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# Photochemical transformations of 5-perfluoroalkenyl uracils

Tomasz Cytlak, Henryk Koroniak *

*Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60780 Poznan, Poland*

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In dedication to Professor Alain Tressaud on the occasion of his 70th birthday.

ABSTRACT

Photochemical behavior of 1,3-dimethyl-5-trifluorovinyluracil **1** has been studied in polar, nucleophilic solvents (water and anhydrous methanol). Photoirradiation of **1** with UV light ($\lambda > 300$ nm) provides additional insight on previously suggested mechanism of phototransformations. Electrocyclization leading to cyclobutene intermediate **3** is a primary reaction; next addition of nucleophile (molecule of methanol or water) occurs, giving access to products.



## 1. Introduction

Some uracil and uridine analogues substituted with alkenyl chain at the C5-position are of great biological importance showing significant antiviral activities [1]. Since the fluorine presence is often involved in the biological activity of organic compounds, the development of new synthetic methodologies to create fluorinated unsaturated derivatives of uridine is of great interest in organic chemistry [2]. In the course of our studies we were able to synthesize a series of new derivatives of uracil with C5-perfluoroalkenyl groups which along with the endocyclic 5,6 double bond might be considered as a diene system [3]. This has an obvious influence on the structural as well as other properties of studied system. In this paper we would like to present our findings on photochemical behavior of some 5-fluoropropenyl uracils, as a good example of use of fluorinated diene in the synthesis of some fluorinated systems.

## 2. Results and discussion

Previously we have reported the preliminary results of our studies dealing with photochemical properties of 1,3-dimethyl-5-trifluorovinyluracil in water [4]. The unexpected transformations of this system prompted us to carry on more complete research on this topic. In the case of 1,3-dimethyl-5-trifluorovinyluracil, electrocyclization of diene system (exocyclic trifluorovinyl group and endocyclic C5–C6 double bond) is a primary dominant reaction, followed by ring opening caused by nucleophilic action of water (Scheme 1). This reaction proves to be almost quantitative, showing no formation of other side products.

The mechanism of this reaction involves photochemical cyclization leading to cyclobutene intermediate **3**, and then a Michael type addition–elimination reaction of water molecule occurs. In the next step, the more stable keto tautomer **5** reacts with another molecule of water, giving the most thermodynamically stable product, difluoroacetic acid derivative **2**. It is worth mentioning that intermediate **3** should be significantly stabilized by fluorine atoms [5], however we were able neither to isolate nor to observe this intermediate spectroscopically.

We suggest that the keto **5**–enol **4** equilibrium should favor the keto tautomer **5**. The DFT calculations support this expectation, showing that keto form **5** is 0.4 kcal/mol (1.7 kJ/mol) more stable than the enol form **4**. In the case of molecules containing fluorine only *ab initio* and DFT computational methods give reliable data concerning thermodynamic stability [6]. In our case B3LYP/6-31G* calculations were used to determine the equilibrium **4** versus **5**. The calculated, very small, $\Delta G^{\circ} = 0.4$ kcal/mol for the keto–enol equilibrium is surprising, however, the presence of fluorine atoms should significantly stabilize the enol form **4**.

In our further studies we have tried to confirm previously suggested mechanism of bimolecular nucleophilic reaction with molecule of solvent, as observed in the case of **1**. Similarly to photoirradiation of **1** with UV light ($\lambda > 300$ nm) in water, we led analogous photoreaction of **1** in anhydrous methanol (Scheme 2). Using methanol as a solvent, which acts also as a nucleophile, we should preclude keto–enol equilibrium. Analogically, the first step

* Corresponding author. Tel.: +48 618291303; fax: +48 618291505.
*E-mail address:* koroniak@amu.edu.pl (H. Koroniak).

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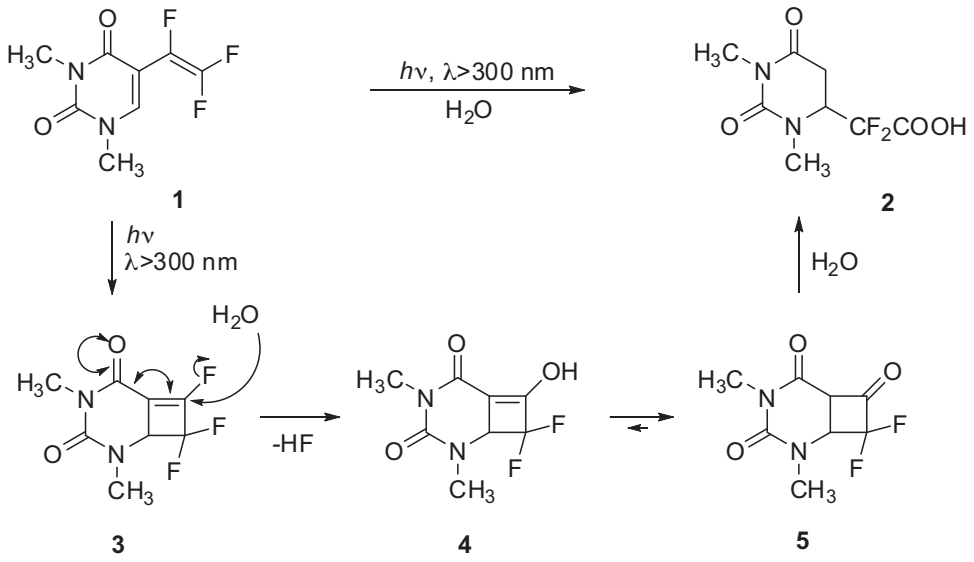
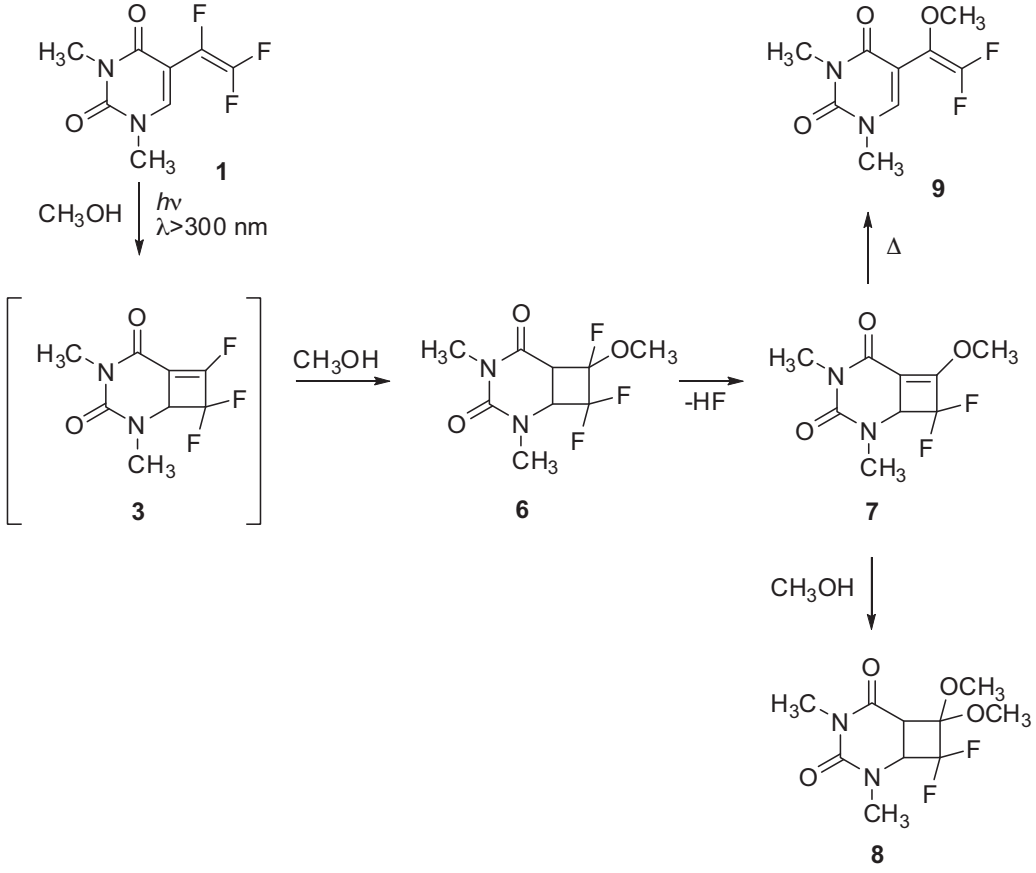
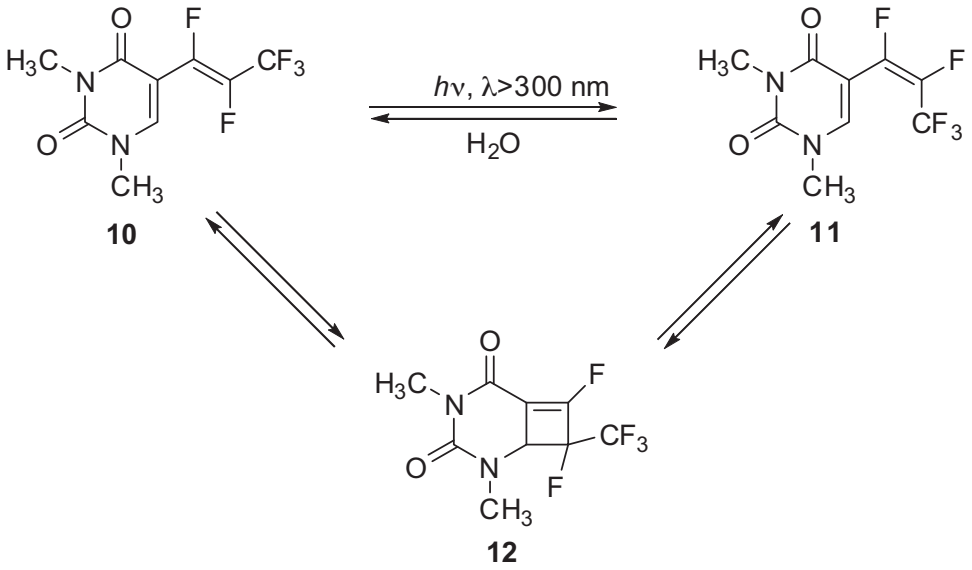



**Scheme 1.**

of reaction was electrocyclization to cyclobutene intermediate **3**. After photoirradiation, HPLC analysis showed the presence of three photoproducts (**6**–**8**). Michael-type addition reaction of methanol to cyclobutene intermediate **3** gave product **6** which is less stable than product **7**. It is formed by elimination of HF molecule in **6**, leading to α,β-unsaturated carbonyl system **7**. Again, compound **7** undergoes transformation to **8** (possibly *via* Michael type addition–elimination reaction) [7] and/or to **9** *via* electrocyclic ring opening of cyclobutene. In our observation it was proved that the formation of both **8** and **9** is parallel with the slight preference of **9**. Since electrocyclic ring opening is a unimolecular reaction (**7** → **9**), while Michael addition elimination reaction is bimolecular process (**7** → **8**) this aspect of suggested mechanism requires further kinetic studies. Analyzing reaction mixture we were able to isolate by HPLC intermediate **7**. Heating of **7** in anhydrous methanol led to ring opening reaction which gave access to a conjugated diene system **9** as well as to the thermodynamically more stable compound **8**. These transformations are in good agreement with our general expectations. Surprisingly however, in the case of 1,3-dimethyl-5-(*E*)-pentafluoropropenyluracil during




**Scheme 2.**




**Scheme 3.**

photoirradiation under the same conditions only *E*–*Z* isomerization was observed. The irradiation of water solution of **10** led to a photostationary state involving equilibration with 1,3-dimethyl-5-(*Z*)-pentafluoropropenyluracil **11** where the more sterically congested **11** was a major product. Photoirradiation of **11** as the starting material also led to the identical photostationary state (Scheme 3). This transformation, although quite obvious from the structural point of view, requires some additional comments. Observed equilibria at photostationary state showed preference of *Z* isomer **11** over more stable (less congested) *E* isomer **10**. At photostationary state the ratio **10**/**11** = 1:1.4 (based on NMR integration) and 1:1.54 (based on HPLC integration). It may be easily assumed that torquoselectivity effect is the important factor in this transformation, but expected preference for the formation of *Z* isomer *via* cyclobutane ring opening should favor this reaction at least by 5–7 kcal/mol [8]. Such kinetic preference should be demonstrated in the composition of reaction mixture, where isomer *Z* should be the only observed product.

It was our expectation that the torquoselectivity of cyclobutene ring opening favouring fluorine atom as a better electron donor rotate outward leading to *Z* isomer will be a dominant process. Obviously large steric effect caused by $CF_3$ group will diminish this effect. One can however on the basis of detailed analysis of the photostationary state conclude that a radical mechanism cannot be excluded as a competitive one [9].

## 3. Conclusions

As a conclusion we have demonstrated the mechanism of phototransformation of **1** in polar, nucleophilic solvents. As we have expected, methanol precluded keto–enol equilibrium observed during addition of water molecule. In general this experiment suggests our original concept on the mechanism of this transformation. In the latter however, the reaction mixture seems to be a consequence of thermodynamical stability of formed products.

## 4. Experimental

### 4.1. General

Methanol was distilled by standard method. Starting materials (**1**, **10**, **11**) were prepared as previously described [3].

$^{19}F$ NMR, $^{13}C$ NMR, $^{1}H$ NMR spectra were recorded in $CD_3OD$ (compounds **6**–**9**) and DMSO-$d_6$ (compound **2**) at respectively 282, 75, 300 MHz. Chemical shifts are given in ppm relative to $CCl_3F$ ($^{19}F$ NMR) or TMS ($^{13}C$ NMR and $^{1}H$ NMR), used as internal reference. Coupling constants are given in Hz. The following abbreviations are used: "s" singlet, "d" doublet, "t" triplet, "q" quartet, "m" multiplet, "br" broad signals.

HPLC separations were performed on a Waters 600E instrument equipped with a Waters 996 Photodiode Array UV detector and Agilent 1100 Series with a Agilent G1315B diode-array detector (UV) using XTerra RP 18 5 μm (19 mm × 100 mm) column at a flow rate 1 mL/min.

Mass spectra were recorded on a Waters 2690 LC/MS equipped with a Micromass ZQ Electrospray detector (ESI), AMD 402 instrument (EI) and AMD 604 (LSIMS).

### 4.2. Photochemistry

Photoirradiations were carried out in a water cooled photoreactor (150 mL) with a 150 W immersed medium pressure mercury lamp using a 1 mm Pyrex filter which provided UV light with $\lambda > 300$ nm in atmosphere of dry argon. The concentrations of the irradiated water solutions of **1, 10, 11** were 1 mM, due to the solubility of the starting material. The phototransformations were followed by HPLC analysis. The irradiations of **1** were continued until the loss of substrates were observed. After 1.5 h (in water) or 2 h (in methanol) of irradiation of **1**, the solution was concentrated *in vacuo* and photoproducts (**2**, **6**–**9**) were isolated by HPLC. In case of compounds **10** and **11**, irradiations were continued until photostationary state was observed (about 1 h). The analytical and spectral data of the photoproducts (**2**, **6**–**9**) are presented below.

#### 4.2.1. 2-(1,3-Dimethyl-5,6-dihydrouracil-6-yl)-2,2-difluoroacetic acid (2)

White solid (55%). $^{19}F$ NMR: $\delta$ −109.7 (dd, 1F, $^{2}J_{FF}$ = 243.0 Hz, $^{3}J_{FH}$ = 18.3 Hz, CFF), −105.2 (dd, 1F, $^{2}J_{FF}$ = 243.0 Hz, $^{3}J_{FH}$ = 8.5 Hz, CFF). $^{13}C$ NMR: $\delta$ 26.8 ($^{3}N$–$CH_3$), 30.3 (d, $^{3}J_{CF}$ = 4.6 Hz, $CH_2$), 36.8 (d, $^{4}J_{CF}$ = 3.3 Hz, $^{1}N$–$CH_3$), 55.1 (t, $^{2}J_{CF}$ = 34.0 Hz, CH), 117.2 (t, $^{1}J_{CF}$ = 260.0 Hz, C-2), 153.0 ($^{2}C$=O), 163.6 (t, $^{2}J_{CF}$ = 24.6 Hz, C-1), 168.1 ($^{4}C$=O). $^{1}H$ NMR: $\delta$ 2.57–2.63 (2H, br m, $CH_2$), 2.96 (3H, s, $^{3}N$–$CH_3$), 3.00 (3H, d, $J$ = 0.8 Hz, $^{1}N$–$CH_3$), 4.02–4.16 (1H, m, CH). MS (LSIMS) $m/z$: 235 $[M-H]^-$.

#### 4.2.2. 7,8,8-Trifluoro-7-methoxy-2,4-dimethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione (6)

$^{19}$F NMR: $\delta$ −128.0–127.6 (m, 1F, CF), −125.4 (dt, 1F, $^{2}J_{FF}$ = 204.6 Hz, $J_{FF/FH}$ = 6.3 Hz, CFF), −113.8 (ddd, 1F, $^{2}J_{FF}$ = 204.5 Hz, $^{3}J_{FF}$ = 13.9 Hz, $^{4}J_{FH}$ = 7.7 Hz, CFF). $^{1}$H NMR: $\delta$ 3.07 (3H, s, $^{4}$N–CH$_3$), 3.18 (3H, d, $J$ = 0.4 Hz, $^{2}$N–CH$_3$), 3.64 (3H, d, $J$ = 1.6 Hz, OCH$_3$), 3.91–4.02 (1H, m, H-1), 4.36 (1H, ddd, $J$ = 11.0, 7.5, 5.6 Hz, H-6). LC–MS (ESI) $m/z$: 253 [M+H]$^+$.

#### 4.2.3. 8,8-Difluoro-7-methoxy-2,4-dimethyl-2,4-diazabicyclo[4.2.0]oct-6-ene-3,5-dione (7)

$^{19}$F NMR: $\delta$ −128.6 (d, 1F, $^{2}J_{FF}$ = 205.9 Hz, CFF), −102.7 (dd, 1F, $^{2}J_{FF}$ = 205.9 Hz, $^{3}J_{FH}$ = 1.2 Hz, CFF). $^{1}$H NMR: $\delta$ 2.75 (3H, s, $^{4}$N–CH$_3$), 3.01 (3H, s, $^{2}$N–CH$_3$), 4.10 (3H, s, OCH$_3$), 5.22 (1H, d, $J$ = 1.7 Hz, H-1). LC–MS (ESI) $m/z$: 233 [M+H]$^+$.

#### 4.2.4. 8,8-Difluoro-7,7-dimethoxy-2,4-dimethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione (8)

White solid (18%). $^{19}$F NMR: $\delta$ −122.2 (d, 1F, $^{2}J_{FF}$ = 213.0 Hz, CFF), −108.6 (dd, 1F, $^{2}J_{FF}$ = 213.0 Hz, $^{3}J_{FH}$ = 2.8 Hz, CFF). $^{13}$C NMR: $\delta$ 27.7 ($^{4}$N–CH$_3$), 29.6 (br d, $^{4}J_{CF}$ = 1.1 Hz, $^{2}$N–CH$_3$), 52.0 (OCH$_3$), 61.6 (dd, $^{2}J_{CF}$ = 23.4 Hz, $^{2}J_{CF}$ = 21.2 Hz, C-1), 61.7 (br s, C-6), 109.7 (dd, $^{2}J_{CF}$ = 21.2 Hz, $^{2}J_{CF}$ = 12.9 Hz, C-7), 120.45 (dd, $^{1}J_{CF}$ = 288.9 Hz, $^{1}J_{CF}$ = 281.6 Hz, C-8), 149.0 (br dd, $^{4}J_{CF}$ = 4.2 Hz, $^{4}J_{CF}$ = 2.2 Hz, C-3), 162.7 (dd, $^{4}J_{CF}$ = 6.7 Hz, $^{4}J_{CF}$ = 4.3 Hz, C-5). $^{1}$H NMR: $\delta$ 2.72 (d, 3H, $J$ = 1.1 Hz, $^{4}$N–CH$_3$), 2.76 (3H, d, $J$ = 3.5 Hz, $^{2}$N–CH$_3$), 3.75 (3H, s, OCH$_3$), 4.21 (3H, s, OCH$_3$), 4.62 (1H, br s, H-6), 5.41 (1H, d, $J$ = 2.5 Hz, H-1). LC–MS (ESI) $m/z$: 265 [M+H]$^+$. MS (EI) 70 eV, $m/z$ (rel. int.): 264.1 [M]$^+$ (12), 249.1 (39), 192.1 (100).

#### 4.2.5. 5-(2,2-Difluoro-1-methoxyvinyl)-1,3-dimethyluracil (9)

Pale yellow oil (48%). $^{19}$F NMR: $\delta$ −109.8 (d, 1F, $^{2}J_{FF}$ = 63.7 Hz, CFF), −100.5 (d, 1F, $^{2}J_{FF}$ = 63.7 Hz, CFF). $^{13}$C NMR: $\delta$ 29.1 ($^{3}$N–CH$_3$), 33.5 ($^{1}$N–CH$_3$), 60.2 (OCH$_3$), 104.1 (dd, $^{2}J_{CF}$ = 36.9 Hz, $^{2}J_{CF}$ = 18.0 Hz, COCH$_3$), 106.4 (t, $^{3}J_{CF}$ = 4.1 Hz, C-5), 134.1 (dd, $^{1}J_{CF}$ = 288.1 Hz, $^{1}J_{CF}$ = 274.1 Hz, CF$_2$), 147.5 (dd, $^{4}J_{CF}$ = 3.7 Hz, $^{4}J_{CF}$ = 1.8 Hz, C-6), 151.4 (C-2), 163.4 (dd, $^{4}J_{CF}$ = 3.4 Hz, $^{4}J_{CF}$ = 1.4 Hz, C-4). $^{1}$H NMR: $\delta$ 2.88 (3H, s, $^{3}$N–CH$_3$), 3.05 (3H, s, $^{1}$N–CH$_3$), 3.53 (3H, s, OCH$_3$), 7.82 (1H, s, H-6). LC–MS (ESI) $m/z$: 233 [M+H]$^+$.

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