

Published

With international search report.

(54) Title: PROCESS FOR THE PURIFICATION OF SUBSTITUTED P-NITRODIPHENYLETHERS

(57) Abstract

A process for the purification of a compound of general formula (I), wherein R1 is hydrogen or C1–C6 alkyl, C2–C6 alkyl or C2–C6 alkenyl, any of which may optionally be substituted with one or more substituents selected from halogen and hydroxy; or COOR4, COR4, CONR4R5 or CONHSO2R4; R4 and R5 independently represent hydrogen or C1–C4 alkyl optionally substituted with one or more halogen atoms; R6 is a halogen atom or a group R4; R2 is hydrogen or halogen; and R3 is C1–C4 alkyl, C2–C4 alkenyl or C2–C4 alkynyl, any of which may optionally be substituted with one or more halogen atoms; or halogen; or, where appropriate, a salt thereof; from a mixture containing the compound of general formula (I) together with one or more isomers or di-nitrated analogues thereof; the process comprising dissolving the mixture in a suitable crystallisation solvent and recrystallising the product from the resulting crystallisation solution wherein the crystallisation solution contains not more than 25% loading of the compound of general formula (I) and wherein the temperature to which the solution is cooled for crystallisation is not greater than about 30°C; wherein, after the addition of the crystallisation solvent but before recrystallisation, the crystallisation solution is subjected to at least one wash with an aqueous solution having an acid pH. The process is particularly useful for purifying acifluorfen.
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<table>
<thead>
<tr>
<th>AL</th>
<th>Albania</th>
<th>ES</th>
<th>Spain</th>
<th>LS</th>
<th>Lesotho</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>Armenia</td>
<td>FI</td>
<td>Finland</td>
<td>LT</td>
<td>Lithuania</td>
</tr>
<tr>
<td>AT</td>
<td>Austria</td>
<td>FR</td>
<td>France</td>
<td>LU</td>
<td>Luxembourg</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>GB</td>
<td>United Kingdom</td>
<td>LV</td>
<td>Latvia</td>
</tr>
<tr>
<td>AZ</td>
<td>Azerbaijan</td>
<td>GE</td>
<td>Georgia</td>
<td>MC</td>
<td>Monaco</td>
</tr>
<tr>
<td>BA</td>
<td>Bosnia and Herzegovina</td>
<td>GH</td>
<td>Ghana</td>
<td>MD</td>
<td>Republic of Moldova</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GN</td>
<td>Guinea</td>
<td>MG</td>
<td>Madagascar</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>GR</td>
<td>Greece</td>
<td>MK</td>
<td>The former Yugoslav Republic of Macedonia</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>HU</td>
<td>Hungary</td>
<td>ML</td>
<td>Mali</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>IE</td>
<td>Ireland</td>
<td>MN</td>
<td>Mongolia</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>IL</td>
<td>Israel</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>IS</td>
<td>Iceland</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>IT</td>
<td>Italy</td>
<td>MX</td>
<td>Mexico</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>JP</td>
<td>Japan</td>
<td>NE</td>
<td>Niger</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>KE</td>
<td>Kenya</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>KG</td>
<td>Kyrgyzstan</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>KP</td>
<td>Democratic People’s Republic of Korea</td>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d’Ivoire</td>
<td>KR</td>
<td>Republic of Korea</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>KZ</td>
<td>Kazakhstan</td>
<td>PT</td>
<td>Portugal</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>LC</td>
<td>Saint Lucia</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>CU</td>
<td>Cuba</td>
<td>LI</td>
<td>Liechtenstein</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>LK</td>
<td>Sri Lanka</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>LR</td>
<td>Liberia</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>SI</td>
<td>Slovenia</td>
<td>SG</td>
<td>Singapore</td>
</tr>
<tr>
<td>EE</td>
<td>Estonia</td>
<td>SK</td>
<td>Slovakia</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>ES</td>
<td>Spain</td>
<td>SZ</td>
<td>Swaziland</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>FI</td>
<td>Finland</td>
<td>TD</td>
<td>Chad</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>FR</td>
<td>France</td>
<td>TG</td>
<td>Togo</td>
<td>SG</td>
<td>Singapore</td>
</tr>
<tr>
<td>GB</td>
<td>United Kingdom</td>
<td>TJ</td>
<td>Tajikistan</td>
<td>SI</td>
<td>Slovenia</td>
</tr>
<tr>
<td>GE</td>
<td>Georgia</td>
<td>TM</td>
<td>Turkmenistan</td>
<td>SK</td>
<td>Slovakia</td>
</tr>
<tr>
<td>GH</td>
<td>Ghana</td>
<td>TR</td>
<td>Turkey</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>GN</td>
<td>Guinea</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
<td>SZ</td>
<td>Swaziland</td>
</tr>
<tr>
<td>GR</td>
<td>Greece</td>
<td>UA</td>
<td>Ukraine</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>HU</td>
<td>Hungary</td>
<td>UG</td>
<td>Uganda</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>IE</td>
<td>Ireland</td>
<td>US</td>
<td>United States of America</td>
<td>TJ</td>
<td>Tajikistan</td>
</tr>
<tr>
<td>IL</td>
<td>Israel</td>
<td>UA</td>
<td>Ukraine</td>
<td>TM</td>
<td>Turkmenistan</td>
</tr>
<tr>
<td>IS</td>
<td>Iceland</td>
<td>TR</td>
<td>Turkey</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>IT</td>
<td>Italy</td>
<td>UA</td>
<td>Ukraine</td>
<td>UG</td>
<td>Uganda</td>
</tr>
<tr>
<td>JP</td>
<td>Japan</td>
<td>US</td>
<td>United States of America</td>
<td>VN</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>KE</td>
<td>Kenya</td>
<td>YU</td>
<td>Yugoslavia</td>
<td>ZW</td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>
PROCESS FOR THE PURIFICATION OF SUBSTITUTED P-NITRODIPHENYLETHERS

The present invention relates to a process for the purification of diphenyl ether compounds which are useful as herbicides or as intermediates in the synthesis of herbicides. In particular, it relates to a process for obtaining particular nitrated isomers of diphenyl ether compounds from mixtures containing other nitrated isomers.

In WO 9710200 the prior art on the production and purification of certain herbicidal nitro substituted diphenyl ethers is reviewed and it is concluded that none of the prior art methods are particularly satisfactory for use on an industrial scale because they all have the common problem that the processes yield a mixture of the required product and other nitrated isomers. Nitrated isomers of diphenyl ether compounds are often extremely difficult to separate from one another and the quantity of other isomers is often too high for the final product to fulfil the requirements of the regulatory authorities for herbicides. The problem tends to be further exacerbated if the nitrated product is an intermediate in the synthesis of a herbicide rather than the required herbicide itself because the mixture of nitrated compounds means that larger quantities of other reagents must be used than would be necessary if the nitrated isomers could be separated satisfactorily. It is therefore important to ensure that the nitration process produces a product mixture containing the highest possible proportion of the desired isomer.

There is disclosed in WO 9710200 a process for the purification of a compound of general formula I:

I

wherein \( R^1 \) is hydrogen or \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl or \( C_2-C_6 \) alkynyl, any of which may optionally be substituted with one or more substituents selected from halogen and hydroxy; or \( COOR^4 \), \( COR^5 \), \( CONR^4R^5 \) or \( CONH\text{SO}_2R^4 \);

\( R^4 \) and \( R^5 \) independently represent hydrogen or \( C_1-C_4 \) alkyl optionally substituted with one or more halogen atoms;
R⁴ is a halogen atom or a group R⁴;
R¹ is hydrogen or halo; and
R¹ is C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl, any of which may optionally be substituted with one or more halogen atoms; or halo;

or, where appropriate, a salt thereof;

from a mixture containing the compound of general formula I together with one or more isomers or di-nitrated analogues thereof; the process comprising dissolving the mixture in a suitable crystallising solvent and recrystallising the product from the resulting crystallisation solution wherein the crystallisation solution contains not more than 25% loading of the compound of general formula I and the temperature to which the solution is cooled for crystallisation is not greater than about 30°C.

In WO 9710200 and in the present specification, loading is defined as:

\[
\frac{\text{weight of pure compound of formula I} \times 100}{\text{weight of pure compound of formula I} + \text{weight of solvent}}
\]

In order to calculate the loading of the crystallisation solution, it is therefore essential to know the amount of isomer of general formula I present in the product mixture.

It has now been found that significant improvements in the yield of pure compound can be obtained by adding an extra step to the process described in WO 9710200. Thus after the addition of the crystallising solvent but before recrystallisation, the crystallisation solution is subjected to at least one wash with an aqueous solution having an acid pH.

Therefore there is provided a process for the purification of a compound of general formula I:

\[\text{I}\]

wherein R¹ is hydrogen or C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, any of which may optionally be substituted with one or more substituents selected from halogen and hydroxy; or COOR⁴, COR⁴, CONR⁴R⁴ or CONHSO₂R⁴;
R¹ and R⁴ independently represent hydrogen or C₁-C₄ alkyl optionally substituted with one or more halogen atoms;
R⁵ is a halogen atom or a group R⁴;
R² is hydrogen or halo; and
R³ is C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl, any of which may optionally be substituted with one or more halogen atoms; or halo;
or, where appropriate, a salt thereof;
from a mixture containing the compound of general formula I together with one or more isomers or di-nitrate analogues thereof; the process comprising dissolving the mixture in a suitable crystallising solvent and recrystallising the product from the resulting crystallisation solution wherein the crystallisation solution contains not more than 25% loading of the compound of general formula I and the temperature to which the solution is cooled for crystallisation is not greater than about 30°C; wherein, after the addition of the crystallising solvent but before recrystallisation, the crystallisation solution is subjected to at least one wash with an aqueous solution having an acid pH.

The yield of pure compound of general formula I increases as the number of washes increases. Therefore it is often desirable to wash the crystallisation solution up to, for example, five times, e.g. twice or three times.

All washes comprise preferably 0.2 to 2.0 times the volume of the organic phase, and more preferably about 0.5 times the volume of the organic phase.

The washes are preferably conducted at a temperature of from 50 to 90°C, e.g. at about 80°C.

It has also been found that the pH range of the washing liquid appears to be of significance to the yield of the compound of general formula I which can be obtained. The aqueous solution used for washing the crystallisation solution preferably has a pH of 4.5 or less.

In a preferred embodiment of the invention the crystallisation solution is washed with an aqueous solution having a pH of from 3 to 3.8, more preferably an aqueous solution having a pH of from 3.3 to 3.5.

If the wash pH is greater than 3.8, the final yield may be reduced. This may be because above pH 3.8, there is salt formation in aqueous solution and the presence of salts in the product solution tends to inhibit the crystallisation of the free acid. If the pH of the
washing solution is lower than 3, there may be no significant improvement in the yield of the purified compound obtained. This may be due to the presence in the crude solution containing the compound of general formula I of the impurity of formula (4) which can be removed by the washing procedure described. The efficiency of removal of this impurity increases as the pH of the wash increases.

In a further preferred embodiment of the invention the crystallisation solution is washed with an aqueous solution having a pH of between 3.0 and 4.5, e.g. pH 3.5 to 4.5, followed by an additional wash at a pH of <2.0, e.g. pH 1.

In this embodiment use of an aqueous solution having a higher pH avoids the difficulty of controlling the pH at precisely 3 to 3.8, and the use of the final wash at pH <2.0 removes the adverse effect of the higher pH and converts any salt which is formed back to the free acid.

In a further preferred embodiment the process of the invention includes a first wash at pH <2.0, e.g. pH 1, followed by one to three washes at a pH of 3.0 to 4.5, followed by a final wash at pH <2.0, e.g. pH 1.

Washes having a pH of <2.0 may be prepared using a mineral acid, e.g. hydrochloric, sulfuric or phosphoric acid, to obtain the desired pH. Washes having a pH of 3.0 to 4.5 may be prepared by adding an alkali, e.g. an alkali metal hydroxide or carbonate, or a buffer, for example a salt of an acid having a pKa in the range 2–5, e.g. formate/formic acid, to give the desired pH.

Because the pH controlled washes also take out some compound of formula I as well as impurities, doing more than one wash leads to an increased loss of compound of formula I but this is more than compensated for by the benefit of impurity removal.

Surprisingly however, it has been found that if the aqueous layers resulting from the pH controlled washes are adjusted to a suitable pH and then back extracted with fresh solvent, most (90-95%) of the compound of formula I can be recovered without re-extracting the impurities (<5%).

Therefore there is provided a process for the purification of a compound of general formula I as defined above from a mixture containing the compound of general formula I together with one or more isomers or di-nitrated analogues thereof; the process comprising dissolving the mixture in a suitable crystallising solvent and recrystallising the product from the resulting crystallisation solution wherein the crystallisation solution contains not more
than 25% loading of the compound of general formula I and the temperature to which the solution is cooled for crystallisation is not greater than about 30°C; wherein, after the addition of the crystallising solvent but before recrystallisation, the crystallisation solution is subjected to at least one wash with an aqueous solution having an acid pH and the aqueous wash is back extracted with fresh crystallising solvent.

The resulting extracts are preferably recycled into the crystallisation process.

If multiple pH controlled washes are carried out, the washes are preferably combined prior to back-extraction.

The volume of solvent used for back extraction is not critical but generally the process uses preferably 0.2-3 times the volume of the aqueous phase, and preferably about 0.5-1 times the volume of the aqueous phase.

The back extraction is preferably conducted at a temperature of from 50 to 90°C, e.g. at about 80°C and may be performed at pH 3.2-4.2 preferably at pH 3.5-3.8.

In a preferred embodiment of the invention the process includes the use of multiple, preferably two to three, pH controlled washes followed by back extraction of the combined washings. Additional yield gains are of the order of 3-4% may be obtained by this embodiment.

That back extraction is so beneficial is most surprising since the skilled person would not have been expected it to be so selective since the original pH controlled washing of the compound of formula I with crystallising solvent was so selective, in the opposite direction (i.e. for impurities not for compound of formula I).

Using the process of the present invention, it is possible to obtain a product of greater than 90% purity. This is a significant advantage when the product is a herbicide as regulatory authorities usually demand an active ingredient of a very high level of purity with minimal impurities. The advantage may be even greater when the product produced is an intermediate and additional steps must be carried out as reagents are not wasted in reacting with unwanted by-products.

In the context of the present invention, the term “C₁-C₆ alkyl” refers to a saturated straight or branched hydrocarbon chain containing from 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, t-butyl, n-pentyl and n-hexyl. The term “C₁-C₄ alkyl” is a subset of C₁-C₆ alkyl and refers to an alkyl group having up to 4 carbon atoms.
The term "C₂-C₆ alkenyl" refers to a straight or branched hydrocarbon chain containing from 2 to 6 carbon atoms and having at least one double bond. Examples include ethenyl, allyl, propenyl and hexenyl. The term "C₂-C₄ alkenyl" is a subset of C₂-C₆ alkenyl and refers to an alkenyl group having up to 4 carbon atoms.

The term "C₂-C₆ alkylnyl" refers to a straight or branched hydrocarbon chain containing from 2 to 6 carbon atoms and having at least one triple bond. Examples include ethynyl, propynyl and hexynyl. The term "C₂-C₄ alkylnyl" is a subset of C₂-C₆ alkylnyl and refers to an alkylnyl group having up to 4 carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine and the corresponding term "halo" refers to fluoro, chloro, bromo or iodo.

Although the process of the invention may be used for the purification of any compound of general formula I, it is especially preferred that R² is chloro and R³ is trifluoromethyl. Particularly preferred compounds of general formula I are those in which R¹ is COOH or CONHSO₂CH₃. These compounds are 5-(2-chloro-α,α,α-trifluoro-4-tolyloxy)-2'-nitrobenzoic acid (acifluorfen) and 5-(2-chloro-α,α,α-trifluoro-4-tolyloxy)-N-methanesulfonyl-2'-nitro-benzamide (fomesafen), both of which are potent herbicidal compounds.

In the context of the present invention, compounds of general formula I are designated 4'-nitro isomers.

Other components of the product mixture which may be present include the 2'-nitro isomer of general formula:

\[
\begin{align*}
R^3 & \quad \text{O} \\
& \quad \text{NO}_{2} \\
& \quad \text{R}^1
\end{align*}
\]

the 6'-nitro isomer:

\[
\begin{align*}
R^3 & \quad \text{O} \\
& \quad \text{O}_2\text{N} \\
& \quad \text{R}^1
\end{align*}
\]

and the dinitro isomers (1) and (2):
Further unwanted by-products include compound (3) which is formed by nitration of an isomer present as an impurity in the reactant:

and compound (4):

It is particularly important that purification of the desired product of general formula I should remove all, or substantially all, of the 2'-nitro isomer since this is the most difficult isomer to separate from the product by other methods. In addition, if the compound of general formula I is to be used as starting material in a further reaction, other nitrated isomers are also likely to react and this causes wastage of reagents. Again, the 2'-nitro isomer is a particularly important impurity as many of its reaction products are also difficult to separate from the reaction products of compounds of general formula I.
Impurities of formula (4) tend to be present when the compound of general formula I has been produced via a route starting from an alkylphenol (for example m-cresol when the compound of general formula I is acifluorfen or fomesafen). For this reason, although this route uses less expensive starting materials and should be more economic to operate, it has often been avoided in the past and the compound of general formula I produced instead via a route starting from 3-hydroxybenzoic acid. Indeed, this is the route recommended by the authors of both US 5446197 and GB-A-2103214. The impure mixture containing the compound of general formula I used in the testing of the present invention was produced via the route starting from a 3-alkyl phenol and contains the impurity of formula (4).

Only a narrow range of solvents is suitable for use in the present invention with examples being aromatic hydrocarbons, such as xylenes or mixtures of xylenes, and haloaromatics such as o-chlorotoluene, p-chlorotoluene, benzotrifluoride, 3,4-dichlorobenzotrifluoride, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, bromobenzene, and 2-fluorotoluene. Mixtures of any of the above solvents may also be suitable and also mixtures containing aromatic hydrocarbons with a co-solvent which may be one of the solvents mentioned above but may, alternatively be chosen from a much wider range of solvents including aliphatic hydrocarbons, esters, ethers, nitriles and halohydrocarbons.

Xylenes have been found to be particularly suitable solvents for use in the present invention with o-xylene giving better results than other xylenes or mixtures of xylenes.

The optimum loading of the crystallisation varies considerably according to the solvent which is chosen but is, in any case, not greater than about 25%. More typically, optimum loading is from 8% to 20%. For many solvents, for example xylenes, the loading may be, for example, from about 15 to 20% but with a few solvents it is necessary to reduce the loading even further with a product mixture loading of about 8 to 10% being used.

Although the temperature to which the solution is cooled to effect crystallisation may be as high as 30°C, the purity of the product may be increased considerably by reducing the temperature somewhat. It is greatly preferred, therefore that the temperature to which the solution is cooled to achieve crystallisation is not above 20°C, preferably about 0° to 15°C with 0° to 5°C being an optimal range.

A further factor which has been found to affect the purity of the product is the length of time for which the mixture is allowed to stand after crystallisation before recovery of the
product. It has been found that many 2'-nitro isomers of general formula I are metastable in solution and tend to crystallise slowly, contaminating the desired product and reducing its purity after crystallisation. Therefore, it is preferred that the product slurry, after achieving crystallisation temperature, is not held for more than about four hours, more preferably for less than 2 hours and most preferably from about 1 to 2 hours, before physical separation of the product from the mother liquors.

Crystallisation may be achieved by any suitable method such as seeding the crystallisation solution with crystals of a pure compound of general formula I. It may be advantageous to carry out the seeding in several stages starting when the crystallisation solution is still hot and adding further crystals as it cools. In some circumstances, seeding of the crystallisation solution may not be necessary and cooling of the solution will cause crystallisation of the product.

The product may be separated from the slurry after crystallisation by any appropriate method but filtration is very often the most convenient way of doing this.

The mixture to be purified may be the crude product of a process for the nitration of a compound of general formula II:

\[
\begin{align*}
\text{II} & \\
R^1 & \text{ } \\
R^2 & \text{ } \\
R^3 & \text{ }
\end{align*}
\]

wherein \( R^1, R^2 \) and \( R^3 \) are as defined for general formula I.

Any conventional nitration method may be used, for example the nitration method disclosed in GB-A-2103214.

In one suitable method, the nitration agent may be nitric acid or a mixture of nitric and sulphuric acids although other types of nitrating agent may also be used. The reaction may take place in an organic solvent and suitable solvents include halogenated solvents such as dichloromethane (DCM), ethylene dichloride (EDC), chloroform, tetrachloroethylene (perk lone) and dichlorobenzotrifluoride (DCBTF). Alternatively, solvents such as acetic acid, acetic anhydride, acetonitrile, ethers such as tetrahydrofuran (THF) or dioxane, sulfolane, nitrobenzene, nitromethane, liquid sulphur dioxide or liquid carbon dioxide. It is also advantageous to conduct the reaction in the presence of acetic anhydride and, in this
case, it is preferred that the molar ratio of acetic anhydride to compound of general formula II is from about 1:1 to 3:1. The reaction temperature may be from about -15° to 15°C, more usually from about -10° to 10°C.

After the nitration reaction, the crude product must be removed from the reaction solvent and taken up in the crystallisation solvent. This may be achieved by washing with water to remove any acetic anhydride, acetic acid or mineral acid and then stripping off the reaction solvent completely, melting the product mixture and then taking up the melt in the crystallisation solvent. Alternatively, the product can be extracted from the nitration solvent as a salt (for example the sodium salt) into water and the solvent separated off for recycling. The salt solution may then be acidified in the presence of the hot recrystallisation solvent in order to extract the product for recrystallisation. When acidifying the salt solution, it has been found that adjusting the pH to 1 or less produces the most favourable results. Indeed, it seems that there may be an increase in yield of about 10% when the salt solution is at pH 1 compared with an identical process in which the salt solution is at pH 3. This process in which the impure product is not isolated and in which the pure product is obtained directly from an aqueous solution of the salt is especially useful as it simplifies the work up process after the nitration reaction. It is certainly a considerable improvement on the process described in US 5446197 in which it is necessary to isolate a crude wet paste containing the compound to be purified.

When the nitration process is combined with either of these work-ups and the purification process of the invention, it is possible to obtain a product of over 90% purity in a yield of greater than 70%.

The step of taking up the crude product in the crystallisation solvent may be preceded by an initial purification step. This partial purification comprises removing the reaction solvent and treating the resultant crude product with a mixture of water and a water-miscible polar solvent.

In one method of achieving partial purification, any acetic anhydride may be hydrolysed with water to give acetic acid and this, or acetic acid from any other source, may be left in the reaction mass to act as the polar solvent. The reaction solvent may then be removed by distillation or steam distillation leaving a molten crude product containing some acetic acid which may then be treated with additional quantities of acetic acid and water to facilitate partial purification without substantial dissolution of the required isomer.
Alternatively, the crude product of the nitration reaction, after washing and removal of the reaction solvent, may be treated with a mixture of a polar solvent and water to achieve partial dissolution of impurities and isomers without substantial loss of the desired product which can then be recovered by filtration. In this case, suitable polar solvents include solvents such as formic acid, acetic acid, propionic acid, methanol, acetonitrile and acetone.

The proportion of polar solvent to water may be in the range of from about 3:7 to 7:3, more particularly from about 2:3 to 3:2, and the amount of crude nitrated isomer mixture in the polar solvent/water solution may be from about 10 to 80% by weight, preferably about 15 to 30% by weight. The initial purification step may be carried out at a temperature of from about 10\(^\circ\) to 60\(^\circ\)C, more usually from about 15\(^\circ\) to 30\(^\circ\)C.

An initial purification process such as those described above leads to an improvement in the quality of the crude nitration product from about 70% strength (i.e. 70% by weight of the desired isomer of general formula I) to about 80% strength. A nitration process followed by the initial purification step and the purification process of the invention is high yielding with a recovery of the desired isomer of greater than 90% and often greater than 95%, especially with the use of back extraction of the aqueous acid washes.

In addition to being a herbicide in its own right, acifluorfen may also serve as an intermediate in the synthesis of fomesafen. The acifluorfen may be converted to its acid chloride which may then be reacted with methane sulphonamide to give fomesafen. Both of these steps may be carried out by conventional methods, for example as set out in EP-A-0003416. It is a particular advantage when using this method to start out with pure acifluorfen as the reaction with methane sulphonamide is an expensive process and it is highly desirable not to waste reagents by sulphonamidating unwanted nitro-isomers to produce unwanted isomers of fomesafen.

The present invention therefore provides a route for the synthesis of pure acifluorfen and its subsequent conversion to pure fomesafen.

As already mentioned, one of the particular advantages of the purification process of the present invention is that it can be used to purify acifluorfen produced from m-cresol and 3,4-dichlorobenzyltrifluoride (DCBTF). As discussed above, m-cresol is less expensive than 3-hydroxybenzoic acid, which is an alternative starting material, but the route starting from m-cresol tends to yield acifluorfen of insufficient purity for use as a herbicide or as an intermediate to other compounds such as fomesafen. However, using the purification
process of the present invention, it has proved possible to purify acifluorfen produced by the m-cresol route.

Therefore, in a further aspect of the present invention, there is provided a process for the preparation of 5-(2-chloro-\(\alpha,\alpha,\alpha\)-trifluoro-4-tolyloxy)-2'-nitrobenzoic acid (acifluorfen), the process comprising the steps of:

a) reacting m-cresol with DCBTF to produce 3-(2-chloro-\(\alpha,\alpha,\alpha\)-trifluoro-4-tolyloxy)toluene;

b) oxidising 3-(2-chloro-\(\alpha,\alpha,\alpha\)-trifluoro-4-tolyloxy)toluene to give 3-(2-chloro-\(\alpha,\alpha,\alpha\)-trifluoro-4-tolyloxy)benzoic acid;

c) nitrating 3-(2-chloro-\(\alpha,\alpha,\alpha\)-trifluoro-4-tolyloxy)benzoic acid to give acifluorfen; and

d) purifying the acifluorfen by a method according to the methods described above.

The invention will now be further illustrated with reference to the following examples.

Example 1

Acifluorfen Acid Washing and Recrystallisation Procedure

1. First Wash

o-Xylene (263 g), concentrated HCl (16 g) and crude acifluorfen sodium salt solution (116 g, 39.3% strength) were mixed and heated to 80°C. The pH of the aqueous phase was adjusted, if necessary, to pH 1 or less with a further addition of concentrated HCl. The resulting mixture was agitated for 15 min then allowed to separate. The lower aqueous phase was then removed.

2. Subsequent Washes With Aqueous Solutions Having an acid pH

Water (65 g) was added to the organic phase and the mixture agitated and reheated to 80°C. The pH of the mixture was then adjusted to the target value by addition of concentrated HCl or 25% sodium hydroxide solution. The mixture was agitated at the target pH for 15 min then allowed to separate for 15 min before removal of the aqueous layer. This procedure was repeated as indicated in Tables I and II. After washing, the organic phase was cooled to 50°C at a rate of 20°C/hour with seeding at 50°C and 45°C, then held at 5°C for 1 hour. The purified acifluorfen was filtered off, washed with chilled o-xylene (25 g) and the wet cake dried in a vacuum oven.
The results of various washing procedures performed in this manner are illustrated in Tables I and II below.

**TABLE I**

<table>
<thead>
<tr>
<th>No of first washes at pH 1.0</th>
<th>No of subsequent washes at controlled pH (and pH value)</th>
<th>Average results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Product Str. %</td>
<td>2'-Nitro %</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>95.2</td>
<td>0.21</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>95.9</td>
<td>0.13</td>
</tr>
<tr>
<td>1</td>
<td>1 (pH 3.3)</td>
<td>94.8</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>2 (pH 3.3)</td>
<td>94.6</td>
<td>1.36</td>
</tr>
<tr>
<td>1</td>
<td>2 (pH 3.5)</td>
<td>93.2</td>
<td>3.3</td>
</tr>
<tr>
<td>1</td>
<td>3 (pH 3.3)</td>
<td>90.4</td>
<td>5.64</td>
</tr>
<tr>
<td>1</td>
<td>1 (pH 4.0)</td>
<td>96.3</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE II**

<table>
<thead>
<tr>
<th>First wash pH</th>
<th>Second wash pH</th>
<th>Third wash pH</th>
<th>Average results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Product Str. %</td>
<td>2'-Nitro %</td>
</tr>
<tr>
<td>3.5</td>
<td>3.5</td>
<td>-</td>
<td>96.5</td>
<td>-</td>
</tr>
<tr>
<td>4.0</td>
<td>1.0</td>
<td>-</td>
<td>94.7</td>
<td>0</td>
</tr>
<tr>
<td>3.5</td>
<td>3.5</td>
<td>1.0</td>
<td>95.5</td>
<td>0</td>
</tr>
<tr>
<td>1.0</td>
<td>4.0</td>
<td>1.0</td>
<td>94</td>
<td>0.2</td>
</tr>
<tr>
<td>1.0</td>
<td>3.8</td>
<td>1.0</td>
<td>95.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Example 2

A. Purification of acifluorfen acid using acid washes without back extraction

Step 1. o-Xylene (195g), 36% HCl (17.3g), and 99.5g and crude acifluorfen sodium salt solution (99.5g 40.26% strength) were mixed in a 1 litre reactor and heated to 80°C. The pH of the aqueous phase was adjusted if necessary to be <1 with the further addition of HCl. After settling the lower aqueous phase was removed.
Step 2. Water (98g) was added to the organic phase and 25% NaOH (3g) was added. After heating to 80°C the pH was adjusted to 3.8-4.0, by the addition of further NaOH if necessary. After settling the lower aqueous phase was removed.

Step 3. Water (98g) was added to the organic phase for the second wash (a small charge of NaOH was added if necessary to adjust the pH of the mixture to 3.8-4.0) and heated to 80°C. After settling the lower aqueous phase was removed.

Step 4. Water (33g) and 98% H₂SO₄ (2g) were added to the organic phase to bring the pH below 2 and the mixture heated to 80°C. After settling the lower aqueous phase was removed.

Step 5. Fresh o-Xylene (32g) was added to bring the acifluorfen acid loading in xylene to 15%.

Step 6. The mixture was cooled to 5°C. During cooling, seeding with pure acifluorfen was begun at about 45°C. The slurry was held at 5°C for 0.5 to 1 hour and then filtered and dried under reduced pressure.

B. Purification of acifluorfen acid using acid washes and back extraction

Step 1. The first two water washes from a double wash acifluorfen acid purification run were taken and fresh o-xylene (195g) was added and the mixture heated to 80°C.

Step 2. The pH of the mixture was adjusted to about 3.6 by adding 10% HCl (1.3g).

Step 3. After settling the lower aqueous phase was removed and the xylene layer which contains the recovered acifluorfen acid is recycled to the purification process described in A, step 1 above.
### Results

<table>
<thead>
<tr>
<th>Process Used</th>
<th>Yield %</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AA Str. %</td>
</tr>
<tr>
<td>Double pH adjusted wash, no back extraction</td>
<td>77</td>
<td>93.7</td>
</tr>
<tr>
<td>Double pH adjusted wash, with back extraction</td>
<td>81.9</td>
<td>95.1</td>
</tr>
</tbody>
</table>
1. A process for the purification of a compound of general formula I:

![Chemical structure](image)

wherein R¹ is hydrogen or C₁-C₆ alkyl, C₂-C₆ alkenyl or C₇-C₆ alkynyl, any of which may optionally be substituted with one or more substituents selected from halogen and hydroxy; or COOR⁵, COR⁶, CONR⁴R⁴ or CONHSO₃R⁴;

R⁴ and R⁵ independently represent hydrogen or C₁-C₄ alkyl optionally substituted with one or more halogen atoms;

R⁶ is a halogen atom or a group R⁴;

R² is hydrogen or halo; and

R³ is C₁-C₄ alkyl, C₂-C₄ alkenyl or C₇-C₆ alkynyl, any of which may optionally be substituted with one or more halogen atoms; or halo;

or, where appropriate, a salt thereof;

from a mixture containing the compound of general formula I together with one or more isomers or di-nitrat ed analogues thereof; the process comprising dissolving the mixture in a suitable crystallising solvent and recrystallising the product from the resulting crystallisation solution wherein the crystallisation solution contains not more than 25% loading of the compound of general formula I, loading being defined as:

\[
\frac{\text{weight of pure compound of formula I}}{\text{weight of pure compound of formula I} + \text{weight of solvent}} \times 100
\]

and the temperature to which the solution is cooled for crystallisation is not greater than about 30°C wherein, after the addition of the crystallising solvent but before recrystallisation, the crystallisation solution is subjected to at least one wash with an aqueous solution having an acid pH.
2. A process as claimed in claim 1, wherein the crystallisation solvent comprises an aromatic hydrocarbon, such as a xylene or mixture of xylenes, a haloaromatic such as o-chlorotoluene, p-chlorotoluene, benzotrifluoride, 3,4-dichlorobenzotrifluoride, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, bromobenzene or 2-fluorotoluene, a mixture of any of the above solvents or a mixture containing an aromatic hydrocarbon with a co-solvent comprising an aliphatic hydrocarbon, ester, ether, nitrile or a halohydrocarbon.

3. A process as claimed in claim 2, wherein the crystallisation solvent is o-xylene.

4. A process as claimed in claim 1, wherein the loading of the crystallisation solution is from about 8% to 20%.

5. A process as claimed in claim 1, wherein the temperature to which the solution is cooled to effect crystallisation is not greater than 20°C.

6. A process as claimed in claim 1, wherein, after crystallisation, the mixture is allowed to stand for no more than two hours before recovery of the product.

7. A process as claimed in claim 1, wherein the mixture to be purified is the crude product of a process for the nitration of a compound of general formula II:

\[
\begin{align*}
\text{II} \\
R^1 & \quad R^2 \\
\end{align*}
\]

wherein \( R^1, R^2 \) and \( R^3 \) are as defined for general formula I.

8. A process as claimed in claim 1, which includes up to five aqueous washes at an acid pH.
9. A process as claimed in any of the preceding claims, wherein the crystallisation solution is washed with an aqueous solution having a pH of from 3 to 3.8.

10. A process as claimed in claim 9, wherein the crystallisation solution is washed with an aqueous solution having a pH of from 3.3 to 3.5.

11. A process as claimed in any one of claims 1 to 8, wherein the crystallisation solution is washed with an aqueous solution having a pH of between 3.0 and 4.5, followed by an additional wash at a pH of <2.0.

12. A process as claimed in any one of claims 1 to 8, which includes a first wash at pH <2.0, followed by one to three washes at a pH of 3.0 to 4.5, followed by a final wash at pH <2.0.

13. A process as claimed in any of the preceding claims wherein the aqueous wash is back extracted with fresh crystallising solvent.

14. A process according to claim 13 wherein the crystallising solvent is recycled into the crystallisation process.

15. A process according to claim 13 or claim 14 in which the washings from multiple pH controlled washes are combined prior to back-extraction.

16. A process according to any of the preceding claims wherein the compound of general formula I is 5-(2-chloro-α,α,α-trifluoro-4-tolyloxy)-2’-nitrobenzoic acid (acifluorfen) or 5-(2-chloro-α,α,α-trifluoro-4-tolyloxy)-N-methanesulfonyl-2’-nitro-benzamide (fomesafen).

17. A process as claimed in claim 16, wherein the compound of general formula I is acifluorfen and the process further comprises converting the acifluorfen to its acid chloride and reacting the acid chloride with methane sulfonamide to give fomesafen.
18. A process according to claim 17 wherein the acifluorfen is prepared by a process comprising the steps of:
   a) reacting m-cresol with DCBTF to produce 3-(2-chloro-α,α,α-trifluoro-4-tolyloxy)toluene;
   b) oxidising 3-(2-chloro-α,α,α-trifluoro-4-tolyloxy)toluene to give 3-(2-chloro-α,α,α-trifluoro-4-tolyloxy)benzoic acid; and
   c) nitrating 3-(2-chloro-α,α,α-trifluoro-4-tolyloxy)benzoic acid to give acifluorfen.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C201/16 C07C303/44

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)
IPC 6 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)

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>
<tbody>
<tr>
<td>A</td>
<td>US 5 446 197 A (M. SANDISON ET AL) 29 August 1995 see claim 1</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>DE 32 27 846 A (RHONE-POULENC) 10 February 1983 see claim 1</td>
<td>1</td>
</tr>
<tr>
<td>P, A</td>
<td>WO 97 10200 A (ZENeca) 20 March 1997 cited in the application see claim 1</td>
<td>1</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Data of the actual completion of the international search
25 May 1998

Date of mailing of the international search report
04/06/1998

Name and mailing address of the ISA
European Patent Office, P.B. 5816 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eipo nl
Fax (+31-70) 340-3016

Authorized officer
Voylazoglou, D

Form PCT/ISA/210 (second sheet) (July 1993)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DE 69408843 D</td>
<td>09-04-1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BE 893942 A</td>
<td>26-01-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 8204352 A</td>
<td>19-07-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 1203811 A</td>
<td>29-04-1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH 652710 A</td>
<td>29-11-1985</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 333582 A</td>
<td>28-01-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2510102 A</td>
<td>28-01-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 2103214 A,B</td>
<td>16-02-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 58038235 A</td>
<td>05-03-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LU 84297 A</td>
<td>22-03-1984</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL 8202995 A</td>
<td>16-02-1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 75324 B</td>
<td>29-11-1985</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4594440 A</td>
<td>10-06-1986</td>
</tr>
<tr>
<td>WO 9710200 A</td>
<td>20-03-1997</td>
<td>AU 6664096 A</td>
<td>01-04-1997</td>
</tr>
</tbody>
</table>