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SYNTHESIS OF 5-SUBSTITUTED NUCLEOSIDES VIA THE REGIOSELECTIVE LITHIATION OF 2'-DEOXYURIDINE

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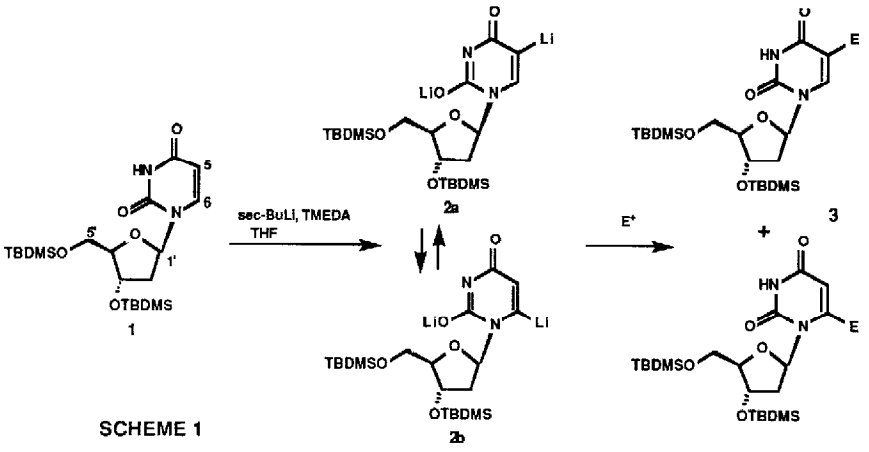
Summary: *Treatment of 2'-deoxy-3',5'-bis-O-[(1,1-dimethylethyl)dimethylsilyl]-uridine with sec-BuLi in the presence of TMEDA resulted in a highly regioselective lithiation at C-5. The lithiated derivative was treated with a number of electrophiles to afford 5-substituted 2'-deoxyuridines.*

In the course of our work on the synthesis of substituted 2-'deoxyuridine derivatives, we required a simple and direct method of introducing mercapto, sulfide, and disulfide substituents at C-5. The methods currently available involve the condensation of bis(trimethylsilyl) derivatives of blocked 5-mercaptouracil substrates with suitably activated sugars affording α and β mixtures of nucleosides,[1] addition of methyl hypobromite/sodium sulfide to 2'-deoxyuridine derivatives followed by reduction of the resulting disulfides,[2] or chemoselective alkylation at the more acidic mercapto-moiety of preformed 5-mercaptonucleosides.[3] The regioselectivity is generally dictated by the substitution of the starting nucleoside (or pyrimidine) which involves a multistep synthesis. We wish to report that 5-substituted-2'-deoxiuridines may be obtained by a simple one-pot deprotonation/alkylation of the readily available nucleoside **1**.

Although lithiation of uridines has been previously studied,[4] very little has been reported on the 2'-deoxyuridine series[4,5]. Metal-halogen exchange of 5-bromo-2'-deoxyuridine was used to synthesize 14C-labelled thymidine in low yields due to the low solubility of the tetra-lithio intermediate.[5a] The 3',5'-bis-O-(trimethylsilyl) derivative of 2'-deoxy-5-bromouridine was converted to the di-lithio intermediate with *n*-BuLi and condensed with vinyl halides to afford 5-vinyl-substituted products.[6] In both cases the regioselectivity was controlled by the halogen substitution of the starting material. Miyasaka[4] has studied the competitive C-5/C-6 deprotonation of uridines and has found that the ratio is governed by the protecting groups on the sugar. In general, deprotonation occurs exclusively at the thermodynamically more acidic C-6 hydrogen[7] in the case of less bulky substituents such as the 2',3'-O-isopropylidene derivative. On the other hand, when a freely rotating t-butyldimethylsiloxy substituent is present at C-2', only C-5 deprotonation is observed. We have found that under similar conditions deprotonation is virtually exclusive at C-5 in the 2'-deoxyuridine series (SCHEME 1).



SCHEME 1

The starting nucleoside 2'-deoxy-3',5'-bis-O-[(1,1-dimethylethyl)dimethylsilyl]-uridine **1** was obtained in quantitative yield from 2'-deoxyuridine[8] using standard methodology[9] (TBDMSCl, DMF, imidazole, 50°C.). Deprotonation in THF at -78°C with 2 equiv. sec-BuLi in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) afforded the bis-lithio derivatives **2a** and **2b** which were then treated with MeOD resulting in a 5:1 ratio of C-5/C-6 deuterium incorporation (48% recovery) as judged by 1H NMR. When the dianion **2** was quenched with either benzyl- or p-methoxybenzyldisulfide, C-5 substituted products **3b,c** were obtained with >99% regioselectivity! (Table I). This high selectivity was also observed when **2** was treated with benzoyl chloride resulting in the C-5 acylated derivative **3d.** Lower selectivity was observed when **2** was treated with MeI, resulting in a 3:1 ratio of C-5/C-6 alkylated products. In no cases was a C-5/C-6 difunctionalized product observed.

TABLE I

Electrophile	Yield[a]	Ratio C-5/C-6[b]	Product
MeOD	48%	5:1	**3a**
Benzyldisulfide	58%	>99:1	**3b**
p-OMe-Benzyldisulfide	49%	>99:1	**3c**
Benzoylchloride	45%	>99:1	**3d**
MeI	55%	3:1	**3e**

[a]isolated yields; [b]based on $^1H/^{13}C$ NMR analysis of mixture

The regioselectivity of the products was readily established by comparison with the 1H NMR shifts of **1** where the hydrogens at C-5 (5.59, d, J= 8.1Hz) and C-6 (7.79, d, J= 8.1Hz) are well resolved doublets (Table II). In the case of the C-

5 sulfide derivatives **3b,c** as well as the acyl derivative **3d** the upfield doublet disappears and a well resolved singlet appears.[10] The sulfides **3b,c** were also correlated to 2'-deoxy-3',5'-di-O-acetyl-5-thioacetyluridine prepared by a different route.[1a] The silyl blocking groups on the methylated product **3e** were removed (tetrabutylammonium fluoride, THF, rt, 95%) to afford thymidine as the major component which was identical by 1H, 13C NMR, and IR with an authentic sample. Thymidine was also converted to **3e** (TBDMSCl, DMF, imidazole, 99%) which was identical spectroscopically with synthetic (**1**→**2**→**3e**) material.

TABLE II. 1H NMR chemical shiftsa of **3**

Compound	R	H-5	H-6
1	H	5.59 (d)	7.79 (d)
3b	SCH_2Ph		7.56 (s)
3c	SCH_2PhOMe		7.59 (s)
3d	COPh		8.30 (s)
3e	Me(C-5)		7.47 (s)
3e	Me(C-6)	5.56 (s)	

a1H NMR (200 MHz) shifts are referenced to $CDCl_3$

Other conditions were also investigated (sec-BuLi/l IMPA, tert-BuLi/TMEDA) but in general they gave the same or lower overall yields. No deprotonation was observed with LDA. The lithium salt of tetramethylpiperidine in the presence of TMEDA afforded exclusively C-5 alkylated product **3b** but in low yields (9%). We have briefly addressed the cause of the moderate yields observed[11] and it appears that instability of the protecting groups towards the strongly basic conditions are a factor. We have recovered a complex mixture of what appears to be desilylated products with the uracil moiety intact. Subjecting **1** to sec-BuLi/TMEDA for 5 min. at -78°C followed by aqueous workup afforded only 82% of **1**.

It has been proposed[4] that the rigid monolithio derivative **4** undergoes lithiation/alkylation at C-6 in all cases except those where a freely-rotating bulky group X (*tert*-butyldimethylsilyl-oxy) prevents approach of the base resulting in exclusive C-5 functionalization. If a similar monolithio derivative exists in the 2'-deoxy series (X=H), deprotonation cannot be dictated by the bulky silyl-oxy group and incorporation of the electrophile at C-6 might actually be favored. We have found that for the 2'-deoxy series preferential C-5 functionalization is observed. In both series selective alkylation at C-5 is a result of kinetic deprotonation with sec-BuLi at this carbon. CPK models of **2** indicate that the C-6 position remains sterically hindered regardless of what conformer is preferred.

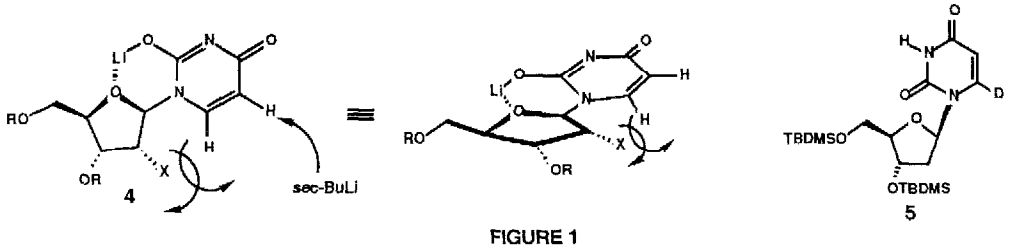


FIGURE 1

In order to address the possibility of an exchange occurring between the C-5 and C-6 protons (compounds **2a** and **2b**) prior to incorporation of the electrophile, we synthesized the selectively deuterated 2'-deoxyuridine derivative **5** according to the method of Fox.[12] Using typical deprotonation conditions (see below) followed by alkylation with benzyl disulfide, no scrambling of the deuterium label was observed.[13] Incorporation of the electrophile reflects the regioselectivity of deprotonation. It is possible that the C-2' oxygen directs an aggregate of the base to the C-6 hydrogen in all cases except those where no oxygen is present (deoxy series) or where a bulky protecting group (silyl ether) interferes sterically.

A typical experiment is as follows: To a THF (1mL) solution of **1** (38 mg, 0.083mmol, 1.0 equiv) at -78°C under N_2 was added TMEDA (27.6uL, 0.183mmol, 2.2 equiv) followed by sec-BuLi (182uL, 0.183mmol, 2.2 equiv). After 30 min, a THF (1mL) solution of benzyl disulfide (102.3mg, 0.415mmol, 5.0 equiv) was added and the reaction was allowed to warm to rt to afford after usual workup and chromatography 28mg (58%) of **3b**.

The lithiated intermediate **2** was condensed with sulfur[14] followed by $NaBH_4$ reduction in order to obtain directly the 5-mercapto derivative but all attempts resulted in a complex mixture of products. Hydrogenation of **3c** (H_2, Pd/C, MeOH, rt.) afforded a 12% yield of the 5-mercapto product. Attempts to remove the p-OMe-benzyl group under acidic conditions[15] resulted in decomposition of product.

We are currently investigating the scope and limitations of this reaction, in particular, the synthesis of unsymmetrical C-5 substituted disulfides. Even though the yields are moderate, this method affords an extremely rapid entry into 5-substituted-2'-deoxyuridines and complements existing methods.[16]

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[10]^{1}H NMR (200 MHz) shifts are referenced to TMS in $CDCl_3$. 3',5'-bis-O-acetyl-5-thioacetyl-2'-deoxyuridine was obtained by a completely different route (ref 1a).

[11]Thin layer chromatography (30% EtOAc in hexanes) of the reaction mixture shows only **1** and **3** with no baseline material.

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[13]The actual incorporation of deuterium at C-6 is only about 90% and partial deuteration also occurs at C-5, but these ratios remain the same in the product.

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