Communications to the Editor

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A NOVEL AND REGIOSPECIFIC ROUTE TO 5-ACYLURIDINES VIA AN AMIDE α-ANION DERIVED FROM 5,6-DIHYDROURIDINE

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Upon lithiation with LDA, 2',3'-O-isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine has been shown to serve as an "amide α-anion". Thus, acylation of the resulting dianion took place regiospecifically at the C-5 position. The subsequent phenylselenenylation and oxidative elimination afforded 5-acyluridines.

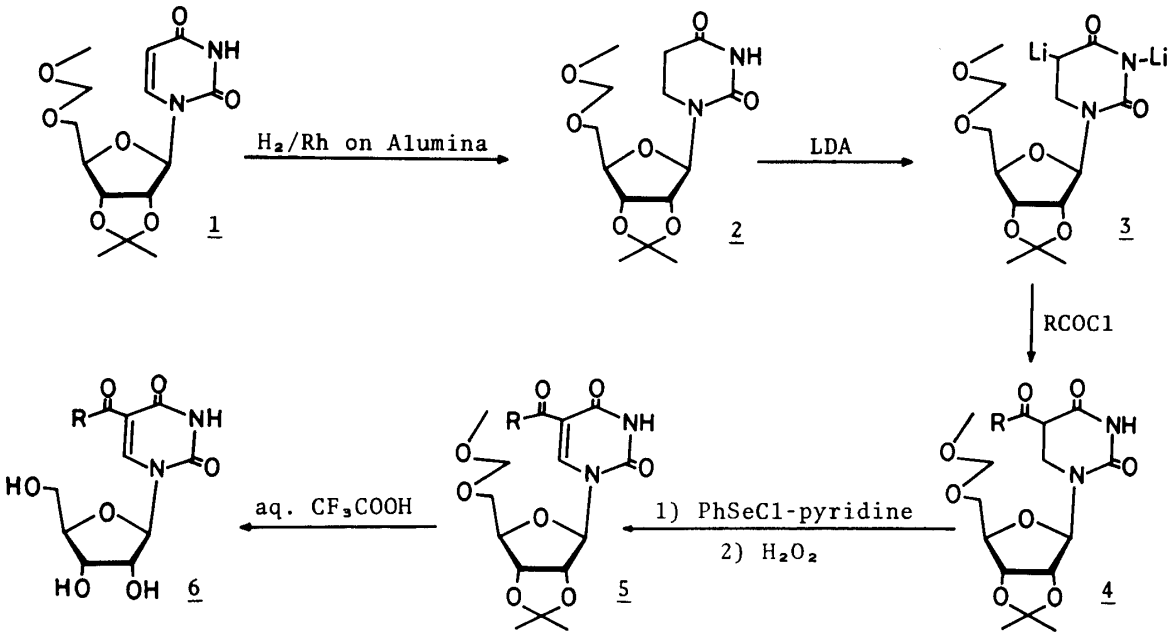
KEYWORDS—— amide α-anion; phenylselenenylation; oxidative elimination; uridine derivatives; 5-acyluridines; lithiation; 5,6-dihydrouridine derivative

Lithiation of organic molecules has come to be recognized as an important tool for carbon-carbon bond forming reactions. In the field of nucleoside chemistry, however, lithiation has been used less frequently. This may be related to the fact that the published results[1] are not very practical from the preparative standpoint.

In the course of our studies on the lithiation of uridine derivatives,[2] we found that the metalation of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1) with LDA takes place at the C-6 position in an essentially regiospecific manner. We have already reported the usefulness of this method for the general synthesis of 6-substituted uridines.[3] In this communication, we wish to demonstrate another successful example of lithiation of a 5,6-dihydrouridine derivative which permits regiospecific synthesis of 5-acyluridines.

Because butyllithium is thought to act by a "coordination mechanism",[4] we initially considered that the direct metalation of 1 with this reagent could lead to the preferential formation of the C-5 lithiated species. Compound 1 was treated with 2.5 eq of butyllithium in THF below -70°C. After quenching with CD_3OD, the PMR spectrum of the product showed that the deuterium incorporation occurred with a preference of about 2:1 for the C-6 position. Although this is quite interesting as compared with the result reported by Pichat and co-workers in the case of tris-trimethylsilyluridine,[1] lack of the desired regioselectivity in the above reaction prompted us to devise another route. Our next study, which is the subject of the present communication, was concerned with the lithiation of a 5,6-dihydrouridine derivative which lacks the 5,6-double bond, thereby possibly facilitating the selective generation of the C-5 anion.

Scheme



RCO: a) Benzoyl, b) Propionyl, c) Isobutyryl,
d) Pivaloyl, e) Ethoxycarbonyl.

Table I

	RCOX	Yields (%) of products 4	5	6	Partial PMR data (D_2O,DSS,δ) of 6 H-1'	H-6	R
a	PhCOCl	79.6	89.7	84.3	5.93	8.52	Phenyl 7.45∿7.79
b	CH_3CH_2COCl	72.3	82.7	83.0	5.91	8.88	CH_3 1.06 CH_2 2.93
c	$(CH_3)_2CHCOCl$	80.0	88.0	90.6	5.92	8.86	CH_3 1.09 CH 3.43∿3.71
d	$(CH_3)_3CCOCl$	94.4	64.4*	82.3	5.91	8.22	CH_3 1.22
e	CH_3CH_2OCOCl	80.5	99.2	93.4	5.91	9.00	CH_3 1.31 CH_2 4.27

* requires heating during phenylselenenylation.

Catalytic hydrogenation (5% Rh on alumina) of 1 in MeOH gave 2',3'-O-isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (2; M^+ m/z: 330; H-1' δ: 5.71 doublet) in nearly quantitative yield. When 2 in THF was treated with 2.5 eq of LDA below -70°C, a clear solution of 3 resulted. Subsequent addition of benzoyl chloride (2.0 eq, below -70°C, 1 h) to the anion solution furnished 5-benzoyl-5,6-dihydrouridine derivative 4a as an epimeric mixture (M^+ m/z: 434; H-1' δ: 5.69 and 5.93, each as a doublet) in 79.6% yield after column chromatography on silica gel (1% EtOH in $CHCl_3$). As shown in Table I, other acylating agents, including ethyl chloroformate, work equally well to afford 4b~e.[5] The available experimental evidence indicates that, if the 5,6-double bond could be regenerated, an "amide α-anion" of 2 would be a highly effective candidate for the synthesis of C-5 substituted uridines. With this objective, we utilized some recent advances in the preparation of unsaturated β-dicarbonyl compounds,[6] namely phenylselenenylation of 4 and successive oxidative elimination.

The phenylselenenylation of 4a was carried out in the presence of 1.1 eq of PhSeCl-pyridine complex in CH_2Cl_2 (0°C→ room temperature, overnight). After removal of the pyridine, the mixture was allowed to react with 30% H_2O_2 in CH_2Cl_2 (0°C, 2 h) without isolation of the intermediate selenide. Chromatographic purification through a silica gel column (1% EtOH in $CHCl_3$) gave 5a (M+1 m/z: 433) in 89.7% yield. The PMR spectrum of 5a (H-1' δ: 6.04 doublet) exhibited a sharp singlet at δ 8.39 corresponding to its H-6, providing evidence of regeneration of the 5,6-double bond having occurred. Similarly, 4b~e gave the corresponding protected 5-acyluridines (5b~e)[7] in high yields. Although the reaction of 4 with PhSeCl/pyridine was relatively slow, it is worth noting that the β-dicarbonyl compounds bearing an amide or imide group were able to function as a suitable substrate in the above transformation (4→ 5).

In the final step of our sequence, concurrent deprotection of the isopropylidene and methoxymethyl groups in 5 was performed in 50% aqueous trifluoroacetic acid, giving rise to the unprotected 5-acyluridines (6a~e)[8,9] in high yields.

The synthetic route described herein has disclosed a new anion chemistry in the nucleoside field. This can certainly be applied to the synthesis of a wider range of 5-substituted uridines. We are currently evaluating its scope and limitation.

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5) All the 5-acyl-5,6-dihydrouridine derivatives (4a∿e) were obtained as sirup and gave physical data consistent with their structures.

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7) All the protected 5-acyluridines (5a∿e) were obtained as sirup and gave physical data consistent with their structures.

8) Typical examples for synthesizing 5-acyluridines and their 2'-deoxy analogues are given below: a) A. Holý, Collect. Czech. Chem. Commun., 37, 1555 (1972); b) N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg, and G. Shaw, J. Chem. Soc. Perkin I, 1973, 1720; c) A. Kampf, C. J. Pillar, W. J. Woodford, and M. P. Mertes, J. Med. Chem., 19, 909 (1976); d) V. Armstrong, H. Sternbach, and F. Eckstein, "Methods in Enzymology," Vol. 46, ed. by W. B. Jakoby and M. Wilcheck, Academic Press, New York, San Fransisco, and London, 1977, pp. 346∿352; e) H. Inoue, M. Takada, M. Takahashi, and T. Ueda, Heterocycles, 8, 427 (1977); f) P. J. Barr, P. Chananont, T. A. Hamor, A. S. Jones, M. K. O'Leary, and R. T. Walker, Tetrahedron, 36, 1269 (1980).

9) All the 5-acyluridines (6a∿e) were obtained as crystals and gave physical data consistent with their structures. Melting points of 6a∿e are given below: 6a mp 210∿211°C; 6b mp 180∿181°C (Lit.[8e] mp 186∿187°C); 6c mp 168∿169°C; 6d mp 129∿130°C; 6e mp 205∿206°C (Lit.[8a] mp 199∿201°C).

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