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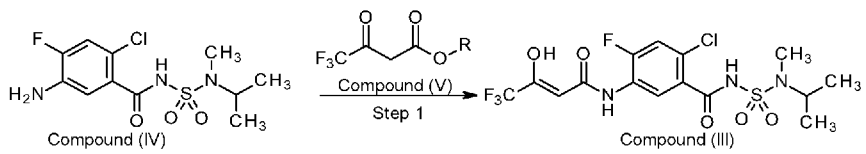
(54) Title: PROCESS FOR PREPARING A SAFLUFENACIL INTERMEDIATE



(57) Abstract: A process for preparing the compound of formula (III), wherein the compound of formula (IV) is reacted in the presence of a base with a compound of formula (V), wherein R is methyl, ethyl, or phenyl, to obtain the compound of formula (III).

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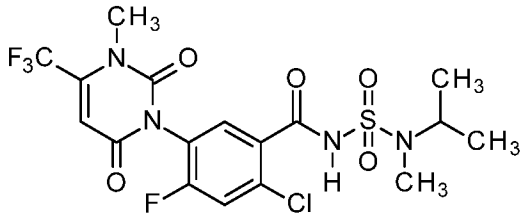
Process for preparing a Saflufenacil intermediate

The present invention relates to a new and highly efficient process for the production of the herbicide Saflufenacil.

Saflufenacil (Compound (I)) is the common name of the compound 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1-(2H)pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)-amino]sulfonyl]benzamide, which is herbicidally active, inhibiting the plant enzyme protoporphyrinogen oxidase (PPO).



(I)

Saflufenacil as described herein includes also different forms of the compound, such as crystalline or particle forms.

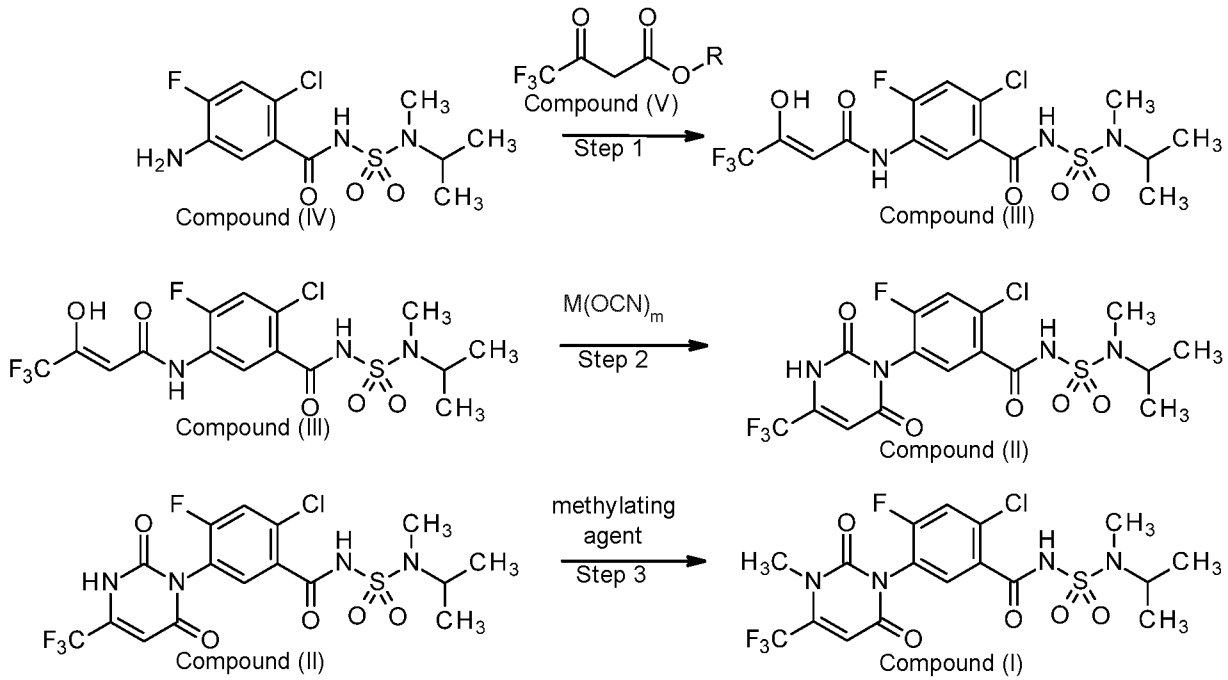
The synthesis of Saflufenacil has been described in WO2001/083459. Further processes for its preparation were described in WO2003/097589, WO2005/054208, WO2006/010474, WO2006/125746 and WO2008/043835. WO2005/054208 in particular teaches the reaction of a phenylisocyanate with an enamine to form a 3-phenyluracil compound.

US2019/0263780, JP2021091638 and EP1397958 disclose processes for the manufacture of certain uracil compounds, such as the PPO inhibitor Epyrifenacil, by reacting an aniline compound with an alkyl trifluoroacetoacetate in the presence of an inorganic base, cyclization of the resulting acetanilide with a cyanate in the presence of a protonic acid, and subsequent methylation to obtain the final product. The reaction of an aniline compound with ethyl 4,4,4-trifluoroacetoacetate without any base, and subsequent cyclization reaction with KOCN in acetic acid is also described in WO2023/017518.

Saflufenacil is particularly useful for preplant applications and selective preemergence weed control in multiple crops, including corn and soybean. However, the purity and yield obtained through the methods described in the literature are not always satisfactory. For crop protection products in general, there is a high demand to save raw materials, to reduce cost and to minimize the environmental impact of the respective chemical processes.

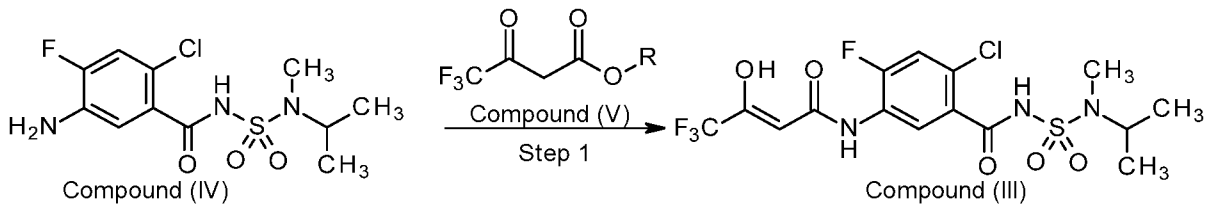
Accordingly, an object of the present invention is to provide an inexpensive, economically viable and safe process, suitable for industrial scale use, for preparing Saflufenacil (I). In addition, an object of the present invention is to provide an inexpensive, economically viable and safe process, suitable for industrial scale use, for preparing the intermediate compounds (II) and (III).

Accordingly, the present invention is directed to a process for preparing Saflufenacil (I), comprising three chemical reaction steps (Steps 1, 2, and 3), a process for preparing the intermediate compound (II), comprising Steps 1 and 2, and a process for preparing the intermediate compound (III), comprising Step 1 (see Scheme 1).

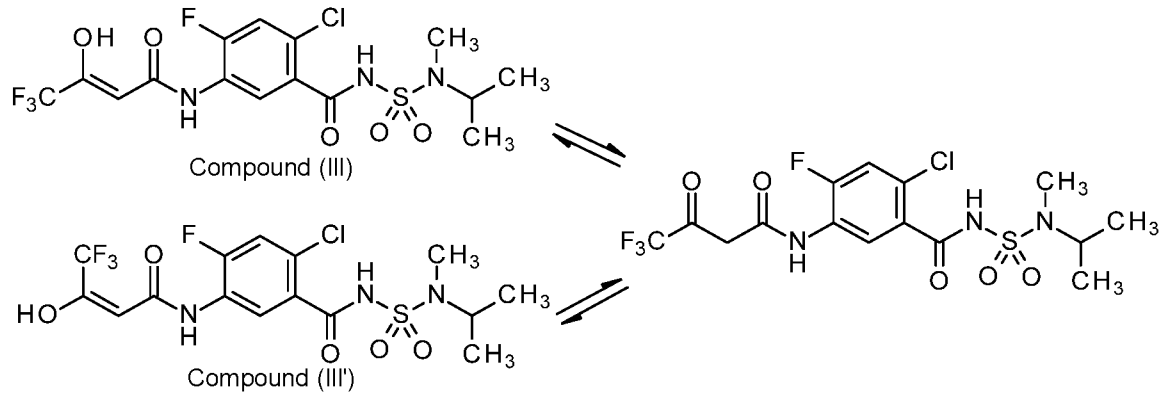


Scheme 1

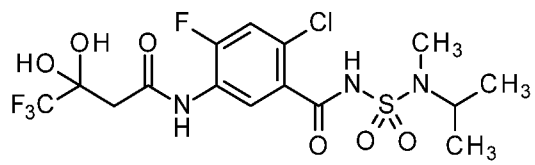
Step 1:



Compound (III) and its stereoisomer (III') are in equilibrium with the corresponding keto form. Both stereoisomers (III) and (III') and the respective tautomer are subject of the present invention:



The corresponding hydrate form is also subject of the present invention:



Compound (III)-hydrate

Compound (IV) is known in the prior art, can be prepared according to the methods described in the prior art, e.g. in WO2004/39768, and can be used in Step 1 with or without further purification.

Compound (V), wherein R is methyl, ethyl, or phenyl, is commercially available, e.g. from Sigma-Aldrich and many other vendors. In a preferred embodiment, Compound (V) is ethyl 4,4,4-trifluoro-3-oxo-butanoate (R is ethyl).

The reaction of Compound (IV) with Compound (V) is usually carried out in an inert organic solvent. Suitable solvents for this reaction are -depending on the temperature range-hydrocarbons, such as pentane, hexane, cyclopentane, cyclohexane, heptane, octane, toluene, xylene; chlorinated hydrocarbons, such as chlorobenzene, 1,2-, 1,3- or 1,4-dichlorobenzene, ethers, such as 1,4-dioxane, anisole; glycol ethers, such as dimethyl glycol ether, diethyl glycol ether, diethylene glycol dimethyl ether; carboxamides, such as N,N-dimethylformamide, N-methylpyrrolidone; nitrated hydrocarbons, such as nitrobenzene, nitroxylenes; tetraalkylureas such as tetraethylurea, tetrabutylurea, dimethylethyleneurea, dimethylpropyleneurea; nitriles, such as acetonitrile, propionitrile, butyronitrile or isobutyronitrile; or else mixtures of individual solvents.

Preferably, the solvent is not miscible with water. Examples for solvents, which are not miscible with water include aromatic hydrocarbons such as toluene, ethylbenzene, o-xylene, m-xylene, p-xylene, and mesitylene; halogenated aromatic hydrocarbons such as chlorobenzene and bromobenzene; nitrile compounds such as benzonitrile; nitro compounds such as nitrobenzene; aliphatic hydrocarbons such as heptane and octane; ether compounds such as dibutyl ether, and anisole; and mixtures thereof.

Most preferred aromatic solvents in the process of Step 1 are chlorobenzene, toluene, xylenes or mixtures thereof.

In one embodiment, o-, m-, p-xylene or a mixture thereof is used as solvent for the reaction of Compound (IV) with Compound (V) in Step 1.

In another embodiment, toluene is used as solvent for the reaction of Compound (IV) with Compound (V).

The reaction of Compound (IV) with Compound (V) can be carried out without the presence of a base. Usually, the reaction of Compound (IV) with Compound (V) is carried out in the presence of a base, which can be an organic or an inorganic base.

Non-limiting examples for suitable inorganic bases are sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, sodium methoxide, or potassium methoxide.

Non-limiting examples for suitable organic bases are tertiary amines such as triethylamine (TEA), diisopropylethylamine, and triethylenediamine (TEDA or DABCO), or pyridine.

Preferably, an organic base is employed in Step 1 of the process according to the invention, more preferably a tertiary amine.

In the most preferred embodiment, the base in Step 1 of the process according to the invention is triethylamine, which provides better conversions and faster kinetics than equal molar amounts of inorganic bases.

The reaction time can vary in a wide range and depends on a variety of factors such as pressure, temperature, solvents or the reagents and auxiliary substances used. Typical reaction times are in the range of from 1 to 20 hours, preferably from 2 to 15 hours and more preferably from 3 to 10 hours.

Step 1 of the process according to the present invention can be carried out under atmospheric pressure or under slightly elevated or reduced pressure. Typically, the atmospheric pressure is employed.
In one embodiment, the alcohol R-OH produced in Step 1 is distilled off under reduced pressure, e.g. between 10 kPa and 90 kPa, 30 kPa and 70 kPa, or 40 kPa and 60 kPa.

Depending on the solvent, the reaction temperature will generally not exceed 180°C and is preferably up to 120°C, and in particular up to 100°C, and will generally be at least 40°C, and preferably at least 50°C.

Frequently, at least the major part of Compound (V) will be added at a low temperature, for example in the range from 0 to 40°C, in particular from 10 to 40°C, and especially from 20 to 30°C, and the mixture will be heated during or after the addition to a temperature in the range from 40 to 180°C, in particular from 50 to 120°C, and especially from 70 to 100°C, e.g. 90°C, until the reaction has gone to completion, and depending on the vapor pressure of the solvent used, the solvent can be refluxed under reduced pressure, e.g. the pressure is from 20 to 90 kPa.

The weight ratio of the solvent to compound (IV) is generally from 100:1 to 1:1, preferably from 50:1 to 1:1, more preferably from 20:1 to 2:1, and most preferably from 10:1 to 3:1.
The molar ratio of compound (IV) to the base, if present, generally is from 1:0.01 to 1:3, preferably from 1:0.1 to 1:2 and most preferably from 1:0.5 to 1:1.5. More base can be added to push reaction to completion if needed.
The molar ratio of compound (IV) to Compound (V) generally is from 1:1 to 1:5, preferably from 1:1 to 1:4, more preferably from 1:1 to 1:2. More compound (V) can be added to push reaction to completion.

In one embodiment, Compound (IV), the base, e.g. TEA, and the solvent (e.g. toluene or xylene) are added to the reactor. The mixture is agitated and heated to 50°C to 140°C, or 70 to 100°C, e.g. 90°C. Compound (V), dissolved in the same solvent as is already present in the reactor or in another suitable solvent, is then added to the reactor. Reaction is then heated to desired temperature and held until reaction is deemed complete via HPLC.

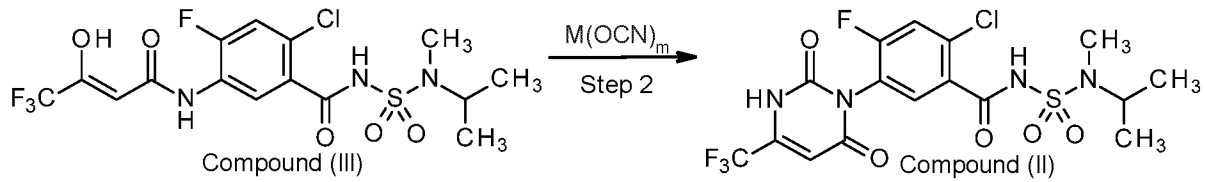
In a preferred embodiment, the reaction of the Compound (IV) with Compound (V) to Compound (III) comprises the steps of

(a) Providing a first mixture comprising Compound (IV), the base (e.g. TEA) and the solvent (e.g. toluene or xylene);
(b) Adding Compound (V) to the first mixture under agitation to form a second mixture, and
(c) Agitating the second mixture.

Usually, the reaction mixture is refluxed with solvent taken overhead in a receiver until reaction is complete. In one embodiment R-OH (methanol, ethanol, or phenol) origination from Compound (V) is taken overhead, pushing the reaction forward. Progress of the reaction can be monitored e.g. by HPLC until Compound (IV) is deemed converted. The product of the reaction, Compound (III) is either isolated in this step or, as in most cases, used as is in the next step, i.e. without work-up.

Work-up of the reaction mixture to obtain Compound (III) can be carried out by methods customary for this purpose. Generally, the alcohol formed during Step 1, e.g. ethanol, in case Compound (V) is ethyl 4,4,4-trifluoro-3-oxo-butanoate, can be removed by distillation or rectification. In addition, or alternatively, the alcohol can be extracted with water and separated from the water-immiscible solvent. The solvent used is removed by suitable processes, for example by distillation or rectification. For further purification, it is possible to use usual processes such as crystallization, precipitation or chromatography.

Step 2:



Compound (III) Compound (II)

In Step 2, Compound (III) is reacted with an isocyanate compound in the presence of an organic acid to obtain Compound (II).

Isocyanate compounds of the general formula $M(OCN)_m$ are employed, wherein m is 1 or 2, and M is an alkali metal, alkaline earth metal or ammonium. In a preferred embodiment, isocyanate compounds of the general formula $M(OCN)_m$, are employed, wherein m is 1, and M is an alkali metal selected from lithium, sodium and potassium, in particular M is sodium or potassium. These compounds are commercially available from Sigma Aldrich and similar vendors and chemical suppliers.

Generally, the reaction is carried out in the presence of a quaternary ammonium salt as a phase transfer catalyst. Suitable quaternary ammonium salts are tetrabutylammonium salts, e.g. tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, or tetrabutylammonium hydrogensulfate.

These compounds are commercially available from Sigma Aldrich and similar vendors and chemical suppliers.

In step 2 of the process according to the present invention, preferred quaternary ammonium salt phase transfer catalysts are tetrabutylammonium chloride and tetrabutylammonium bromide, in particular tetrabutylammonium bromide.

The reaction of Compound (III) with the isocyanate compound in the presence of the quaternary ammonium salt is usually carried out in an inert organic solvent. Suitable solvents for this reaction are -depending on the temperature

range- hydrocarbons, such as pentane, hexane, cyclopentane, cyclohexane, heptane, octane, toluene, xylene; chlorinated hydrocarbons, such as methylene chloride, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, chlorobenzene, 1,2-, 1,3- or 1,4-dichlorobenzene, ethers, such as 1,4-dioxane, anisole; glycol ethers, such as dimethyl glycol ether, diethyl glycol ether, diethylene glycol dimethyl ether; esters, such as ethyl acetate, propyl acetate, methyl isobutyrate, isobutyl acetate; carboxamides, such as N,N-dimethylformamide, N-methylpyrrolidone; nitrated hydrocarbons, such as nitrobenzene; tetraalkylureas such as tetraethylurea, tetrabutylurea, dimethylethyleneurea, dimethylpropyleneurea; nitriles, such as acetonitrile, propionitrile, butyronitrile or isobutyronitrile; or else mixtures of individual solvents.

Preferably, the solvent is not miscible with water. Examples for solvents, which are not miscible with water include aromatic hydrocarbons such as toluene, ethylbenzene, o-xylene, m-xylene, p-xylene, and mesitylene; halogenated aromatic hydrocarbons such as chlorobenzene and bromobenzene; nitrile compounds such as benzonitrile; nitro compounds such as nitrobenzene; aliphatic hydrocarbons such as heptane and octane; ether compounds such as dibutyl ether, and anisole; and mixtures thereof.

Most preferred aromatic solvents in the process of Step 2 are chlorobenzene, toluene, xylenes or mixtures thereof.

In one embodiment, o-, m-, p-xylene or a mixture thereof is used as solvent for the reaction of Compound (III) with the isocyanate compound in Step 2.

In another embodiment, toluene is used as solvent for the reaction of Compound (III) with the isocyanate compound.

The reaction of Compound (III) with the isocyanate compound is usually carried out in the presence an organic acid. Non-limiting examples for suitable organic acids are formic acid, acetic acid, propionic, butyric acid, and benzoic acid.

In the most preferred embodiment, the acid in Step 2 of the process according to the invention is acetic acid, which provides better yield and ease of removal.

The reaction time can vary in a wide range and depends on a variety of factors such as, for example pressure, temperature, solvents or the reagents and auxiliary substances used. Typical reaction times are in the range of from 1 to 30 hours, preferably from 2 to 20 hours and more preferably from 3 to 10 hours.

Step 2 of the process according to the present invention can be carried out under atmospheric pressure or under slightly elevated or reduced pressure. Typically, the atmospheric pressure is employed.

Depending on the solvent, the reaction temperature will generally not exceed 180°C and is preferably up to 120°C, and in particular up to 100°C, and will generally be at least 40°C, and preferably at least 50°C.

Frequently, at least the major part of Compound (III) will be added at once or over a period of several hours at a low temperature, for example in the range from 0 to 40°C, in particular from 10 to 40°C, and especially from 20 to 30°C, e.g. at room temperature, and the mixture will be heated during or after the addition to a temperature in the range from 40 to 180°C, in particular from 50 to 120°C, and especially from 70 to 100°C, e.g. 90°C, until the reaction has

gone to completion, and depending on the vapor pressure of the solvent used, the solvent can be refluxed under reduced pressure, e.g. the pressure is from 20 to 90 kPa.

The weight ratio of compound (III) to the solvent generally, is from 1:1 to 1:20, preferably from 1:2.5 to 1:10.
The molar ratio of compound (III) to the isocyanate compound $M(OCN)_m$ generally is from 1:1 to 1:6 preferably from 1:1 to 1:5, most preferably from 1:1 to 1:4.
The molar ratio of compound (III) to quaternary ammonium salt generally is from 1:0.01 to 1:1, more generally 1:0.01 to 1:0.1 and most preferably from 1:0.02 to 1:0.08.
The molar ratio of compound (III) to the acid generally is from 1:0.01 to 1:30, preferably from 1:0.1 to 1:20, more preferably from 1:1 to 1:15.

In one embodiment, Compound (III), the quaternary ammonium salt, e.g. tetrabutylammonium bromide, the isocyanate compound $M(OCN)_m$, e.g. KOCN, the solvent (e.g. toluene or xylene), and the acid, e.g. acetic acid, are added to the reactor. Reaction is then held at temperature with agitation until deemed complete by HPLC.
In a preferred embodiment, the acid, e.g. acetic acid, is added last to the reactor, preferably dropwise.

Step 2 of the process according to the invention can be conducted either independently of Step 1 or directly after Step 1 without isolation or purification of Compound (III).

In the latter case, the reactor already contains the product of Step 1, Compound (III) in a solvent, e.g. toluene or xylene. The quaternary ammonium salt, e.g. tetrabutylammonium bromide, the isocyanate compound $M(OCN)_m$, e.g. KOCN, and optionally more solvent (e.g. toluene or xylene), and the acid, e.g. acetic acid, are added to the reactor, containing Compound (III).
In a preferred embodiment, the acid, e.g. acetic acid, is added last to the reactor, preferably dropwise.

In a preferred embodiment, the reaction of the Compound (III) with the isocyanate compound $M(OCN)_m$ to Compound (II) comprises the steps of

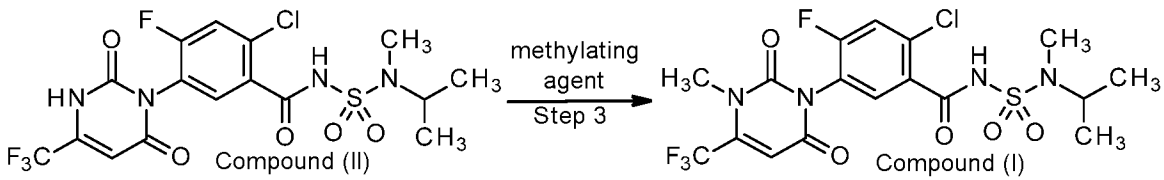
(a) Providing a first mixture comprising Compound (III) and the solvent (e.g. toluene or xylene);
(b) Adding the isocyanate compound $M(OCN)_m$, e.g. KOCN, and the quaternary ammonium salt, e.g. tetrabutylammonium bromide, to the first mixture under agitation to form a second mixture, and
(c) Adding the acid, e.g. acetic acid, to the second mixture under agitation to form a third mixture.

Progress of the reaction can be monitored e.g. by HPLC until Compound (III) is deemed converted. The product of the reaction, Compound (II) is either isolated in this step or, as in most cases, used as is in the next step, i.e. without work-up.

Work-up of the reaction mixture to obtain Compound (II) can be carried out by methods customary for this purpose. Progress of the reaction can be monitored e.g. by HPLC until Compound (III) is deemed converted. In general, the

solvent used is removed by suitable processes, for example by distillation. For further purification, it is possible to use usual processes such as crystallization, precipitation or chromatography.

Step 3:



In Step 3, Compound (II) is reacted with a methylation agent in the presence of a base to obtain Compound (I), Saflufenacil.

Suitable methylating agents are for example dimethyl sulfate, methyl iodide, methyl bromide, methyl chloride, or methyl sulfonate. A particularly preferred methylating agent is dimethyl sulfate.

Suitable bases are inorganic base such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate; sodium hydrogen carbonate, potassium hydrogen carbonate, sodium hydroxide, potassium hydroxide, tripotassium phosphate and trisodium phosphate, and aqueous solutions thereof.

Generally, the reaction is carried out in the presence of a quaternary ammonium salt as a phase transfer catalyst. Suitable quaternary ammonium salts are tetrabutylammonium salts, e.g. tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, or tetrabutylammonium hydrogensulfate.
These compounds are commercially available from Sigma Aldrich and similar vendors and chemical suppliers.
In step 3 of the process according to the present invention, preferred quaternary ammonium salt phase transfer catalysts are tetrabutylammonium chloride and tetrabutylammonium bromide, in particular tetrabutylammonium bromide.

The reaction of Compound (II) with the methylation agent is usually carried out in an inert organic solvent. Suitable solvents for this reaction are -depending on the temperature range- hydrocarbons, such as pentane, hexane, cyclopentane, cyclohexane, heptane, octane, toluene, xylene; chlorinated hydrocarbons, such as methylene chloride, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, chlorobenzene, 1,2-, 1,3- or 1,4-dichlorobenzene, ethers, such as 1,4-dioxane, anisole; glycol ethers, such as dimethyl glycol ether, diethyl glycol ether, diethylene glycol dimethyl ether; esters, such as ethyl acetate, propyl acetate, methyl isobutyrate, isobutyl acetate; carboxamides, such as N,N-dimethylformamide, N-methylpyrrolidone; nitrated hydrocarbons, such as nitrobenzene; tetraalkylureas such as tetraethylurea, tetrabutylurea, dimethylethyleneurea, dimethylpropyleneurea; nitriles, such as acetonitrile, propionitrile, butyronitrile or isobutyronitrile; or else mixtures of individual solvents.

Preferably, the solvent is not miscible with water. Examples for solvents, which are not miscible with water include aromatic hydrocarbons such as toluene, ethylbenzene, o-xylene, m-xylene, p-xylene, and mesitylene; halogenated aromatic hydrocarbons such as chlorobenzene and bromobenzene; nitrile compounds such as benzonitrile; nitro compounds such as nitrobenzene; aliphatic hydrocarbons such as heptane and octane; ether compounds such as dibutyl ether, and anisole; and mixtures thereof.
In one embodiment, toluene and THF are used as solvent in a biphasic reaction for the reaction of Compound (II) with the methylating agent.

The reaction time can vary in a wide range and depends on a variety of factors such as, for example pressure, temperature, solvents or the reagents and auxiliary substances used. Typical reaction times are in the range of from 1 to 20 hours, preferably from 2 to 15 hours and more preferably from 3 to 10 hours.

Step 3 of the process according to the present invention can be carried out under atmospheric pressure or under slightly elevated or reduced pressure. Typically, the atmospheric pressure is employed.

Frequently, at least the major part of Compound (II) will be added at a low temperature, for example in the range from 0 to 70°C, in particular from 10 to 60°C, and especially from 20 to 40°C, and the mixture will be heated during or after the addition to a temperature in the range from 20 to 70°C, in particular from 30 to 60°C, and especially from 40 to 50°C, until the reaction has gone to completion.

The weight ratio of compound (II) to the solvent generally, is from 1:0.3 to 1:20, preferably from 1:1 to 1:15, most preferably form 1:3 to 1:10.
The molar ratio of compound (II) to the methylation agent is from 1:1 to 1:3, preferably from 1:1 to 1:2 and most preferably for 1:1 to 1:1.5.
The molar ratio of compound (II) to quaternary ammonium salt generally is from 1:0.01 to 1:1, more generally 1:0.01 to 1:0.1 and most preferably from 1:0.02 to 1:0.08.

Amount of base is added such that the pH of the reaction is kept between pH 2.5 and 8.0, and most preferably between 4.2 and 6.0.

In one embodiment, Compound (II), is dissolved in solvent (toluene/THF) and water is added as well as the quaternary ammonium salt, e.g. tetrabutylammonium bromide, and methylating agent. The base is then added dropwise such that the desired pH range is achieved and so that the reaction proceeds to completion (monitored by HPLC).

Work-up of the reaction mixture to obtain Compound (I) can be carried out by methods customary for this purpose. In general, the solvent used is removed by suitable processes, for example by distillation. Compound (I) can then be taken up in a water-immiscible organic solvent, any impurities are then extracted using water which, if appropriate, is

acidified. Upon phase separation, the organic phase comprising the product is dried, and the solvent is removed under reduced pressure. For further purification, it is possible to use usual processes such as crystallization, precipitation or chromatography.

- In one embodiment (E1), the intermediate produced in Step 1, Compound (III), is separated from the reaction mixture and purified to obtain a solid.
- In another embodiment (E2), the reaction mixture comprising the intermediate produced in Step 1, Compound (III), is employed without further purification in Step 2.
- In another embodiment (E3), the intermediate produced in Step 2, Compound (II), is separated from the reaction mixture and purified to obtain a solid.
- In another embodiment (E4), the reaction mixture comprising the intermediate produced in Step 2, Compound (II), is employed without further purification in Step 3.
- In another embodiment (E5), Steps 1 and 2 are carried out sequentially as a one-pot synthesis without intermediate work-up, as a telescoping synthesis.
- Preferably, Steps 1, 2 and 3 are carried out sequentially as a one-pot synthesis (E6) without intermediate work-up, as a telescoping synthesis.
- More preferably, Steps 1, 2 and 3 are carried out sequentially in the same solvent, as a one-pot synthesis (E7) without intermediate work-up, as a telescoping synthesis.

EXAMPLES:

Example 1 (Step 1)

In one example of the reaction 67g of Compound (IV) (0.2 mol) was added to a 2L round bottom flask and had 350g of o-xylene added. Triethylamine (20.7g, 0.2 mol) was subsequently added and the reaction was heated to 90°C. To this was added ethyl 4,4,4-trifluoro-3-oxo-butanoate (45.7g, 0.248 mol) in 42.7g o-xylene over 30 min maintaining the 90°C temp in the reactor. The reaction was monitored by HPLC (Compound (III) RT 6 min) and heated for 3 hrs with ethanol being collected in a Dean Stark trap. When reaction was deemed complete 200g of o-xylene was distilled off with vacuum. And 20 ml of DMF added followed by 200g of 10%HCl. After 30 min of agitation the reaction was filtered via Buchner funnel to give a sand like material which was a little sticky. This was washed with hexanes (3 x 100g). Mother liquor and wash show no product. The material was dried in 70ºC vac oven for 3 days. Yielding 97g of 98% pure material (Compound (III).

HPLC method:

Column: Zorbax® Eclipse™ XDB-C18 150 mm x 4.6 mm x 3.5 µm; T 30°C; 2ml/min flow rate; Mobile phase: 66% water: 34 % Acetonitrile, 0.25 ‰ formic acid (88%).

Example 2 (Telescoped Steps 1 and 2)

To a round bottom flask was added 16 g of Compound (IV) (0.049mol, 98.2% pure) and 84 g of m-xylene. TEA (4.95 g, 0.049 mol) was then added and reaction became homogenous. The reaction was then heated to 90ºC and 10.9 g

(0.059 mol) of ethyl 4,4,4-trifluoro-3-oxo-butanoate in 42.7g Xylene was then added over time such that the reaction temp was kept at 90ºC with Ethanol allowed to leave overhead via a Dean Stark Trap. The reaction was then monitored over time by HPLC for completion (done in 3 hrs). 50g of m-xylene was added to the reaction and then distilled off to remove any unreacted ethyl 4,4,4-trifluoro-3-oxo-butanoate. Reaction was sampled for completion and appeared to give 98.2% conversion to Compound (III) by HPLC. HPLC as in Example 1.

The above reaction was then cooled down to 40ºC. Potassium isocyanate (14.75g, 0.18 mol) and tetrabutylammonium bromide (0.05 g, 1.55 10^{-4} mol) were added and 10.6 g (0.177 mol) of Acetic Acid was then added dropwise over 30 min. The temp was then raised to 85ºC were 10.8 g (0.18 mol) of Acetic Acid was added over 3.5 hrs. Reaction was monitored by HPLC over 7 hours. Upon completion, 65 g of liquid (Xylene and Acetic acid mixture) was distilled off under vacuum. The residue was dissolved in 65 g of DMF and then added dropwise to 1 L of water at 10ºC. This provided an easily filterable slurry via Buchner funnel. Upon drying in 50ºC vac oven, 28.6g of 79.7% pure Compound (II) was obtained (96.4% yield from Compound (IV).

Example 3 (Step 2)

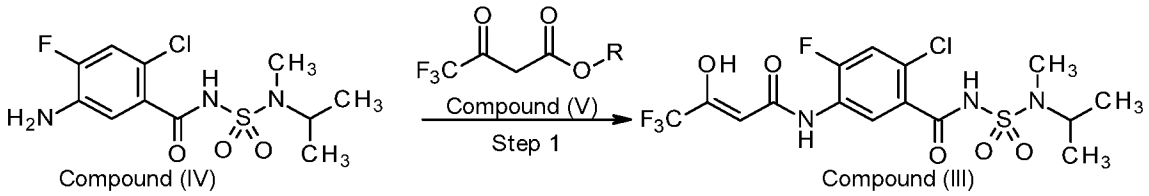
In another reaction 55 g of Compound (III) ((72.9% pure, 0.087 mol) was dissolved in toluene (101.3 g) in a round bottom flask. To this was added 16.1 g (0.198 mol) KOCN, 1.4 g (4.3 10^{-3} mol) TBABr and 19.1g (0.32 mol) AcOH. The reaction was heated to 85ºC and held there for 16hrs. At this point, 90g of a two phase distillate were distilled off at 33torr and 63ºC. To the resulting slurry was added 80g DMF. The DMF mixture was then added dropwise to a 1L of Water chilled to 10ºC. After total addition the water was pH adjusted to 1.7 with 1N HCl and the white solid was filtered via Buchner Funnel and washed with water. The material was then dried in a vac-oven at 50ºC. This provided 43.6g of Compound II (86.1% pure) in 87.2% yield.

Example 4 (Step 3)

In another reaction, Compound II (19.5g, 72.5% pure, 0.03 mol) was added to an automated reactor equipped with pH control. 126.5g of toluene and 25.3 g THF were also added. The mixture was heated to 25-40°C with agitation until the Uracil was dissolved, Water (16.23g) was then added (initial pH of solution was 5.27). 1.95 g of a 50% aq (0.003 mol) Tetrabutylammoniumbromide solution was then added. The reaction was heated to 40°C And the reaction was adjusted to pH 5.2 using 10% NaOH. Dimethyl sulfate (5.15g, 0.0408 mol) was then added in one portion. Held the reaction at 40ºC for 1hr maintaining pH 5.2 by adding 10% NaOH as necessary. Then held the reaction at 40ºC at pH 4.2 with 10% NaOH for 5.5 hrs. Once reaction was deemed complete, a few drops of 93% sulfuric acid was added to adjust pH to 1.46. Reaction was heated to 60ºC for 0.5 hr and the biphasic reaction was split at this temp. The organic layer was then also washed with 16.9 g of water. The organic phase (168 g) was then distilled under vacuum to adjust the concentration of Saflufenacil (Compound (I)) in solution to 15% by mass (in this reaction 67g of solvents distilled off to leave 100.7 g of organic. THF and Toluene solvent matrix was also adjusted (desired ratio is 95:5 Tol:THF). This slurry was then filtered, washed with 5% THF in toluene and dried in 70ºC vac-oven. This yielded an off-white solid 11.7 g of 91.9% Compound (I) (71% yield).

CLAIMS

1. A process for preparing the compound of formula (III), comprising the following step:
Step 1: reacting the compound of formula (IV) in the presence of a base with a compound of formula (V), wherein R is methyl, ethyl, or phenyl, to obtain the compound of formula (III):



2. The process as claimed in claim 1, wherein the base is an organic base.

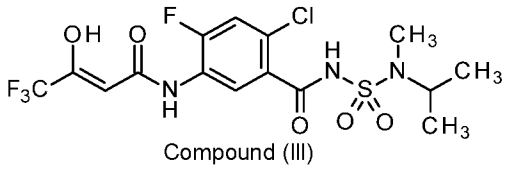
3. The process as claimed in claim 2, wherein the organic base is a tertiary amine or pyridine.

4. The process as claimed in claim 3, wherein the organic base is triethylamine (TEA).

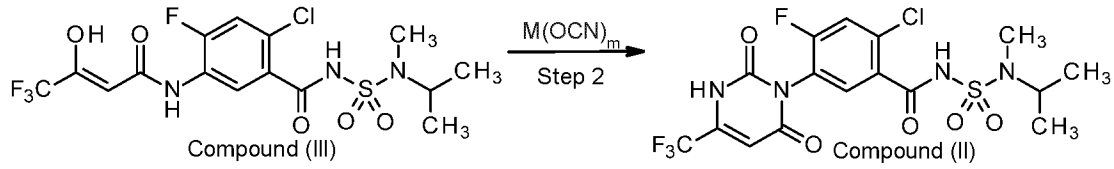
5. The process as claimed in anyone of claims 1 to 4, wherein the molar ratio of the compound of formula (IV) to the base is from 1:0.1 to 1:2.

6. The process as claimed in anyone of claims 1 to 5, wherein the reaction is carried out in an inert organic solvent, preferably in chlorobenzene, toluene, xylenes, or mixtures thereof.

7. The compound of formula (III), including its stereoisomer, its tautomer, and its hydrate



8. A process for preparing the compound of formula (II), comprising the following steps:
Step 1: preparing the compound of formula (III) according to anyone of claims 1 to 6; and
Step 2: reacting the compound of formula (III) with $M(OCN)_m$, wherein M is an alkali metal, alkaline earth metal or ammonium, m is 1 or 2, in the presence of a phase transfer catalyst and an organic acid, to obtain the compound of formula (II):



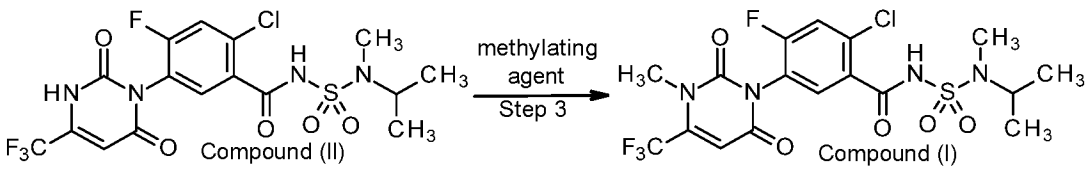
9. The process as claimed in claim 8, wherein the organic acid is acetic acid.

10. The process as claimed in claim 8 or 9, wherein the molar ratio of the compound of formula (II) to the organic acid is from 1:0.1 to 1:20.

11. The process as claimed in any one of claims 8 to 10, wherein the reaction is carried out in an inert organic solvent, preferably in chlorobenzene, toluene, xylenes or mixtures thereof.

12. The process as claimed in any one of claims 8 to 11, wherein Step 1 and Step 2 are carried out sequentially as a one-pot synthesis, without intermediate work-up, as a telescoping synthesis.

13. A process for preparing the compound of formula (I), comprising the following steps:
Step 1: preparing the compound of formula (III) according to anyone of claims 1 to 6;
Step 2: preparing the compound of formula (II) according to anyone of claims 8 to 12; and
Step 3: reacting the compound of formula (II) with a methylating agent in the presence of a base to obtain the compound of formula (I):



14. The process as claimed in 13, wherein Steps 1 to 3 are carried out sequentially as a one-pot synthesis, without intermediate work-up, as a telescoping synthesis.

15. The process as claimed in claim 12 or 14, wherein Steps 1 and 2 or Steps 1 to 3 are carried out in the same solvent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/084211

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/54 C07C303/34
ADD.

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)
C07D 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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/054208 A1 (BASF AG [DE]) 16 June 2005 (2005-06-16) page 22 claims; examples	1-15
Y	EP 1 397 958 A1 (SUMITOMO CHEMICAL CO [JP]) 17 March 2004 (2004-03-17) page 30, paragraph [164] - page 31, paragraph [0167]	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2024	07/01/2025

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/084211

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005054208 A1	16-06-2005	AT E381547 T1	15-01-2008
		BR PI0417052 A	06-02-2007
		CN 1890222 A	03-01-2007
		DK 1692115 T3	25-03-2008
		EP 1692115 A1	23-08-2006
		ES 2295957 T3	16-04-2008
		IL 175713 A	30-12-2010
		JP 4528306 B2	18-08-2010
		JP 2007513110 A	24-05-2007
		KR 20060120187 A	24-11-2006
		US 2006293520 A1	28-12-2006
		WO 2005054208 A1	16-06-2005
EP 1397958 A1	17-03-2004	BR 0117036 A	27-07-2004
		CA 2447845 A1	12-12-2002
		DE 60125985 T2	12-07-2007
		EP 1397958 A1	17-03-2004
		EP 1736052 A2	27-12-2006
		US 2004138063 A1	15-07-2004
		US 2006234865 A1	19-10-2006
		WO 02098228 A1	12-12-2002