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6-ALKYL- AND 5,6-DIALKYL-2-METHOXY-4(3H)-PYRIMIDINONES IN THE TRANSFORMATIONS OF PYRIMIDINES. REGIOSPECIFIC 1-N-ACYLATION OF PYRIMIDINES.

Maurizio Botta*, Francesco De Angelis, Gabriella Finizia, Rosario Nicoletti*
Dip. Chimica, Università "La Sapienza", P.le A. Moro 5-00185 Roma, Italy.

Maurizio Delfini

Ist. Chimica e Tecnologia dei Radioelementi, CNR, Padova, Italy.

Summary: Transformation of 6- and 5,6-dialkyl-2-methoxy-4(3H)-pyrimidinones (1a and 1b) into 1-N-acylated-pyrimidine derivatives 3(a-f) under Friedel-Craft like conditions is presented. In different acylation conditions 4-O-acylated--pyrimidines (5a and 5b) are also obtained. Compounds (3c) and (3f) can be directly converted into 1-N-acyl-protected-isouridine analogues (8a and 8b).

The regioselective single-N-acylations of uracils and its derivatives has always received specific attention[1] since this reaction opens the possibility to obtain selectively alkylated and/or nucleoside derivatives of such compounds. A recent paper of Reese and co-workers describes the synthesis of 1-N and 3-N-benzoyl derivatives of uracil and thymine.[2]

To the best of our knowledge no records are available in the literature dealing with the regiospecific N-benzoylation of 6-alkyl and 5,6-dialkyluracils and it is well known that the presence of a 6-alkyl group lowers the reactivity of 1-N. Actually some experiments of benzoylation of 6-methyluracil, using the cited Reese method, gave poor results in our hands.

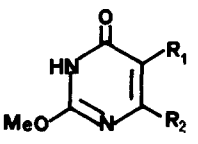
Our interest in the chemistry of 2-methoxy-4(3H)-pyrimidinones (1) as possible starting materials in selective reactions at the pyrimidine nucleus[3,4] prompted us to study the acylation reaction under Friedel-Crafts like conditions on 1a and 1b.

Compounds (1a and 1b), prepared as previously reported,[4] were silylated in the usual way.[5] Reagents in excess were removed in vacuo and the crude material, dissolved in CH_3CN, was reacted with the appropriate aroyl chloride (1.2 mole/ equivalent) by gently warming for 0.5 hr in the presence of $SnCl_4$ (1.6 mole/

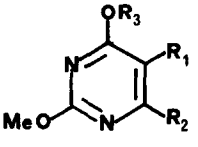
equivalent). The usual work-up gave the crude product which was purified by flash chromatography. Results are reported in the table.

Compound	Yield(%)	mp (°C)(solv.)	Compound	Yield(%)	mp (°C) (solv.)
3a	80	163-5 (MeOH)	3d	70	186-8 ($CHCl_3$)
b	57	168-70(MeOH)	e	58	156-8 ($CHCl_3$)
c	63	160-3 ($CHCl_3$)	f	93	195-7 ($CHCl_3$)

The correctness of structures 3 can be argued from ^{13}C n.m.r. spectra. With reference to 1 in fact, in 3 an upfield shift is exhibited by 6-C(10 p.p.m.), 6-C-$\underline{C}H_3$(7 p.p.m.) and 2-C (2 p.p.m.) whilst 5-C and OCH_3 resonance signals exhibited a small downfield shift.[7]



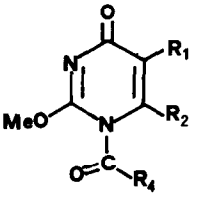
1a: R_1=H ; R_2=Me
b: R_1=R_2=$-(CH_2)_4-$



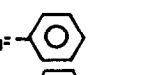
2a : R_1=H; R_2=Me ; R_3=Si(Me)$_3$
b : R_1-R_2=$-(CH_2)_4-$; R_3-Si(Me)$_3$

4 : R_1=H ; R_2=Me; R_3=Si(Me)$_2$ ^{t}Bu

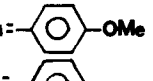
5a : R_1=H; R_2=Me; R_3= Ac
b : R_1=H; R_2=Me; R_3= Bz



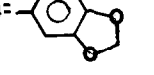
3a: R_1=H ; R_2=Me; R_4=



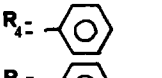
b: R_1=H ; R_2=Me; R_4=



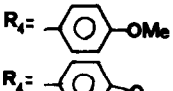
c: R_1=H; R_2=Me; R_4=



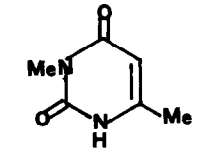
d: R_1-R_2=$-(CH_2)_4$; R_4=



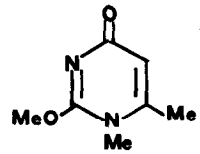
e R_1=R_2=$-(CH_2)_4$; R_4=



f R_1=R_2=$-(CH_2)_4$; R_4=



6



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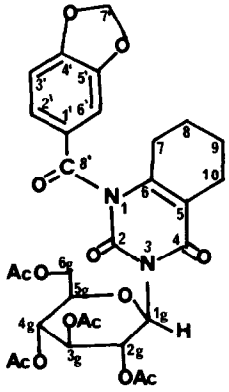
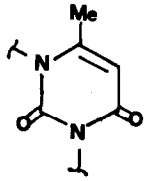


8b



8a

In the case of compound (3c)[8] the site of substitution was confirmed by converting it into the 3-N-methyluracil (6). Hydrolysis of the methoxyl by treating 3c with an aqueous solution of $NaHCO_3$,[9] 3-N-alkylation with CH_3I and re-

moval of the piperonyl by methanolysis gave (6) which was identified by comparison with an authentic sample available in our laboratory.[10]

No reaction took place when alkyl acid chlorides were used instead. Under forced conditions we could observe only a transmethylation reaction. Along with some desmethylated product (44%) we obtained the 1,6-dimethyl-2-methoxy-4-pyrimidinone(7, 45%)identified by hydrolysis and comparison with an authentic sample. This was the only result we could obtain with different Lewis acid ($AlCl_3$, BF_3, $TiCl_4$, $ZnBr_2$).Different results were obtained by using as acylating agent the mixed anhydride obtained by mixing acetic acid (one mmole), trifluoroacetic anhydride (3 mmoles) and phosphoric acid 85% (1.1 mmoles).[11] 2-Methoxy-4-t-butyldimethylsilyloxy-6-methylpyrimidine (4, lack of carbonyl absorbtion in the i.r.), was prepared by stirring for three days a mixture of 1a (1 mmole), t-butyl dimethylsilyl chloride (1.2 mmoles) and imidazole (2.5 mmoles) in CH_3CN. 4 was then added to the acylating reagent previously mentioned and the mixture was gently warmed (50°C) under stirring. When the reaction did not proceed further (t.l.c.) the mixture was diluted with ether and the organic phase washed with ice, water and an aqueous solution of $NaHCO_3$. Preparative t.l.c. afforded 5a, identified as 2-methoxy-4-acetoxy-6-methyl pyrimidine (32%, m.p. 121-122°C) along with some starting material 1a. The site of attack was established by n.m.r. (downfield shift of 5-H proton resonance of 5a with respect to the same proton in 1a, 6.53 vs 5.99) by i.r. (presence of only one carbonyl absorbtion at ν=1750 cm^{-1}, instead of 1660 in 1a) and confirmed by its rate of ammonolysis.[12] Same reaction was carried out with the mixed anhydride of benzoic acid and 2-methoxy-4-benzoyloxy-6-methyl pyrimidine (5b) was obtained (40%, m.p. 137-139°C).

Once more the presence[3,4] in 3 of the 2-methoxy group turns to be useful for regioselective functionalization at 3-N. As example, 3c and 3f were reacted with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in the modified Hilbert-Johnson conditions.[13] 8a and 8b were obtained in good yields (as oils). They were characterised through their n.m.r. spectra.[14] It is interesting to note that this is the first straightforward route to 1-N-acyl-protected-3 -D--glucopyranosyl-6-alkyl and 5,6-dialkyluracils (isouridine analogues).

REFERENCES AND FOOTNOTES

1) L. B. Spector, and Z. B. Keller, J. Biol. Chem., 232, 185 (1958); R. W. Chambers, Biochemistry, 4, 219 (1965), see refs. 2 and refs. there cited
2) K. A. Cruickshank, J. Jiricny, and C. B. Reese, Tetrahedron Lett., 681(1984)
3) M. Botta, F. De Angelis, G. Finizia, A. Gambacorta, and R. Nicoletti, Synth. Commun., 15, 27 (1985).

4) M. Botta, M. Cavalieri, D. Ceci, F. De Angelis, G. Finizia, and R. Nicoletti, Tetrahedron, 40, 3313 (1984)
5) See for example L. Birkofer and A. Ritter, Angew. Chem., Int. Edit., 4, 417 (1965)
6) Satisfactory microanalyses and spectroscopic data were obtained for all new compounds described.
7) As examples ^{13}C n.m.r. and ^{1}H n.m.r. spectra of 3c and 3f are reported. Compound 3c ^{13}C n.m.r. ($CDCl_3$) δ : 17.70 (Me-C-6), 55.91 (Me-C-2), 102.81 (C-7'), 107.73 (C-5), 108.89 (C-6'), 109.37 (C-3'), 125.65 (C-1'), 127.81 (C-2'), 147.57 (C-4'), 149.14 (C-5'), 154.63 (C-2), 156.14 (C-6), 166.49 (C-4), 170.76 (C-8') ^{1}H n.m.r. ($CDCl_3$) δ:2.07 (3H, s, Me-C-6), 3.90 (3H, s, OMe), 5.91 (1H, s, H-C-5), 6.18 (2H, s, H_2-C-7'), 6.95 (1H, J=1.8 Hz, H-C-3'), 7.35 (1H, s, H-C-6'), 7.45 (1H, q, J=8 Hz, H-C-3'). Compound 3f ^{13}C n.m.r. ($CDCl_3$) δ : 21.60 (C-8 and C-9), 22.20 (C-10), 22.40 (C-7), 55.60 (Me-C-2), 102.40 (C-7'), 108.80 (C-6'), 109.20 (C-3'), 115.20 (C-5), 125.60 (C-1'), 127.20 (C-2'), 143.60 (C-4'), 148.60 (C-5'), 153.80 (C-6), 154.60 (C-2), 164.20 (C-4), 168.20 (C-8'); ^{1}H n.m.r. ($CDCl_3$) δ :1.75 (4H, m, H_2-C-9 and H_2-C-8), 2.30-2.50 (4H, m, H_2-C-10 and H_2-C-7), 3.85 (3H, s, OMe), 6.14 (2H, s, H_2-C-7'), 6.95 (1H, d, J=1.8 Hz, H-C-3'), 7.35 (1H, s, H-C-6'), 7.45 (1H, q, J=8 Hz, H-C-2').
8) The piperonyl moiety used by us as 3-N-protector proved to be more stable as compared to the other acyl-derivatives.
9) The resulting 1-piperonyl-3-methyluracil showed to be stable for over 48 hr when treated with a 1.5 molar solution of ammonia in methanol-water.
10) In addition the U.V. spectrum of 6 showed a bathochromic shift typical of the 3-N-alkylated compounds λ_{max} (H_2O, pH=7) = 260 n.m. ($\varepsilon = 47x10^3$), λ max (0.01 N, NaOH, pH=12)= 278 n.m. ($\varepsilon = 4 \times 10^3$), lit. D. Shugar, and J. J. Fox, Biochim. Biophys. Acta, 9, 199 (1952)
11) C. Galli, Synthesis, 303 (1979)
12) In the same conditions ammonolysis of 5a and 5b are instantaneous while same reaction on 3a and 3c occurs in 12 hr.
13) U. Niedballa, and H. Vorbruggen, J. Org. Chem., 39, 3660 (1974)
14) Compound 8a: ^{13}C n.m.r. ($CDCl_3$), δ : 20.47 (Me acetyls and Me-C-6), 61.40 (C-6g), 67.93 (C-4g), 69.80 (C-2g), 69.94 (C-3g), 89.59 (C-5), 70.36 (C-5g), 90.06 (C-1g), 102.07 (C-7), 108.31 (C-3'), 109.67 (C-6'), 122.69 (C-6), 126.12 (C-2'), 126.43 (C-1'), 148.06 (C-4'), 152.56 (C-5'), 163.72 (C-4),169.42, 169.79, 169.91 (C = O acetyls), 170.22 (C-2), 170.65 (C-8'). ^{1}H n.m.r. ($CDCl_3$) δ : 1.95-2.10 (15H, m, Me acetyls and Me-C-6), 3.98-4.35 (4H, m, H-C-4 g + H-C-2 g + H-C-3 g + H-C-5), 4.98-5.25 (2H, m, H_2-C-6 g), 5.62 (1H, m, H-6-5 g) 6.12 (2H, s, H_2-C-7'), 6.30 (1H, d, J=4.2 Hz,H-C-1 g), 6.94 (1H, d, J=1.8 Hz, H-C-3'), 7.50 (1H, d, J=1.8 Hz, H-C-6'), 7.67 (1H, q, J=8.4 Hz, H-C-2). Compound 8b: ^{13}C n.m.r. ($CDCl_3$) δ: 20.45 (Me acetyl and tetrahydroquinaxoline alifatic ring carbons), 61.38 (C-6g), 67.35 (C-4g), 69.34 (C-2g), 69.77 (C-3g), 70.33 (C-5g), 89.55 (C-5), 90.06 (C-1g), 102.07 (C-7'), 108.28 (C-3'), 109.64 (C-8'), 122.52 (C-6'), 126.09 (C-2'), 126.41 (C-1'), 148.05 (C-4'), 152.52 (C-5'), 163.74 (C-4), 169.47, 169.87 (C=O acetyls), 170.53 (C-2), 170.64 (C-8'), ^{1}H n.m.r. ($CDCl_3$) δ : 1.98-2.10 (20H, m, Me acetyls + tetrahydroquinaxoline protons), 4.00-4.45 (3H, m, H_2-C-6g + H-C-4g), 4.88-5.35 (2H, m, H-C-2g + H-C-5g), 5.50-5.63 (1H, m, H-C-3g), 6.10 (2H, s, H_2-C-7'), 6.33 (1H, d, J=4.2 Hz, H-C-1g), 6.93 (1H, d, J=1.8 Hz, H-C-3'), 7.50 (1H, d, J=1.8 Hz, H-C-6'), 7.67 (1H, q, J=8.4 Hz, H-C-2').

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