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DYNAMIC ASPECTS IN THE LDA LITHIATION OF AN ARABINOFURANOSYL DERIVATIVE OF 4-ETHOXY-2-PYRIMIDINONE: REGIOSELECTIVE ENTRY TO BOTH C-5 AND C-6 SUBSTITUTIONS

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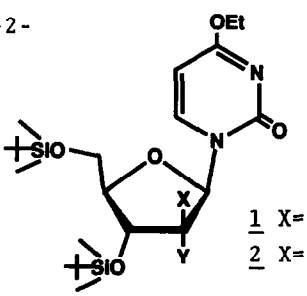
Summary Regioselectivity (C-5 vs. C-6) in the LDA lithiation of 1-[2,3,5-tris-O-(tert-butyldimethylsilyl)-β-D-arabinofuranosyl]-4-ethoxy-2-pyrimidinone can be controlled simply by changing the reaction conditions, providing a route to both the 5- and 6-substituted derivatives.

Lithiation chemistry has now been widely recognized to be a method of choice to construct multi-functionalized aromatic compounds, since its regiochemical outcome can be anticipated with some degree of certainty by considering directing ability of substituents.[1] Our lithiation studies of uridine derivatives proved that LDA (lithium diisopropylamide), which is known to act through an "acid-base mechanism,"[2] was a highly effective reagent to deprotonate the more acidic H-6 specifically.[3] In consequence, this approach furnished a simple method for synthesizing a variety of 6-substituted uridines.[4]

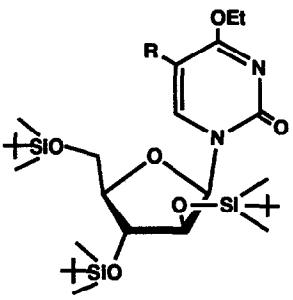
We thought this methodology should allow a ready access to otherwise unavailable analogues of 1-β-D-arabinofuranosylcytosine (Ara-C), their 6-substituted derivatives. However, when the sugar hydroxyls of Ara-C were protected with tert-butyldimethylsilyl (TBDMS) group and subjected to the lithiation with LDA in THF at −80°C, no lithiation could be observed after deuteration.[5-7] We therefore turned to the use of 4-ethoxy-2-pyrimidinone derivative 1 as a starting material, for it can readily be transformed to the cytosine derivative upon ammonolysis. In the present communication, we describe on dynamic aspects of the LDA lithiation of 1, where both regioselective C-5 and C-6 metallations can be accomplished simply by changing the reaction conditions.



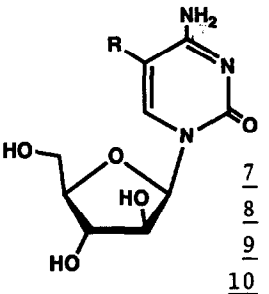
1 X= OTBDMS, Y= H
2 X= H, Y= OTBDMS

When 1 was treated with 1 equiv of LDA in THF at −80°C for 5 min and then quenched with MeOD, a 24% of D-incorporation to the C-5 position was observed without any detectable incorporation to the desired C-6 position. Use of 4 equiv of the reagent increased the extent of C-5 deuteration to 90% (recovery: 91%). The lithiation of ribofuranosyl counterpart 2 (1 equiv of LDA, at −80°C for 5 min), on the other hand, took place regiospecifically at the C-6 position (54%).[8] These results indicate that spatial shielding exerted by the "2'-up" substituent would be an important determinant of the above regiochemistry of 1.

The C-5 lithiated species prepared from 1 and 4 equiv of LDA was reacted with electrophiles such as MeI, HCO_2Et, PhCOCl, and Et_2NCOCl. Yields of the



3 R= Me (82%)
4 R= CHO (60%)
5 R= COPh (71%)
6 R= $CONEt_2$ (45%)



7 R= Me
8 R= CHO
9 R= COPh
10 R= $CONEt_2$

products (3-6) are shown in parentheses. Deprotection followed by ammonolysis gave the corresponding 5-substituted Ara-C (7-10).[9]

During the preparation of 3-6, when the reaction temperature had not been kept below −70°C, a small amount of the 6-substituted product often accompanied. This led us to re-examine the LDA lithiation of 1 more precisely by changing reaction temperature and by following time-course. The results obtained by using 4 equiv of LDA are shown in Fig. 1 and 2 by D-incorporation. As can be

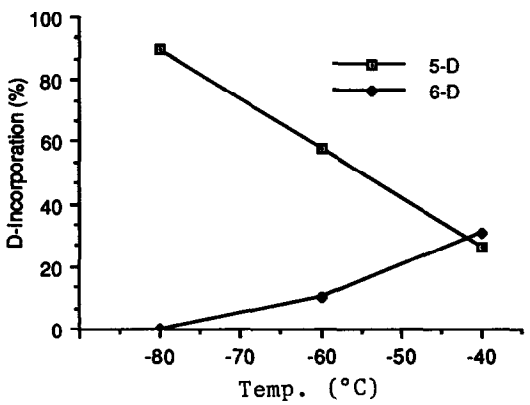


Fig. 1 Effect of reaction temperature on the regioselectivity in LDA (4 equiv) lithiation of 1 (for 5 min).

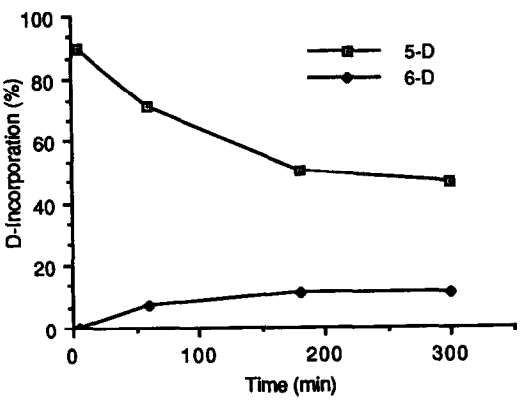


Fig. 2 Time-course of the regioselectivity in LDA (4 equiv) lithiation of 1 (at −80°C).

seen from these results, on raising the temperature and with the elapse of time, the C-6 lithiation became an observable event at the expense of the C-5 lithiation level. Thus, it can be assumed that deprotonation at the C-5 position of 1 would be a kinetically-controlled process while the reaction at the C-6 position would be thermodynamically favoured.

To accomplish the initially-intended synthesis of the 6-substituted derivatives, attempts were made for regiospecific C-6 lithiation. "Catalyzed metallation" known to encourage thermodynamic deprotonation[10] failed in the present system. That is, when 1 was treated with 4 equiv of MeLi in the presence of 0.07 equiv of diisopropylamine (at −80°C for 5 min), both the C-6 and C-5 posi-

tions were deuterated to almost equal extents (ca. 15%). Moreover, a by-product isolated in 16% yield appeared to be one resulted from nucleophilic addition of the MeLi across the 5,6-double bond.

We finally found that, simply by using 1 equiv of LDA at an elevated temperature of −40°C, the C-6 position could be lithiated to a considerable extent without concomitant metallation at the C-5 position (Fig. 3). It should be

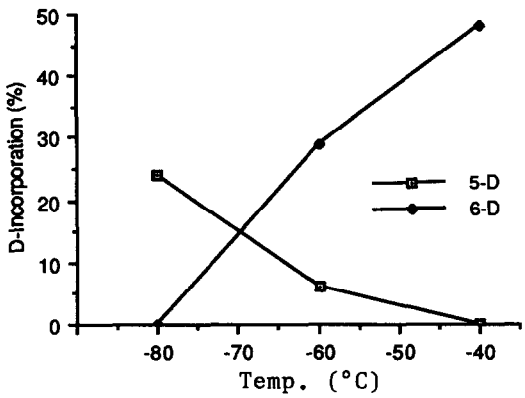


Fig. 3 Effect of reaction temperature on the regioselectivity in LDA (1 equiv) lithiation of 1 (for 5 min).

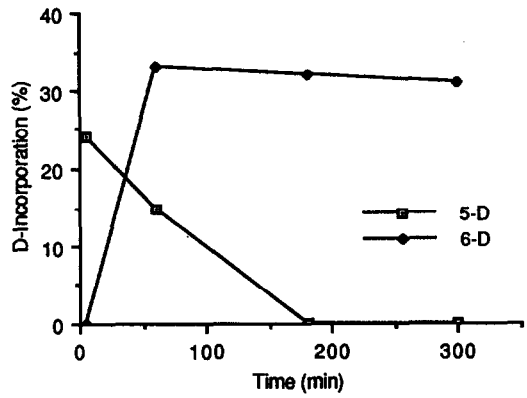
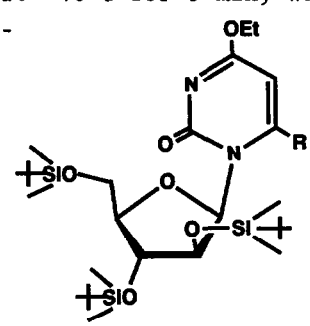


Fig. 4 Time-course of the regioselectivity in LDA (1 equiv) lithiation of 1 (at −80°C).

noted that, in contrast to the results given in Fig. 2, the use of stoichiometrical amount of LDA encouraged a substantial shift from the C-5 to the C-6 lithiation even at −80°C (Fig. 4). Though the absence of excess LDA is certainly disadvantageous for the more basic C-5 lithiated species to survive, it is not clear if the dominant formation of the C-6 lithiated species is simply ascribable to its less basic nature. The C-6 lithiated species prepared under optimum conditions (1 equiv of LDA, at −40°C for 5 min) was reacted with MeI, HCO_2Me, PhCOCl, and Et_2NCOCl, respectively. Non-carbon electrophiles, $(PhS)_2$ and iodine, were also used. The corresponding 6-substituted products (11-15) were obtained in a moderate yield as shown in parentheses.[11] In the case of Et_2NCOCl, the starting material (1) was recovered quantitatively, presumably due to the less nucleophilic character of the lithiated species than that of its C-5 counterpart.



11 R= Me (46%)
12 R= CHO (52%)
13 R= COPh (52%)
14 R= SPh (52%)
15 R= I (45%)

In conclusion, the present study has revealed that 5- or 6-substituted arabinofuranosyl pyrimidine nucleosides can be synthesized separately using a common starting material (1), simply by changing the reaction temperature and the amount of LDA. Although there have been several reports dealing with dynamic aspects of metallation and some have employed them for synthetic purpose,

we are not aware of any example of their successful control without changing the reagent[12] or the polarity of medium.[13]

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5) Lithiation of cytidine derivatives with butyllithium was reported, but no detailed description has been available: L. Pichat, J.-P. Gilbert, and M. H. Normant, C. R. Acad. Sci. Paris Ser. C, 277, 115 (1973).
6) In the present study, lithiation levels were determined based on ^{1}H-NMR spectroscopy after deuteration of lithiated species by MeOD.
7) When N^4-benzoyl-1-(2,3,5-tris-O-TBDMS-β-D-arabinofuranosyl)cytosine was lithiated with 5 equiv of LDA, both the C-5 and C-6 positions were metallated (ca. 5%).
8) When 1-(2,3,5-tris-O-TBDMS-β-D-arabinofuranosyl)uracil was lithiated with 5 equiv of LDA under similar conditions, no metallation could be observed. This clearly indicates that LDA is not basic enough to deprotonate H-5 of uracil ring.
9) The ammonolysis was carried out with NH_3/MeOH in a sealed tube. The reaction temperature and time required were found to be dependent on the electronic nature of each C-5 substituent (e.g. 7: 100°C for 48 h; 9: 50°C for 13 h).
10) For an example: F. Trecourt, M. Mallet, F. Marsais, and G. Queguiner, J. Org. Chem., 53, 1367 (1988).
11) The yield of 11 was determined based on ^{1}H-NMR spectroscopy, for this compound could not be separated from 1.
12) H. O. House, M. Gall, and H. D. Olmstead, J. Org. Chem., 36, 2361 (1971); A. K. Beck, M. S. Hoejstra, and D. Seebach, Tetrahedron Lett., 1187 (1977); E. J. Corey and A. W. Gross, ibid., 25, 495 (1984).
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