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MILD FLUORINATION OF URACIL DERIVATIVES BY CAESIUM FLUOROXYSULPHATE

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Abstract *1,3-Dimethyl and 1,3-dimethyl-5-halo substituted uracil derivatives reacted with $CsSO_4F$ under mild reaction conditions. Reactions carried out in an acetonitrile/water mixture or in a wide range of alcohols (methanol, ethanol, isopropanol and tert.butanol) resulted in the regioselective formation of the 5-fluoro-6-hydroxy or 5-fluoro-6-alkoxy-1,3-dimethyl-5,6-dihydrouracil derivatives, respectively, while the stereochemistry of the reaction was strongly syn predominant. Uracil was converted to 5-fluorouracil, and uridine to 5-fluorouridine, while the reaction of barbituric acid with $CsSO_4F$ in acetonitrile as solvent produced 5,5-difluorobarbituric acid.*

In last three decades many efforts have been made to achieve the direct introduction of a fluorine atom into organic molecules, and this field of considerable importance from the chemical as well as the biological point of view[1] has recently been covered by excellent reviews[2]. The fluorofunctionalisation of organic molecules, by a variety of reagents developed so far, requires a vacuum line, low temperatures and special laboratory equipment, so that the choice of reagent for selective and mild fluorination is still limited. Caesium fluoroxysulphate ($CsSO_4F$) is, after xenon difluoride[3], one of the mildest and easiest handling fluorinating reagents and has already been tested upon aromatics[4], alkenes[5], alkynes[6], and alkanes[7]. It was shown that the reaction course strongly depends on the structure of the organic molecule and the functional groups present, the reagent to substrate molar ratio, solvent polarity, temperature and the general reaction procedure .

Fluorosubstituted pyrimidine derivatives are of considerable interest because of the biological activity and clinical use of 5-fluorouracil and related compounds[1d] which were for a long time available only by incovenient indirect synthesis using highly toxic fluoroacetate as a precursor. Therefore many methods for the direct introduction of a fluorine atom into pyrimidine derivatives were developed in the last decade using elementary fluorine[8] or fluoroxy compounds[9] as fluorinating agents. We now report an investigation of the regio and stereoselectivity of direct fluorofunctionalisation of some uracil derivatives by caesium fluoroxysulphate.

RESULTS AND DISCUSSION

We have chosen 1,3-dimethyluracil (1a, Scheme) as a model substrate for regio and stereochemical studies of $CsSO_4F$ fluorination reactions with uracil derivatives. 1.3-Dimethyluracil derivatives are soluble in a wide range of solvents, which allows better detection of all posible reaction products, and simplifies both reaction and isolation parameters and product structure determination .

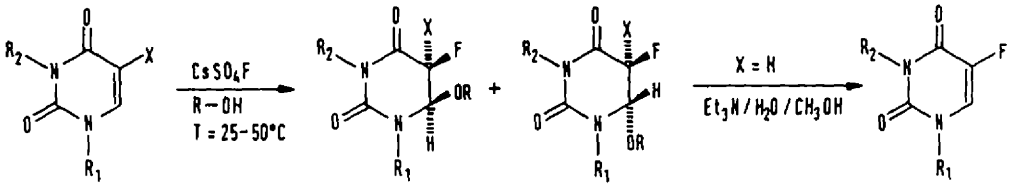
The reaction of 1a with $CsSO_4F$ in acetonitrile medium at room temperature resulted in a complex reaction mixture in which only a low yield of fluorine-containing products could be detected. However, the use of a 10:1 CH_3CN/H_2O mixture considerably enhanced the formation of two fluoro-hydroxy-1,3-dimethyluracil derivatives, having in their ^{19}F nmr spectra doublet of doublet signals at δ=-203.0 ppm ($^2J_{FH}$=47Hz, J_{FH}=2Hz) and δ=-193.0 ppm($^2J_{FH}$=47Hz, $^3J_{FH}$=7Hz), respectively, with a 8:1 relative intensity ratio. The treatment of the crude product mixture with aqueous triethylamine in methanol at room temperature for two hours produced a 5-fluoro-1,3-dimethyluracil (1b), thus proving that regioselectively 5-fluoro-6-hydroxy-5,6-dihydro-1,3-dimethyluracil derivatives (3a, 6a, Scheme) were formed. On the basis of arguments citated in the literature [9d,9e] which were proved by single crystal X-ray analysis[9c], we assigned the isomer with the smaller F_5-H_6 vicinal coupling constant as cis-5-fluoro-6-hydroxy-1,3-dimethyl-5,6-dihydrouracil (3a), and the isomer with the larger F_5-H_6 coupling constant as trans-5-fluoro-6-hydroxy-1,3-dimethyl-5,6-dihydrouracil (6a). We also reconfirmed the correct assignment by independent synthesis of both isomers[10].

Even better yields (80-85%, determined by octafluoronaphthalene as internal standard) of fluorine-containing uracil derivatives 3 and 6 were obtained when methanol (R=CH_3) or ethanol (R=CH_2CH_3) were used as the reaction medium. The relative yield ratio between cis-5-fluoro-6-alkoxy (3) and trans-5-fluoro-6-alkoxy (6) derivatives formed was 11:1 after $CsSO_4F$ fluorination carried out in methanol, and 15:1 after reaction in ethanol, while later treatment of the crude isomer mixtures by aqueous Et_3N resulted in 5-fluoro-1,3-dimethyluracil formation as well.

It is thus evident that fluorination of 1,3-dimethyluracil (1a) with $CsSO_4F$ in a nucleophilic medium (H_2O or alcohols) leads regioselectively to 5-fluoro-6-alkoxy-5,6-dihydro derivatives where the solvent is the source of the nucleophile and highly predominant syn addition takes place, which is, after the almost stereoselective reaction, in agreement with our previously reported results on $CsSO_4F$ fluorination of phenyl substituted alkenes[5a,b].

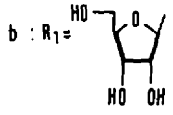
Further, we studied the effect of a halogen atom (X=F, X=Br), bonded at position 5 of the 1,3-dimethyluracil, on the course of the fluorination with $CsSO_4F$ in various hydrophilic solvents. The reactions of 5-fluoro-1,3-dimethyluracil (1b, X=F) with $CsSO_4F$ carried out in a 10:1 CH_3CH/H_2O mixture or in various alcohols (methanol: R=CH_3; ethanol: R=CH_2CH_3; isopropanol: R=$CH(CH_3)_2$ or tert.-butanol: R=$C(CH_3)_3$) produced regioselectively 5,5-difluoro-6-hydroxy (4a) or 5,5-difluoro-6-alkoxy-1,3-dimethyl-5,6-dihydrouracil (4b-e) derivatives in high yield. The only

SCHEME



1 : $R_1 = R_2 = CH_3$
a : X = H
b : X = F
c : X = Br

2 : R_1 = X = H
a : R_2 = H
b : R_1 =



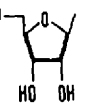
3 : $R_1 = R_2 = CH_3$; X = H
a : R = H
b : R = CH_3
c : R = CH_2CH_3

4 : $R_1 = R_2 = CH_3$; X = F
a : R = H
b : R = CH_3
c : R = CH_2CH_3
d : R = $CH(CH_3)_2$
e : R = $C(CH_3)_3$

5 : $R_1 = R_2 = CH_3$; X = Br
a : R = H
b : R = CH_3
c : R = CH_2CH_3
d : R = $CH(CH_3)_2$

6 : $R_1 = R_2 = CH_3$; X = H
a : R = H
b : R = CH_3
c : R = CH_2CH_3

7 : R_2 = H
a : R_1 = H
b : R_1 =



product, isolated in high yield, after the reaction of 5-bromo-1,3-dimethyluracil (1c, X=Br) with $CsSO_4F$ in water containing acetonitrile, has a singlet signal in its ^{19}F nmr spectra at δ=-146.0 ppm, and in its ^1H nmr spectra a singlet signal for H_6 at δ=5.7 ppm. On the basis of the nmr signal shape (no geminal FH coupling) we established that 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil derivative (5a), was formed, regioselectively, while the relative steric position of the 5-fluoro and 6-hydroxy groups is cis, considering the 5-fluoro 6-hydro trans position, which is shown by the F_5H_6 vicinal coupling size (<1Hz). The reactions of 1c with $CsSO_4F$ in methanol (R=CH_3), ethanol (R=CH_2CH_3) or isopropanol (R=$CH(CH_3)_2$) resulted regio and stereoselectively in (±) r-5-bromo-5-fluoro-t-6-alkoxy-1,3-dimethyl-5,6-dihydro uracil derivatives (5b-d). We also independently prepared products 5b-d by the bromination of 5-fluoro-1,3-dimethyluracil (1b) in alcohols, which was reported to result in trans-5-bromo-6-alkoxy uracil adducts[9c], thus proving the established cis-5-fluoro-6-alkoxy orientation in adducts 5 obtained by $CsSO_4F$ fluorination.

The structure of the alcohol had considerable influence on the reaction rate in the reactions of 1b and 1c with $CsSO_4F$. Reactions in methanol were slightly exothermic at the beginning, while fluorinations in ispropanol or tert.-butanol needed a moderate increase of reaction temperature (40-50°C) and prolongation of reaction time.

Optimisation of the reaction parameters for the fluorination of uracil (2a) and uridine (2b) was achieved by application of a 1:1 methanol/acetic acid solvent mixture in the case of uracil (30 ml/mmol 2a) and methanol (15ml/mmol) in the case of uridine (2b). Treatment of the crude products obtained after reactions with $CsSO_4F$, with aqueous triethylamine in methanol (Et_3N/H_2O/MeOH 1:4.5:4.5) gave 5-fluorouracil (7a) or 5-fluorouridine (7b) in reasonable overall yield.

Reaction of barbituric acid, as an example of a saturated uracil derivative, with $CsSO_4F$ under these reaction condition failed, while $CsSO_4F$ in 2.4 fold molar excess using acetonitrile as the solvent readily converted barbituric acid to 5,5-difluoro barbituric acid in good yield when the reaction was carried in a sealed glass tube at 100 °C for two hours.

EXPERIMENTAL SECTION

IR spectra were recorded with a Perkin-Elmer 277 B spectrometer and ^1H and ^{19}F nmr spectra by a JEOL-JNM-PS 100 instrument, with Me_4Si or CCl_3F as internal standards. Mass spectra and high resolution measurements were taken on a CEC-21-110 spectrometer and thin layer chromatographic separations were carried out on Merck PSC-Fertigplatten silica gel F-254. Commercially available uracil, uridine and barbituric acid were used, while 1,3-dimethyluracil[11], 5-fluoro-1,3-dimethyluracil[11], 5-bromo-1,3-dimethyluracil[12] and $CsSO_4F$[4e,13] were prepared according to the literature.

Fluorination of 1,3-dimethyluracil derivatives (1a-c) with $CsSO_4F$. General procedure.

1 mmol of 1,3-dimethyluracil derivative (1a-c) was dissolved in 2 ml of appropriate solvent (CH_3CN/H_2O 10:1 or freshly distilled and dry R-OH) and with stirring at room temperature, 320 mg (1.3 mmol) of $CsSO_4F$ was added slowly over a 5 minute period. The reaction mixture was then stirred at room or moderately increased temperature (40-50°C for the reactions of 1a-b in 2-propanol or t-butanol, and 1c in acetonitrile or alcohols) for an additional 1 to 4 hours (for 1c), 20 ml CH_2Cl_2 was added, the insoluble residue was filtered off , the filtrate was washed with water, the organic layer dried over anhydrous Na_2SO_4, and the solvent evaporated in vacuo. The crude reaction mixtures were analysed by ^1H and ^{19}F nmr. The products were isolated by TLC (SiO_2, $CHCl_3/CH_3OH$ 9.5:0.5) and identified according to the spectroscopic data.

Fluorination of 1,3-dimethyluracil (1a)

The crude reaction mixtures obtained by the fluorination process in the above mentioned solvents, after nmr analyses, were dissolved in 10 ml of an $Et_3N/H_2O/CH_3OH$ 1:4.5:4.5 mixture, and stirred at room temperature for 2 hours. Evaporation of the solvents in vacuo and crystallisation of the residue from ethanol produced 120-150 mg (63-74%) of 5-fluoro-1,3-dimethyluracil (m.p.=131-133°C), in all respects, identical with an authentic sample.

Fluorination of 5-fluoro-1,3-dimethyluracil (1b)

After fluorination of 1b in an appropriate solvent, the following pure products were isolated by TLC from the crude reaction mixtures:

5,5-Difluoro-6-hydroxy-1,3-dimethyl-5,6-dihydrouracil (4a): 125mg(64.5%) of white crystals m.p.=104.5-105.5°C; nmr($CDCl_3$): δ_F=-114.0ppm (dd, $^2J_{FF'}$=294Hz, $^3J_{FH6}$=7Hz, 1F), $\delta_{F'}$=-130.0ppm (dd, J=294Hz, $^3J_{F'H6}$=2Hz, 1F), δ_{H6}=5.1ppm(dd, J=7Hz,J=2Hz, 1H), δ_H=3.05ppm (s,3H), δ_H=3.15ppm (s,3H); mass. spectrum calcd. for $C_6H_8N_2O_3F_2$ m/z 194.0503, found m/z 194.0505, m/z 194(M^+,100%), 177(12), 128(13), 109(78), 107(15), 92(22), 91(19), 80(90), 79(35), 78(38), 60(20), 59(23), 56(32), 42(78).

5,5-Difluoro-6-methoxy-1,3-dimethyl-5,6-dihydrouracil (4b): 150mg(72.1%) of oily product; nmr($CDCl_3$): δ_F=-111.0ppm (dd, $^2J_{FF'}$=300Hz, $^3J_{FH6}$=7Hz, 1F) $\delta_{F'}$=-128.0ppm (d, J=300Hz, 1F), δ_{H6}=4.6ppm (dd, J=7Hz, J=1Hz, 1H), δ_H=3.6ppm (s,3H), δ_H=3.25ppm (s, 6H); mass spectum calcd. for $C_7H_{10}N_2O_3F_2$ m/z 208.0659, found m/z 208.0660, m/z 208(M^+,100%), 177(54), 123(72), 120(65), 119(15), 108(17), 107(17), 94(80), 93(20), 92(85), 91(34), 85(16), 83(24), 73(15), 72(30), 63(15), 58(37), 56(45),51(21), 43(30),42(90).

5,5-Difluoro-6-ethoxy-1,3-dimethyl-5,6-dihydrouracil (4c): 160mg (72.1%) of oily product; nmr($CDCl_3$): δ_F=-111.0ppm (dd, $^2J_{FF'}$=294Hz, $^3J_{FH6}$=6Hz, 1F), $\delta_{F'}$=-129.0ppm (d, J=294Hz, 1F), δ_{H6}=4.7ppm (dd, J=6Hz, $^3J_{H6F'}$=1Hz, 1H), δ_H=3.8ppm (q,J=7Hz, 2H), δ_H=1.3ppm (t, 3H), δ_H=3.18ppm (s, 3H), δ_H=3.25ppm(s, 3H); mass spectrum calcd. for $C_8H_{12}N_2O_3F_2$ m/z 222.0728, found m/z 222.0725; m/z 222(M^+,100%), 177(195), 165(20), 137(85), 120(95), 93(20), 92(80), 91(20), 50(53), 79(20), 78(20), 58(81), 42(95).

5,5-Difluoro-6-isopropoxy-1,3-dimethyl-5,6-dihydrouracil (4d): 165mg (70%) of white crystals, m.p.=78-80°C; nmr($CDCl_3$): δ_F=-109.5ppm (dd, $^2J_{FF'}$=294Hz, $^3J_{FH6}$=5Hz, 1F), $\delta_{F'}$=-128.5ppm (d, J=294Hz, 1F), δ_{H6}=4.7ppm (dd, J=5Hz, $^3J_{H6F'}$=1Hz, 1H), δ_H=3.9ppm (m, 1H), δ_H=1.2ppm (d, J=7Hz, 6H), δ_H=3.1ppm (s,3H), δ_H=3.20 ppm (s,3H); mass spectrum calcd. for $C_9H_{14}N_2O_3F_2$ m/z 236.0972, found m/z 236.0970; m/z 236(M^+,48%), 177(63), 128(12), 120(54), 109(90), 92(53), 91(12), 80(12), 58(52), 56(13), 43(55), 42(100), 41(31).

5,5-Difluoro-6-tert.butoxy-1,3-dimethyl-5,6-dihydrouracil (4e): 170mg(68%) of white crystals, m.p.=93-94°C; nmr($CDCl_3$): δ_F=-113.0ppm (dd, $^2J_{FF'}$=288Hz, $^3J_{FH6}$=5Hz, 1F), $\delta_{F'}$=-128.0ppm (d,J=288Hz, 1F), δ_{H6}=4.8ppm (dd,J=5Hz, $^3J_{H6F'}$=1.5Hz, 1H), δ_H=3.08ppm (s,3H), δ_H=3.20ppm (s,3H), δ_H=1.1ppm (s,9H); mass spectrum calcd. for $C_{10}H_{16}N_2O_3F_2$ m/z 250.1129, found 250.1130 m/z; m/z 250(M^+,12%), 194(46), 177(57), 128(10), 120(42), 109(52), 92(36), 58(30), 57(100), 42(23), 42(78), 41(42).

Fluorination of 5-bromo-1,3-dimethyluracil (1c)

After fluorination of 1c in an appropriate solvent the following pure products were isolated by TLC from the crude reaction mixtures:

(±)-r-5-Bromo-5-fluoro-t-6-hydroxy-1,3-dimethyl-5,6-dihydrouracil (5a): 150mg(59%) of white crystals, m.p.=128-130°C; nmr(acetone d_6): δ_F=-146.0ppm (s), δ_{H6}=5.7ppm (s, 1H), δ_H=3.30ppm (s,3H), δ_H=3.35ppm (s,3H); mass spectrum calcd. for $C_6H_8N_2O_3BrF$ m/z 253.9703, found m/z 253.9710; m/z 256(M^++2, 5%), 254(M^+,5%), 175(31), 143(10), 119(12), 117(12), 90(11), 89(11), 58(70), 56(17), 43(12), 4(100).

(±)-r-5-Bromo-5-fluoro-t-6-methoxy-1,3-dimethyl-5,6-dihydrouracil (5b): 180mg(67.1%) of white crystals m.p.=46-47°C; nmr($CDCl_3$): δ_F=-138.5ppm (s), δ_{H6}=4.8ppm (s,1H), δ_H=3.6ppm (s,3H), δ_H=3.2ppm (s,6H); mass spectrum calcd. for $C_7H_{10}N_2O_3BrF$ m/z 267.9859, found m/z 267.9860; m/z 270(M^++2, 95%), 268(M^+,95%), 239(40), 237(40), 182(40), 180(40), 158(55), 156(26), 154(62), 153(200, 152(27), 151(20), 140(50), 138(45), 103(40), 101(50), 73(60), 72(52), 63(32), 60(29), 58(30), 56(62), 45(25), 44(15), 42(100).

(±)-r-5-Bromo-5-fluoro-t-6-ethoxy-1,3-dimethyl-5,6-dihydrouracil (5c): 180mg(63.8%) of oily product; nmr($CDCl_3$): δ_F=-137.0ppm(s), δ_{H6}=4.8ppm(s,1H), δ_H=3.7ppm (q,J=7Hz, 2H), δ_H=1.3ppm (t,3H), δ_H =3.25ppm (s,3H), δ_H=3.20ppm (s,3H); mass spectrum calcd. for $C_8H_{12}N_2O_3BrF$ m.z 282.0016, found 282.0010; m/z 284(M^++2, 62%), 282(M^+,62%), 239(55), 237(55), 182(35), 180(35), 158(4), 154(15), 152(15), 140(28), 138(18), 119(15), 118(28), 117(17), 101(30), 82(10), 73(28), 72(10), 60(10), 58(32), 56(20), 43(17), 42(100).

(±)-r-5-Bromo-5-fluoro-t-6-isopropoxy-1,3-dimethyl-5,6-dihydrouracil (5d): 180mg (60,8%) of white crystals, m.p.=77-79°C; nmr($CDCl_3$): δ_F=-131.0ppm (s), δ_{H6}=5.1ppm (s,1H), δ_H=3.9ppm (m,1H), δ_H=1.1ppm (d,J=7Hz, 6H), δ_H=3.1ppm (s,6H); mass spectrum calcd. for $C_9H_{14}N_2O_3BrF$ m/z 296.0172, found m/z 296.0163; m/z 298(M^++2, 63%), 296(M^+,63%), 239(72), 237(72), 182(45), 180(45), 175(100), 171(28), 169(28), 158(50), 154(12), 152(12), 147(10), 101(25), 90(10), 73(100), 58(17), 43(40), 42(100), 41(95).

Fluorination of uracil (2a)

One mmol of uracil (2a) was dissolved in 20 ml of methanol/acetic acid (1/1 solvent mixture), 450 mg (1.8 mmols) of $CsSO_4F$ were added and the reaction mixture was stirred at 40°C for 2 hours, the insoluble inorganic residue was filtered off, the filtrate evaporated in vacuo, the solid crude products dissolved in 10 ml of $Et_3N/CH_3OH/H_2O$ 1:4.5:4.5 solvent mixture and stirred at room temperature for 3 hours. The solvent was distilled off under reduced pressure, and crystallisation of the crude solid residue from water produced 70 mg (53.8%) *5-fluorouracil* (7a), m.p.=278-280°C (dec.).

Fluorination of uridine (2b)

80 mg (0.33 mmol) of uridine (2b) were dissolved in 5 ml of methanol, 150 mg (0.6 mmols) of $CsSO_4F$ were addded and the reaction mixture was stirred at 40°C for 2 hours, the insoluble inorganic residue filtered off, 5 ml of water and 1 ml of Et_3N added to the filtrate and the mixture stirred at room temperature for 3 hours. The solvent was distilled off under reduced pressure and 68 mg (78.6%) of *5-fluorouridine* (7b) were isolated by preparative TLC (SiO_2, $CH_3OH/CHCl_3$ 2:1). The product (7a) has nmr[9a,c] and ms[14] spectroscopic data as already published.

Fluorination of barbituric acid

A mixture of 600 mg (2.4 mmols) of $CsSO_4F$, 5 ml of acetonitrile and 130 mg (1 mmol) of barbituric acid was heated in a sealed glass tube at 100°C for 2 hours. The reaction suspension was then diluted with 15 ml of acetonitrile, filtered and the filtrate evaporated in vacuo. Crystallisation of the crude solid residue from water produced 105 mg (64%) of *5,5-difluorobarbituric acid*[9b] : m.p.=205-208°C (dec.);, δ_F= -113.4ppm(s); m/z 164(M^+,23%), 128(23), 98(18), 78(100), 70(23), 65(21), 60(15), 59(100), 50(60), 46(55), 45(40), 44(20), 43(82), 42(98), 41(90).

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