Efficient Synthesis of 5-Hydroxymethyl Pyrimidines and their Nucleosides Using Microwave Irradiation

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This paper dedicated to Prof. H. S. El Khadem on the occasion of his 80th birthday.

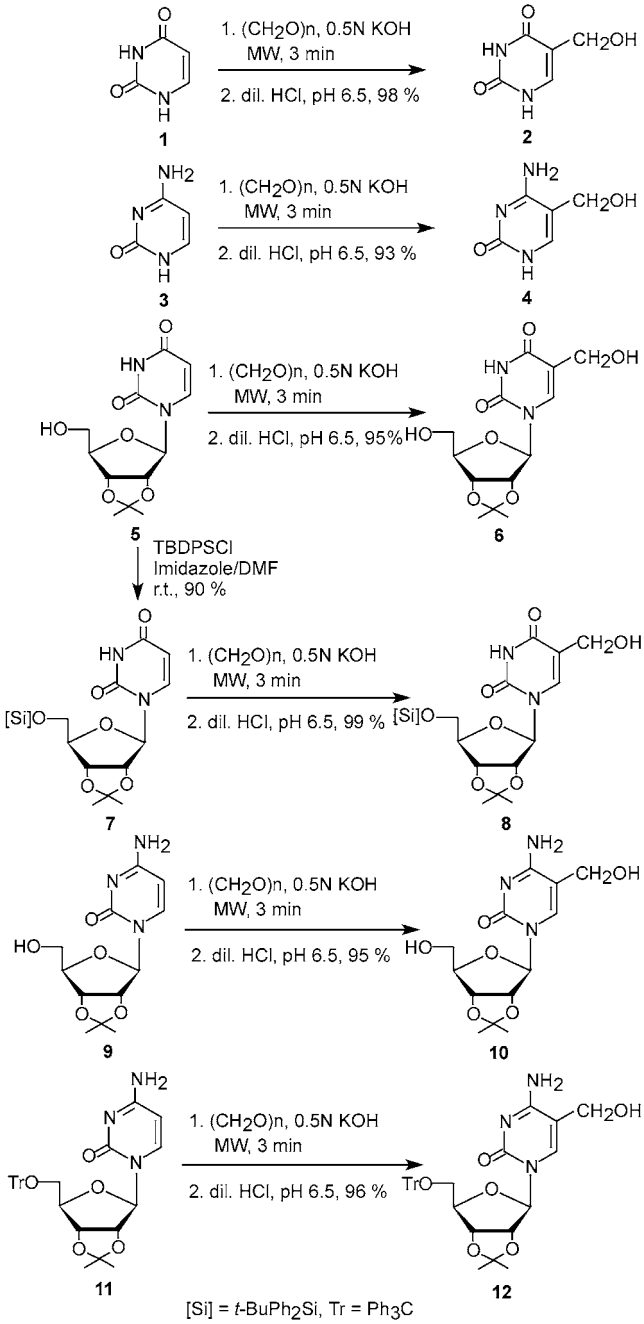
Abstract: Hydroxymethylation of uracil (**1**), cytosine (**3**), 5-hydroxymethyl-2′,3′-*O*-isopropylideneuridine (**5**), 5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-*O*-isopropylideneuridine (**7**), 2′,3′-*O*-isopropylidenecytidine (**9**) and 2′,3′-*O*-isopropylidene-5′-*O*-tritylcytidine (**11**) was efficiently carried out with paraformaldehyde in alkaline medium under microwave irradiation in very high yield.

Key words: microwave, uracil, cytosine, 5-hydroxymethyluracil, uridine, cytidine, formaldehyde addition

There has been increasing interest in the application of microwave irradiation to chemical reactions over recent years.[1–3] Although reactions have been reported to proceed at equal rates under both microwave and conventional heating at the same temperature,[4–6] speculation about the influence of microwaves on reaction rates have been reported whereby the reaction could proceed faster than that under conventional conditions at the same temperature.[7–11]

Addition products of formaldehyde with pyrimidines are of considerable interest in connection with problems of nucleic acid metabolism.[12,13] The 5-hydroxymethyl-2′-deoxyuridine triphosphate has been found to be a substrate for SP10c DNA replication and is present in SP10c phage-infected *Bacillus Subtilis*.[14] This has attracted the attention towards the synthesis of its analogues. Consequently, the 5-hydroxymethyl analogues of uracil,[15] cytosine,[16] 2′,3′-*O*-isopropylideneuridine,[17] and 2′,3′-*O*-isopropylidenecytidine[18] were prepared by treating of uracil (**1**), cytosine (**3**), 2′,3′-*O*-isopropylideneuridine[19] (**5**), and 2 ′,3′-*O*-isopropylidenecytidine[19] (**9**) with paraformaldehyde in alkaline medium for one to three days (Scheme 1).

We report here an efficient and easy method for the synthesis of 5-hydroxymethyluracil (**2**), 5-hydroxymethylcytosine (**4**), 5-hydroxymethyl-2′,3′-*O*-isopropylideneuridine (**6**), 5′-*O*-*tert*-butyldiphenylsilyl-5-hydroxymethyl-2′,3′-*O*-isopropylideneuridine (**8**), 5-hydroxymethyl-2′,3′-*O*-isopropylidenecytidine (**10**) and 5-hydroxymethyl-2′,3′-*O*-isopropylidene-5′-*O*-tritylcytidine (**12**) in 93–99% yield by the hydroxymethylation of **1**, **3**, **5**, **7**, **9**



Scheme 1

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and **11** with paraformaldehyde in 0.5 N potassium hydroxide solution under microwave irradiation for 3 minutes followed by acidification by dilute hydrochloric acid. Each of the ^{1}H NMR spectra[20] of **2**, **4**, **6**, **8**, **10** and **12** showed a singlet at δ = 4.11, 3.51, 4.12, 4.15, 3.49 or 3.50 ppm corresponding to the CH_2 group, indicated the successful hydroxymethylation.

In conclusion, a succesful hydroxymethylation of pyrimidines and their nucleosides using microwave irradiation has been achieved. Moreover, various protecting groups in the nucleosides have not been affected under such conditions, which could allow further chemical modifications on them. Furthermore, the method saves time, the products were easily isolated, giving high yield, economic and it is friendly to the environment.

General Procedure

To 2 mL of 0.5 N KOH was added 1 mmol of **1**, **3**, **5**, **7**, **9** or **11** and paraformaldehyde (0.04 g, 1.2 mmol) and each mixture was taken in a round-bottom flask and irradiated in MW oven (Master KOG 840-P, output 1500 W) for 3 min. The reaction mixture was acidified by diluted HCl (pH ~ 6.5) and then reprecipitated from acetone and water (2:1) to afford pure products of **2**, **4**, **6**, **8**, **10** and **12** in 93–99% yields.

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(20) **Selected Physical Data: 2**: White powder; mp >300 °C (H_2O); TLC ($CHCl_3$–MeOH, 8.5:1.5 v/v): R_f 0.59. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.11 (s, 2 H, CH_2), 7.24 (s, 1 H, H-6), 10.71 (br s, 1 H, NH), 11.05 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75.04 MHz): δ = 55.7 (CH_2), 112.6 (C-5), 138.1 (C-6), 151.3 (C-2), 163.7 (C-4). **4**: White powder; mp >300 °C (H_2O); TLC ($CHCl_3$–MeOH, 8:2 v/v): R_f 0.35. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.51 (s, 2 H, CH_2), 7.12 (br s, 2 H, NH_2), 8.15 (s, 1 H, H-6), 11.18 (br s, 1 H, NH). **6**: White powder; mp 170–172 °C (H_2O); TLC ($CHCl_3$–MeOH, 8.5:1.5 v/v): R_f 0.50. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.36 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 3.85 (d, 1 H, J_{gem} = 12.1 Hz, H-5′$_a$), 3.97 (d, 1 H, J_{gem} = 12.1 Hz, H-5′$_b$), 4.12 (s, 1 H, CH_2), 4.80 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = 2.4 Hz, H-4′), 4.95 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{2',3'}$ = 6.2 Hz, H-3′), 4.98 (brs, 1 H, OH), 5.01 (dd, 1 H, $J_{2',3'}$ = 6.2 Hz, $J_{1',2'}$ = 2.5 Hz, H-2′), 5.67 (d, 1 H, $J_{1',2'}$ = 2.5 Hz, H-1′), 7.57 (s, 1 H, H-6), 9.01 (br s, 1 H, NH). **7**: White foam; TLC ($CHCl_3$–MeOH, 9.5:0.5 v/v): R_f 0.61. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.08 (s, 9 H, 3 CH_3), 1.34 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 3.94 (d, 1 H, J_{gem} = 12.4 Hz, H-5′$_a$), 3.96 (d, 1 H, J_{gem} = 12.4 Hz, H-5′$_b$), 4.26 (dd, 1 H, $J_{3',4'}$ = 3.3 Hz, $J_{4',5'}$ = 2.6 Hz, H-4′), 4.75 (m, 1 H, H-3′), 4.82 (m, 1 H, H-2′), 5.44 (d, 1 H, $J_{1',2'}$ = 3.1 Hz, H-1′), 5.97 (d, 1 H, $J_{5,6}$ = 5.0 Hz, H-5), 7.34–7.41 (m, 5 H, Ar-H), 7.44–7.65 (m, 6 H, Ar-H, H-6), 9.51 (br s, 1 H, NH). ^{13}C NMR ($CHCl_3$, 75.04 MHz): δ = 19.3 (Me_3C), 25.3 (CH_3), 26.9 (Me_3C), 27.2 (CH_3), 63.9 (C-5′), 80.1 (C-3′), 84.9 (C-2′), 86.4 (C-4′), 91.5 (C-1′), 102.4 (Me_2C), 114.3 (C-5), 127.8, 127.9, 129.9, 130.0, 132.2, 132.7, 135.3, 135.5 (Ar-Carbons), 140.6 (C-6), 150.1 (C-2), 163.3 (C-4). **8**: White foam; TLC ($CHCl_3$–MeOH, 9:1 v/v): R_f 0.58. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.10 (s, 9 H, 3 CH_3), 1.35 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 3.90 (d, 1 H, J_{gem} = 12.2 Hz, H-5′$_a$), 3.94 (d, 1 H, J_{gem} = 12.2 Hz, H-5′$_b$), 4.15 (s, 2 H, CH_2), 4.15 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = 2.7 Hz, H-4′), 4.77 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, $J_{2',3'}$ = 6.3 Hz, H-3′), 4.80 (dd, 1 H, $J_{2',3'}$ = 6.3 Hz, $J_{1',2'}$ = 3.2 Hz, H-2′), 5.50 (d, 1 H, $J_{1',2'}$ = 3.2 Hz, H-1′), 7.35–7.44 (m, 5 H, Ar-H), 7.50–7.60 (m, 5 H, Ar-H), 8.01 (s, 1 H, H-6), 10.32 (br s, 1 H, NH). **10**: Pale yellow foam; TLC ($CHCl_3$–MeOH, 9:1 v/v): R_f 0.45. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.36 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.49 (s, 2 H, CH_2), 4.01 (m, 2 H, H-5′), 4.31 (m, 1 H, H-4′), 4.39 (m, 1 H, H-3′), 4.78 (m, 1 H, H-2′), 5.51 (d, 1 H, $J_{1',2'}$ = 2.8 Hz, H-1′), 7.21 (br s, 2 H, NH_2), 8.01 (s, 1 H, H-6). **12**: Yellow foam; TLC ($CHCl_3$–MeOH, 9:1 v/v): R_f 0.65. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.50 (s, 2 H, CH_2), 3.79 (m, 2 H, H-5′), 4.33 (m, 1 H, H-4′), 4.95 (m, 1 H, H-3′), 5.09 (m, 1 H, H-2′), 5.60 (d, 1 H, $J_{1',2'}$ = 2.9 Hz, H-1′), 7.09–7.25 (m, 8 H, NH_2, Ar-H), 7.29–7.38 (m, 9 H, Ar-H), 8.06 (s, 1 H, H-6).