

CHEMISTRY OF ORGANO HALOGENIC MOLECULES. PART 100. COMPARATIVE BEHAVIOUR OF XENON DIFLUORIDE AND CAESIUM FLUOROXYLSULPHATE IN THE FLUORINATION OF ENOL ACETATES AND KETONES

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Abstract - Xenon difluoride and caesium fluoroxy sulphate reacted in methylene chloride or acetonitrile with various enol acetates, diketones, and ketones, yielding mainly α -fluoro ketones, the course of the reaction depending on the reagent and the structure of the organic molecule. Enol acetates from cycloalkanones were converted with caesium fluoroxy sulphate to α -fluorocycloalkanones in high yield. Xenon difluoride and caesium fluoroxy sulphate converted enol acetates of benzocycloalkanones-1 to α -fluorobenzocycloalkanones, while the reactivity of enol acetates of benzocycloalkanones-2 depended on the reagent used. 1,3-Diphenylpropane-1,3-dione and its enol acetate were converted with XeF_2 and $CsSO_4F$ to mono and difluoro substituted products, the course of the reaction being dependent on the reagent. Xenon difluoride converted 1-indanone to rearranged 2,2-difluorochromane, while caesium fluoroxy sulphate reacted to 1-fluoro-2-indanone with 2-indanone.

Introduction of fluorine into organic molecules is important from various points of view, but the problem differs considerably from those concerning other halogen atoms¹. This important field of investigation has been covered in recent years by excellent reviews².

The best information about the reactivity of different new reagents can be obtained by reacting them with organic molecules which by their well studied reactivity with other reagents permit a valuable comparison of their behaviour, and also offer the possibility of improved knowledge about the mechanism of halogenation. 1,1-Diphenylethene, cis and trans stilbene, indene, norbornene, diphenylacetylene, benzene, and phenanthrene, are only a few of such molecules, which already merited special attention. Great differences in the reactivity of fluorinating reagents, tested on the above mentioned substrates, was thus established^{1,2}.

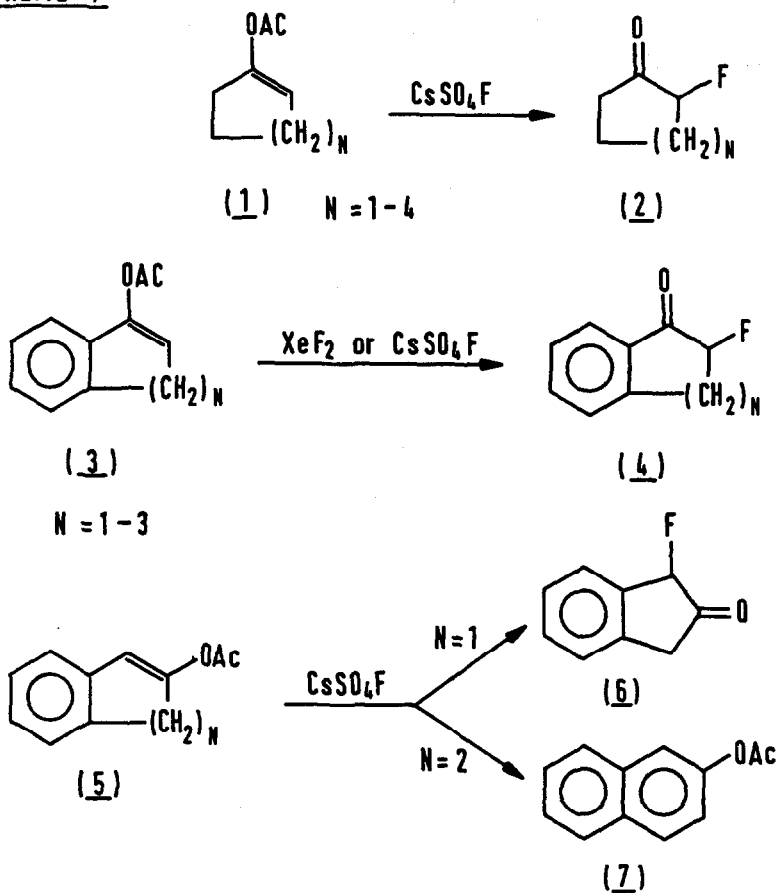
In the last three decades many efforts have been made to find a fluorinating agent which would selectively introduce fluorine into organic molecules under mild conditions. A variety of the reagents discovered require special laboratory equipment, with a vacuum line and low temperatures usually necessary. Two of the mildest and the easiest handled fluorinating reagents are xenon difluoride and caesium fluoroxy sulphate, and their behaviour in the presence of organic molecules has also been reviewed³.

Our continuing interest in the fluorination of organic molecules with XeF_2 and $CsSO_4F$ was thus directed to exploring the differences in their behaviour in reactions with enol acetates, diketones, and ketones.

RESULTS AND DISCUSSION

Rozen and Filler have reviewed possibilities for the preparation of α -fluorocarbonyl compounds⁴. We have already demonstrated that XeF_2 reacted with some enol acetates and diketones, the course of the reaction depending on the catalyst used⁵. Tsushima with coworkers⁶ and Filler⁷ have also shown that XeF_2 converted silyl enol ethers to α -fluoro-ketones.

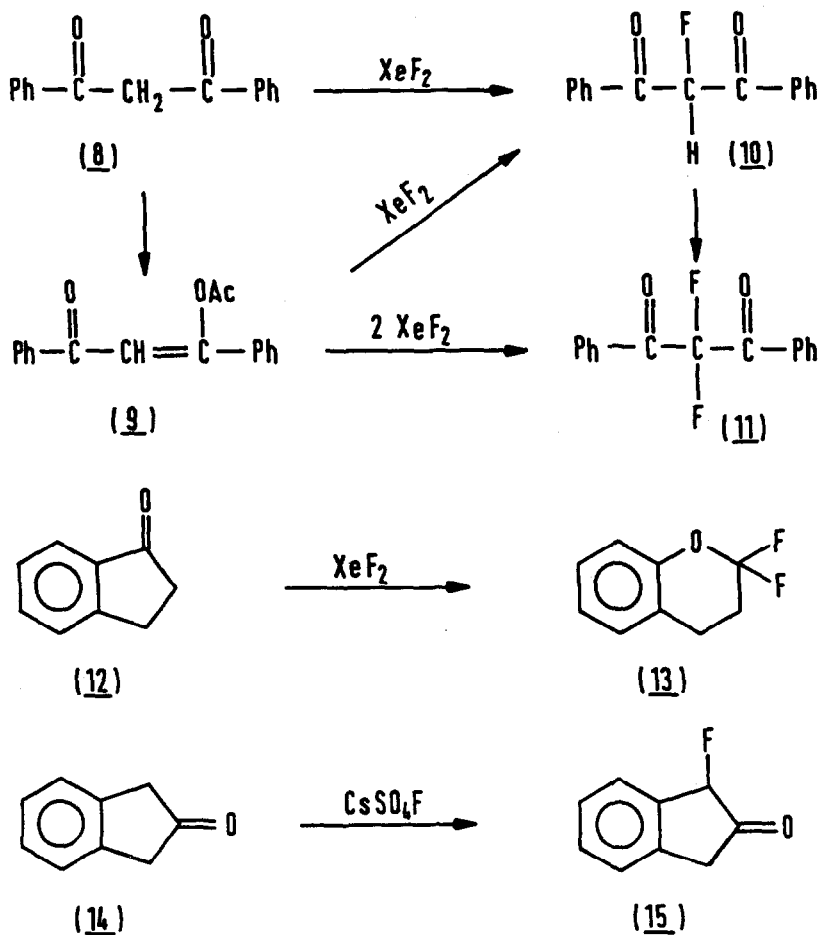
SCHEME 1



Caesium fluoroxysulphate (CsSO_4F) readily reacted with enol acetates prepared from cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone in methylene chloride at 35°C to form α -fluorocycloalkanones (2). Analysis of the crude reaction mixture by ^{19}F NMR spectroscopy showed that 70-80% of fluorosubstituted product was formed. The enol acetate of 4-*tert.*-butylcyclohexanone gave two α -fluoro products with a slight predominance of axially bonded fluorine. Comparison of the results obtained with those obtained in the fluorination with xenon difluoride⁵ shows that fluorination with CsSO_4 avoided the problem of hydrolysis of enol acetate to ketone caused by the presence of HF when

XeF₂ was used. Sensitivity of the enol acetate to hydrolysis diminishes with increasing size of the ring. Both, xenon difluoride and caesium fluoroxysulphate reacted with the enol acetates of benzocyclo-1-ones (3, Scheme 1) in methylene chloride, and in all cases more than 80% of α -fluoro product 4 was formed. Decomposition of enol acetates to ketones in the HF-catalysed reaction with XeF₂, in no case exceeding more than 5%, was thus much less pronounced than in the case of enol acetates of cycloalkanones (1). By contrast, the behaviour of the two reagents differed toward the enol acetates of benzocyclo-2-ones (5) and 1-acetoxy-1-phenylethene. Thus, the course of the reaction of 5 with CsSO₄F depended on the size of the ring, leading to 1-fluoro-2- indanone in the case of a five membered ring, while with the six membered ring, 2-acetoxynaphthalene was formed. Room temperature HF-catalysed reaction of xenon difluoride with 5 (N = 1), resulted in a mixture containing at least three fluoro substituted products, α -fluoro-cycloindanone-2 (6) being accompanied by aromatic ring substituted products, while 5 (N = 2) gave an α -fluoro product, which rapidly decomposed further.

SCHEME 2



The reaction of CsSO₄F with 1-acetoxy-1-phenylethene gave α -fluoro and α,α -difluoro acetophenone in the ratio of 2.3:1, while the reaction with XeF₂ resulted in a complex mixture of up to six products.

The reaction of enol acetate (9), prepared from 1,3-diphenyl-propane-1,3-dione, with XeF₂ gave mono (10) or difluoro (11) substituted products (Scheme 2), depending on the molar ratio, while the corresponding reaction with CsSO₄F resulted in a complex reaction mixture. 1,3-Diphenylpropane-1,3-dione (8) reacted with xenon difluoride to form the mono (10) or difluoro (11) substituted product, depending on the molar ratio, the monofluoro product (10) also converting into the difluoro product (11) with XeF₂. Reaction of 8 with CsSO₄F gave both mono (10) and difluoro (11) products in the ratio of 4:1. We have already demonstrated⁵ that XeF₂ reacts with acetophenone to form 3-fluoro or 3,3-difluoropentane-2,4-dione, depending on the reaction conditions, while the reaction with CsSO₄F led to 3-fluoropentane-2,4-dione and 1,3-difluoropentane-2,4-dione in the ratio of 1.7:1, again demonstrating the difference between the reagents. Fluorination of 5,5-dimethyl-cyclohexa-1,3-dione with CsSO₄F gave 2-fluoro-3-hydroxy-5,5-dimethyl-2-cyclohexenone in high yield, while further reaction with CsSO₄F resulted in 2,2-difluoro-5,5-dimethyl-cyclohexa-1,3-dione.

Further, we studied the reactions of XeF₂ and CsSO₄F with 1-indanone and 2-indanone: the reaction of CsSO₄F with 1-indanone failed, while XeF₂ reacted to the rearranged product 2,2-difluorochromane (13), in contrast to 2-indanone, which converted to 1-fluoro-2-indanone with CsSO₄F, while reaction with XeF₂ led to only 10% conversion of the starting material.

The present results demonstrate again the important role of the structure of the organic molecule on the course of fluorination with the mild fluorinating agents XeF₂ and CsSO₄F.

EXPERIMENTAL SECTION

IR spectra were recorded with a Perkin-Elmer 277 B spectrometer and ¹H and ¹⁹F NMR spectra by a JEOL-JNM-PS 100 instrument, with Me₄Si or CCl₃F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas-liquid partition chromatography was carried out on Varian Aerograph Models 2700 and 3700, and TLC on Merck PSC-Fertigplatten silica gel F-254. Enol acetates were prepared from the corresponding ketones using isopropenyl acetate⁸.

Fluorination of Enol Acetates with Caesium Fluoroxysulphate

2 mmols of enol acetates were dissolved in 4 ml of distilled methylene chloride and under stirring at 35°C CsSO₄F was added at 15 minute intervals until none of the starting enol acetate was present in the reaction mixture. In all cases except 1-acetoxy-1-phenylethene, where 4 mmols of CsSO₄F were needed for the conversion of the starting substrate, 2.8 mmols of CsSO₄ were necessary for the complete conversion of the enol acetate. The reaction mixture was diluted with 20 ml of methylene chloride, any insoluble residue filtered off, the organic layer washed with water (15 ml), dried over anhydrous Na₂SO₄, the solvent evaporated in vacuo, and the crude reaction mixture analysed by ¹⁹F NMR, glc, or tlc. It was established that 1.6 - 1.8 mmols of 2-fluorocycloalkanones-1 were present in the reaction mixture (octafluoronaphthalene or hexafluorobenzene were used as internal standards to determine the amount of 2-fluorocycloalkanone-1). Pure 2-fluorocycloalkanones were isolated by preparative glc or tlc.

Fluorination of 1-Acetoxy-cyclo-1-enes (1, N = 1-4)

Products were isolated by preparative glc (FFAP 30%, Chromosorb W AW 60/80, T = 160-180°C) and 35-40% of pure 2-fluorocycloalkan-1-one (2, N = 1-4) were obtained, and their spectroscopic data were in agreement with those already published^{5,9}.

Fluorination of 1-Acetoxybenzocycloalkan-1-enes (3, N = 1-3)

Products were isolated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 1:4).

2-Fluoro-1-Indanone (4; N = 1)

The product was crystallized from petrolether and 47% of crystalline product, mp = 54-56°C (mp_{lit}⁷ = 59°C) was obtained; NMR δ_F -192.5 (ddd, ²J_{FH2} = 50 Hz, ³J_{FH3} = 22.5 Hz, ³J_{FH3} = 9 Hz), δ_H 2.7-4.0 (m, 2H), δ_{H2} 5.2 (ddd, J = 50 Hz, 8 Hz, 4 Hz, 1H), δ_{Ph} 7.2 - 7.8 (m, 4H); mass spectrum, m/z 150 (M⁺, 81), 149 (28), 122 (100), 121 (25), 104 (24), 103 (13), 102 (45), 101 (33), 96 (29), 77 (17), 76 (61), 75 (13), 74 (31), 63 (28), 62 (15), 51 (35).

2-Fluoro-1-Tetralone (4, N = 2)

The product was crystallized from petrolether and 70% of crystalline product, mp = 38-40°C (mp_{lit}¹⁰ = 38°C) was obtained; NMR δ_F -192 (dm, ²J_{FH2} = 47.5 Hz), δ_H 2.5 (m, 2H), δ_H 3.1 (m, 2H), δ_{H2} 5.1 (ddd, J = 47.5 Hz, 12 Hz, 6 Hz, 1H), δ_{Ph} 7.2-8.2 (m, 4H); mass spectrum, m/z 164 (M⁺, 80), 118 (100), 90 (60), 89 (20).

2-Fluoro-1-Benzosuberone (4, N = 3)

56% of oily product; NMR δ_F -183 (dt, ²J_{FH2} = 50 Hz, ³J_{FH3} = 17 Hz), δ_H 1.7-3.2 (m, 6H), δ_{H2} 5.2 (dm, J = 50 Hz, 1H), δ_{Ph} 7.2-7.9 (m, 4H); mass spectrum calcd. for C₁₁H₁₁OF m/z 178.0793, found m/z 178.0791; m/z 178 (M⁺, 100), 150 (26), 131 (40), 104 (38).

Fluorination of 2-Acetoxy-1-Indene (5, N = 1)

The pure product was isolated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 1:4) and 50% of oily 1-fluoro-2-indanone (6) was isolated; NMR δ_F -179.5 (d, ²J_{FH1} = 52 Hz), δ_H 3.5 (s, 2H), δ_{H1} 5.55 (d, J = 52 Hz, 1H), δ_{Ph} 7.3 (m, 4H); mass spectrum calcd. for C₉H₇FO m/z 150.0481, found m/z 150.0484; m/z 150 (M⁺, 15), 123 (10), 122 (100), 121 (18), 103 (10), 102 (10), 101 (12), 96 (18), 86 (30), 84 (50), 51 (10), 50 (10), 49 (12), 47 (15).

Fluorination of 2-Acetoxy-3,4-Dihydronaphthalene (5, N = 2)

Pure 2-acetoxynaphthalene (7), identical with a commercially available sample, was isolated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 1:4) and crystallization from ethanol in 78% yield.

Fluorination of 1-Acetoxy-1-Phenylethene

The crude reaction mixture was separated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 9:1).

Phenyl-Fluoromethylketone

43.5% of solid product, mp = 23°C (mp_{lit}¹¹ 25-26°C); NMR δ_F -238 (t, J = 46 Hz), δ_H 5.4 (t, J = 46 Hz, 2H), δ_{Ph} 7.3-7.9 (m, 5H); mass spectrum m/z 138 (M⁺, 15), 105 (100), 77 (80), 51 (45), 50 (20).

Phenyl-Difluoromethylketone

16% of oily product¹²; NMR δ_F -121 (d, J = 47 Hz), δ_H 6.2 (t, J = 47 Hz, 1H), δ_{Ph} 7.4 - 8.0 (m, 5H); mass spectrum, m/z 156 (M^+ , 15), 105 (100), 77 (90), 51 (45), 50 (20).

Fluorination of Enolacetates with Xenon Difluoride

1 mmol of enolacetate (**3**, N = 1-3) was dissolved in 4 ml of distilled methylene chloride, 0.95-1.1 mmol of xenon difluoride was added and a catalytic amount of hydrogen fluoride (5-8 mg) was introduced. The reaction mixture was stirred at room temperature for 50 minutes to 2 hours, 10 ml of methylene chloride were added, the reaction mixture was washed with aqueous NaHCO₃ and water (twice) and dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo, the crude reaction mixture was analysed by ¹⁹F and ¹H NMR and glc, and pure α -fluoroketones were isolated by preparative tlc:

2-Fluoro-1-Indanone (4, N = 1): 61% of solid product, mp = 55-57°C;

2-Fluoro-1-Tetralone (4, N = 2): 77.4% of solid product, mp = 37-38°C;

2-Fluoro-1-Benzosuberone (4, N = 3): 71.5% of oily product.

2-Fluoro-1,3-Diphenylpropane-1,3-Dione (10)

The pure product was isolated by preparative tlc (SiO₂, CH₂Cl₂: n-hexane 1:1) and 70.7% of solid product, mp = 65-67°C (mp_{lit}¹³ = 74-76°C); NMR δ_F -185.7 (d, ²J_{FH} = 48 Hz), δ_H 6.4 (d, J = 48 Hz, 1H), δ_{Ph} 7.35-7.90 (m, 10H); mass spectrum, m/z 242 (M^+ , 24), 241 (20), 106 (13), 105 (100), 77 (75), 51 (16).

Fluorination of 1-Indanone (12) with Xenon Difluoride

2 mmols of 1-indanone (**12**) were dissolved in 2 ml of distilled methylene chloride, 1 mmol of xenon difluoride was added and under stirring a catalytic amount of hydrogen fluoride (5-8 mg) was introduced into the reaction mixture. After 24-hours stirring at room temperature, the reaction mixture was diluted with 10 ml of methylene chloride, washed with aqueous NaHCO₃, water (twice), dried over anhydrous sodium sulphate and the solvent evaporated in vacuo. The crude reaction mixture was analysed by ¹⁹F and ¹H NMR and glc, and the pure product isolated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 3:1) and 18% (based on the amount of xenon difluoride) of oily 2,2-difluorochromane (**13**) was isolated; NMR δ_F -70.2 (t, J = 9 Hz), δ_{H3} 2.32 (tt, J = 9 Hz, 7 Hz, 2H), δ_{H4} 3.0 (t, J = 7 Hz, 2H), δ_{Ph} 7.3 (m, 4H); mass spectrum calcd. for C₉H₈F₂O m/z 170.0543, found m/z 170.0540; m/z 171 (M^+ + 1, 10), 170 (M^+ , 100), 169 (14), 151 (12), 149 (26), 106 (30), 86 (11), 84 (18), 78 (58), 77 (17), 51 (20), 39 (16).

In order to increase the amount of 2,2-difluorochromane formed, a larger amount of xenon difluoride was used. However, besides the larger amount of **13**, aromatic ring-substituted products were also observed.

Fluorination of 1,3-Diphenylpropane-1,3-Dione (8) and 2-Fluoro-1,3-Diphenylpropane -1,3-Dione (10) with Xenon Difluoride

1 mmol of diketone was dissolved in 2-15 ml of distilled methylene chloride. 0.95-2.2 mmol of xenon difluoride was added, and under stirring a catalytic amount of hydrogen fluoride was introduced into the reaction mixture. The reaction mixture was stirred at room temperature for 30 minutes to 24

hours, diluted with 10 ml of methylene chloride, washed with aqueous NaHCO₃, water (twice), dried over anhydrous Na₂SO₄, and the solvent evaporated in vacuo. The crude reaction mixture was analysed by ¹⁹F and ¹H NMR and the pure products were isolated by preparative tlc (SiO₂, CH₂Cl₂: n-hexane 1:1) and recrystallized from methanol.

2-Fluoro-1,3-Diphenylpropane-1,3-Dione (10): 66% of crystalline product, mp = 65-67°C.

2,2-Difluoro-1,3-Diphenylpropane-1,3-Dione (11): 68% of crystalline product, mp = 56-57°C (mp lit¹⁴ = 59-59.5°C), NMR δ_F -102 (broad s), δ_{Ph} 7.4-8.2 (m); mass spectrum, m/z 260 (M⁺, 6), 105 (100), 77 (49), 51 (11).

2,2-Difluoro-1,3-diphenylpropane-1,3-dione (11) was also isolated in 65% yield when 1 mmol of enol acetate 9 was fluorinated with 2.6 mmols of xenon difluoride. Difluoro product 11 was also isolated in 71% yield when 1 mmol of 8 was fluorinated with 2.2 mmols of xenon difluoride.

Fluorination of Ketones and 1,3-Diketones with Caesium Fluoroxysulphate

2.8 - 3.6 mmols of caesium fluoroxysulphate were suspended in 4 ml of acetonitrile, stirred at room temperature for 5 minutes and then 2 mmols of ketone or diketone were added and the reaction mixture stirred for 2 hours at 30°C. Then 20 ml of methylene chloride were added, the insoluble residue filtered off, the organic layer washed with water, dried over anhydrous Na₂SO₄, the solvent evaporated in vacuo, and the crude reaction mixture analysed by ¹⁹F NMR. Pure products were isolated by preparative tlc.

Fluorination of 2-Indanone (14)

1-Fluoro-2-indanone (15) was isolated by preparative tlc in 46.5% yield as an oily product.

Fluorination of 1,3-Diphenylpropane-1,3-dione (8)

Pure products were isolated by preparative tlc (SiO₂, petrolether: CH₂Cl₂ 4:1) and 37% of solid *2-fluoro-1,3-diphenylpropane-1,3-dione* (10) and 9.5% of solid *2,2-difluoro-1,3-diphenylpropane-1,3-dione* (11) were obtained.

Fluorination of 5,5-Dimethylcyclohexa-1,3-Dione

Reaction of 2 mmols of diketone and 2.4 mmols of CsSO₄F, after the usual work-up procedure, resulted in a crude reaction mixture, which after preparative tlc isolation (SiO₂, petrolether: CH₂Cl₂ 1:1) gave 66.5% of solid *2-fluoro-3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one*, mp = 145-147°C (mp lit¹³ = 149-150°C); NMR δ_F -172 (broad s), δ_H 1.1 (s,6H), δ_H 2.3 (s,2H), δ_H 2.4 (s,2H); mass spectrum m/z 158 (M⁺, 34), 143 (17), 130 (13), 102 (62), 101 (18), 83 (100), 74 (10), 73 (15), 60 (70), 56 (24), 55 (54), 54 (20), 53 (10), 51 (10), 43 (18), 42 (10), 41 (45); IR(KBr) ν = 3500 cm⁻¹, 1640 cm⁻¹.

2,2-Difluoro-5,5-Dimethylcyclohexane-1,3-Dione

The reaction of 2 mmols of 5,5-dimethylcyclohexane-1,3-dione with 4.8 mmols of CsSO₄F, after the usual work-up procedure, gave a crude reaction mixture and by preparative glc (SE-30 10 %, Chromosorb A 45/60, T = 210°C) 48% of solid *2,2-difluoro-5,5-dimethylcyclohexane-1,3-dione* was isolated⁵.

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