A Highly Convenient Procedure for the Synthesis of 5-(2-Acylvinyl)uracils, a Group of Novel 5-Substituted Uracils[2]

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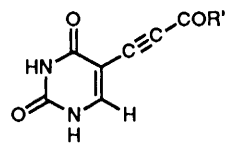
An unambiguous and efficient method has been developed for the synthesis of a number of 5-(2-acylvinyl)uracils, which are of interest as anticancer, antiviral, and anti-AIDS agents.

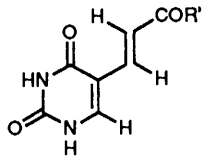
We have been interested in the development of novel 5-substituted uracils[1] the importance of which as anticancer (5-fluorouracil),[3] antiviral [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine, BVDU][4] and anti-AIDS (azidothymidine, AZT)[5] agents needs no emphasis.[6,7]

Recently, we reported[8] a versatile synthesis of 5-(2-

acylethynyl)uracils (5-AEUs) (**1**): an alternative, general procedure for the synthesis of these has also been developed by us.[9]

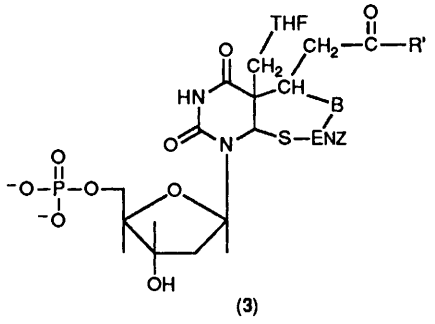


(1)



(2)

R′ = Alkyl or aryl group



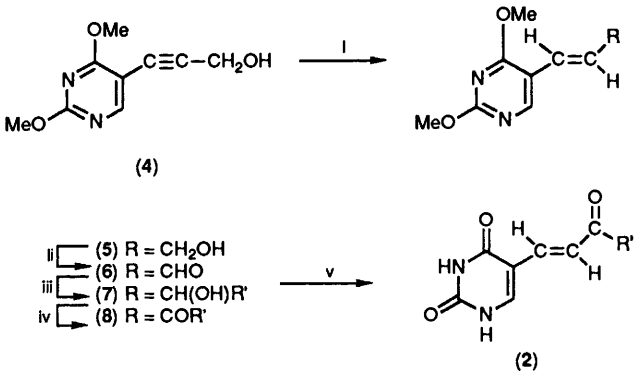
(3)

One of the proposed enzyme-inhibitor complexes (**3**) (–CH_2–THF, methylene tetrahydrofolate; B, a basic group on TS enzyme)

The 5-AEUs have strong antitumour properties and presumably act as inhibitors of thymidylate synthetase;[10] we have now become interested in the corresponding vinyl analogues, *e.g.* 5-(2-acylvinyl)uracils (5-AVUs) (**2**). In these the highly active 5-substituents lead to activation of the 5,6-double bond of the uracil ring by inductive and mesomeric effects. Hence, in the reaction of thymidylate synthetase (TS) enzyme[11] (a crucial enzyme in cellular multiplication processes) with the 2′-deoxyribonucleotides derived from (**2**), the addition of the cysteine mercapto group of TS to C-6 of the uracil ring will be highly facilitated. Addition of other nucleophilic groups in the TS enzyme to the side chain double bond of (**2**) will also help to form a tight enzyme–inhibitor complex (**3**).

Furthermore, hydrophobic interactions between the enzyme and aromatic part (R′ = aryl) of the AVUs will strengthen the complex. Similar considerations apply as well to 5-AEUs. However, the AVUs differ from the AEUs in the stereoelectronic characteristics of their side chains. Thus, their interactions with TS are expected to be different from those of AEUs with the TS enzyme. Hence, the synthesis of the AVUs is highly desirable in order to develop the best inhibitors of thymidylate synthetase.

In spite of the potentialities of the nucleotides of 5-(2-acylvinyl)uracils as inhibitors of TS and other enzymes, there are very few reports of their synthesis,[12] and their biological properties remain mostly unexplored. Hence, we undertook a programme to synthesize a number of the AVUs and to study their biological properties extensively. No general methods for the synthesis of the AVUs are known. Partial reduction of the AEUs to the AVUs has not been successful in our hands and led to the completely saturated compounds. Also, the reaction of substituted 5-halogenopyrimidines with methyl vinyl ketone in the presence of palladium catalysts usually led to a poor yield of the corresponding 5-(2-acetylvinyl)pyrimidines. The corresponding saturated derivatives were the major products.[13] This prompted us to develop a general and simplified method for the synthesis of 5-(2-acylvinyl)uracils and the present communication reports an extremely facile and unambiguous method for the synthesis of the AVUs as shown in the Scheme.



(4)

(2)

Scheme. i, LAH in THF; ii, MnO_2 in CH_2Cl_2; iii, RMgX in THF; iv, MnO_2 in CH_2Cl_2; v, Me_3SiCl, NaI in CH_3CN.

5-(2-Hydroxymethylethynyl)-2,4-dimethoxypyrimidine (**4**), synthesized by a novel procedure[9] and used to prepare 5-(2-acylethynyl)uracils, has also proved to be crucial in the synthesis of 5-(2-acylvinyl)uracils. On reduction with lithium aluminium hydride in tetrahydrofuran, compound (**4**) gave the corresponding vinyl analogue (**5**) (85%). The *E*-configuration was established from its ^1H NMR spectra where the two vinylic hydrogens were coupled (*J* 16 Hz). Mild oxidation of (**5**) with manganese dioxide in dichloromethane led to (**6**) (65%). Treatment of the latter with Grignard reagents gave a number of 5-[3-alkyl- or, 3-aryl-(3-hydroxy)propenyl]-2,4-dimethoxypyrimidines as gums: (**7a**; R′ = Me) (88%), (**7b** R′ = Et) (87%), (**7c**; R′ = Pr) (92%), (**7d**; R′ = Pr^i) (77%), (**7e**; R′ = Bu) (81%), (**7f**; R′ = Ph) (68%), (**7g**; R′ = C_6H_4Me-*p*) (80%), and (**7h**; R′ = C_6H_4OMe-*p*) (72%). To avoid rearrangements, the vinyl alcohols were oxidised with a mild reagent, *e.g.* neutral manganese dioxide in dichloromethane to the corresponding vinyl ketones, *e.g.* 5-(2-acylvinyl)-2,4-dimethoxypyrimidines: (**8a**; R′ = Me), m.p. 94–95 °C (75%); (**8b**; R′ = Et), m.p. 82–84 °C (65%); (**8c**; R′ = Pr), m.p. 62 °C (73%); (**8d**; R′ = Pr^i), m.p. 82–84 °C (71%); (**8e**; R′ = Bu), m.p. 50–52 °C (82%); (**8f**; R′ = Ph), m.p. 134 °C (73%); (**8g**; R′ = C_6H_4Me-*p*), m.p. 160–162 °C (61%); (**8h**; R′ = C_6H_4OMe-*p*), m.p. 122–123 °C (71%).

The *O*-dealkylation of alkoxypyrimidines, particularly with sensitive functional groups at C-5 position, has always posed serious problems[14] and although iodotrimethylsilane is a versatile reagent for ether cleavage[15,16] its use with alkoxypyrimidines has not been extensively explored.[17] We found that 5-ethynyl-2,4-dimethoxypyrimidine was converted into 5-acetyluracil or treatment with iodotrimethylsilane in chloroform.[18] With 5-(2-acylethynyl)-2,4-dimethoxypyrimidines, use of 6M hydrochloric acid or iodotrimethylsilane in chloroform gave demethylation with concurrent addition of hydrogen halide to the triple bond to give 5-(1-halogeno-2-acylvinyl)-uracils.[8] However, when 6M hydrochloric acid was used for the deblocking of 5-(2-acylvinyl)-2,4-dimethoxypyrimidines (**8**), normal deblocked products could not be obtained for (**8a**) and (**8b**). Chlorotrimethylsilane and sodium iodide have been used for the removal of ether functionality.[19] We found that treatment of 5-(2-acylvinyl)-2,4-dimethoxypyrimidines (**8**) with chlorotrimethylsilane and sodium iodide in acetonitrile at room temperature followed by treatment with water, gave smooth demethylation without concurrent addition to the double bond. This reagent was found to be superior to iodotrimethylsilane in this respect. We believe this is the first successful report of *O*-dealkylation of alkoxypyrimidines having sensitive C-5 substituents to the corresponding uracil derivatives without

any change in the functional groups. Thus, a number of 5-(2-acylvinyl)uracils were obtained: (**2a**; R′ = Me), m.p. 279 °C (74%); (**2b**; R′ = Et), m.p. 240–242 °C (57%); (**2c**; R′ = Pr), m.p. 248–250 °C (73%); (**2d**; R′ = Pr^i), m.p. 268–270 °C (66%); (**2e**; R′ = Bu), m.p. 254–256 °C (79%); (**2f**; R′ = Ph), m.p. 286–288 °C (78%); (**2g**; R′ = C_6H_4Me-*p*), m.p. 296–298 °C (80%), and (**2h**; R′ = C_6H_4OMe-*p*), m.p. 286–288 °C (88%).

Preliminary biological studies have shown that 5-(2-*p*-toluoylvinyl)uracil inhibits the growth of L1210/0 mouse leukemia cells in culture (IC_{50} = 5.7 μM) and inhibits the TS enzyme in intact L1210/0 cells.[10]

Experimental

Typical Procedure.—To an ice-cold solution of a Grignard reagent [made from *p*-bromotoluene (1.7 g, 9.94 mmol) and magnesium turnings (240 mg, 10 m atom) in tetrahydrofuran (THF; 20 ml)], compound (**6**) (500 mg, 2.6 mmol) in THF (20 ml) was added dropwise. The reaction mixture was heated at reflux for 1 h and THF was distilled off, with continuous addition of benzene. After cooling, decomposition with saturated aqueous NH_4Cl, extraction with ether, and purification of the residue after solvent removal by column chromatography on neutral alumina (eluant chloroform–ethyl acetate = 9:1) compound (**7g**) (590 mg, 80%) gave a gum.

Compound (**7g**) (100 mg, 0.35 mmol) in CH_2Cl_2 (15 ml) was oxidised with active manganese dioxide (600 mg, 6.9 mmol) by stirring at room temperature (28–30 °C) for 16 h. Work-up and column chromatography on neutral alumina (chloroform as eluant), gave (**8g**) (0.21 mmol, 60%) as a crystalline compound, m.p. 160–162 °C. A mixture of (**8g**) (150 mg, 0.53 mmol), chlorotrimethylsilane (0.2 ml, 1.39 mmol), and sodium iodide (170 mg, 1.13 mmol) in dry acetonitrile (6 ml) was stirred at room temperature (28 °C) for 24 h under nitrogen atmosphere. After removal of the solvent, the residue was treated with water (1 ml) and aqueous sodium metabisulphite (10%), and the solution filtered and dried to yield 5-(2-*p*-toluoylvinyl)uracil (**2g**), (108 mg, 80%); this crystallized from methanol and water as pale yellow crystals, m.p. 296–298 °C.

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References

1 R. S. Bhatt, N. G. Kundu, T. L. Chwang, and C. Heidelberger, *J. Heterocycl. Chem.*, 1981, **18**, 771; N. G. Kundu, S. Sikdar, R. P. Hertzberg, S. A. Schmitz, and S. G. Khatri, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1293.
2 Part 14 of the series 'Studies on Uracil Derivatives and Analogues': for Part 12, see ref. 14, and part 13, N. G. Kundu, B. Das, C. P. Spears, A. Majumdar, and S.-I. Kang, *J. Med. Chem.*, in press.
3 C. Heidelberger in Cancer Medicine, eds. J. F. Holland and E. Frei, Lea and Febiger, Philadelphia, 1984, 801; C. Heidelberger, P. V. Danenberg and R. G. Moran, 'Fluorinated Pyrimidines and their Nucleosides in Advances in Enzymology and Related Areas in Molecular Biology,' ed. A. Meister, Wiley, New York, 1983, 57.
4 E. DeClercq, J. Descamps, P. DeSomer, P. J. Barr, A. S. Jones, and R. T. Walker, *Proc. Natl. Acad. Sci. USA*, 1979, **76**, 2947.
5 R. Dagani, *Chem. Eng. News*, 1987, **65**, 41; E. DeClercq, *J. Med. Chem.*, 1986, **29**, 1561; P. Herdewijn, J. Balzarini, E. DeClercq, R. Pauwels, M. Baba, S. Broder, and H. Vanderhaeghe, *ibid.*, 1987, **30**, 1270; T.-S. Lin, J.-Y. Guo, R. F. Schinazi, C. K. Chu, J.-N. Xiang, and W. H. Prusoff, *ibid.*, 1988, **31**, 336.
6 J. Cairns, *Sci. Am.*, 1985, **253**, No. 5, 31.
7 R. C. Gallo, *Sci. Am.*, 1987, **256**, No. 1, 45; R. M. Baum, *Chem. Eng. News*, 1988, July 11, 7; R. C. Gallo and L. Montagnier, *Sci. Am.*, 1988, **259**, No. 4, 25.
8 N. G. Kundu, B. Das, A. Majumdar, and L. N. Chaudhuri, *Tetrahedron Lett.*, 1987, **28**, 5543.
9 N. G. Kundu, L. N. Chaudhuri, and B. Das, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1165.
10 Observations from our laboratory and the laboratory of Dr. C. P. Spears, University of Southern California Comprehensive Cancer Centre, Los Angeles, USA.
11 L. W. Hardy, J. S. Finer-Moore, W. R. Montfort, M. Jones, D. V. Santi, and R. M. Stroud, *Science*, 1987, **235**, 448.
12 E. C. Ressner, P. Fraher, M. S. Edelman, and M. P. Mertes, *J. Med. Chem.*, 1976, **19**, 194.
13 A. Wada, H. Yasuda, and S. Kanatomo, *Synthesis*, 1988, **10**, 771.
14 N. G. Kundu, B. Das, and A. Majumdar, *Synthesis*, 1990, in press.
15 M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 1977, **42**, 3764.
16 T.-L. Ho and G. A. Olah, *Angew. Chem.*, 1976, **88**, 847; *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 774.
17 R. B. Silverman, R. E. Radak, and N. P. Hacker, *J. Org. Chem.*, 1979, **44**, 4970.
18 N. G. Kundu and S. A. Schmitz, *J. Heterocycl. Chem.*, 1982, **19**, 463.
19 G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, 1979, **44**, 1247.

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