Title: PROCESS FOR THE PREPARATION OF BENZOIC ACID DERIVATIVES VIA A NEW INTERMEDIATE OF SYNTHESIS

Abstract: The object of the invention is the preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid and derivatives thereof, by nitration of 2-chloro-4-fluorobenzotrichloride and the conversion of the novel synthetic intermediate thus obtained into its acid form or derivatives thereof; a further object of the invention is the conversion of benzotrichloride synthetic intermediates into the corresponding benzotrifluoride derivatives.
“Process for the preparation of benzoic acid derivatives via a new intermediate of synthesis”

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FIELD OF THE INVENTION
The subject-matter of the present invention is the preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid and derivatives thereof, including the acyl chloride thereof and a novel synthetic intermediate. In particular, the subject-matter of the invention is a process for the preparation of the above-mentioned derivatives by nitration of 2-chloro-4-fluorobenzotrichloride and the transformation of the novel synthetic intermediate thus obtained into the acid and derivatives thereof, including the corresponding acyl chloride, or by a process comprising the nitration and simultaneous hydrolysis of said 2-chloro-4-fluorobenzotrichloride. A subject of the invention is likewise the transformation of the benzotrichloride synthetic intermediates into the corresponding benzotrifluoride derivatives.

TECHNICAL BACKGROUND
2-chloro-4-fluoro-5-nitrobenzoic acid is a known product. Its preparation is described in the literature, solely by nitration of 2-chloro-4-fluorobenzoic acid, just as reported, for example, in WO87/07602, EP0863142 and WO01/83459.

The reaction described has considerable drawbacks, including the fact that the starting product, 2-chloro-4-fluorobenzoic acid is a solid, and hence not so easily handled compared to a liquid compound at room temperature. Furthermore, its nitration requires significant volumes of sulfuric acid and, by no means least, nitration of 2-chloro-4-fluorobenzoic acid leads to the production of considerable amounts of impurities, such as unwanted by-products.

SUMMARY OF THE INVENTION
The aim of the present invention is to provide an alternative synthetic process for 2-chloro-4-fluoro-5-nitrobenzoic acid and derivatives thereof including the acyl chloride, by a novel and original preparation process, with respect to the nitration process described in the aforementioned references, furthermore obviating the drawbacks of said nitration.
Indeed, it has now been found that it is possible to prepare 2-chloro-4-fluoro-5-nitrobenzoic acid by nitration, not of the corresponding non-nitrated acid, but of 2-chloro-4-fluorobenzotrichloride, the reaction proceeding via 2-chloro-4-fluoro-5-nitrobenzotrichloride, a novel and versatile reaction intermediate which is easily converted into the desired acid or the acyl chloride thereof or into other possible compounds.

**DETAILED DESCRIPTION OF THE INVENTION**

Hence, according to one aspect thereof, the object of the present invention relates to a process for the preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid and derivatives thereof, of formula (I):

\[
\begin{align*}
\text{R} & \quad \text{Cl} \\
\text{O}_2\text{N} & \quad \text{F}
\end{align*}
\]

wherein
- R is a -COOH, -COOR’, -CO-Hal, -CONR’”R’”, -COSR’” or -CN group,
- Hal represents a halogen atom,
- R’ represents a linear or branched alkyl, alkenyl or alkynyl group; an optionally substituted aryl group;
- R’” and R’”” represent, independently, a hydrogen atom; a linear or branched alkyl, alkenyl or alkynyl group; an optionally substituted aryl or arylalkyl group;

comprising:

a) reacting 2-chloro-4-fluorobenzotrichloride of formula (II):

\[
\begin{align*}
\text{CCl}_3 & \quad \text{Cl} \\
\text{F} & \quad \text{Cl}
\end{align*}
\]
with a sulfinic mixture to give the intermediate compound 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III):

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{O}_2\text{N} \\
\text{F} \\
\text{CCl}_3
\end{array}
\]

(III)

b) hydrolysing the intermediate to give the acid of formula (I) wherein R is -COOH; and optionally
c) converting the acid thus obtained into a derivative thereof.

According to the present invention, by halogen is meant a substituent selected from chlorine, bromine, fluorine and iodine, with chlorine being a particularly preferred substituent.

In particular, the preparation of the compound of formula (I) wherein R is -COCl (R = -CO-Hal with Hal = Chlorine) may proceed according to any of the following steps, including:

\( c' \) treating the acid of formula (I) wherein R is -COOH with classic chlorinating agents; or alternatively

\( c'' \) reacting 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with 2-chloro-4-fluoro-5-nitrobenzoic acid (formula (I) wherein R is OH) in approx. 1:1 molar ratios; or alternatively still

\( c''' \) reacting the 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with water in the presence of a suitable catalyst or in a weakly acidic medium,

said stages (\( c' \), \( c'' \) and \( c''' \)) providing the compound of formula (I) wherein R is -COCl.

Examples of linear or branched alkyl, alkenyl and alkynyl groups include lower alkyIs such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, iso-pentyl, etc., optionally, whenever possible, mono- or poly-unsaturated.

Examples of optionally substituted aryl and arylalkyl groups include phenyl, naphthyl, diphenyl, benzyl, etc., optionally mono or poly-substituted with linear or
branched alkyl, alkenyl or alkynyl groups, with halogens or with functional groups such as carboxyls (optionally esterified), primary, secondary or tertiary amines etc.

The starting product, 2-chloro-4-fluorobenzotrichloride of formula (II), is a liquid, easily measurable product, the preparation of which is described in the literature for example in US 4,711,905 (column 17) in which it is synthesised via the photochlorination of the corresponding toluenic derivative.

According to the present invention, by “sulfonitic mixture” is meant a mixture composed of concentrated nitric acid and either concentrated sulfuric acid or oleum, wherein the nitric acid content in said sulfonitic mixture is approx. 30% by weight with respect to the total mixture weight.

According to one advantageous aspect of the invention, the nitric acid content in the sulfonitic mixture is less than 30% by weight, for example comprised of between 15 and 30%. Indeed, it has been observed that said sulfonitic mixture is particularly advantageous when used on an industrial scale.

According to one advantageous aspect, the nitration step (a) is performed with a nitric acid/compound of formula (I) ratio greater than 1/1, even better if greater than 2/1 (mol/mol), for example with a ratio of 2.2/1 or even 3/1 or higher.

The temperature of the nitration reaction (a) is at least slightly lower than room temperature, advantageously comprised of between 0 and 20°C, for example comprised of between 10 and 20°C or between 0°C and 10°C. Temperatures less than 0°C may likewise be used but involve longer reaction times, while temperatures above room temperature do not always give the selective nitration of the desired position in the benzene ring.

In particular, it has been observed that using a temperature comprised of between 0-10°C, for example around 0-5°C, is particularly advantageous, above all when operating in the presence of a sulfonitic mixture with a nitric acid content of less than 30% by weight, allowing greater handleability of the reaction mixture with reduced production of by products.

Hydrolysis (b) of the compound of formula (III) to give the acid form, is generally performed in an acid medium, for example in the presence of hydrochloric, hydrobromic, acetic and/or sulfuric acid, at a temperature comprised of between
room temperature and the reaction mixture reflux temperature, for example at a
temperature greater than 50°C, advantageously comprised of between 80 and 120°C.
With certain types of hydrolysis, it may be possible to add a suitable catalyst, such as
for example FeCl₃. The technical details of the hydrolysis step (b) are provided in the
experimental section of this description.
If desired, or indeed necessary, the acid of formula (I) (wherein R = -COOH) may be
purified according to known techniques, for example by washing with water,
advantageously in a water/alcohol mixture.
For the good outcome of the process of the invention according to the
aforementioned steps (a), (b), (c’), (c’’) or (c’’’), it is essential that the sulfonitric
mixture be used in pre-mixed form, instead of the starting product being dissolved
firstly in sulfuric acid with nitric acid then being added later.
Indeed, it has been observed that when the starting product of formula (II) comes into
contact firstly with sulfuric acid or oleum and then with nitric acid, then besides the
desired nitration, the hydrolysis of the trichloride group to the acid form is also
obtained without the formation of the 2-chloro-4-fluoro-5-nitrobenzotrichloride
intermediate of formula (III), which as already mentioned, is a novel, potentially
versatile compound with wide range of potential uses in the synthesis of organic
compounds, that may be useful for example in the preparation of derivatives of said
acid and particularly the compound of formula (I) wherein R is as defined previously
but other than -COOH.
The process for the preparation of the compound of formula (I) wherein R is -COOH
by the nitration and simultaneous hydrolysis of 2-chloro-4-fluorobenzotrichloride of
formula (II) comprising of the addition of said compound of formula (II) in sulfuric
acid or oleum, with the subsequent addition of an appropriate quantity of nitric acid
to the mixture, represents however a further aspect of the present invention. The
details of this synthetic process are provided in the experimental section of the
present description.
In general, for carrying out the process of stage (a) of the invention, the starting
product of formula (II) may be added slowly (over several hours, for example around
2-3 hours) into the pre-chilled sulfonitric mixture and kept at a temperature
comprised of between 0 and 10°C, the reaction mixture may then be left at said temperature for several hours until the nitration reaction is complete. Those skilled in the art are naturally able to check the progress of the reaction by means of conventional chromatographic techniques.

Once the reaction is complete (i.e. when the starting product can no longer be detected) the reaction mixture may be treated according to known techniques for the isolation of the intermediate product of formula (III). For example, the desired product may be precipitated by treatment with ice water, and then isolated by filtration or be extracted from the suspension formed by using an appropriate solvent immiscible in water, for example a chlorinated solvent. Afterwards, using conventional isolation techniques, the compound of formula (III) may be obtained with good yield and high purity. Said compound may be used directly for subsequent transformations without any further purification.

2-Chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) is a novel compound and represents a further aspect of the present invention.

The acid obtained from step (b) may be transformed into a derivative thereof (R is as defined above but ≠ -COOH) according to techniques well known to those skilled in the art and/or described in the literature.

The transformation of the acid of formula (I) wherein R is -COOH into the acyl chloride thereof of formula (I) wherein R is -COCl (R = -CO-Hal with Hal = Chlorine) may be particularly useful. Said reaction may be carried out either by chlorination of the corresponding acid according to conventional techniques, for example through the action of chlorinating agents such as thionyl chloride, under reaction conditions well known to those skilled in the art or, according to a further aspect of the present invention, by reacting 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with 2-chloro-4-fluoro-5-nitrobenzoic acid.

Thus, according to a further aspect thereof, the present invention also relates to a process for the preparation of the compound of formula (I) wherein R is -COCl comprising reacting the 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) and 2-chloro-4-fluoro-5-nitrobenzoic acid (formula (I) wherein R is -COOH) in a molar ratio of 1/1, preferably in the presence of a Lewis acid, such as for example
FeCl₃ or ZnCl₂, at a temperature comprised of between room temperature and 150-160°C, for example around 50°C or more advantageously around 80°C. The reaction is exothermic and produces hydrochloric acid. The technical details of said preparation are reported in the following experimental section.

Alternatively, it is possible to react the 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with water in the presence of a catalyst such as FeCl₃ or FeSO₄, or even in a weakly acidic medium, for example in the presence of dilute sulfuric acid, to obtain the of 2-chloro-4-fluoro-5-nitrobenzoic acid chloride; in this case, it is advantageous to operate at temperatures ranging between approx. 120 and 160°C and the measured quantity of water must be added slowly and constantly in order to avoid inactivation of the catalyst and hydrolysis of the compound into its acid form.

As already mentioned, the novel compound of formula (III) is a particularly versatile chemical intermediate and may be used, for example, as a starting product for the preparation of 2-chloro-4-fluoro-5-nitrobenzotrifluoride, for example by halogen exchange reaction with hydrofluoric acid (HF).

2-chloro-4-fluoro-5-nitrobenzotrifluoride is itself a novel product and constitutes a further subject-matter of the present invention.

This product may likewise be obtained by nitration of 2-chloro-4-fluorobenzotrifluoride, which may in turn be obtained from the 2-chloro-4-fluorobenzotrichloride of formula (II) by means of the halogen exchange reaction with HF.

Thus, according to another aspect thereof, a subject-matter of the invention is a process for the preparation of a compound of formula (IV)

![Diagram](IV)

wherein R° is a hydrogen atom or a –NO₂ group,

comprising reacting a compound of formula (V):

7
wherein $R^o$ is as defined above, with hydrofluoric acid (HF), optionally isolating the product and/or optionally subjecting the product of formula (IV), wherein $R^o$ is H, to a nitration reaction under the conditions of step (a) described above.

According to one embodiment of the invention, the above described fluorination reaction is carried out using an excess of HF and heating in an autoclave, for example up to 90°C for the amount of time necessary for conversion, which may be assessed for example by monitoring the production of gaseous hydrochloric acid. The fluorinated product of formula (IV) may then be isolated according to known techniques, for example by neutralising the reaction mixture using bases such as a solution of sodium bicarbonate and then distilling the product, or by crystallising it from a suitable solvent.

The various aspects of the invention will now be non-limitingly illustrated by means of the following examples.

**EXPERIMENTAL SECTION**

**EXAMPLE 1**

Preparation of 2-chloro-4-fluoro-5-nitrobenzotrichloride (formula (III)) (according to step (a))

Into a 500 ml 4-necked round-bottomed flask, equipped with mechanical means of stirring, means of cooling, thermometer and dropping funnel, 150.2 g of 30% oleum, and 60.2 g of concentrated nitric acid (99%) are added while maintaining the temperature below 10°C. To the sulphonitic mixture thus obtained 115.6 g of 2-chloro-4-fluorobenzotrichloride are added over approx. 2.5 hours while maintaining the temperature between 0 and 10°C. The reaction is left at said temperature for a further 2 hours to achieve completion, then poured into an ice/water mixture and the precipitation of a white solid is immediately observed. Approx. 300 g of dichloromethane is added to the mixture and the phases separated, the organic phase
is washed with a solution of NaHCO₃, then dried over magnesium sulfate, filtered and evaporated to dryness. 132 g of the title product (titre by GC = 93.7%, yield 93%) are obtained as a white solid.
M.P. = 65-68°C

GC-MS identifies ion 256-262 [M-Cl]⁺

¹H NMR (spectra have been performed in CD₂COCD₃)
doublet signal at 7.91 ppm ³J_HF 9.91 Hz
doublet signal at 8.93 ppm ⁴J_HF 7.63 Hz
(reference 2.03 ppm on the central line of the residual acetone signal)

¹⁹F NMR
Singlet signal at −113.68 ppm
(trifluoroacetic acid reference, the signal of which is given at −77.00 ppm)

¹³C NMR (coupled spectrum)

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EXAMPLE 2

Preparation of 2-chloro-4-fluoro-5-nitrobenzotrichloride (formula (III)) (according to step (a))

Into a 500 ml 4-necked, cryostatically cooled round-bottomed flask equipped with mechanical means of stirring, a thermometer, dropping funnel and a acidic gas traps, 602.8 g of sulfinic mixture containing 22% nitric acid are loaded, and the temperature cryostatically cooled to 0°C. 251.8 g of 2-chloro-4-fluorobenzotrichloride are added by means of the dropping funnel while maintaining the temperature between 0 and 2°C. The addition is completed over 4.5 hours, and the well-stirred, homogeneously appearing mixture has a pale yellow colour. The reaction mixture is left, still at 0-4°C, for a further 2 hours for the reaction to go to
completion. The reaction is monitored by GC, following the disappearance of the reagent, and the acids are then diluted with 150.4 g of deionised water. The process is performed using external cooling in order to maintain the temperature below 10°C. 20 minutes after the addition of the water to dilute the acids, still with cooling, the reaction mixture is filtered under reduced pressure to give 651.6 g of filtered acids and 328.5 g of a damp, pale yellow, coarse grained solid which is washed by stirring with deionised water for one hour. The desired product is filtered to give 304.1 g of a pale yellow coloured product upon drying.

Nitrination molar yield: 96.2%.

Melting point (°C): 59-62

EXAMPLE 3

Preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid (according to step (b))

Into a 250 ml reaction vessel 41.6 g of 96% H₂SO₄ are loaded and 8.4 g of water added dropwise (to adjust the acid concentration to 80%). The temperature of the acid is adjusted to approx. 70°C and the portionwise addition of 10 g of purified 2-chloro-4-fluoro-5-nitrobenzotrichloride (titre by GC = 99.5%) commenced. The temperature is then set to 100-110°C, observing the progressive formation of a white solid product dispersed in the mixture. The temperature is kept for approx. 3 ore, then the reaction mixture cooled to approx. 50°C and diluted with 100 g of water, and the product then extracted with 40 g of ethyl acetate at room temperature. The phases are separated and the organic solution washed with 46 g of water. Finally, the solvent is evaporated to give 7 g of the title product, as a white solid.

Titre by HPLC = 94.5%, molar yield 88%.

Melting point (°C): 148-151.

EXAMPLE 4

Preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid (according to step (b))

Into a 250 ml reaction vessel inside a 1 l glass equipped with mechanical means of stirring, thermometer, bubble condenser, thermostatically controlled oil heater, acid vapour water traps, 750 g of 96% sulfuric acid are loaded and 75 g of deionised water added dropwise to dilute the acid to 85%. The operation is completed over 1.5 hours, reaching a maximum temperature of 45°C. The acid is then heated to 80-90°C,
and the portionwise addition of 302.6 g of crude 2-chloro-4-fluoro-5-nitrobenzotrichloride commenced. The production of HCl may be observed immediately, both in the reaction mixture (seen by foaming), and in the water absorption traps. The reaction is moderately exothermic, however, the portionwise addition continues in safety, avoiding the accumulation of gas with vigorous stirring. The temperature is kept between 80-100°C for the entire duration of the reaction, and for ¾ of the duration, the reaction has the appearance of a solution, then the acid product begins to form a suspension despite the high temperature. Addition of the organic component is completed in 3 hours 45 minutes, divided into 15 minute periods with the addition of 20-30 g each. The reaction mixture is kept stirring at 100°C for a further 3 hours, until the reaction is complete. The gas absorbed in the traps (approx. 97.5 g) is an indication of the state of completion of the reaction. The reaction mixture is then cooled to 20°C, and then the product filtered to give 233 g of a creamy white, damp solid. It is then further purified by washing with water, filtration and drying to obtain 171.0 g of product.

Hydrolysis molar yield: 82%.
Melting point (°C): 148-152.

EXAMPLE 5

Preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid (according to step (b))

Into a 250 ml reaction vessel 50 g of 96% sulfuric acid are loaded then diluted to 80% by the addition of 10 g of water. The mixture is then heated to approx. 70°C and then the portionwise addition of 12 g of crude nitration product 2-chloro-4-fluoro-5-nitrobenzotrichloride (titre by GC = 98%) commenced. The reaction mixture is heated to 100-110°C and kept at said temperature for approx. 3 hours to promote the formation of the hydrolysis product. While cooling, it is diluted with the addition of 50 g of water and 50 g of ice, and the product extracted with 60 g of ethyl acetate. Following separation of the phases, the organic phase is washed with 60 g of water, and the ethyl acetate concentrated under reduced pressure. 10 g of heptane are then added and 8 g of title product isolated as a white solid.

Titre by HPLC = 96.5%, molar yield 91%.
Melting point (°C): 150-153.
EXAMPLE 6

Preparation of the chloride salt of 2-chloro-4-fluoro-5-nitrobenzoic acid (according to step (c*))

Into a 100 ml reaction vessel 30 g of 2-chloro-4-fluoro-5-nitrobenzotrichloride and 0.85 g of FeCl₃ are loaded. The mixture is heated to approx. 50°C and 22.4 g of 2-chloro-4-fluoro-5-nitrobenzoic acid added. The temperature increases to 85°C with strong release of gaseous hydrochloric acid. The mixture becomes completely fluid and the reaction is left for approx. 1.5 hours to proceed to completion. The disappearance of the starting product and the corresponding appearance of the title compound are monitored by gas chromatography (GC).

Final GC analysis: 94.7% the chloride salt of 2-chloro-4-fluoro-5-nitrobenzoic acid (via the methyl ester).
Melting point (°C): 53-57.

EXAMPLE 7

Preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid
(by simultaneous nitration and hydrolysis of 2-chloro-4-fluoro-5-nitrobenzotrichloride)

Into a 3 litre round-bottomed flask equipped with mechanical means of stirring, means of cooling, thermometer and dropping funnel 2900 g of concentrated sulfuric acid are loaded which is then cooled to 0/5°C. 500 g of 2-chloro-4-fluorobenzotrichloride are then added of approx. 2 hours. The formation of a solid is observed, along with the liberation of gas (hydrochloric acid). 255 g of concentrated nitric acid (again at 0°C) are then added slowly and after 3 hours, the temperature of the mixture is allowed to return to 20°C and the reaction left stirring at this temperature for as further 17 hours. The reaction mixture is poured into ice water and the precipitate thus formed filtered then washed firstly with water, filtered once more and treated with a warm ethyl acetate and heptane mixture. Following cooling, the precipitate is filtered to give 340 g of title product in the form of a white solid.
Titre by HPLC = 97.2%, molar yield 76%.
Melting point (°C): 151-154.

EXAMPLE 8
Illustrative preparation of 2-chloro-4-fluoro-5-nitrobenzotri fluoride

2-chloro-4-fluoro-5-nitrobenzotrichloride is loaded into an autoclave and an excess of hydrofluoric acid added (>100% molar), with a maximum pressure of 12 bar, at a maximum temperature of 90°C. When the release of gaseous hydrochloric acid has ceased (after approx. 10-15 hours) the contents of the autoclave are unloaded, neutralised with a solution of sodium bicarbonate and the product isolated by distillation.

Melting point (°C): 44.5°C


NMR characterisation of the compound:

\[ \text{NMR spectra in CDCl}_3 \]

\[ ^{19}\text{F} : -64.53 \text{ s, CF}_3 ; \text{ s} -110.92 \text{ s, F} \]

\[ ^{1}H \text{ NMR} \]

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\[ ^{13}C \text{ NMR (proton coupled)} \]

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CLAIMS

1. A process for the preparation of 2-chloro-4-fluoro-5-nitrobenzoic acid and/or the chloride derivative thereof of formula (I):

\[
\begin{align*}
\text{(I)} \\
\text{wherein} \\
- R & \text{ is a } -\text{COOH, } -\text{COOR}, -\text{CO-Hal, } -\text{CONR}''\text{R''', } -\text{COSR''' or } -\text{CN group,} \\
- \text{Hal represents a halogen atom,} \\
- R' & \text{ represents a linear or branched alkyl, alkenyl or alkynyl group; an optionally substituted aryl group;} \\
- R'' \text{ and R'''} & \text{ represent, independently, a hydrogen atom; a linear or branched alkyl, alkenyl or alkynyl group; an optionally substituted aryl or arylalkyl group,} \\
\text{characterised in that:} \\
a) \text{ reacting 2-chloro-4-fluorobenzotrichloride of formula (II):}
\end{align*}
\]

\[
\begin{align*}
\text{(II)} \\
\text{with a sulfonitric mixture to give the intermediate compound 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III):}
\end{align*}
\]

\[
\begin{align*}
\text{(III)} \\
\end{align*}
\]
b) hydrolysing the intermediate to give the acid of formula (I) wherein R is -OH; and optionally
c) the acid thus obtained is transformed into a derivative thereof.

2. The process according to claim 1 characterised in that said nitration mixture
   is a mixture composed of concentrated nitric acid and concentrated sulfuric
   acid or oleum and wherein the nitric acid content in said nitration mixture is
   approx. 30% by weight with respect to the total mixture weight.

3. The process according to claims 1 or 2 characterised in that the nitric acid
   content in the nitration mixture is less than 30% by weight.

4. The process according to claims 1 to 3 characterised in that the nitration step
   (a) is carried out with a nitric acid/compound of formula (I) ratio of no less
   than 2:1 (mol/mol).

5. The process according to claims 1 to 4 characterised in that the temperature
   of the nitration reaction (a) is between approx. 0 and approx. 20ºC.

6. The process according to claims 5 characterised in that the temperature of the
   nitration reaction (a) is between approx. 0 and approx. 10ºC.

7. The process according to claims 1 to 6 characterised in that the hydrolysis (b)
   is performed in an acidic medium.

8. The process according to claims 1 to 7 for the preparation of the product of
   formula (I) wherein R is –COCl, characterised in that any of the following
   steps are performed:
   c') treating the acid of formula (I) wherein R is -COOH with classic
      chlorinating agents; or alternatively
      c'') reacting 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with
      2-chloro-4-fluoro-5-nitrobenzoic acid (formula (I) wherein R is -COOH)
      in approx. 1/1 molar ratios; or alternatively still
      c''') reacting 2-chloro-4-fluoro-5-nitrobenzotrichloride of formula (III) with
      water in the presence of a suitable catalyst or in a weakly acidic medium.

9. The process according to claim 8 characterised in that thionyl chloride is used
    in step (c').

10. The process according to claim 8 characterised in that step (c'') is performed
in the presence of a Lewis acid.

11. A compound which is 2-chloro-4-fluoro-5-nitrobenzotrichloride.

12. A process for the preparation of the compound of formula (I):

\[
\text{(I)} \quad \begin{array}{c}
\text{Cl} \\
\text{R} \\
\text{O}_2\text{N} \\
\text{F}
\end{array}
\]

wherein R is -COOH, characterised in that the compound of formula (II):

\[
\text{(II)} \quad \begin{array}{c}
\text{CCl}_3 \\
\text{Cl} \\
\text{Cl} \\
\text{F}
\end{array}
\]

is measured into sulfuric acid or oleum and subsequently concentrated nitric acid is added to the mixture.

13. A process for the preparation of a compound of formula (IV)

\[
\text{(IV)} \quad \begin{array}{c}
\text{CF}_3 \\
\text{Cl} \\
\text{R}^\circ \\
\text{F}
\end{array}
\]

wherein R\(^\circ\) is a hydrogen atom or a \(-\text{NO}_2\) group, comprising reacting a compound of formula (V):

\[
\text{(V)} \quad \begin{array}{c}
\text{CCl}_3 \\
\text{Cl} \\
\text{R}^\circ \\
\text{F}
\end{array}
\]

wherein R\(^\circ\) is as described above, with an excess of HF, optionally isolating the product and/or optionally subjecting the product of formula (IV), wherein
R° is H, to a nitration reaction.

14. A compound which is 2-chloro-4-fluoro-5-nitrobenzotrifluoride.
# INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

C07C201/08  C07C205/12  C07C205/58  C07C51/093  C07C63/70

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07C

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)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No.</th>
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<td>WO 87/07602 A (RHONE-POULENC AGROCHIMIE) 17 December 1987 (1987-12-17) cited in the application page 17, lines 8-10, left-hand compound; claims 1 and 41 page 66, reaction scheme; page 71, reaction scheme</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the International search: 13 February 2006

Date of mailing of the International search report: 23/02/2006

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Authorized officer: Sen, A
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