

Regioselective modification of the sugar moiety in pyrimidine nucleosides via a 4',5'-dehydro-2',3'-anhydrouridine intermediate

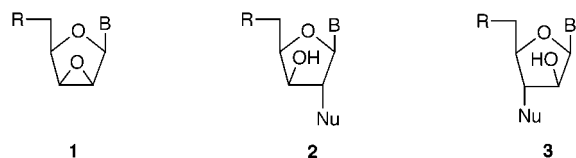
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3'-Substituted pyrimidine nucleoside derivatives are obtained in moderate to high yields by the reaction of 1-(2',3'-anhydro-5'-deoxy-4',5'-didehydro- α -L-erythro-pentofuranosyl)uracil with nucleophiles without the formation of the corresponding 2'-adduct.

Nucleosides modified in the sugar moiety have become important components of both chemotherapeutic agents, as potential antimetabolites,¹ and synthetic oligonucleotide probes.² From a synthetic point of view, it is desirable to develop a common key intermediate. 2',3'-Anhydro- β -D-lyxo-



furanosyl pyrimidine nucleosides **1** first synthesized by Fox *et al.*³ are versatile building blocks, which through a nucleophilic ring-opening reaction can function as precursors of enantiomerically pure and biologically interesting pyrimidine nucleoside derivatives, and a number of reports for the application of **1** have appeared in the literature.⁴ However, it is well known that the nucleophilic addition of **1** gave a mixture of 2'- and 3'-adducts (**2** and **3**) in most cases.

During our studies on the nucleophilic modification of 2',3'-epoxy derivatives **1** and related compounds, we have discovered that the treatment of 2',3'-epoxy-5'-iodouridine **4**^{3c} with MeONa afforded 4',5'-dehydro-5'-deoxy-3'-methoxy derivative **5a** in 96% yield as the sole product (Scheme 1). The possible reaction intermediates, 1-(2',3'-anhydro-5'-deoxy-

4',5'-didehydro- α -L-erythro-pentofuranosyl)uracil **6** and 5'-iodo-3'-methoxy derivative **7**, were prepared. The epoxide **6** reacted regioselectively with MeONa to give the corresponding 3'-adduct **5a** in 80% yield via regioselective nucleophilic attack of the methoxide anion at the highly reactive allylic 3'-position of **6**. On the other hand, only 2',5'-anhydro derivative **8** was accessible from 5'-iodo-3'-methoxy derivative **7** without the formation of **5a** (Scheme 1).

We have now worked out an efficient synthetic method for the epoxide **6**, possessing contiguous enol ether and epoxide moieties in the molecule, which acts as a prominent precursor for a variety of 3'-adducts **5** and that can be incorporated into 3'-modified pyrimidine nucleosides. The synthesis of 2',3'-anhydrouridine **6** was achieved in 92% yield by the reaction of **4** with LiHMDS (2.2 equiv.) in dry DMF (0 °C, 4 h). The efficiency of **6** as the precursor of the modified sugar moiety was demonstrated in the nucleophilic addition using various nucleophiles (Table 1). With the exception of two examples (Table 1, entries 1 and 2), which needed reflux temperatures for the completion of the reaction, all other additions were achieved at room temperature, and the yields of the 3'-adduct **5** were in the range of 52–81%. In the reaction with NaN₃ or PhSH as a comparatively soft nucleophile, 5'-adduct (**9g** or **9h**)⁵ was also formed as a side product (3 or 11% yield) via S_N2' addition⁶ together with a major product, the 3'-adduct (**5g** or **5h**).

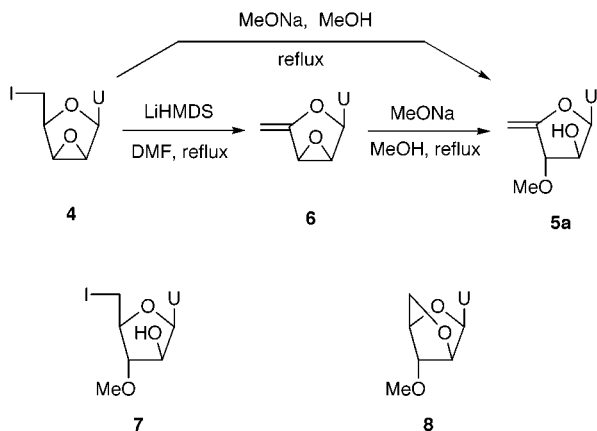
In addition, when Et₂AlCN was used as a nucleophile, isomerized product **11** was obtained in 58% yield due to the activation of 3'-hydrogen of intermediate **10** by the strong electron-withdrawing cyano group (Scheme 2).

Next, we examined the hydroboration reaction of **5a**, aiming to convert it into the 5'-hydroxy derivatives **12** and **13**. When **5a** was refluxed with 18 equiv. of BH₃–THF in dry THF and then subsequently treated with H₂O₂–NaOH, the α -isomer **12** was obtained as the major product (53%) together with the β -isomer

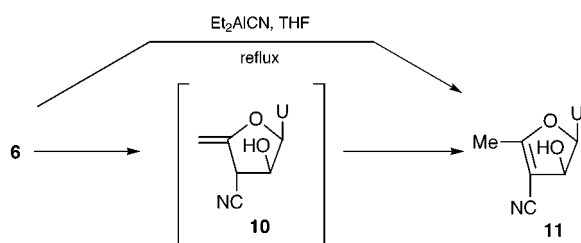
Table 1 Nucleophilic addition to **6**

Entry	Nucleophile	Solvent ^a	t/h	R	Product	Yield (%) ^b	
						5	9
1	MeONa	MeOH ^c	2	OMe	a	80	ND ^d
2	Me ₃ Al	CH ₂ Cl ₂ ^c	12	Me	b	81	ND ^d
3	BnNH ₂	CH ₂ Cl ₂	24	NHBn	c	81	ND ^d
4	NaCH(CO ₂ Me) ₂	MeOH	12	CH(CO ₂ Me) ₂	d	69	ND ^d
5	BzOH ^e	CH ₂ Cl ₂	1	OBz	e	61	ND ^d
6	BzSH ^e	CH ₂ Cl ₂	48	SBz	f	52	ND ^d
7	NaN ₃	DMF	3	N ₃	g	63	3
8	PhSH	Et ₃ N	1	SPh	h	80	11

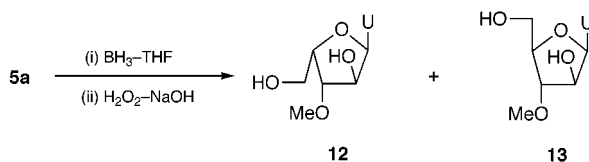
^a Unless otherwise noted, the reactions were carried out at room temperature. ^b Isolated yields after chromatographic separation; all the reaction products were fully characterized by elemental analysis and spectroscopic data. ^c The reactions were carried out under reflux conditions. ^d Not detectable. ^e Reactions were performed in the presence of Et₃N as base.



Scheme 1



Scheme 2



Scheme 3

13 as a minor product (17%) (Scheme 3). This isomer ratio may be interpreted by invoking the steric hindrance effects of the methoxy group at the 3'-position.

In conclusion, we have developed a regioselective method for the synthesis of 3'-substituted pyrimidine nucleoside derivatives **5**, **11**, **12** and **13** using 1-(2',3'-anhydro-5'-deoxy-4',5'-didehydro- α -L-erythro-pentofuranosyl)uracil **6** as a key inter-

mediate without the formation of the corresponding 2'-adduct. The results presented herein provide a novel entry into a variety of sugar-modified pyrimidine nucleosides.

Notes and references

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