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REGIOSPECIFIC C-ALKYLATION OF URIDINE: A SIMPLE ROUTE TO 6-ALKYLURIDINES

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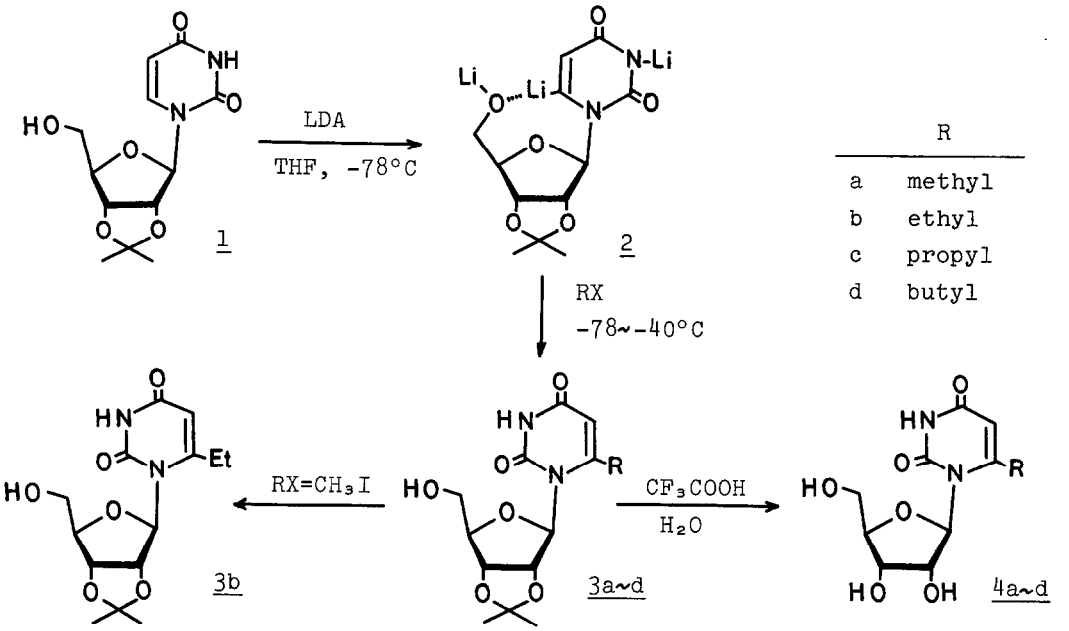
Summary 6-Alkyluridines were conveniently synthesized by lithiation and successive alkylation from 2',3'-O-isopropylideneuridine with complete regioselectivity.

The glycosidic conformation of 6-methylpyrimidine nucleosides in solution has been shown to be syn, being affected by steric influence of the 6-methyl group.[1] Several authors also mentioned the inability to achieve enzymic reaction of these nucleosides which would be the main reflection of the presence of a 6-alkyl substituent.[2] The stereochemical and biological aspects of 6-alkylpyrimidine nucleosides would be interesting to prompt further investigation but no particular progress has been reported in this field, which could be attributed to the difficult accessibility of the bulky and higher homologs.

Although several methods are known for synthesizing 6-alkyluridines,[3] the simplest strategy might be the metalation-alkylation reaction sequence. We wish to report here an excellent alternative for 6-alkyluridines with complete regioselectivity using the above process.

As pointed out earlier by Pichat and co-workers,[4] lithiation of tris-trimethylsilyluridine occurs at both C-5 and C-6, 28% and 14% respectively, of the uracil ring. However, we found that the lithium salt of 2',3'-O-isopropylideneuridine in tetrahydrofuran (THF) upon reaction with excess of alkyl halide[5] at -78°C afforded 6-alkyl-2',3'-O-isopropylideneuridine (3) as the sole product (46~60% in isolated yield). None of the 5-alkyl isomer nor N^3- and/or 5'-O-alkylated product was detected in the reaction mixture under these conditions (confirmed by PMR).



It seemed likely that in this case, where the 5'-hydroxyl group can easily participate in the stabilization of the 6-lithio derivative (2), as depicted in the above scheme, metalation took place in a regiospecific manner to give 3 after alkylation. In the case of methyl iodide, especially on a large scale (10 mmol or more of 1), concomitant formation of 6-ethyl derivative (3b) was also observed. Acetonides (3) thus obtained were treated with trifluoroacetic acid-water at room temperature to remove the protecting group leading to the desired free nucleosides[6] (4). PMR data of the compounds 3 and 4 are summarized in the table.

In a typical procedure, a solution of 1 (2.84 g) in THF (100 ml) was added dropwise to a solution of lithium diisopropylamide (50 mmol) in THF (30 ml) at -78°C under nitrogen atmosphere (about 1 hr). Stirring was continued another 45 min to yield a cloudy pale yellow solution of 2. The lithium salt solution was then treated with an excess of butyl bromide (6.4 ml) at -78°C and the mixture was allowed to stand overnight at -40°C. Evaporation of the solvent followed by purification of the residue by silica gel column chromatography (2%-MeOH in $CHCl_3$) gave 2.03 g (59.6% yield) of 3d as a homogeneous amorphous solid.

Table. PMR data of compound 3 ($CDCl_3$, TMS) and 4 (D_2O, DSS)
Chemical shifts in ppm (90 MHz)

	3a	3b	3c	3d	4a	4b	4c	4d
NH	9.78	9.73	9.84	9.87	—	—	—	—
H-5	5.60	5.63	5.61	5.61	5.76	5.69	5.70	5.71
H-1'	5.67	5.70	5.67	5.68	5.67	5.63	5.59	5.62
H-2'	5.28	5.28	5.29	5.29	4.83	4.78	4.76	4.78
H-3'	5.02	5.06	5.07	5.06	4.40	4.38	4.37	4.39
H-4'	4.23	4.23	4.24	4.24	4.01	3.98	3.94	3.98
CH_2-5'	3.84	3.85	3.84	3.82	3.87	3.84	3.82	3.84
HO-5'	2.96	2.84	3.13	3.33	—	—	—	—
isop.	1.58	1.58	1.57	1.57	—	—	—	—
	1.35	1.37	1.36	1.36	—	—	—	—
R	2.33	2.62	2.56	2.57	2.41	2.70	2.63	2.70
		1.30	1.71			1.27	1.46	
			1.06	1.89~1.13			0.99	1.83~1.20
				0.98				0.96

The solution of 3d in CF_3COOH-H_2O (1:1, 30 ml) was kept for 2 hr at room temperature. The reaction mixture was evaporated and the residue was passed through a silica gel column (10%-EtOH in $CHCl_3$) to furnish 6-butyluridine (4d), 1.49 g (83.2% yield).

Our method provides a simplest route from uridine to 6-substituted uridines and presumably other electrophiles could be used in a similar manner Various functionalizations of 2 are currently under investigation in our laboratory.

REFERENCES AND NOTES

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5. Alkyl halides used were methyl iodide, ethyl bromide, propyl bromide, and butyl bromide.
6. High resolution mass spectrometric data of compounds 4 are as follows :

		Calcd.	Found
4a			
M-H_2O	$C_{10}H_{12}N_2O_5$	240.0746	240.0806
B+2	$C_5H_7N_2O_2$	127.0507	127.0497
B+1	$C_5H_6N_2O_2$	126.0429	126.0412
4b			
M+1	$C_{11}H_{17}N_2O_6$	273.1086	273.1116
B+CHOH	$C_7H_9N_2O_3$	169.0613	169.0614
B+2	$C_6H_9N_2O_2$	141.0664	141.0659
B+1	$C_6H_8N_2O_2$	140.0585	140.0581
4c			
M-H_2O	$C_{12}H_{16}N_2O_5$	268.1059	268.1064
B+CHOH	$C_8H_{11}N_2O_3$	183.0769	183.0783
B+2	$C_7H_{11}N_2O_2$	155.0820	155.0841
B+1	$C_7H_{10}N_2O_2$	154.0742	154.0757
4d			
M+1	$C_{13}H_{21}N_2O_6$	301.1399	301.1415
B+CHOH	$C_9H_{13}N_2O_3$	197.0926	197.0929
B+2	$C_8H_{13}N_2O_2$	169.0977	169.1009
B+1	$C_8H_{12}N_2O_2$	168.0898	168.0938

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