Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Sep 2006.

To cite this article: Lech Celewicz , Krzysztof Ciszewski & Krzysztof Golankiewicz (1991) The Efficient Synthesis of N^4-Substituted 1-Methylcytosines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:14, 1489-1500, DOI: 10.1080/00397919108016423

To link to this article: http://dx.doi.org/10.1080/00397919108016423

SYNTHETIC COMMUNICATIONS, 21(14), 1489-1500 (1991)

THE EFFICIENT SYNTHESIS OF N^4-SUBSTITUTED 1-METHYLCYTOSINES

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ABSTRACT: An improved procedure for the preparation of 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine is described. This compound appeared to be an excellent substrate for the synthesis of N^4-substituted 1-methylcytosines.

Cytosine derivatives have attracted considerable attention due to their various biological effects, especially, antiviral and anticancer properties of appropriate nucleosides.[1-5] Among the large number of known cytosine analogs, N^4-substituted cytosine derivatives are of special interest as naturally occurring constituents of ribonucleic acids (RNA's).[6] 1-Methylcytosine and its derivatives have proved to be useful model compounds in the

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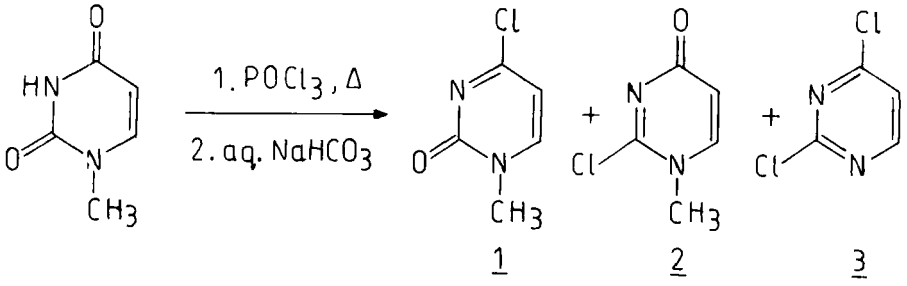
studies of physicochemical properties and chemical reactions of the corresponding cytosine nucleosides.[7,8] The preparation of N^4-substituted 1-methylcytosines has been usually achieved via nucleophilic displacement of alkoxy or alkylthio substituents at the 4 position of appriopriate pyrimidine precursors with the use of amines.[8-10] These methods however, require heating of reagents at high temperatures (often in sealed tubes or autoclaves), particularly, when aromatic amines are used as substrates.[11,12] We have reported that N-(1H-2-oxo-4-pyrimidinyl)amino acids undergo photochemical decarboxylation and this process can be used for the facile synthesis of N^4-substituted cytosines[13] and N^4-(1-deuterioalkyl)cytosines[14] with substituents derived from amino acids.

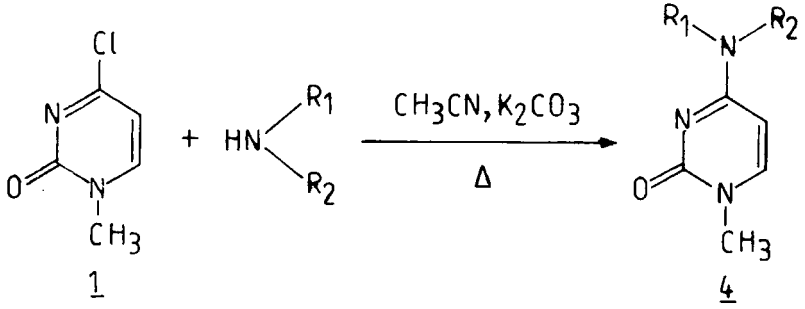
In continuation of our studies of biologically active pyrimidines we present an improved method for preparation of 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine **1** and an efficient method of synthesis of N^4-substituted 1-methylcytosines, employing as the synthetic precursor **1** and aliphatic as well as aromatic amines. To our knowledge, little information concerning the reactions of 1-alkyluracils with phosphoryl halides has been published. 4-Chloro-1,2-dihydro-1-methyl-2-oxopyrimidine **1** was originally prepared by Todd and co-workers[15] in 28% yield from 1-methyluracil and phosphoryl chloride heated under reflux. We have found that the reaction of 1-methyluracil with phosphoryl chloride under reflux gives three products: 4-chloro-1-methyl-2-oxopyrimidine **1** (35% isolated yield), 2-chloro-1-methyl-4-oxopyrimidine **2** (20% isolated yield) and 2,4-dichloropyrimidine **3**

(20% isolated yield). When the reaction temperature is lowered to 70°C, predominantly product **1** is formed in 75% yield, product **2** in 20% yield, whereas product **3** is not observed.



It should be mentioned that the increased yield of **1** is also due to change of work-up procedure of the reaction mixture.

The 4-chloro-1-methyl-2-oxopyrimidine **1** undergoes efficient reaction with amines in acetonitrile in the presence of potassium carbonate.



TABLE

Product			Isolated Yield (%)
4a	R_1 = H	R_2 = CH_3	90
4b	R_1 = H	R_2 = CH_2CH_3	85
4c	R_1 = H	R_2 = $CH_2CH_2CH_3$	84
4d	R_1 = H	R_2 = $CH_2(CH_2)_2CH_3$	92
4e	R_1 = H	R_2 = $CH_2(CH_2)_4CH_3$	90
4f	R_1 = H	R_2 = $C(CH_3)_3$	83
4g	R_1 = H	R_2 = $CH_2CH = CH_2$	78
4h	R_1 = H	R_2 = cyclohexyl	76
4i	R_1 = H	R_2 = CH_2Ph	82
4j	R_1 = CH_3	R_2 = CH_3	72
4k	R_1 = CH_2CH_3	R_2 = CH_2CH_3	84
4l	R_1 = H	R_2 = Ph	61
4m	R_1 = H	R_2 = p-tolyl	60

The reaction proceeds with aliphatic non-branched chain amines even in temperatures 25-50°C within 1 hour to give N^4-substituted cytosines in high yields. In the case of sterically hindered t-butylamine and aromatic amines the reaction is performed at reflux (about 82°C). In comparison with the widely used synthetic precursors for N^4-substituted 1-methylcytosines 4-methoxy- and 4-methylthio-1-methyl-2-oxopyrimidines, **1** is much more reactive and gives desired products in higher yields.

In conclusion, we highly recommend the presented method as the most convenient and effective for the synthesis of N^4-substituted 1-methylcytosines. The scope of the method was demonstrated by the synthesis of thirteen compounds **4a-m**.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Satisfactory microanalyses were obtained on an elemental analyser Perkin-Elmer 240. UV spectra were recorded on a Shimadzu UV-160 spectrophotometer. ^1H- and ^{13}C-NMR spectra were determined on Jeol FX 90 Q spectrometer. Mass spectra were made on a Jeol JMS-D-100 mass spectrometer.

Synthesis of 4-chloro-1,2-dihydro-1-methyl-2-oxopyrimidine 1

A mixture of 1-methyluracil (2 g, 15.9 mmol) and phosphoryl chloride (8 ml, 85.8 mmol) was stirred at 70°C for 4 h. The excess of phosphoryl chloride was removed under reduced pressure. The residue was cooled in dry ice-isopropanol bath and neutralized with saturated solution of sodium bicarbonate. The resulting precipitate was filtered off, dissolved in acetonitrile and dried with magnesium sulphate. The solution was evaporated and dried in vacuo over phosphorus pentaoxide to give 1.72 g of product **1**, yield 75%. Analytically pure samples of **1** were obtained by crystallization from acetonitrile. The filtrate (remaining after removal of the precipitate of product **1**) was extracted with

chloroform (15 x 30 ml), the first two extracts were discarded and the further were combined, dried over magnesium sulphate and evaporated to give 0.46 g of product **2**, yield 20%. It appeares that compound **2**, whose structure was established by NMR and MS spectroscopy, is very sensitive to moisture. During standard purification by column chromatography or crystallization small amounts of 1-methyluracil always were detected.

1[15]: m.p. 207-208°C

^{1}H-NMR ($CDCl_3$) δ 3.51 (s, 3H, CH_3), 6.37 (d, 1H, J = 6.8 Hz, C^5-H), 7.63 (d, 1H, J = 6.8 Hz, C^6-H).

^{13}C-NMR ($CDCl_3$) δ 38.7, 102.1, 105.1, 145.0, 148.4.

MS, m/z (rel. int.) 146 (32), 145 (19), 144 (100), 143 (37), 116 (19), 115 (20), 109 (33), 81 (20), 80 (13).

2: ^{1}H-NMR (CD_3CN) δ 3.61 (s, 3H, CH_3), 6.03 (d, 1H, J = 7.4 Hz, C^5-H), 7.49 (d, 1H, J = 7.4 Hz, C^6-H).

MS, m/z (rel. int.) 146 (32), 145 (17), 144 (100), 143 (35), 116 (24), 115 (19), 109 (38), 81 (18), 80 (13).

Synthesis of N^4-substituted 1-methylcytosines 4a-m

To a solution of **1** (2 g, 13.8 mmol) in acetonitrile (220 ml) were added appropriate amine (41.4 mmol) and potassium carbonate (4 g, 28.9 mmol). The reaction mixture was stirred at 50°C for 1 h (in the case of **4f**, **4l** and **4m** the reaction mixture was refluxed for 6 h). The solids were filtered off and washed with acetonitrile. The filtrate was evaporated and the residue was crystallized from acetonitrile **4a-j** or water - methanol **4l** and **4m**.

The product **4m** before crystallization was purified by flash chromatography on silica gel column (ethyl acetate - ethanol 50:1).

4a[8,9,15]: m.p. 177-178°C

UV (CH_3OH) λ_{max} 273 nm, ε_{max} 7100

^{1}H-NMR (CD_3OD) δ 2.88 (s, 3H, N^4-CH_3), 3.35 (s, 3H, N^1-CH_3), 5.81 (d, 1H, J = 7.3 Hz, C^5-H), 7.45 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 27.7, 37.6, 96.6, 146.2, 159.8, 166.4.

MS, m/z (rel. int.) 139 (100), 109 (21), 97 (34).

4b: m.p. 135-137°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 9600

^{1}H-NMR (CD_3OD) δ 1.17 (t, 3H, J = 7.2 Hz, CH_3), 3.35 (s, 3H, N^1-CH_3), 3.38 (m, 2H, N^4-CH_2), 5.79 (d, 1H, J = 7.3 Hz, C^5-H), 7.44 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 14.5, 36.4, 37.6, 96.7, 146.2, 159.9, 165.8.

MS, m/z (rel. int.) 153 (100), 138 (28), 125 (44), 109 (15), 95 (29), 83 (37).

4c: m.p. 157-158°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 10000

^{1}H-NMR (CD_3OD) δ 0.94 (t, 3H, J = 7.2 Hz, CH_3), 1.6 (m, 2H, CH_2), 3.35 (s, 3H, N^1-CH_2), 3.37 (m, 2H, N^4-CH_2), 5.81 (d, 1H, J = 7.3 Hz, C^5-H), 7.44 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 11.7, 23.2, 37.6, 43.3, 96.7, 146.2, 159.9, 166.0.

MS, m/z (rel. int.) 167 (58), 152 (42), 139 (25), 138 (75), 125 (100), 109 (25), 95 (75), 83 (51).

4d: m.p. 125-126°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 9400

^{1}H-NMR (CD_3OD) δ 0.94 (t, 3H, J = 7.0 Hz, CH_3), 1.51 (m, 4H, CH_2-CH_2), 3.38 (s, 3H, N^1-CH_3), 3.39 (m, 2H, N^4-CH_2), 5.87 (d, 1H, J = 7.3 Hz, C^5-H), 7.46 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 14.0, 20.8, 31.9, 37.8, 41.2, 96.9, 146.2, 159.9, 165.7.

MS m/z (rel. int.) 181 (54), 166 (9), 152 (52), 139 (74), 138 (69), 125 (100), 109 (24), 95 (45), 83 (34).

4e: m.p. 91-92°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 10800

^{1}H-NMR (CD_3OD) δ 0.89 (t, 3H, J = 7.0 Hz, CH_3), 1.33 (m, 8H, CH_2), 3.33 (m, 2H, N^4-CH_2), 3.36 (s, 3H, N^1-CH_3), 5.85 (d, 1H, J = 7.2 Hz, C^5-H), 7.46 (d, 1H, J = 7.2 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 14.4, 23.6, 27.7, 30.0, 32.7, 37.6, 41.6, 96.7, 146.2, 160.0, 165.9.

MS, m/z (rel. int.) 209 (42), 194 (8), 180 (18), 166 (34), 152 (62), 139 (90), 138 (70), 125 (100), 109 (28), 95 (43), 83 (37).

4f: m.p. 255-257°C

UV (CH_3OH) λ_{max} 272 nm, ε_{max} 9900

^{1}H-NMR (CD_3OD) δ 1.44 (s, 9H, CH_3), 3.33 (s, 3H, N^1-CH_3), 5.79 (d, 1H, J = 7.3 Hz, C^5-H), 7.37 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 28.0, 37.6, 52.8, 97.8, 145.6, 159.6, 165.8.

MS, m/z (rel. int.) 181 (34), 166 (15), 125 (100), 83 (32).

4g: m.p. 159°C

UV (CH_3OH) λ_{max} 275 nm, ε_{max} 10300

^{1}H-NMR (CD_3OD) δ 3.35 (s, 3H, N^1-CH_3), 3.99 (m, 2H, N^4-CH_2), 5.04-5.34 (m, 2H, =CH_2), 5.71-6.13 (m, 1H, -CH=), 5.83 (d, 1H, J = 7.3 Hz, C^5-H), 7.46 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 37.6, 43.8, 96.5, 116.4, 135.3, 146.6, 159.8, 165.9.

MS, m/z (rel. int.) 165 (100), 164 (69), 150 (32).

4h: m.p. 193°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 10500

^{1}H-NMR (CD_3OD) δ 1.25-2.03 (m, 10H, CH_2), 3.33 (s, 3H, N^1-CH_3), 3.91 (m, 1H, CH), 5.76 (d, 1H, J = 7.2 Hz, C^5-H), 7.41 (d, 1H, J = 7.2 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 26.0, 26.7, 33.6, 37.6, 50.2, 96.9, 146.2, 160.0, 165.1.

MS, m/z (rel. int.) 207 (36), 178 (6), 164 (13), 150 (19), 126 (52), 125 (100), 83 (17).

4i: m.p. 195-196°C

UV (CH_3OH) λ_{max} 274 nm, ε_{max} 11200

^{1}H-NMR (CD_3OD) δ 3.32 (s, 3H, N^1-CH_3), 4.55 (s, 2H, CH_2), 5.84 (d, 1H, J = 7.3 Hz, C^5-H), 7.22-7.35 (m, 5H, Ph), 7.42 (d, 1H, J = 7.3 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 37.7, 45.2, 96.6, 128.2, 128.7, 129.4, 139.8, 146.6, 159.9, 166.0.

MS, m/z (rel. int.) 215 (45), 106 (37), 91 (100).

4j[8,9,15]: m.p. 181°C

UV (CH_3OH) λ_{max} 281 nm, ε_{max} 11300

^{1}H-NMR (CD_3OD) δ 3.12 (s, 6H, N^4-CH_3), 3.39 (s, 3H, N^1-CH_3), 6.08 (d, 1H, J = 7.6 Hz, C^5-H), 7.60 (d, 1H, J = 7.6 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 37.8, 38.0, 93.5, 147.5, 159.2, 165.4.

MS, m/z (rel. int.) 153 (100), 138 (36), 124 (31), 123 (45), 109 (12), 95 (17).

4k: m.p. (oil)

UV (CH_3OH) λ_{max} 281 nm, ε_{max} 12600

^{1}H-NMR (CD_3OD) δ 1.18 (t, 3H, J = 7.0 Hz, CH_3), 3.38 (s, 3H, N^1-CH_3), 3.58 (m, 2H, N^4-CH_2), 6.02 (d, 1H, J = 7.5 Hz, C^5-H), 7.61 (d, 1H, J = 7.5 Hz, C^6-H).

^{13}C-NMR (CD_3OD) δ 13.3, 37.7, 43.7, 93.5, 147.5, 159.4, 164.1.

MS, m/z (rel. int.) 181 (49), 166 (8), 152 (100), 138 (33).

4l[11,12]: m.p. 265-267°C (lit.[11,12] 256-258°C)

UV (CH_3OH) λ_{max} 297 nm, ε_{max} 17300

^{1}H-NMR (DMSO-d_6) δ 3.29 (s, 3H, N^1-CH_3), 5.91 (d, 1H, J = 7.2 Hz, C^5-H), 6.93-7.42 (m, 3H, CH), 7.71-7.82 (m, 2H, CH), 7.72 (d, 1H, J = 7.2 Hz, C^6-H), 9.57 (br s, 1H, NH).

^{13}C-NMR (DMSO-d_6) δ 37.0, 94.3, 120.0, 122.7, 128.4, 139.3, 146.7, 155.7, 162.2.

MS, m/z (rel. int.) 201 (89), 200 (100), 159 (21).

4m: m.p. 269-270°C

UV (CH_3OH) λ_{max} 298 nm, ε_{max} 20400

^{1}H-NMR (DMSO-d_6) 2.26 (s, 3H, CH_3), 3.28 (s, 3H, N^1-CH_3), 5.88 (d, 1H, J = 7.4 Hz, C^5-H), 7.11 (d, 2H, J = 8.4 Hz, CH), 7.62 (d, 2H, J = 8.4 Hz, CH), 7.69 (d, 1H, J = 7.4 Hz, C^6-H), 9.49 (br s, 1H, NH).

^{13}C-NMR (DMSO-d_6) δ 20.5, 37.0, 94.3, 120.1, 128.9, 131.7, 136.8, 146.5, 155.8, 162.1.

MS, m/z (rel. int.) 215 (81), 214 (100), 173 (31).

ACKNOWLEDGEMENTS

The authors are indebted to Mrs Halina Thiel-Pawlicka for technical assistance. This work was supported by the Grant II/2.

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(Received in UK 8 April, 1991)