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STEREOSELECTIVE SYNTHESIS OF N^1-6-METHYLURIDINE AND RELATED 2-SUBSTITUTED ANALOGUES

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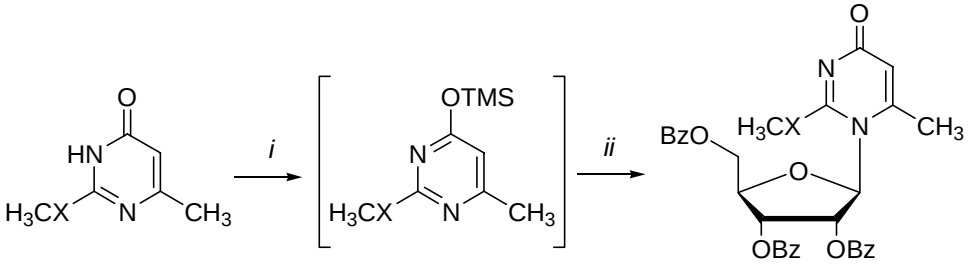
Abstract – Coupling reaction of 2-substituted-6-methyl-4(3*H*)-pyrimidinones (**1a,b**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (ABR) afforded the corresponding N^1-2,6-disubstituted nucleosides (**2a,b)** without any trace of the N^3-isomer. The 2-methylthio-6-methyl derivative (**2b)** has then proved to be a key intermediate for the synthesis of N^1-6-methyluridine (**4)** and the corresponding N^1-2-amino-6-metyhl derivative (**5)**, suggesting the possibility to obtain different 2,6-disubstituted derivatives by means of methylthio nucleophilic substitution. A successful solid phase application was also shown.

To date, the main efforts in the discovery of novel antiviral and anticancer nucleosides were generally devoted to the functionalization of the sugar moiety while base modified nucleoside have received so far little attention. In this context, base-modified pyrimidine nucleosides have generally been substituted at C-5 position (i.e. BVDU, CEDU)[1] probably because of the easiness of functionalization at this site (i.e. electrophilic substitution) which could be related to the highest single coefficient in the HOMO of C-5. While the methods for the preparation of 5-substituted pyrimidine nucleosides are well established, there is a need for yet a easier access to 6-derivatized analogues which, being constrained into a non natural *syn*-conformation, are of interest as potential antimetabolites. Uridine derivatives bearing a 6-vinyl substituent as well as a 6-fluoromethyl substituent have in fact shown to posses interesting antitumor activity.[2] However, according to the results published so far from Vorbrüggen et al.,[3] very subtle steric as well as energetic factors seem to drive the formation of N^1- and N^3- nucleosides by condensation of 6-substituted nucleobases with the suitable sugar. As a result, a complex mixture of N^1- and N^3-isomers, which requires tedious purification, is always obtained.

In order to drive the coupling reaction between 6-substituted pyrimidines and the activated sugar derivative to the exclusive formation of the N^1-nucleoside, few different strategies have been developed so far: the

most common method requires a preliminary protection of the amide moiety of the pyrimidine base to give the corresponding N^3-benzyl derivative, subsequent silylation, condensation with the activated sugar, removal of the benzyl group and final deprotection of the sugar moiety. Otherwise, the formation of the N^3-nucleoside during the condensation reaction is prevented by transforming the 6-substituted pyrimidines into a 4,6-disubstituted derivatives so that the NH moiety of the nucleobase is no more available for the coupling with the sugar.[2b] The continued interest of our research group in the synthesis of unnatural nucleosides has prompted us to investigate the synthesis of 6-substituted nucleoside in order to find out a new method for maximal yields or exclusive formation of the N^1-isomer.[4] Since steric factors seem to be of primary importance in the formation of either N^1- or N^3-nucleosides in the coupling reaction between silylated 6-methyluridine and the activated sugar, initially we decided to study the effects of a reduced bulkiness around the N^1 atom on the outcome of the coupling reaction. Accordingly, a methoxy group was introduced in the C-2 position of 6-methyluracil. The *O*-methyl group is chemically very similar to *O*-trimethylsilyl group of the silylated nucleobase but its smaller size could influence the outcome of the coupling reaction.



1a: X = O
1b: X = S

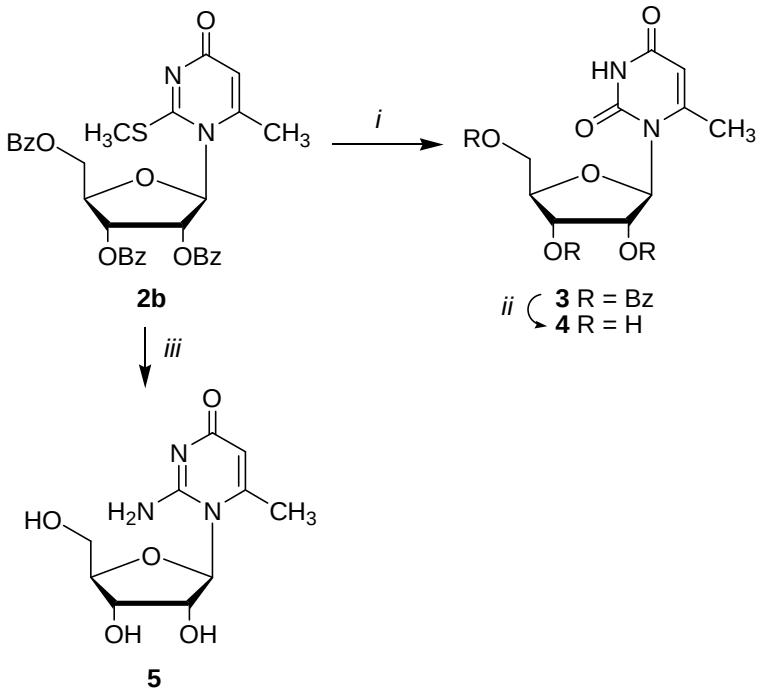
2a: X = O
2b: X = S

Scheme 1. Reagents and conditions: *i.* HMDS, $(NH_4)_2SO_4$; *ii*. ABR, TMSOTf, MeCN

Following the Vorbrüggen's procedure,[5] 2-methoxy-6-methyl-4(3*H*)-pyrimidinone (**1a**) was reacted with hexamethyldisilazane (HMDS) in the presence of catalytic ammonium sulfate (Scheme 1) to give the corresponding 4-trimethylsilyl derivative. The latter intermediate was then reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (ABR) in the presence of trimethylsilyl triflate (TMSOTf) as a catalyst to give compound (**2a)** as the only product in 61% yield which configuration was established through 1D NOE difference spectrometry (NOEDS) NMR experiments: irradiation of the anomeric proton (H1') in (**2a)** gave a significative NOE effect both on C6 methyl group and H4', characteristic for a β-N^3-nucleoside. The same stereoselectivity in the outcome of the coupling reaction was observed using the 2-methylthio-6-methyl-4(3*H*)-pyrimidinone (**1b)** even if nucleoside (**2b)** was obtained

with lower yields (49%) probably due to the bigger size of the sulfur atom. The configuration of (**2b)** was established through the irradiation of the anomeric proton in a 1D NOE experiment.

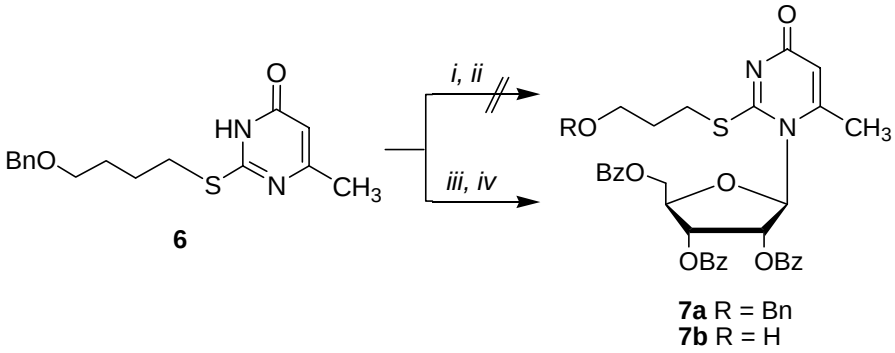
In order to get the desired N_1-6-methyluridine (**4)**, compound (**2b)** was reacted with 3 equivalents of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane followed by aqueous workup obtaining compound (**3)** in 72% yield (Scheme 2). Final deprotection with methanolic ammonia afforded N_1-6-methyluridine (**4)** which chemico-physical properties and NMR data were identical with that of an authentic sample.[6] The methylthio group in C-2 played therefore a key role for the stereoselectivity of the coupling reaction and was moreover an interesting site for further functionalization: reacting in fact compound (**2b)** directly with methanolic ammonia at room temperature for 48 hours, methylthio displacement and sugar deprotection took place at the same time giving the 2-amino-4-methyluridine (**5)** in 68% yield.



Scheme 2. Reagents and conditions: *i*. *m*-CPBA (3 eq.), CH_2Cl_2, r.t.; *ii*. MeOH/NH_3, r.t.; *iii*. MeOH/NH_3, r.t.

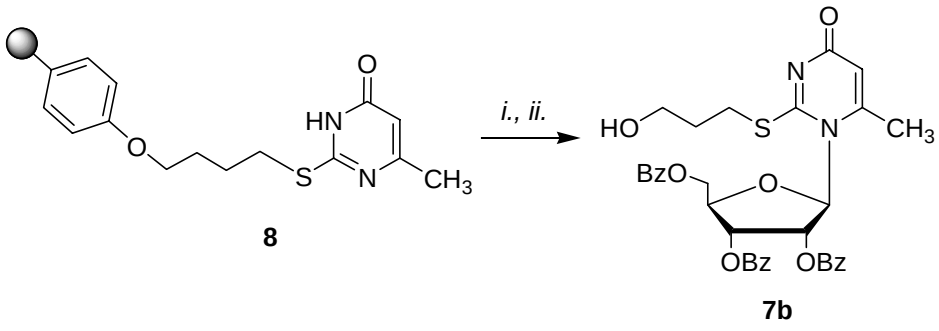
Our interest turned then into the development of additional 2,6-disubstituted nucleosides since, to the best of our knowledge, they represent a new class of unnatural nucleosides which may display interesting biological activity. A further increase in the steric hindrance of the C2 side chain of the nucleobase (compound **6**) did not afford however the expected coupling product (**7a)** following the Vorbrüggen's procedure (Scheme 3). Nevertheless, a modified coupling procedure allowed to obtain the desired compound: one pot silylation with TMSOTf and TMSI catalyzed coupling reaction with ABR let us to

obtain (**7a)** in a 54% yield (using 1 eq. of TMSI) while (**7b)** was obtained in a 30% yield using an excess of TMSI (2 eq.) (Scheme 2).



Scheme 3. Reagents and conditions: *i.* HMDS, $(NH_4)_2SO_4$; *ii*. ABR, TMSOTf, CH_3CN; *iii*. Collidine, TMSOTf, CH_2Cl_2; *iv*. ABR, TMSI (1 eq. for **7a** and 2 eq for **7b**).

As a further extension of our previous work on the solid phase synthesis of pyrimidine nucleosides,[4e] the latter modified coupling procedure was also proved to be an interesting approach for the contemporary coupling with the sugar and releasing of the 2,6-disubstituted nucleoside (**7b)** from the solid support (Scheme 3) since our previously developed Oxone® cleavage methodology was not effective on solid supported 6-substituted nucleosides. The application of the modified Vorbrüggen's procedure using 3 equivalents of TMSI gave, after 72h, the expected nucleoside (**7b)** in a good 42% yield.



Scheme 4. Reagents and conditions: *i*. Collidine, TMSOTf, CH_2Cl_2; *ii*. ABR, TMSI (2 eq).

In conclusion, the present work has initially pointed out the interesting role played by the reduced steric hindrance on the C-2 position of 6-methyluracil derivatives on the outcome of the coupling reaction. The stereoselective formation of nucleosides (**2a,b)** was thus obtained. Subsequent reaction of (**2b)** with *m*-CPBA and final deprotection, afforded N^1-6-methyluridine as single isomer after only three steps starting from (**1b)**. It was moreover observed how, reacting compound (**2b)** with methanolic ammonia for long time, it was possible to obtain both sugar deprotection and methylthio displacement achieving in this way compound (**5)**. Finally, a modified Vorbrüggen's procedure was successfully applied to the

solid-supported nucleobase (**8)** obtaining the contemporary coupling with the sugar and releasing of the 2,6-disubstituted nucleoside (**7b)** from the solid support. Both solution and solid phase approaches could therefore be conveniently employed to obtain further 2,6-disubstituted nucleosides in order to study the antimetabolite properties of this new class of compounds.

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