Abstract:

Title: PROCESS FOR THE MANUFACTURE OF FLUORINATED COMPOUNDS

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(54) Title: PROCESS FOR THE MANUFACTURE OF FLUORINATED COMPOUNDS

(57) Abstract: A process for the manufacture of a fluorinated organic compound of formula R-F wherein R is an organic residue, which comprises reacting a starting material of general formula R-X wherein X is a leaving group with SO₂F₂. Addition of an amine/hydrofluoride complex enhances the reaction speed.
Process for the manufacture of fluorinated compounds

The present invention which claims benefit of US provisional patent application number 60/910295 filed on April 5th, 2007 the complete content of which is incorporated herein by reference, concerns a process for the manufacture of fluorinated organic compounds, especially enantiopure fluorinated organic compounds. Organic fluorinated compounds are useful inter alia as pharmaceuticals, agrochemicals and building blocks thereof.

The patent application WO 96/13474 discloses the reaction of a hydroxyaliphate with perfluorobutanesulphonyl fluoride or perfluoroocotanesulphonyl fluoride in the presence of an organic base in an inert organic solvent. The fluorination reagent used is highly expensive.

It was desirable to have available a fluorination method which allows for economical production notably of high value added pharmaceutical compounds or intermediates. It was particularly desirable to have available a fluorination method which allows for efficient manufacture of optically active fluorinated organic compounds having high enantiomeric purity.

The invention concerns in consequence a process for the manufacture of a fluorinated organic compound of formula R-F wherein R is an organic residue, which comprises reacting a starting material of general formula R-X wherein X is a leaving group, with SO$_2$F$_2$.

In the process according to the invention, the leaving group X is preferably a hydroxy group.

The process of the present invention is suited especially to substitute a fluorine atom for a leaving group in compounds wherein the respective C atom (to which the leaving group is bound) is sp$^3$ hybridized.

Starting compounds suitable for use in the process of the present invention are preferably compounds with a primary or secondary leaving group X. A suitable class of such compounds can be represented by the general formula R$^1$R$^2$CH-X. R$^1$ and R$^2$ are independently selected from the group consisting of branched or linear aliphatic groups, alicyclic groups, araliphatic groups, aromatic groups, hydrogen, branched or linear fluoroaliphatic groups, fluoroaraliphatic groups, and fluoroaromatic groups. Preferably, R$^1$ and R$^2$ stand for branched or linear aliphatic groups, alicyclic groups, araliphatic groups, branched or linear
fluoroaliphatic groups, or fluoroaraliphatic groups. These groups may contain
catenary (in-chain) hetero atoms (such as oxygen, nitrogen, or sulfur) and/or one,
two or even more olefinic double bonds. Any fluorosubstituted moieties or
compounds may be partially or perfluorinated. The groups R¹ and R² can be
substituted by hetero atoms such as oxygen, nitrogen or sulfur. The may also be
substituted by one or more substituents of the general formula O-Z wherein Z is,
for example, a hydrogen atom, an alkyl group or a protecting group, for example,
a benzoyl group. The groups R¹ and R² may form a ring which can contain
catenary hetero atoms (such as oxygen, nitrogen, or sulfur) and/or one, two or
even more olefinic double bonds.

X preferably stands for the OH group. The process according to the
invention can for example be carried out with primary or secondary alcohols.
These can be, for example, carbinols or polyols.

For example, the process of the present invention can be applied using the
compounds as disclosed in US-A 6,248,829 which is incorporated herein by
reference. In these compounds, a hydroxy group is substituted by a fluorine
atom. Especially, referral is made to those compounds disclosed in that US
patent in column 4, line 5 to column 5, line 18 which can be reacted according to
the process of the present invention.

According to a preferred embodiment, the process of the present invention
is applied to prepare fluoro compounds from respective compounds containing at
least one hydroxy group and at least one keto or ester group. Preferably, the
starting compound has the general formula R³-C(O)OR⁴ wherein R³ is a Cl to
C25 aliphatic hydrocarbaryl group which contains at least one hydroxyl group,
and, optionally, one, two or more olefinic double bonds. Preferably, R³ is a Cl to
C⁵ aliphatic hydrocarbaryl group substituted by at least one hydroxy group.
Especially preferably, R³ is a Cl to C3 group substituted by one hydroxy group.
R⁴ is preferably a Cl to C5, especially preferably a Cl to C3, aliphatic
hydrocarbaryl group. For example, the methyl ester, ethyl ester and i- or n-propyl
esters of lactic acid can be applied as starting compound and are reacted to form
the respective ester compounds comprising a fluorine atom on the carbon atom
adjacent to the keto group.

In another preferred embodiment, the starting compounds are selected from
the group generally known as carbohydrates or "sugars", and the product can be
named "fluorosugar". The starting compound, for example, can be a
monosaccharide, a disaccharide, an oligosaccharide or a polysaccharide. It may
be an aldose or ketose. It may be a triose, tetrose, pentose, hexose or be based on a group with an even higher number of carbon atoms. Often, a part of the hydroxy groups of the "sugar" is alkylated (e.g. with a methyl or ethyl group) and/or substituted by a protective group, for example, the benzoyl group. This enables to substitute only the desired hydroxy group or groups by a fluorine atom according to the present invention. The introduction of protective groups, for example, the benzoyl group, is generally known to the expert.

In a particularly advantageous embodiment of the process according to the invention, the leaving group X is attached to a stereogenic centre and the starting material R-X is enantiomerically pure. It has been found that in this embodiment optically active fluorinated organic compounds having high enantiomeric purity can be obtained. Examples of starting material comprising the leaving group X attached to a stereogenic center are the lactic acid esters and the compounds of the sugar group mentioned above. Of course, if desired, racemic mixtures may be converted into the respective racemic fluorinated compounds, if desired.

In the process according to the invention the reaction temperature is generally from about 0°C to about 150°C, preferably from about 10°C to about 100°C and more preferably from about 20°C to about 80°C.

In the process according to the invention, the reaction pressure is generally from about 1 to about 30 bars, preferably from about 2 to about 20 bars and more preferably from about 3 to about 10 bars. The reaction pressure can be adjusted by pressurizing with gaseous SO₂F₂.

In the process according to the invention, excess SO₂F₂ can be recovered from the reaction medium and recycled to subsequent runs. For example, a gaseous stream containing SO₂F₂ can be withdrawn from the reaction medium, at least SO₂F₂ is liquefied under pressure and the fraction obtained can be introduced into the reaction.

In the process according to the invention, the reaction can be carried out in a solvent. Organic aprotic solvents such as acetonitrile are suitable. Other suitable solvents are, for example, aromatic hydrocarbons, for example, toluene, benzene, xylene, anisol, aliphatic hydrocarbons or mixtures thereof, for example, hexane, ethers, for example, diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, diglyme, halogenated ethers, for example, heptafluoropropyl ethyl ether, heptafluoropropyl methyl ether, 2-(trifluoromethyl)hexafluoropropyl methyl ether, 2-(trifluoromethyl)hexafluoropropyl ethyl ether, esters, for
example, acetic acid ethyl ester, halogenated hydrocarbons, for example, dichloromethane or perfluorohydrocarbons, for example, perfluorohexane, and sulfolane. A solvent is especially advantageous if any of the reactants or additives (especially the amine/hydrofluoride complex) is solid and/or has a low solubility or even is insoluble in the reaction mixture.

In the process according to the invention, the reaction time can be adjusted to achieve the desired conversion and is typically from about 1 hour to about 20 hours in a batch process. In a continuous process the appropriate residence time should be adjusted.

In the process according to the invention, the reaction is suitably carried out in the presence of a base. Those bases are especially suitable which are aprotic. The base must enable the formation of the sulfate ester in the first step of the reaction, but it must not be so basic that an undesired split of HF would occur. Often, bases are very suitable which have a have a \( \text{pK}_a \) which is equal to or greater than 9.5, especially equal to or greater than 10. For example, the base can be an organic amine, preferably a tertiary amine. A trialkylamine is particularly suitable. Preferably, the alkyl groups are the same or different and are preferably selected from aliphatic saturated C1 to C4 groups. The alkyl groups are preferably selected from methyl, ethyl, propyl and butyl. In this case, the amine is preferably selected from triethylamine and tributylamine. Other suitable amines are, for example, tri-n-propylamine, tri-i-propyl amine, and i-propyl-diethyl amine. Other strong amine bases with a \( \text{pK}_a \) equal to or greater than 12, especially guanidines, for example, N,N,N',N',N"-pentamethyl guanidine, and 1,5-diaza-bicyclo[4.3.0]non-5-ene ("DBN") and 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU").

When a base is used, the molar ratio of the base to the starting material is generally equal to or greater than about 1 preferably equal to or greater than about 1.05 and more preferably equal to or greater than about 1.1. In the process according to the invention the molar ratio of the base to the starting material is generally equal to or less than about 10. Preferably, it is equal to or less than about 5. More preferably, it is equal to or less than 3.5. It can especially preferably be equal to or less than about 2.

In a particular embodiment, which has given good results the process according to the invention is carried out in the substantial absence of hydrogen fluoride. In particular, this embodiment can be carried out without addition of hydrogen fluoride to the reactants.
In another embodiment, the reaction is carried out in the presence of an amine/hydrogen fluoride complex. In this embodiment the amine is often as described herein before.

In this embodiment, the molar ratio hydrogen fluoride/amine is often from about 0.1 to about 3 and preferably from about 0.5 to about 1.5.

If an amine/hydrofluoride complex and an amine base is added to the reaction mixture, the amine of the amine base and the amine in the amine/hydrofluoride complex may be different, but preferably are the same.

If desired, the amine/hydrofluoride complex can be prepared before it is added to the starting material or introduced into a reactor, for example, simply by adding HF to the amine or by adding amine to the HF in the desired molar ratio. Alternatively or additionally, the amine/hydrofluoride complex can be prepared in situ in the reactor. For example, amine can be added, and HF is then introduced. This can be done before any starting material or solvent is introduced into the reactor, and/or during or after any starting material or solvent is introduced into the reactor.

In a preferred embodiment, the amine/hydrofluoride complex is added to before starting the reaction and/or after the reaction was started.

The process according to the invention is particularly suitable when the starting material is ethyl lactate and the fluorinated organic compound is 2-fluoropropionic acid ethyl ester. More particularly, good results have been obtained when the starting material is (L)-ethyl lactate and the fluorinated organic compound is (R)-2-fluoropropionic acid ethyl ester.

The process is also very suitable when the starting material is a disaccharide or a derivative thereof, for example, a derivative some of the hydroxy groups of which are alkylated (preferably, by methyl, ethyl or propyl) and/or protected by protective groups, e.g. protected by benzoyl groups or acetyl groups. A preferred group of starting compounds are discarharides of pentoses and/ hexoses. For example, methyl glucopyranoside is a suitable starting material. A very preferred starting compound is methyl 2,3,6-O-benzoyl-α-D-galactopyranoside, and the fluorinated organic compound is 4-deoxy-4-fluoro-methyl 2,3,6-O-benzoyl-α-D-galactopyranoside. These compounds are intermediates for the preparation of fluorosugar derivatives of antibiotic macrolides suitable to treat, for example, fungal infections. This is described in WO 93/18049. This international patent application also gives examples of many other fluorosugars which can be prepared according to the present invention.
Of course, the expert knows that he will not apply starting compounds, solvents or other constituents in the reaction mixture which react with sulfuryl fluoride and/or the amine/hydrofluoride complex (if the latter is present) in an undesired manner. Compounds interfering in an undesirable manner can easily be found out by performing initially small scale test reactions to check the basic suitability of the compounds involved.

The inventors have found out that the presence of an amine/HF complex is not mandatory in the process of the present invention. But often, the presence of amine/hydrofluoride complexes improves the yield or reaction speed allowing the reaction to be performed at lower temperatures. Whereas the presence of an amine/hydrofluoride complex is very advantageous in the process of the present invention as described above, it can also advantageously be applied in processes where a fluorinated organic sulfonyl fluoride is applied as fluorinating agent instead of (or additionally to) sulfuryl fluoride.

Accordingly, an aspect of the present invention is a process for the manufacture of a fluorinated organic compound of formula R-F wherein R is an organic residue, which comprises reacting a starting material of general formula R-X, wherein X is a leaving group, with a fluorinated organic sulfonyl fluoride or SO₂F₂ in the presence of an added amine/hydrofluoride complex. In this aspect of the invention, preferred embodiments correspond to those given above.

X is preferably a hydroxy group. Thus, the presence of an amine/hydrofluoride is especially advantageous if the hydroxy group of organic compounds (wherein the hydroxy group is preferably attached to an sp³ hybridized carbon atom) is substituted by fluorine when the starting compound is reacted with at least one fluorinated, saturated aliphatic or alicyclic sulfonyl fluoride; preferably in the presence of a strong organic base. Also here, those bases are especially suitable which are aprotic and enable the formation of the sulfate ester in the first step, but it must not be so basic that an undesired split of HF would occur. Also in this embodiment, bases which have a $p_K_a$ which is equal to or greater than 9.5, preferably equal to or greater than 10, are especially suitable. Concrete examples for suitable bases are given above. Trialkyl amines, for example, tripropylamine, and especially triethyl amine and tributyl amine, are very suitable. Generally, a useful class of such sulfonyl fluorides can be represented by the general formula R₃SO₂F. Here, R₃ is selected from the group consisting of perfluorinated alkyl groups having from 1 to about 10 carbon atoms (this group is the preferred one); partially fluorinated alkyl groups having from 1
to about 10 carbon atoms; unsubstituted or perfluoralkyl substituted,
perfluorinated cycloalkyl groups having from 4 to 8 carbon atoms; and
unsubstituted or perfluoralkyl substituted, partially fluorinated cycloalkyl groups
having from 4 to 8 carbon atoms. Representative examples of suitable sulfonyl
fluorides are given in US-A 6,248,889, which is incorporated herein in its
entirety, in column 3, especially lines 16 to 34. Perfluorobutane sulfonyl
fluoride, perfluorohexane sulfonyl fluoride, perfluorooctane sulfonyl fluoride
and their mixtures are highly preferred. These compounds are commercially
available, or they can prepared for example by electrochemical fluorination of
the respective sulfonyl fluorides, as, for example, is described in US-A 6,248,889
in column 3, lines 1 to 34.

In this aspect of the invention, the amine/hydrofluoride complex can be
added before the reaction is started, and/or after the reaction has started. The
preferred composition of the complex is given above, the molar ratio of
amine/hydrofluoride complex to starting compound is preferably equal to or
greater than 0.1, more preferably equal to or greater than 0.5, especially
preferably equal to or greater than 1. It is preferably equal to or lower than 3.

It is a further advantage that the process of the present invention can be
performed with trialkyl amines as base which are cheap and not as basic as very
strong bases. According to the state of the art, only very strong bases (pK_a equal
to or greater than 12), for example, DBN, DBU or guanidines, were considered
to be suitable bases.

Examples
The examples hereafter illustrate the invention without however limiting
its scope.

Examples 1 to 8: Reactions with amine*HF complex and SO_2F_2
In a 100 ml autoclave, (L)-ethyl lactate was mixed with different quantities
of different ammonium hydrogen fluorides. The quantities were adjusted in that
way that 70 % of the reactor volumes were used. Afterwards, SO_2F_2 was
introduced and stirred for definite reaction times at RT. Samples were taken by
time and were analyzed by GC. All data are summarized in the following table 1:
<table>
<thead>
<tr>
<th>No</th>
<th>amine</th>
<th>Amine quantity (eq)</th>
<th>Ratio HF/amine</th>
<th>Solvent Type</th>
<th>Pressure $\text{SO}_2\text{F}_2$ (bar)</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>selectivity (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEA</td>
<td>3.8</td>
<td>1.0</td>
<td>MeCN b</td>
<td>5</td>
<td>20</td>
<td>99.5</td>
<td>99.5</td>
<td>99.0</td>
</tr>
<tr>
<td>2</td>
<td>TEA</td>
<td>3.8</td>
<td>1.0</td>
<td>MeCN b</td>
<td>5</td>
<td>1</td>
<td>99.5</td>
<td>99.7</td>
<td>99.2</td>
</tr>
<tr>
<td>3</td>
<td>TBA</td>
<td>2.0</td>
<td>1.5</td>
<td>-</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>97.8</td>
<td>97.8</td>
</tr>
<tr>
<td>4</td>
<td>TBA</td>
<td>2.0</td>
<td>1.5</td>
<td>-</td>
<td>1</td>
<td>20</td>
<td>99.0</td>
<td>98.0</td>
<td>97.0</td>
</tr>
<tr>
<td>5</td>
<td>TBA</td>
<td>1.9</td>
<td>1.5</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>91.6</td>
<td>99.3</td>
<td>91.0</td>
</tr>
<tr>
<td>6</td>
<td>TBA</td>
<td>1.3</td>
<td>1.3</td>
<td>-</td>
<td>4</td>
<td>3</td>
<td>68.7</td>
<td>99.7</td>
<td>68.5</td>
</tr>
<tr>
<td>7</td>
<td>TBA</td>
<td>2.0</td>
<td>1.5</td>
<td>-</td>
<td>4</td>
<td>20</td>
<td>89.8</td>
<td>100.0</td>
<td>89.8</td>
</tr>
<tr>
<td>8a</td>
<td>TBA</td>
<td>2.0</td>
<td>1.5</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>32.2</td>
<td>100</td>
<td>32.2</td>
</tr>
</tbody>
</table>

a at 65 °C, b 3ml/mmol, c ee determined: 98.5 %, TEA: triethylamine, TBA: tributylamine
Examples 9 and 10: Reactions only with amine and SO$_2$F$_2$

In a 100 ml autoclave, (L)-ethyl lactate was mixed with different quantities of tributylamine. The quantities were adjusted in that way that 70 % of the reactor volumes were used. Afterwards, SO$_2$F$_2$ was introduced and stirred for definite reaction times at 65 °C. Samples were taken by time and were analyzed by GC. All data are summarized in the following table 2:

<table>
<thead>
<tr>
<th>No</th>
<th>amine</th>
<th>Amine quantity (eq.)</th>
<th>Solvent Type</th>
<th>Pressure SO$_2$F$_2$ (bar)</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>selectivity (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>TBA</td>
<td>1.9</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>95.0</td>
<td>100</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>TBA</td>
<td>1.1</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>94.4</td>
<td>100</td>
<td>94.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Reaction No 10 was performed two times. With the combined reaction mixtures, a work up was performed. The product was isolated by simple vacuum distillation of the crude reaction mixture after degassing in 90 % recovery yield and 95 % purity.

Examples 11 to 13: Synthesis of methyl 4-deoxy-4-fluoro-2,3,6-O-benzoyl-α-D-galactopyranoside (4FTBGP") from methyl 2,3,6-O-benzoyl-α-D-galactopyranoside ("TBGP")

General procedure: 4.04 g (7.98 mmol, 1.0 eq.) of TBGP, triethyl amine, 50 ml of the solvent and - if applied - the amine/HF complex were charged into an autoclave. The reaction temperature was adjusted to 60 °C and 4 bars of sulfuryl chloride were then injected. The sulfuryl fluoride pressure was maintained during all the reaction time. After cooling the reaction mixture back to room temperature (RT), the excess of sulfuryl fluoride was released and the reaction mixture was poured into 50 ml of water and 40 ml of diethyl ether. The aqueous layer was extracted with 2 times 20 ml of diethyl ether, and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude reaction product was then analyzed by LC-MS. Data are compiled in the following table 3:
The data of table 3 demonstrate that the reaction between the modified carbohydrate compound (certainly a complex molecule) and sulfuryl fluoride can be performed in the absence of the amine/hydrofluoride complex, but that the added complex drastically improves the yield.

Further tests have shown that triethyl amine is far superior to pyridine or imidazole under the conditions of examples 11 to 13.

<table>
<thead>
<tr>
<th>No</th>
<th>Amine quantity</th>
<th>Amine/HF complex</th>
<th>Solvent</th>
<th>Pressure SO$_2$F$_2$</th>
<th>Recovered solid mass</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(eq.)</td>
<td>(eq.)</td>
<td>Type</td>
<td>(bar)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>11</td>
<td>1.1</td>
<td>--</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>86</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>3.0</td>
<td>Net$_3$·3HF</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.35 eq.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>3.0</td>
<td>Net$_3$·3HF</td>
<td>CH$_3$CN</td>
<td>4</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.42 eq.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CL A I M S

1 - A process for the manufacture of a fluorinated organic compound of formula R-F wherein R is an organic residue, which comprises reacting a starting material of general formula R-X wherein X is a leaving group with SO₂F₂.

2 - The process according to claim 1, wherein the reaction is carried out in the presence of a base.

3 - The process according to claim 2, wherein the base is an organic amine.

4 - The process according to claim 3, wherein the organic amine is a tertiary amine.

5 - The process according to claim 4, wherein the tertiary amine is a trialkylamine, preferably selected from triethylamine and tributylamine.

6 - The process according to anyone of claims 2 to 5, wherein the molar ratio of the base to the starting material is from about 1 to about 10, preferably from about 1.05 to about 5 and more preferably from about 1.1 to about 2.

7 - The process according to claim 1, wherein the reaction is carried out in the presence of an amine/hydrogen fluoride complex.

8 - The process according to claim 7 wherein the amine is as described in anyone of claims 3 to 5.

9 - The process according to claims 7 or 8 wherein the molar ratio hydrogen fluoride/amine is from about 0.1 to about 3 and preferably from about 0.5 to about 1.5.

10 - The process according to any one of claims 1 to 9, wherein the reaction temperature is from about 0°C to about 150°C, preferably from about 10°C to about 100°C and more preferably from about 20°C to about 80°C.

11 - The process according to any one of claims 1 to 10 wherein the reaction pressure is from about 1 to about 30 bars, preferably from about 2 to about 20 bars and more preferably from about 3 to about 10 bars.
12 - The process according to claim 11 wherein the reaction pressure is adjusted by pressurizing with gaseous SO₂F₂.

13 - The process according to anyone of claims 1 to 12 wherein the leaving group X is a hydroxy group.

14 - The process according to anyone of claims 1 to 13 wherein the leaving group X is attached to a stereogenic centre and the starting material R-X is enantiomerically pure.

15 - The process according to anyone of claims 1 to 13 wherein the starting material is ethyl lactate and the fluorinated organic compound is 2-fluoropropionic acid ethyl ester, or wherein the starting material is methyl 2,3,6-O-benzoyl-α-D-galactopyranoside and the fluorinated compound is methyl 4-deoxy-4-fluoro-2,3,6-O-benzoyl-α-D-galactopyranoside.

16 - The process according claim 15 wherein the starting material is (L)-ethyl lactate and the fluorinated organic compound is (R)-2-fluoropropionic acid ethyl ester.

17. - A process for the manufacture of a fluorinated organic compound of formula R-F wherein R is an organic residue, which comprises reacting a starting material of general formula R-X wherein X is a leaving group with a fluorinated organic sulfonyl fluoride or SO₂F₂ in the presence of an added amine/hydrofluoride complex.
A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC:

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched:

Electronic data base consulted during the international search (name of data base and, where practical, search terms used):

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| X        | DATABASE WPI Week 200668  
Thomson Scientific, London, GB; AN  
2006-659829  
XP002492576  
-WO 2006/098444 A (CENTRAL GLASS CO LTD)  
21 September 2006 (2006-09-21)  
abstract | 1-17 |
claims 1,2; example 3 | 1-17 |

D. Further documents are listed in the continuation of Box C. See patent family annex.

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search: 19 August 2008

Date of mailing of the international search report: 28/08/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer: Kleidernigg, O l iver
<table>
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<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
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