

Synthesis of monofluorinated C₄-building blocks based on methallyl chloride

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Abstract

Halofluorination of methallyl chloride using *N*-halosuccinimides in combination with triethylamine trihydrofluoride (Et₃N·3HF) gave in each case more than 98% of the Markovnikov products and <2% of the regioisomers in good yield. The formal addition of methanesulfonyl fluoride with the combination of dimethyl(methylthio)sulfonium fluoroborate (DMTSF) and Et₃N·3HF gave a 94:6 mixture of both regioisomers. Only small phenylsulfenyl fluorination of methallyl chloride has been observed when treated with *N*-phenylthiophthalimide (NPTP) and Olah's reagent. With benzenesulfonyl chloride, 1,3-dichloro-2-methyl-2-(phenylthio)propane is formed which on treatment with Olah's reagent at 0 °C or with Et₃N·3HF at 60 °C rearranges to 1,2-dichloro-2-methyl-3-(phenylthio)propane. Treatment of 1,3-dichloro-2-methyl-2-(phenylthio)propane with silver fluoride in methylene chloride at -30 °C gave 1-chloro-2-fluoro-2-methyl-3-(phenylthio)propane which was also obtained by reaction of 1-bromo-3-chloro-2-fluoro-2-methylpropane with thiophenolate.

Chlorofluorination of methallylphenylthio ether using NCS/Et₃N·3HF failed, while corresponding reactions with NBS or NIS and Et₃N·3HF gave mainly the bromo- or iodo-fluorides with Markovnikov orientation in 61% or 35% yields. Related halofluorinations of methallylphenyl ether gave the halofluorides in good yield. All attempts to obtain chromanes or thiochromanes bearing a 3-fluorine substituent by cyclization of these halofluorinated ethers or thio ethers failed using different Lewis acids. However, the benzyl protected *o*-allylphenol which was bromofluorinated with NBS/Et₃N·3HF in good yield gave on catalytic hydrogenation over Pd/C the 3-fluoro-2*H*-chromane in nearly quantitative yield.

Keywords: Electrophilic addition; Halofluorination; Sulfonylfluorination; *N*-Halosuccinimides; Dimethyl(methylthio)sulfonium tetrafluoroborate; Triethylamine trihydrofluoride

1. Introduction

Monofluorinated organic compounds are important as biologically active substances or intermediates for syntheses [1]. However, the selective introduction of a single fluorine substituent into unsaturated compounds by addition of anhydrous hydrogen fluoride is usually difficult, e.g. because of rearrangement or oligomerization of the substrate; amine/HF complexes often have similar disadvantages or do not react at all with ethylenic compounds [2].

More advantageously, softer electrophiles than the proton, such as halonium ions, and sulfur or selenium cationic species, may be used in combination with fluoride donors. Several possibilities for halofluorinations [2,3], sulfonylfluorinations [4–6] or selenenylfluorinations [6–8] of alkenes or alkynes have been described.

From these additionally heterosubstituted organofluorides a lot of consecutive reactions can be made to produce useful fluorinated final products. On the other hand, it can be of some advantage to have several different potential leaving groups for further transformations. This can be realized, for example, using allyl-substituted alkenes as starting materials.

This work was designated to synthesize monofluorinated compounds using so-called 'three-components reactions' [9] (substrate, electrophile, nucleophile) based on methallyl chloride (**1**) and some related substituted compounds.

Principally, electrophilic three-component reactions with **1** are known to give mostly Markovnikov-oriented products. Depending on the electrophilic species used and the nucleophilic partner to some extent, anti-Markovnikov products and compounds are obtained arising by an addition–elimination mechanism (formal substitution). Thus, addition of hypochlorous acid gave mainly 1,3-dichloro-2-methylpropan-2-ol

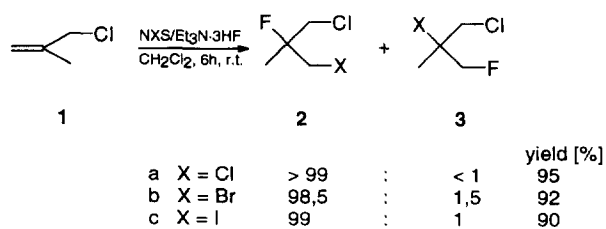
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and some 2,3-dichloro-2-methylpropan-1-ol with traces of unsaturated products, depending on the reaction conditions and the source of hypochlorous acid [10–12]. Analogously, hypobromous acid and hypoiodous acid yielded the corresponding halohydrins [10]. Bromoacetoxylation of **1** with NBS in acetic acid leads mainly to the Markovnikov product (80%) and two formal substitution products, 3-bromo-2-chloro-methylpropene and 3-bromo-1-chloro-2-methylpropene [13], while for the addition of 3,5-dinitrobenzenesulfonyl chloride in acetic acid the formation of the Markovnikov product was described as the sole product [14]. In contrast, by liquid-phase chlorination, significant amounts of 1,3-dichloro-2-methylenepropane and isomeric 1,3-dichloro-2-methylpropenes were formed by deprotonation of the intermediary cation in addition to the normal addition product [15].

2. Results

Combinations of electrophilic agents with triethylamine trifluorohydrofluoride ($\text{Et}_3\text{N} \cdot 3\text{HF}$) or Olah's reagent ($\text{py} \cdot 9\text{HF}$) create versatile methods for halofluorination [16–18], sulfonylfluorination [4,6] and selenenylfluorination [6,8] of unsaturated substrates.

Reactions of methallyl chloride (**1**) with *N*-halosuccinimides and $\text{Et}_3\text{N} \cdot 3\text{HF}$ in methylene chloride at room temperature gave the corresponding 2-fluoro-1-halo-2-methylpropanes **2** (Markovnikov orientation)¹ in good yield and with more than 98% regioselectivity [20], reflecting the better stabilization of the intermediary tertiary cationic species, while bromofluorination of allyl chloride with NBS/HF in tetrahydrofuran gave a 4:1 mixture of the regioisomers in 35% overall yield [21].

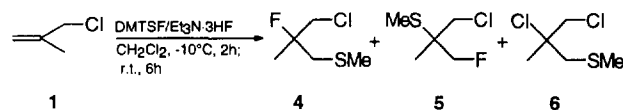


Formal substitution products like those formed in liquid-phase chlorination [15,22] or bromoacetoxylation [10] of **1** have not been observed in this work. This fact is in agreement with observations by Smit et al. [23] for reaction of **1** with nitronium tetrafluoroborate in liquid sulfur dioxide (–40

¹ 1,3-Dichloro-2-fluoro-2-methylpropane (**2a**) has already been synthesized in a mixture with 1,1-dichloro-2-fluoro-2-methylpropane, e.g. from 2-butene with $\text{SF}_4/\text{HF}/\text{Cl}_2$ (65% selectivity, 83% overall yield) [19a]; 1-bromo-3-chloro-2-fluoro-2-methylpropane (**2b**) has been synthesized by reaction of 1,2-bromo-3-chloro-2-methylpropane with chlorine monofluoride (88% yield) [19b] or with hexachloromelamine in liquid HF at –15 °C in 59% yield [19c] and in 37% yield by treatment of **1** with bromine trifluoride [19d].

°C) leading to 1-chloro-2-fluoro-2-methyl-3-nitropropane (60%), without traces of 2-chloromethyl-3-nitropropene.

The combination of DMTSF (Trost's reagent) and $\text{Et}_3\text{N} \cdot 3\text{HF}$ has been shown to be a versatile method for the addition of the elements of methanesulfonyl fluoride to alkenes [4]. Treatment of **1** using this combination of reagents at –10 °C in methylene chloride produced the regioisomers **4** and **5** in 94:6 ratio (^{19}F NMR) and 86% overall yield before separation. In addition, 5% of the dichloride **6** were isolated and another monofluoro compound (1%) and a difluorinated substance (6%) were also found by ^{19}F NMR spectroscopy.

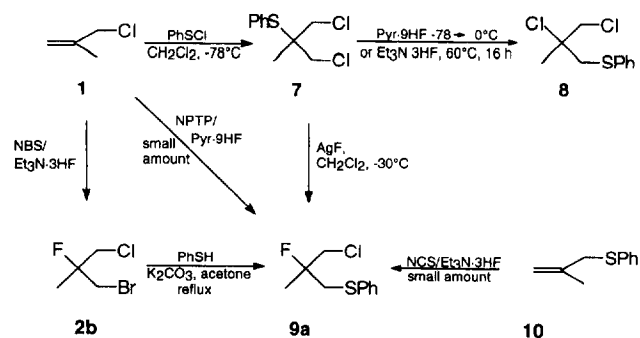


On the other hand, no benzenesulfonyl fluorination to form **9a** has been observed when **1** is treated with benzenesulfonyl chloride at room temperature in the presence of $\text{Et}_3\text{N} \cdot 3\text{HF}$, only a mixture of **7** and **8** being obtained. This behaviour may be attributed to the much stronger nucleophilic properties of chloride compared to fluoride in the amine/HF reagents. Even treatment of **1** with *N*-phenylthiophthalimide (NPTP)/Olah's reagent in methylene chloride at room temperature gave only small amounts (3%, GC) of **9a** and mainly **8** besides a significant amount of methallylphenylthio ether (**10**) and several other, unidentified compounds. The second chlorine atom in **8** can either originate from a second molecule of **1** or may be connected to the formation of **10** or from the solvent.

Reaction of **1** with benzenesulfonyl chloride in methylene chloride at –78 °C gave pure dichloride **7** (anti-Markovnikov product), which on addition of Olah's reagent at this temperature and allowing to warm up to room temperature or heating with $\text{Et}_3\text{N} \cdot 3\text{HF}$ for 16 h at 60 °C rearranges to the thermodynamically more stable Markovnikov product **8**². A sulfur-assisted chlorine–fluorine exchange which has been observed on treatment of other β -chloroalkylphenylthio ethers with $\text{Et}_3\text{N} \cdot 3\text{HF}$ at elevated temperature [25] was not realized with **7** (or **8**) and seems to be caused by the influence of the neighbouring chlorine substituent.

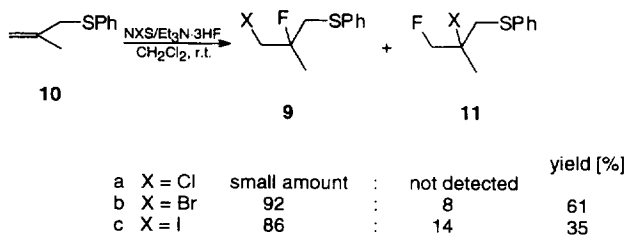
On the other hand, treatment of **7** with silver fluoride in methylene chloride at –30 °C and allowing to warm up to room temperature gave the substitution product **9a** as the main product with subsequent rearrangement of the anti-Markovnikov to the Markovnikov structure. Additionally, five other fluorinated compounds (total yield about 10%) were formed. More economically, **9a** was formed in 53% yield from **2b** by nucleophilic substitution on heating with thiophenol and potassium carbonate in acetone for 8 h.

² A mixture of **7** and **8** has been prepared already [24].

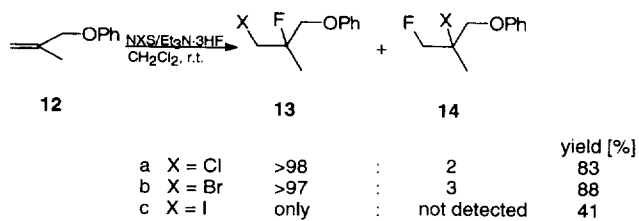


However, the yield was not good and we also tried to obtain **9a** by chlorofluorination of methallylphenylthio ether (**10**) which is available in 93% yield by reaction of thiophenol with **1** and potassium carbonate in acetone. However, treatment of **10** with NCS and $\text{Et}_3\text{N} \cdot 3\text{HF}$ gave a mixture of 10 compounds. The main component (40%, GC) of this mixture was the formal substitution product 2-chloromethyl-3-phenylthiopropene and only small quantities (6%, GC) of **9a** were detected by GC/MS-coupling experiments. This type of addition–elimination is known for other reactions of trisubstituted or terminally disubstituted alkenes with NCS [26] in the presence of even more nucleophilic partners than the fluoride ion in $\text{Et}_3\text{N} \cdot 3\text{HF}$, and is also known for chlorination of methallyl halides [27].

In contrast, bromofluorination with NBS and iodofluorination with NIS and $\text{Et}_3\text{N} \cdot 3\text{HF}$ gave the desired halofluorides **9b** and **9c** in quite good regioselectivity of 12:1 or 6:1, respectively (GC), with the regioisomers **11**, but with only moderate or low yields (61% or 35%).



Analogously, halofluorination of methallylphenyl ether (**12**) was successful with all of the three tested halosuccinimides giving the respective chloro- and bromofluorides **13** and **14** in good yield (83% or 88%) and with much better regioselectivity of 80:1 and 40:1. The reaction of **12** with NIS and $\text{Et}_3\text{N} \cdot 3\text{HF}$ gave **13c** in 41% yield; its regioisomer **14c** was not detected.

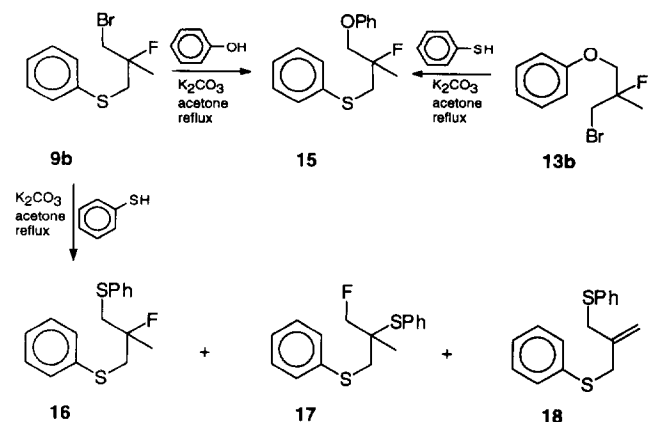


Next we tried to cyclize the thio ether **9a** and the ethers **13a** and **13b** under Lewis acid catalysis in analogy to the

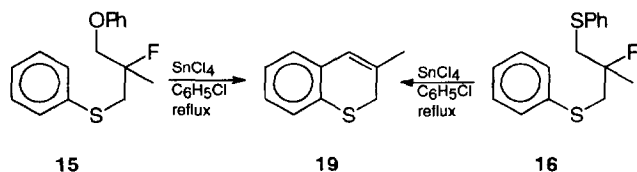
known [28] formation of chromane from 1-chloro-3-phenoxypropane with tin tetrachloride, to obtain chromanes or thiochromanes with a fluorine substituent in the 3-position. However, all attempts using catalytic amounts of antimony pentachloride, tin tetrachloride, zinc dichloride, boron trifluoride etherate or aluminium trichloride in different solvents like methylene chloride, chloroform, cyclohexane or chlorobenzene at different temperatures and high dilution showed no reaction with **13a** at room temperature and gave multicomponent mixtures with SnCl_4 or AlCl_3 at higher temperature. Compound **13b** did not react with AlCl_3 at room temperature, but showed mainly elimination of hydrogen fluoride and concomitant rearrangements at higher temperature. In cases of reaction of **13a** and **13b** with strong Lewis acids, oligomerization seems to be the main process. We never observed Friedel–Crafts-like cycloalkylations.

As an alternative, we used another method already known for the formation of chromane by cyclization of 1,3-diphenoxypropane with aluminium chloride [29]. In this context, we synthesized 2-fluoro-2-methyl-1-phenoxy-3-(phenylthio)propane (**15**) by heating **9b** with phenol in the presence of potassium carbonate, or with higher yield and better purity (because of the better selectivity in the synthesis of **13b** compared to **9b**) in 82% yield from **13b** by treatment with thiophenol under related conditions (only 2% of the regioisomer **14**, 5% of diphenyldisulfide and 4% of an unfluorinated, unidentified by-product were found in the crude mixture).

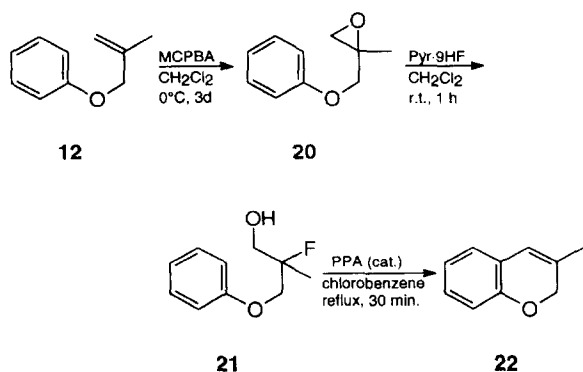
Reaction of **9b** with thiophenol under the same conditions was not so straightforward, giving a mixture of the desired bis-thioether **16** (40%), the regioisomer **17** (20%), the dehydrofluorination product **18** (20%) and 10% of unidentified by-products.



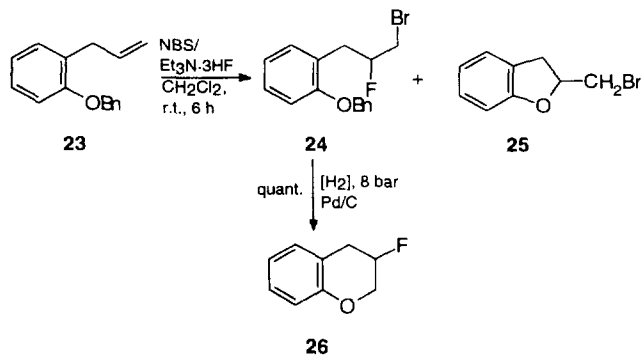
Treatment of **15** with SnCl_4 in hot chlorobenzene after 2 min gave 80% (GC) of 3-methyl-2*H*-thiochromene (**19**) [30] which was also formed, however, with <20% yield from the mixture of **16**–**18**. Other Lewis acids, such as ZnCl_2 , AlCl_3 , $\text{BF}_3 \cdot \text{OEt}_2$, or different solvents (methylene chloride, chloroform, cyclohexane) either gave mainly the HF-elimination product **19** or — at low temperature — usually no reaction occurred.



Among the methods described in the literature for the synthesis of chromanes is also the cyclization of 3-phenoxypropan-1-ols with polyphosphoric acid (PPA) [31]. We tried to use this method starting with the fluorinated alcohol **21**. First, the corresponding epoxide **20** [32] was formed in nearly quantitative yield from **12** by reaction with MCPBA in methylene chloride at 0 °C. Ring-opening of **20** using Olah's reagent [33] gave **21** with 86% yield without contamination with the other regioisomer. However, cyclization with catalytic amounts of PPA in chlorobenzene proceeded again with loss of hydrogen fluoride to give mainly 3-methyl-2*H*-chromene (**22**) (70%–80% depending on the conditions) and some by-products from which **22** [34] was separated by chromatography.



Finally, we succeeded in synthesizing 3-fluorochromane (**26**) starting with *o*-allylphenol. We protected the OH function with a benzylic group. Bromofluorination of the benzyl ether **23** with NBS/Et₃N·3HF in methylene chloride for 6 h gave the bromofluoride **24** (67% yield). In the crude product, 12% of the regioisomer of **24** and 14% (GC) of 2-bromo-methyl-benzofuran (**25**) were detected. Compound **25** was, as already known for other electrophilic additions to **23** [35], the sole product of treatment with NBS in CH₂Cl₂. Deprotection of **24** with 8 bar hydrogen over palladium on carbon gave a nearly quantitative yield of **26** by simultaneous cyclization.



3. Experimental details

All operations with Et₃N·3HF were carried out in usual glassware, while reactions with Olah's reagent were performed in polypropylene flasks. The experiments were undertaken under an efficient hood.

¹H (300 MHz) and ¹³C NMR spectra (75.5 MHz) were obtained using a Bruker WM-300 instrument with ca. 15% solutions in CDCl₃. Chemical shifts (δ) are reported in ppm using TMS for ¹H and CDCl₃ for ¹³C NMR as internal standards. ¹⁹F NMR spectra were obtained using a Bruker AC-200 (188 MHz) or a Bruker WP-80 (75 MHz) instrument with CFCl₃ as internal standard. GLC was performed on a Hewlett Packard 5890 II gas chromatograph with a 0.33 mm × 25 m quartz capillary column filled with 0.52 μm HP-1 employing nitrogen as the carrier gas. Mass spectra (70 eV) were obtained using GLC/MS-coupling with a Varian GC 3400/Varian Saturn IT (Ion Trap) instrument with an NIST data system. Elemental analyses were carried out by the Mikroanalytisches Laboratorium, Organische Chemie, Universität Münster. Thin layer chromatography was performed with Merck silica gel DC 60 F₂₅₄ plates and flash chromatography with Merck silica gel 60 with solvent mixtures of petroleum ether and ethyl acetate as specified for the special case in the procedures. All solvents were purified by distillation and stored over molecular sieves. CH₂Cl₂ was dried by distillation from P₂O₅ and stored over A4 molecular sieves (0.4 nm).

3.1. Halofluorination of methallyl chloride (**1**)

A mixture of 1.81 g (20 mmol) of methallyl chloride (**1**) and 10 ml (50 mmol) of Et₃N·3HF in 20 ml of CH₂Cl₂ was treated in portions with stirring with 22 mmol of the *N*-halosuccinimide at 0 °C and allowed to warm up to room temperature over 2 h. After continued stirring at this temperature for 16 h, the mixture was poured into 50 ml of ice water and neutralized with 28% aqueous ammonia. The organic layer was separated and the aqueous phase extracted three times with 30 ml of CH₂Cl₂. The combined organic extracts were washed with 0.1 N HCl and a 5% aq. solution of NaHCO₃ and dried over Na₂SO₄. After removal of the solvent, the residue was distilled or purified by column chromatography (silica gel, petroleum ether/ethyl acetate 50:1).

1,3-Dichloro-2-fluoro-2-methylpropane (**2a**) [19a]: Yield, 2.75 g (95%, crude product) (spectroscopic data, cf. Table 1).

1-Bromo-3-chloro-2-fluoro-2-methylpropane (**2b**) [19b, c,d]: Yield, 3.48 g (92%), b.p. 57 °C/12 mmHg (spectroscopic data, cf. Table 1).

1-Chloro-2-fluoro-3-iodo-2-methylpropane (**2c**): Yield, 4.21 g (90%, crude product) (spectroscopic data, cf. Table 1).

3.2. Reaction of methallyl chloride (**1**) with DMTSF/ $\text{Et}_3\text{N} \cdot 3\text{HF}$

To a solution of 3.92 g (20 mmol) of DMTSF and 8.5 ml (50 mmol) of $\text{Et}_3\text{N} \cdot 3\text{HF}$ in 20 ml of CH_2Cl_2 a solution of 1.81 g (20 mmol) of **1** in 10 ml of CH_2Cl_2 was added with stirring at -10°C . Stirring was continued for 2 h at this temperature and for an additional 6 h at room temperature. Then the reaction mixture was poured into 100 ml of ice water, neutralized with diluted NH_3 and after separation of the organic layer the aqueous phase was extracted three times with 30 ml portions of CH_2Cl_2 . The combined organic extracts were washed with water and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography (silica gel, petroleum ether/diethyl ether).

1-Chloro-2-fluoro-2-methyl-3-(methylthio)propane (**4**): Yield, 2.35 g (75%) (spectroscopic data, cf. Table 1).

1-Chloro-3-fluoro-2-methyl-2-(methylthio)propane (**5**): Yield, 131 mg (4%). ^1H NMR (300 MHz) δ : 1.63 (d, 2H, $^4J_{\text{HF}} = 2.0$ Hz); 2.11 (s, 3H, SCH_3); 3.80 (s, 2H, $-\text{CH}_2\text{Cl}$); 4.50 (dd, 2H, $^2J_{\text{HF}} = 47$ Hz, $-\text{CH}_2\text{F}$) ppm. ^{13}C NMR (75 MHz) δ : 18.1 (SCH_3); 25.5 ($^3J_{\text{CF}} = 3.0$ Hz, CH_3); 39.5 ($^2J_{\text{CF}} = 25.0$ Hz, Cq); 49.6 (CH_2Cl); 86.6 ($^1J_{\text{CF}} = 180.3$ Hz, CH_2F) ppm. ^{19}F NMR δ : -216.0 ($^2J_{\text{HF}} = 47$ Hz) ppm.

1,2-Dichloro-2-methyl-3-(methylthio)propane (**6**): Yield, 162 mg (5%). ^1H NMR (300 MHz) δ : 1.71 (s, 3H, $-\text{CH}_3$); 2.26 (s, 3H, $-\text{SCH}_3$); 3.03, 3.04 (AB, 2H, $-\text{CH}_2\text{S}$); 3.80, 3.95 (AB, 2H, $-\text{CH}_2\text{Cl}$) ppm. ^{13}C NMR (75 MHz) δ : 18.1 (SCH_3); 27.7 (CH_3); 45.3 (CH_2S); 51.6 (CH_2Cl); 71.23 (Cq) ppm.

3.3. Reaction of methallyl chloride (**1**) with benzenesulfonyl chloride

A solution of 1.81 g (20 mmol) of methallyl chloride (**1**) in 20 ml of CH_2Cl_2 was treated under stirring with 2.88 g (20 mmol) of benzenesulfonyl chloride at -78°C . After stirring at this temperature for 3 h, a 1 ml sample was taken and the solvent removed. The ^1H NMR spectrum showed pure **7**.

1,3-Dichloro-2-methyl-2-(phenylthio)propane (**7**) [24]: ^1H NMR (60 MHz) δ : 1.30 (s, 3H, CH_3); 3.70 (s, 4H, CH_2Cl); 7.47 (m, 5H, arom.) ppm.

3.3.1. 1,2-Dichloro-2-methyl-3-(phenylthio)propane (**8**) [24]

The remaining solution of **7** was treated with 1 ml of Olah's reagent at -78°C and stirred while allowing it to warm up to room temperature when it was stirred for 2 h at this temperature. The solvent was removed giving pure **8** after column chromatography (silica gel, petroleum ether/ether, 5:1). ^1H NMR (300 MHz) δ : 1.78 (s, 3H, CH_3); 3.46, 3.54 (AB, $J = 13.8$ Hz, $-\text{CH}_2\text{SPh}$); 3.82, 3.95 (AB, $J = 11.4$ Hz, $-\text{CH}_2\text{Cl}$); 7.30–7.45 (m, 3H, arom.); 7.55–7.60 (m, 2H, arom.) ppm. ^{13}C NMR (CDCl_3) δ : 27.7 (CH_3); 45.8 ($\text{CH}_2\text{-S}$); 51.9 ($\text{CH}_2\text{-Cl}$); 70.5 (Cq); 127.1 (*p*-C); 129.2 (*m*-C); 130.8 (*o*-C); 135.9 (*ipso*-C) ppm.

3.3.2. 1-Chloro-2-fluoro-2-methyl-3-(phenylthio)propane (**9a**)

Method A: By nucleophilic substitution of **2b**

A mixture of 1.9 g (10 mmol) of **2b**, 1.1 g (10 mmol) of thiophenol and 1.4 g (10 mmol) K_2CO_3 in 15 ml of acetone was refluxed for 8 h. After cooling, the mixture was poured into 50 ml of water and extracted three times with 25 ml of ether. The combined organic phases were extracted with 3 ml of 1 N NaOH and dried with Na_2CO_3 . Evaporation of the solvent gave 1.2 g (53%) of **9a**.

Method B: By nucleophilic substitution of **7**

A mixture of 1.17 g (5 mmol) of **7** in 20 ml of CH_2Cl_2 was treated with 1.92 g (15 mmol) of AgF at -30°C and stirred at this temperature for 3 h. After warm-up to room temperature, the precipitate was filtered off and the solvent removed giving 1.11 g (92%) of **9a** contaminated with about 5% of **8** (spectroscopic data, cf. Table 1).

3.4. Nucleophilic substitution of 1-bromo-2-fluoro-2-methyl-3-phenoxypropane (**13b**) with thiophenol

A mixture of 2.47 g (10 mmol) of **13b**, 1.1 g (10 mmol) of thiophenol and 1.40 g (10 mmol) of K_2CO_3 in 15 ml of acetone was refluxed for 8 h. After cooling, the mixture was poured into 50 ml of water and extracted three times with 25 ml of ether. The combined organic phases were extracted with 3 ml of 2 N NaOH and dried with Na_2CO_3 . Evaporation of the solvent gave 2.65 g (96%) of crude **15** contaminated (GC) with **14** (2%), diphenyldisulfide (5%) and an unidentified by-product (4%). Purification of the crude product by column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1) gave 2.25 g (82%) of pure **15**.

2-Fluoro-2-methyl-1-phenoxy-3-(phenylthio)propane (**15**): for spectral and analytical data, cf. Table 1.

3.5. Nucleophilic substitution of 1-bromo-2-fluoro-2-methyl-3-(phenylthio)propane (**9b**) with thiophenol

Using the procedure given above for the synthesis of **15** by reaction of **9b** with thiophenol, a mixture of 40% of **16** and 20% of **17** was obtained in addition to 20% of **18**. The mixture was not separated.

3.6. Synthesis of 3-methyl-2H-thiochromene (**19**)

Compound **15** (270 mg, 1 mmol) was added to a boiling solution of five drops of SnCl_4 in 10 ml of chlorobenzene. After 2 min, the solution was poured into 50 ml of water and neutralized with 2 N NaOH. The organic layer was separated and the aqueous phase extracted with 20 ml of CH_2Cl_2 . The combined extracts were washed with 1% HCl and 5% NaHCO_3 solutions, dried with Na_2SO_4 and the solvent removed in vacuum. The remaining crude yellowish residue (150 mg, 92%) did not show ^{19}F signals, but contained 80%

Table 1
Spectroscopic and analytical data for disubstituted 2-fluoro-2-methylpropanes^a

Compound	2a	2b	2c	4	Compound	13a	13b	–	–					
X=	Cl	Br	I	SMe	X=	Cl	Br	Br ^b	Br ^c					
¹⁹ F NMR	–151.4	–148.2	–143.5	–144.8	¹⁹ F NMR	–156.3	–152.9	–153.2	–152.5					
¹ H NMR	δ J	δ J	δ J	δ J	¹ H NMR	δ J	δ J	δ J	δ J	δ J	δ J	δ J	δ J	
CH ₃	1.54 21.4	1.55 21.0	1.63 21.0	1.52 21.4	CH ₃	1.65 21.5	1.60 21.5	1.65 21.5	1.68 21.2					
CH ₂ Cl	3.70 15.4	3.70 15.4	3.48 16.3	3.73 14.7	CH ₂ O	4.18	4.10	4.20	4.53					
CH ₂ X	3.70 15.4	3.57 14.5	3.75 14.2	2.85 17.9	CH ₂ X	3.87	3.66 15.7	3.73	3.74					
(SMe)	–	–	–	2.20	aryl	7.05	6.93	6.96	7.00					
						7.40	7.28	7.22	8.20					
								7.36	8.45					
MS (m/z)	156 (5%)				MS (m/z)	202 (39%)	246 (36%)	282 (47%)	n.d.					
¹³ C NMR	δ J	δ J	δ J	δ J	¹³ C NMR	δ J	δ J	δ J	δ J	δ J	δ J	δ J	δ J	
CH ₃	21.4 23.4	21.9 23.5	23.0 23.4	22.6 23.5	CH ₃	20.5 23.4	21.3 23.0	21.4 23.4	21.2 22.6					
CH ₂ Cl	46.7 29.3	47.3 28.1	48.7 29.0	48.3 29.7	CH ₂ O	89.8 27.9	70.3 28.0	71.4 29.4	71.7 28.7					
CH ₂ X	46.7 29.3	34.9 28.5	9.6 26.5	40.9 24.2	CH ₂ X	46.7 28.7	35.2 28.5	35.2 27.9	34.5 28.0					
(SMe)	–	–	–	17.5 2.2	CF	94.0 175.9	93.4 176.0	93.4 175.9	93.5 176.0					
CF	94.1 179.0	93.4 178.8	93.0 179.1	96.4 176.3	aryl	114.7	114.6	113.7 130.3	111.9 142.0					
					o	121.5	121.4	122.2 153.7	113.8 159.4					
					m	129.3	129.5	123.3	124.6					
					p	158.2	158.2	127.5	129.0					
					q									
Elemental analysis					C	H	C	H	C	H	C	H	C	H
Calc. (%)					59.26	5.97	48.61	4.89	42.66	3.94	32.37	2.72		
Found (%)					58.93	6.11	48.47	5.02	42.55	3.95	32.07	2.87		

^a δ in ppm; J in Hz.

^b 1-Bromo-3-(2-chlorophenoxy)-2-fluoro-2-methylpropane.

^c 1-Bromo-3-(2-bromo-4-nitrophenoxy)-2-fluoro-2-methylpropane.

of **19** [30]. MS *m/z*: 162 (M^+ , 61%); 161 ($M^+ - 1$, 50%); 147 ($M^+ - CH_3$, 100%); 128 ($M^+ - H_2S$, 11%). ¹H NMR (300 MHz) δ: 1.95 (s, 3H, –CH₃); 3.32 (s, 2H, CH₂–S); 6.24 (s, 1H, =CH–); 6.94–7.18 (m, 4H, arom.) ppm. {Lit. value [29]: ¹H NMR (CCl₄) δ: 1.90 (bs, 1H); 3.20 (bs, 2H); 6.18 (m, 1H); 6.8–7.2 (m, 4H) ppm.} ¹³C NMR (75 MHz) δ: 23.8 (q, –CH₃); 29.5 (t, –CH₂S–); 109.8 [s, =C(CH₃)–]; 120.4 (s, arom.); 124.2 (d); 125.4 (d); 126.4 (d); 126.9 (d); 127.2 (d); 132.9 (s) ppm.

3.7. Epoxidation of methallyl chloride (**1**)

Into a mixture of 8.0 g (35 mmol) of 75% *m*-chloroperbenzoic acid in 75 ml of CH₂Cl₂, a solution of 4.44 g (30 mmol) of **12** in 25 ml of CH₂Cl₂ was dropped under stirring at 0 °C. The mixture was allowed to warm up slowly to room

temperature and stirred for 3 d at 20 °C. Then 50 ml of 2 N NaOH were added in portions at 0 °C with vigorous stirring. The precipitated *m*-chlorobenzoic acid dissolved. The organic layer was separated and washed again with 2 N NaOH and water. After drying with MgSO₄, the solvent was removed yielding 4.85 g (99%) of **20** (99% purity, GC).

2,3-Epoxy-2-methyl-1-phenoxypropane (**20**) [32]: MS *m/z*: 164 (M^+ , 100%); 148 (3); 134 (22); 133 (13); 119 (8); 107 (25); 94 (80); 77 (26); 71 (25); 43 (20). ¹H NMR (300 MHz) δ: 1.48 (s, 3H, –CH₃); 2.72 (d, 1H, H-3); 2.84 (d, 1H, H-3); 3.96 (q, 2H, ³J = 11 Hz, H-1); 6.90–6.97 (m, 3H, arom.); 7.2–7.3 (m, 2H, arom.) ppm. ¹³C NMR (75 MHz) δ: 18.3 (q, –CH₃); 51.7 (t, C3); 55.3 (s, C1); 114.5 (d); 120.9 (d); 129.3 (d); 158.5 (s) ppm. Analysis: C₁₀H₁₂O₂ (164.2) requires: C, 73.15; H, 7.37%. Found: C, 73.43; H, 7.61%.



13c		15		21		Compound	9a		9b		9c	
I		SPh		OH		X =	Cl		Br		I	
-148.2		-150.0		-163.8		¹⁹ F NMR	-145.0		-141.6		-136.6	
δ	J	δ	J	δ	J	¹ H NMR	δ	J	δ	J	δ	J
1.64	21.5	1.54	21.8	1.45	21.0	CH ₃	1.60	21.4	1.55	21.2	1.59	22.5
4.12		4.05		4.08		CH ₂ S—	3.27	14.0 (<i>J</i> _{AB})	3.35	18.3	3.37	18.0
							3.35	15.0 (<i>J</i> _{HF})				
3.54	15.0	3.39		3.80	18.0	CH ₂ X	3.72	11.9 (<i>J</i> _{AB})	3.56	-3.64	3.65	-3.80
							3.75	15.0 (<i>J</i> _{HF})				
6.95				6.90		aryl	7.22	-7.55				
7.30				7.25								
294 (100%)		276 (77%)		184 (19%)		MS (<i>m/z</i>)	218		262		310	
δ	J	δ	J	δ	J	¹³ C NMR	δ	J	δ	J	δ	J
22.5	23.4	21.9	24.4	19.2	18.8	CH ₃	22.7	23.3	23.3	23.3	24.2	23.4
71.2	27.9	70.9	27.2	69.7	24.4	CH ₂ S—	41.2	24.9	41.9	25.1	42.8	24.9
9.2	26.4	40.5	24.9	65.7	20.1	CH ₂ X	48.6	28.6	37.1	28.3	11.7	27.2
92.8	176.6	95.4	175.1	95.8	173.4	CF	94.5	178.2	94.7	178.2	94.3	174.0
114.7		114.5	126.4	114.6		aryl <i>o</i>	126.9		126.7		126.7	
120.7		121.2	128.9	121.3		<i>m</i>	129.2		129.0		128.9	
129.4		129.3	129.8	129.4		<i>p</i>	130.2		130.2		130.2	
158.2		158.2	136.1	158.4		<i>q</i>	136.0		135.7		135.6	
C	H	C	H	C	H		C	H	C	H	C	H
40.84	4.11	69.53	6.20	65.20	7.11		54.91	5.63	45.63	4.60	38.72	3.90
40.63	4.20	69.58	6.41	64.94	7.24		54.91	5.24	45.51	4.58	38.68	3.96

3.7.1. 2-Fluoro-2-methyl-3-phenoxypropan-1-ol (**21**)

In a polypropylene Erlenmeyer flask, 2 ml (75 mmol) of Olah's reagent were added to a solution of 1.7 g (10 mmol) of **20** in 25 ml of CH₂Cl₂ with stirring at 0 °C. After continuous stirring for 45 min at 0 °C, the mixture was poured into 50 ml of ice water and neutralized with 2 N NaOH. The organic layer was separated and the aqueous layer extracted with 25 ml of CH₂Cl₂. The combined extracts were washed with 2 N NH₃ solution, 1% HCl and 5% NaHCO₃ solution. After drying with MgSO₄, the solvent was removed giving 1.8 g (98%) of crude **21** (86% purity, GC) (spectroscopic and analytical data, cf. Table 1).

3.7.2. 3-Methyl-2H-chromene (**22**) [34]

To a boiling solution consisting of 0.5 g of polyphosphoric acid in 40 ml of chlorobenzene was added 368 mg (2 mmol) of **21** and the mixture refluxed for 30 min. After cooling, 10

ml of 2 N HCl were added, the organic layer separated and washed with 25 ml of 2 N NaOH and water. Drying and distillation of the solvent gave 280 mg (95%) of crude **22** (about 75% purity). Pure **22** was obtained by column chromatography (silica gel, petroleum ether). MS *m/z*: 146 (*M*⁺, 68%); 145 (*M*⁺ - 1, 75%); 131 (*M*⁺ - 15, 100%); 115 (*M*⁺ - 31, 26%). ¹H NMR (300 MHz) δ: 1.7 (s, 3H, -CH₃); 4.60 (s, 2H, -CH₂O-); 6.07 (s, 1H, =CH-); 6.5–6.8 (m, 4H, arom.) ppm (in agreement with data in Ref. [34]).

3.8. Synthesis of 3-fluorochromane (**26**) via 2-(3'-bromo-2'-fluoropropyl)phenylbenzyl ether (**24**)

A mixture consisting of 5.36 g (40 mmol) of 2-allylphenylbenzyl ether (**23**) and 16.1 g (100 mmol) of Et₃N·3HF in

40 ml of methylene chloride was treated in portions under stirring with 7.83 g (44 mmol) of NBS at 0 °C and allowed to warm up to room temperature during 2 h. After continued stirring at this temperature for 6 h, the mixture was poured into 100 ml of ice water and neutralized with 28% aqueous ammonia. The organic layer was separated and the aqueous phase extracted three times with 50 ml of CH₂Cl₂. The combined organic extracts were washed with 0.1 N HCl and a 5% aq. solution of NaHCO₃ and dried over Na₂SO₄. Removal of the solvent gave a mixture of compounds involving **24** (62%) and **25** (14%) as the main components. In addition, two other bromofluorinated compounds (regioisomers of **24**) were found in GC/MS coupling experiments, but could not be isolated. Distillation of the crude mixture gave in the first fraction mainly the benzofuran **25**, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 50:1) and shown to be identical with that prepared according to a literature procedure [36]. The main fraction contained mainly the bromofluoride **24** (82%) and its isomer (5%) and 6% of **25**. Compound **24** was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 50:1).

2-(3'-Bromo-2'-fluoropropyl)phenylbenzyl ether (**24**): B.p. 60 °C/0.01 mmHg. MS *m/z*: 322/324 (M⁺, 7%); 302/304 (M⁺ – HF, 0.2%); 243 (M⁺ – Br, 0.1%); 224 (M⁺ – Br – HF, 0.7%); 197 (0.3%); 195 (0.3%); 181 (0.3%); 178 (0.3%); 165 (0.4%); 152 (2%); 133 (1%); 131 (1.5%); 109 (1%); 107 (1%); 91 (100%). ¹H NMR (300 MHz) δ: 3.15 (dd, ³J_{HF} = 21 Hz, 2H, –CH₂Br); 3.45 (dm, ³J_{HF} = 20 Hz, 2H, –CH₂–CHF); 4.95 (dm, ²J_{HF} = 54 Hz, 1H, –CHF); 5.05 (s, 2H, –CH₂–O); 6.95 (m, 2H, arom.); 7.25 (m, 2H, arom.); 7.35 (m, 5H, arom.) ppm. ¹³C NMR (75 MHz) δ: 34.0 (C-1', ²J_{CF} = 23 Hz); 34.7 (C-3', ²J_{CF} = 22 Hz); 70.1 (–CH₂O–); 91.0 (–CHF–, ¹J_{CF} = 177 Hz); 111.8, 121.0, 124.4 (C–CH₂CHF); 127.3, 127.5, 128.3, 128.7, 128.9, 129.0, 131.8, 136.9 (C–CH₂–O); 156.6 (C–O–CH₂) ppm.

2-(3'-Bromo-2'-fluoropropyl)phenylbenzyl ether (**24**) (3.22 g, 10 mmol) was dissolved in 80 ml of methanol. 350 mg palladium on carbon (10%) were added and the mixture stirred under 8 bar hydrogen pressure for 24 h. The catalyst was separated and washed twice with small portions of methanol. The solvent and by-products were removed giving 3-fluorochromane (**26**) almost quantitatively. Yield: 1.5 g (99%, crude). ¹H NMR (300 MHz) δ: 3.0–3.2 (m, 2H, –CH₂–); 4.1 (dd, 1H, ³J_{HF} = 30 Hz, H_{2a}); 4.3 (m, 1H, –CH₂O–); 5.08 (dm, ²J_{HF} = 47.5 Hz, –CHF); 6.83 (m, 2H, arom.); 7.1 (m, 2H, arom.) ppm. ¹³C NMR (75 MHz) δ: 30.9 (dd, ²J_{CF} = 18 Hz, C-4); 67.2 (dd, ²J_{CF} = 18 Hz, C-2); 84.4 (dd, ¹J_{CF} = 175.2 Hz, C-3); 116.0 (dd, ⁴J_{CF} = C-5); 118.4 (s, C-4a); 121.5 (d, C-8); 128.0 (d); 130.2 (d, C-6 and C-7); 153.8 (s, C-8a) ppm. ¹⁹F NMR δ: –186.5 ppm.

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References

- [1] J.F. Liebmann, A. Greenberg and W.R. Dolbier, Jr. (eds.), *Fluorine-containing Molecules*, VCH Publishers Inc., New York, 1988; J.T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; R. Filler, K. Kobayashi and L.M. Yagupolskii (eds.), *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, 1993.
- [2] G.A. Olah and X.-Y. Li, in G.A. Olah, R.D. Chambers and G.K.S. Prakash (eds.), *Synthetic Fluorine Chemistry*, Wiley, New York, 1992, p. 163.
- [3] N. Yoneda, *Tetrahedron*, 47 (1991) 5329; J.A. Wilkinson, *Chem. Rev.*, 92 (1992) 505.
- [4] G. Haufe, G. Alvernhe, D. Anker, A. Laurent and C. Saluzzo, *J. Org. Chem.*, 57 (1992) 714.
- [5] A.S. Gybin, W.A. Smit, M.Z. Krimer, N.S. Zefirov, L.A. Novgorodtseva and N.K. Sadovaya, *Tetrahedron*, 36 (1980) 1361; S.T. Purrington and I.D. Correa, *J. Org. Chem.*, 51 (1986) 1080.
- [6] C. Saluzzo, A.M. La Spina, D. Picq, G. Alvernhe, D. Anker, D. Wolf and G. Haufe, *Bull. Soc. Chim. Fr.*, 131 (1994) 831.
- [7] K.C. Nicolaou, N.A. Petasis and D.A. Claremon, *Tetrahedron*, 41 (1985) 4835; C. Saluzzo, G. Alvernhe, D. Anker and G. Haufe, *Tetrahedron Lett.*, 31 (1990) 663; C. Saluzzo, G. Alvernhe, D. Anker and G. Haufe, *Tetrahedron Lett.*, 31 (1990) 2127.
- [8] S. Tomoda and Y. Usuki, *Chem. Lett.*, (1989) 1235; J.R. McCarthy, D.P. Matthews and C.L. Barney, *Tetrahedron Lett.*, 31 (1990) 973; K. Uneyama and M. Kanai, *Tetrahedron Lett.*, 31 (1990) 3583; Y. Usuki, M. Iwaoka and S. Tomoda, *Chem. Lett.*, (1992) 1507; H. Poleschner, M. Heydenreich, K. Spindler and G. Haufe, *Synthesis*, (1994) 1043.
- [9] G. Beger, *J. Prakt. Chem.*, 333 (1991) 677.
- [10] C.D. Hurd and J.L. Abernethy, *J. Am. Chem. Soc.*, 63 (1941) 976.
- [11] P. Ballinger and P.B.D. de la Mare, *J. Chem. Soc.*, (1957), 1481, and refs. cited therein.
- [12] M. Mühlstädt, K. Schulze and G. Winkler, *J. Prakt. Chem.*, 317 (1975) 166.
- [13] I.V. Bodrikov and S.V. Spiridonova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Technol.*, 21 (1988) 1088.
- [14] V.G. Collin, U. Jahnke, G. Just, G. Lorenz, W. Pritzkow, M. Rolling, L. Winguth, P. Dietrich, C.E. Döring, H.-G. Hauthal and A. Wiedenhöft, *J. Prakt. Chem.*, 311 (1969) 238.
- [15] L.F. Hatch, J.J. Russ and L.B. Gordon, *J. Am. Chem. Soc.*, 69 (1947) 2614; K. Schulze, S. Hartmann, H. Krüger, M. Mühlstädt, C. Richter and H. Richter, *J. Prakt. Chem.*, 326 (1984) 433.
- [16] G.A. Olah, J.T. Welch, Y.D. Vankar, M. Nojima, I. Kerekes and J.A. Olah, *J. Org. Chem.*, 44 (1979) 3872.
- [17] A. Gregoric and M. Zupan, *J. Org. Chem.*, 49 (1984) 333.
- [18] G. Alvernhe, A. Laurent and G. Haufe, *Synthesis*, (1987) 562.
- [19] (a) B.V. Kumshenko, Yu.A. Ostanin and L.M. Yagupolskii, *Zh. Org. Khim.*, 29 (1993) 1927; (b) L.S. Boguslavskaya, N.N. Chuvatkin, I.Y. Panteleeva and L.A. Ternovskoi, *Zh. Org. Khim.*, 18 (1982) 938; (c) N.N. Chuvatkin and L.S. Boguslavskaya, *Zh. Org. Khim.*, 19 (1983) 1107; (d) L.S. Boguslavskaya, N.N. Chuvatkin, A.V. Kartashov and L.A. Ternovskoi, *Zh. Org. Khim.*, 23 (1987) 262.
- [20] Presented in part at the 13th Int. Symp. Fluorine Chem., Bochum, 1991, cf. G. Haufe, K. Schulze and G. Alvernhe, *J. Fluorine Chem.*, 54 (1991) 264, and at the 14th Int. Symp. Fluorine Chem., Yokohama, 1994, cf. U. Weßel, D. Wolf, C. Saluzzo, G. Alvernhe and G. Haufe, Abstracts of papers, p. 218.
- [21] W.R. Dolbier, Jr., T.A. Grey, J.J. Keaffaber, L. Celewicz and H. Koronijak, *J. Am. Chem. Soc.*, 112 (1990) 363.

- [22] I.V. Bodrikov and Z.S. Smolyan, *Usp. Khim.*, 35 (1966) 853.
- [23] A.G. Talybov, U.G. Mursakulov, M.M. Gusejnov and V.A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1982) 654.
- [24] B. Giese and P. Mazumdar, *Chem. Ber.*, 114 (1981) 2859.
- [25] C. Saluzzo, G. Alvernhe, D. Anker and G. Haufe, *J. Fluorine Chem.*, 47 (1990) 467.
- [26] K. Schulze, G. Haufe and G. Köhler, *Z. Chem.*, 29 (1989) 167.
- [27] I.V. Bodrikov, S.V. Spiridonova, Z.S. Smolyan and A.I. Subbotin, *Zh. Org. Khim.*, 6 (1970) 684.
- [28] P. Maitte, *Ann. Chim.*, 9 (1954) 433.
- [29] L.W. Deady, R.D. Topsom and J. Vaughan, *J. Chem. Soc.*, (1963) 2094.
- [30] B.D. Tilak, H.S. Desai, C.V. Deshpande, S.K. Jain and V.M. Vaidya, *Tetrahedron*, 22 (1966) 7; A.G. Hortmann, R.L. Harris and J.A. Miles, *J. Am. Chem. Soc.*, 96 (1974) 6199.
- [31] I.J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G.J. Williams, *J. Org. Chem.*, 31 (1966) 3032.
- [32] G.A. Gartman, V.I. Proshutinskii, A.Y. Chervinskii, P.G. Neifeld and G.G. Kudymov, *Zh. Strukt. Khim.*, 31 (1990) 133.
- [33] G.A. Olah and D. Meidar, *Isr. J. Chem.*, 17 (1978) 148; G. Alvernhe, A. Laurent and G. Haufe, *J. Fluorine Chem.*, 34 (1986) 147; H. Suga, T. Hamatani and M. Schlosser, *Tetrahedron*, 46 (1990) 4247; J. Umezawa, O. Takahashi, K. Furuhashi and H. Nohira, *Tetrahedron Asymm.*, 4 (1993) 2053; A. Sattler and G. Haufe, *J. Fluorine Chem.*, 69 (1994) 185.
- [34] E.E. Schweizer, A.T. Wehmann and D. Meeder Nycz, *J. Org. Chem.*, 38 (1973) 1583.
- [35] M. Mühlstädt, Ch. Schubert and E. Kleinpeter, *J. Prakt. Chem.*, 327 (1985), 270, and refs. cited therein.
- [36] R. Adams and R.E. Rindfusz, *J. Am. Chem. Soc.*, 41 (1919) 648.