Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5767–5769

Tetrahedron Letters

Photochemical behaviour of 5-perfluoroalkenyl uracils

Henryk Koroniak,* Piotr Karwatka and Tomasz Cytlak

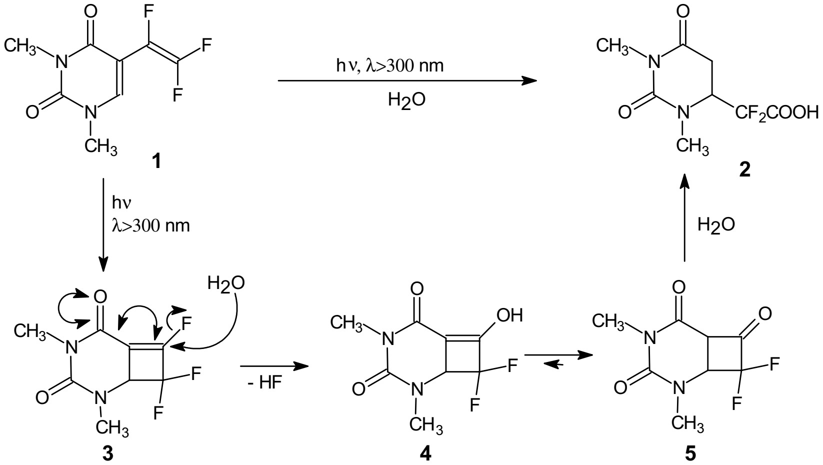
Adam Mickiewicz University, Faculty of Chemistry, Grunwalszka 6, 60-780 Poznań, Poland

Received 7 August 2003; revised 21 April 2004; accepted 30 April 2004
Available online 15 June 2004

Abstract—Phototransformations of derivatives of 5-fluoroalkenyl uracils depend strongly on the fluorinated substituents. 1,3-Dimethyl-5-trifluorovinyluracil when irradiated in water with UV light ($\lambda > 300$ nm) gives 1,3-dimethyl-(5,6-dihydrourac-6-yl)-difluoroacetic acid as the only product, while the analogous 1,3-dimethyl-5-(*E*-pentafluoropropenyl)uracil isomerizes to its *Z* isomer. It is suggested that the first transformation is *thermodynamically* controlled while the second one is *kinetically* controlled, the difference being due to *torquoselectivity*.

It is known that modified uracils with an unsaturated exocyclic side chain in position 5 display significant antiviral activity.[1] Recently, we studied extensively synthetic methodology to access 5-fluorinated alkenyl uracils as well as to determine their structural properties.[2] One of the reasons for our research is the potential biological activity of fluorinated 5-alkenyl uracils. This expectation is based on the geometrical similarity of hydrogen and fluorine. The therapeutic properties are attributed to the structural similarity of fluorine and hydrogen-containing molecules (e.g., the 5-fluorouracil analogue of uracil) to such an extent that these molecules are quite often not indistinguishable by enzymes.[3] In our studies we were able to synthesize a series of new derivatives of uracil with 5-perfluoroalkenyl groups, which along with the endocyclic 5,6 double bond, form a diene system.[2]

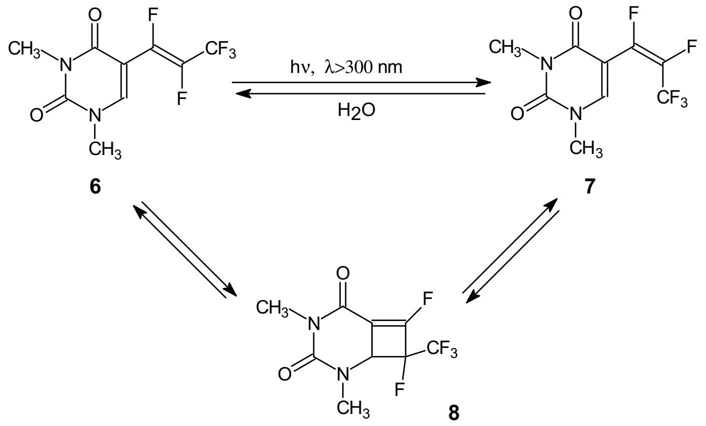
The photochemical properties of 1,3-dimethyl-5-(trifluorovinyl)uracil **1** were studied, assuming that the electrocyclization of the *diene* would be a dominant reaction. The intermediate, a cyclobutene derivative,



Keywords: Uracil; 5-Trifluorovinyl uracil; 5-Pentafluoropropenyl uracil; Photorearrangement.

* Corresponding author. Tel.: +48-61-8291303; fax: +48-61-8291507; e-mail: koroniak@main.amu.edu.pl

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.187



was expected to undergo further transformations. Moreover the presence of fluorine atoms in the cyclobutene moiety should stabilize its structure.[4a] Surprisingly, during irradiation[5] of **1** with UV light ($\lambda > 300\,\mathrm{nm}$) in water, we isolated 1,3-dimethyl-(5,6-dihydrourac-6-yl)-difluoroacetic acid **2**, as the only stable product.[6] Irradiation of the same substrate **1** with higher energy light ($\lambda = 254\,\mathrm{nm}$) led to cleavage of the C(5)–C(trifluorovinyl) bond and gave 1,3-dimethyluracil as the sole product.

The mechanism of these transformations seems to involve a Michael type addition–elimination reaction after the photochemical electrocyclization. The more stable keto **5** versus enol **4** tautomer then reacts with a nucleophile (water) leading to the most thermodynamically stable product—a derivative of difluoroacetic acid **2**. In the case of irradiation with higher energy light (low-pressure mercury lamp, $\lambda = 254\,\mathrm{nm}$) simple cleavage of a C–C bond occurs.

It would appear that the final product **2** is formed via the labile intermediate **3**, the structure of which we were not able to determine experimentally. We suggest that the keto **5**–enol **4** equilibrium should favour the keto tautomer **5**, which can sometimes be reversed.[4] On the basis of DFT calculations, however, keto form **5** is 0.4 kcal/mol (1.7 kJ/mol) more stable than the enol form **4**.[7]

These findings are in contrast to the photochemical transformations of 1,3-dimethyl-5-(*E*-pentafluoropropenyl)uracil. It is surprising, that in this case only *E–Z* isomerization was observed. No traces of intermediates analogous to **4** or **5** were found in the reaction mixture. The irradiation of a water solution of **6** led to a photostationary state involving equilibration with 1,3-dimethyl-5-(*Z*-pentafluoropropenyl)uracil **7**, where the more sterically congested **7** is the major product (HPLC ratio **6**/**7** = 1:1.54).[9] Irradiation of **7** as the starting material also led to the identical photostationary state.

This experimental observation suggests that the unimolecular transformation is much faster than the bimolecular nucleophilic reaction with molecules of solvent (water), as observed in the case of **1**. Although *trans–cis* photochemically induced isomerization is a well-known reaction, we believe that in this case torquoselectivity[10] seems to be an important and dominating factor. It seems that in the ring opening of the intermediate cyclobutene **8**, among the two substituents $-CF_3$ and –F responsible for the isomerization, the fluorine being an efficient π-electron donor will preferentially rotate outward, forcing the CF_3 group to rotate inward. As a result formal *trans–cis* isomerization is observed. It is just another experimental example supporting the torquoselectivity prediction based on computational calculations.[10]

References and notes

1. (a) De Clerq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Sci. U.S.A.* **1979**, *76*, 2947–2951; (b) Jones, A. S.; Rahim, S. G.; Walker, R. T. *J. Med. Chem.* **1981**, *24*, 759–760; (c) Coe, P. L.; Harnden, M. R.; Jones, A. S.; Noble, S. A.; Walker, R. T. *J. Med. Chem.* **1982**, *25*, 1329–1334; (d) De Clerq, E.; Desgranges, C.; Herdewijn, P.; Sim, I. S.; Jones, A. S.; McLean, M. J.; Walker, R. T. *J. Med. Chem.* **1986**, *29*, 213–217.
2. (a) Koroniak, H.; Fiedorow, P.; Pluskota, D.; Karwatka, P.; Abboud, K. A. *J. Mol. Struct.* **1994**, *323*, 215–221; (b) Koroniak, H.; Karwatka, P.; Pluskota, D.; Fiedorow, P.; Jankowski, J. *J. Fluorine Chem.* **1995**, *71*, 135–137.
3. Welch, J.; Eswarakrishan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons, 1991.
4. (a) Lemal, D. M. *Acc. Chem. Res.* **2001**, *34*, 662–671; (b) Lindner, P. E.; Correa, R. A.; Gino, J.; Lemal, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 2556–2563; (c) Lindner, P. E.; Lemal, D. M. *J. Org. Chem.* **1996**, *61*, 5109–5115.
5. Photoirradiations were carried out in a water cooled reactor with an immersed medium pressure mercury lamp using a 1 mm Pyrex filter which provided UV light with $\lambda > 300\,\mathrm{nm}$. The phototransformations were followed by HPLC analysis. The concentration of the irradiated water solutions of **1**, **6** and **7** was in the range of 10^{-3} M (usually 1 mM), due to the solubility of the starting material.
6. Pure **2** was isolated from the irradiated solution of **1**. After 1.5 h irradiation of **1**, the solvent (water) was removed in vacuo. The solid precipitate was collected and showed to consist of **2** and unreacted traces of **1**. After column chromatography (to remove unreacted **1**) and recrystallization, samples of pure **2** (purity checked by HPLC, reverse phase C-18 column) were submitted for analysis. Yield (isolated) 55%. ^{1}H NMR, (DMSO-d_6, in ppm in δ scale downfield from TMS), 2.60 (br m, 2H, C^5–H_2), 2.96

(s, 3H, $\mathrm{N^3{-}C}H_3$), 3.00 (s, 3H, $\mathrm{N^1{-}C}H_3$), 4.10 (m, 1H, $\mathrm{C^6{-}}H$). ^{19}F NMR, (DMSO-d_6, in ppm in φ scale upfield from $\mathrm{CFCl_3}$) 105.2 (1F, dd, $^2J_{\mathrm{F-F}} = 243\,\mathrm{Hz}$, $^3J_{\mathrm{F-H}} = 8.5\,\mathrm{Hz}$), 109.7 (1F, dd, $^2J_{\mathrm{F-F}} = 243\,\mathrm{Hz}$, $^3J_{\mathrm{F-H}} = 18\,\mathrm{Hz}$); LSIMS in negative mode showed the $[\mathrm{M-H}]^-$ ion at m/z (relative intensity) = 235 (50).

7. In the case of molecules containing fluorine only ab initio and DFT computational methods give reliable data concerning thermodynamic stability.[8] In our case B3LYP/6-31G* calculations were used to determine the equilibrium **4** versus **5**. The calculated, very small, $\Delta G^o = 0.4\,\mathrm{kcal/mol}$ for the keto–enol equilibrium is surprising, however, the presence of fluorine atoms should significantly stabilize the enol form **4**.[4]
8. Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K. *J. Mol. Struct. (THEOCHEM)* **1997**, *398*, 169–179.
9. The ^{19}F NMR spectra of fluorinated alkenes are of great importance for determining their structure. The coupling constants, $^3J_{\mathrm{F-F}}$ of fluorine atoms at the C=C bond have useful analytical value. Generally $^3J_{trans\ \mathrm{F-F}} \approx 120$–$150\,\mathrm{Hz}$, while $^3J_{cis\ \mathrm{F-F}} \approx 10$–$45\,\mathrm{Hz}$. In our case: **6**: ^{19}F NMR, ($\mathrm{CDCl_3}$, in ppm in φ scale upfield from $\mathrm{CFCl_3}$), 67.4 (3F, dd, $\mathrm{C{=}CFC}F_3$, $^3J_{\mathrm{CF_3-F}} = 11\,\mathrm{Hz}$, $^4J_{\mathrm{CF_3-F}} = 21\,\mathrm{Hz}$), 135.0 (1F, dq, $\mathrm{C}F\mathrm{{=}CFCF_3}$, $^3J_{trans\ \mathrm{F-F}} = 139\,\mathrm{Hz}$, $^4J_{\mathrm{CF_3-F}} = 21\,\mathrm{Hz}$), 164.0 (1F, dq, $\mathrm{CF{=}C}F\mathrm{CF_3}$, $^3J_{trans\ \mathrm{F-F}} = 139\,\mathrm{Hz}$, $^4J_{\mathrm{CF_3-F}} = 11\,\mathrm{Hz}$); **7**: ^{19}F NMR, ($\mathrm{CDCl_3}$, in ppm in φ scale upfield from $\mathrm{CFCl_3}$), 66.4 (3F, dd, $\mathrm{C{=}CFC}F_3$, $^3J_{\mathrm{CF_3-F}} = 13\,\mathrm{Hz}$, $^4J_{\mathrm{CF_3-F}} = 8\,\mathrm{Hz}$), 111.1 (1F, m, $\mathrm{C}F\mathrm{{=}CFCF_3}$), 148.1 (1F, dq, $\mathrm{CF{=}C}F\mathrm{CF_3}$, $^3J_{cis\ \mathrm{F-F}} = 10\,\mathrm{Hz}$, $^4J_{\mathrm{CF_3-F}} = 13\,\mathrm{Hz}$). At photostationary state the ratio **6/7** 1:1.4 (based on NMR integration).
10. Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471–477.