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Synthesis of some 5-perfluoroalkenyl derivatives of uracil

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Abstract

1,3-Dimethyl-5-iodouracil reacts smoothly with perfluorovinyl- (and *E*/*Z*-pentafluoropropenyl)-zinc iodides in the presence of Pd^0 as a catalyst yielding the appropriate 5-perfluoroalkenyl derivatives of uracil at high and moderate yield. In an analogous reaction, 1,3-dimethyl-6-iodouracils did not yield the expected coupling products.

Keywords: Synthesis; Perfluoroalkenyl uracils; NMR spectroscopy; Coupling products; Palladium catalyst

1. Introduction

It has been shown that uracil derivatives having unsaturated substituents at the 5-position display significant biological activity. For example, 5-bromovinyl uracil (and its analogues) are potent antiviral agents [1–7]. The synthetic approach for obtaining several such derivatives has been based, in general, on coupling organometallic unsaturated fragments with aromatic species. In most cases palladium(0) or palladium(II) have been employed as catalysts. Using this method organozinc [8,9], organocopper [10–13] and organomercurials [14] have been used as well as substituted alkenes [15], ethers [16] or α,β-unsaturated ketones [17]. The basic idea behind the synthesis of some fluorinated analogues of molecules of this type lies in the observation that fluorine should not influence the geometry of the molecule (when compared with a hydrocarbon analogue) but it can dramatically change its biological activity due to the changed electronic properties.

2. Results and discussion

In this communication we would like to report a simple, one-step synthesis of 5-perfluoroalkenyl derivatives of uracil (**1–6**) as fluorinated analogues of the above described species and of potential synthons of appropriate nucleosides.

Preparation of these species may be accomplished through the use of the method introduced by Burton and Heinze [18,19] who used palladium(0) as a catalyst. As model compounds for eventual adaptation in nucleosides synthesis, we have used 1,3-dimethyl-5-iodouracils which can be readily prepared from uracil (see Experimental details). Methylation of the N-1 and N-3 positions in the uracil moiety was important as a means of protecting the relatively acidic functions of the N–H protons, whereas the methyl group at the N-1 position of uracil can also be treated as a substitute for a sugar.

The coupling reaction of 1,3-dimethyl-5-iodouracils proceeded smoothly and in high yield. In the preparation of the 5-perfluoroalkenyl derivatives, the *E* or *Z* geometry of the reacting pentafluoropropenylzinc iodides was fully preserved. The reaction was much slower when 6-methyluracil was used, which can easily be explained by the steric effect of a methyl group in the 6-position of uracil (Scheme 1).

Success with this methodology led us to attempt the preparation of some 6-perfluoroalkenyl-substituted uracils using an analogous approach. After synthesis of the 1,3-dimethyl-6-iodouracil (see Experimental details), however, the coupling reaction did not give the expected product. The reaction mixture contained unreacted starting material and traces of 1,3-dimethyluracil (isolated on TLC and characterized). After prolonged reaction time and the use of higher reaction

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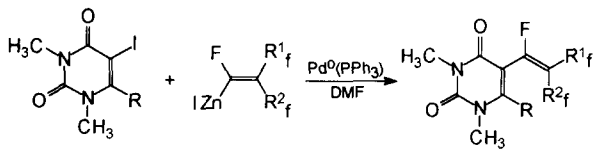
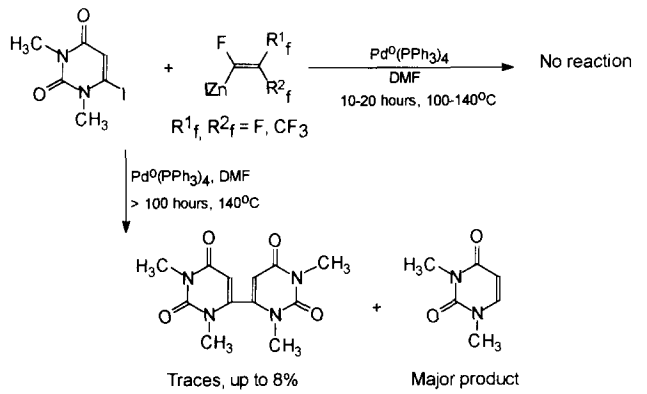


R = H, CH_3 R^1_f, R^2_f = F, CF_3

1	R=H	R^1_f = F	R^2_f = F
2	R=H	R^1_f = CF_3	R^2_f = F
3	R=H	R^1_f = F	R^2_f = CF_3
4	R=CH_3	R^1_f = F	R^2_f = F
5	R=CH_3	R^1_f = CF_3	R^2_f = F
6	R=CH_3	R^1_f = F	R^2_f = CF_3

Scheme 1.



Scheme 2.

temperatures (140 °C vs. 110 °C), the products isolated were 6,6′-bis(1,3-dimethyluracil) – a product expected in an Ullmann-type reaction – and 1,3-dimethyluracil. Formation of the later compound can be explained as a result of the reduction of 1,3-dimethyl-6-iodouracil (Scheme 2).

The reason for this failure is not completely clear and is probably due to the electrophilic vs. nucleophilic character of the 5- and 6-positions in uracil. One can provide a reasonable rationale by pointing out that the 5-position in uracil is very similar to that in aromatic compounds (i.e. suitable for electrophilic attack) whereas the 6-position in uracil is nucleophilic in character. This means that despite obvious structural similarities its reactivity in coupling reactions is very low.

Although we did not get satisfactory results in the preparation of 6-substituted uracils, the presented method seems to be very efficient for the preparation of 5-perfluoroalkenyl-substituted uracils.

3. Experimental details

^{1}H and ^{19}F NMR spectra have been obtained on a Varian Gemini VT 300 MHz spectrometer using $CDCl_3$ as solvent. TMS was the internal standard in ^{1}H NMR and $CFCl_3$ was used as reference for ^{19}F NMR. Chemical shifts for ^{1}H NMR are reported in ppm on the δ scale downfield from TMS and in ^{19}F NMR on the φ scale upfield from $CFCl_3$. Melting points were determined on a Boetius hot plate microscope and are uncorrected. All compounds (**1–6**) had satisfactory combustion analyses.

Trifluorovinylzinc iodide and *E*- and *Z*-pentafluoropropenylzinc iodides were prepared in dry DMF according to the procedure of Heinze and Burton [19]. After preparation in DMF, perfluoroalkenylzinc iodides were stored under argon and proved to be stable for long periods. For each coupling reaction the appropriate amount of DMF solution of the perfluoroalkenylzinc iodides was taken by means of a syringe.

Tetrakis(triphenylphosphine)palladium $Pd^0(PPh_3)_4$, was used as the catalyst in the coupling procedures and was freshly prepared according to the method of Coulson [20]. As suggested by Heinze and Burton [19], it has been found that the 'yellow' catalyst is much more reactive than the 'green' one. The colour change is probably due to partial oxidation of phosphorus in the molecule.

1,3-Methylation of uracil was accomplished as a one-step process using dimethyl sulfate as described previously [21]. 5-Iodouracil was obtained by direct iodination using the method described previously [22], whereas 6-iodouracil was prepared by reacting iodine with in-situ generated 6-uracil carbanion [23].

3.1. General procedure for coupling perfluorozinc iodides with iodouracils

In a 250 ml round-bottomed flask equipped with a reflux condenser and magnetic stirrer, 3.2 g (12 mmol) of 1,3-dimethyl-5-iodouracil was dissolved in 120 ml of dry DMF. To the flask was then added 350 mg (0.3 mmol) of tetrakis(triphenylphosphine)palladium(0) along with a few milligrams of copper chloride CuCl. The reactants were kept under an argon atmosphere. To the reaction vessel about 20 mmol (1.5 molar excess) of perfluoroalkenylzinc iodide was added by means of a syringe as a solution in DMF (usually the concentration of the solution was kept at about 0.9–1.0 M, thus about 20 ml of the solution of perfluorozinc iodides in DMF was added to the reaction mixture). Under stirring, the reaction mixture was then heated to about 100–110 °C for 10–20 h. The course of the reaction was followed by TLC checking of the loss of starting 1,3-dimethyl-5-iodouracil. After cooling to ambient temperature, the oily reaction mixture was extracted with hexane/ethyl acetate mixture (3:7 v/v) and after removing excess solvent was purified by column chromatography (silica gel, ethyl acetate/hexane, 7:3, v/v). The product was recrystallized from water or water/methanol solvents.

Compound of **1**: Yield, 60%; m.p. 69–71 °C. ^{1}H NMR δ: 3.39 (3, s, N^1-CH_3); 3.47 (3, s, N^3-CH_3); 7.42 (1, s, C^6-H) ppm. ^{19}F NMR ϕ: 98.0 (1, dd, C=CF*F*, $^3J_{cis\text{-}FF}=30$ Hz, $^2J_{gem\text{-}FF}=68$ Hz); 114.2 (1, dd, C=C*F*F, $^3J_{trans-FF}=116$ Hz, $^2J_{gem\text{-}FF}=68$ Hz); 165.5 (1, dd, C*F*=CFF, $^3J_{trans\text{-}FF}=116$ Hz, $^3J_{cis\text{-}FF}=30$ Hz) ppm.

Compound **2**: Yield, 45%; m.p. 87–89 °C. ^{1}H NMR δ: 3.39 (3, s, N^1-CH_3); 3.48 (3, s, N^3-CH_3); 7.54 (1, s, C^6-H) ppm. ^{19}F NMR ϕ: 67.4 (3, dd, C=CFC*F*$_3$, $^4J_{FCF_3}=21$ Hz, $^3J_{CF_3F}=11$ Hz); 135.0 (1, dq, C*F*=CFCF$_3$, $^4J_{FCF_3}=21$ Hz, $^3J_{trans\text{-}FF}=139$ Hz); 164.0 (1, dq, CF=C*F*CF$_3$, $^3J_{FCF_3}=11$ Hz, $^3J_{trans\text{-}FF}=139$ Hz) ppm.

Compound **3**: Yield, 40%; m.p. 105–107 °C. ^{1}H NMR δ: 3.38 (3, s, N^1-CH_3); 3.49 (3, s, N^3-CH_3); 7.45 (1, s, C^6-H) ppm. ^{19}F NMR ϕ: 66.4 (3, dd, C=CFC*F*$_3$, $^4J_{FCF_3}=8$ Hz, $^3J_{FCF_3}=13$ Hz); 111.1 (1, m, dq?, C*F*=CFCF$_3$); 148.1 (1, dq, C=C*F*CF$_3$, $^3J_{FCF_3}=13$ Hz, $^3J_{cis\text{-}FF}=10$ Hz) ppm.

Compound **4**: Yield, 23%; m.p. 65–68 °C. ^{1}H NMR δ: 2.66 (3, s, C^6-CH_3); 3.43 (3, s, N^1-CH_3); 3.55 (3, s, N^3-CH_3) ppm. ^{19}F NMR ϕ: 98.5 (1, dd, C=CF*F*, $^3J_{cis\text{-}FF}=30$ Hz, $^2J_{gem\text{-}FF}=67$ Hz); 114.0 (1, dd, C=C*F*F, $^3J_{trans\text{-}FF}=118$ Hz, $^2J_{gem\text{-}FF}=67$ Hz); 161.5 (1, dd, C*F*=CFF, $^3J_{trans\text{-}FF}=118$ Hz, $^3J_{cis\text{-}FF}=30$ Hz) ppm.

Compound **5**: Yield, 20%; m.p. 63–65 °C. ^{1}H NMR δ: 2.35 (3, s, C^6-CH_3); 3.38 (3, s, N^3-CH_3); 3.51 (3, s, N^3-CH_3) ppm. ^{19}F NMR ϕ: 67.5 (3, dd, C=CFC*F*$_3$, $^4J_{FCF_3}=21$ Hz, $^3J_{FCF_3}=11$ Hz); 128.2 (1, dq, C*F*=CFCF$_3$, $^4J_{FCF_3}=21$ Hz, $^3J_{trans\text{-}FF}=143$ Hz); 161.0 (1, dq, C=C*F*CF$_3$, $^3J_{FCF_3}=11$ Hz, $^3J_{trans\text{-}FF}=143$ Hz) ppm.

Compound **6**: Yield, 15%; m.p. 65–67 °C. ^{1}H NMR δ: 2.35 (1, s, C^6-CH_3); 3.38 (3, s, N^1-CH_3); 3.49 (3, s, N^3-CH_3) ppm. ^{19}F NMR ϕ: 68.4 (3, dd, C=CFC*F*$_3$, $^4J_{FCF_3}=8$ Hz, $^3J_{FCF_3}=13$ Hz); 108.8 (1, m, dq?, C*F*=CFCF$_3$); 148.4 (1, dq, C=C*F*CF$_3$, $^3J_{FCF_3}=13$ Hz, $^3J_{cis\text{-}FF}=10$ Hz) ppm.

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