethyltin and 58 mg (0.05 mmol) of tetrakis(triphenylphosphine)palladium(0) in 5 mL of hexamethylphosphoric triamide was stirred for 16 h at 60°C under nitrogen. The reaction mixture was poured into $H_2O$ (50 mL) and extracted with $Et_2O$ (50 mL). The organic solution was dried, evaporated and the protecting groups were removed with sodium methanolate in methanol. After chromatographic purification ($CHCl_3$-MeOH 90-10) thymidine (3a) was obtained as crystalline material in 76 % yield (91 mg, 0.38 mmol) [(mp 186-187°C), $\lambda_{max}$ 267 nm (ε=9.800)].

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