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FLUORINATION WITH CAESIUM FLUOROXYSULPHATE. ROOM TEMPERATURE FLUORINATION OF PHENYL SUBSTITUTED OLEFINS

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Abstract - Room-temperature fluorination of 1,1-diphenylethene with caesium fluoroxysulphate in methylene chloride resulted in an addition elimination process, thus yielding 1,1-diphenyl--2-fluoroethene, while in the presence of nucleophile containing species, i.e., hydrogen fluoride, methanol, or acetic acid, either vicinal difluorides, methoxy fluorides or acetoxy fluorides were formed. Reaction with norbornene in the absence of a nucleophile gave only 7-fluoronortricyclane and 7-syn-fluoronorborn-2-ene, while similar reaction with 2-phenylprop--1-ene gave 3-fluoro and 3,3-difluoro-2-phenylprop-1-ene. 1,1-diphenylprop-1-ene, 1,1-diphenyl-2-fluoroethene and 1,1-diphenyl--2-bromoethene were converted with caesium fluoroxysulphate in the presence of various nucleophile donating species, i.e. hydrogen fluoride, methanol, or acetic acid, to adducts with nucleophile bonding following Markovnikov type regioselectivity.

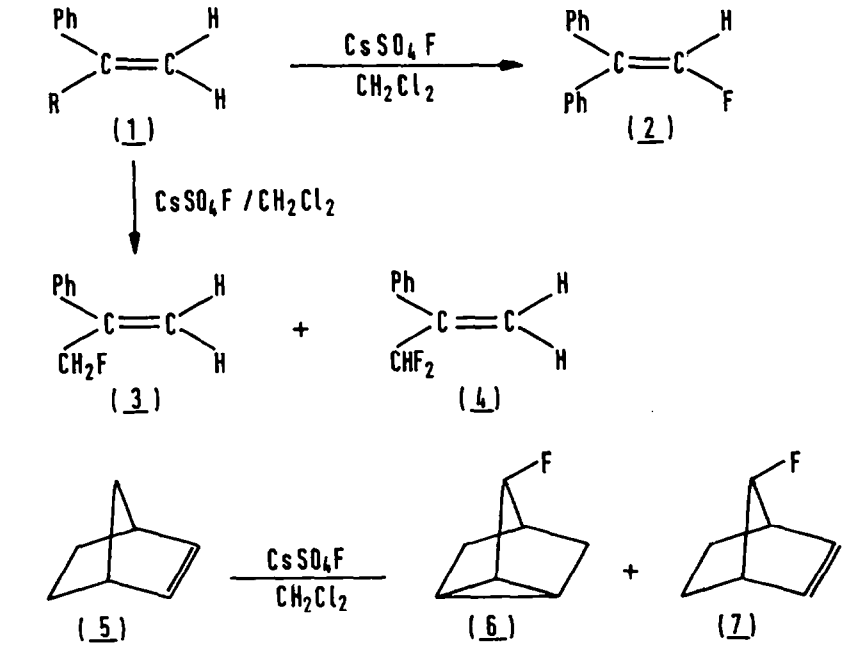
Introduction of fluorine into organic molecules is important from the chemical and pharmaceutical point of view but the problem differs considerably from those concerning other halogen atoms[1]. The choice of reagent for room-temperature introduction of fluorine into organic molecules is limited. Fluoroxy trifluoromethane was explored for introduction of fluorine into various types of organic molecules with varying success[2], while recently fluorinations with trifluoroacetyl hypofluorite[3] and acetyl hypofluorite[4,5] were reported, but reactions with these types of reagents demand safety precautions because of their toxicity, with low temperatures usually required.

Xenon difluoride is the most easily handled fluorinating agent known up to now[6,7,8], but high price is its greatest disadvantage. Appelman and coworkers reported the first preparation and characterisation of caesium and rubidium fluoroxysulphate[9], and found that it reacted with several benzene derivatives[10,11]. We have studied room-temperature fluorination with caesium fluoroxysulphate of various organic molecules[12,13,14]. We now wish to report our investigations of room-temperature reactions with various phenyl substituted olefines and norbornene.

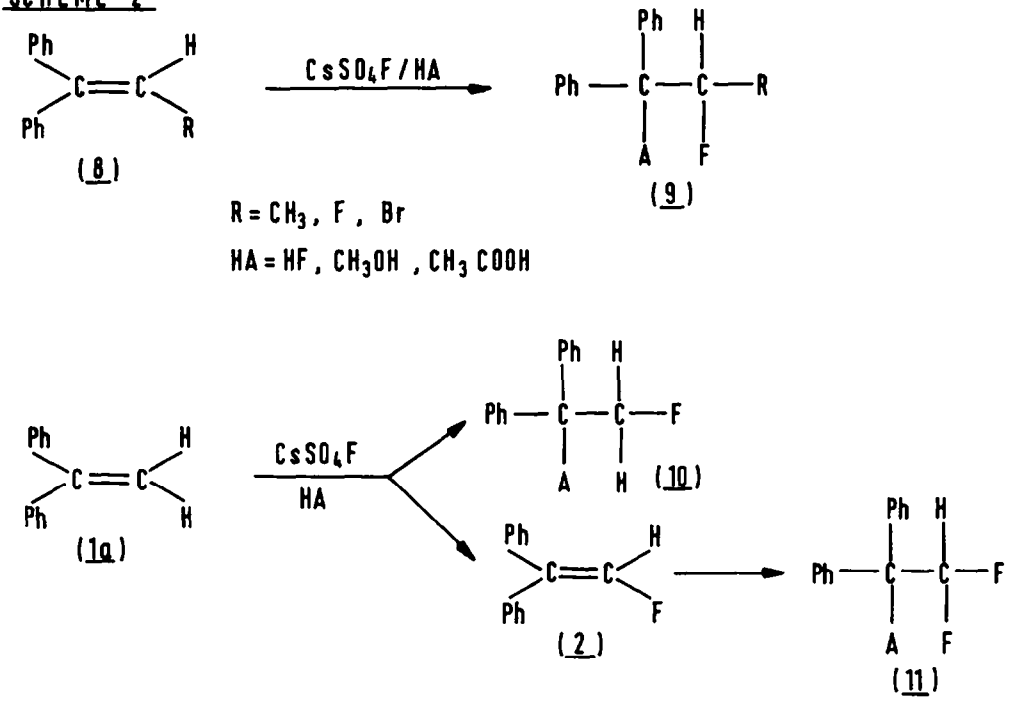
Results and Discussion

Valuable information about the reactivity of a new fluorinating agent can be obtained by studying its reactions with organic molecules which have already been investigated with other reagents. Many fluorinating agents have been tested on 1,1-diphenylethene and up to now all reagents gave different products. Low temperature reactions with fluorine led to addition elimination products and three products were obtained[16], while the course of room-temperature fluorination with xenon difluoride depended on the catalyst used: vicinal difluorides were formed in high yields in the presence of a catalytic amount of hydrogen fluoride[17] whereas vicinal difluorides were accompanied with fluoro-trifluoroacetates when the reaction was catalyzed by trifluoroacetic acid[18]. A complex mixture of five products was observed on reaction of 1,1-diphenylethene with fluoroxy trifluoromethane[19], while rearranged geminal difluorides were isolated in the reaction with aryliodo (III) difluoride[20,21] and with a mixture of lead tetraacetate and hydrogen fluoride[22]. As evident, the structure of the fluorinating agent plays the major role in the fluorination of organic molecules.

SCHEME 1



SCHEME 2



In a typical experiment carried out in a polyethylene vessel a solution of olefin in methylene dichloride was added to a stirred suspension of caesium fluoroxysulphate in methylene dichloride and stirred at room temperature. After the usual work-up procedure, the crude reaction mixtures were analyzed by ^{19}F nmr spectroscopy and the products isolated by gas or thin layer chromatography. Reaction with 1,1-diphenylethene (1a) resulted after 3 hours in an addition-elimination product 2, while reaction with 2-phenylprop-1-ene (1b) gave a mixture of two products: 3-fluoro-2-phenylprop-1-ene (3) and 3,3-difluoro-2-phenylprop-1-ene (4). The ratio of products 3 and 4, as determined by ^{19}F nmr, depended on the molar ratio of 2-phenylprop-1-ene (1b) to caesium fluoroxysulphate. In a reaction where 1 mmol of 1b and 1.3 mmol of caesium fluoroxysulphate were used the ratio of 3 : 4 was 1.9 to 1, increasing the amount of caesium fluoroxysulphate (1.8 mmol) resulted in formation of a greater amount of difluoride, the ratio of 3 : 4 being 0.8 to 1. ^{19}F nmr spectra of crude reaction mixtures obtained by fluorination of 2-phenylprop-1-ene (1b) showed, besides signals for products 3 and 4, only two signals corresponding to the formation of trace amounts of Z and E-1-fluoro-2-phenylprop-1-ene. It is evident that fluorination of 1,1-diphenylethene with caesium fluoroxysulphate in methylene dichloride markedly differs from that with other fluorinating agents.

The reaction of norbornene has also been used on several occasions as a mechanistic device to elucidate the mechanism and stereochemistry of diverse reactions[23]. The different reactivity of caesium fluoroxysulphate from other fluorinating agents stimulated us to study its reaction with norbornene. 3-hours reaction of norbornene (5) in methylene dichloride gave only two products, 6 and 7, in the ratio of 1 : 1.1 which were isolated by preparative glc. On the basis of spectroscopic data,

TABLE

THE EFFECT OF REACTION VARIABLES ON FLUORINATION OF 1,1-DIPHENYLETHENE (1a)

HA	HA : 1a (m mol)	$CsSO_4F$: 1a (m mol)	Conversion of 1a (%)	Product distribution 10 (%)	2 (%)	11 (%)
HF	1	1.2	67	83	17	-
HF	3	2	100	80	-	20
CH_3COOH	1	0.8	45	9	91	-
CH_3COOH	4	1.2	60	43	53	4
CH_3COOH	10	2	100	86	-	14
CH_3OH	1	1	60	33	67	-
CH_3OH	4	1	64	47	47	6
CH_3OH	10	1.6	90	60	23	17
CH_3OH	50	1.6	90	63	12	25
CH_3OH	solvent	0.8	43	61	31	8
CH_3OH	solvent	1.6	85	66	21	13
CH_3OH	solvent	2	100	78	-	22

which were in agreement with those of authentic samples[24], we established that 7-fluoronortricyclane (6) and 7-syn-fluoronorborn-2-ene (7) were formed. The reactivity of caesium fluoroxysulphate again markedly differs from other reagents for introduction of fluorine into organic molecules[22,24].

Further, we studied the influence of nucleophilic species present in the reaction mixture on the course of the reaction of 1,1-diphenylalkenes with caesium fluoroxysulphate at room temperature and two types of reactions were observed. Reactions with olefins (Scheme 2, 8) having a substituent bonded to C-2 favoured the formation of adducts (9), with the nucleophile adding according to Markovnikov's rule. The reactions were run under slightly different reaction conditions, i.e. olefin was dissolved in methylene dichloride and mixed with a nucleophile-containing substrate: hydrogen fluoride, methanol, or acetic acid, and under stirring at room temperature caesium fluoroxysulphate was slowly added to the reaction mixture. The yields of adducts were between 70 and 90 %, pure products were isolated by preparative gas chromatography and the structures of the products determined on the basis of spectroscopic data.

Reactions with 1,1-diphenylethene in the presence of nucleophiles depended on the type of nucleophile, on the ratio of nucleophile to 1,1-diphenylethene and on the ratio of caesium fluoroxysulphate to 1,1-diphenylethene. The effects of variables on the course of the reactions are presented in the Table. Reactions in the presence of hydrogen fluoride mainly favour the formation of vicinal difluorides, and only 17 - 20 % of elimination process accompanied the addition reaction. In contrast, reaction in the presence of acetic acid favoured the addition-elimination process, while an increase in the amount of acetic acid resulted in a predominantly vicinal fluoro acetoxy adduct. The effect of methanol as nucleophile or even as solvent is presented in the Table.

The present study shows that caesium fluoroxysulphate is a mild fluorinating agent for the fluorination of alkenes and extensive work is now in progress to establish the mechanism of these reactions.

Experimental Section

Ir spectra were recorded using a Perkin Elmer 727 B spectrometer and ^{1}H 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 Varian Aerograph Models 2700 and 3700, and TLC on Merck PSC-Fertigplatten Silicagel F-254.

Fluorination of 1,1-Diphenylethene (1a)

1.25 g (5 mmols) of $CsSO_4F$ was stirred in 8 ml of CH_2Cl_2 for five minutes at room temperature under a dry argon atmosphere, then 0.9 g (5 mmols) of 1,1-diphenylethene (1a) dissolved in CH_2Cl_2 (2 ml) was added and stirred for 1 hour at 35°C, then four more additions of 1.25 g (5 mmols) of $CsSO_4F$ were made at half hour intervals. The reaction was slightly exothermic. After 1 hour of additional stirring another 20 ml of CH_2Cl_2 were added, the insoluble precipitate was filtered off, the filtrate washed with water, the organic layer dried with anhydrous Na_2SO_4, and the solvent evaporated in vacuo. The crude reaction mixture was analyzed by ^{19}F nmr and glc and 74 % of 2-fluoro-1,1-diphenylethene (2) was established to be present in the reaction mixture, the rest being the unconverted 1,1-diphenylethene. 2-fluoro-1,1-diphenylethene (2) was isolated by preparative glc (FFAP 30 %, Chromosorb W H/P 80/100, T = 210°C) and 380 mg (38 %) of liquid product were obtained. The spectroscopic data were in agreement with those in the literature[16,18].

Fluorination of 2-Phenylprop-1-ene (1b)

0.9 g (3.6 mmols) of $CsSO_4F$ was stirred in 3 ml of CH_2Cl_2 for 5 minutes at room temperature, then 0.236 g (2 mmols) of 2-phenylprop-1-ene (1b) dissolved in CH_2Cl_2 (1 ml) was added and the reaction mixture was stirred for 3 hours at 35°C. After the usual work-up procedure, the crude reaction mixture (240 mg) was analyzed by ^{19}F nmr spectroscopy and gas chromatography and 3-fluoro-2-phenylprop-1-ene (3) and 3,3-difluoro-2-phenylprop-1-ene (4) were isolated by preparative glc (SE-30 10 %, Chromosorb W H/P 80/100, T = 110°C):

80 mg (29.5 %) of 3 was isolated as a liquid product, and the spectroscopic data were in agreement with those in the literature[18]. 100 mg (32.5 %) of liquid product 4 was isolated; NMR: δF = - 114.7 ppm (d, J_{FH} = 60 Hz), δCH = 6.22 ppm (t, 1H), δCH_2 = 5.5 ppm (m, 2H), δPh = 7.2 ppm (m, 5H); mass spectrum calcd. for $C_9H_8F_2$ m/e 154.0594, found m/e 154.0597, m/e 154 (M^+, 80), 103 (100), 77 (50).

Fluorination of Norbornene (5)

0.65 g (2.6 mmols) of $CsSO_4F$ was stirred in 7 ml of CH_2Cl_2 for 5 minutes at room temperature, then 0.188 g (2 mmols) of norbornene (5), dissolved in 1 ml of CH_2Cl_2, was added and stirred at room temperature for 2 hours. The solvent was evaporated down to 1 ml and the rest was analyzed by ^{19}F nmr and gas chromatography. 7-syn-fluoronortricyclane (6) and 7-syn-fluoronorborn-1-ene (7) were formed in the ratio 1 : 1.1; pure products were isolated by preparative glc (FFAP 30 %, Chromosorb W H/P 80/100, T = 80°C) and 50 mg (22.3 %) of 6 and 52 mg (23.2 %) of 7 as solid compounds were obtained. The spectroscopic data of 6 and 7 were in agreement with those of the independently synthesized compounds and with those in the literature[22,24].

Fluorination of Alkenes in the Presence of Hydrogen Fluoride

1 mmol of alkene (1a, 8) was dissolved in 2 ml of CH_2Cl_2, 1 - 3 mmol of hydrogen fluoride was introduced, and under stirring 1.3 mmol of $CsSO_4F$ was added. The reaction was slightly exothermic; the reaction mixture was stirred at room temperature for 1 hour. After the usual work-up procedure, the crude reaction mixtures were analyzed by ^{19}F nmr and glc. Pure products were isolated according to literature procedures and spectroscopic data were in agreement with those of independently prepared compounds: 1,2-difluoro-1,1-diphenylethane[18], 1,1-diphenyl-1,2-difluoropropane[18], 1,1-diphenyl-1,2,2-trifluoroethane[18], and 1,1-diphenyl-1,2-difluoro-2-bromoethane[25]. The yields of the isolated products were between 50 and 80 %.

Fluorination of Alkenes in Methanol

1 mmol of alkene (1a, 8) was dissolved in 2 ml of dry methanol and under stirring in a nitrogen atmosphere at room temperature, 1.3 - 2 mmols of $CsSO_4F$ was added slowly over a period of 5 min (2 mmols was required only in the case of 1,1-diphenylethene in order to enhance the conversion of starting material). The reaction mixture was stirred at room temperature for an additional hour; the reaction was slightly exothermic. After the usual work-up the crude reaction mixture was analyzed by ^{19}F nmr and pure products were isolated by preparative gas or thin layer chromatography.

Reaction with 1,1-Diphenylethene

The following products were isolated by preparative glc (FFAP 30 %, Chromosorb W H/P 80/100, T = 200°C):

36,5 % of 2-fluoro-1-methoxy-1,1-diphenylethene, mp 22 - 23°C, NMR: $\delta F = -218$ ppm (t, $J_{FH} = 51$ Hz), $\delta H = 5.05$ ppm (d, 2H, J = 51 Hz), $\delta OCH_3 = 3.3$ ppm (s, 3H), $\delta Ph = 7.4$ ppm (m, 10 H); mass spectrum calcd. for $C_{15}H_{15}FO$ m/e 230.1107, found m/e 230.1103, m/e 230 (M^+, 2), 198 (17), 197 (100), 167 (10), 165 (15), 105 (45), 77 (40), 51 (19)

and 12 % of oily 2,2-difluoro-1-methoxy-1,1-diphenylethane,

NMR: δF = - 125 ppm (d, J_{FH} = 54 Hz), δH = 6.3 ppm (t, 1H, J_{FH} = 54 Hz), δOCH_3 = 3.2 ppm (s, 3H), δPh = 7.3 ppm (m, 10H); mass spectrum calcd. for $C_{15}H_{14}F_2O$ m/e 248.1013, found 248.1015, m/e 248 (M^+, 2), 198 (18), 197 (100), 165 (16), 105 (12), 77 (44), 51 (20).

Reaction with 1,1-Diphenylprop-1-ene

63 % of liquid 2-fluoro-1-methoxy-1,1-diphenylpropane was isolated by preparative tlc (SiO_2, petrolether: $CHCl_3$ 8 : 2), NMR: δF = - 178.0 ppm (dq, J_{FH} = 50 Hz, 24.5 Hz), δCH_3 = 1.12 ppm (dd, 3H, J_{FH} = 24.5 Hz, J_{HH} = 6 Hz), δH = 5.3 ppm (dq, 1H, J_{FH} = 50 Hz, J_{HH} = 6 Hz), δPh = 7 ppm (m, 10 H); mass spectrum calcd. for $C_{16}H_{17}FO$ m/e 244.1263, found m/e 244.1268, m/e 244 (M^+, 1), 198 (17), 197 (100), 105 (25), 77 (25), 61 (12).

Reaction with 1,1-Diphenyl-2-Fluoroethene

70.5 % of oily 2,2-difluoro-1-methoxy-1,1-diphenylethane was isolated by preparative tlc (SiO_2, petrolether: $CHCl_3$ 9 : 1).

Reaction with 1,1-Diphenyl-2-Bromoethene

68 % of 2-fluoro-2-bromo-1-methoxy-1,1-diphenylethane, mp = 36-37°C, was isolated by preparative tlc (SiO_2, petrolether: $CHCl_3$ 8 : 2); NMR: δF = - 140 ppm (d, J_{FH} = 51 Hz), δH = 7.3 ppm (d, 1H, J_{FH} = 51 Hz), δOCH_3 = 3.3 ppm (s, 3H), δPh = 7.5 ppm (m, 10H); mass spectrum calcd. for $C_{15}H_{14}BrFO$ m/e 308.0212, found m/e 308.0215, m/e 310 (M^+ + 2, 4), 308 (M^+, 4), 198 (18), 197 (100), 165 (12), 105 (32), 77 (44), 51 (9).

Fluorination of Alkenes in Acetic Acid

1 mmol of alkene (1,1-diphenylethene; 1,1-diphenylprop-1-ene or 1,1-diphenyl-2-fluoroethene) was dissolved in 1.5 ml of CH_2Cl_2, 5 mmols of dry acetic acid were added and under stirring in a nitrogen atmosphere 1.3 mmol of $CsSO_4F$ was added at room temperature. The reaction mixture was stirred for 1 hour at room temperature and after the usual work-up procedure, the crude reaction mixture was analyzed by ^{19}F nmr and the products were isolated by preparative thin layer chromatography.

Fluorination of 1,1-Diphenylethene

48 % of liquid 2-fluoro-1-acetoxy-1,1-diphenylethane was isolated (SiO_2, petrolether: $CHCl_3$ 7 : 3); NMR: δF = - 234 ppm (t, J_{FH} = 51 Hz), δH = 5.5 ppm (d, 2H, J_{FH} = 51 Hz), δCH_3 = 2.2 ppm (s, 3H), δPh = 7.4 ppm (m, 10H); mass spectrum calcd. for $C_{16}H_{15}FO_2$ m/e 258.1056, found m/e 258.1059, m/e 258 (M^+, 6), 238 (17), 196 (40), 195 (22), 184 (10), 183 (80), 105 (100), 77 (65), 43 (50).

Fluorination of 1,1-Diphenylprop-1-ene

60.5 % of liquid 2-fluoro-1-acetoxy-1,1-diphenylpropane was isolated (SiO_2, petrolether: $CHCl_3$ 7 : 3); NMR: $\delta F = -179$ ppm (dq, $J_{FH} = 48$ Hz, 24 Hz), $\delta CH_3 = 1.3$ ppm (dd, 3H, $J_{FH} = 24$ Hz, $J_{HH} = 4.5$ Hz), $\delta COCH_3 = 2$ ppm (s, 3H), $\delta H = 6.1$ ppm (dq, 1H, $J_{FH} = 48$ Hz, $J_{HH} = 4.5$ Hz), $\delta Ph = 7.2$ ppm (m, 10H); mass spectrum calcd. for $C_{17}H_{17}FO_2$ m/e 272.1212, found m/e 272.1216, m/e 272 (M^+, 5), 225 (12), 184 (15), 183 (100), 105 (63), 77 (41), 61 (13), 51 (13), 43 (58).

Fluorination of 1,1-Diphenyl-2-Fluoroethene

61.5 % of 2,2-difluoro-1-acetoxy-1,1-diphenylethane, mp = 40 - 41°C was isolated (SiO_2, petrolether: $CHCl_3$ 7 : 3); NMR: $\delta F = -126.5$ ppm (d, $J_{FH} = 54$ Hz), $\delta H = 7.3$ ppm (t, 1H, $J_{FH} = 54$ Hz), $\delta CH_3 = 2.2$ ppm (s, 3H), $\delta Ph = 7.4$ ppm (m, 10H); mass spectrum calcd. for $C_{16}H_{14}F_2O_2$ m/e 276.0962, found m/e 276.0964, m/e 276 (M^+, 12), 256 (10), 194 (15), 184 (15), 183 (100), 165 (19), 105 (58), 77 (78), 51 (15), 43 (42).

Fluorination of 1,1-Diphenylethene in the Presence of Various Nucleophiles

To 1 - 50 mmols of methanol or acetic acid, methylene dichloride was added, so that the combined volume totalled 2 ml (in the case of hydrogen fluoride in 2 ml of CH_2Cl_2, 1 - 3 mmols of HF were introduced), 1 mmol of 1,1-diphenylethene was added and under stirring at room temperature in a nitrogen atmosphere, various amounts of $CsSO_4F$ were added. The reaction mixture was stirred for 1 hour at room temperature and after the usual work-up, the crude reaction mixture was analyzed by NMR spectroscopy and glc. The effect of the variables on conversion of 1,1-diphenylethene and the product distribution is presented in the Table.

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