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PALLADIUM-CATALYSED SYNTHESIS OF SOME BIOLOGICALLY ACTIVE 5, 6-DISUBSTITUTED URACILS[1]

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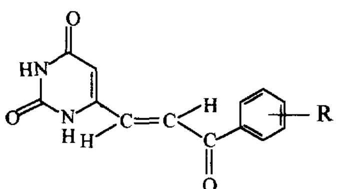
Abstract. Synthesis of some 5-halo-[E]-6(2-*p*-toluoylvinyl)uracils and some 5-alkynyl-[E]-6-(2-*p*-toluoylvinyl)uracils through palladium-catalysed procedure and cytotoxicities of the former and [E]-6-(2-*p*-toluoylvinyl)uracils are reported.

Uracil derivatives substituted either at C-5 or C-6 position and their nucleosides have considerable importance in the field of chemotherapy. Among the important 6-substituted uracils, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT)[2] and its derivatives have emerged as new anti-HIV-1 agents. Another group of 6-substituted uracils, *viz.* 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs)[3] behave as non-nucleoside reverse transcriptase inhibitors (NNRTIs). The excellent biological activities exhibited by both 5-substituted and 6-substituted uracil derivatives provided the impetus to explore chemistry and biological activities of 5,6-disubstituted uracils.[4,5] Also, recently it was shown that introduction of a halogen substitution at 5-position of 6-vinyluracil increased the susceptibility of the resulting compounds towards thiols, but did not produce a corresponding increase in activity in cell culture assay.[6]

Chemistry

Previously we synthesised a number of uracil compounds substituted by either an acetylenic ketone or a vinylic ketone moiety at C-5 position leading to 5-acylethynyluracils (5-AEUs)[7] or 5-acylvinyluracils (5-AVUs)[8] respectively. The 5-AEUs particularly exhibited promising antitumor properties against various tumor cell lines *in vitro*. Recently, we reported[9] a facile one step synthesis of [E]-6-(2-acylvinyl)uracils (6-AVUs) from



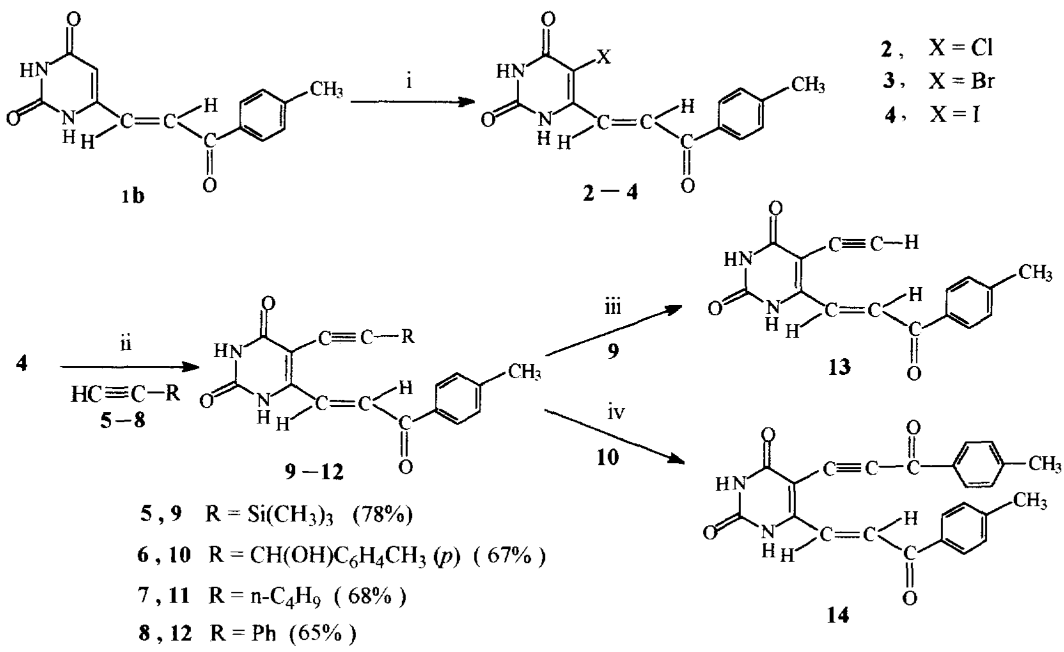
1a-c

1a , R = H
1b , R = CH_3 (*p*)
1c , R = OCH_3 (*p*)

6-iodouracil and acetylenic carbinols in the presence of bis(triphenylphosphine)palladium(II) chloride and CuI. However their biological properties were not reported. This letter describes the synthesis of 5-halo- and 5-alkynyl-[E]-6-(2-acylvinyl)uracils and the biological evaluation of the 6-AVUs and 5-halo-6-AVUs.

Palladium-catalysed reactions have been extensively utilised for carbon-carbon bond formation .[10,11] We have used this procedure for the synthesis of both 5- and 6-substituted uracils and their nucleosides[9,12] starting from the corresponding iodouracils or their derivatives. However, in our attempts to synthesise the 5,6-disubstituted uracils by palladium-catalysed reactions of 5,6-diiodouracil with acetylenic carbinols, the desired 5,6-disubstituted uracils could not be obtained. Hence, we developed a facile two step procedure for the synthesis of the disubstituted uracils as shown in the Scheme.

Scheme



Reaction condition : I) N-chlorosuccinimide (NCS), acetic acid, 80°C, 8h or N-bromosuccinimide (NBS), acetic acid, 80°C, 8h, or iodine monochloride (ICl), aq. MeOH, 80°C, 16h; ii) $(Ph_3P)_4Pd$, CuI, DMF, TEA, N_2, 50°C, 4h; iii) NaOMe, MeOH, r.t., 4h; iv) Jones reagent, DMF.

The 6-substituted uracils and their nucleosides were synthesised either through a Wittig reaction[13] or by a lithiation procedure.[14] Compound **1b**[9] on treatment with N-chloro- or N-bromosuccinimide in acetic acid or with iodine monochloride in aqueous methanol (1:1) led smoothly to the corresponding 5-halo-[E]-6-(2-acylvinyl)uracils **2-4**. 5-Iodo-[E]-6-(2-*p*-toluoylvinyl)uracil (**4**) underwent palladium catalysed reactions with the copper (I) iodide leading to the 5-alkynyl-[E]-6-(2-*p*-toluoylvinyl)uracils **9-12**.[15] The catalyst $(Ph_3P)_4Pd(0)$ was found to be specific for this reaction. Other catalysts, *e.g.*,$(Ph_3P)_2PdCl_2$-CuI or $PdCl_2$-PPh_3-CuI failed to yield the condensation products. The 5-trimethylsilyl derivative **9** could be easily desilylated with sodium methoxide in methanol to 5-ethynyl-[E]-6-(2-*p*-toluoyl)vinyluracil (**13**), whereas **10** on oxidation with Jones reagent yielded 5-(*p*-toluoylethynyl)-[E]-6-(2-*p*-toluoylvinyl)uracil (**14**) in excellent yield. Thus, a very convenient palladium-catalysed method has been developed for the synthesis of a number of novel 5.6-disubstituted uracils **9-14**. It appears a bulky 6-substituent does not hinder palladium-catalysed reactions at the C-5 position of the uracil ring. The method is easily adaptable for the synthesis of other 5,6-disubstituted uracils.

Biology

Biological studies on [E]-6-(2-acylvinyl)uracils (6-AVUs) **1a-1c** and 5-halo-[E]-6-(2-*p*-toluoylvinyl)uracils **2-4** were carried against CCRF-CEM human lymphoblastoid cells in culture[16] and the results are shown in Table. All of the 6-AVUs **1a-c** exhibited excellent antitumor activities, of which the *p*-toluoylvinyl derivative **1b** was the most potent. Among the 5-halo derivatives **2-4**, the 5-chloro-6-AVU **2** was found to be the least active, whereas the corresponding 5-bromo derivative **3** exhibited activity comparable with 6-AVUs **1a-c**. Interestingly the 5-iodo-[E]-6-(2-*p*-toluoylvinyl)uracil (**4**) emerged as the most potent compound in the series, even more potent than 5-FU in this cell culture system. Further studies on the other disubstituted uracils are in progress.

Table. *In vitro* activity of 6-AVUs (**1a-c**) and 5-halo-6-AVUs (**2-4**) against CCRF-CEM cells

Compound	R	X	IC_{50} μM
1a	H	H	2.6
1b	Me (*p*)	H	1.8
1c	OMe(*p*)	H	2.2
2	Me (*p*)	Cl	12.2
3	Me (*p*)	Br	2.6
4	Me (*p*)	I	1.4
5-FU	-	-	2.0

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15. **Typical procedure : Synthesis of 5-Iodo-[E]-6-(2-*p*-toluoylvinyl)uracil (4).** To a suspension of [E]-6-(2-*p*-toluoylvinyl)uracil (**1**, 500 mg, 1.95 mmol) in aqueous methanol (1:1), iodine monochloride was added and refluxed for 16h. The resulting yellow solid was then filtered , washed with sodium thiosulfate solution and methanol respectively to obtain compound **4** (610 mg, 1.596 mmol, 81.8 %), which was crystallised from methanol (m.p. >260°C).
Synthesis of 5-Phenylethynyl-[E]-6-(2-*p*-toluoylvinyl)uracil) (12). A mixture of compound **4** (200 mg, 0.52 mmol), phenylacetylene (**8**, 80 mg, 0.78 mmol), tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol), copper(I) iodide (10 mg, 0.052 mmol) and triethylamine (150 mg, 1.48 mmol) in N, N-dimethyl-formamide (10 ml) was stirred under nitrogen atmosphere at 50^0C for 4h. After removal of the solvent under reduced pressure, the residue was triturated with acetone (10 ml) to afford **12** (120 mg, 0.336 mmol, 64.8%), crystallised from methanol-DMF (m. p. 262-264^0C). Satisfactory spectroscopy data (IR, UV, ^{1}H NMR,) were obtained for all the compounds synthesised; typical data for **12** : ν_{max} / cm^{-1} 3130, 3030, 1715, 1660, 1620, 1610, 1570; λ_{max} / nm 422.4 (logε = 3.93), 288.4 (logε = 4.40); δ_H[600 MHz, DMSO-d_6], 2.40 (s, 3H, $ArCH_3$), 7.42 (d, 2H, J = 8.46 Hz, $COArH_m$), 7.46 (m, 3H, $ArH_{m,p}$), 7.52 (m, 2H, ArH_o), 7.74 (d, 1H, J = 15.50 Hz, -C=CH-COAr), 8.06 (d, 2H, J = 8.46 Hz, $COArH_o$), 8.34(d, 1H, J = 15.51 Hz, ura-CH=C-CO), 11.55 (s, 1H, NH), 11.70 (s, 1H, NH); elemental analyses were satisfactory.

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