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Selective Electrochemical Aromatic Fluorination of Acetophenone and Benzophenone

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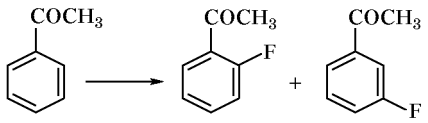
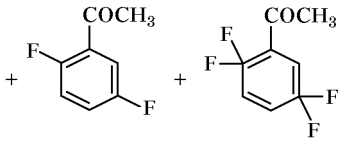
Abstract—Electrochemical fluorination of acetofenone and benzophenone was studied in anhydrous HF and in solutions. The electrochemical fluorination of acetophenone in HF occurred exclusively in the ring and furnished *ortho*- and *meta*-isomers of fluoroacetophenone, 2,5-difluoroacetophenone, and 1-(3,3,6,6-tetrafluoro-1,4-cyclohexadienyl)-1-ethanone. The fluorination of benzophenone in anhydrous HF furnished predominantly *m*-fluorobenzophenone, whereas in the presence of chloroform only chlorination products were obtained. The electrochemical fluorination of acetophenone in acetonitrile gave rise only to mono- and difluorinated products. The reasons for readily occurring oxidative fluorination of aromatic compounds into polyfluoro-1,4-cyclohexadienes were discussed, and the decomposition paths of fluorinated products under electron impact were considered.

Fluorination of aromatic compounds with various fluorinating agents under different conditions for a long time have attracted the attention of researchers as a way to fluoroaromatic products. The direct fluorination with elemental fluorine of various aromatic compounds was investigated [1], and also the oxidative fluorination thereof with higher metal fluorides (AgF_2, CoF_3 etc.) [2]. At the same time we did not find any publications on electrochemical fluorination of aromatic ketones. With aliphatic-aromatic ketones the interesting problem is whether the fluorination would occur into the side chain or into the aromatic ring, and with benzophenone and its analogs either "unsymmetrical" polyfluorination into one ring or "symmetrical" process in both rings are presumable. In this connection and in extension of our previous studies in this field [3, 4] we carried out electrochemical fluorination of acetophenone (**I**) and benzophenone (**II**) in anhydrous HF and in solutions in chloroform and acetonitrile.

Liquid products from electrochemical fluorination of acetophenone were separated by preparative GLC. Their analysis by ^{1}H, ^{13}C, ^{19}F NMR and GC-MS methods revealed that the electrochemical fluorination, similar to oxidative fluorination with the higher metal fluorides [2] took place exclusively in the ring and left intact the acetyl group. The main fluorination products were *ortho*-and *meta*-isomers of fluoroacetophenone (**III**) and (**IV**), 2,5-difluoroacetophenone (**V**) (not detected in the products of fluorination with HF in the presence of CoF_3 or PbO_2 [2]), and 1-(3,3,6,6-tetrafluoro-1,4-cyclohexadienyl)-1-ethanone (**VI**).



I **III** **IV**



V **VI**

The structure of all products was unambiguously proved by their ^{1}H, ^{13}C, ^{19}F NMR spectra, in particular, by characteristic splitting of signals in proton and carbon spectra due to coupling with one, two, or four fluorine atoms. As additional evidence for assignment of isomers **III** and **IV** served the presence of long-range coupling with constants $^5J_{HF}$ 4.9 Hz (publ.: 4.8 Hz [5]) and $^4J_{CF}$ 7.3 Hz in the ^{1}H and ^{13}C NMR spectra of *ortho*-isomer **III** and the lack of this coupling in the *meta*-isomer **IV**. According to ^{1}H and ^{19}F NMR data the ratio of isomers **III** and **IV** in the reaction mixture was 2 : 1. The GC-MS method detected in the reaction mixture alongside 2,5-difluoroacetophenone (**V**) another isomer of difluoroacetophenone, but the insignificant amount of the latter prevented estimation of its structure by spectral methods. In tetrafluoride **VI** the proton signal

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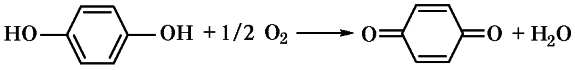
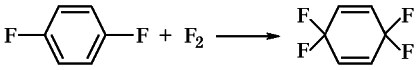
of methyl group appears as a triplet due to coupling with fluorine atoms in position *3* with a long-range coupling constant $^5J_{HF}$ 1.5 Hz (publ.: 1 Hz [2]). Analysis of the published [2, 6, 7] and our own experimental data shows that formation of 1-substituted 3,3,6,6-tetrafluoro-1,4-cyclohexadienyl derivatives of **VI** type is a general way of fluorination for various aromatic substances. Insofar as this process consists in oxidative addition with aromaticity distortion which is not common to aromatic compounds, apparently a certain driving force should exist that makes up for the energy loss due to destruction of the aromatic system. This driving force is likely a formation of four very strong C–F bonds, and if the difluoromethyl group would be regarded as an analog of a carbonyl group, then the ease of the oxidative fluorination of 2,5-difluoroacetophenone **V** into 1-(3,3,6,6-tetrafluoro-1,4-cyclohexadienyl)-1-ethanone (**VI**) would be similar to the readily occurring oxidation of hydroquinone into quinone.

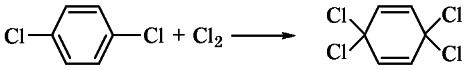
It should be noted that this result is specific just for difluoromethyl group in contrast to the other dihalomethyl groups. We carried out comparative calculation of heat evolution in the oxidation of hydroquinone and the oxidative halogenation of 1,4-dihalobenzenes (equations 1–3). The calculation of reagents and reaction products was performed by the procedure B3LYP/6-311G(d,p) with full geometry optimization.



ΔE = –35.3 kcal/mol (1)

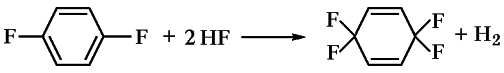


ΔE = –95.2 kcal/mol (2)



ΔE = –1.4 kcal/mol (3)

The oxidative fluorination turned out to be far more exothermic than the hydroquinone oxidation unlike the oxidative chlorination which should occur virtually without heat evolution. Notice however that reaction (2) only formally describes the electrochemical fluorination of acetophenone. The actual process of electrochemical fluorination in liquid HF is more close to reaction (4)



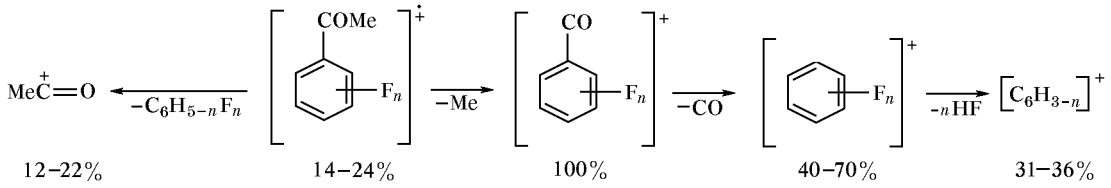
(4)

This reaction turned out to be endothermic, ΔE = 28.4 kcal mol^{-1}, but this effect is evidently compensated by entropy increase due to molecular hydrogen evolution. The similar chlorination reaction is nearly twice as endothermic, ΔE = 49.8 kcal mol^{-1}.

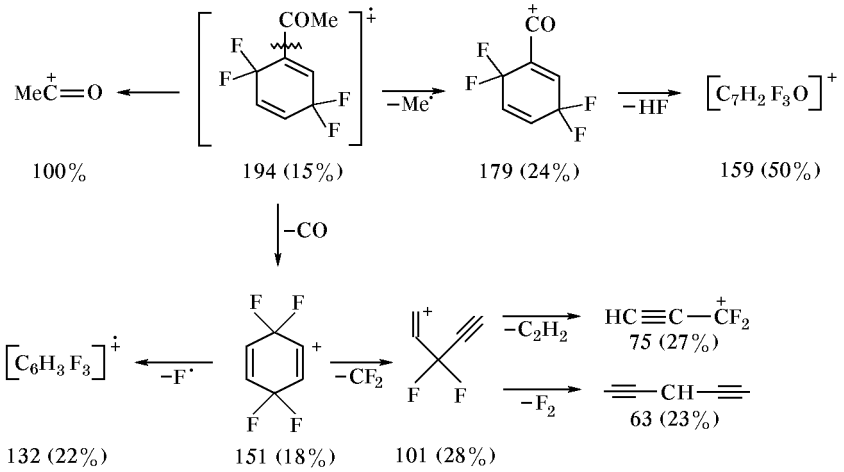
The electrochemical fluorination of acetophenone in acetonitrile gave rise to *ortho*- and *meta*-isomers of fluoroacetophenone (**III**) and (**IV**), the latter prevailing, 2,5-difluoroacetopheneone (**V**), and likely 3,5-difluoroacetophenone. The main difference of the "hard" fluorination in anhydrous HF from the "soft" fluorination in acetonitrile solution is the composition of the products: under conditions of "hard" fluorination the ratio of *ortho*-isomer (**III**) to *meta*-isomer (**IV**) is 2 : 1, and the main reaction product is tetrafluoride **VI**, whereas the "soft" fluorination afforded compounds **III** and **IV** in 1 : 2 ratio, and tetrafluoride **VI** was not detected even in traces.

The absence of polyfluorinated compound **VI** in the products of the "soft" fluorination is consistent with the general rule that electrochemical fluorination in solvents affords prevailingly monofluorinated substances [8]. As to the direction of monofluorination and its dependence on the solvent, note that no *para*-isomers were obtained in electrochemical fluorination both of acetophenone and of phenyl methyl sulfone that we had studied earlier [4]. We believe that this fact testifies to the operation of ECEC-mechanism (Electrochemical-Chemical-Electrochemical-Chemical) where on the first stage occurs the one-electron oxidation of the substrate to the corresponding cation-radical [9]. The calculation of cation-radicals of both substrates by AM1 procedure showed that the electron density on carbon atom of

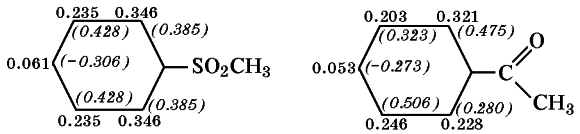
Scheme 1.



Scheme 2.



aromatic ring increased as its distance from the electron-withdrawing substituent grew (see figure). This means that the *ortho*- and *meta*-positions should possess comparable activity with respect to a nucleophile that should considerably exceed the activity of the *para*-position. The change in the *ortho*–*meta* ratio depending on the solvent may be due to the charge control of the reactivity under conditions of the "hard" fluorination leading to prevailing formation of *ortho*-isomer **III**, whereas in the process of the "soft" fluorination the spin density plays an important role, and since it is higher in the *meta*-position, under these conditions *meta*-isomer **IV** is predominant.



Charges (overall charges on carbon atoms and hydrogens linked thereto) and spin density (in italics in parentheses) in cation-radicals of phenyl methyl sulfone and acetophenone calculated by AM1 procedure.

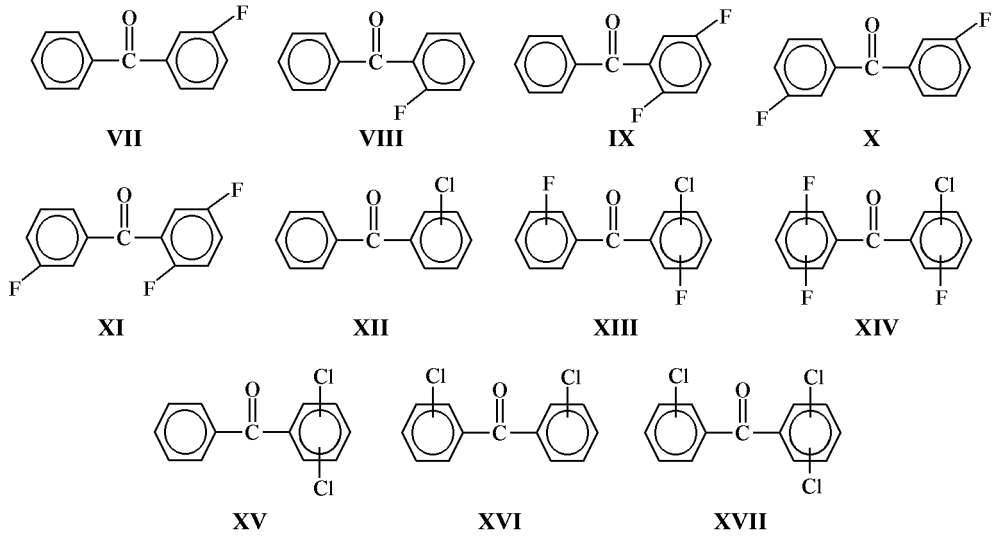
Under electron impact compounds **III**–**V** undergo rupture predominantly at the Me–CO bond with positive charge localization on the aromatic fragment followed by further fragmentation of the fluoro-substituted benzoyl-cations with ejection of CO and HF molecules (Scheme 1).

On the contrary, nonaromatic tetrafluoride **VI** suffered fragmentation mostly at the bond C_{ar}–CO with localization of the charge mainly on the acetyl group. The fragmentation of the molecular ion with the charge localization on the cyclohexadiene fragment is less probable and in a way resembles the fragmentation of the molecular ion of methyl 3,3,6,6-tetrafluoro-1,4-cyclohexadienyl sulfone [4].

The electrochemical fluorination of benzophenone proceeded slowly, with considerable tarring; within 10 h the conversion did not exceed 30%. The composition and structure of fluorinated products were established by ^{13}C and ^{19}F NMR spectroscopy and GC-MS method. The main product was *meta*-fluorobenzophenone (**VII**) as confirmed by its mass spectrum (*m/z* of molecular ion 200), by the presence of two CH signals in the ^{13}C NMR spectrum with a characteristic geminal coupling constant $^2J_{CF}$ 22 Hz (C^2 and C^4), and a doublet of triplets in the ^{19}F NMR spectrum which might appear only in a *meta*-isomer. As a minor monofluorination product was obtained *ortho*-fluorobenzophenone (**VIII**). The di- and trifluorinated products were present in insignificant amounts, but just the composition of fragment ions in their mass spectra revealed the fluorination direc-

tion. Mass spectra of two isomeric difluorides **IX** and **X** with *m/z* of molecular ions 218 are quite different. In the prevailing isomer the following fragment ions were observed: s *m/z* 141 $[M\text{-Ph}]^+$ 113 $[M\text{-PhCO}]^+$, 105 $[PhCO]^+$, 77 $[Ph]^+$ evidencing, that subsequent fluorination occurred into already fluorinated ring affording $PhCOC_6H_3F_2$. In the mass spectrum of the minor difluorinated product the above cited peaks were lacking, but were present peaks with *m/z* 123 $[M\text{-}C_6H_4F]^+$ and 95 $[C_6H_4F]^+$ suggesting the symmetrical structure of difluoride (**X**) $(C_6H_4F)_2CO$. The lack of peaks with *m/z* 105 and 77 in the spectrum of trifluoride **XI** also indicates a structure with both rings fluorinated, $C_6H_3F_2COC_6H_4F$.

To suppress the precipitation of tar on the electrodes that decreased current the reaction mixture containing fluorinated products **VII–XI** was diluted with chloroform, and the process was carried on. However the electrochemical fluorination of this mixture did not result in higher yield of products **VII–XI**, but afforded only monochlorinated products **XII–XIV**. Their composition and the distribution of fluorine atoms between the rings was established by GC-MS method.



If to the electrochemical fluorination was subjected a solution of pure benzophenone in chloroform, the fluorination products were totally absent, and only products of benzophenone chlorination were obtained: **XII** (two isomers) and **XV–XVII** in a ratio (%) (**XII**-°)–(**XII**-*m*)–(**XV**)–(**XVI**)–(**XVII**), 21 : 48 : 10 : 12 : 9. The reaction was slow: conversion within 12 h was only 13%. The formation of only chlorinated products and no mixed products with F and Cl, **XIII** and **XIV**, means that cation-radical of benzophenone arising in the first stage does not react with HF and only abstracts chlorine from the chloroform molecule for the C–Cl bond is weaker than the H–F bond.

Unlike the above process the electrochemical fluorination in acetonitrile proceeded fairly selectively affording as the main product *meta*-fluorobenzophenone (**VII**) (^{19}F NMR data).

In the mass spectra of all fluorinated products containing an unsubstituted phenyl group the most abundant peak was that of ion $[PhCO]^+$. Thus the fragmentation predominantly occurred by rupture of the bond between the fluorinated ring and the carbonyl group $C_6H_{5-n}F_n$-COPh with charge localization on the nonfluorinated fragment.

EXPERIMENTAL

^1H, ^{13}C and ^{19}F NMR spectra are registered on spectrometer Bruker DPX 400 (at operating frequencies 400, 100, and 376 MHz respectively) from solutions in $CDCl_3$, internal reference HMDS, chemical shifts are reported with respect to TMS (^1H, ^{13}C) and CCl_3F (^{19}F). GC-MS analysis was carried out on Hewlett Packard HP 5971A instrument (70 eV) coupled with a column Ultra-2 (5% phenylmethylsilicone), vaporizer temperature 250°C, oven temperature programming from 70 to 280°C at a rate 20 deg min^{-1}. GLC analysis was performed on chromatograph LKhM-8, column 2000 × 3 mm, stationary phase 15% polymethylphenylsilicone oil on Chromaton N-AW, detector katharometer, carrier

gas helium. Preparative separation was carried out on chromatograph PAKhV 07, columns 5000 × 8 mm, stationary phase 5% SE 30 on Chromaton N-AV DMCS.

Electrochemical fluorination was carried out in an electrolyzer of stainless steel of 130 cm^3 capacity with nickel anodes of overall surface 63 cm^3. The electrolyzer was equipped with an inlet for charging HF, an outlet for discharge of fluorination products, and a reflux condenser filled with acetone–ether mixture (1 : 1) cooled with liquid nitrogen to –20°C. Into the cooled electrolyzer cell was charged 120 g of anhydrous HF and 15 g of acetophenone. The electrolysis was carried out for 18 h (17.7 A·h) at anode current density 1.6 dm^{-2}, cell voltage 6.2–7.4 V, cell temperature ~5°C. On completing the electrolysis the reaction mixture was discharged, HF was evaporated, NaF was added to the residue to scavenge the residual HF, then the mixture was extracted with ether, the extract was dried over $CaCl_2$. The ether was distilled off, the residue was distilled under reduced pressure, bp 70–80°C (10 mm Hg), and the products were separated by the preparative GLC.

Electrochemical fluorination of acetophenone in acetonitrile was performed in the similar fashion 100 ml of HF, 20 ml of CH_3CN, 10 g of acetophenone, 12 h, 12.3 A–h, 1.6 dm^{-2}, 6.2–7.4 v, ~8°C).

1-(2-Fluorophenyl)-1-ethanone (III). ^{1}H NMR spectrum, δ, ppm: 2.62 d (3H, CH_3, $^5J_{HF}$ 4.9 Hz), 7.11 d.d.d (1H, H^3, $^3J_{HF}$ 11.2, $^3J_{HH}$ 8.3, $^4J_{HH}$ 1.1 Hz), 7.20 d.d.d (1H, H^5, $^3J_{HH^6}$ 7.7, $^3J_{HH^4}$ 7.3 Hz), 7.49 d.d.d.d (1H, H^4, $^4J_{HF}$ 5.0, $^4J_{HH}$ 1.9 Hz), 7.85 t.d (1H, H^6, $^4J_{HF}$ 7.7 Hz). ^{13}C NMR spectrum, δ, ppm: 31.35 d (CH_3, $^4J_{CF}$ 7.3 Hz), 116.60 d (C^3, $^2J_{CF}$ 24.1 Hz), 124.32 d (C^5, $^4J_{CF}$ 3.4 Hz), 128.38 d (C^1, $^2J_{CF}$ 26.3 Hz), 130.54 d (C^6, $^3J_{CF}$ 2.2 Hz), 134.61 d (C^4, $^3J_{CF}$ 9.1 Hz), 162.20 d (C^2, $^1J_{CF}$ 254.7 Hz), 195.87 d (C=O, $^3J_{CF}$ 3.0 Hz). ^{19}F NMR spectrum, δ, ppm: –109.38 m (publ.: –110.0 [1, 8]).

1-(3-Fluorophenyl)-1-ethanone (IV). ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 7.23 t.d.d (1H, H^4, $^3J_{HF}$ 8.2, $^3J_{HH}$ 8.2, $^4J_{HH}$ 1.0 Hz), 7.41 t.d (1H, H^5, $^3J_{HH^6}$ 8.0, $^4J_{HF}$ 5.5 Hz), 7.60 d.d.d (1H, H^2, $^3J_{HF}$ 9.5, $^4J_{HH^4}$ 2.6, $^4J_{HH^6}$ 1.6Hz), 7.70 d.d.d (1H, H^6). ^{13}C NMR spectrum, δ, ppm: 26.56 (CH_3), 114.85 d (C^2, $^2J_{CF}$ 22.0 Hz), 120.02 d (C^4, $^2J_{CF}$ 21.6 Hz), 124.05 d (C^6, $^4J_{CF}$ 2.6 Hz), 130.19 d (C^5, $^3J_{CF}$ 7.8 Hz), 139.14 d (C^1, $^3J_{CF}$ 6.0 Hz), 162.78 d (C^3, $^1J_{CF}$ 247.8 Hz), 196.64 d (C=O, $^4J_{CF}$ 2.1 Hz). ^{19}F NMR spectrum, δ, ppm: –111.91 m (publ.: –112.35 [10]).

1-(2,5-Difluorophenyl)-1-ethanone (V). ^{1}H NMR spectrum, δ, ppm: 2.57 m (3H, CH_3), 7.14 m (2H, $H^{2,4}$), 7.48 m (1H, H^5). ^{13}C NMR spectrum, δ, ppm: 31.18 d (CH_3, $^4J_{CF}$ 7.6 Hz), 115.99 d.d (C^2, $^2J_{CF}$ 25.0, $^3J_{CF}$ 3.0 Hz), 117.76 d.d (C^5, $^2J_{CF}$ 27.2, $^3J_{CF}$ 7.8 Hz), 120.95 d.d (C^4, $^2J_{CF}$ 24.6, $^3J_{CF}$ 9.5 Hz), 126.66 d.d (C^1, $^2J_{CF}$ 15.7, $^3J_{CF}$ 6.3 Hz), 157.79 d.d (C^3, $^1J_{CF}$ 251.1, $^4J_{CF}$ 1.9 Hz), 158.18 d.d (C^6, $^1J_{CF}$ 244.6, $^4J_{CF}$ 1.9 Hz), 194.46 d (C=O, $^3J_{CF}$ 3.4 Hz). ^{19}F NMR spectrum, δ, ppm: –112.90 m (F^6), –115.31 m (F^3) (publ.: –115.42 and –118.04 [11]).

1-(3,3,6,6-Tetrafluoro-1,4-cyclohexadienyl)-1-ethanone (VI). ^{1}H NMR spectrum, δ, ppm: 2.60 t (3H, CH_3, $^5J_{HF}$ 1.5 Hz), 6.32 m (2H, $H^{4,5}$), 7.00 m (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 28.87 t (CH_3, $^4J_{CF}$ 2.6 Hz), 128.32 t.t (C^5, $^2J_{CF}$ 29.6, $^3J_{CF}$ 9.3 Hz), 129.71 t.t (C^4, $^2J_{CF}$ 30.6, $^3J_{CF}$ 9.3 Hz), 133.08 t.t (C^1, $^2J_{CF}$ 36.7, $^3J_{CF}$ 11.5 Hz), 133.82 t.t (C^2, $^2J_{CF}$ 31.4, $^3J_{CF}$ 7.0 Hz), 192.37 s (C=O). ^{19}F NMR spectrum, δ, ppm: –92.62 s (F^3), –93.89 s (F^6) (publ.: –95.27 and –96.77 [2]).

Electrochemical fluorination of benzophenone in HF, chloroform, and acetonitrile were carried out as described above for acetophenone. After removal of HF the reaction mixtures were analyzed by NMR spectroscopy and GC-MS method.

(3-Fluorophenyl)(phenyl)methanone (VII). ^{13}C NMR spectrum, δ, ppm: 116.43 d (C^2, $^2J_{CF}$ 22.4 Hz), 119.16 d (C^4, $^2J_{CF}$ 21.6 Hz), 125.61 d (C^6, $^4J_{CF}$ 3.0 Hz), 162.24 d (C^3, $^1J_{CF}$ 247.8 Hz), 194.87 d (C=O, $^4J_{CF}$ 1.7 Hz). We failed to identify the signals of C^1 and C^5 atoms. ^{19}F NMR spectrum, δ, ppm: –111.71 d.t ($^3J_{HF}$ 8.5, $^4J_{HF}$ 5.7 Hz).

(2-Fluorophenyl)(phenyl)methanone (VIII). ^{19}F NMR spectrum, δ, ppm: –110.99 m.

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