ORGANIC LETTERS

2004
Vol. 6, No. 11
1793−1795

Lithiation at the 6-Position of Uridine with Lithium Hexamethyldisilazide: Crucial Role of Temporary Silylation

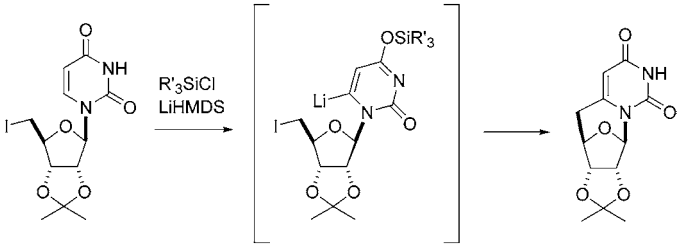
Yuichi Yoshimura,*,† Hiroki Kumamoto,‡ Ayuka Baba,‡ Shingo Takeda,‡ and Hiromichi Tanaka‡

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-Ku, Sendai, 981-8558, Japan, and School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

yoshimura@tohoku-pharm.ac.jp

Received March 17, 2004

ABSTRACT



Lithium hexamethyldisilazide (LiHMDS) can mediate silylation at the 6-position of uridine, although LiHMDS alone is not able to generate the C-6-lithiated uridine. Experimental results showed that temporary silylation of O-4 (or N-3) of the uracil ring triggers the C-6 lithiation with LiHMDS. This finding allowed us to develop an efficient intramolecular alkylation of 5′-deoxy-5′-iodouridine to furnish 6,5′-*C*-cyclouridine.

LiHMDS is an amide base that is widely used in organic synthesis. Although the usefulness of LiHMDS is ascribed to its stability and low sensitivity to air, its major drawback is its weaker basicity (pK_a 29.5 in THF) in comparison to LDA (pK_a 35.7 in THF).[1] LDA abstracts the H-6 proton of uridine and generates the C-6 lithio derivative, which serves as a versatile synthetic intermediate for various types of 6-substituted uridines.[2] Replacement of LDA with LiHMDS did not give any products resulting from C-6 lithiation. This is consistent with a recent report regarding the acidity of the H-6 of 1,3-dimethyluracil, the pK_a value of which is estimated as 34.[3]

One curious experimental result is the fact that treatment of compound **1** with LiHMDS in the presence of Me_3SiCl gave 6-trimethylsilyluridine **2** in good yield[4] (data not shown). Use of other electrophiles (e.g., Bu_3SnCl) in this reaction gave none of the 6-substituted product. Also, it was confirmed that quenching of LiHMDS-treated **1** with CD_3-OD did not give any trace of the C-6-deuterated derivative **4** as evidenced by ^{1}H NMR spectroscopy (Scheme 1).

These results show that LiHMDS alone cannot lithiate the C-6-position of **1** and that only in the presence of an appropriate silylating agent is LiHMDS able to effect the C-6-lithiation. In this paper, we report several experimental results that suggest that the silylating agent plays a crucial role through masking the acidic N-3−H in the C-6-lithiation with LiHMDS.

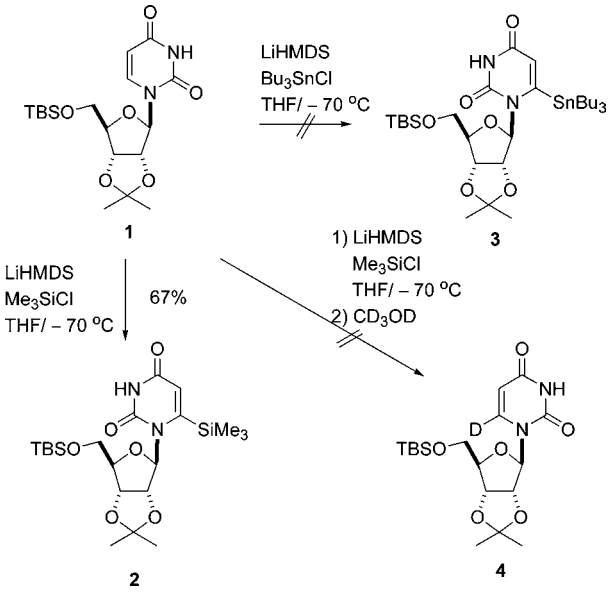
We hypothesized the reaction mechanism shown in Scheme 2. In the reaction involving LiHMDS and the silylating agent, the O-4 of the uracil moiety would temporarily be silylated. The H-6 of the silylated intermediate must be much more acidic than that of the starting uracil

† Tohoku Pharmaceutical University.
‡ Showa University.

(1) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 3127−3229.
(2) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635−2642.
(3) Sievers, A.; Wolfenden, R. *J. Am. Chem. Soc.* **2002**, *124*, 13986−13987.
(4) Ogamino, J.; Kumamoto, H.; Mizunuma, H.; Takeda, S.; Tanaka, H. *Nucleic Acids Res., Supplement 1* **2001**, 3−4.

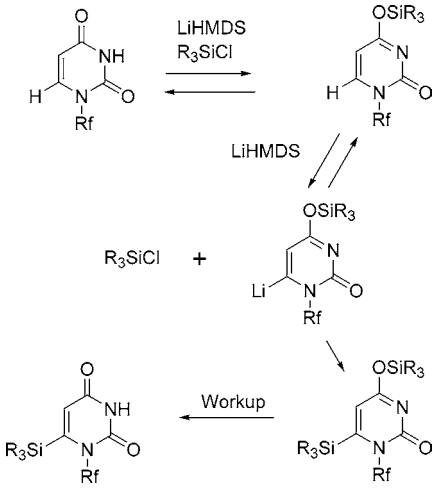
10.1021/ol049500d CCC: $27.50
Published on Web 05/05/2004

Scheme 1



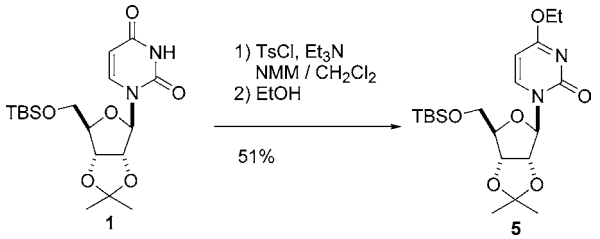
derivative, since the negative charge on the N-3-position is absent. Under these circumstances, LiHMDS is able to generate the C-6-lithio derivative, which, upon silylation followed by aqueous workup, gives the 6-silyluridine derivative.

Scheme 2



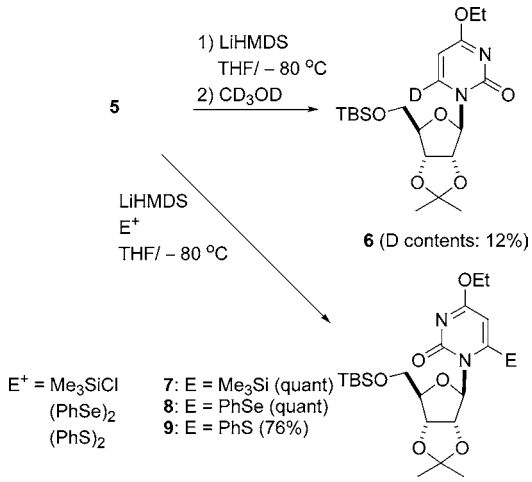
To prove this hypothesis, we examined lithiation of 4-*O*-ethyluridine (**5**) as a mimic of the proposed 4-*O*-silyl intermediate. Compound **5** was prepared by slight modification of the reported method:[5] reaction of **1** with *p*-toluenesulfonyl chloride (TsCl), Et_3N, and *N*-methylmorpholine (NMM) in dichloromethane, followed by treatment with ethanol (Scheme 3).

Scheme 3



Reaction of **5** with LiHMDS (4.8 equiv, in THF at −80 °C for 30 min) was followed by quenching with CD_3OD. The ^1H NMR spectrum of the resulting product **6** showed deuterium incorporation of 12% into the C-6-position (Scheme 4). Although the observed deuterium incorporation level was low, we anticipated that a more appropriate choice of electrophiles could shift the reaction bias to a considerable level of product formation, since an equilibrium does exist in the above acid−base reaction. As shown in Scheme 4, the use of Me_3SiCl, $(PhSe)_2$, and $(PhS)_2$ as an electrophile in the reaction with the LiHMDS-treated **5** gave the respective 6-substituted products in good to excellent yields. In contrast, reactions of the LiHMDS-treated **1** with these electrophiles under the same conditions gave little or none of the products.[6]

Scheme 4



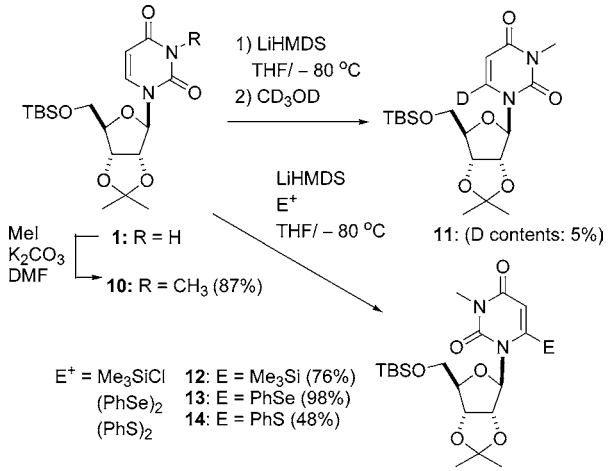
Similar results were obtained by using the *N*-3-methyluridine derivative **10** as a substrate for the LiHMDS lithiation (Scheme 5): despite only 5% deuterium incorporation observed in **11**, high yields of the 6-$SiMe_3$ (**12**)-, 6-SePh (**13**)-, and 6-SPh (**14**)-substituted products were formed.

The possibility of applying the present LiHMDS lithiation to an intramolecular alkylation was next examined: synthesis of 6,5′-*C*-cyclouridine[7] **16**, a conformationally fixed nucleo-

(5) Tsuchiya, K.; Komatsu, H. *Nucleic Acids Res., Supplement 2* 2002, 135−136.

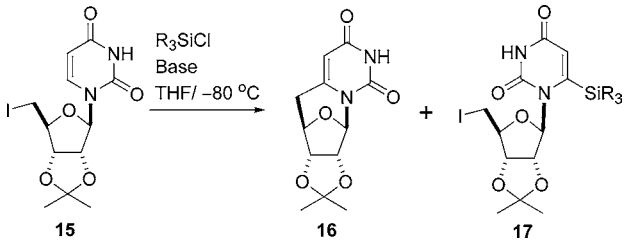
(6) Use of $(PhS)_2$ resulted in complete recovery of **1**, while $(PhSe)_2$ gave the corresponding 6-SePh derivative in 2% yield.

Scheme 5



side analogue, from 5′-deoxy-5′-iodouridine[8] (**15**). It should be noted that our previously reported LDA lithiation,[2] when applied to **15**, gave a complex mixture of products, from which **16** was isolated only in 8% yield, presumably due to the higher basicity of LDA.

Scheme 6



As mentioned earlier, simple LiHMDS treatment of **15** gave none of the desired 6,5′-*C*-cyclouridine (Table 1, entry 1). In contrast to this, the presence of 3.0 equiv of trimethylsilyl chloride in the reaction medium gave 6,5′-*C*-cyclouridine **16** and 6-TMS derivative **17** in 56 and 42% yields, respectively (entry 2). Other silyl chlorides such as $Me(Ph)_2SiCl$ and Ph_2SiCl_2 can also be used in this cyclization reaction (entries 3 and 4). Actually, these bulky silyl chlorides gave higher yields of **16** by rendering the competing 6-silylation a comparatively sluggish event.

Table 1. LiHMDS-Mediated Cyclization of **15** in the Presence of Trialkylsilyl Chloride

			yield	
entry	base[a]	R_3SiCl (equiv)	**16** (%)	**17** (%)
1	LiHMDS		0	0
2	LiHMDS	TMSCl (3.0)	56	42
3	LiHMDS	$Me(Ph)_2SiCl$ (1.5)	83	trace
4	LiHMDS	Ph_2SiCl_2 (3.0)	88	trace

[a] Performed with 4.8 equiv of the corresponding amide base.

In conclusion, we have found that LiHMDS combined with Me_3SiCl can lithiate the C-6-position of uridine derivatives through temporarily removing acidic N-3−H by silylation. One advantage of using this weaker base for the C-6-lithiation of uridine derivatives is clearly exemplified in the case of 5′-deoxy-5′-iodouridine (**15**) as a substrate that has a leaving group in the molecule. Consequently, a high-yield preparation of 6,5′-*C*-cylouridine (**16**) has become possible in a single step.

Supporting Information Available: Experimental procedure and characterization data for **5**−**14**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049500D

(7) Ueda, T.; Usui, H.; Shuto, S.; Inoue, H. *Chem. Pharm. Bull.* **1984**, *32*, 3410−3416.
(8) Levene, P. A.; Tipson, R. S. *J. Biol. Chem.* **1934**, *106*, 113−124.