Tetrahedron Letters Vol. 21, pp 1105 - 1108 0040-4039/80/0315-1105$02.00/0

A NEW SYNTHESIS OF N-BLOCKED DIHYDROURACIL AND DIHYDROOROTIC ACID DERIVATIVES USING LITHIUM TRI-SEC-BUTYL BOROHYDRIDE AS REDUCING AGENT

Stephen J. Hannon, Nitya G. Kundu*, Robert P. Hertzberg, Ram S. Bhatt, and Charles Heidelberger

LAC-USC Cancer Center Research Laboratory, and School of Pharmacy
University of Southern California,
Los Angeles, California 90033.

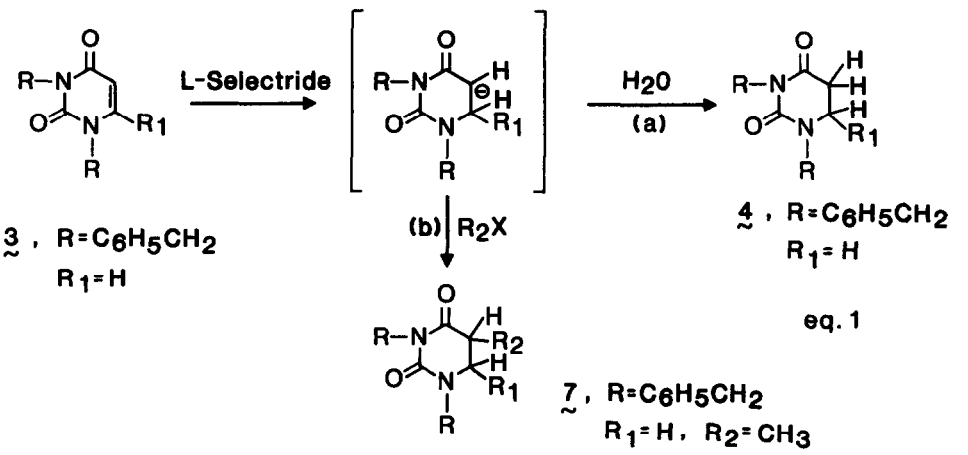
Summary: 1,3-Di-N-substituted uracil and its derivatives have been reduced with lithium-tri-sec-butyl borohydride to the corresponding 5,6-dihydro compounds in excellent yields. Alkylation of 5-position of uracil is also very conveniently accomplished.

5,6-Dihydrouracils are known to be intermediates in the catabolism of uracils [1-3] whereas 5,6-dihydroorotic acid is an important intermediate in the biosynthesis of pyrimidine nucleotides. [4-5] In view of our interest in the development of compounds which will act as inhibitors of dihydrouracil dehydrogenase, dihydroorotase, and dihydroorotate dehydrogenase[5], we have been seeking methods for the synthesis of 5-substituted -5,6-dihydrouracil and orotic acid derivatives.

The usual chemical methods for the synthesis of 5,6-dihydrouracils and 5,6-dihydroorotic acid derivatives have been either by a low yield cyclization process[6], or by catalytic hydrogenation[7] of the corresponding uracil or orotic acid derivatives, which frequently has led to the elimination of desired functionality[8]. The dearth of convenient methods for the reduction of uracils encouraged us to look at new reagents for the specific reduction of the uracil 5,6-double bond. Lithium tri-sec-butyl borohydride (L-Selectride)[9] has been found to be a versatile reagent for the stereoselective reduction of cyclic ketones[10-11]. Recently[12-13] it has also been successfully used for the reduction of α,β-unsaturated ketones and esters to the corresponding saturated ketones and esters.

Application of L-Selectride to uracil derivatives provided us with a mild method for the reduction of 5,6-double bond of N-blocked uracils (sequence a, equation 1). A "one-pot" reduction-alkylation leading to N-blocked 5-substituted-5,6-dihydro uracil derivatives, e.g., compounds 7,8,9,10 and 11, (sequence b, equation 1) has also been accomplished. This method avoids subjecting a 5-substituted uracil to hydrogenation conditions which could remove or alter the C-5 substituent. It also eliminates subjecting base-sensitive dihydrouracils to basic nucleophiles which may open up the ring[14].

Uracil itself could not be reduced with L-Selectride in tetrahydrofuran, dimethyl formamide (DMF) or liquid ammonia. However, protection of the N-1 and N-3 nitrogens with methyl, benzyl[15] or benzyloxy methyl [16,17] groups afforded derivatives which were easily reduced with L-Selectride. N-protection provided the good THF solubility of the compounds, and also locked them in the "ene-one" form essential for reduction with the Selectride. Table I lists the compounds which have been reduced with this reagent, the nature of products formed and the yields for the reactions.



eq. 1

This method of reduction provides us with a mild and efficient process for the reduction of 5,6-double bond of uracil and orotic acid derivatives. Also, 5-alkyl uracils can be conveniently synthesized by this procedure. Combined with some efficient N-deblocking agent[18-23] this method could be suitable for the synthesis of 5,6-dihydro-5-substituted uracils and orotic acid derivatives. A typical experimental procedure follows.

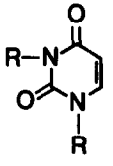
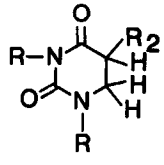
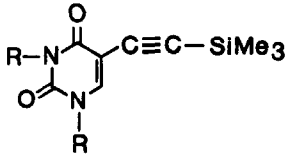
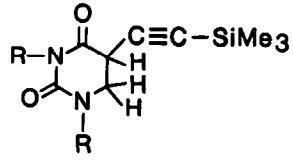
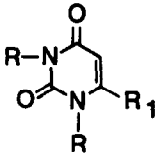
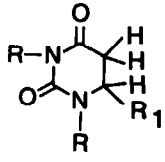
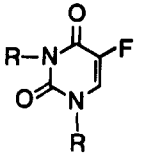
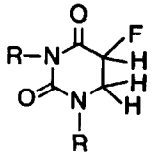
N_1, N_3-dialkyluracils were made by stirring the uracil (1 mmole) in DMF at room temperature with anhydrous potassium carbonate (2.5 mmole) and excess methyl iodide or benzyl bromide or benzyl chloromethyl ether (2.2 mmole); the reaction at room temperature with uracil and benzyl bromide took 2 days.

N_1,N_3-dibenzyluracil (1 mmole) in dry THF (5 ml) under an argon atmosphere was cooled in a dry ice-acetone bath and 1.1 equivalent of L-Selectride (1.1 ml of 1M solution in THF) was added by syringe. The reaction was stirred for 5-10 minutes, after which the alkylating reagent in excess was added to the reaction at low temperature, and the mixture was allowed to reach room temperature with stirring over 10 minutes. The reaction was quenched with saturated aqueous ammonium chloride solution, extracted into chloroform, washed, dried and the solvent removed. To avoid oxidative workups that might oxidize the dihydrouracils, preparative TLC was used to separate mixtures and to remove residual borane. The yields reported are those obtained after purification. N_1, N_3-dibenzyluracil (3) on L-Selectride reduction yielded N_1, N_3-dibenzyl-5,6-dihydrouracil (4), mp 80-81°C, in 94% yield.

Acknowledgement: We thank Mr. Surendra Khatri for technical assistance, and Dr. H. Boettger of the Jet Propulsion Laboratory, Pasadena, Calif., for mass spectral data. This investigation was supported by Contract Number NO 1-CM-67084, from the National Cancer Institute, National Institutes of Health.

TABLE I

Compounds Reduced with Lithium Tri-sec-Butyl Borohydride

Compounds[15,24,26]	Compounds No	Electrophile	Products[25,26]	Products No	Yield %
	1, R=CH_3	H_2O		2, R=CH_3, R_2=H	72
	3, R=C_6H_5-CH_2	H_2O		4, R=$C_6H_5CH_2$, R_2=H	94
	5, R=C_6H_5-CH_2-O-CH_2	H_2O		6, R=C_6H_5-CH_2-O-CH_2,R_2=H	80
	3, R=C_6H_5-CH_2	CH_3I		7,R=C_6H_5-CH_2,R_2=CH_3	88
	1, R=CH_3	CH_3I		8, R=R_2=CH_3,	67
	3, R=C_6H_5-CH_2	C_6H_5-CH_2-Br		9, R=R_2=$C_6H_5CH_2$	79
	3, R=C_6H_5-CH_2	C_2H_5Br		10, R=C_6H_5-CH_2,R_2=C_2H_5	67
	3,R=C_6H_5-CH_2	HC≡C-CH_2Br		11,R=C_6H_5-CH_2,R_2=HC≡C-CH_2	89
	12, R=C_6H_5-CH_2	H_2O		13, R=C_6H_5-CH_2	41
	14, R=C_6H_5-CH_2 R_1=$CO_2C_2H_5$	H_2O		15,R=C_6H_5-CH_2 R_1=$CO_2C_2H_5$	62
	16, R=$C_6H_5CH_2$	H_2O		17, R=C_6H_5-CH_2	47
	18, R=C_6H_5-CH_2-O-CH_2	H_2O		19, R=$C_6H_5CH_2$-O-CH_2	29

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22b. Drs. W. Wolf and A. Ghanbarpour have converted compound 19 to 5-fluoro-5,6-dihydrouracil by catalytic hydrogenation on 10% Pd/C. This synthesis is being reported by them elsewhere.
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26. N_1, N_3-dibenzyl uracil[15], 3, mp 61-63°C; N_1N_3-dibenzyloxymethyl uracil, 5, mp 54-56°C; ethyl N_1, N_3-dibenzyl orotate, 14, mp 75-76°C; N_1, N_3-dibenzyloxymethyl-5-fluorouracil[17], 18, mp 79°C; N_1, N_3-dimethyl-5,6-dihydrouracil[25], 2; N_1, N_3-dibenzyl-5,6-dihydrouracil, 4, mp 80-81°C; compounds 12, 16 and the other N_1, N_3-dialkyl-5,6-dihydrouracils were obtained as thick oils which did not crystallize. All new compounds had spectral data consistent with assigned structures. Some typical NMR data(δ) are as follows - compound 4, 2.60 (t, 2H, J=6Hz, C_5-methylene), 3.19 (t, 2H, J = 6Hz, C_6-methylene), 4.58 (s, 2H, $-CH_2-$), 4.98 (s, 2H, $-CH_2-$), 7.23 (s, 10H, aro-H); compound 6, 2.42 (t, 2H, J = 6Hz, C_5-methylene), 3.18 (t, 2H, J = 6Hz, C_6-methylene), 4.52 (s, 2H, - CH_2 -), 4.7 (s, 2H, - CH_2 -), 4.9 (s, 2H, - CH_2 -), 5.35 (s, 2H, - CH_2 -), 7.35 (s, 10H, aro-H).

(Received in USA 13 November 1979)