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REACTION OF ORGANOMETALLIC REAGENTS WITH 2'- AND 3'-KETOURIDINE DERIVATIVES: SYNTHESIS OF URACIL NUCLEOSIDES BRANCHED AT THE 2'- AND 3'-POSITIONS

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The reaction of organolithium, Grignard, and organoaluminum reagents with 2'- and 3'-ketouridine derivatives was examined. For the reaction of 2',5'-bis-O-(tert-butyldimethylsilyl)-3'-ketouridine, both organolithiums and organoaluminums seem to be practically useful. But only organoaluminums gave satisfactory yields in the reaction of 3',5'-O-(tetraisopropyldisiloxan-1,3-diyl)-2'-ketouridine.

KEYWORDS —— organoaluminum reagent; organolithium reagent; Grignard reagent; ketouridine; branched-chain sugar nucleoside; arabinofuranosyluracil; xylofuranosyluracil

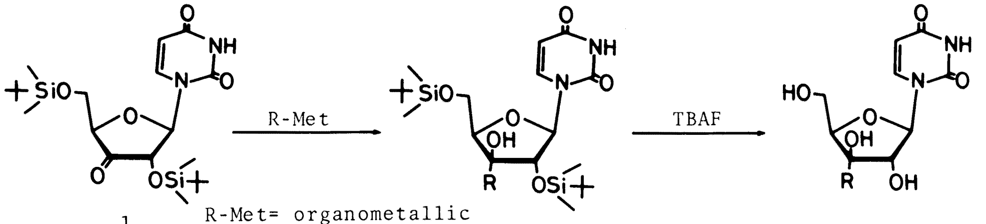
Since the first report[1)] on the synthesis of 2'- and 3'-C-methyladenosines, nucleosides bearing branched-chain sugars have been known to be an important family, not only as biologically active compounds[2,3)] but also for elucidation of enzyme recognition of substrates.[4-6)] Most compounds in this category have been synthesized by the classical condensation method.[1-5)] However, the usefulness of this approach is limited by the number of steps required to prepare the requisite branched-chain sugars. Less frequently these compounds have been prepared from easily accessible naturally-occurring nucleosides.[7)]

One may easily anticipate that the reaction of organometallic reagents with ketonucleosides would constitute a simple and straightforward entry to these compounds. However, Cook and Moffatt reported that an attempt to treat 2',5'-di-O-trityl-3'-ketouridine with either methyl Grignards or methyllithium under various conditions did not give any alkylation product. Only borohydride reduction was successful.[8)] Since then, no investigation has dealt with such an approach to branched-chain sugar nucleosides, to the best of our knowledge.[9)]

As part of our continuing work on the use of organometallics for the modification of nucleosides,[10)] we thought that the reported reactions of 3'-ketouridine should be reinvestigated by changing the protecting group in the sugar moiety, since organometallics such as Grignard reagents and alkyllithiums can be regarded as Lewis acids.[11)]

With the success of the tert-butyldimethylsilyl (TBDMS) protecting group in our lithiation studies, 2',5'-bis-O-TBDMS-3'-ketouridine (1)[12)] was selected as a starting material in the present study.

When 1 was treated with 3 eq of MeLi in THF for 3 h at below –70°C, the expected alkylation product (2) was obtained in 79% yield after quenching with AcOH followed by chromatographic purification through a Florisil® column (benzene:EtOAc = 10:1). Though similar treatment of 1 with PhLi gave a comparable yield (Table I, entry 2), the use of BuLi significantly decreased the yield (entry 3), giving several decomposition products.[13] This could be rationalized in terms of a higher basicity of BuLi which would alter the reaction course in favour of elimination.



1 R-Met= organometallic reagent

2 R= Me, 3 R= Ph,
4 R= Bu, 5 R= Et,
6 R= C≡CPh

7 R= Me, 8 R= Ph,
9 R= Bu, 10 R= Et,
11 R= C≡CPh

Chart 1

Table I. Synthesis of 3'-C-Substituted 2',5'-bis-O-TBDMS Xylofuranosyluracils

Entry	Organometallic reagent	R	Product	Yield(%)
1	MeLi	Me	2	79
2	PhLi	Ph	3	72
3	BuLi	Bu	4	33
4	MeMgBr	Me	2	37
5	EtMgBr	Et	5	24
6	PhMgBr	Ph	3	30
7	Me_3Al	Me	2	64
8	Ph_3Al	Ph	8	26*
9	$PhC≡CAlEt_2$	C≡CPh	6	58

* Overall yield of 8 from 1.

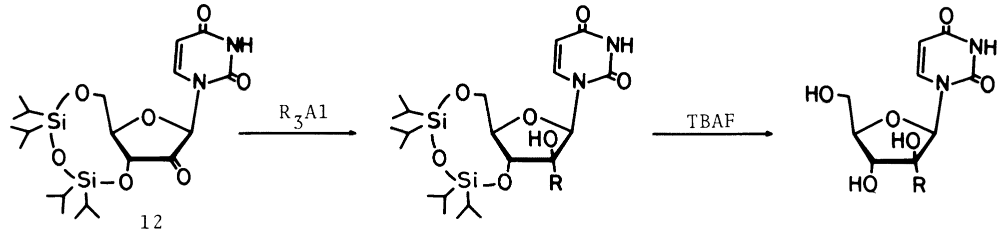
On the other hand, when Grignard reagents (3 eq) were used in the above reaction, hardly any decomposed products were formed. But as can be seen from Table I (entries 4, 5, and 6), the yields of products (2, 3, and 5) were uniformly low.[14]

The reaction of 1 with organoaluminum reagents was examined next using CH_2Cl_2 as a solvent. Though 1 was not susceptible to the reaction of Me_3Al (3 eq) at below –70°C, the expected carbalumination was achieved by conducting the reaction at room temperature, producing 2 in good yield (entry 7). Ph_3Al and $PhC≡CAlEt_2$ also worked to effect carbalumination of 1 (entries 8 and 9). It should be noted that even when these reactions were conducted at refluxing temperature, essentially no decomposition took place, showing the highly oxygenophilic character of organoaluminum reagents.

The products 2-6 obtained in the above reaction were deprotected in THF with tetrabutylammonium fluoride (TBAF) to give the corresponding free 3'-C-substituted xylofuranosyluracils (7-11) in high yields.

Application of this approach to the synthesis of 2'-C-substituted arabinofuranosyluracils was then investigated using the organometallics listed in Table I and 3',5'-O-(tetraisopropyldisiloxan-1,3-diyl)-2'-ketouridine (12).15)

As was expected from the reported instability of 2'-ketouridine,8) both the organolithium and the Grignard reagents were practically inefficient, giving a complex mixture of products. Especially in the reactions of organolithium reagents, instantaneous precipitation occurred upon addition of the reagent to a THF solution of 12 (below −70°C).



12

Chart 2

13 R= Me
14 R= C≡CPh
15 R= Ph

16 R= Ph
17 R= Me
18 R= C≡CPh

In contrast, the use of organoaluminum reagents again gave satisfactory results. Thus, when 12 was treated with 3 eq of Me_3Al in CH_2Cl_2 at room temperature for 1 h, the corresponding 2'-C-methylated product (13) was obtained in 98% yield. A similar reaction with $PhC\equiv CAlEt_2$ gave a 79% yield of 14. With Ph_3Al, the initially formed 15 could not be isolated in pure form, but deprotection with TBAF gave 2'-C-phenyl arabinofuranosyluracil (16) in 30% overall yield from 12. Compounds 13 and 14 were also treated with TBAF to furnish 17 and 18, respectively, in high yields.

Finally, the stereochemical reaction course of all of the organometallics involved in the present study was assumed to be alpha in corroboration with the X-ray crystallographic analysis of 16,16) the result of which is depicted in Fig. 1.

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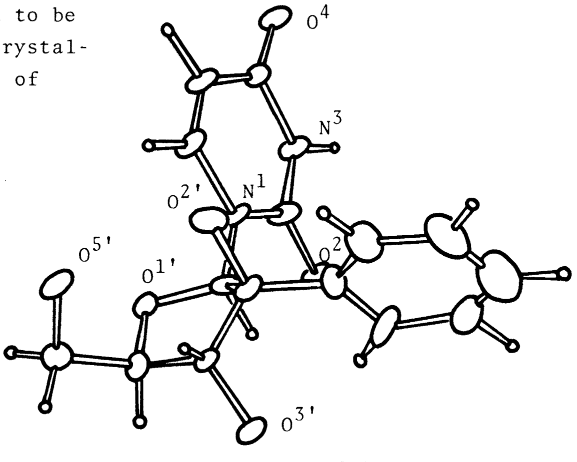

Fig. 1. Molecular Structure of 2'-C-Phenyl Arabinofuranosyluracil (16)17)

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13) Formation of uracil was confirmed by ^{1}H-NMR and MS spectroscopy.

14) When these reactions were carried out at room temperature, a complex mixture of products resulted, most of the starting material being consumed.

15) Preparation and a Wittig reaction of **12** have been reported: T. Ueda, S. Shuto, M. Sato, and H. Inoue, *Nucleosides and Nucleotides*, **4**, 401 (1985).

16) The observed crystal data of **16** are as follows: molecular formula $C_{15}H_{16}N_2O_6$; molecular weight 320, space group $P3_2$, Z= 3, a= 13.722, b= 13.722, c= 7.030 Å. The final R value was 0.11 including anisotropic thermal parameters for non-hydrogen atoms.

17) Hydrogens are located on the calculated positions.

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