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FLUORINATION WITH CAESIUM FLUOROXYSULPHATE. PART XI.

MILD FUNCTIONALIZATION OF SATURATED HYDROCARBONS

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ABSTRACT – Several hydrocarbons reacted with caesium fluoroxysulphate in acetonitrile at 35°C yielding mono and disubstituted products. Fluorocyclohexane, fluorocycloheptane, and 2-exo-fluoronorbornane formed in the reactions with the corresponding hydrocarbons were accompanied by up to 15% of other unidentified fluoro products, but their amount was strongly diminished when fluorination was performed in the presence of nitrobenzene. Fluorination of adamantane resulted in 1-fluoro, 2-fluoro, and 1,3-difluoro substituted products, with the substitution at the tertiary carbon atom strongly predominating. The presence of nitrobenzene did not influence the rate of reaction and the product distribution when the reaction was carried out in acetonitrile, while the introduction of methanol or methanol and nitrobenzene into the reaction mixture slowed down the reaction, with no evidence of the presence of methoxy derivatives.

The choice of reagents for mild introductions of fluorine into organic molecules is very limited. Many reagents studied require at least vacuum lines and low temperatures, which makes the introduction of fluorine into organic molecules considerably different from the conditions connected with other halogen atoms[1]. Xenon difluoride and caesium fluoroxysulphate are two of the most easily handled fluorinating agents known up to now[2,3]. It has been demonstrated that $CsSO_4F$ reacted with various organic molecules, its reactivity being strongly influenced by the structure of the molecule and the appropriateness of the reaction conditions[4-12]. We now report an investigation of the introduction of fluorine into several saturated hydrocarbons with $CsSO_4F$.

RESULTS AND DISCUSSION

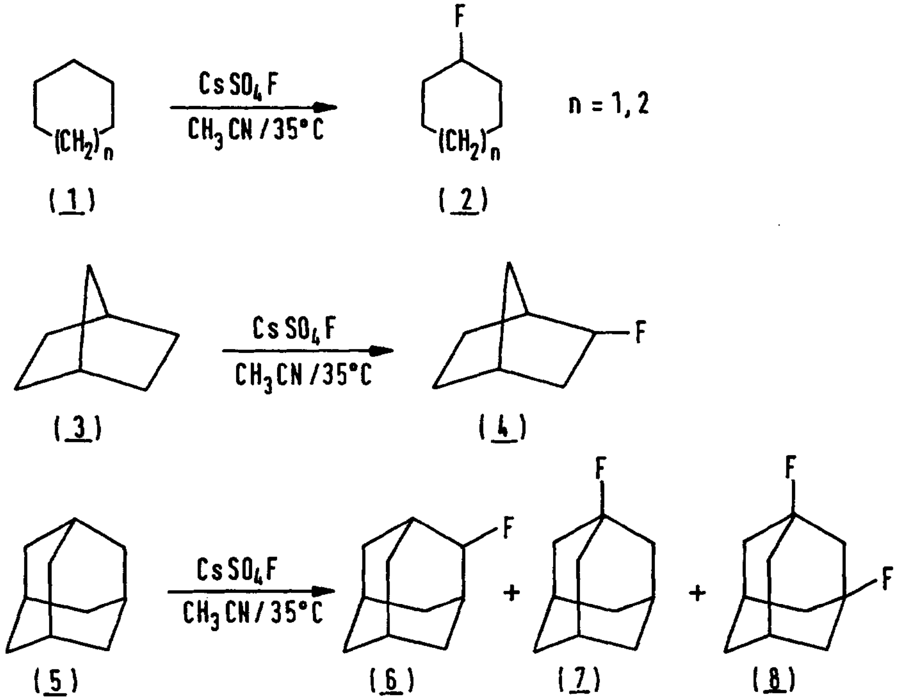
One of the most important subjects in organic chemistry is the functionalization of unreactive sites in an organic molecule. Direct substitution of hydrogen at the saturated carbon atom by fluorine represents a different problem from that of the introduction of chlorine and bromine[13], and several techniques have been developed[1]. Adcock and coworkers[14] made an important contribution to the direct introduction of fluorine at lower temperatures in aerosol suspension of hydrocarbons. Barton and coworkers[15] found that functionalization of saturated hydrocarbon atoms with elemental fluorine, diluted with nitrogen, is also possible at lower temperatures in the liquid phase, and this concept was explored by Rozen and coworkers[16].

In a typical experiment 1 mmol of hydrocarbon was dissolved in 2 ml of acetonitrile and under stirring at 35°C 1.3 mmol of $CsSO_4F$ was added stepwise, while the reaction temperature was kept under control because of the exothermic nature of the reaction. After completing addition of $CsSO_4F$, the reaction mixture was stirred for 0.5 hour at 35°C, and after the work-up procedure, it was analysed by glc and ^{19}F nmr. The reaction mixture obtained by the reaction of $CsSO_4F$ with cyclohexane, cycloheptane, or norbornane (Scheme) contained up to 85% of monofluoro substituted product, i. e. fluorocyclohexane, fluorocycloheptane, or 2-exo-fluoronorbornane, and up to 15% of other products, whose structures, because of the greater number of products in small amounts, were not determined. However, the number and the amount of the unidentified products were strongly reduced when the reaction was carried out in the presence of the free-radical inhibitor nitrobenzene. The yields of monofluoro products were much higher than those observed by thermically initiated fluorinations of hydrocarbons with xenon difluoride[17].

Free-radical functionalization of adamantane, with special attention to regioselectivity, was studied in detail. Regioselectivity strongly depends on the reagent used and the following patterns were found: reaction with $R_2N^{+\cdot}H$ proceeds 99% at C_1[18], reaction with $^{\cdot}CCl_3$ 86% at C_1[18], fluorination with XeF_2 85% at C_1[17], fluorination with F_2 or CF_3OF proceeds mainly at C_1, with the ratio to other products formed depending on the reaction conditions and the presence of free-radical inhibitors[15], while chlorination in CCl_4 yields 1- and 2-chloroadamantane in nearly equivalent amounts[18]. Fluorination of 1 mmol of adamantane with 1.3 mmol of $CsSO_4F$ resulted in 80% conversion of the starting hydrocarbon and 1-fluoroadamantane, 2-fluoroadamantane, and 1,3-difluoroadamantane were found in 3.8 : 1 : 1.4 ratio in the crude reaction mixture. In order to study the effect of solvent and free-radical inhibitor on the course of the reaction, we ran the reaction with a smaller amount of $CsSO_4F$ (0.7 mmol) for 0.5 hour. As evident from the Scheme, the presence of a free-radical inhibitor had no effect on the reaction rate and the product distribution. Fluorination carried out in a mixture of acetonitrile and methanol resulted in a lower conversion of adamantane and in diminished regioselectivity, while no formation of methoxy derivatives was established. Introduction of a free-radical inhibitor increased the regioselectivity when fluorination was carried out in a mixture of methanol and acetonitrile (Scheme).

Finally, we studied the fluorination of n-hexane and found that 2-fluoro and 3-fluorohexane formed in the ratio 1.5 : 1 represent 85% of the products present in the crude reaction mixture. It is interesting that no formation of 1-fluorohexane was found, which was observed to be present in 28% relative yield in the fluorination with XeF_2[17].

SCHEME



THE EFFECT OF REACTION CONDITIONS ON FLUORINATION OF ADAMANTANE [a]

REACTION CONDITIONS	CONVERSION OF (5) [%]	PRODUCT DISTRIBUTION [%] (6)	(7)	(8)
CH_3CN	43	16.5	62.0	21.5
$CH_3CN / C_6H_5NO_2$ [c]	41	14.5	61.0	24.5
CH_3CN / CH_3OH [d]	32	22.0	65.5	12.5
$CH_3CN / CH_3OH / C_6H_5NO$ [e]	28	13.5	60.0	26.5

a) Adamantane: 1mmol; $CsSO_4F$: 0.7mmol; solvent: 1ml; reaction temperature: 35°C : reaction time 30 min.

b) Determined by glc ; c) Nitrobezene : 0.1mmol; d) $CH_3CN : CH_3OH = 3:1$

e) $CH_3CN : CH_3OH = 3:1$; nitrobenzene : 0.1 mmol

EXPERIMENTAL SECTION

Ir spectra were recorded using a Perkin Elmer 727 B spectrometer and ^1H and ^{19}F nmr spectra by a Jeol-JNM-PS 100, with Me_4Si or CCl_3F 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 a Varian Aerograph, Models 2700 and 3700, and TLC on Merck PSC Fertigplatten Silicagel F-254.

General Fluorination Procedure

A 1 mmol sample of hydrocarbon was dissolved in 2 ml of acetonitrile and with stirring at 35°C, 1.3 mmol of $CsSO_4F$ was added slowly, while the reaction temperature was kept under control by cooling because the reaction is exothermic. After the completion of the addition of $CsSO_4F$, the reaction mixture was stirred for a further 0.5–1 hour at 35°C, cooled to room temperature, diluted with 15 ml of methylene chloride, the solid residue was filtered off, the filtrate washed with water (10 ml), the organic layer dried over anhydrous Na_2SO_4 and the solvent was partially evaporated in vacuo. The crude reaction mixture was analysed by ^{19}F nmr (octafluoronaphthalene was added as internal standard to determine the amount of fluorinated products), and also by glc. Pure products were isolated by preparative glc and identified on the basis of comparison of the spectroscopic data with those already published.

Fluorination of Cyclohexane

The crude reaction mixture containing 0.76 mmol of fluorocyclohexane was separated by preparative glc (OV 17 10%, Chromosorb A 45/60, T=60°C) and pure fluorocyclohexane was isolated in 30% yield. Spectroscopic data were in agreement with those already published[19].

Fluorination of Cycloheptane

The crude reaction mixture containing 0.71 mmol of fluorocycloheptane was separated by preparative glc (OV 17 10%, Chromosorb A 45/60, T=60°C) and pure fluorocycloheptane was isolated in 34% yield. Spectroscopic data were in agreement with those already published[20].

Fluorination of Norbornane

The crude reaction mixture containing 0.78 mmol of 2-exo-fluoronorbornane, was separated by preparative glc (OV 17 10%, Chromosorb W H/P 60/80, T=60°C) and pure 2-exo-fluoronorbornane was isolated in 48% yield. Spectroscopic data were in agreement with those already published[21].

Fluorination of Adamantane

The crude reaction mixture was separated by preparative glc (OV 17 10%, Chromosorb W H/P 60/80, T=90°C) and 1-fluoroadamantane[22] (26% yield), 2-fluoroadamantane[23] (6.5% yield) and 1,3-difluoroadamantane[22] (10% yield) were isolated. Spectroscopic data were in agreement with those already published[22,23].

Effect of a Free-Radical Inhibitor on the Fluorination of Hydrocarbons

1 mmol of hydrocarbon and 0.1 mmol of nitrobenzene were dissolved in 1 ml of acetonitrile (or a 3 : 1 mixture of acetonitrile : methanol) and with stirring at 35°C, 0.7 mmol (or 1.3 mmol) of $CsSO_4F$ was slowly added. The reaction mixture was stirred for an additional 0.5 hour and after the usual work-up the crude reaction mixture was analysed by ^{19}F nmr and glc. In the case of cyclohexane, cycloheptane, and norbornane, side-products almost disappeared, while in the case of adamantane, the effect of the free-radical scavengers on the product distribution and the conversion of starting material is evident from the Scheme.

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