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Chemo-Enzymatic Synthesis of 2'-Deoxynucleoside Urethanes

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Abstract: *2'-Deoxynucleoside 5'- and 3'-(N-alkyl) carbamates were synthesized in a two step procedure, using lipases to catalyze the first regioselective vinyloxycarbonylation step.*

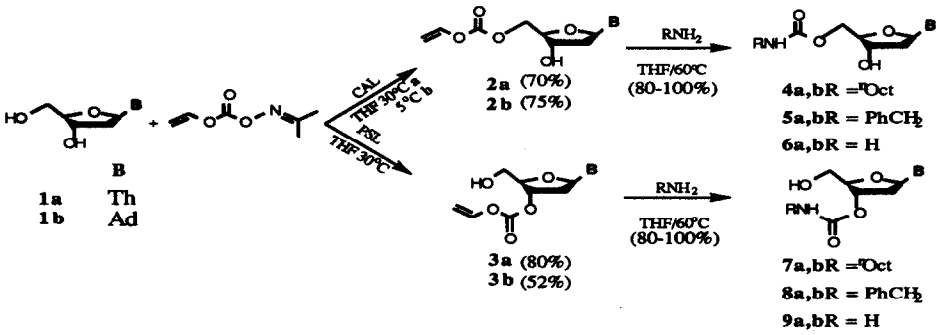
One of the most widespread groups in chemotherapy is the carbamate moiety, which occurs among others, in several classes of antitumorous products.[1] It is also used for increasing permeation through biological membranes of cytotoxic compounds [2] and β-blockers.[3]

On the other hand, *O*-carbamate has been used to replace phosphate linkages in oligonucleotides,[4] since it was found to be able to simulate them *in vitro*.[5] These nucleotide analogues with carbamate internucleoside linkages were shown to effect strong hibridization with complementary DNA sequences,[4] and therefore can be worthy for the study of genetic mechanisms, the treatment of viral diseases and other therapeutic aims.

Bearing this in mind, and as a part of our ongoing research on the modified nucleosides' field,[6-7] we decided to carry out the synthesis of 5'-*O*- and 3'-*O* -alkylcarbamoyl-2'-deoxynucleosides in a regioselective way, using enzymes to avoid cumbersome and time consuming protection/deprotection steps. When testing several lipases, they were found to be unable to catalyze the reaction between vinyl carbamates and thymidine (some carbamates have been shown to inhibit many serine-hydrolases),[8] and then we thought fit to plan the synthesis in a two-step procedure, involving the enzymatic obtention of a carbonate and the later reaction with an amine.

3'- and 5'-methyl, allyl, and benzyl carbonates of thymidine were obtained in accordance with previous works [7] and then subjected to the amination step in THF or dioxane at 60°C, but no carbamates could be detected. Nonetheless, when vinyl or acetonoxime carbonates were tested, carbamates could be isolated in almost quantitative yields. This must be underlined since alkyl vinyl carbonates in these conditions only yield alkylcarbamates in the presence of lipases.[9]

Hence, we chose acetone *O*-(vinyloxycarbonyl)oxime as the carbonylating agent, which in presence of the suitable enzyme[7] (Scheme) allowed to get the corresponding 5'-*O*- or 3'-*O*- vinyloxycarbonyl 2'-deoxynucleosides in good yields (moderate in the case of **3b**). Temperature was optimized in order to improve the regioselectivity/yield ratio. In agreement with previous works,[6-7] total regioselectivity is obtained in the presence of PS lipase, and small amounts of **3a,b** appear when the reaction is catalyzed by CA lipase.



Scheme

The amination step was stopped when complete disappearance of the initial vinylcarbonates **2a-b**, **3a-b** was observed by TLC. Products were purified and isolated by flash chromatography, and characterized by ^{1}H, ^{13}C NMR and mass spectrometry.

To sum up, we have shown a mild, simple and fast procedure to synthesize purine and pyrimidine 2'-deoxynucleoside urethanes in good yields, in a regioselective way, and without previous protection steps.

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