A General Procedure for the Synthesis of Dimethoxypyrimidines and Uracils with Highly Functionalised C-5 Substituents[1]

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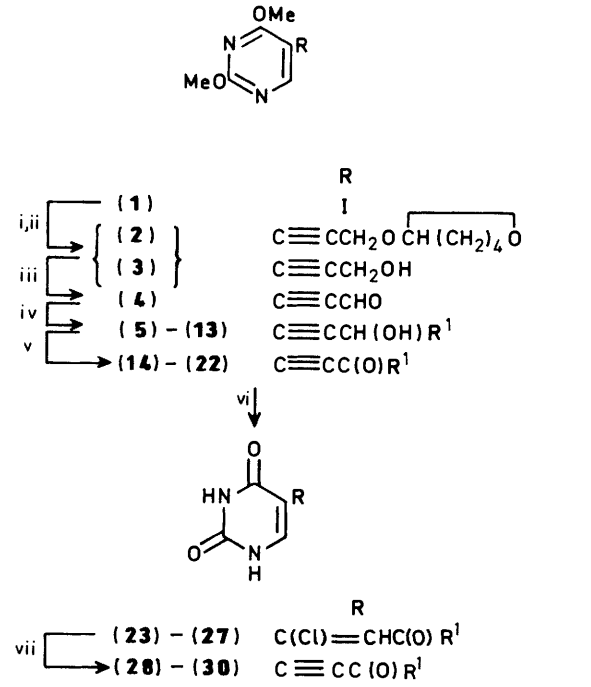
A versatile method for the synthesis of 5-[(3-alkyl or, 3-aryl-3-hydroxy)propynyl]-2,4-dimethoxypyrimidines (**5**)—(**13**), 5-(2-acyl-ethynyl)2,4-dimethoxypyrimidines (**14**)—(**22**), 5-(2-acyl-chlorovinyl)uracils (**23**)—(**27**) and 5-(2-acylethynyl)uracils (**28**)—(**30**) is described.

Whilst the importance of 5-substituted uracils as anticancer and antiviral agents is well established,[2,3] such compounds have acquired increased importance because of the effectiveness of some of them against AIDS.[4] Inherent in the choice of these compounds as anticancer and antiviral agents is their role as inhibitors of thymidylate synthetase and other enzymes essential for cellular multiplication processes.[5] We have a long term interest in the development of inhibitors of thymidylate synthetase and dihydro-orotate dehydrogenase, essential enzymes required for the growth of cells and have developed methods for the synthesis of various 5- and 6-substituted derivatives of uracil[6] and dihydrouracil.[7]

Recently we became interested in novel 5-substituted uracils where the 5-substituent contains an ethynyl or vinyl group conjugated with an acyl or other functional groups. We felt such molecules (after being converted into the corresponding 2'-deoxyribonocleotides) could act as potent inhibitors of thymidylate synthetase or other enzymes, and hence could be of use as anticancer and antiviral agents. With that objective, we have reported[8] a method for the synthesis of a few 5-(2-acylethynyl-uracils. In view of the promising biological properties of these compounds,[9] and lack of methods for the synthesis of uracil derivatives with highly functionalised C-5-substituents, it became imperative to develop alternative methods for the synthesis of uracil derivatives with an activated 5-ethynyl or 5-vinyl substituent. Here, we report a versatile method for the synthesis of such compounds.

Copper(I) 3-tetrahydropyranyloxyprop-1-ynide has been a useful reagent for the synthesis of aromatic and heterocyclic ethynyl substituted compounds.[10] We have utilised this unique reagent for the introduction of a protected ethynyl side-chain on the pyrimidine ring. 5-Iodo-2,4-dimethoxypyrimidine[11] (**1**) when refluxed with copper(I) 3-tetrahydropyranyloxyprop-1-ynide in pyridine for 2.5 h gave 2,4-dimethoxy-5-(3-tetrahydropyranyloxypropyn-1-yl)pyrimidine (**2**) as a gum (87%). This when deblocked with toluene-*p*-sulphonic acid in methanol (reflux, 1 h) yielded 5-(2-hydroxymethylethynyl)-2,4-dimethoxypyrimidine (**3**) as a crystalline solid (m.p. 122 °C; 81%), which on oxidation with Swern reagent[12] gave 5-(2-formylethynyl)-2,4-dimethoxypyrimidine (**4**) (m.p. 130 °C, 76%). Compound (**4**) has proved to be a very crucial compound in our synthetic strategy. On treatment of (**4**) with various Grignard reagents a number of 5-[(3-alkyl or aryl-3-hydroxy)-propyn-1-yl]-2,4-dimethoxypyrimidines were obtained in excellent to satisfactory yields: (**5**; R′ = Me), m.p. 110 °C (90%); (**6**; R′ = Et), m.p. 75 °C (83%); (**7**; R′ = Pr^i), gum (20%); (**8**; R′ = Bu), m.p. 66 °C (46%); (**9**; R′ = CH=CH$_2$), m.p. 78 °C (55%); (**10**; R′ = Ph), gum (74%); (**11**; R′ = C$_6$H$_4$Me-*p*), m.p. 110 °C (70%); (**12**; R′ = C$_6$H$_4$OMe-*p*), m.p. 116—117 °C (80%); and (**13**; R′ = 3,4-dimethoxyphenyl), gum (47%). The acetylenic alcohols were readily oxidised with Collins' reagent[13] or with manganese dioxide in dichloromethane. The following acetylenic ketones were obtained: (**14**; R′ = Me), m.p. 96 °C (61%); (**15**; R′ = Et), m.p. 76 °C (64%); (**16**; R′ = Pr^i), m.p. 92 °C (50%): (**17**; R′ = Bu), gum (71%); (**18**; R′ = CH=CH$_2$), m.p. 110—112 °C (61%); (**19**; R′ = Ph), m.p. 124—125 °C (54%); (**20**; R′ = C$_6$H$_4$Me-*p*), m.p. 140—141 °C (91%); (**21**; R′ = C$_6$H$_4$OMe-*p*), m.p. 136 °C (50%); (**22**; R′ = C$_6$H$_3$(OMe)$_2$-3,4), m.p. 142—144 °C (39%). Although iodotrimethylsilane or chlorotrimethylsilane and sodium iodide have been utilised by us[8] to deblock 5-(2-acylethynyl-2,4-dimethoxyprimidines, we found 6M hydrochloric acid conveniently converted compounds (**14**), (**15**), (**19**)—(**21**) into the corresponding 5-(2-acyl-1-chlorovinyl)uracils: (**23**; R′ = Me), m.p. 236 °C (67%); (**24**; R′ = Et), m.p. 236 °C (75%); (**25**; R′ = Ph), m.p. 240—242 °C (84%); (**26**; R′ = C$_6$H$_4$Me-*p*), m.p. 246—250 °C (87%), and (**27**; R′ = C$_6$H$_4$OMe-*p*), m.p. 234—235 °C (86%). The 5-(2-acyl-1-



Scheme. *Reagents and conditions:* i, Cu^I–C≡C–CH$_2$OCH(CH$_2$)$_4$O (1.3 mol equiv.)–Py, 2.5 h, reflux; ii, *p*-TSA, MeOH, 1 h, reflux; iii, oxalyl chloride (1.3 mmol equiv.), DMSO (1 ml), Et$_3$N (5 ml) dropwise addition at −78 °C, then brought to room temp.; iv, RMgX (2 equiv. in ether or THF); v, CrO_3 (3 mol equiv.) in pyridine; vi, 6M HCl, heat at 90 °C for 4 h; vii, KOH (2M) in dioxane, stirring at room temp. for 24 h.

* For details of the Supplementary publication see 'Introduction for Authors (1989)', *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

chlorovinyl)uracils which were found to be stable and easier to handle than the corresponding 1-iodo analogues, were easily converted into 5-(2-acylethynyl)uracils on treatment with potassium hydroxide in dioxane: (**28**; R′ = Ph), m.p. >290 °C (69%); (**29**; R′ = C_6H_4Me-*p*), m.p. >290 °C (70%); and (**30**; R′ = C_6H_4OMe-*p*, m.p. >290 °C (57%). Preliminary biological studies on some of the synthesised 5-substituted uracils have been extremely encouraging: compounds (**25**) and (**26**) led to 57% and 74% inhibition respectively whereas compounds (**28**) and (**29**) led to 100% inhibition of growth of Ehrlich ascites carcinoma cells in Swiss Albino mice.

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