# Palladium-catalysed Synthesis of 6-(2-Acylvinyl)uracils, a group of Novel 6-Substituted Uracils of Biological Significance[1]

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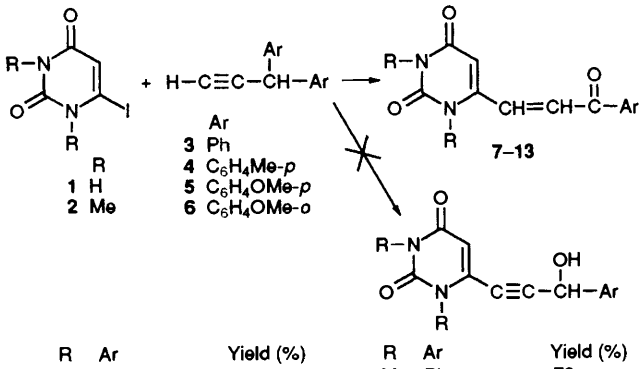
The palladium-catalysed synthesis of novel 6-substituted uracils of biological significance is described.

5-Substituted uracils and their nucleosides have been of immense biological significance because of their use in the chemotherapy of cancer [*e.g.* FU (5-fluorouracil), FUdR (5-fluoro-2′-deoxyuridine)][2] and viral diseases {$F_3$TdR (trifluorothymidine), BVDU [*E*-5-(2-bromovinyl-2′-deoxyuridine)] and AZT (3′-azido-3′-deoxythymidine)}.[3–6] Also, many 5-substituted uracils have been developed as enzyme inhibitors[7] and been used in the synthesis of modified nucleotides.[8]

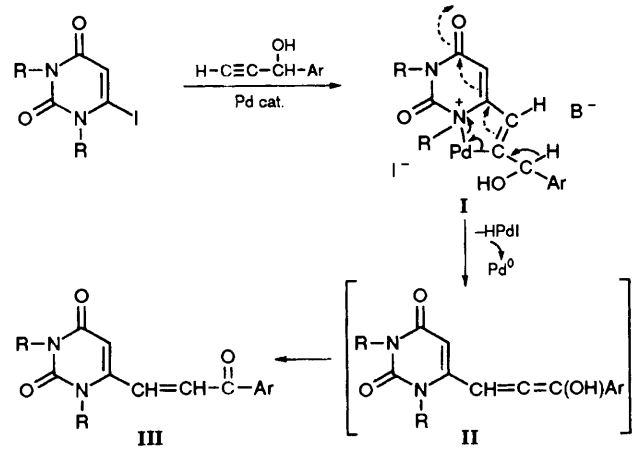
In contrast to the extensive studies which have been done on 5-substituted uracils and their nucleosides, there has been less emphasis on the development of novel 6-substituted uracils, although orotic acid (6-carboxyuracil) plays an important role in pyrimidine biosynthesis. Only a limited number of 6-substituted uracils have been synthesised and their biological activities explored.[9] Recently, however, a 6-substituted uracil derivative 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT)[10–12] has attained considerable significance as a specific inhibitor of HIV-1, a causative agent of AIDS.[13]

In connection with our studies on uracil derivatives which could be of use as anticancer and antiviral agents, we recently developed a series of novel 5-substituted uracil derivatives, *e.g.* 5-acylethynyluracils (5-AEUs) and (*E*)-5-(2-acylvinyl)uracils (5-AVUs) which showed promising activities against L1210/0 mouse leukaemia and CCRF-CEM human lymphoblastoid cells in culture.[14,15] In view of the interesting biological activities of 5-AEUs and 5-AVUs and the fact that an acyl substituent in the C-2 position of the ethynyl group attached to the C-5 of the uracil ring potentiates the biological activities of the 5-substituted uracils, we were prompted to introduce acylvinyl and acylethynyl groups at the C-6 position of the uracil ring and study the biological properties of the derived compounds. In this communication, we report on the results we have obtained so far.




| | R | Ar | Yield (%) | | R | Ar | Yield (%) |
|---|---|---|---|---|---|---|---|
| 7 | H | Ph | 39 | 11 | Me | Ph | 76 |
| 8 | H | $C_6H_4Me$-*p* | 60 | 12 | Me | $C_6H_4Me$-*p* | 80 |
| 9 | H | $C_6H_4OMe$-*p* | 57 | 13 | Me | $C_6H_4OMe$-*p* | 58 |
| 10 | H | $C_6H_4OMe$-*o* | 35 | | | | |

Scheme 1




Scheme 2

When a mixture of 6-iodouracil **1** or $N^1$,$N^3$-dimethyl-6-iodouracil **2** and an acetylenic carbinol **3–6** was heated in the presence of dichlorobis(triphenylphosphine)palladium(II), copper(I) iodide and a base ($Et_3N$) in dimethylformamide at 55 °C for 6 h,† 6-(2-acylvinyl)uracils **7–10** and the corresponding $N^1$,$N^3$-dimethyl derivatives **11–13** were obtained in modest to good yields‡ instead of the expected 6-[(3-aryl-3-hydroxy)-propyn-1-yl]uracils (Scheme 1). However, the reactions of **1** or **2** with prop-2-yn-1-ol **14** or 3-acetoxy-3-(*p*-methoxy)phenylprop-1-yne **15** failed under various conditions. Also, the reactions of **1** or **2** with 1-(*p*-anisyl)prop-2-yn-1-one **16** (H–C≡C–C(O)$C_6H_4OMe$-*p*) or with 3-(*p*-anisyl)-3-oxoprop-1-ene failed to yield any 6-substituted uracil derivatives in contrast to the reactions of 5-iodouracil derivatives with **15** and **16** which led to the 5-(*p*-anisoylethynyl) or (*E*)-5-(2-*p*-anisoylvinyl)uracil derivatives in good yields respectively.[1,15] Thus, the above method constitutes a very general and useful method for entry into novel 6-substituted uracil derivatives.

The palladium-catalysed reaction of nitrogen heterocycles containing iodine on a carbon atom next to the nitrogen atom with acetylenic alcohols leading to the chalcones has been explained simply through a base-catalysed rearrangement.[16] We, however, believe the proximal nitrogen atom must have a role in the rearrangement process which probably takes place through an intermediate **I** (Scheme 2).[17] The formation of the palladated complex **I** helps in the ionisation of C–H of the CHOH group leading to the allenol **II**. Formation of **I** is also facilitated by electromerisation in the enone system of the uracil ring (dotted arrows). The allenol **II** then rearranges to the acylvinyl ketone **III**.

Thus, we have described the first successful synthesis of 6-(2-acylvinyl)uracils through palladium-catalysed reactions. These compounds or their $N^1$- or $C^5$-substituted counterparts could be of use as anticancer and/or anti-AIDS agents. Studies are in progress towards that direction.

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## Footnotes

† Typical reactions: *e.g.* synthesis of **8**; a mixture of 6-iodouracil (0.84 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol, 6.8 mol%), CuI (0.11 mmol, 12.5 mol%) and triethylamine (3.85 mmol) in dimethylformamide (3 ml) was stirred under a nitrogen atmosphere at room temp. for 10 min. 1-(*p*-

Tolyl)-prop-2-yn-1-ol (1.23 mmol) was then added and the mixture was heated at 55 °C for 6 h. The solvents were then removed under reduced pressure and the residue was triturated with acetone (3–5 ml) and filtered to yield 6-(2-*p*-toluoylvinyl)uracil (0.5 mmol, 60%) as a light yellow solid; crystallisation from methanol, mp >280 °C.

‡ Satisfactory spectroscopic data (IR, UV and $^1$H NMR) were obtained for all the compounds synthesized; typical data, **8**, mp >280 °C; $\nu_{max}$/cm$^{-1}$ 3115, 3000, 1720, 1625, 1610, 1590; $\delta_H$ [100 MHz, $(CD_3)_2SO$] 2.48 (s, 3H, Ar–$CH_3$), 6.12 (s, 1H, C$^5$-H), 7.12–7.60 (m, 3H, $H_m$ and C=CH–CO), 7.96–8.36 (m, 3H, $H_o$ and Ura–C*H*=C), 11.16 (brs, 2H, N$^1$H and N$^3$H); elemental analyses were satisfactory.

From preliminary studies compounds **7** and **8** were found to be active against CCRF-CEM human lymphoblastoid cells *in vitro* with $IC_{50}$ being 50 μmol dm$^{-3}$ for both compounds.

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