The Synthesis of 5-Carboxymethylaminomethyluridine and 5-Carboxymethylaminomethyl-2-thiouridine

Colin B. Reese* and Yogesh S. Sanghvi

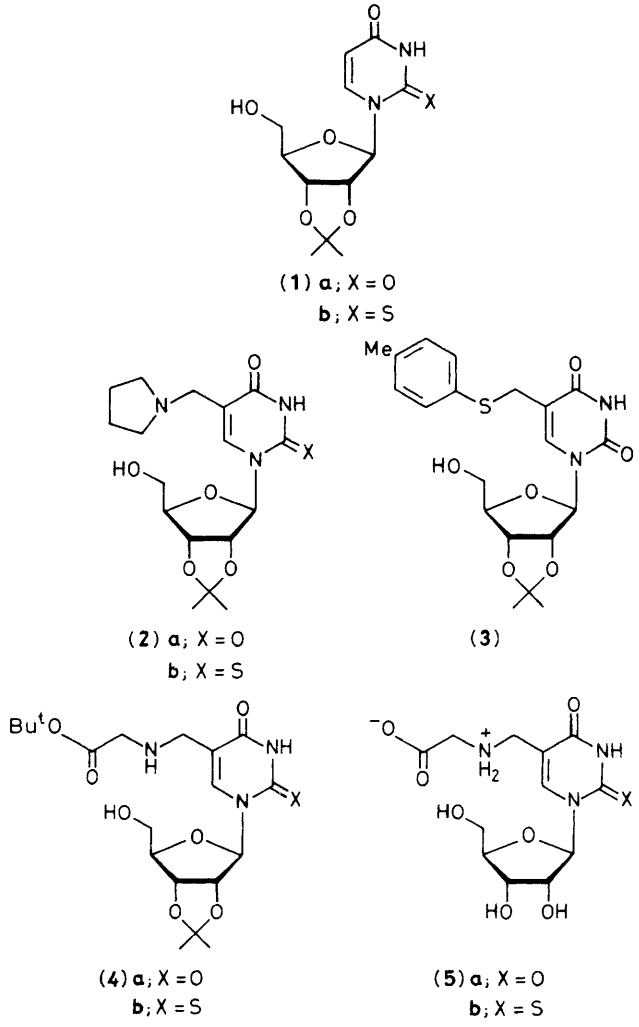
Department of Chemistry, King's College, Strand, London WC2R 2LS, U.K.

2′,3′-*O*-Isopropylideneuridine (**1a**) and 2′,3′-*O*-isopropylidene-2-thiouridine (**1b**) are converted in 4 steps, *via* the corresponding Mannich bases (**2a**) and (**2b**), into the modified nucleosides (**5a**) and (**5b**), respectively.

We recently found[1,2] that when 2′,3′-*O*-isopropylideneuridine (**1a**) is heated with 5 mol. equiv. each of pyrrolidine and formaldehyde in aqueous solution for 1 h, under reflux, 2′,3′-*O*-isopropylidene-5-pyrrolidinomethyluridine (**2a**) is obtained. We further showed[1] that when this Mannich base (**2a**) is heated with an excess of toluene-*p*-thiol in acetonitrile solution, it is smoothly converted into 2′,3′-*O*-isopropylidene-5-(*p*-tolylthiomethyl)uridine (**3**), a valuable intermediate in the synthesis of 5-methyluridine.

It seemed to us that nucleoside Mannich bases were likely to find other uses as synthetic intermediates. In support of this we now report the conversion of (**2a**) and its 2-thio analogue (**2b**) into 5-carboxymethylaminomethyluridine[3] (**5a**) and 5-carboxymethylaminomethyl-2-thiouridine[4] (**5b**), respectively. The latter two modified nucleosides [5] occupy the first positions in the anticodon triplets of *B. subtilis* $tRNA^{Gly}$ and *B. subtilis* $tRNA^{Lys}$, respectively.[6]

The Mannich base (**2a**), which was prepared as described previously,[1] was treated with 10 mol. equiv. of methyl iodide in acetonitrile at room temperature. After 16 h, the products were concentrated under reduced pressure to give the putative methiodide of (**2a**). This material was redissolved in acetonitrile and allowed to react with 3 mol. equiv. of glycine t-butyl ester[7] at room temperature for 16 h. Following work-up and chromatography of the products, (**4a**) was isolated as a pure crystalline solid† (from ethanol), m.p. 85 °C, in 50% yield. When (**4a**) was treated with trifluoroacetic acid–water (95 : 5 v/v) for 5 h at room temperature, the protecting groups were removed and 5-carboxymethylaminomethyluridine (**5a**) was obtained. The latter compound (**5a**) crystallized from aqueous ethanol as colourless prisms,‡ m.p. 197 °C decomp., and was isolated in 70% yield.



The Mannich base (**2b**) was prepared by heating 2′,3′-*O*-isopropylidene-2-thiouridine[8] (**1b**) with 5 mol. equiv. each of

† Satisfactory microanalytical and spectroscopic data were obtained for all crystalline compounds described.

‡ δ_H[$(CD_3)_2SO$, 250 MHz] 3.20 (2H, s), 3.5—3.75 (4H, m), 3.84 (1H, m) 4.00 (1H, m), 4.07 (1H, m), 5.77 (1H, d, *J* 5.0 Hz), 8.09 (1H, s); λ_{max} (0.1 M HCl) 265 (ε 9500), λ_{min} 232 nm (ε 1800); R_F 0.34 [propan-2-ol–ammonia (*d* 0.88)–water (7 : 1 : 2) on Merck No. 5642 h.p.t.l.c. plates].

formaldehyde and pyrrolidine in aqueous solution, under reflux, for 1 h; it was isolated as a crystalline solid (from acetone), m.p. 131 °C, in 70% yield. This Mannich base (**2b**) was converted into (**4b**) by the same two-step procedure as was used (see above) in the conversion of (**2a**) into (**4a**), except that the methylation step was carried out in acetone rather than in acetonitrile solution. When (**4b**), which was isolated as a colourless glass in 59% yield, was treated as above with trifluoroacetic acid–water (95 : 5 v/v), 5-carboxymethylaminomethyl-2-thiouridine (**5b**) was obtained. Compound (**5b**) was isolated as a crystalline solid,§ m.p. 211—212 °C decomp., in 60% yield. Preliminary studies suggest that this approach to the synthesis of 5-alkylaminomethyl derivatives of uridine and 2-thiouridine is of general application.

§ δ_H [$(CD_3)_2SO$, 250 MHz] 3.22 (2H, s), 3.5—3.8 (4H, m), 3.92 (1H, m), 4.03 (1H, m), 4.09 (1H, m), 6.51 (1H, d, *J* 3.1 Hz), 8.34 (1H, s); λ_{max} (95% EtOH) 277 (ε 12 900), λ_{min} 245 nm (ε 4 020); R_F 0.41 [propan-2-ol–ammonia (*d* 0.88)–water (7 : 1 : 2) on Merck No. 5642 h.p.t.l.c. plates].

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