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THE FACILE SYNTHESIS OF N(1), N(4) - DIMETHYL-5-SUBSTITUTED CYTOSINES

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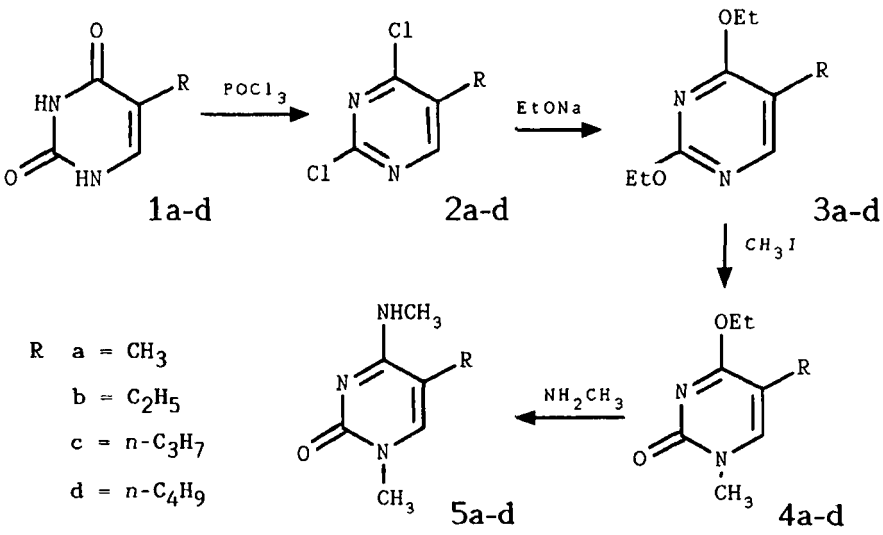
ABSTRACT: A facile, high yield synthesis of N(1),N(4)-dimethyl-5-alkyl (methyl, ethyl, *n*-propyl, *n*-butyl) cytosines has been described. This method seems to be an alternative and universal route to N(1),N(4)-methylated cytosines with any 5-substituent.

Alkylated cytosines[1,2,3,4,5] and cytidines[6,7,8,9,10,11,12,13,14] besides their great importance in the studies of biological interactions are also very interesting from the synthetic point of view. The general method of preparation of these species employs 4-thio, 4-alkyl-thio or 4-alkoxy derivatives of uracil as a substrates and finally expected cytosines are formed in the reactions with appropriate amines[7,15,16]. The several modified cytosines, mostly having an alkyl or aryl substituents placed at N(1) and/or N(4) are of special interest as a nucleotide models. The synthesis of these species has been developed and improved previously in our laboratory[17,18,19]. In a recent paper Golankiewicz

et al.[20] offered an efficient synthesis of N(4)-substituted-N(1)-methyl cytosines *via* preparation of 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine as a substrate for final nucleophilic replacement with amines. This methodology, however, failed in case of synthesis of 5-substituted cytosines (especially in the case of bulky n-propyl and n-butyl groups). Proposed intermediate has been produced with very low yield and a reaction work-up required tedious procedures of separation and purification.

In this communication we would like to describe simple and facile method of preparation of N(1),N(4) dimethylcytosines having an alkyl (methyl, ethyl, n-propyl and n-butyl) substituents using alternative methodology, which seems to be an universal way of preparation of N(1),N(4)-dimethyl-5-alkyl cytosines.

Our alternative method of the synthesis of N(1),N(4)-dimethyl-5-alkyl cytosines is depicted below:



The 5-substituted uracils **1a-d** (commercially available **1a** R=CH_3) or prepared previously[21], have been reacted with phosphoryl trichloride yielding 2,4-dichloro-5-alkyl uracils **2a-d** with practically quantitative yield. After distilling off the excess of phosphoryl trichloride the reaction residue was reacted with sodium ethoxide giving 2,4-diethoxy-5-alkyl uracil **3a-d**. The following Hilbert-Johnson reaction[15] with methyl iodide allowed us to introduce methyl group in N(1) position. Finally, bomb reaction with methyl amine in methanol yielded the expected product. Surprisingly the reactions proceed smoothly with high yield and almost none side products were observed. It the initial step N(1)-methyl-5-alkyl-4-ethoxy uracils **4a-d** were prepared practically as a one-pot reaction. The final bomb (autoclave) reaction with volatile methyl amine yielded required cytosines with a high yield. The simple recrystalization (from ethyl acetate) gave analytically pure N(1),N(4)-dimethyl-5-alkyl cytosines **5a-d**. Although we did not tested that, it seems that the proposed procedure might be an universal one in the preparation of a variety of N(1)-methyl-N(4)-alkyl(aryl)-5-alkyl cytosines.

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus and are uncorrected. All ^{1}H-NMR and ^{13}C-NMR spectra were performed on VARIAN Gemini 300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard (unless indicated otherwise). Chemical shifts δ are reported in ppm downfield from TMS. The satisfactory elemental analyses were determined on Perkin Elmer 240 apparatus.

General Procedure of Synthesis of N(1)-methyl-5-alkyl-4-ethoxy uracils **4a-d**

0.1 mole of 5-alkyl-uracil **1a-d** was placed in 250 ml round botom flask equipped with reflux condenser and drying tube. To the flask 0.5 mole of phosphoryl trichloride was added, as well as 0.15 mole of N,N-diethyl aniline. The reaction mixture was kept at about 110^0C for about 10 hours until the starting 5-alkyl uracil was completelly dissolved. The excess of phosphoryl cholride was distilled off, the reaction mixture was cooled down to a room temperature and poured on ice (about 100 g). The water layer was extracted with ethyl ether. Extracts were combined and dried with calcium chloride. Finally solvent was evaporated yielding oily residue - crude 2,4 dichloro-5-alkyl uracil **2a-d** (yield of crude product over 90%). 2,4-Dichloro-5-alkyl uracil **2a-d** was dissolved in 50-100 ml of dry ethanol and to this solution 200 ml of sodium ethoxide in ethanol (2.0 equivalents of sodium ethoxide in 200 ml of ethanol *per* 1 equivalent of crude 2,4-dichloro-5-alkyl uracil **2a-d**) was added. The reaction mixture was warmed up to about 60^0C for 15 minutes. Next sodium chloride was filtered off, ethanol was removed on rotavap yielding crude 2,4-diethoxy-5-alkyl uracil **3a-d**. This material was dissolved again in ethyl ether, washed with water, dried and finally ethyl ether was removed under vacuo. To the oily residue 0.15 mole (9 ml) of freshly distilled methyl iodide was added and the reaction mixture was kept 1-2 days at 0^0C in refrigerator. The crystalline precipitate-desired N(1)-methyl-5-alkyl-4-ethoxyuracils **4a-d** were pure and their structures have been proved on the basis of ^{1}H- and ^{13}C-NMR spectra. From the filtrate excess of methyl iodide was removed and the residues (contaminated with the traces of diethylaniline) were used in the next reaction without further purification.

Compound **4a** R= CH_3 , yield 88%(crude)

^{1}H-NMR ($CDCl_3$) δ_H 1.38 (3H,t,^{3}J=7.1Hz,O-C-CH_3), 1.94 (3H,s,C^5-CH_3), 3.46 (3H,s, N^1-CH_3), 4.45 (2H,q,^{3}J=7.1Hz,O-CH_2), 7.20 (1H,s,C^6-H)

^{13}C-NMR ($CDCl_3$) δ_C12.05; 14.31; 37.63; 63.12; 104.38; 144.42; 156.80; 170.23;

Compound **4b** R= C_2H_5, yield 91%(crude)

^{1}H-NMR ($CDCl_3$) δ_H 1.13 (3H,t,^{3}J=7.5Hz,C^5-C-CH_3), 1.37 (3H,t, ^{3}J=7.1Hz, O-C-CH_3), 2.36 (2H,q,^{3}J=7.5Hz,C^5-CH_2), 3.47 (3H,s,N^1-CH_3), 4.48 (2H,q, ^{3}J=7.1Hz, O-CH_2), 7.16(1H,s,C^6-H)

^{13}C-NMR ($CDCl_3$) δ_C13.17; 14.28; 19.80; 37.71; 63.01; 110.34; 143.59; 156.93; 169.93;

Compound **4c** R=*n*-C_3H_7, yield 85%(crude)

^{1}H-NMR ($CDCl_3$) δ_H 0.93 (3H,t,^{3}J=7.3Hz,C^5-C-C-CH_3), 1.37 (3H,t, ^{3}J=7.1Hz,O-C-CH_3), 1.52 (2H,sextet,^{3}J=7.3Hz,C^5-C-CH_2), 2.29 (2H,t, ^{3}J=7.3Hz,C^5-CH_2), 3.46 (3H,s,N^1-CH_3); 4.44 (2H,q,^{3}J=7.1Hz,O-CH_2), 7.16(1H,s,C^6-H)

^{13}C-NMR ($CDCl_3$) δ_X13.71; 14.29; 22.01; 28.59; 37.71; 63.02; 108.77; 144.29; 156.93; 170.05;

Compound **4d** R= *n*-C_4H_9, yield 82%(crude)

^{1}H-NMR ($CDCl_3$) δ_H 0.93 (3H,t,^{3}J= 7.3Hz,C^5-C-C-C-CH_3), 1.25-1.40 (5H, m,O-C-CH_3 and C^5-C-C-CH_2), 1.48 (2H,m,C^5-C-CH_2), 2.31 (2H,t, ^{3}J=7.3Hz, C^5-CH_2), 3.46 (3H,s,N^1-CH_3), 4.44 (2H,q,^{3}J= 7.1Hz,O-C-CH_2), 7.15 (1H,s,C^6-H)

^{13}C-NMR ($CDCl_3$) δ_C13.90; 14.29; 22.28; 26.21; 31.00; 37.71; 63.03; 109.02; 144.15; 156.93; 170.04;

General Synthesis of N(1),N(4)-dimethyl-5-alkyl cytosines **5a-d**

0.1 mole of prepared N(1)-methyl-5-alkyl-4-ethoxyuracil **3a-d** was placed in a bomb and 40 ml of 33% of methyl amine in methanol was added. The bomb

was placed at 110^{0}C for 24 hours. Next, after cooling to the room temperature, bomb was open and all volatile materials were removed yielding oily residue which crystallized after addition of a few drops of ethyl ether. Recrystalization from ethyl acetate gave analitically pure product N(1),N(4)-dimethyl-5-alkyl cytosine **5a-d**.

Compound **5a** R=CH_3 ,(78%), m.p.182-184^{0}C

^{1}H-NMR ($CDCl_3$) δ_H 1.96 (3H,s,C^5-CH_3), 3.05 (3H,d,^{3}J=4.5Hz, N^4-CH_3), 3.40 (3H,s,N^1-CH_3), 5.07 (1H,s,N^4-H), 7.00 (1H,s,C^6-H)

^{13}C-NMR ($CDCl_3$) δ_C 12.77; 28.32; 37.35; 101.36; 142.39; 157.44; 164.07

Elemental Analysis (for $C_7H_{11}N_3O$) C,H,N

Compound **5b** R= C_2H_5, (81%), m.p.128-130^{0}C

^{1}H-NMR ($CDCl_3$), δ_H 1.04 (3H,t,^{3}J=7.4Hz,C^5-C-CH_3), 2.20 (2H,q, ^{3}J=7.4Hz,C^5-CH_2), 2.88 (6H,d,^{3}J=4.5Hz,N^4-CH_3), 3.27 (3H,s,N^1-CH_3), 5.79 (1H,d,^{3}J=4.5Hz,N^4-H), 6.82 (1H,s,C_6-H)

^{13}C-NMR ($CDCl_3$) δ_C11.96; 19.45; 27.98; 37.09; 107.55; 140.63; 157.37; 163.37

Elemental Analysis (for $C_8H_{13}N_3O$) C,H,N

Compound **5c** R= *n*-C_3H_7, (75%), m.p.127-129^{0}C

^{1}H-NMR ($CDCl_3$) δ_H 0.97 (3H,t,^{3}J=7.5Hz,C^5-C-C-CH_3), 1.56 (2H,sextet, ^{3}J=7.5Hz,C^5-C-CH_2), 2.20 (2H,t,^{3}J=7.5Hz,C^5-CH_2), 3.04 (3H,d, ^{3}J=4.5Hz, N^4-CH_3), 3.41 (3H,s,N^1-CH_3), 5.30 (1H,d,^{3}J=4.5Hz,N^4-H), 6.95 (1H,s, C^6-H)

^{13}C-NMR ($CDCl_3$) δ_C 13.77; 21.11; 28.33; 28.56; 37.47; 105.62; 142.03; 157.45; 163.60

Elemental Analysis (for $C_9H_{15}N_3O$) C,H,N

Compound **5d** R=*n*-C_4H_9, (75%) m.p.159-161^{0}C

^{1}H-NMR ($CDCl_3$) δ_H 0.79 (3H,t,^{3}J=7.5Hz,C^5-C-C-C-CH_3), 1.15-1.45 (4H,m,C^5-C-CH_2CH_2), 2.14 (2H,t,^{3}J=7.5Hz,C[illegible]I_2), 2.90 (3H,d, ^{3}J=4.8Hz,

N^4-CH_3), 3.26 (3H,s,N^1-CH_3), 5.71(1H,d,^3J=4.8Hz, N^4-H), 6.82 (1H,s, C^6-H)
^{13}C-NMR ($CDCl_3$) δ_C 13.58; 22.08; 26.30; 28.00; 29.78; 37.06; 106.15; 141.33; 157.30; 163.40
Elemental Analysis (for $C_{10}H_{17}N_3O$) C,H,N

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