A Photochemical Synthon for the 5-Uracil Carbanion. Application to the Direct Functionalization of Unprotected Uracils

By ALLAN WEXLER, ROBERT J. BALCHUNIS, and JOHN S. SWENTON*
(*Department of Chemistry, The Ohio State University, Columbus, Ohio* 43210)

Summary The photocycloaddition of 5-fluorouracil to enol acetates followed by base catalysed fragmentation affords a ready, mild procedure for functionalization at C-5 of unprotected uracils.

RECENTLY there has been much chemical and biological interest in 5-substituted uracils and uridines.[1] Classical synthetic approaches involve reactions of protected 5-lithiouracils, reduction of protected 6-chlorouracils, or direct synthesis from α-formyl esters.[2] We report that appropriate 5-substituted uracils can be obtained under mild conditions from commercially available 5-fluorouracil by a two-step photoaddition–fragmentation sequence. This method is preferable for synthesis of many 5-substituted uracils and is potentially useful for direct functionalization of readily available 5-fluorinated nucleoside derivatives[3] and as a synthetic route to C-nucleoside analogues.

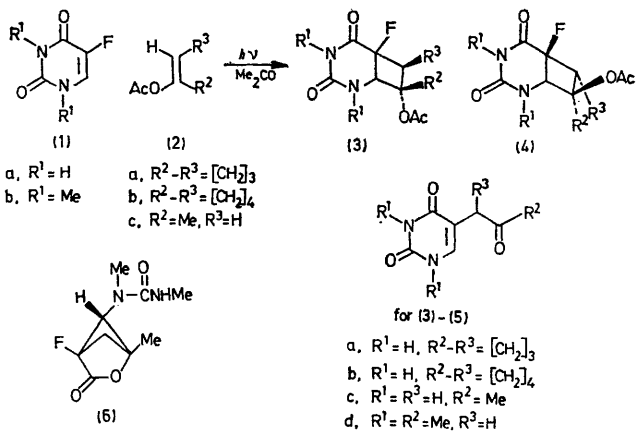

TABLE. Yields of photoadducts and functionalized uracils

Uracil/M × 10²	Enol acetate/M × 10²	Yield/% and (ratio) adducts[a] of (3) : (4)	Yield uracil/%
(1a) (6·7)[b]	(2a) (67·0)	(3a) 64[d] (93 : 7) m.p. 224—226°	(5a)[f] 72 m.p. 252—253°
(1a) (6·7)[b]	(2b) (67·0)	38[d] (66 : 12) (3b) m.p. 261—264° (4b) m.p. 188—190°	(5b)[f] 76 m.p. 280—283°
(1a) (6·7)[b]	(2c) (67·0)	57[e] (3 : 7) (3c) m.p. 219—222° (4c) m.p. 252—254°	(5c)[g] 37 m.p. 254—255°
(1b) (4·7)[c]	(2c) (47)	58[e] (1 : 2) (3b) liquid; (4d) m.p. 83·5°	(5d)[f] 66 m.p. 112—114°

[a] Irradiations of 3 mmol of the uracil in 150 cm³ of solvent were performed for 1·5—3 h with Corex-filtered light from a 450 W Hanovia medium-pressure source. [b] Acetone solvent. [c] Acetonitrile–acetone (6 : 2) solvent. [d] Yield of the major adduct from direct recrystallization of the reaction mixture. [e] Yield of the adduct mixture after silica gel chromatography. [f] The yield is reported for fragmentation of the major adduct. [g] The fragmentation was performed on the adduct mixture. The low isolated yield in this instance largely reflects the difficulty in the recrystallization of this material.

Acetone-sensitized irradiation of 5-fluorouracil (**1a**) to cyclopentenyl acetate, followed by recrystallization, yielded 64% of the adduct (**3a**). When a solution of (**3a**) was refluxed for 10 min in methanolic NaOH (3 equiv.), followed by acidification and recrystallization, (**5a**) (72%) was obtained. To demonstrate the generality of the method the acyclic isopropenyl acetate (**2c**) and the more flexible cyclohexenyl acetate (**2b**) were subjected to the same sequence (see Table). That the photoadditions were clean and of high regioselectivity was apparent from the ^{19}F-n.m.r. spectra of the crude reaction mixture, since the only other detectable fluorine compounds arose from dimerization of the 5-fluorouracil.

The stereochemistry of the intervening cycloadducts was established from either straightforward analysis of their ^{19}F-n.m.r. spectra or degradative methods. Thus, the ^{19}F-n.m.r. spectra of adducts (**3a**), (**3b**), (**4a**), and (**4b**) all exhibited the X-portion of an ABX system, and the stereochemistry could be assigned on the known variation of J_{HF} with dihedral angle.[4] For the isopropenyl acetate adducts, the *endo*-configuration of (**3d**) was established by its anomolous base cleavage to (**6**). The same type of reaction can be realized from the *endo*-adduct of 1,3-dimethyluracil (**1b**) and vinyl acetate, provided more stringent hydrolysis conditions than those reported previously are used.[5] The stereochemistry of the related cycloadducts (**3c**) and (**4c**) was assigned by comparison of their ^{19}F-n.m.r. chemical shifts and coupling constants with those of (**3d**) and (**4d**).

The unique ability of fluorine to remain intact in these photoaddition reactions contrasts with the lability of chlorine and bromine under these conditions† and suggests that this photochemical stability of the vinylic fluoride may considerably extend the synthetic scope of photoannelation *via* cyclobutane intermediates.[6]

We thank the Camille and Henry Dreyfus Fund for partial support.

(*Received, 14th April* 1975; *Com.* 427.)

† All attempts at photoaddition of 5-bromo- or 5-chloro-uracil to enol acetates and enol ethers gave complex mixtures. These experiments will be detailed in a full paper. We note that reports of photoadditions to $\alpha\beta$-unsaturated enones bearing halogen substituents on the double bond are rare.

[1] H. Hayashi, K. Nakanishi, C. Brandon, and J. Marmur, *J. Amer. Chem. Soc.*, 1973, **95**, 8749; T. Kulikowski and D. Shugar, *J. Medicin. Chem.*, 1974, **17**, 269; K. Gerzon, D. C. DeLong, and J. C. Kline, *Pure Appl. Chem.*, 1971, **28**, 489; J. D. Fissekis and F. Sweet, *J. Org. Chem.*, 1973, **38**, 1963; C. H. Evans, A. S. Jones, and R. T. Walter, *Tetrahedron*, 1973, **29**, 1611.

[2] For a summary of these methods see: N. J. Leonard and R. L. Cundall, *J. Amer. Chem. Soc.* 1974, **96**, 5904. A photochemical procedure specific to 5-(formylmethyl)uracil has recently been published. D. E. Bergstrom and W. C. Agosta, *Tetrahedron Letters*, 1974, 1087.

[3] M. J. Robins and S. R. Naik, *J. Amer. Chem. Soc.*, 1971, **93**, 5277; *J.C.S. Chem. Comm.*, 1972, 18; D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, 1972, **37**, 329.

[4] K. L. Williamson, Y. F. Li, F. H. Hall, and S. Swager, *J. Amer. Chem. Soc.*, 1966, **88**, 5678.

[5] J. S. Swenton and J. A. Hyatt, *J. Amer. Chem. Soc.*, 1972, **94**, 7605; 1974, **96**, 4885.

[6] For synthetic applications of photoannelations *via* cleavage of cyclobutanes see B. D. Challand, H. Hikino, G. Kornes, G. Lange, and P. DeMayo, *J. Org. Chem.*, 1969, **34**, 794 and references cited therein; N. R. Hunter, G. A. MacAlpine, H. J. Liu, and Z. Valenta, *Canad. J. Chem.*, 1970, **48**, 1436; P. T. Ho, S. F. Lee, D. Chang, and K. Wiesner, *Experientia*, 1971, **27**, 1377.