Reactions Between Methiodides of Nucleoside Mannich Bases and Carbon Nucleophiles

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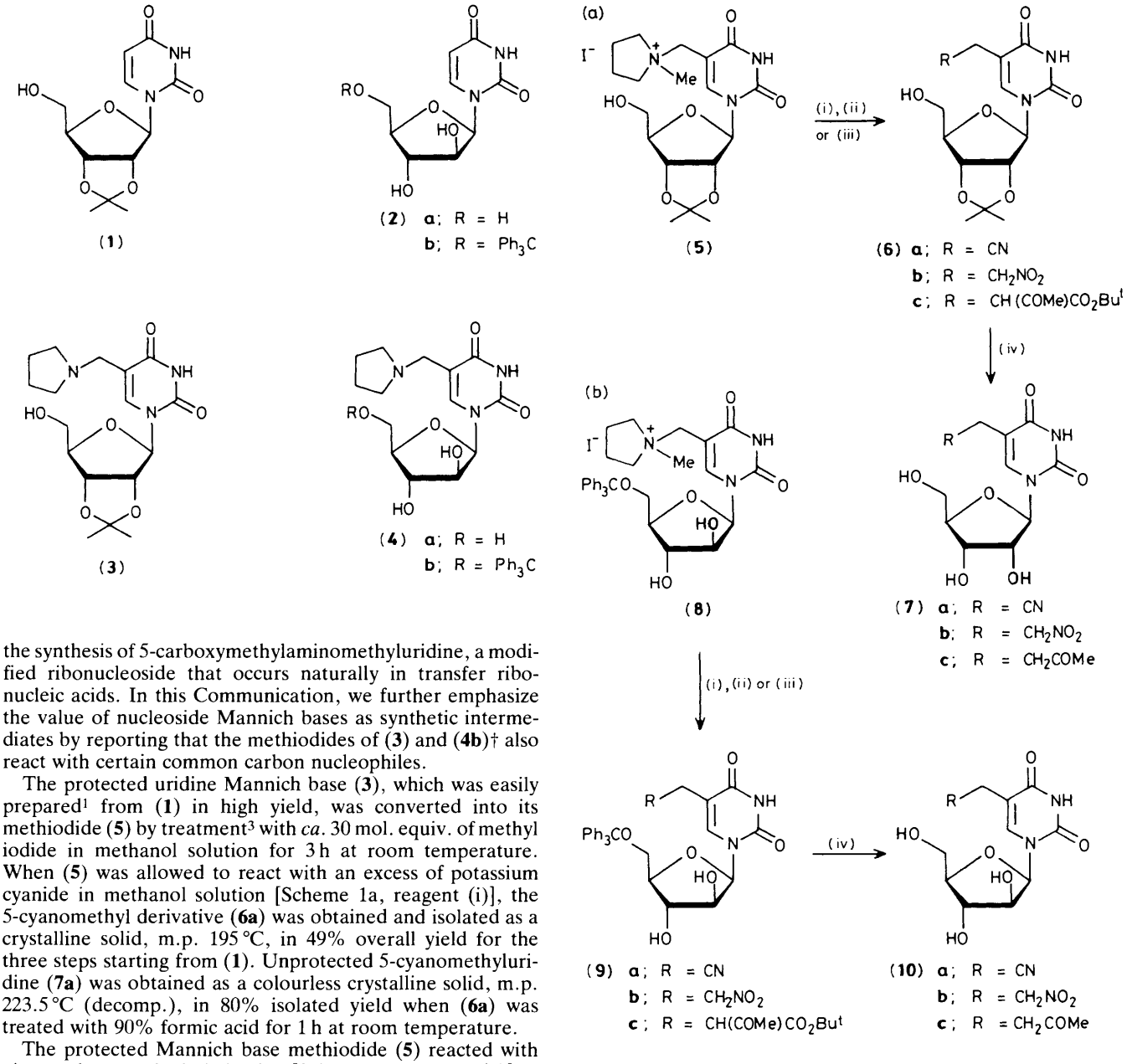
The conversion of the Mannich base methiodide (**5**) into the 5-substituted uridine derivatives [(**7a**), (**7b**), and (**7c**)] is described; (**8**) is similarly converted into the 5-substituted 1-β-D-arabinofuranosyluracil derivatives [(**10a**) and (**10c**)].

2′,3′-*O*-Isopropylideneuridine (**1**) and 1-β-D-arabinofuranosyluracil (**2a**) have been found[1,2] to react readily with formaldehyde and pyrrolidine in boiling aqueous solution to give the corresponding Mannich bases [(**3**) and (**4a**), respectively] in good yields. The latter compounds are valuable synthetic intermediates; thus they both react[1,2] with toluene-4-thiol, a sulphur nucleophile, to give the corresponding 5-(4-tolylthiomethyl) derivatives which are intermediates in very convenient preparations of 5-methyluridine[1] and 1-β-D-arabinofuranosylthymine.[2] The methiodide of (**3**) was also found[3] to react with nitrogen nucleophiles; for example, its reaction with glycine t-butyl ester was recently exploited[3] in



Scheme 1. *Reagents and Conditions*: (i) KCN (5.0 mol. equiv.)–MeOH, 4 h, r.t. (room temperature); (ii) Et_3N–$MeNO_2$ (1 : 5 v/v), 18 h, r.t.; (iii) $MeCOCH_2CO_2Bu^t$ (5.0 mol. equiv.), $(Me_2N)_2C{=}NH$ (5.0 mol. equiv.)–Me_2NCHO, 2 h, r.t.; (iv) (a) HCO_2H–H_2O (9 : 1 v/v), 30—90 min, r.t.; (b) [for (**6c**) and (**9c**) only] CF_3CO_2H–MeCN (1 : 3 v/v), 16 h, r.t.

the synthesis of 5-carboxymethylaminomethyluridine, a modified ribonucleoside that occurs naturally in transfer ribonucleic acids. In this Communication, we further emphasize the value of nucleoside Mannich bases as synthetic intermediates by reporting that the methiodides of (**3**) and (**4b**)† also react with certain common carbon nucleophiles.

The protected uridine Mannich base (**3**), which was easily prepared[1] from (**1**) in high yield, was converted into its methiodide (**5**) by treatment[3] with *ca.* 30 mol. equiv. of methyl iodide in methanol solution for 3 h at room temperature. When (**5**) was allowed to react with an excess of potassium cyanide in methanol solution [Scheme 1a, reagent (i)], the 5-cyanomethyl derivative (**6a**) was obtained and isolated as a crystalline solid, m.p. 195 °C, in 49% overall yield for the three steps starting from (**1**). Unprotected 5-cyanomethyluridine (**7a**) was obtained as a colourless crystalline solid, m.p. 223.5 °C (decomp.), in 80% isolated yield when (**6a**) was treated with 90% formic acid for 1 h at room temperature.

The protected Mannich base methiodide (**5**) reacted with nitromethane and triethylamine [Scheme 1a, reagent (ii)] to give the corresponding 5-(2-nitroethyl) derivative (**6b**), which was then treated with 90% formic acid to give unprotected 5-(2-nitroethyl)uridine (**7b**) as a crystalline solid, m.p. 168—172 °C. The modest isolated yield of the latter compound (**7b**) [16% overall, for the four steps starting from 2′,3′-*O*-isopropylideneuridine (**1**)] was due partly to the fact that the last step [*i.e.* step (iv)] proceeded in only 43% yield. The yield obtained in the conversion of (**5**) into (**7c**) was, however, much more satisfactory. When (**5**) was allowed to react with t-butyl acetoacetate and N^1,N^1,N^3,N^3-tetramethylguanidine in dimethylformamide solution [Scheme 1a, reagent (iii)] and the intermediate alkylated acetoacetate derivative (**6c**) treated first with 90% formic acid to remove the 2′,3′-*O*-isopropylidene protecting group and then with trifluoroacetic acid in acetonitrile, 5-(3-oxobutyl)uridine (**7c**) was obtained as a colourless crystalline solid, m.p. 211 °C, in 44% overall yield based on (**1**) as starting material.

5′-*O*-Triphenylmethyl-1-β-D-arabinofuranosyluracil (**2b**) was converted into the Mannich base (**4b**) by heating it, under reflux, with *ca.* 5 mol. equiv. each of pyrrolidine and formaldehyde in 2-methoxyethanol–water (1 : 1 v/v) solution for 3 h. The latter compound (**4b**) was converted into its methiodide (**8**) which was, in turn, converted [Scheme 1b,

† Reactions between (**4b**) [rather than (**4a**)] and carbon nucleophiles were investigated in order to facilitate the fractionation of the products by chromatography on silica gel. Satisfactory microanalytical and spectroscopic data were obtained for all new crystalline compounds prepared.

reagents (i) and (iii)] into crystalline 5-cyanomethyl-1-β-D-arabinofuranosyluracil (**10a**) [m.p. 230 °C (decomp.)] and crystalline 5-(3-oxobutyl)-1-β-D-arabinofuranosyluracil (**10c**) [m.p. 209.5 °C] in 45 and 29% overall yields, respectively, based on (**2b**) as starting material. While the reaction between (**8**), nitromethane, and triethylamine [Scheme 1b, reagent (ii)] proceeded in satisfactory yield [*ca.* 60% for the three steps starting from (**2b**)], difficulty was encountered in the isolation of (**10b**), following treatment with 90% formic acid [step (iv)]. It would appear from the studies involving both (**6b**) and (**9b**) that 90% formic acid is probably an unsatisfactory reagent to use in the unblocking of nucleosides derived from 5-(2-nitroethyl)uracil. An alternative approach to the direct 5-alkylation of uridine has very recently been reported.[4]

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