Pergamon

Tetrahedron, Vol. 53, No. 20, pp. 7045-7056, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00402-X

Reactivity of Lithium Trimethylsilyldiazomethane and Diazomethane Toward the 5,6-Double Bond of Uracil and Uridine Derivatives

Raffaele Saladino,[a]* Luigi Stasi,[c] Claudia Crestini,[a] Rosario Nicoletti[c] and Maurizio Botta,[b]*

[a]Dipartimento Agrochimico Agrobiologico, Università degli studi di Viterbo "La Tuscia", via San Camillo de Lellis, 01100 Viterbo, Italy.

[b]Dipartimento Farmaco Chimico Tecnologico, Banchi di Sotto 55, Università degli Studi, 53100 Siena, Italy.

[c]Dipartimento di Chimica, p.le Aldo Moro 5, Università "La Sapienza", 00185, Roma, Italy.

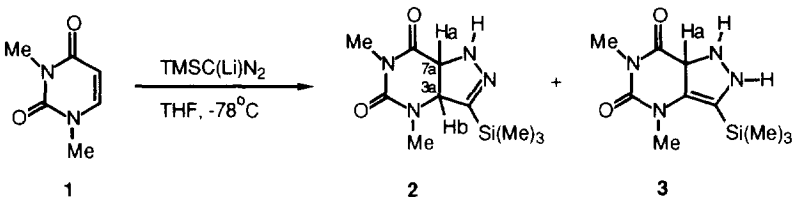
Abstract: The reaction of lithium trimethylsilyldiazomethane [TMS(Li)N_2] with uracil and uridine derivatives is reported; this provides a general method for the synthesis of several new annulated and fused heterocyclic systems. The unexpected cycloaddition of diazomethane (CH_2N_2) to the C-5,6 double bond of 5-nitrouracil and 5-nitrouridine derivatives is also reported. © 1997 Elsevier Science Ltd.

Lithium trimethylsilyldiazomethane [TMS(Li)N_2], easily prepared from trimethylsilyldiazomethane ($TMSCHN_2$) and n-butyllithium,[1] is a quite useful [C-N-N] synthon for the preparation of azoles.[2] Aoyama and coworkers showed that the pyrazole nucleus may be conveniently constructed by the reaction of TMSC(Li)N_2 with α,β-unsaturated nitriles[3] and α,β-unsaturated sulfones[4]. The reaction proceeds by nucleophilic attack of TMSC(Li)N_2 on the β-carbon followed by cyclization and subsequent elimination of lithium cyanide.[3] Moreover, 4-trimethylsilyl-1,2,3-triazoles have been prepared by the reaction of TMSC(Li)N_2 with ketenimines.[5] In particular, ketenimines bearing electron-withdrawing groups give 4-amino-3-trimethylsilylpyrazoles.[6] The same authors reported[7] that the reaction of TMSC(Li)N_2 with β-amino-α,β-unsaturated ketones gives 3- or 5-acylpyrazoles, while the reaction with β-pyrrolidino derivatives mainly affords 1,2-diazabicyclo[3.2.0]hepta-2,6-dienes.

Although the cycloaddition reaction is one of the most versatile tools for the synthesis of annulated and fused heterocyclic systems,[8] only a few examples of their application to the synthesis and modification of uracil and uridine derivatives are reported in the literature. For instance, Noguchi and coworkers reported the preparation of pyrazolo [3',4':4,5]pyrido[2,3-d]pyrimidines *via* nitrile imines[9] and *via* azomethine imines.[10] Prajapati and coworkers described the preparation of isoxazolo[3',4':4,5]pyrido[2,3-d]pyrimidines *via* nitrile oxides and nitrones.[11] Finally, Sasaki and coworkers reported the 1,3-dipolar cycloaddition of azide to pyrimidine rings activated by the presence of a 5-nitro or 5-bromo substituent,[12] and the intramolecular

cycloadditions of 5'-azido-5'-deoxyuridine derivatives.[13]

In a continuation of our studies about the reactions of the β-amino-α,β-unsaturated carbonyl moiety present in the 2,4(1H,3H)-pyrimidinedione system with ozone,[14] dimethyldioxirane[15] and organometallic reagents,[16] we studied the cycloaddition of TMSC(Li)N_2 to the 5,6-double bond of uracil and uridine derivatives. TMSC(Li)N_2 (1.5 mmol), prepared from trimethylsilyldiazomethane and n-butyllithium, was allowed to react with 1,3-dimethyluracil[17] **1** (1 mmol) in dry terahydrofuran (THF) at -78°C for 0.5h. The reaction products were found to be a mixture of 3a,7a-dihydro-4,6-dimethyl-3-trimethylsilyl-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **2** and the pyrazoline derivative **3** (58% and 29% yield, respectively), as shown in Scheme 1.



1 **2** **3**

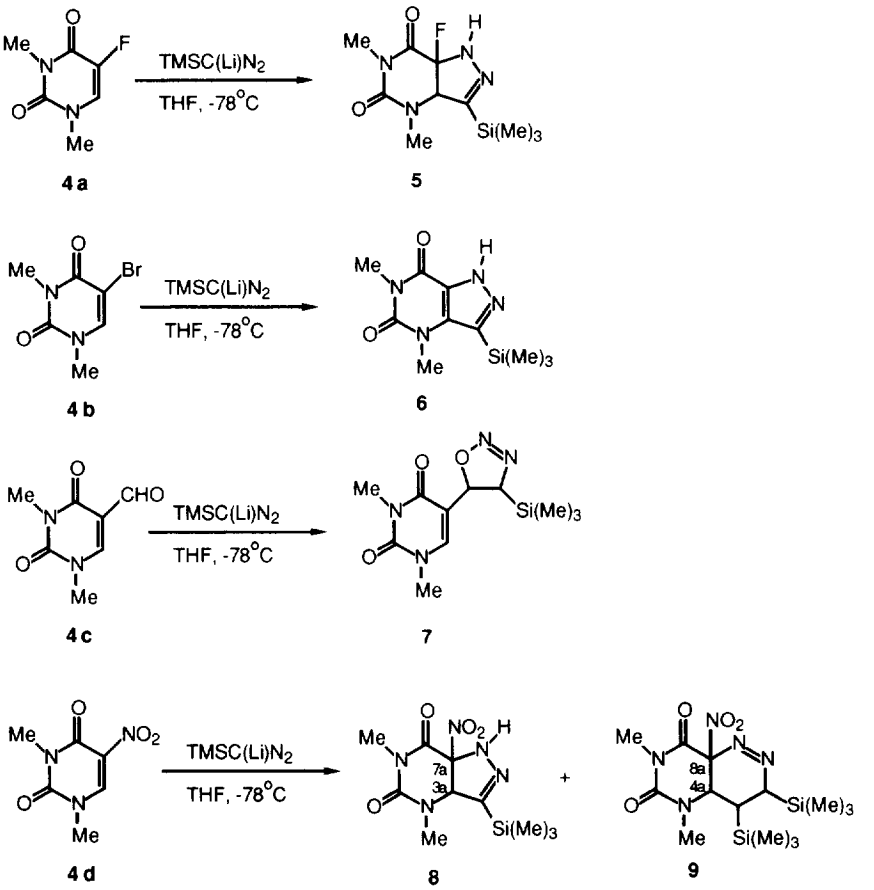
Scheme 1

When the reaction was carried out under similar experimental conditions using an excess of TMSC(Li)N_2 (2.5 mmol) the yield of **3** increased (45%), and **2** was isolated in 30% yield. The stereochemistry of the 3a and 7a-positions for **2** (numeration as reported in Scheme 1) was assigned to be cis on the basis of the coupling constant value (J 9.14 Hz) between protons Ha and Hb.

Probably, the reaction proceeds through a nucleophilic attack of TMSC(Li)N_2 on the β-carbon of the β-amino-α,β-unsaturated carbonyl moiety followed by cyclization and subsequent rearrangement to give **2**.[3] In the presence of an excess of TMSC(Li)N_2 the concomitant removal of the Hb proton in the 3a-position, followed by protonation during the work-up of the reaction, may explain the formation of the pyrazoline derivative **3**. The latter hypothesis is further confirmed by the quantitative transformation of **2** into **3** using a small excess of lithium bis(trimethylsilyl)acetamide in THF at -78°C (not shown).

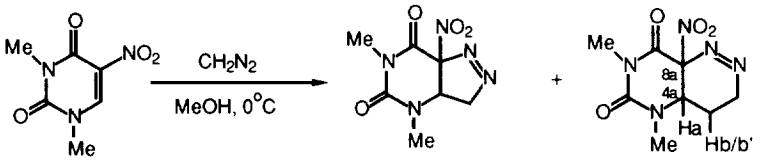
To evaluate the generality of this transformation and to study the effect of C-5 electron withdrawing substituents on the reaction pathway, we performed the reaction of some 5-substituted 1,3-dimethyluracil derivatives with TMSC(Li)N_2, under similar experimental conditions. Thus, the reaction of 5-fluoro-1,3-dimethyluracil **4a** with TMSC(Li)N_2 (1.2 mmol) in tetrahydrofuran (THF), at -78°C for 1h, gave the 3a,7a-dihydro-4,6-dimethyl-7a-fluoro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **5** as only recovered product in 68% yield (Scheme 2). In this reaction pyrazoline derivatives could not be detected. The reaction of 5-bromo-1,3-dimethyluracil **4b** with TMSC(Li)N_2 (1.2 mmol) in THF at -78°C gave 4,6-dimethyl-3-trimethylsilyl-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **6** in 54% yield. The use of an excess of TMSC(Li)N_2 (2.0 mmol) under similar experimental conditions increased the yield of **6** (78%). On the basis of these data, it is reasonable to

suggest that **6** might be formed by elimination of the bromine atom from the 7a position in the corresponding 1H-pyrazole intermediate (not isolated in our experimental conditions). 5-Formyl-1,3-dimethyluracil **4c** reacts with TMSC(Li)N_2 (1.2 mmol) in THF at -78°C to give a complex reaction mixture from which 5-(4',5'-dihydro-4-trimethylsilyl-1,2,3-oxadiazol-5'-yl)uracil **7** was the only recovered product in 25% yield. Noteworthy, products of addition on the β-carbon were not recovered in this case. The reaction of 5-nitro-1,3-dimethyluracil **4d** with TMSC(Li)N_2 (1.2 mmol) in THF at -78°C also gave a complex reaction mixture; the 3a, 7a-dihydro-4,6-dimethyl-7a-nitro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **8** and the pyridazine derivative **9** were the only isolated products (7% and 13% yield, respectively). The pyridazine derivative **9** could arise from an unexpected addition and subsequent cyclization of two molecules of TMSC(Li)N_2 with loss of one nitrogen molecule (Scheme 2).



Scheme 2

The high reactivity showed by 5-nitro-1,3-dimethyluracil **4d** with TMSC(Li)N_2 prompted us to investigate its behaviour with a less powerful dipolarophile, such as CH_2N_2. When **4d** was treated with an excess of CH_2N_2 (prepared from nitrosomethylurea in the presence of ether and 30% KOH aqueous solution and stored over KOH) in MeOH at 0°C, the 3a, 7a-dihydro-4,6-dimethyl-7a-nitro-Δ^1-pyrazolino[4,3-d]pyrimidin-5,7-dione **10** was obtained as main product (39%) and the 4a,8a-dihydro-5,7-dimethyl-8a-nitropyridazino[5,4-d]pyrimidin-6,8-dione **11** (28%) as by-product (Scheme 3). Compound **10** was found to be stable when treated with an excess of CH_2N_2. The stereochemistry of the 4a and 8a positions in compound **11** was determined by nuclear magnetic spectroscopy experiments. The conformational analysis of 5,6-dihydrouracil derivatives showed[18] that these compounds present a half-chair conformation, the [N-CO-N-CO] moiety being approximately in a coplanar fashion.

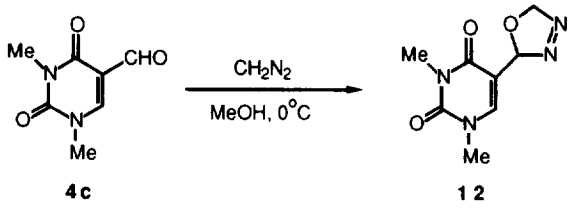


4d **10** **11**

Scheme 3

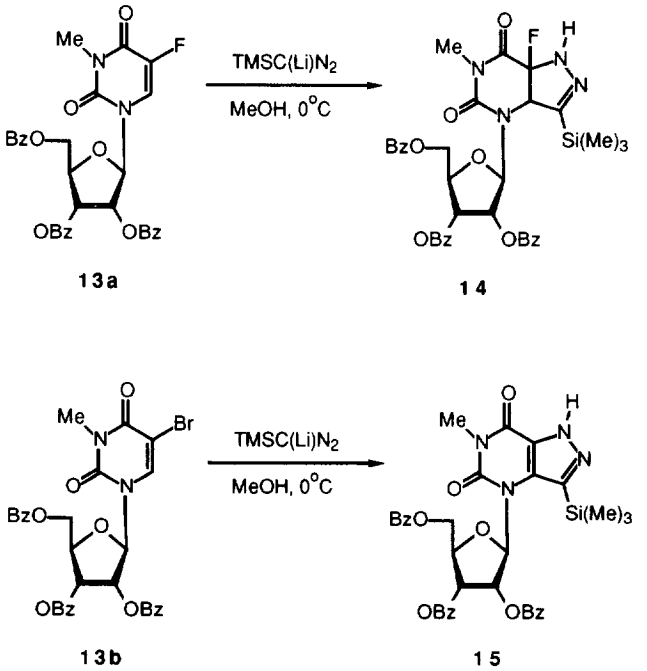
In the case of **11**, the proton Ha, present in the 4a position (Scheme 3), is in axial position as shown by the presence of an axial-axial (Jax-ax=9.33 Hz) and an axial-equatorial (Jax-eq=3.24 Hz) coupling constants for the ABX system. The irradiation of the Ha proton signal gave a ca. 5% enhancement of the N(5)-Me proton signal in NOE experiments. Furthermore, the absence of any detectable NOE effect between the N(5)-Me and the Hb/b' protons led to the assignement of a cis stereochemistry. We can put forward only hypotheses on the pathway leading to compound **11**. Parham and coworkers reported[19] that, when CH_2N_2 reacted with nitrostyrene an addition product was obtained in quantitative yield; however, the product appeared to be polymeric. It was also observed that secondary nitroolefines did not show the same behaviour yielding the expected pyrazoline derivatives. In our case, in accord with the results obtained in the reaction of **4d** with TMSC(Li)N_2, it is possible to suggest that **11** might be formed by the addition and subsequent cyclization of two molecules of CH_2N_2 with loss of one nitrogen molecule. The C-5 nitro substituent seems to play an important role in the reaction pathway. In fact, the pyridazine derivative is not recovered in the reactions of TMSC(Li)N_2 with uracil derivatives bearing other C-5 electron withdrawing substituents. This hypothesis might be further confirmed by the complete unreactivity of 1,3-dimethyluracil **1** and uracil derivatives **4a-b** toward CH_2N_2 under analogous experimental conditions.

The reaction of **4c**, in the presence of a small excess of CH_2N_2 in MeOH at -10°C, gave the 1,3,4-oxadiazole derivative **12** (53%) as the only recovered product (Scheme 4). It is interesting to note that, in the latter case, the orientation of CH_2N_2 addition to the carbonyl moiety is opposite to that previously observed for the addition of TMSC(Li)N_2 to **4c**.



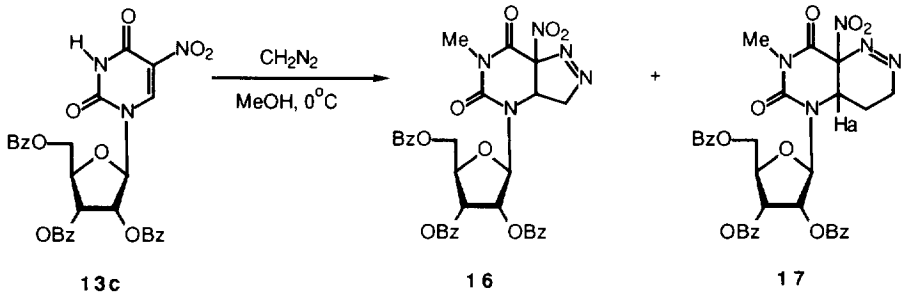
Scheme 4

Diazomethane has been added to a large number of conjugated olefins to give pyrazoline derivatives,[20] but only a few examples[21] have been reported of the formation of products resulting from the addition to the carbonyl group. It is noteworthy that the orientation in the 1,3-dipole addition to the carbonyl group of **4c** is opposite to that previously obtained by us in the reaction of 1,3-dimethyl-6-formyluracil with CH_2N_2.[22] In that case, the 1,3-dimethyl-6-oxiranyluracil (not shown) was obtained. These data show that the position of the formyl moiety on the 5,6-double bond of the uracil ring is an important feature for the orientation of the addition of CH_2N_2 to the carbonyl group.



Scheme 5

To test the generality of the reaction of uracil derivatives with TMSC(Li)N_2 and CH_2N_2, we studied the reaction of some uridine derivatives under analogous experimental conditions. The reaction of 2',3',5'-tri-O-benzoyl-N(3)-methyl-5-fluorouridine **13a**, prepared starting from 5-fluorouracil using the procedure described by Vorbruggen[23] (and subsequent alkylation of the N(3) nitrogen atom according to the procedure reported by Reese)[24] with TMSC(Li)N_2 (1.5 mmol) in THF at -78°C for 1h, afforded the 3a,7a-dihydro-6-methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **14**, as the only recovered product in 63% yield. 2',3',5'-Tri-O-benzoyl-N(3)-methyl-5-bromouridine **13b** reacted with an excess of TMSC(Li)N_2 (2.2 mmol) in THF at -78°C to give 6-methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **15** in 78% yield (Scheme 5). In accordance with the results obtained in the reaction of **4b** with TMSC(Li)N_2, compound **15** may be formed by elimination of the bromine atom from the 7a-position in the corresponding 1H-pyrazole nucleoside intermediate (not isolated in our case). When 2',3',5'-Tri-O-benzoyl-5-nitrouridine **13c** was treated with an excess of CH_2N_2 in MeOH at 0°C, the 3a,7a-dihydro-6-methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-7a-nitro-Δ^1-pyrazolino[4,3-d]pyrimidin -5,7-dione **16** and the pyridazine nucleoside derivative **17** were recovered in acceptable yields (45% and 33% yield, respectively) [Scheme 6].



Scheme 6

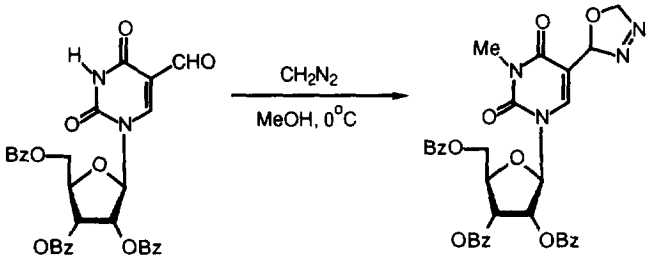
In the case of **17**, the proton Ha in the 4a position is axial as shown by the presence of an axial-axial (Jax-ax=10.5 Hz) and an axial-equatorial (Jax-eq=2.7 Hz) coupling constants for the ABX system. 2',3',5'-Tri-O-benzoyl-5-bromouridine and 2',3',5'-tri-O-benzoyl-5-fluorouridine (not shown) did not react with CH_2N_2 under analogous experimental conditions.

The reaction of nucleic acids and their components with diazomethane has been extensively studied[25] in connection with the possible relationship between the mechanism of mutagenesis and carcinogenesis.[26] In all cases products of alkylation of the heteroatoms present on the nucleic bases were described; the only side reaction, observed in the case of some pyrimidine nucleosides, being the methylation of the sugar residue.[27]

To the best of our knowledge, the reaction of 5-nitrouracil and 5-nitrouridine with CH_2N_2 is the first report in the literature of the dipolar cycloaddition of CH_2N_2 to the 5,6-double bond of the uracil ring.

Finally, in accordance with the results previously shown in the case of 1,3-dimethyl-5-formyluracil, the

reaction of 2',3',5'-tri-O-benzoyl-5-formyluridine **13d**, with an excess of CH_2N_2 in MeOH at 0°C, gave the 2',3',5'-tri-O-benzoyl-N(3)-methyl-5(2"-2,4-dihydrooxazol-2-yl)uridine derivative **18** in 68% yield (Scheme 7).



Scheme 7

This result confirms that in the cycloaddition of CH_2N_2 to uracil derivatives, bearing a formyl group on the C-5 position of the uracil ring, the carbonylic carbon is the most electrophilic center. Further work in this area is in progress in our laboratories.

Experimental

NMR spectra were recorded on a Bruker (200 MHz) spectrometer and are reported in δ values. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed with a 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 uncorrect. 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-Dimethyluracil **1**, and 1,3-dimethyl-5-bromouracil **4b** were synthesized according to the procedure reported by Allen;[17] 1,3-dimethyl-5-fluorouracil **4a**, and 1,3-dimethyl-5-nitrouracil **4d** were synthesized according to the procedure reported by Hedayatullah;[28] 1,3-dimethyl-5-formyluracil **4c** was synthesized according to the

procedure reported by Botta;[29] 2',3',5'-tri-O-benzoyl-N(3)-methyl-5-fluorouridine **13a**, 2',3',5'-tri-O-benzoyl-N(3)-methyl-5-bromouridine **13b**, and 2',3',5'-Tri-O-benzoyl-5-nitrouridine **13c** were synthesized according to the procedure reported by Vorbruggen[23] (when necessary, the alkylation of the N(3) nitrogen atom was performed according to the procedure reported by Reese);[24] 2',3',5'-tri-O-benzoyl-5-formyluridine **13d** was synthesized according to the procedure reported by Mertes.[30]

Reaction of compounds **1**, **4a-d**, and **13a-b** with lithium trimethylsilyldiazomethane [TMSC(Li)N_2]. General procedure.

The reactions were carried out by adding TMS(Li)N_2 (1.2 mmol), prepared from trimethylsilyldiazomethane ($TMSCHN_2$) and n-butyllithium,[1] to solutions of the required substrate (1.0 mmol) in dry THF (5 ml) at -78°C, until the substrate disappeared (TLC chloroform:methanol=9.5:0.5).The mixture was decomposed by addition of NH_4Cl s.s. The organic layer diluted with EtOAc was then separated, washed with $NaHCO_3$ s.s., and brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash-chromatography using CH_2Cl_2:EtOAc=9.0:1.0 as eluant.

3a,7a-Dihydro-4,6-dimethyl-3-trimethylsilyl-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **2**-(147 mg, 58%), m. p. 105-110 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 3400 (NH), 1720 (CO), 1650 (CO) cm^{-1}. Anal. Calcd. for $C_{10}H_{18}N_4O_2Si$: C, 47.20; H, 7.10; N, 22.0. Found: C, 47.31; H, 7.10; N, 22.08.^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.20 (9H, s, CH_3), 3.15 (3H, s, CH_3), 3.25 (3H, s, CH_3), 4.05 (1H, d, J 9.14 Hz, H-6), 4.55 (1H, d, J 9.14 Hz, H-5), 6.78 (1H, b. s., NH); m/z 254 (M^+, 39%).

Pyrazolidine derivative **3**- (74 mg, 29%), m. p. 101-103 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 3380 (NH), 1735 (CO), 1640 (CO) cm^{-1}. Anal. Calcd. for $C_{10}H_{18}N_4O_2Si$: C, 47.20; H, 7.10; N, 22.0. Found: C, 47.18; H, 7.08; N, 22.13. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.28 (9H, s, CH_3), 2.91 (3H, s, CH_3), 3.51 (3H, s, CH_3), 6.80 (1H, s, H-5), 9.20 (1H, b. s., NH), 11.20 (1H, b.s., NH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.02 (CH_3), 27.14 (CH_3), 34.58 (CH_3), 125.86 (CH), 162.12 (C), 166.57 (C), 178.05 (C); m/z 254 (M^+, 43%).

3a,7a-Dihydro-4,6-dimethyl-7a-fluoro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **5**- (185 mg, 68%), m. p. 181-186 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 3536 (NH), 3392 (NH), 1725 (CO), 1645 (CO) cm^{-1}. Anal. Calcd. for $C_{10}H_{17}FN_4O_2Si$: C, 44.10; H, 6.30; N, 20.60. Found: C, 44.18; H, 6.25; N, 20.68. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.45 (9H, s, CH_3), 3.37 (1H, d, $J_{H/F}$ 6.10 Hz, CH), 3.42 (3H, s, CH_3), 3.58 (3H, s, CH_3), 7.20 (1H, b. s., CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.01 (CH_3), 28.20 (CH_3), 34.28 (CH_3), 115.42 (CH), 129.61 (C), 151.94 (C), 157.85 (C); m/z 272 (M^+, 43%).

4,6-Dimethyl-3-trimethylsilyl-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **6**- (136 mg, 54%), m. p. 189-192 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 3600 (OH), 1680 (CO) cm^{-1}. Anal. Calcd. for $C_{10}H_{16}N_4O_2Si$:

C, 47.60; H, 6.40; N, 22.20. Found: C, 47.55; H, 6.40; N, 22.13. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.45 (9H, s, CH_3), 3.50 (3H, s, CH_3), 3.65 (3H, s, CH_3), 12.72 (1H,b. s., NH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.02 (CH_3), 28.75 (CH_3), 35.0 (CH_3), 129.10 (C), 130.20 (C), 135.60 (C), 151.20 (C), 158.15 (C); m/z 252 (M^+, 78%).

5-(4',5'-Dihydro-4-trimethylsilyl-1,2,3-oxadiazol-5'-yl)uracil **7**- (70.5 mg, 25%), m. p. 99-101 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 1740 (CO), 1680 (CO) cm^{-1}. Anal. Calcd. for $C_{11}H_{18}N_4O_3Si$: C, 46.80; H, 6.40; N, 19.80. Found: C, 46.87; H, 6.42; N, 19.84. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.31 (9H, s, CH_3), 3.15 (3H, s, CH_3), 3.25 (3H, s, CH_3), 4.05 (1H, d, J 8.98 Hz, CH), 4.55 (1H, d, J 8.98 Hz, CH), 6.80 (1H, s, H-6); m/z 282 (M^+, 28%).

3a, 7a-Dihydro-3-trimethylsilyl-4,6-dimethyl-7a-nitro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **8**- (21 mg, 7%), oil. I.R. ($CHCl_3$) ν_{max}: 1735 (CO), 1680 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.85 (9H, s, CH_3), 3.30 (3H, s, CH_3), 3.40 (3H, s, CH_3), 4.60 (1H, s, CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.01 (CH_3), 29.66 (CH_3), 35.66 (CH_3), 70.01 (CH), 84.70 (C), 153.0 (C), 162.20 (C); m/z 299 (M^+, 19%).

Pyridazine derivative **9**- (50 mg, 13%), oil. I.R. ($CHCl_3$) ν_{max}: 1745 (CO), 1680 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.88 (9H, s, CH_3), 2.60 (1H, m, CH), 2.95 (3H, s, CH_3), 3.19 (3H, s, CH_3), 4.71 (1H, s, CH), 5.18 (1H, m, CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.01 (CH_3), 14.06 (CH), 22.62 (CH_3), 31.55 (CH_3), 35.66 (CH), 57.13 (CH), 85.16 (C), 153.60 (C), 163.15 (C); m/z 385 (M^+, 26%).

3a,7a-Dihydro-3-trimethylsilyl-7a-fluoro-6-methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)1H-pyrazolo[4,3-d]pyrimidin-5,7-dione **14**- (442 mg, 63%), m.p. 199-203 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 1718 (CO), 1680 (CO), 1530 (C=N) cm^{-1}. Anal. Calcd. for $C_{35}H_{35}FN_4O_9Si$: C, 59.80; H, 5.0; N, 8.0. Found: C, 59.82; H, 5.11; N, 8.10. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.40 (9H, s, CH_3), 3.40 (3H, s, CH_3), 4.73 (3H, m, H-4' and H-5'/5"), 4.85 (1H, d, $J_{H/F}$ 7.5 Hz, CH), 5.80 (1H, m, H-3'), 6.30 (1H, m, H-2'), 6.55 (1H, d, J 6.8 Hz, H-1'), 7.60 (15H, m, Ph-H); m/z 702 (M^+, 51%).

6-Methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)1H-Pyrazole[4,3-d]pyrimidin-5,7-dione **15**- (531 mg, 78%), m.p. 206-208 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 1718 (CO), 1680 (CO), 1580 (C=C and C=N) cm^{-1}. Anal. Calcd. for $C_9H_{12}N_4O_2Si$: C, 61.60; H, 5.0; N, 8.20. Found: C, 61.64; H, 5.11; N, 8.15. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.41 (9H, s, CH_3), 3.42 (3H, s, CH_3), 4.81 (3H, m, H-4' and H-5'/5"), 5.80 (1H, m, H-3'), 6.35 (1H, m, H-2'), 6.53 (1H, d, J 8.5 Hz, H-1'), 7.50 (15H, m, Ph-H); m/z 682 (M^+, 74%).

Reaction of compounds **4c-d**, and **13c-d** with diazomethane [CH_2N_2]. General procedure.
The reactions were carried out by adding CH_2N_2, prepared from nitrosomethylurea in the presence of ether and 30% KOH aqueous solution and stored over KOH,[1] to solutions of the required substrate (1.0 mmol) in MeOH (5 ml) at 0°C, until the substrate disappeared (TLC chloroform:methanol=9.5:0.5).The mixture was decomposed by addition of a small amount of acetic acid and the organic layer careful evaporated under reduced pressure. The residue was purified by flash-chromatography using CH_2Cl_2:EtOAc=9.0:1.0 as eluant.

3a,7a-Dihydro-4,6-dimethyl-7a-nitro-Δ^1-pyrazolino[4,3-d]pyrimidin-5,7-dione **10**- (63 mg, 28%), oil. I.R. ($CHCl_3$) ν_{max}: 1730 (CO), 1675 (CO), 1620 (NO_2) cm^{-1}. Anal. Calcd. for $C_7H_9N_5O_4$: C, 37.0; H, 4.0; N, 30.80. Found: C, 37.10; H, 4.0; N, 30.71. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 1.49 (1H, m, CH), 2.63 (1H, t J 8.0 Hz, CH), 3.15 (3H, s, CH_3), 3.19 (3H, s, CH_3), 3.59 (1H, m, CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 0.02 (CH_3), 20.34 (CH_2), 29.52 (CH_3), 35.24 (CH_3), 41.03 (CH), 83.10 (C), 148.25 (C), 161.10 (C); m/z 227 (M^+, 32%).

4a, 8a-Dihydro-5,7-dimethyl-8a-nitropyridazine[5,4-d]pyrimidin-6,8-dione **11**- (94 mg, 39%), oil. I.R. ($CHCl_3$) ν_{max}: 1738 (CO), 1680 (CO), 1610 (NO_2) cm^{-1}. Anal. Calcd. for $C_8H_{11}N_5O_4$: C, 39.80; H, 4.60; N, 29.0. Found: C, 39.71; H, 4.60; N, 29.19. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 2.42 (2H, m, CH_2), 3.05 (3H, s, CH_3), 3.13 (3H, s, CH_3), 4.56 (2H, m, CH_2), 5.28 (1H, dd Jax-ax 9.33 Hz and Jax-eq 3.24 Hz, CH); δ_C ppm: 0.01 (CH_3), 29.39 (CH_2), 29.68 (CH_3), 31.18 (CH_3), 69.42 (CH_2), 82.92 (CH), 149.53 (C), 151.01 (C), 183.20 (C); m/z 241 (M^+, 27%).

1,3,4-Oxadiazole derivative **12**- (96 mg, 53%), m.p. 88-90 °C (from n-hexane/EtOAc). I.R. ($CHCl_3$) ν_{max}: 1718 (CO), 1680 (CO) cm^{-1}. Anal. Calcd. for $C_8H_{10}N_4O_3$: C, 45.70; H, 4.80; N, 26.70. Found: C, 45.81; H, 4.82; N, 26.73. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 3.30 (3H, s, CH_3), 3.37 (3H, s, CH_3), 3.48 (2H, s, CH2), 5.30 (1H, s, H-6), 7.39 (1H, s, CH); δ_C ppm: 27.68 (CH_2), 37.03 (CH_3), 37.15 (CH_3), 54.45 (CH), 98.92 (CH), 110.87 (C), 141.46 (C), 162.37 (C); m/z 182 (M^+- N_2, 27%).

3a,7a-Dihydro-6-methyl-4(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)7a-nitro-Δ^1-pyrazolino[4,3-d]pyrimidin - 5,7-dione **16**- (296 mg, 45%), oil. I.R. ($CHCl_3$) ν_{max}: 1728 (CO), 1680 (CO), 1625 (NO_2) cm^{-1}. Anal. Calcd. for $C_{32}H_{27}N_5O_{11}$: C, 58.40; H, 4.10; N, 10.60. Found: C, 58.43; H, 4.12; N, 10.62.^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 1.56 (1H, m, CH), 2.31 (1H, m, CH_2), 3.18 (3H, s, CH_3), 3.90 (1H, m, CH), 4.60 (3H, m, H-4' and H-5'/5"), 5.89 (2H, m, H-2' and H-3'), 6.40 (1H, d, J 7.0 Hz, H-1'), 7.80 (15H, m, Ph-H); δ_C ppm: 28.61 (CH_2), 36.10 (CH_3), 62.20 (CH_2), 64.18 (CH), 70.25 (CH), 71.48 (CH), 80.03 (CH), 87.03 (CH), 128.44 (CH), 129.68 (CH), 133.76 (C), 149.50 (C), 158.10 (C), 165.70 (C), 166.80 (C); m/z 657 (M^+, 43%).

Pyridazine nucleoside derivative **17**- (221 mg, 33%), oil. I.R. ($CHCl_3$) ν_{max}: 1718 (CO), 1680 (CO), 1637 (NO_2) cm^{-1}. Anal. Calcd. for $C_{33}H_{29}N_5O_{11}$: C, 59.0; H, 4.40; N, 10.40. Found: C, 59.08; H, 4.42; N, 10.36. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 2.54 (2H, m, CH_2), 3.73 (2H, m, CH_2), 3.90 (3H, s, CH_3), 4.77 (3H, m, H-4' and H-5'/5"), 5.49 (1H, dd, Jax-ax 10.5 Hz and Jax-eq 2.7 Hz, CH), 5.83 (2H, m, H-2' and H-3'), 6.20 (1H, d, J 7.8 Hz, H-1'),7.80 (15H, m, Ph-H); δ_C ppm: 21.10 (CH_2), 28.61 (CH_2), 38.40 (CH_2), 61.15 (CH), 63.47 (CH), 70.25 (CH_2), 71.48 (CH), 80.03 (CH), 87.03 (CH), 128.56 (CH), 129.61 (C), 129.68 (C), 133.76 (CH), 148.50 (C), 165.10 (C), 166.23 (C); m/z 671 (M^+, 43%).

2',3',5'-Tri-O-benzoyl-N(3)-methyl-5(1,3,4-oxadiazol-2-yl)uridine derivative **18**- (435 mg, 68%), oil. I.R. ($CHCl_3$) ν_{max}: 1718 (CO), 1680 (CO), 1560 (C=C and N=N) cm^{-1}. Anal. Calcd. for $C_{33}H_{28}N_4O_{10}$: C, 61.90; H, 4.40; N, 8.70. Found: C, 61.81; H, 4.33; N, 8.66. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 3.10 (3H, s, CH_3), 3.30 (1H, s, CH), 4.55 (2H, m, CH_2), 4.80 (3H, m, H-4' and H-5'/5"), 5.83 (2H, m, H-2' and H-3'), 6.43 (1H, d, J 9.8 Hz, H-1'), 7.80 (16H, m, Ph-H + H-6); m/z 640 (M^+, 33%).

Acknowledgements: financial support from Italian MURST is acknowledged.

References and Notes.

1. Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth.* **1990**, 68, 1.
2. (a) Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, 30, 3450. (b) Aoyama, T.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, 30, 3380.
3. Aoyama, T.; Inoue, S.; Shioiri, T. *Tetrahedron Lett.* **1984**, 25, 433-436.
4. Asaki, T.; Aoyama, T.; Shioiri, T. *Heterocycles* **1988**, 27, 343-346.
5. Aoyama, T.; Katsuta, S.; Shioiri, T. *Heterocycles* **1989**, 28, 133.
6. Aoyama, T.; Nakano, T.; Marumo, K.; Uno, Y.; Shioiri, T. *Synthesis* **1991**, 1163-1167.
7. Ito, T.; Hatano, K.; Kurono, Y.; Aoyama, T.; Shioiri, T. *Heterocycles* **1993**, 35, 41-46.
8. Padwa, A. in "1,3-Dipolar cycloaddition chemistry"; Padwa, A., Ed.; John Wiley and Sons, New York, **1984**, Vol. 2, p 277.
9. Noguchi, M.; Nagata, S.; Kajigaeshi, S. *Chem. Pharm. Bull.* **1986**, 34, 3994.
10. Noguchi, M.; Yamada, K. *Synthesis* **1993**, 145-148.
11. Prajapati, D.; Bhuyan, P.; Sandhu, J.S. *J. Chem. Soc, Perkin Trans I* **1988**, 607: see also; Kim, J.N.; Ryu, E.K. *J. Org. Chem.* **1992**, 57, 1088-1092.
12. (a) Sasaki, T.; Minamoto, K.; Kino, M.; Mizuno, T. *J. Org. Chem.* **1976**, 41, 1100. (b) Blank, H.U.; Wempen, I.; Fox, J. *J. Org. Chem.* **1969**, 35, 1131.
13. (a) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, 36, 865. (b) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Am. Chem. Soc.* **1978**, 100, 2248.
14. Saladino, R.; Crestini, C.; Occhionero, F.; Nicoletti, R. *Tetrahedron* **1995**, 12, 3607-3616.

15. (a) Saladino, R.; Bernini, R.; Mincione, E.; Tagliatesta, P.; Boschi, T. *Tetrahedron Lett.* **1996**, 37, 2647-2650. (b) Saladino, R.; Bernini, R.; Crestini, C.; Mincione, E.; Bergamini, A.; Marini, S.; Palamara, A.T. *Tetrahedron* **1995**, 27, 7561-7578.
16. Botta, M.; Saladino, R.; Gambacorta, A.; Nicoletti, R. *Heterocycles* **1991**, 32, 1537-1545.
17. Scannel, J.P.; Crestfield, A.M.; Allen, F.W. *Biochim. Biophys. Acta* **1958**, 32, 406.
18. (a) Chabre, M.; Gagnaire, C.; Nofre, C. *Bull. Soc. Chim.* **1965**, 1749. (b) Rouillier, P.; Delmau, J.; Duplan, J.; Nofre, C. *Tetrahedron Lett.* **1966**, 35, 4189-4194.
19. Parham, W.E.; Bleasdale, J.L. *J. Am. Chem. Soc.* **1950**, 72, 3843-3846.
20. (a) Gutsche, A. *Org. Reactions* **1954**, 8, 364-429. (b) Parham, W.E.; Blake, F.D.; Theissen, D.R. *J. Chem. Soc.* **1962**, 27, 2415-2419. (c) Ledwith, A.; Parry, D. *J. Chem. Soc. (B)* **1966**, 1408. (d) Huisgen, R. *J. Org. Chem.* **1975**, 41, 403-419. (e) King, R.R. *J. Org. Chem.* **1982**, 47, 5397-5398.
21. Smith, L.I.; Pings, W.B. *J. Org. Chem.* **1937**, 2, 95.
22. Botta, M.; Saladino, R.; Gambacorta, A.; Nicoletti, R. *Tetrahedron Asymmetry* **1990**, 1, 441-444.
23. Niedballa, U.; Vorbruggen, H. *J. Org. Chem.* **1974**, 39, 3654-3660.
24. Haines, J.A.; Reese, C.B.; Lord Todd, A.R. *J. Chem. Soc.* **1964**, 1406.
25. (a) Miles, H.T. *Biochim. Biophys. Acta* **1956**, 22, 247. (b) Miles, H.T. *J. Am. Chem. Soc.* **1957**, 79, 2565. (c) Haines, J.A.; Reese, C.B.; Todd, A.R. *J. Chem. Soc.* **1964**, 1406. (d) Roosevelt, T.; Fleyscher, M.H.; Hall, R.H. *J. Med. Chem.* **1965**, 8, 486. (e) Wong, J.L.; Fuchs, D.S. *J. Org. Chem.* **1971**, 36, 848-850.
26. (a) Ueda, T.; Fox, J.J. *Advan. Carbohyd. Chem.* **1967**, 22, 382. (b) Brimacombe, R.L.C., Griffin, B.E., Haines, J.A.; Haslam, W.J.; Reese, C.B. *Biochemistry* **1965**, 4, 2452. (c) Magee, P.N.; Barnes, J.M. *Advan. Cancer. Res.* **1967**, 10, 227.
27. Reese, C.B.; Sulston, J.E. *Biochim. Biophys. Acta* **1967**, 149, 293.
28. Hedayatullah, M. *J. Heterocycl. Chem.* **1981**, 18, 339.
29. Botta, M.; De Angelis, F.; Corelli, F.; Meninchincheri, M.; Nicoletti, R.; Marongiu, M.E.; Pani, A.; La Colla, P. *Arch. Pharm. (Weinheiren)* **1991**, 324, 203-207.
30. Kampf, A.; Pillar, C.J.; Woodford, W.J.; Mertes, M.P. *J. Med. Chem.* **1976**, 7, 909-915

(*Received in UK* 7 *March* 1997; *revised* 4 *April* 1997; *accepted* 7 *April* 1997)