CHEMISTRY LETTERS, pp. 1401-1404, 1985.

REGIOSELECTIVITY IN THE LITHIATION OF URIDINE. EFFECT OF THE SUGAR PROTECTING GROUPS

Hiroyuki HAYAKAWA, Hiromichi TANAKA, Yuko MARUYAMA, and Tadashi MIYASAKA*
School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142

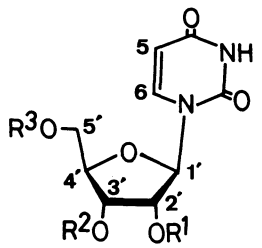
Efficiency and regioselectivity in the lithiation of uridine derivatives with lithium dialkylamides are dramatically affected by the protecting groups in their sugar moiety, results suggesting that the metallation proceeds through their syn-conformers.

We have been studying on the utilization of lithiation for synthetic purpose in nucleoside field.[1-4] The regiospecific lithiation at the C-6 position of uridine was accomplished by treating 2',3'-O-isopropylidene-5'-O-methoxymethyl-uridine (1) with LDA (lithium diisopropylamide).[1] Though this offers a general method for the preparation of 6-substituted uridines of various types,[5] which have so far been known to be difficult to synthesize, factors governing the regiospecificity are unknown.

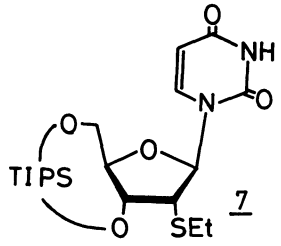
In this communication, we would like to report results of our recent work which has been undertaken to elucidate the mechanism of the lithiation of uridine derivatives with lithium dialkylamides.

In Table 1 are presented the results of lithiation with LDA followed by deuteration. We initially assumed that the extent of the lithiation of 1 with LDA (Run 1) would be affected by changing the 5'-O-protecting group (R^3), since uridine is known to exist in anti-conformation in solution[6] and since protection with 2', 3'-O-isopropylidene group allows the 5'-position to approach the C-6 as reported in the case of hydroxymethylation of uridine derivatives.[7]

However, replacement of the methoxymethyl group in 1 by a bulky silyl group, TBDMS (tert-butyldimethylsilyl), did not give any difference both in terms of efficiency and regioselectivity (Run 2). Use of the cyclohexylidene derivative (3) gave essentially the same result within experimental error (Run 3). On the other hand, when all the three hydroxyl groups were protected with TBDMS, neither the C-6 nor the C-5 was lithiated (Run 4). The situation was similar when TIPS (1,1,3,3-tetraisopropyldisiloxan-1,3-diyl) group[8] was used for the simultaneous protection of 3'- and 5'-hydroxyl groups, except the result of Run 5 where the C-6 lithiation was observed in an appreciable extent.



Compd.	Protecting group
1	R^1=R^2= 2',3'-O-isopropylidene, R^3= methoxymethyl
2	R^1=R^2= 2',3'-O-isopropylidene, R^3= TBDMS
3	R^1=R^2= 2',3'-O-cyclohexylidene, R^3= TBDMS
4	R^1=R^2=R^3= TBDMS
5	R^1= TBDMS, R^2=R^3= 3',5'-O-TIPS
6	R^1= H, R^2=R^3= 3',5'-O-TIPS



7

Table 1. Deuterium incorporation(%)[a] upon treatment with LDA[b]

Run	Compd.	C-5	C-6
1	1	0	87
2	2	0	87
3	3	0	85
4	4	0	0
5	5	0	9
6[c]	6	0	0
7	7	0	0

Table 2. Deuterium incorporation(%)[a] upon treatment with LTMP[b]

Run	Compd.	C-5	C-6
8	1	9	80
9	2	10	64
10	3	12	69
11	4	26	0
12	5	27	38
13[c]	6	8	0
14[d]	6	35	0
15	7	30	0

a) Deuterium incorporation was analyzed by ^{1}H-NMR spectroscopy using H-1' as a standard.
b) Reactions were performed in THF at below -70 °C for 1 h with 3 equiv. of LDA or LTMP and then quenched with CD_3OD. In all cases, recoveries after silica gel column chromatography were more than 90%.
c) 4 Equiv. of LDA or LTMP was used.
d) 10 Equiv. of LTMP was used.

These observations can be interpreted only when the initially formed N(3)-lithiated species is assumed to exist in the syn-conformation, which is fixed by intramolecular chelation as depicted in Chart 1. On the basis of this assumption, approach of the lithiating agent to the C-6 position may be interfered by a C-2' substituent which rotates about the C(2')-O bond. The results of Runs 4-7 may be a reflection of such steric hindrance imposed by the C-2' substituents.[9] In the cases of Runs 1-3, free rotation about C(2')-O bond is impossible. As lithium dialkylamides are thought to act through an "acid-base" mechanism,[10] the available data in Table 1 indicate that LDA is not basic enough to deprotonate the less acidic H-5.[11]

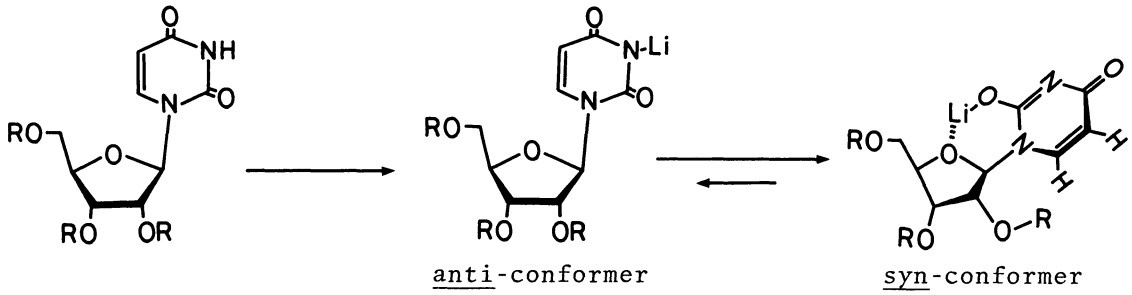
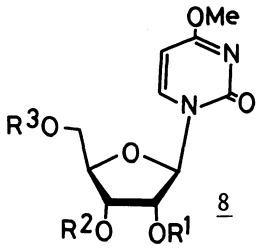


Chart 1.

The above considerations led us to examine the efficiency and regioselectivity of these reactions with a more basic lithium dialkylamide, LTMP (lithium 2,2,6,6-tetramethylpiperidide).[12] That is, in case where the C-6 position is sterically blocked, the regiospecific C-5 metallation could be achieved by the use of LTMP.

The results of lithiation with LTMP are summarized in Table 2. As expected, regiospecific lithiation of the C-5 positions was observed for the compounds having free rotational C-2' substituents (Runs 11, 13, 14, and 15). Only one exception is Run 12. At present time, we do not have a satisfactory explanation for the decrease of regioselectivity in Run 12 but it is certainly consistent with the result of Run 5 (Table 1). The results of Runs8-10 in which C-6 lithiation was predominant are also in accord with our assumption. Although Pichat and co-workers[13] proposed the presence of 5,6-dilithiated species of uridine in halogen-lithium exchange reaction, we could not detect the formation of such species throughout these reactions.[14]

Finally, the mechanism proposed herein would be further corroborated by the following fact. When 4-methoxy-1-(2,3,5-tris-O-TBDMS)-β-D-ribofuranosyl pyrimidin-2-one (8: $R^1=R^2=R^3=$ TBDMS), which has no imino hydrogen in its base moiety, was treated with LDA, the C-6 lithiated species was generated to the extent of 71%.



8

While lithiation has been used extensively as an important tool in organic synthesis, little is known on its mechanistic aspect. Our work described above demonstrates that lithiation of uridine derivatives proceeds through their syn-conformers and that, in principle, direct and regiospecific generation of the C-5 anion is possible by changing the protecting group in sugar moiety.[15]

References

1) H. Tanaka, H. Hayakawa, and T. Miyasaka, Tetrahedron, 38, 2635 (1982).

2) H. Tanaka, Y. Uchida, M. Shinozaki, H. Hayakawa, A. Matsuda, and T. Miyasaka, Chem. Pharm. Bull., 31, 787 (1983).
3) H. Hayakawa, H. Tanaka, and T. Miyasaka, Tetrahedron, 41, 1675 (1985).
4) H. Tanaka, M. Hirayama, A. Matsuda, T. Miyasaka, and T. Ueda, Chem. Lett., 1985, 589.
5) An application of our method has been reported: H. Ikehira, T. Matsuura, and I. Saito, Tetrahedron Lett., 25, 3325 (1984).
6) For example: M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, J. Am. Chem. Soc., 95, 3770 (1973).
7) D. V. Santi and C. F. Brewer, J. Am. Chem. Soc., 90, 6236 (1968) and references cited therein.
8) W. T. Markiewicz, J. Chem. Res. (M), 1979, 181.
9) Anionic repulsion between the C-2' alkoxide and the lithiating agent may be responsible in the reactions of compound 6.
10) H. W. Gschwend and H. R. Rodriguez, "Organic Reactions," ed by W. G. Dauben, John Wiley and Sons, Inc., New York, Chichester, Brisbane, and Toronto (1979), Vol. 26, pp. 1-360.
11) The mechanism of H-6 exchange in pyrimidine nucleosides is thought to involve the direct abstraction by base: J. A. Rabi and J. J. Fox, J. Am. Chem. Soc., 95, 1628 (1973).
12) LTMP is reported to be 1.6 pK units more basic than LDA: R. R. Fraser, A. Baignée, M. Bresse, and K. Hata, Tetrahedron Lett., 23, 4195 (1982).
13) L. Pichat, B. Massé, J. Deschamps, and P. Dufay, Bull. Soc. Chim. Fr., 1971, 2102.
14) An example of ortho-dilithiated species: U. D. G. Prabhu, K. C. Eapen, and C. Tamborski, J. Org. Chem., 49, 2792 (1984).
15) Recently, TBDMS group has been used in lithiation reaction to inhibit the directive effect of an oxygen substituent: B. M. Trost and M. G. Saulnier, Tetrahedron Lett., 26, 123 (1985).

(Received June 27, 1985)