RESEARCH ON ANTIVIRAL AGENTS. 5.[1] LITHIATION OF 6-METHYLURACIL AS A NEW AND EFFICIENT ENTRY TO C(6)-SUBSTITUTED URACILS

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Abstract- Synthesis of numerous C(6)-substituted uracils can be effected by lithiation of N(1), N(3)-substituted 6-methyluracils (1) and (4) with LiHMDS, followed by the reaction of the resulting lithio derivatives with carbon, sulfur, and selenium electrophiles. The unexpected migration of the N(1)-benzoyl group in the metalation-alkylation and the high stereoselectivity obtained in the reaction with substituted cyclohexanones are also reported.

In spite of several syntheses described in literature[2] for the preparation of uracil derivatives, little attention has been paid to the synthesis and the chemistry of 6-substituted uracils, mainly because of the following reasons: i) 6-substituted uracils are not good substrates towards N-1 glycosylation procedures to obtain 6-substituted nucleosides;[3] ii) 6-substituted uracils are not substrates for the enzymes involved in neoplastic diseases;[4] and iii) 6-substituted uracils are not prepared in good yields using the general methods reported for other uracil derivatives.[5] Recently the chemistry of 6-substituted uracils has been subjected to renewed interest, due to the unexpected antiviral activity shown by some of these compounds; as for example, 1-[2-hydroxyethoxymethyl]-6-phenylthiothymine (HEPT)[6] and 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidine (DABO),[7] which are "non-nucleoside" reverse transcriptase inhibitors of the human immunodeficiency virus (HIV)-associated reverse transcriptase.[8]

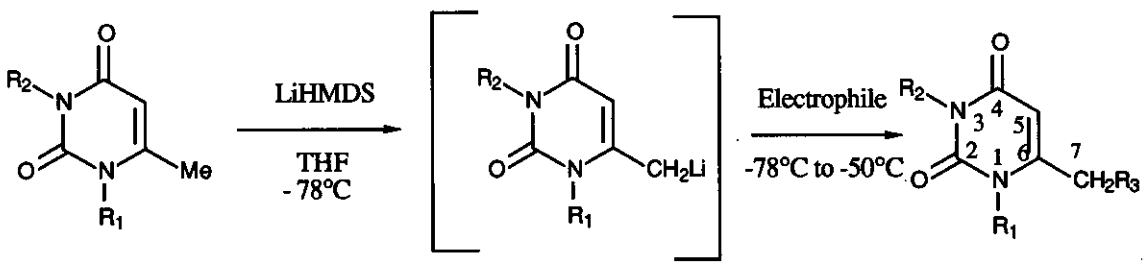
6-Substituted uracils are usually synthesized *via* cyclization of β-keto ester derivatives with O-methylisourea,[9] thiourea, or alkylisothioureas.[10, 11] The shortcomings of these methods are the preparation of the appropriate β-keto esters through procedures that are not necessarily straighforward, and the low yields obtained in the presence of bulky substituents.

Our previous work on the synthesis of bipyrimidinones and bipyrimidinylmethane derivatives showed that the metalation with 2-methylfuryllithium of 2-methoxy-6-methyl-4(3*H*)-pyrimidinone takes place at the methyl in the 6-position in an essentially regiospecific manner.[12] Having recently been involved in the

synthesis and biological evaluation of 6-substituted uracil derivatives,[13] we became interested in developing a new and efficient procedure for the metalation-alkylation sequence of easily available 1,3,6-trimethyluracil (**1**) and 1,3-dibenzoyl-6-methyluracil (**4**) with carbon, sulfur and selenium electrophiles. We describe the preparation of several types of 6-substituted uracils, proving the uselfulness of the above procedure. Moreover, the unexpected migration of the N(1)-benzoyl group in the metalation-alkylation and the high stereoselectivity obtained in the reaction with substituted cyclohexanones are also discussed.

Disulfides are used as a label for estimating the extent of metalation, especially in the case of lithiation with dialkylamides, where substitution by deuterium may be low.[14] We first examined the reaction of **2**, prepared from 1,3,6-trimethyluracil (**1**) with 1.3 eq. of lithium base [lithiumdiisopropyl amide (LDA), lithium hexamethyldisilazane (LHMDS), and 2-methylfuryllithium] in THF, with diphenyl disulfide in order to evaluate the extent of the lithiation. Treatment of **2** with 1.5 eq. of diphenyl disulfide (below -70°C for 6 h) afforded 1,3-dimethyl-6-(methylenephenylthio)uracil (**3a**) in variable yields, the most active LHMDS was chosen as a lithium base to prepare lithium intermediates (**2**) and (**5**) in the Entry 1-17 (48% yield) [Scheme, Table 1, Entry 1].

Scheme

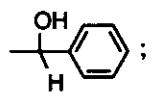


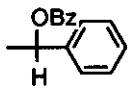
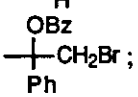
1: R_1=R_2= Me
4: R_1=R_2= Bz

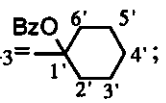
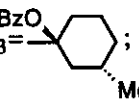
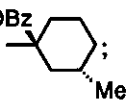
2: R_1=R_2= Me
5: R_1=R_2= Bz

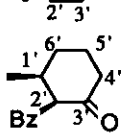
3a-c, 3e-h: R_1=R_2= Me
6a-d: R_1=R_2= Bz
6e-i: R_1=H, R_2= Bz

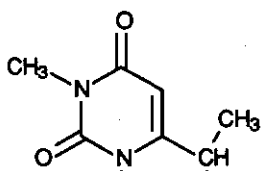
3a, 6a: R_3= S-Ph; **3b, 6b**: R_3= Me; **3c**: R_3= Et;

3e, 6c: R_3= S-2'-Py; **3f, 6d**: R_3= Se-Ph; **3g**: R_3=  ;

3h: R_3=  ; **6e**: R_3=  ; **6f**: R_3=  ;

6g: R_3=  ; **6h**: R_3=  ; **6h-(1'S, 3'R)**: R_3=  ;

6i: R_3= 



3d

We then investigated the reaction of **2**, with several carbon, sulfur and selenium electrophiles. The reaction

of **2** with 1.5 eq. of alkyl iodides (methyl iodide and ethyl iodide) in THF at -50 °C afforded 1,3-dimethyl-6-ethyluracil (**3b**) and 1,3-dimethyl-6-n-propyluracil (**3c**) in acceptable yields; in the first case, the concomitant formation of 1,3-dimethyl-6-isopropyluracil (**3d**) was observed (Scheme, Table 1, Entries 2-3). The reaction of **2**, under similar experimental conditions, with 2,2'-dipyridinyl disulfide, phenylselenenyl bromide, benzaldehyde, and 2-bromoacetophenone: as electrophiles afforded compounds (**3e-h**) in 41-79% yields as main products (Scheme, Table, Entries 4-7) and unreacted **1** as by products (30-15% yields). It is noteworthy that in the case of 2-bromo acetophenone the alkoxy moiety formed upon addition of the lithium salt to the carbonyl electrophile afforded an internal nucleophilic substitution to give the C(6)-oxiranylmethyl derivative (**3h**) as the only isolated product (Table 1, Entry 7).

In order to enhance the synthetic utility of this procedure, our attention was next turned to the metalation-alkylation sequence of 1,3-dibenzoyl-6-methyluracil (**4**). Benzoyl group may be easily removed using 1.5 N-ammonia in wet methanol as deacylating agent.[15] Moreover, N(1)-benzoyluracils undergo deacylation at rates which may be as much as four orders of magnitude faster than the rates of the corresponding N(3)-benzoyl derivatives, thus providing a good chemoselectivity for the removal of the benzoyl group.[15]

Table 1: Reactions of lithium intermediates (**2**) and (**5**) with carbon, sulfur and selenium electrophiles.

Entry	Product(s)	Electrophile	Temperature (°C)	Yield (%)
1	**3a**	$(S\text{-}Ph)_2$	-78	48
2	**3b** (**3d**)	MeI	-50	45 (16)
3	**3c**	EtI	-50	43
4	**3e**	$(S\text{-}2'\text{-}Py)_2$	-78	41
5	**3f**	Br-Se-Ph	-78	50
6	**3g**	PhCHO	-78	68
7	**3h**	$PhCOCH_2Br$	-50	79
8	**6a**	$(S\text{-}Ph)_2$	-78	69
9	**6b**	MeI	-50	58
10	**6c**	$(S\text{-}2'\text{-}Py)_2$	-78	37
11	**6d**	Br-Se-Ph	-50	48
12	**6e**	PhCHO	-78	75
13	**6f**	$PhCOCH_2Br$	-78	80
14	**6g**	Cyclohexane	-78	65
15	**6h**	3-Methylcyclohexanone	-78	48
16	**6h-(1'S,3'R)**	(R)-(+)-3-Methylcyclohexanone	-78	63
17	**6i**	2-Cyclohexen-1-one	-78	43

We first examined the reaction of the lithium intermediate (**5**), prepared from 1,3-dibenzoyl-6-methyluracil (**4**) with 1.3 eq. of LiHMDS, with diphenyl disulfide. Treatment of **5** with 1.5 eq. of diphenyl disulfide (below -70 °C for 6 h) afforded 1,3-dibenzoyl-6-methylenphenylthiouracil (**6a**) in 69% yield (Scheme, Table 1, Entry 8). It seemed likely that, in this case, the N(1)-benzoyl group can participate in the stabilization of the lithio derivative (**5**), and the metalation-alkylation sequence took place in better yield than the same reaction carried out in the presence of the N(1)-methyl moiety. These data are in accord with the results described by Tanaka[16] on the partecipation of the 5'-OH sugar moiety in the C(6)-selective lithiation of uridine derivatives. Under similar experimental conditions, the reaction of **5** with carbon, sulfur and selenium electrophiles afforded compounds (**6b-i**) in good yields (Scheme, Table 1, Entries 9-16). Unexpectedly, compound (**6e**) was obtained as only isolated product when benzaldehyde was used as electrophile, probably as a result of the migration of the N(1)-benzoyl group to the C(1')-oxygen formed after the addition of **5** on the carbonyl moiety (Scheme, Table 1, Entry 12). Moreover, in the case of 2-bromo acetophenone, the migration of the N(1)-benzoyl group was faster than the previously observed internal nucleophilic substitution, to give compound (**6f**) as the only isolated product (Scheme, Table 1, Entry 13). A possible explanation for this finding lies in the susceptibility of the N(1)-benzoyl group toward nucleophilic substitution by C(1')-oxygen in the low energy, six member transition state (Figure 1), obtained by an energy minimization of the input geometry (**6e**) to convergence, followed by a statistical Monte Carlo conformational analysis (performed using the MM2 force field as implemented in Model).[17]

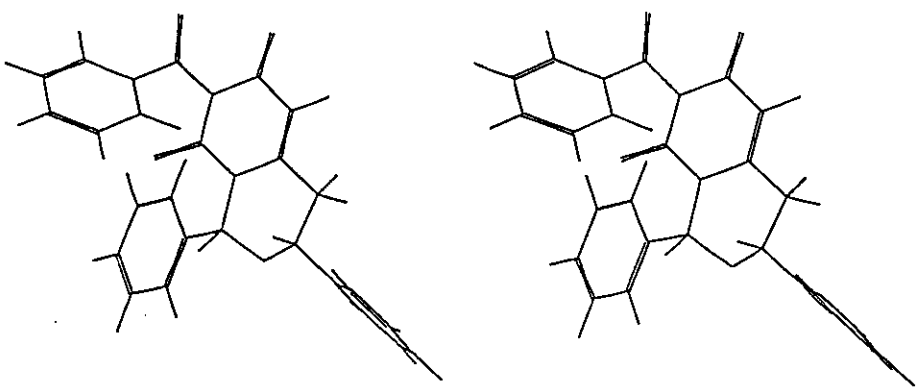


Figure 1. Energy minimization of the input geometry (**6e**) to convergence, followed by a statistical Monte Carlo conformational analysis performed using the MM2 force field as implemented in Model.[17]

Table 2. Correlated ^{1}H-nmr and ^{13}C-nmr data for compound (**6h**).

Position	δc	δH ^{1}J correlated proton[a]	^{2}JH,C and ^{3}JH,C correlated carbon
OCO	168.57	—	—
NCO	166.81	—	—
C-4	162.35	—	—
C-6	150.83	—	—
C-2	150.19	—	—
C-4"	135.12	7.65 (1H, br t, 7)	—
C-4"'	133.53	7.59 (1H, br t, 7)	—
C-1"	131.40	—	—
C-2"', 6"'	130.45x2	7.90 (2H, br d, 8)	—
C-1"'	130.11	—	—
C-2", 6"	129.67x2	8.01(2H, br d, 8)	—
C-3"', 5"'	129.11x2	7.48 (2H, br t, 7)	—
C-3", 5"	128.60x2	7.46 (2H, br t, 7)	—
C-5	102.45	5.62 (1H, s)	$^{2}J_{6}$
C-1'	82.76	—	—
C-2'	43.22	2.48 (1H, br d, 13)[b]	$^{2}J_{1'}$
		1.01 (1H, br t, 12, 5)	$^{2}J_{1'}$
C-7	42.81	3.11 (2H, s)	$^{2}J_{6}$ $^{2}J_{1'}$ $^{3}J_{5}$
C-4'	34.60	2.48 (1H, br d, 13)[b]	—
		1.27 (2H, dt, 13,5)	—
C-6'	33.75	1.72 (1H, m)	—
		0.84 (2H, dt, 12,5)	—
C-3'	27.80	1.70 (1H, m)	—
Me	22.19	0.90 (3H, d, 6)	$^{2}J_{3'}$
C-5'	21.40	1.60 (2H, m)	—

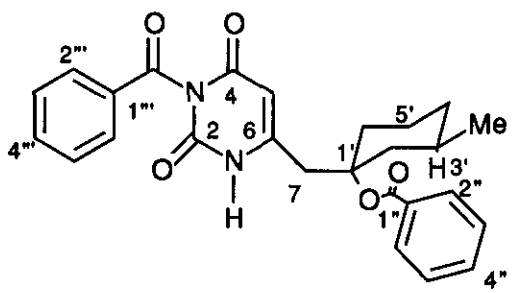
[a]Carbon and proton signals were correlated by an HECTOR measurement. By this experiment the geminal protons for each carbon were also determined. [b]H-2'eq and H-4'eq protons gave in C_5D_5N two different signals at δ 2.79 and 2.69, respectively. The chemical shift assignment was supported by a series of decoupling experiments.

The reaction proceeded similarly with cyclic ketones, and in the case of racemic 3-methylcyclohexanone, only one racemic diastereoisomer, compound (**6h**) (Figure 2, Table 2), was obtained (single signals in the

300 MHz ^{1}H-nmr spectra) in good yield (Table 1, Entry 15).[15,16]

A complete carbon and proton chemical-shift assignment (Table 2) was performed by a series of 1D- and 2D-nmr measurements. The geminal pair of protons for each carbon of the cyclohexane ring was evidenced by the HETCOR measurement and confirmed by decoupling experiments. In particular, DIF NOE experiments, partly run in C_5D_5N solution to better distinguish some signals, showed no increase between the signal of 7-methylene group (see Figure 2 for numbering) and those of the protons belonging to the cyclohexane moiety. Accordingly, the proximity of H-3' proton (which gave an isolated 1H multiplet in C_5D_5N solution) and H-2"/H-6" protons was revealed by their mutual NOE effect. These findings require the 7-methylene group to be in equatorial position and the benzoyloxy substituent in axial position.

Figure 2



6h-(1'S, 3'R)/(1'R, 3'S)

When the reaction was performed with chiral R-(+)-3-methylcyclohexanone only one enantiomer, compound **[6h-(1'S, 3'R)]**, was isolated in the reaction mixture (Table 1, Entry 16) with a high enantioselectivity (e.e.> 98%; $[\alpha]_D$ -12.75°; c. 1.2, $CHCl_3$). In particular, only peaks characteristic of an enantiomerically pure diastereoisomer were found both in the ^{1}H-nmr spectrum and in hplc chromatograms performed using several chiral columns. The stereoselectivity obtained for the reaction of **5** with 3-methylcycloexanone and R-(+)-3-methylcyclohexanone is in accord with the data reported in literature about the factors which govern the direction of addition of organometallic compounds to monosubstituted cyclohexanones.[18] In fact, although the stereoselectivity is usually not high, there is a preference for attack from the equatorial direction with the substituent in the equatorial position, to give the axial alcohol; this preference for equatorial attack increases with the size of the alkyl group. Furthermore, a possible role of the concerted migration of the N(1)-benzoyl in the enhancement of the stereoselectivity can not be completely rejected. Finally, compound (**6i**) was obtained from a Michael-like addition when 2-cyclohexen-1-one was used as electrophile (Table 1, Entry 17). It is noteworthy that the migration of the N(1)-benzoyl group to the C(2')-position of the cyclohexanone ring (see Scheme for numbering of C-6 substituents) occurs with cis-stereochemistry with respect to the newly formed carbon-carbon bond as

unequivocally shown by ^{1}H-nmr coupling costant value ($J_{H\text{-}1',H\text{-}3}$= 9.0 Hz). These data are in accord with the previously proposed low energy, six membered transition state model.

EPERIMENTAL

^{1}H-Nmr and ^{13}C-nmr spectra were recorded on a Bruker (200 MHz) and on a Varian Gemini (300 MHz) spectrometers and are reported in δ values. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed by C. Erba 1106 analyzer. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. $[\alpha]_D$ was performed on a Perkin-Elmer 241 Polarimeter. All solvents were ACS reagent grade and were redistilled and dried according to standard procedures. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh for flash technique. Thin layer chromatography was carried out using Merck platten Kieselgel 60 F254.

Starting Compounds

1,3,6-Trimethyluracil (**1**) was synthesized according to the procedure reported by Scannell;[19] 1,3-dibenzoyl-6-methyluracil (**4**) was synthesized according to the procedure reported by Reese.[15]

Metalation-alkylation reaction sequence for compounds (**1**) and (**4**). General procedure.

To a solution of the substrate (1 mmol) in dry THF (7 ml) cooled to -78°C lithium examethyldisilazane (1.3 mmol) was added dropwise under nitrogen atmosphere. After the mixture was stirred for 1 h, the electrophile (1.5 mmol) was added, while maintaining the temperature below -70°C. The mixture was stirred for 6 h at variable temperature depending on the electrophile used (from -78°C to -50°C), quenched with NH_4Cl saturated solution (2 ml), and allowed to warm to room temperature. The organic layer diluted with EtOAc (100 ml) was then separated, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography using chloroform:methanol=9.5:0.5 as mobile phase.

1,3-Dimethyl-6-(methylenphenilthio)uracil (**3a**)- (126 mg, 48%); mp 40-42°C; ir ($CHCl_3$) ν_{max}: 1758, 1673, and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 7.30-7.15 (5H, m, Ar-H), 5.35 (1H, s, H-5), 3.75 (2H, s, CH_2), 3.45 (3H, s, CH_3), 3.25 (3H, s, CH_3); ^{13}C-nmr ($CDCl_3$) δ ppm 161.91 (C), 152.61 (C), 149.67 (C), 132.81 (C), 132.82 (CH), 129.43 (CH), 128.68 (CH), 128.30 (CH), 102.14 (CH), 37.64 (CH_2), 31.50 (CH_3), 28.02 (CH_3); m/z=263 (M^+, 55%). Anal. Calcd for $C_{13}H_{15}N_2O_2S$: C, 59.52; H, 5.38; N, 10.69. Found: C, 59.65; H, 5.35; N, 10.75.

1,3-Dimethyl-6-ethyluracil (**3b**)- (76 mg, 45%); oil; ir ($CHCl_3$) ν_{max}: 1760, 1680, and 1630 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 5.59 (1H, s, H-5), 3.36 (3H, s, CH_3), 3.29 (3H, s, CH_3), 2.50 (2H, q, J 7.0 Hz, CH_2), 1.20 (3H, t, J 7.0 Hz, CH_3); m/z=168 (M^+, 37%). Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13 ; H, 7.19 ; N, 16.65. Found: C, 57.20 ; H, 7.21 ; N, 16.73 .

1,3-Dimethyl-6-n-propyluracil (**3c**)- (78 mg, 43%); oil; ir ($CHCl_3$) ν_{max}: 1781, 1677, and 1625 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 5.60 (1H, s, H-5), 3.37 (3H, s, CH_3), 3.33 (3H, s, CH_3), 2.42 (2H, t, J 7.2 Hz, CH_2), 1.63 (2H, m, CH_2), 1.01 (3H, t, J 6.8 Hz, CH_3); m/z=182 (M^+, 12%). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32 ; H, 7.74 ; N, 15.37 . Found: C, 59.28 ; H, 7.81 ; N, 15.47.

1,3-Dimethyl-6-isopropyluracil (**3d**)- (29 mg, 16%); oil; ir ($CHCl_3$) ν_{max}: 1782, 1675, and 1630 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 5.63 (1H, s, H-5), 3.41 (3H, s, CH_3), 3.30 (3H, s, CH_3), 2.75 (1H, m, CH), 1.19 (6H, d, J 7.7 Hz, CH_3); m/z=182 (M^+, 33%). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32 ; H, 7.74 ; N, 15.37 . Found: C, 59.29 ; H, 7.80 ; N, 15.43.

1,3-Dimethyl-6-(methylen[pyridin-2'-yl]thio)uracil (**3e**)- (108 mg, 41%); oil; ir ($CHCl_3$) ν_{max}: 3090, 1763, 1679, and 1630 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 8.50 (1H, m, Ar-H), 7.60-7.0 (3H, m, Ar-H), 5.95 (1H, s, H-5), 4.25 (2H, s, CH_2), 3.35 (3H, s, CH_3), 3.20 (3H, s, CH_3); ^{13}C-nmr ($CDCl_3$) δ ppm.: 162.36 (C), 154.75 (C), 150.92 (C), 149.49 (CH), 136.54 (CH), 122.67 (CH), 121.60 (C), 120.55 (CH), 102.11 (CH), 30.23 (CH_2), 27.99 (CH_3), 31.59 (CH_3); m/z=263 (M^+, 23%). Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98 ; N, 15.96 . Found: C, 54.80 ; H, 5.02 ; N, 15.89.

1,3-Dimethyl-6-methylenephenilseleniumuracil (**3f**)- (154.4 mg, 50%); mp= 72-74°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3110, 1768, 1671, and 1622 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 7.30 (3H, m, Ar-H), 7.55 (2H, m, Ar-H), 5.20 (1H, s, H-5), 3.72 (2H, s, CH_2), 3.30 (3H, s, CH_3), 3.50 (3H, s, CH_3); ^{13}C-nmr ($CDCl_3$) δ ppm.: 162.28 (C), 153.02 (C), 151.23 (C), 135.80 (C), 127.42 (CH), 129.70 (CH), 129.69 (CH), 129.54 (CH), 101.66 (CH), 31.49 (CH_3), 28.55 (CH_2), 28.09 (CH_3); m/z=309 (M^+, 23%). Anal. Calcd for $C_{13}H_{14}N_2O_2Se$: C, 50.49; H, 4.56; N, 9.06 . Found: C, 50.43 ; H, 4.57 ; N, 9.09 .

1-Phenyl-1-hydroxy-2-(1,3-dimethyluracil-6-yl)ethane (**3g**)- (176 mg, 68%); oil; ir ($CHCl_3$) ν_{max}: 3400, 3060, 1777, 1678, and 1622 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 7.35 (5H, m, Ar-H), 5.62 (1H, s, H-5), 4.23 (1H, m, CH), 3.42 (3H, s, CH_3), 3.29 (3H, s, CH_3), 2.91 (2H, d, J 7.7 Hz, CH_2); m/z=260 (M^+, 21%). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.19; N, 10.76. Found: C, 64.49; H, 6.21; N, 10.87.

1,2-Oxiranyl-2-phenyl-3-(1,3-dimethyluracil-6-yl)propane (**3h**)- (215 mg, 79%); mp= 74-76°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3100, 1766, 1679, and 1630 cm^{-1}; ^1H-nmr ($CDCl_3$) δ ppm 7.30 (5H, m, Ph-H), 5.60 (1H, s, H-5), 3.40 (3H, s, CH_3), 3.28 (3H, s, CH_3), 3.25 (2H, m, CH_2), 2.90 (2H, m, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm.: 162.24 (C), 152.55 (C), 149.93 (C), 138.38 (C), 128.96 (CH), 128.80 (CH), 125.38 (CH), 103.10 (CH), 57.09 (C), 53.86 (CH_2), 37.64 (CH_2), 32.10 (CH_3), 27.69 (CH_3);

m/z=272 (M^+, 21%). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92 ; N, 10.28 . Found: C, 66.23 ; H, 5.87 ; N, 10.33 .

1,3-Dibenzoyl-6-(methylenphenilthio)uracil (**6a**)- (305 mg, 69%); mp 87-89°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3033, 1780,1760, 1678, and 1623 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 8.10-7.25 (15H, m, Ar-H), 5.75 (1H, s, H-5), 4.15 (2H, s, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm.: 169.04 (C), 167.78 (C), 160.85 (C), 151.06 (C), 149.55 (C), 132.76 (C), 132.41 (C), 131.49 (CH), 131.15 (CH), 130.56 (CH), 130.50 (CH), 129.64 (CH), 129.32 (CH), 129.14 (CH), 104.28 (CH), 36.04 (CH_2); m/z=442 (M^+, 67%). Anal. Calcd for $C_{25}H_{18}N_2O_4S$: C, 67.86 ; H, 4.10; N, 6.33. Found: C, 67.80 ; H, 4.10 ; N, 6.37.

1,3-Dibenzoyl-6-ethyluracil (**6b**)- (202 mg, 58%); oil; ir ($CHCl_3$) ν_{max}: 1760, 1680, and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 7.60-8.20 (10H, m, Ph-H), 6.0 (1H, s, H-5), 2.40 (2H, q, J 9.76 Hz, CH_2), 1.25 (3H, t, J 9.76 Hz, CH_3); ^{13}C-nmr ($CDCl_3$) δ ppm 168.36 (C), 167.90 (C), 161.64 (C), 156.37 (C), 149.32 (C), 135.68 (CH), 135.23 (CH), 130.40 (CH), 128.32 (C), 126.23 (C), 129.52 (CH), 129.19 (CH), 100.48 (CH), 24.98 (CH_2), 11.03 (CH_3); m/z=348 (M^+, 37%). Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96 ; H, 4.63 ; N, 8.04. Found: C, 67.0 ; H, 4.61 ; N, 8.08 .

1,3-Dibenzoyl-6-methylene[pyridin-2'-yl]thiouracil (**6c**)- (164 mg, 37%); oil; ir ($CHCl_3$) ν_{max}: 3013, 1810, 1757, 1680, and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 7.55-7.0 (14H, m, Ar-H), 6.22 (1H, s, H-5), 4.33 (2H, s, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 189.10 (C), 180.02 (C), 161.24 (C), 155.27 (C), 152.14 (C), 149.52 (C), 136.52 (CH), 135.23 (CH), 132.51 (C), 131.11 (C), 130.45 (CH), 129.01 (CH), 122.56 (CH), 120.66 (CH), 103.59 (CH), 29.80 (CH_2); m/z=443 (M^+, 72%). Anal. Calcd for $C_{24}H_{17}N_3O_4S$: C, 65.0; H, 3.86 ; N, 9.47 . Found: C, 65.10 ; H, 3.86 ; N, 9.49.

1,3-Dibenzoyl-6-methylenephenilseleniumuracil (**6d**)- (235 mg, 48%); oil; ir ($CHCl_3$) ν_{max}: 3009, 1798, 1760, 1673, and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 7.95-7.20 (15H, m, Ar-H), 5.51 (1H, s, H-5), 3.95 (2H, s, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 173.10 (C), 169.04 (C), 168.12 (C), 153.12 (C), 152.20 (C), 137.25 (C), 135.19 (CH), 130.74 (CH), 132.79 (C), 130.57 (CH), 130.25 (CH), 129.99 (CH), 129.78 (CH), 129.10 (CH), 103.44 (CH), 29.52 (CH_2); m/z=489 (M^+, 52%). Anal. Calcd for $C_{25}H_{18}N_2O_4Se$: C, 61.36; H, 3.71 ; N, 5.72. Found: C, 61.39; H, 3.71 ; N, 5.75.

1-Phenyl-1-benzoyloxy-2-(N-3-benzoyluracil-6-yl])ethane (**6e**)- (330 mg, 75%); mp= 138-140°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3350, 3010, 1800, 1765, 1680, and 1637 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 11.40 (1H, br s, N(1)-H), 7.20- 8.20 (10H, m, Ar-H), 6.25 (1H, m, CH), 5.65 (1H, s, H-5), 2.50 (3H, d, 8.1 Hz, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 168.48 (C), 165.66 (C), 162.55 (C), 152.19 (C), 152.0 (C), 138.62 (C), 135.85 (CH), 133.52 (CH), 131.39 (C), 130.56 (CH), 130.46 (CH), 129.76 (CH), 126.0 (CH), 129.78 (CH), 102.58 (CH), 73.31 (CH), 40.77 (CH_2); m/z=440 (M^+, 21%). Anal. Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58 ; N, 6.36. Found: C, 70.81 ; H, 4.60 ; N, 6.42.

2-Benzoyloxy-2-phenyl-3-bromo-1-[N-3-benzoyluracil-6-yl])propane (**6f**)- (425 mg, 80%); mp= 75-77°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3298, 3020, 1798, 1760, 1680, and 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 11.38 (1H, br s, N(1)-H), 7.58-7.05 (15H, m, Ph-H), 5.18 (1H, s, H-5), 4.71 (2H, m, CH_2), 3.40 (2H, m, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 168.11 (C), 164.82 (C), 161.90 (C), 150.45 (C), 149.83 (C), 138.06 (C), 135.24 (C), 133.69 (C), 131.13 (C), 130.20 (CH), 129.68 (CH), 129.59 (CH), 128.73 (CH), 128.65 (CH), 124.79 (CH), 102.72 (CH), 82.62 (C), 42.44 (CH_2), 37.08 (CH_2); m/z=532 (M^+, 13%). Anal. Calcd for $C_{27}H_{21}N_2O_5Br$: C, 60.80; H, 3.96; N, 14.98. Found: C, 61.09 ; H, 3.59 ; N, 15.11.

1-Benzoyloxy-1-methylene-[N-3-benzoyluracil-6-yl)]cyclohexane (**6g**)- (281 mg, 65%); mp= 196-198°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3400, 1750, 1710, 1655, and 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 9.60 (1H, br s, N(1)-H), 7.90 (4H, m, Ar-H), 7.50 (6H, m, Ar-H), 5.62 (1H, s, H-5), 3.07 (2H, m, CH_2), 2.40 (2H, m, CH_2), 1.40 (8H, m, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 168.80 (C), 166.81 (C), 162.56 (C), 151.33 (C), 150.73 (C), 135.24 (CH), 133.56 (CH), 131.66 (C), 130.66 (C), 130.56 (CH), 129.76 (CH), 129.65 (CH), 129.24 (CH), 128.70 (CH), 102.44 (CH), 82.48 (C), 41.94 (CH_2), 34.76 (CH_2), 24.76 (CH_2), 21.47 (CH_2); m/z=432 (M^+, 39%). Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.45; H, 5.59 ; N, 6.38.

1-Benzoyloxy-1-methylene-(N-3-benzoyluracil-6-yl)-3-methylcyclohexane [**6h-(1'S,3'R)/(1'R, 3'S)**]- (214 mg, 48%); mp= 188-190°C (from EtOAc/n-Hexane); ir ($CHCl_3$) ν_{max}: 3450, 1750, 1710, 1660, and 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 9.65 (1H, br s, N(1)-H), 7.46-7.65 (10H, m, Ar-H), 5.62 (1H, s, H-5), 3.11 (2H, m, CH_2), 1.01-2.48 (9H, m), 0.90 (3H, m, CH_3); m/z=446 (M^+, 39%). Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.86 ; N, 6.27 . Found: C, 69.91 ; H, 5.84 ; N, 6.33.

(1'S, 3'R)-1-Benzoyloxy-1-methylene-(N-3-benzoyluracil-6-yl)]-3-methylcyclohexane [**6h-(1'S, 3'R)**]- (281 mg, 63%); mp= 188-190°C (from EtOAc); $[\alpha]_D$ -12.75° (c. 1.2, $CHCl_3$); ir ($CHCl_3$) ν_{max}: 3450, 1750, 1710, 1660, and 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ ppm 9.65 (1H, br s, N(1)-H), 7.46-7.65 (10H, m, Ar-H), 5.62 (1H, s, H-5), 3.11 (2H, m, CH_2), 1.01-2.48 (9H, m), 0.90 (3H, m, CH_3); m/z=446 (M^+, 39%). Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.86 ; N, 6.27. Found: C, 69.96 ; H, 5.86 ; N, 6.31.

cis-2-Benzoyl-3-methylene-(N-3-benzoyluracil-6-yl)]cyclohexanone (**6i**)- (185 mg, 43%); mp=189-191°C (from EtOAc); ir ($CHCl_3$) ν_{max}: 3400, 1750, 1710, 1665, and 1590 cm^{-1}; ^{1}H-nmr (DMSO) δ ppm 11.5 (1H, br s, N(1)-H), 7.85 (10H, m, Ar-H), 5.40 (1H, s, H-5), 4.81 (1H, d, J 9.0 Hz, CH_2), 3.34 (2H, s, CH_2), 2.01 (7H, m, CH_2); ^{13}C-nmr ($CDCl_3$) δ ppm 209.09 (C), 198.53 (C), 170.40 (C), 162.46 (C), 155.67 (C), 150.32 (C), 137.75 (C), 135.67 (CH), 133.52 (CH), 131.51 (C), 128.92 (CH), 128.74 (CH), 128.53 (CH), 127.73 (CH), 99.60 (CH), 62.15 (CH), 41.32 (CH_2), 38.72 (CH), 38.02 (CH_2), 29.45 (CH_2), 24.10 (CH_2); m/z=430 (M^+, 28%). Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15 ; N, 6.50 . Found: C, 69.83 ; H, 5.17 ; N, 6.61.

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