Novel C–C Bond Formation at the 5-Position of Uracils. Facile Synthesis of 5-Methoxycarbonylmethyluridine and 5-Carbamoylmethyluridine, Minor Component Nucleosides derived from transfer Ribonuclease

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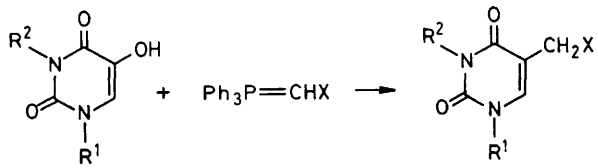
Summary 5-Hydroxyuracil derivatives were treated with stable Wittig reagents to give the corresponding 5-alkyluracil derivatives such as 5-methoxycarbonylmethyluridine and 5-carbamoylmethyluridine.

RECENTLY, C–C bond-formation reactions at the 5-position of uracils have received considerable attention[1] because of the biological activity[2] of 5-carbon substituted 2′-deoxyuridines. We report herein a new synthetic approach to C(5)-substituted uracils and its application to the facile synthesis of minor component nucleosides isolated from transfer ribonuclease (tRNA). Our method involves the use of easily available 5-hydroxyuracils and stable Wittig reagents as starting materials.

Thus, 5-hydroxy-1,3-dimethyluracil (**1a**)[3] was treated with ethoxycarbonylmethylenetriphenylphosphorane (**2a**) (1·2 equiv.) in refluxing acetonitrile for 9 h. After evaporation of the solvent *in vacuo*, the residue was poured into water,



(1) (2) (3)

a; $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = Rf$, $R^2 = H$

a; X = CO_2Et
b; X = CO_2Me
c; X = $CONH_2$
d; X = CN

a; $R^1 = R^2 = Me$, X = CO_2Et
b; $R^1 = R^2 = Me$, X = CO_2Me
c; $R^1 = R^2 = Me$, X = $CONH_2$
d; $R^1 = R^2 = Me$, X = CN
e; $R^1 = Me$, $R^2 = H$, X = CO_2Et
f; $R^1 = Rf$, $R^2 = H$, X = CO_2Me
g; $R^1 = Rf$, $R^2 = H$, X = $CONH_2$

Rf = β-D-ribofuranosyl

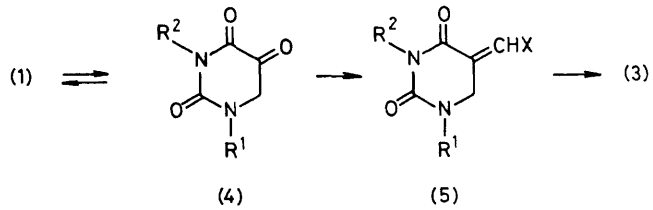
the resulting triphenylphosphine oxide was filtered off, and the filtrate was evaporated to dryness to give 5-ethoxycarbonylmethyl-1,3-dimethyluracil (**3a**)† in 93% yield.

Similarly, compound (**1a**) was treated with other stable Wittig reagents [(**2b**)—(**2d**)] to give the corresponding C(5)-substituted uracils [(**3b**)—(**3d**)] in good yields. However, similar treatment of the uracil (**1a**) with unstable Wittig reagents such as $Ph_3P{=}CH_2$ and $(EtO)_2P(O)CH_2CO_2Et$–NaH resulted in recovery of the starting material.

TABLE

Starting Materials	Product	M.p./°C	Yield/%
(**1a**) + (**2a**)	(**3a**)	78—80	93
(**1a**) + (**2b**)	(**3b**)	99—100	74
(**1a**) + (**2c**)	(**3c**)	255—256	55
(**1a**) + (**2d**)	(**3d**)	116—118	99
(**1b**) + (**2a**)	(**3e**)	126·5—128	83
(**1c**) + (**2b**)	(**3f**)	161	67
(**1c**) + (**2c**)	(**3g**)	227—229	99

The 3-unsubstituted 5-hydroxy-1-methyluracil (**1b**) was converted into compound (**3e**) by treatment with the Wittig reagent (**2a**). This success led us to investigate the synthesis of 5-substituted uridines derived from tRNA. Although the reaction did not proceed when 5-hydroxyuridine (**1c**)[4] was treated with compound (**2b**) in refluxing acetonitrile as described above, the use of dioxan in place of acetonitrile as a solvent afforded the expected minor component of tRNA, 5-methoxycarbonylmethyluridine (**3f**).[5] 5-Carbamoylmethyluridine (**3g**)[6] was similarly obtained. This new synthetic method for the synthesis of minor components of tRNA requires only two steps from the non-protected uridine and yields are far better than those of conventional methods.[5,6]



The mechanism of these transformations probably involves a reaction between the keto-tautomers (**4**) of compounds (**1**) and the Wittig reagents. The resultant methylene compound (**5**) would then rearrange into compounds (**3**).

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† All new compounds gave satisfactory elemental analyses and spectral properties consistent with the assigned structures.

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