Modern Synthetic Procedures for the Fluorination of Organic Molecules

Alois Haas* and Max Lieb

In view of the number and diversity of publications on organofluorine chemistry in the recent years, it is evident that, since presenting the first series «Fluorierungsmethoden in der Organischen Chemie» [1], *fluorination reactions remain of general interest. The objectives of research in the various studies are quite similar. These include selective fluorination of biologically active substances such as steroids, nucleobases, pharmaceuticals, carbohydrates like sugars and glycosides; systematic studies for developing universally applicable fluorinating agents or improving reaction conditions; optimization of yield and selectivity as well as suppression of side reactions. – Elemental fluorine has become increasingly important as a selective fluorinating agent. The critical factor for successful reactions is to suppress radical fluorination which almost exclusively results in perfluorination, fragmentation or oxidative halogenation of heteroatoms or of alkene- and alkyne-bonds. Radical suppression is achieved by diluting fluorine with an inert gas in the presence of a radical-abstractor and in a suitable solvent at low temperature. – Concerning SF_4 and its derivatives, a renaissance has been realized. To date, these compounds are among most important and multifunctional fluorinating agents. New agents with different fluorinating qualities such as $CsSO_4F$, HOF or OF_2 must be added to the list; however, their range of applicability has not yet been fully explored. In the field of CF_3- and CF_3S-substitution, novel, interesting pathways have been presented, in which the selectivity of new CF_3- and CF_3S-donating agents is outstanding. – As a completment to and continuation of the in 1981 published «Fluorierungsmethoden in der Organischen Chemie», new fluorination methods and new variations of known procedures are reviewed.*

1. Fluorinations with Elemental Fluorine

Elemental fluorine has recently been repeatedly used for specific partial fluorination of also complex organic substrates. In many cases very favourable results could be achieved through the choice of specific reaction conditions (degree of dilution, temperature), whereby in many cases an indirect route was postulated via a hypofluorite species of the solvent, such as CF_3OF, CF_3CO_2F, CH_3CO_2F or CH_3OF, as the fluorinating agent proper. In this way by the direct reaction with elemental fluorine a series of fluorinated steroids

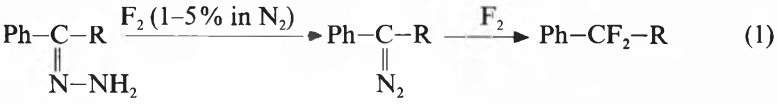
* *Correspondence:* Prof. Dr. A. Haas, Dr. M. Lieb
Lehrstuhl für Anorganische Chemie II
Ruhr-Universität Bochum
Postfach 102148, D-4630 Bochum 1
(Bundesrepublik Deutschland)

The authors:

Alois Haas was born on January 3, 1932 in Czernowitz (Rumania). His early training as a chemical engineer took place at the Staatliche Ingenieurschule Essen (Germany). In 1955 he commenced study of chemistry at the Technische Hochschule Aachen where he received his Dr. rer. nat. in 1960. Postdoctoral work with H. J. Emeléus in Cambridge (England) resulted in the granting of a Ph. D. degree in 1962. He earned his habilitation in 1965 at the University of Göttingen with work on perfluorinated pseudohalogens. Since 1969 he has served as regular Professor for Inorganic Chemistry at the Ruhr-Universität Bochum. His research interests include lower chalcogen fluorides, perfluoroorganochemistry of sulfur, selenium, nitrogen, phosphorus, and mercury, syntheses of perfluoroorganosulfur-substituted heterocycles and their biological properties, fluorination of complex molecules, and developing a periodic system for functional group classification. He has authored eleven volumes of Gmelin's Handbuch der Anorganischen Chemie on «Perfluorohalogenoorgano Element Chemistry». In 1974 he received his D. Sc. (cantab) degree. He has been a corresponding scientific member of the Max-Planck-Gesellschaft since 1975. In 1984 he was awarded Honorary Professorship at the Tongji-University in Shanghai (China).

Max Lieb was born on December 16, 1950 in Essen (F. R. G.). From 1970 to 1976 he studied chemistry at the Ruhr-Universität Bochum. Since 1976 he has been an assistant at the Lehrstuhl für Anorganische Chemie II of this university. He has received his Ph. D. (Chemistry) in 1980 with a dissertation about trifluoromethylthio-substitution on pyrimidines. His current research interests include selective fluorination of organic compounds, perhalogenomethylthio-substitution in heterocyclic systems, and applied organofluorine chemistry.

could be synthesized, such as e.g. 9α- and 14α-fluorosteroids[2] or 16α-,17α-difluoroprogesterone[3], as well as derivatives and precursors of these compounds. Analogously could Δ^4-cholestan-3-one and cholanic acids[10,11] be fluorinated. The antibacterially active pleuromutiline could be transformed into the 2,2-difluoro-pleuromutiline through the intermediate diazo derivative by the action of F_2 at −60 °C in the presence of $CHCl_3$ and KF[4]. In analogy to this also arylketone hydrazones can be transformed into the difluoro-compounds, whereby likewise the diazo-compounds are formed as intermediates.



(1)

This procedure has been adapted to derivatives of neratrol and oestradiol[12]. The direct addition of F_2 to olefins at −78 °C leads to the respective vicinal difluorides in good yields. Addition reactions of this kind were successfully accomplished with perhalogenated olefins[5], vinyl acetate[6], diethyl fumarate[7], 1,1-diphenylethylene[8], and propinylbenzene[9]. The energy, which is liberated at the fluorination, and leads to unselective substitution, carbonization, etc. is removed by working at a low temperature. The reaction of indene and 2-methylindene with stoichiometric amounts of fluorine in $CFCl_3$ at −78 °C affords the vicinal difluorides in good yields[13]. *erythro*-Fluoro-phenylalanine could be synthesized in a like manner[18].

The addition of F_2 to alkynes leads mainly to the appropriate tetrafluoro-derivatives[13]; however, *cis*- and *trans*-difluoro-olefins, as well as tri- and tetra-fluorinated ethanes, could also be isolated – this could be exemplified by various tolane derivatives[14].

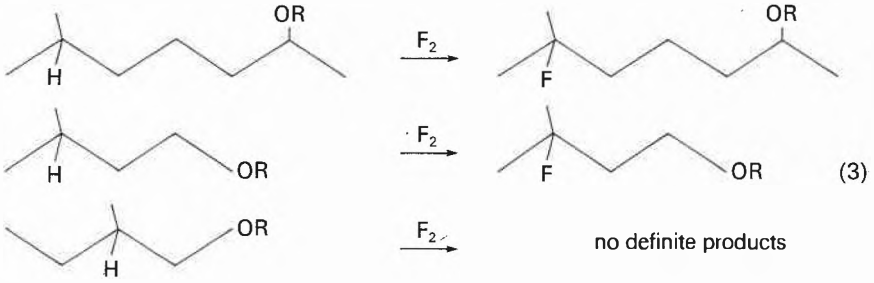
Recently, substitutions on aliphatic systems were also extensively studied. It is to be remarked here, that very dilute F_2 (with N_2 or Ar) and low temperatures had to be used. In this way regiospecific substitutions could be carried out by considering different electron densities.

In experiments with adamantanes a selective fluorination at the tertiary carbon atom was found[15].

In the reaction of *trans*-4-methyl- or *trans*-4-*tert*-butyl-cyclohexyl *p*-nitrobenzoate with 4% F_2 in N_2 at −70 °C, the species fluorinated in the 4-position are obtained in 60 or 50% yield. The *cis*-isomers react analogously[16].

Electrophilic fluorinations of this kind occur preferably at the tertiary carbon atom most distant from an electron withdrawing centre. However, as could be shown in the case of the *p*-nitrobenzoate of menthol, substitution can also occur in the vicinity of electron withdrawing groups, but at any rate the reaction velocity is considerably diminished in comparison with 4-alkyl-cyclohexanols[16].

These results find their corroboration in the case of 6-methyl-2-heptyl-, or 3-methyl-1-butyl *p*-nitrobenzoates. Here substitution occurs in both cases at the tertiary carbon atom, but the yield and reaction rate of the 6-methyl-derivative exceed considerably those of the 3-methyl-species. At further shortening of the C-chain no definite products are obtained[17].

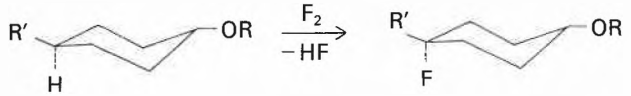


(3)

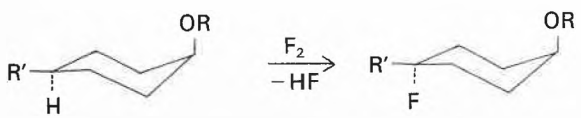
These results were confirmed in an additional study that appeared recently[19].

Fluorinations in aromatic systems were thoroughly studied as depending on various functional groups[20]. A crucial factor in accomplishing all these syntheses is the suppression of radical induced fluorinations, that almost exclusively lead to perfluorination, fragmentation, and oxidative halogenation at heteroatoms, both of alkene and alkyne compounds. For these reasons fluorine is nearly always diluted with an inert gas and worked at a low temperature in the presence of radical captors.

An interesting novel fluorination technique with elemental fluorine has been developed in the very recent time by *Adcock* et al. in the form of aerosol fluorination. The principle of this procedure is, that an aerosol consisting of NaF particles in helium, coated with the substrate to be fluorinated, is introduced into the fluorination reactor[21]. The outstanding property of this procedure is a high yield of highly or perfluorinated compounds. Hydrocarbons[21], adamantanes[22], ketones[23,26], alkyl halides[24,25], as well as ethers[27], were fluorinated according to this procedure. Comprehensive results have been published in two «reports»[28,29].



R = $COC_6H_4NO_2(p)$; R' = Me, *t*-Bu (2)



2. Fluorinations with F_2 in Polar Solvents; Hypofluorite Fluorinations

2.1. In Water

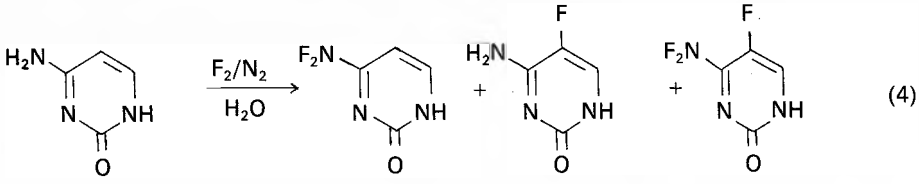
The rate constant of the reaction of water with F_2 has been determined by *Appelman* and *Thompson*[30] as $7 \cdot 10^{-6}$ s^{-1}. The very fast reaction is not influenced either by stirring or by convection, however it is slow enough to allow for reactions with F_2 in H_2O.

Already in 1961 *Grakauskas*[31] reported fluorinations in water. He succeeded in the fluorination of urea dissolved in water to *N*,*N*-difluorourea, $F_2NC(O)NH_2$. Sulfamide behaves the same way: it reacts in an unbuffered aqueous solution with F_2 at 0 to 5 °C to give *N*,*N*-difluorosulfamide[33]. Alkyl carbamates dissolved in water, are converted in about 30% yield to alkyl fluorocarbamates in a reaction with equimolar amounts of F_2 (N_2 diluted) at 0 to 5 °C under stirring. On further fluorination the amount of the unreacted starting compound indeed diminishes, but the yield of alkyl difluorocarbamates is not increased. As a result of hydrolysis difluoroamine is formed. Should one wish to isolate the difluorocarbamates, it is most appropriate to use non-aqueous solvents. Tetrachloromethane, dichloromethane, 1,1,2-trichloro-1,2,2-trifluoroethane, and acetonitrile were used. Owing to the good solubility of the starting materials in acetonitrile and the high stability thereof towards F_2, it is to be preferred over the other solvents. The yields amount to about 45 to 75%[32].

A new example of fluorinations with F_2 in water is the recent success of the synthesis of difluoroamino-pyrimidines[34] (reaction (4)).

2.2. In Acetic acid and Trifluoroacetic acid; Organo-Hypofluorites

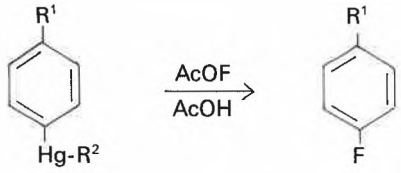
As a consequence of the interesting fluorination properties of trifluoro(fluorooxy)methan[1,2,34] for which, in recent



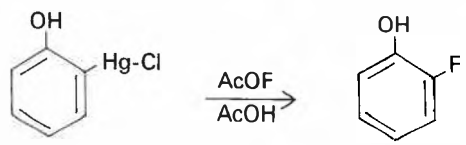
(4)

times too, impressive examples were published[41,45], a search was conducted for easier accessible analogous fluorination agents. By reacting $CF_3C(O)ONa$ with F_2 can $CF_3C(O)OF$ and CF_3CF_2OF be produced and used in situ for fluorination. The reactions of $CF_3C(O)OF$ with stilbenes show an addition behaviour similar to that of CF_3OF[35]. On addition to stilbenes CF_3CF_2OF furnishes *cis*-products and is likewise comparable with CF_3OF[36]. Syntheses of fluorinated steroids, α-fluoroketones[38], and fluorinated *N*-acetyldibenzazepines with CF_3CF_2OF are also known[36,37]. This reaction technique for the production of fluorinating hypofluorite species has also been applied to acetic acid. On passing diluted fluorine through an AcOH/$CFCl_3$ mixture in the presence of salts, such as NaF, CH_3CO_2Na or CF_3CO_2Na at −78 °C, an oxidizing solution is obtained, the fluorinating properties of which are explained by the intermediate appearance of an acetyl-hypofluorite, $CH_3C(O)OF$[39]. The corroboration is based on the fact that the passage of F_2 through sodium acetate in $CFCl_3$ affords identical results[39].

Although up to date no hypofluorite of the RC(O)OF type had been isolated[128] in substance and also no spectroscopic data, as e.g. ^{19}F-NMR shifts, had been published[128], they are at present established as the most versatile fluorinating agents and this is to be attributed to their easy handling and mild properties. Thus, e.g. 1,3-dicarbonyl compounds, malonic ester, and cyclic ketones were fluorinated in partly good yields[40], and also addition reactions to olefinic systems (stilbene)[39] have been studied. The fluorination of activated aromatics with AcOF affords mainly *ortho*-substitution[42,43]; fluorinated nucleosides are also obtainable with AcOF[43]. Interesting new variations are the reactions of organo mercury compounds[43] as, for instance,



(5)



as well as the passing of F_2/N_2 (0.14%) through columns impregnated with $KOAc\cdot(HOAc)_{1.5}$ for the production of AcOF. Not long ago derivatives of fluoroglucose could be formed according to this method[44]. Another feasible application of this procedure is the possibility to synthesize ^{18}F-labeled substances, that are of interest in the diagnostic medicine. Thus antipyrine[46], glucose derivatives[47], and differently substituted aromatic systems[48] were ^{18}F-fluorinated.

3. Fluorinations with Inorganic Hypofluorites

The importance of CF_3OF as an electrophilic fluorination agent has been given a sufficiently extended treatment[1,2,34]. Since the synthesis and the manipulation of this substance are quite commonplace, a search was undertaken for substitute reagents with similar properties. In this connection the application of the fluorooxy-sulfate ion is worth mentioning. The fluorooxysulfates, MSO_4F, prepared in aqueous solution from M_2SO_4 (M = Rb, Cs) and F_2, react with aromatics best in acetonitrile at 20 °C to render fluorine substitution. Thus toluene reacts with this agent to give benzyl fluoride in yields from 40 to 60%. In the fluorination of phenol or anisol, fluorine is introduced mainly in 2-position (about 50 to 80%), barely in 3-position (under 1%), and insignificantly in 4-position (5 to 15%)[48]. Alkoxybenzene and derivatives of naphthalene react analogously with $CsSO_4F$ in CH_3CN[49] in the presence of catalytic amounts of BF_3. A publication that appeared recently[51] reports about the influence of various catalysts, such as HF, H_2SO_4, BF_3, CF_3SO_3H, FSO_3H, and «superacids» on the substitution of aromatics by $CsSO_4F$[51].

Pentane-2,4-dione at 20 °C affords 3-fluoro- and 1,3-difluoro-derivatives. Barbituric acid reacts with $CsSO_4F$ only at 100 °C to give 5,5-difluorobarbituric acid in high yields[50]. A summary of the application potentials of $CsSO_4F$ has appeared very recently[113].

OF_2 can also be conceived as a hypofluorite and employed as a fluorinating agent. However, attention has to be paid to the fact that OF_2 is a more powerful oxygenation agent than all other hypofluorites. For this reason, while employing OF_2, oxygen derivatives have to be considered too. Representative olefines, in $CFCl_3$ solution, are reacted at −78 °C with gaseous OF_2 in such a manner, that the lowering of the pressure of the OF_2 atmosphere is measured. Tetramethylethylene absorbs an equimolar amount OF_2 within one hour and affords 2-fluoro-3-hydroxy-2,3-dimethylbutane in 65 to 70% yield. 1,1-Diphenylethylene absorbs OF_2 within 2.5 h and affords ω-fluoro-acetophenone.

cis-Stilbene is considerably more reactive than the *trans*-isomer, and by OF_2 it is transformed into 17% $C_6H_5C(O)CHFC_6H_5$. *cis*- and *trans*-1-Fluorostilbene are formed as by-products. 1-Butene and 1-propene react with OF_2 in an uncontrollable manner. ^{19}F-NMR spectroscopic studies revealed no evidence of the existence of an intermediate with an OF group. A species of this kind, did either not appear at all, nor even at −78 °C, is it converted to the enol-products.

Alkynes too react sluggishly with OF_2 and form α,α-difluoroketones[52].

Like F_2 and CF_3OF also OF_2 is able to react as an electrophilic fluorination agent. In its reaction with adamantane or with adamantane derivatives, substituted in the 1-position, without an HF captor, oxygenated adamantanes, too, are still produced beside the fluorination products. In the presence of Na_2CO_3 as HF scavenger also 1-fluoro-2-oxa-homoadamantane is formed in addition. The relatively low yields are to be attributed to the persistent formation of unidentifiable tars and additional fluorinated products.

1-Bromoadamantane provides with OF_2 in CH_2Cl_2 at 30 °C (72 h) a complicated mixture, that could not be resolved. 1-Fluoro-3-bromo-adamantane alone could be enriched in as much as to be identified, beyond any doubt.

The preferred formation of bridgehead substituted adamantanes, supports the conclusion about an electrophilic fluorination mechanism like in the case of F_2 and CF_3OF[53]. It is possible to establish a correlation between these three agents with the help of the element displacement principle. Substituting fluorine in F_2 with the parafluorine ligands[54] OF and CF_3 the series F−F, F−OF, CF_3OF of comparable fluorinating behaviour is obtained.

In conclusion, it is appropriate here to point out that hypofluorous acid too has been employed as a fluorinating agent. Thus has succeeded the addition

$$RCH{=}CH_2 + HOF \longrightarrow \underset{F}{RCH}{-}\underset{OH}{CH_2} \quad (6)$$

to olefinic systems, whereas the addition to alkynes affords α-fluoroketones[111].

$$RC{\equiv}CH + HOF \longrightarrow RFC{=}\underset{OH}{\overset{H}{C}} \rightleftharpoons \underset{F}{RCH}{-}\underset{O}{CH} \quad (7)$$

Reactions of HOF with aromatic systems resulted in hydroxy compounds[112].

4. Fluorinations with SF_4 and Analogs

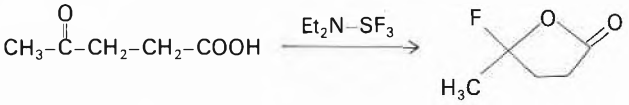
Among the hitherto well-known selective fluorinating agents SF_4 and its derivatives occupy a dominating position. SF_4 is a universally employable agent, very selectively effective and relatively easily accessible; it enables to work also on a preparative scale and it can catalytically be further activated on addition of a Lewis acid. It is therefore not surprising, that the fluorinating properties of SF_4 are the subject of numerous research studies. They led to new conceptions about the results of the reactions of the fluorination of ketones in the presence of catalysts. In the fluorination reactions mentioned by *Smith*[55] in 1962 the Lewis acid serves as a polarizing agent for the C=O group to be fluorinated. The keto-function thus activated facilitates the nucleophilic attack of SF_4 on the positively polarized carbonyl carbon. The end products arise via not isolated nor identified intermediates.

Roughly at the same time *Martin* and *Kagan*[56] put forward an alternative mechanism. Here a mutual effect is envisaged between SF_4 and the Lewis acid. $SF_3^{\oplus}$ or $F_3S^{\delta+}\ldots F\ldots^{\delta-}XF_n$ is assumed as the fluorinating agent.

The detailed investigations of *Dmowski* et al.[57–60] support the latter mechanism. They concluded, that the basicity of the carbonyl oxygen in carboxylic acid fluorides (the first fluorination step of RC(O)OH with SF_4) is correlated with the yield of the trifluorinated product. If the acid fluoride is a weaker base than SF_4, a complex or $SF_3^{\oplus}$ is formed; an increase in XF_n concentration does not lead to any notable increase in the transformation. This occurs in the case of electron withdrawing substituents, as for instance, α- or β-halogenated acid fluorides. However, if the acid fluoride is a stronger base than SF_4, as e.g. benzoyl fluoride, cyclopropanoyl fluoride, or α,β-unsaturated acid fluorides, the formation of mainly $RC(O)F \cdot XF_n$ takes place. In these cases work has to be conducted with an excess of the Lewis acid. An increase in the concentration leads with these substrates to a significant increase in the transformation. Weighty support for this mechanism was furnished by *Wielgat* and *Domagalla*[61], by the capture of α,α-difluorocations with mesitylene in the fluorination of mono- and dichloroacetic acid with SF_4 and also by the ^{19}F-NMR-spectroscopic evidence for the fluorocarbonium ions[62]. This mechanism also explains the repeated appearance of bis(difluoroalkyl)ethers in the fluorination of carboxylic acids with SF_4. The spectrum of the transformations of hydroxy-, aldehyde-, keto-, or carboxylic acid functions into the corresponding F-, CF_2H-, CF_2- or CF_3-compounds by SF_4 or its frequently employed amino-derivative diethylamino-sulfur trifluoride (DAST), Et_2NSF_3, is very widespread.

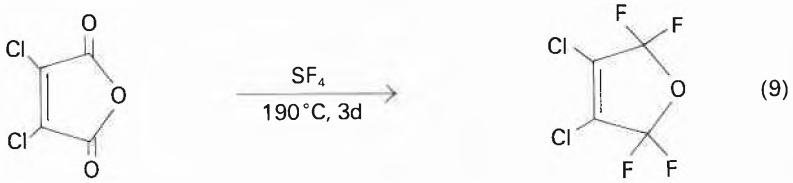
Thus, by the use of DAST[65] the synthesis of fluorinated steroids[63, 64, 66, 71] has succeeded as well as the preparation of α-fluoro-β-amino acids.

Remarkably versatile, too, is the use of DAST for the fluorination of carbohydrates[68], sugars[67, 69], and α-glycosides[70]. 4,4-Difluoro-retinoids[72], as well as 2-fluorobenzodiazepines[73] have also been prepared with the aid of DAST; the same applies to 4,4-difluoro-L-proline, from which fluorine containing peptides can be produced[74]. For the first time prepared were also fluorinated lactones by reacting γ-keto acids with DAST[75].



(8)

Quite abundant are the fluorination examples of oxygen containing heterocycles with SF_4; in this way have dichloromaleic acid anhydride[76] and derivatives of 2,5-dioxodioxane[78] been fluorinated.



(9)

Analogously the synthesis has been accomplished of CF_3-substituted derivatives of furan[77]. For the first time, too, the synthesis was reported of CF_2Cl-ethers by SF_4/HF fluorination in the presence of S_2Cl_2[79].

rated aldehydes; however, rearrangement into the α,β-unsaturated species is observed. Attempts to fluorinate these aldehydes with DAST failed or provided significantly lower yields than with SF_4.

5. Nitrogen Containing Fluorinating Agents

With the synthesis of 1-fluoro-2-pyridone an interesting new fluorinating agent is available[83] and it has been applied to the synthesis of various fluoroma-

$$CH_2Cl{-}CH_2{-}O{-}(CH_2)_2Cl \xrightarrow[55\,^\circ C]{SF_4/HF/S_2Cl_2} CF_2Cl{-}CHF{-}O{-}(CH_2)_2Cl$$
$$\xrightarrow[110\,^\circ C]{} CF_3{-}CHF{-}O{-}(CH_2)_2Cl$$
$$\xrightarrow[200\,^\circ C]{} CF_3{-}CHF{-}O{-}(CH_2)_2F \qquad (10)$$

Likewise for the first time succeeded the preparation of CF_3-*N*-substituted amines from tertiary formamides with SF_4/KF[80, 82].

$$R^1R^2N{-}CHO \xrightarrow{SF_4/KF} R^1R^2N{-}CF_3 \qquad (11)$$

The fluorination of α,β- and β-γ-unsaturated aldehydes has also been investigated and applied to cannabinoles[81].

For studying the influence relative to the position of double-bonds, 3-cyclohexenecarbaldehyde has been fluorinated with SF_4. HF-catalysed trimerisation of the aldehyde is avoided by using dried KF as an HF-abstractor whereby 4-difluoromethylcyclohexene is generated in 72% yield.

By observing the following reaction conditions, α,β-unsaturated aldehydes such as 1-cyclohexencarbaldehyde (see reaction scheme (12)) can also be fluorinated:

1. renunciation of solvents;
2. addition of excess KF;
3. application of stoichiometric threefold excess of SF_4 based on the aldehyde;
4. maintaining a reaction temperature of 20 °C for more than 48 h;
5. addition of steel balls or coils for good homogeneity;
6. removal of volatile compounds in vacuo followed by extraction of the residue with dried solvents and addition of 10% $NaHCO_3$-solution for destroying SF_4/HF-excess.

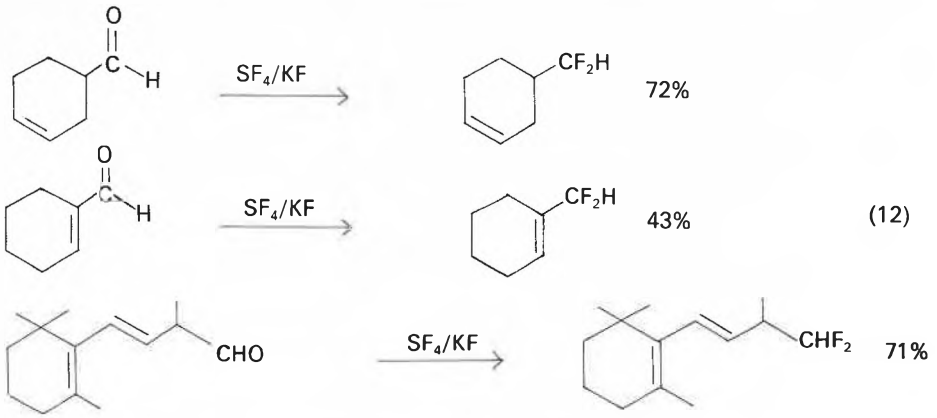
These reaction conditions can also be applied for the fluorination of β,γ-unsaturated aldehydes; however, rearrangement into the α,β-unsaturated species is observed. Attempts to fluorinate these aldehydes with DAST failed or provided significantly lower yields than with SF_4.

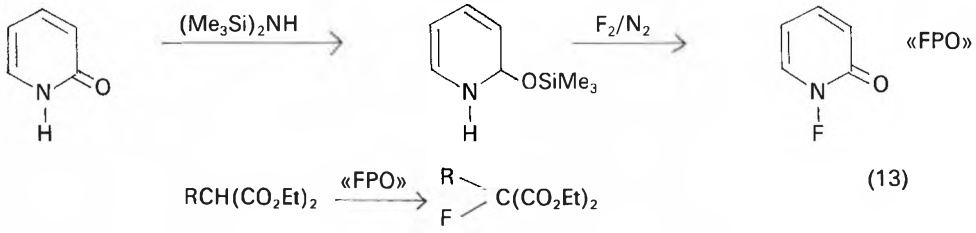
lonates. Likewise, reactions with Grignard reagents and *N*-morpholine-enamines (see reaction (13)) are known[85].

The preparation of a *N*-fluorosuccinimide[84] has been reported, however, fluorinations with this agent are not yet known. The fluorination properties of *N*-fluoro-*N*-alkylsulfonamides easily prepared by fluorination with F_2 and convenient to be dealt with[86] are already used.

Interesting new application examples of tetrabutylammonium fluoride are also presented. Alcoholic functional groups in sugars[86, 88] and steroids[87] have been fluoro-substituted in this way. The preparation of 2-desoxy-2-fluoro-D-glucose succeeds by fluorination with Me_4NF[89].

Halogen- and tosylate-substitution with Bu_4NF by an S_N2 mechanism has been described[90].

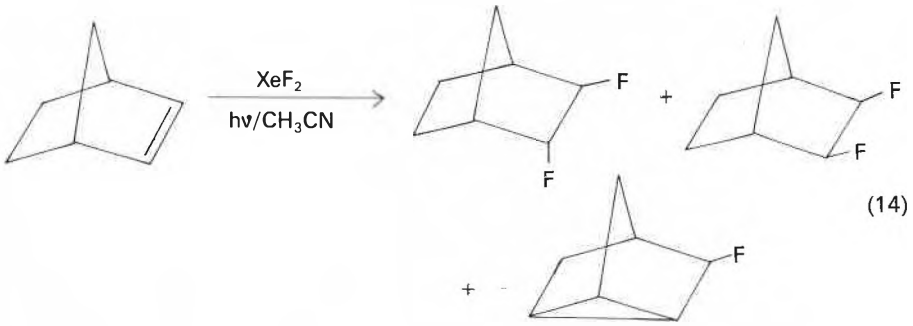




6. Inorganic Fluorinating Agents

Among the inorganic fluorinating agents xenon difluoride, XeF_2, is in the last years perhaps the most mentioned, and its diversity emphasized. New processes have been presented, like:

a) the photochemical addition to norbonene via a clear radical mechanism[91];



b) the fluorodecarboxylation with XeF_2 in the presence of HF[92] which is the first example described of the substitution by fluorine of a carboxylic acid functional group;

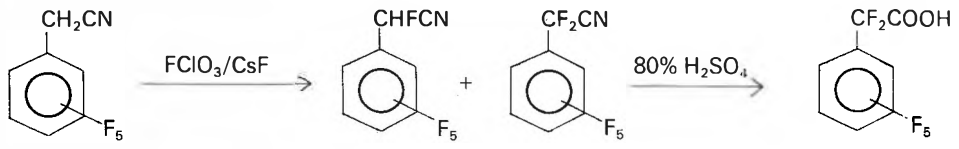
$$RCOOH \xrightarrow{XeF_2,\ HF} RF \qquad (15)$$

c) the partial fluorination of a methylthio-function[93], carried out on methionine.

$$CH_3S- \xrightarrow{XeF_2} FCH_2S- \qquad (16)$$

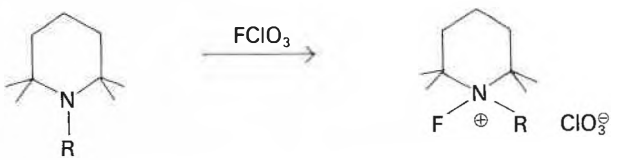
Likewise, fluorinations with XeF_2 of sugars in the presence of BF_3-ether[94,96], chlorine/fluorine replacement reactions[95], HF-catalyzed fluorinations of cyclic enol acetates[97] have been reported, as well as stereospecific additions to olefins[98].

Some Russian papers report fluorinations with «perchlorylfluorides», $FClO_3$. So the synthesis of heptafluorophenylacetic acid was accomplished by the reaction of pentafluorophenylacetonitrile with $FClO_3$/CsF followed by saponification of the nitrile[99] (see reaction (17)).



(17)

N-fluoro salts can be prepared by the treatment of 2,2,4,4,-tetramethyl-*N*-alkylpiperidines with $FClO_3$[100].



Interhalogen compounds have also been applied to fluorinations. Thus for the first time ClF_5 was used as a fluorinating agent for benzene and pyrimidines[101]. ClF is suitable for the synthesis of partially fluorinated ethers from esters[102].

$$RCO_2R' \xrightarrow{ClF,\ HF} RCF_2OR' \qquad (19)$$

$$R = ClCH_2;\ R' = Me,\ Et$$

Iodine monofluoride has been added to cyclohexene derivatives[103] just like IF and BrF to double bonds in steroids in a previous work[104]; analogously can phenyliodosodifluoride be used[110].

More novel examples can also be found for fluorinations with metal fluorides. Thus, by treatment with CoF_3 bromo-adamantanes were converted into the corresponding fluoro-analogs and adamantane itself into perfluoro-adamantane[105]. With CoF_3 pentafluoronitrobenzene and pentafluorobenzaldehyde can be turned into highly fluorinated aliphatic or olefinic species[106]. *N*-fluoro-imines or -amines are inter alia accessible from perfluorinated nitriles by treatment with AgF_2 or CoF_3[107].

$$R_fCN \xrightarrow[CoF_3]{AgF_2} R_fF + R_fCF_3 + R_fCF{=}NF + R_fCF_2{-}NF_2 \qquad (20)$$

α,α-Bis(difluoroamino)aldehydes are obtainable from 1-hydroxy-acetamidine hydrochloride by NaF/nickel fluorination[108].

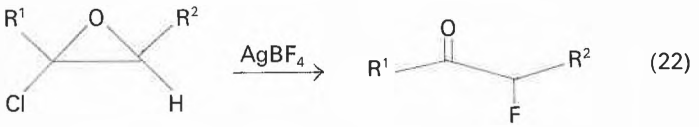
$$HOCH_2{-}\overset{\overset{NH}{\|}}{C}{-}NH_2 \cdot HCl \xrightarrow{NaF/Ni} FC(NF_2)_2R \qquad (21)$$

$$R = CHO,\ CH_2OH$$

An earlier work is to be mentioned here, too, which describes a *cis*-addition of F_2 to olefine steroids by the means of PbF_4[109].

Fluorinations were undertaken also with boron fluorides. Thus silver tetrafluoroborate reacts with chlorinated oxiranes

to furnish α-fluorocarbonyl compounds[114]; similar reactions were reported with α-bromo-aldehydes and -ketones[115].



(22)

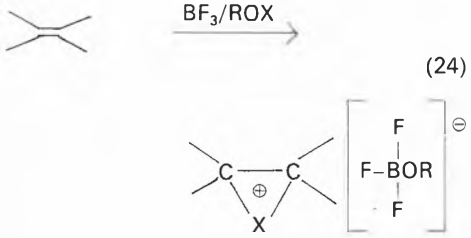
$R^1 = H, CH_3, t\text{-}C_4H_9, C_6H_5$
$R^2 = H, CH_3, C_2H_5, C_6H_5$

Additions of alkyl hypohalogenites in the presence of BF_3 result in α-fluorohalogenides[116],

(23)

X = Cl, Br

the formation of products here being explained mechanistically via a halogenium tetraborate ion pair.

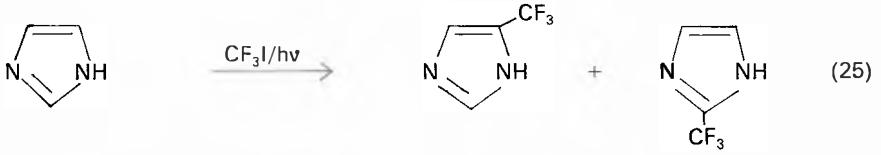


(24)

7. Introduction of CF_3- and CF_3S-Groups

7.1. CF_3-Substitution

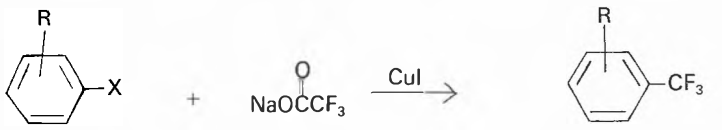
In the field of trifluoromethylation as well, new substitution processes have been put forward. CF_3-imidazols have been synthesized by the treatment with CF_3-radicals, that were produced by irradiation of CF_3I with γ- or UV-rays[117,118].



(25)

Analogously benzene derivatives were CF_3-substituted, but here the CF_3-radicals were produced by the addition of peroxides under heat[119].

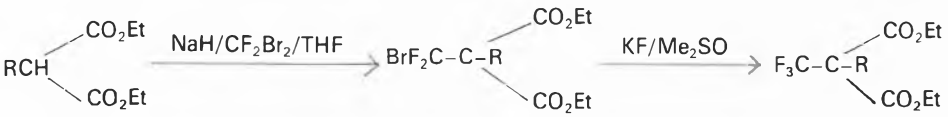
Similar compounds could be synthesized from halogenated (bromine, iodine) aromatics with sodium trifluoroacetate in the presence of copper(I) iodide – here *N*-methylpyrrolidone serves as a solvent[120].



(26)

X = Br, I

CF_3-substituted malonic esters are accessible by difluorobromine-methylation followed by halogen substitution[121].



(27)

7.2. CF_3S- and $ClCF_2$-Substitution

Also in the field of R_fS-substitution were new processes published, of which some start out from mercaptans or their salts.

Thus derivatives of benzene are producible by treatment of the respective thiolates with perhalogenohydrocarbons[122];

$$\text{Aryl-SK} + CF_3Br \rightarrow \text{Aryl-SCF}_3$$
$$\text{Aryl-SK} + CF_2ClBr \rightarrow \text{Aryl-SCF}_2Cl \quad (28)$$

however, here dithioacetates are formed in addition.

By the treatment of mercaptopyrimidines with perfluoroolefins R_fS-substituted 1,3-diazines are attainable[123].

Nucleophilic substitution of iodine atoms in aromatic systems is feasible through the use of Cu-perfluoroalkyl chalcogen salts. In this way were conceived $-SCF_3$-, $-SeCF_3$-, and $-SC_6F_5$-hexa-substituted benzenes[124] as well as pyrimidines[125].

For the first time were CF_3S-functional groups introduced through Wittig or Wittig-Horner reactions and thereby were pyretheroide derivatives synthesized[126].

In the same manner were fluoro(trifluoromethyl)aryl- and (trifluoromethyl)-diaryl-sulfonium salts initiated as trifluoromethylation agents for thiolates[127].

8. Conclusion and Outlook

General interest in preparative organofluorine chemistry has increased in recent years. Elemental fluorine emerges as an important direct or indirect fluorinating agent for organic synthesis. Successes with selectivity and improved yields have been reported, although in many cases these involve hypofluorite intermediates.

Even complicated molecules can be directly fluorinated; however it must be emphasized that a generally applicable procedure has not yet been reported, so that each problem must be solved individually.

Nevertheless, it can be stated, that elemental fluorine, which in former times has been a meer curiosity, now enjoys a certain degree of integrity as a synthetic species. Better selectivity and higher yields are the aims in developing new, mild fluorinating agents and for modifying methods of known ones.

With respect to commercial applications, in fields such as pharmaceuticals and agrochemicals, fluorine chemistry maintains its classical role. New application modes will undoubtedly unfold e.g. ^{18}F-marked biochemical tracers for medical purposes, so that, in future too, interesting results in organofluorine chemistry can be expected.

The authors thank Prof. N. Welcman for the English translation and Prof. Keith E. Peterman for helpful discussion.

Received: April 24, 1985 [FR 8]

[1] A. Haas, M.R.C. Gerstenberger, *Angew. Chem. 93* (1981) 659; *Angew. Chem. Int. Ed. Engl. 20* (1981) 647.
[2] D.H.R. Barton, *Pure Appl. Chem. 49* (1977) 1241.
[3] D.H.R. Barton, J. Lister-James, R.H. Hesse, M.P. Pechet, S. Rozen, *J. Chem. Soc. Perkin Trans. I* (1982) 1105.
[4] H. Vyplet, H. Berner, G. Schulz, *J. Fluorine Chem. 23* (1983) 482.

[5] W.T. Miller, J.D. Stoffer, G. Fuller, A.C. Currie, *J. Am. Chem. Soc. 86* (1964) 51.
[6] A. Yu. Yakubovich, S.M. Rozenshtein, V.A. Ginsberg, USSR-Pat. 162825, *Chem. Abstr. 62* (1965) 451.
[7] A. Yu. Yakubovich, S.M. Rozenshtein, V.A. Ginsberg, S.M. Smirnow, USSR-Pat. 165162, *Chem. Abstr. 62* (1965) 9018.
[8] R.F. Merritt, *J. Org. Chem. 31* (1966) 3871.
[9] R.F. Merritt, *J. Org. Chem. 32* (1967) 609.
[10] R.F. Merritt, T.E. Stevens, *J. Am. Chem. Soc. 88* (1966) 1822.
[11] S. Rozen, Y. Ben-Shushan, *Tetrahedron Lett. 25* (1984) 1947.
[12] T.B. Patrick, P.A. Flory, *J. Fluorine Chem. 25* (1984) 157.
[13] R.F. Merritt, *J. Org. Chem. 32* (1967) 4124.
[14] W.E. McEwen, A.P. Guzikowski, A.P. Wolf, *J. Fluorine Chem. 25* (1984) 169.
[15] D. Alker, D.H.R. Barton, R.H. Hesse, J.L. James, R.E. Markwell, M.M. Pechet, S. Rozen, T. Takeshita, H.T. Toh, *Nouv. J. Chim. 4* (1980) 239.
[16] S. Rozen, C. Gal, Y. Faust, *J. Am. Chem. Soc. 102* (1980) 6860.
[17] C. Gal, G. Ben-Shushan, S. Rozen, *Tetrahedron Lett. 21* (1980) 5067.
[18] T. Tsushima, K. Kawada, J. Nishikawa, T. Sato, K. Tori, T. Tsuji, S. Misaki, *J. Org. Chem. 49* (1984) 1163.
[19] C. Gal, S. Rozen, *Tetrahedron Lett. 25* (1984) 449.
[20] F. Cacace, P. Giacomello, A.P. Wolf, *J. Am. Chem. Soc. 102* (1980) 3511.
[21] J.L. Adcock, K. Horita, E.B. Renk, *J. Am. Chem. Soc. 103* (1981) 6937.
[22] J.L. Adcock, M.L. Robin, *J. Org. Chem. 48* (1983) 3128.
[23] J.L. Adcock, M.L. Robin, *J. Org. Chem. 48* (1983) 2437.
[24] J.L. Adcock, W.D. Evans, L. Heller-Grossman, *J. Org. Chem. 48* (1983) 4953.
[25] J.L. Adcock, W.D. Evans, *J. Org. Chem. 49* (1984) 2719.
[26] J.L. Adcock, M.L. Robin, *J. Org. Chem. 49* (1984) 1442.
[27] J.L. Adcock, M.L. Robin, *J. Org. Chem. 49* (1984) 191.
[28] J.L. Adcock, E.B. Renk, K. Horita, L.H. Grossman, M.L. Robin, Report 1984, Order No. AD-A139958, *Gov. Rep. Announce. Index U.S. 84* (1984) 66.
[29] J.L. Adcock, Report 1984, Order No. AD-A 139987, *Gov. Rep. Announce. Index U.S. 84* (1984) 66.
[30] E.H. Appelman, R.C. Thompson, *Chem. Eng. News 61* (1983) 18.
[31] V. Grakauskas, Am. Chem. Soc. 140. National Meeting, Chicago, Sept. 1961.
[32] V. Grakauskas, K. Baum, *J. Am. Chem. Soc. 91* (1969) 1679.
[33] R.A. Wiesboeck, J.K. Ruff, *Inorg. Chem. 4* (1965) 123.
[34] R.H. Hesse, *Isr. J. Chem. 17* (1978) 60.
[35] S. Rozen, O. Lerman, *J. Org. Chem. 45* (1980) 672.
[36] S. Rozen, O. Lerman, *J. Am. Chem. Soc. 101* (1979) 2782.
[37] S. Rozen, O. Lerman, *J. Org. Chem. 45* (1980) 4122.
[38] S. Rozen, Y. Menahem, *J. Fluorine Chem. 16* (1980) 19.
[39] S. Rozen, O. Lerman, M. Kol, *J. Am. Chem. Soc. Chem. Commun.* (1981) 443.
[40] O. Lerman, S. Rozen, *J. Org. Chem. 48* (1983) 724.
[41] L. Toscano, G. Fioriello, S. Silingardi, M. Inglesi, *Tetrahedron 40* (1984) 2177.
[42] O. Lerman, Y. Tor, D. Hebel, S. Rozen, *J. Org. Chem. 49* (1984) 806.
[43] G.W.M. Visser, B.W. Von Halteren, J.D.M. Herscheid, G.A. Brinkman, A. Hoekstra, *J. Chem. Soc. Chem. Commun.* (1984) 655.
[44] D.M. Jewett J.F. Porocki, R.E. Ehrenkaufer, *J. Fluorine Chem. 24* (1984) 477.
[45] W.J. Middleton, E.M. Bingham, *J. Am. Chem. Soc. 102* (1980) 4845.
[46] C.Y. Shine, A.P. Wolf, *J. Labelled Compds. Radiopharm. 18* (1981) 1059.
[47] S. Levy, E. Livini, D.R. Elmaleh, D.A. Varnum, G.L. Brownell, *Int. J. Appl. Radiat. Isot. 34* (1983) 1560.
[48] D.P. Ip, C.D. Arthur, R.E. Winans, E.H. Appelman, *J. Am. Chem. Soc. 103* (1981) 1964.
[49] S. Stavper, M. Zupan, *J. Chem. Soc. Chem. Commun.* (1981) 148.
[50] S. Stavper, M. Zupan, *J. Chem. Soc. Chem. Commun.* (1983) 563.
[51] E.H. Appelman, *Tetrahedron 40* (1984) 189.
[52] R.F. Merritt, J.K. Ruff, *J. Org. Chem. 30* (1965) 328.
[53] G. Bolte, A. Haas, *Chem. Ber. 117* (1984) 1982.
[54] A. Haas, *Chem.-Ztg. 106* (1982) 239.
[55] W.C. Smith, *Angew. Chem. 74* (1962) 742; *Angew. Chem. Int. Ed. Engl. 1* (1962) 467.
[56] D.G. Martin, F. Kagan, *J. Org. Chem. 27* (1962) 3164.
[57] W. Dmowski, W. Kolinski, *Pol. J. Chem. 47* (1973) 1211.
[58] W. Dmowski, W. Kolinski, *Pol. J. Chem. 48* (1974) 1697.
[59] W. Dmowski, W. Kolinski, *Pol. J. Chem. 52* (1978) 71.
[60] W. Dmowski, W. Kolinski, *Pol. J. Chem. 52* (1978) 547.
[61] J. Wielgat, Z. Domagalla, *J. Fluorine Chem. 20* (1982) 785.
[62] G.A. Olah, V.K. Mo, *Adv. Fluorine Chem. 7* (1973) 69.
[63] J.A. Allan, US-Pat. 4 416 822 (1984).
[64] T. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, *Chem. Pharm. Bull. 30* (1982) 3082.
[65] L. Somekh, A. Shanzer, *J. Am. Chem. Soc. 104* (1982) 5836.
[66] V.K. Ganti, Europ. Pat. Appl. EP 98 583 (1984).
[67] G.H. Klemm, R.H. Kaufman, R.S. Sidhu, *Tetrahedron Lett. 232* (1982) 2927.
[68] A.A. Penglis, *Adv. Carbohydr. Chem. Biochem. 38* (1981) 195.
[69] P.J. Card, *J. Org. Chem. 48* (1983) 393.
[70] P.J. Card, G.S. Reddy, *J. Org. Chem. 48* (1983) 4734.
[71] T.B. Kleine, G.D. Prestwich, *Tetrahedron Lett. 23* (1982) 3043.
[72] A.B. Barna, J.A. Olson, *J. Lipid Res. 25* (1984) 304.
[73] W.J. Middleton, E.M. Bingham, D.H. Smith, *J. Fluorine Chem. 23* (1983) 557.
[74] J.R. Sufrin, W. Korytnik, J.B. Lombardini, D.D. Keith, *Int. J. Pept. Protein Res. 20* (1982) 438.
[75] T.B. Patrick, Y.-F. Poon, *Tetrahedron Lett. 25* (1984) 1019.
[76] M.B. Bancom, US-Pat. 430 554 (1983).
[77] V.V. Lyalin, R.V. Grigorash, L.A. Alekseeva, L.M. Yagupolskii, *Zh. Org. Khim. 20* (1984) 846.
[78] N.N. Muratov, A.I. Burmakov, B.V. Kunshenko, L.A. Alekseeva, L.M. Yagupolskii, *Zh. Org. Khim. 18* (1982) 1403.
[79] N.N. Muratov, B.V. Kunshenko, A.I. Burmakov, L.A. Alekseeva, L.M. Yagupolskii, *Zh. Org. Khim. 20* (1984) 450.
[80] W. Dmowski, M. Kaminski, *J. Fluorine Chem. 23* (1983) 207.
[81] A. Haas, R. Plümer, A. Schiller, *Chem. Ber.*, in press (1985).
[82] W. Dmowski, M. Kaminski, *Pol. J. Chem. 56* (1982) 1369.
[83] S.T. Purrington, W.A. Jones, *J. Org. Chem. 48* (1983) 761.
[84] Ya.L. Yagupolskii, T.I. Savina, *Zh. Org. Khim. 17* (1981) 1330.
[85] S.T. Purrington, W.A. Jones, *J. Fluorine Chem. 26* (1984) 43.
[86] T.-L. Su, R.S. Klein, J.J. Fox, *J. Org. Chem. 46* (1981) 1790.
[87] T.G.C. Bird, G. Felsky, P.M. Fredericks, E.R.H. Jones, G.D. Meakins, *J. Chem. Res. (S)* (1979) 388.
[88] L. Hough, A.K.M.S. Kabir, A.C. Richardson, *Carbohydr. Res. 131* (1984) 335.
[89] T.J. Tewson, *J. Org. Chem. 48* (1983) 3507.
[90] D.Ph. Cox, J. Terpinski, W. Lawrynowicz, *J. Org. Chem. 49* (1984) 3216.
[91] R.A. Hildreth, M.L. Druelinger, S.A. Shackelford, *Tetrahedron Lett. 23* (1982) 1059.
[92] T.B. Patrick, K.K. Jokri, D.H. White, *J. Org. Chem. 48* (1983) 4159.
[93] A.F. Janzen, *J. Fluorine Chem. 22* (1983) 557.
[94] W. Korytnyk, S. Valentekovic-Horvath, C.R. Petri, *Tetrahedron 38* (1982) 2547.
[95] G. Papprott, D. Lentz, K. Seppelt, *Chem. Ber. 117* (1984) 1153.
[96] A.A. Penglis, *Adv. Carbohydr. Chem. Biochem. 38* (1981) 195.
[97] B. Zajc, M. Zupan, *J. Org. Chem. 47* (1982) 573.
[98] A. Gregorčič, M. Zupan, *J. Org. Chem. 49* (1984) 333.
[99] V.V. Burdin, G.G. Furin, G.G. Yakobson, *Zh. Org. Khim. 20* (1984) 567.
[100] I.V. Vigalak, G.G. Petrova, S.G. Lukashina, *Zh. Org. Khim. 19* (1983) 1347.
[101] M.M. Boudakian, G.A. Hyde, *J. Fluorine Chem. 25* (1984) 435.
[102] L.S. Boguslavskaya, *Zh. Org. Khim. 18* (1982) 222.
[103] S. Rozen, M. Brand, *Tetrahedron Lett. 21* (1980) 4538.
[104] A. Bowers, E. Denot, R. Becerra, *J. Am. Chem. Soc. 82* (1960) 4007.
[105] R. Moore, Brit. Pat. 2079273 (1983).
[106] G.S. Phull, R.G. Plevey, J.C. Tatlow, *J. Fluorine Chem. 25* (1984) 111.
[107] G.S. Phull, R.G. Plevey, J.C. Tatlow, *J. Chem. Soc. Perkin Trans. 1 3* (1984) 455.
[108] A.V. Fokin, *Izv. Akad. Nauk SSSR Ser. Khim.* (1982) 1438.
[109] A. Bowers, P.G. Holton, E. Denot, M.C. Loza, R. Urquiza, *J. Am. Chem. Soc. 84* (1962) 1050.
[110] P. Holton, A.D. Cross, A. Bowers, *Steroids* (1964) 71.
[111] K.G. Migliorese, E.H. Appelman, M.N. Tsangaris, *J. Am. Chem. Soc. 101* (1979) 1711.
[112] E.H. Appelman, R. Bonnett, B. Meteen, *Tetrahedron 33* (1977) 2119.
[113] M. Zupan, *Vestn. Slov. Kem. Drus. 31* (1984) 151.
[114] K. Griesbaum, H. Keul, R. Kibar, B. Pfeffer, M. Spraul, *Chem. Ber. 114* (1981) 1858.
[115] A.J. Fry, J. Migron, *Tetrahedron Lett. 20* (1979) 3357.
[116] V.L. Heasley, R.G. Gipe, J.L. Martin, H.C. Wiese, M.L. Oakes, D.F. Shellhammer, G.E. Heasley, B.L. Robinson, *J. Org. Chem. 48* (1983) 3195.
[117] H. Kimoto, S. Fujii, L.A. Cohen, *J. Org. Chem. 47* (1982) 2867.
[118] H. Kumoto, S. Fujii, L.A. Cohen, *J. Org. Chem. 49* (1984) 1060.
[119] L.A. Cohen, *J. Org. Chem. 47* (1982) 2867.
[120] K. Kondo, K. Matsui, E. Tobita, M. Ando, *Chem. Lett.* (1981) 1719.
[121] S.T. Purrington, *Tetrahedron Lett. 25* (1984) 1329.
[122] C. Wakselman, M.J. Tordeux, *J. Chem. Soc. Chem. Commun.* (1984) 12, 793.
[123] T.A. Dashevskaya, Yu. A. Fialkov, V.A. Khranovskii, V.M. Cherkasov, *Khim. Geterosikl. Soedin.* (1984) 402.
[124] N.V. Kontradenko, A.A. Kolomeitsev, V.I. Popov, L.M. Yagupolskii, *Zh. Org. Khim. 19* (1983) 2631.
[125] A. Haas, M. Lieb, unpublished results.
[126] R. Galli, L. Scaglioni, O. Palla, F. Gozzo, *Tetrahedron 40* (1984) 1523.
[127] L.M. Yagupolskii, N.V. Kontradenko, G.N. Timofeeva, *Zh. Org. Khim. 20* (1984) 115.
[128] Meanwhile $CH_3C(O)OF$ has been isolated and characterized: E.H. Appelman, personal communication.