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(54) Title: AN IMPROVED PROCESS FOR THE SYNTHESIS OF STROBILURIN FUNGICIDES VIZ TRIFLOXYSTROBIN AND KRESOXIM-METHYL

(57) Abstract: The present invention relates to an improved process for the synthesis of ii-isomer of compound of formula (5). It further relates to the conversion of formula (5), wherein R is H, to Intermediate (I) and subsequently to substantially pure Trifloxystrobin, compound of formula (I) in good yield.

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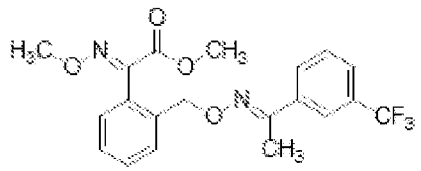
AN IMPROVED PROCESS FOR THE SYNTHESIS OF STROBILURIN FUNGICIDES VIZ TRIFLOXYSTROBIN AND KRESOXIM-METHYL.

FIELD OF INVENTION

The present invention relates to an improved process for the synthesis of strobilurin fungicides viz Trifloxystrobin and Kresoxim-methyl.

BACKGROUND OF THE INVENTION

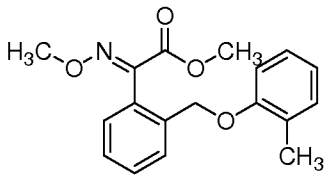
Trifloxystrobin which is (i?)-methoxyimino-{(i?)-2-[l-(3-trifluoromethylphenyl)-ethylideneaminooxymethyl]phenyl} acetic acid methyl ester belongs to the strobilurin class of fungicides. Trifloxystrobin and its process for preparation were first disclosed in **US5238956.** It has the following structural formula:



Formula (I)

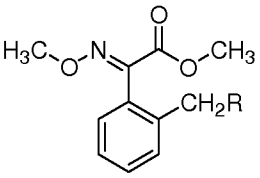
It is most commonly used on bananas, cereals, citrus, coffee, corn, cotton, field beans, grapes, hops, nuts, ornamentals, peanuts, pome fruits, potatoes, rice, small fruits, soybeans, stone fruits, sugar beets, sunflowers, tea, tropical fruits, turf, vegetables and various other crops.

Kresoxim-methyl which is methyl (a£)-a-(methoxyimino)-2-[(2-methylphenoxy) methyl]phenylacetate also belongs to the strobilurin class of fungicides. Kresoxim-methyl was first disclosed in **US4829085.** It has the following structural formula:

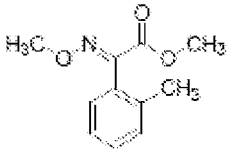


Formula (5b)

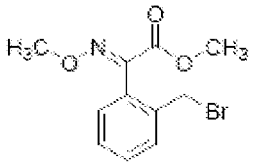
The compound shown below designated as compound of formula (5) is a key intermediate in the synthesis of Trifloxystrobin, when R is substituted as a hydrogen and designated as compound of formula (5a), which subsequently gets converted to Intermediate (I), and Kresoxim-methyl when R is substituted as 2-methylphenoxy and designated as compound of formula (5b).



Formula (5)



(Formula 5a)



Intermediate (I)

US2010/0298593 discloses reaction scheme (A) at page 4 for the preparation of compound of formula (5a) and its conversion to the Intermediate (I) of the present invention. The said publication further cites Rambaud, M. et al., Synthesis; Korean patent publication Nos. 98-83587 and 99-15785 and international patent application No.WO99/07665 in support of Intermediate (I) synthesis.

US5334577 teaches conversion of compound of formula (IV) to compound of formula (VI) at Column 3, line 43 to line 65. It further teaches at Column 3, line 55 to line 68 and column 4, line 1 to line 6, conversion of compound of formula (VI) to formula (III).

US6407100 teaches at column 5; line 32-43, preparation of formula (II). It further discloses at column 4; line 45 to line 67 the process for condensation of formula (II) and formula (III).

US5221762 teaches at column 13, 14 and 15 reaction scheme for the preparation of *E*-isomer of compound of formula (5b) of the present invention.

The prior art processes for the preparation of compound of formula (5) suffer from one or other drawback like low yield, high cycle time, by-product formation and formation of a mixture of Z and *E* isomers. Additionally, recovery of compound of formula (1) is not

possible. This leads to an increase in the effluent treatment load, feasibility and high overall cost.

The processes for the preparation of compound of formula (5) disclosed in the prior art do not yield E-isomer in good yield and high purity.

In a subsequent step, compound of formula (5a) is converted to intermediate (I).

The prior art processes for the preparation of Intermediate (I) suffer from the drawbacks like low yield due to formation of dibromo compound during bromination of compound of formula (5a) using either *N*-bromosuccinimide or bromine in combination with AIBN or benzoyl peroxide or UV light in non-polar chlorinated solvent such as CCl_4 which results in low conversion of compound of formula (5a) into Intermediate (I).

In the light of above disadvantages there is a need to develop an improved process for the preparation of compound of formula (5a) in its E-isomer form in good yield and high purity which can be further converted into Intermediate (I) in good yield and high purity. Intermediate (I) is further used in the preparation of substantially pure Trifloxystrobin in good yield. There is a need to develop a commercially viable process which has the capacity to produce products in good yield, high purity, and which also has the provision to recover useful starting material and reagents from the by-product formed during the course of the reaction.

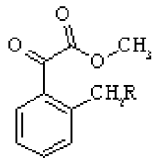
The present inventors have surprisingly developed an improved process for the synthesis of compound of formula (5) and its conversion to Intermediate (I), when R is H, which ameliorates the drawbacks of the prior art.

The present inventors have surprisingly found that the steps of

i) selective hydrolysis,
ii) methoxyimination and
iii) esterification

leading to the formation of compound of formula (5) from the keto compound are critical to recover useful starting material and to obtain the E-isomer in good yield and high purity.

The present inventors have found that the keto compound which is designated as compound of formula (4) contains alpha-substituted-o-toluic acid methyl ester, which is obtained as a by-product during the conversion of compound of formula (3) to compound of formula (4), to the extent of -20%. The process of the present invention proceeds through selective hydrolysis of compound of formula (4) which remains in the aqueous layer as a sodium salt.



Formula (4)

The by-product, i.e. alpha-substituted-o-toluic acid methyl ester, is not hydrolyzed under the above reaction conditions and thus remains in the organic layer which is separated before carrying out next step and hydrolyzed separately using sodium hydroxide in presence of water to recover alpha-substituted-o-toluic acid i.e. compound of formula (1) having purity of -98 % by HPLC which is the starting material of the process of the present invention.

The present inventors have found that selective hydrolysis of compound of formula (4) in the presence of alpha-substituted-o-toluic acid methyl ester leads to recovery of compound of formula (1) i.e. alpha-substituted-o-toluic acid which is the starting material for the process of the present invention, thereby reducing the cost of the process and load on effluent treatment. The recovered compound of formula (1) is used to make compound of formula (5) having same quality as compared to that obtained from compound of formula (1) available commercially.

The present inventors have found that after carrying out the step of methoxyimination on compound of formula (4a), compound of formula (4b) is obtained as a -50:50 mixture of

Z and *E* isomers which on esterification using thionyl chloride and methanol gives compound of formula (5) having E-geometry, exclusively.

The present inventors have found that (Z, E)-isomers of compound of formula (4b) first react with thionyl chloride to form acid chloride. During this reaction, Z-isomer of compound of formula (4b) gets converted into E-isomer of acid chloride of compound of formula (4b), which then reacts with methanol to furnish E-isomer of compound of formula (5), exclusively.

The present inventors have further found that bromination reaction of compound of formula (5a) using sodium bromate in combination with sodium bisulfite (NaBrCb / NaHSCb) in presence of light (UV or ordinary) in biphasic medium of water immiscible "ester class of organic solvents" such as ethyl acetate, n-butyl acetate, isopropyl acetate etc and water results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

The present inventors found that bromination reaction of compound of formula (5a) using *N*-bromosuccinimide in combination with AIBN or benzoyl peroxide in an organic solvent such as acetonitrile, ethyl acetate, dichloromethane, chloroform, chlorobenzene etc, results in higher conversion of compound of formula (5a) to Intermediate (I) giving higher yield as compared to the yield obtained by the use of other solvents such as DCM, EDC, CTC, ethyl acetate, chlorobenzene etc.

The present inventors have further found that bromination reaction of compound of formula (5a) using bromine in presence of light (UV or ordinary) in biphasic reaction medium of dichloromethane and water results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

The present inventors have further found that bromination reaction of compound of formula (5a) using alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, etc in combination with sulphuric acid and hydrogen peroxide (LiBr, NaBr or KBr / H_2SO_4 / H_2O_2) in presence of light (UV or ordinary) in halogenated solvent

such as dichloromethane, chloroform, dichloroethane, etc results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

In the process of the present invention, the crude Intermediate (I) is purified by recrystallization using diisopropyl ether, which, as per the procedures disclosed in the literature, is purified by column chromatography. The purification of Intermediate (I) by recrystallization in diisopropyl ether is a simple, convenient and cost effective method to obtain highly pure Intermediate (I) compared to purification of Intermediate (I) by column chromatography.

The present inventors have developed an improved process in which compounds of formula (2), (3), (4), (4a) and (4b) are not isolated. The compound of formula (4) is subjected to hydrolysis, methoxyimination and esterification, *in situ*, to obtain compound of formula (5) i.e. one pot synthesis of compound of formula (5). The one pot reaction to obtain compound (5) from compound (1) reduces cycle time as the time spent on isolation and purification of each intermediate and solvent recovery is saved. Additionally, the cost of the process is reduced as solvent consumption is minimum and loss in isolation and purification of each intermediate is avoided.

The excess alkali metal carbonate containing by-products generated during the preparation of Trifloxystrobin, compound of formula (I) can be recovered and reused in the subsequent reaction to prepare Trifloxystrobin; compound of formula (I), by condensation of Intermediate (I) and Intermediate (II). In addition, by-product of the reaction i.e. alkali metal bromide such as sodium bromide or potassium bromide etc, recovered after completion of reaction can be reused to carry out bromination reaction of compound of formula (5a) using sulfuric acid and hydrogen peroxide (H_2S0_4 / H_20_2) in presence of light (UV or ordinary).

Recovery of alkali metal bromide by-product and it's reusability for bromination of compound of formula (5a) is a remarkable discovery as it not only reduces cost of the process but also minimizes load on effluent treatment.

OBJECT OF INVENTION

It is an object of the present invention to provide an improved process for the synthesis of Trifloxystrobin and Kresoxim-methyl.

It is an object of the present invention to provide an improved process for the synthesis of E-isomer of compound of formula (5).

It is another object of the present invention to provide an improved process for the synthesis of E-isomer of compound of formula (5) in good yield and high purity.

It is another object of the present invention to recover compound of formula (1) having purity of -98% by HPLC during the synthesis of compound of formula (5).

It is yet another object of the present invention to provide improved processes for conversion of compound of formula (5a) to Intermediate (I) in good yield and high purity.

It is a further object of the present invention to provide an improved process for the synthesis of substantially pure Trifloxystrobin from Intermediate (I) in good yield.

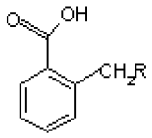
It is another object of the present invention to recover excess alkali metal carbonate along with by-products formed in the synthesis of Trifloxystrobin and reuse it for the synthesis of Trifloxystrobin; compound of formula (I), by condensation of Intermediate (I) and Intermediate (II) in the subsequent batch.

It is another object of the present invention to recover alkali metal bromide by-product formed in the synthesis of Trifloxystrobin; compound of formula (I), and reuse it as a reagent for bromination of compound of formula (5a) to obtain Intermediate (I) in good yield and high purity.

SUMMARY OF INVENTION

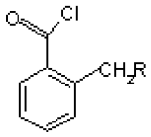
According to an aspect of the present invention there is provided an improved process for the preparation of compound of formula (5) which comprises the steps of:

i. Reacting a compound of formula (1):



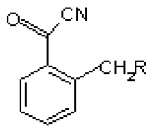
Formula (1)

with thionyl chloride in the presence of dimethylformamide in an organic solvents to obtain compound of formula (2);



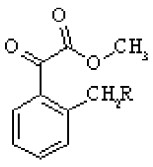
Formula (2)

ii. Converting compound of formula (2) to compound of formula (3) by using metal cyanide in presence of water in an organic solvent;

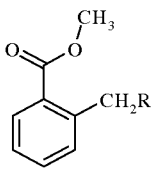


Formula (3)

iii. Converting compound of formula (3) by using dry HCl and methanol in an organic solvent to obtain compound of formula (4) and alpha-substituted-o-toluic acid methyl ester as a by-product;

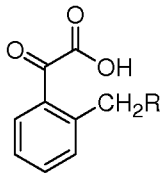


Formula (4)



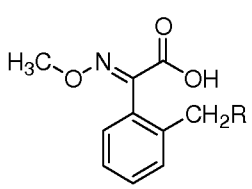
alpha-substituted-o-toluic acid methyl ester

iv. Selective hydrolysis of compound of formula (4) with alkali metal hydroxide in the presence of water in an organic solvent to obtain compound of formula (4a);

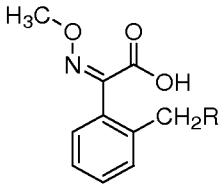


Formula (4a)

v. Methoxyimination of compound of formula (4a) by using methoxyamine hydrochloride in solvents of class chlorinated hydrocarbons such as dichloromethane, dichloroethane, etc to obtain compound of formula (4b) which is a mixture of *E*- and Z-isomers;



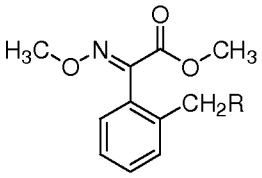
E-isomer



Z-isomer

Formula (4b)

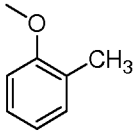
vi. Esterification of compound of formula (4b) using thionyl chloride in the presence of methanol to obtain exclusively E-isomer of compound of formula (5).



Formula (5)

Wherein **R** is **H**

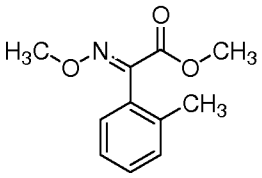
or



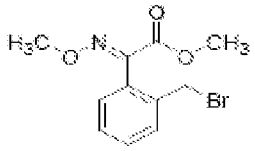
2-methylphenoxy.

According to another aspect of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using sodium bromate in combination with sodium bisulfite, (NaBrCb / NaHSCb) in biphasic medium of water immiscible "ester class of organic solvents" such as ethyl acetate, n-butyl acetate, isopropyl acetate etc and water in presence of light (UV or ordinary).



(Formula 5a)

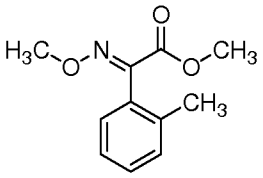


Intermediate (I)

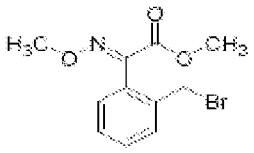
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

According to another aspect of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula 5, wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using *N*-bromosuccinimide in combination with AIBN or benzoyl peroxide in an organic solvent such as acetonitrile, ethyl acetate, dichloromethane, chloroform, chlorobenzene etc;



(Formula 5a)

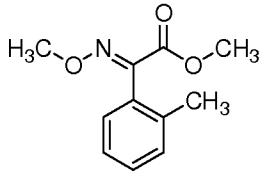


Intermediate (I)

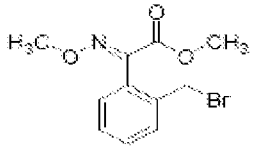
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

According to another aspect of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using bromine in biphasic medium comprising water and one of the halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)

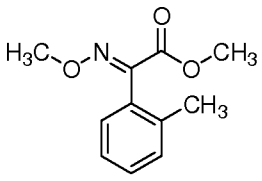


Intermediate (I)

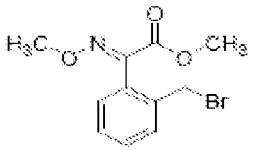
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization using any of the "ether class of organic solvents" such as diethyl ether, *di-n*-propyl ether, di-isopropyl ether, methyl *tert-butyl* ether, etc.

According to another aspect of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, etc in combination with sulphuric acid and hydrogen peroxide (LiBr, NaBr or KBr/ H_2SO_4 / H_2O_2) in halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)

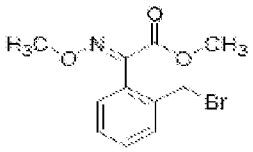


Intermediate (I)

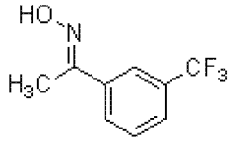
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

According to yet another aspect of the present invention there is provided an improved process for the preparation of Trifloxystrobin, compound of formula (I) having purity more than 98%, which comprises the steps of:

i. Reacting intermediate (II) with intermediate (I) as obtained by the process of the present invention in the presence of base in an organic solvent;

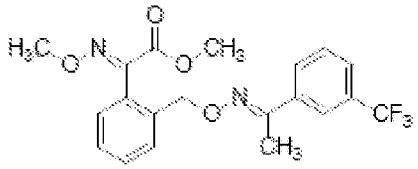


Intermediate (I)



Intermediate II

ii. Purifying the product i.e. Trifloxystrobin, compound of the formula (I) by recrystallization in an organic solvent.



Formula (I)

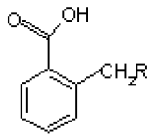
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a robust, efficient and economical synthesis of compound of formula (5) in good yield and high purity. It further relates to the use of compound of

formula (5) (wherein R is Hydrogen) i.e. compound of formula (5a) for the synthesis of Intermediate (I) and its conversion to substantially pure Trifloxystrobin, compound of formula (I) in good yield. Substantially pure Trifloxystrobin means that purity is more than 98%.

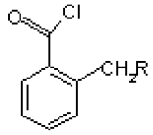
In an embodiment of the present invention there is provided an improved process for the preparation of compound of formula (5) which comprises the steps of:

i. Reacting a compound of formula (1):



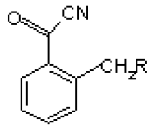
Formula (1)

with thionyl chloride in the presence of dimethylformamide in an organic solvent to obtain compound of formula (2);



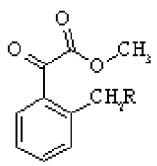
Formula (2)

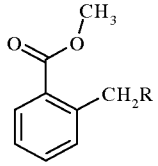
ii. Converting compound of formula (2) to compound of formula (3) by using metal cyanide in presence of water in an organic solvent;



Formula (3)

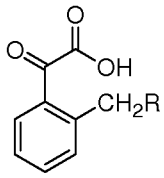
iii. Converting compound of formula (3) by using dry HC1 and methanol in an organic solvent to obtain compound of formula (4) and alpha-substituted-o-toluic acid methyl ester as a by-product;





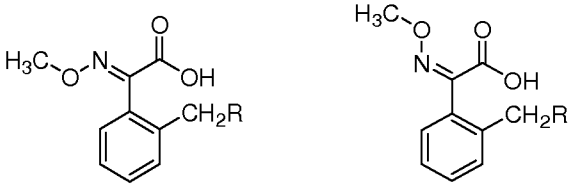
Formula (4) **alpha-substituted-o-toluic acid methyl ester**

iv. Selective hydrolysis of compound of formula (4) with alkali metal hydroxide in the presence of water in an organic solvent to obtain compound of formula (4a);



Formula (4a)

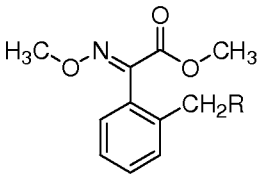
v. Methoxyimination of compound of formula (4a) by using methoxyamine hydrochloride solvents of class chlorinated hydrocarbons such as dichloromethane, dichloroethane, etc to obtain compound of formula (4b) which is a mixture of *E*- and Z-isomers;



E-isomer Z-isomer

Formula (4b)

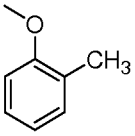
vi. Esterification of compound of formula (4b) using thionyl chloride in the presence of methanol to obtain exclusively E-isomer of compound of formula (5).



Formula (5)

Wherein R is H

or



2-methylphenoxy.

In an embodiment of the present invention metal cyanide used in step (ii) is selected from sodium cyanide, potassium cyanide, cuprous cyanide, etc.

In an embodiment of the present invention alkali metal hydroxide used in step (iv) is sodium hydroxide.

In an embodiment of the present invention organic solvent used in step (i) to step (iv) is selected from toluene, xylene, mesitylene, chlorobenzene, 1,2-dichlorobenzene, etc.

In another embodiment of the present invention compound of formula (4) is converted to compound of formula (5) comprising the steps of (i) selective hydrolysis, (ii) methoxyimination and (iii) esterification which are critical to yield the compound of formula (5) in E-isomer form with good yield and high purity.

Keto compound which is designated as compound of formula (4) contains alpha-substituted-o-toluic acid methyl ester which is obtained as a by-product during the conversion of compound of formula (3) to compound of formula (4) to the extent of -20%. The process of the present invention proceeds through selective hydrolysis of compound of formula (4) which remains in the aqueous layer as a sodium salt.

The by-product i.e. alpha-substituted-o-toluic acid methyl ester, is not hydrolyzed under the above reaction condition and thus remain in organic layer which is separated before carrying out methoxyimination of compound of formula (4a) and hydrolyzed separately using sodium hydroxide in presence of water to recover alpha-substituted-o-toluic acid, compound of formula (1) having purity of -98 % by HPLC which is the starting material of the process of the present invention.

Selective hydrolysis of compound of formula (4) in the presence of alpha-substituted-o-toluic acid methyl ester leads to recovery of compound of formula (1), i.e. alpha-substituted-o-toluic acid which is the starting material for the process of the present

invention, thereby reducing the cost of the process and load on effluent. The recovered compound of formula (1) can be used to make compound of formula (5).

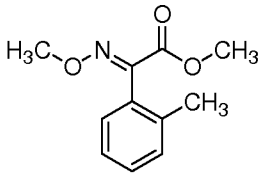
In another embodiment of the present invention, compound of formula (4a) is carried forward to methoxyimination using methoxyamine hydrochloride to obtain compound of formula (4b) which is obtained as a ~50:50 mixture of Z and *E* isomers which on esterification using thionyl chloride and methanol gets converted to compound of formula (5) having E-geometry exclusively.

(Z, E)-Isomers of compound of formula (4b) first react with thionyl chloride to form acid chloride. During this reaction, Z-isomer of compound of formula (4b) gets converted into E-isomer of acid chloride of compound of formula (4b), which then reacts with methanol to furnish E-isomer of compound of formula (5), exclusively.

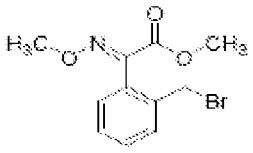
In another embodiment of the present invention compound of formula (2), (3), (4), (4a) and (4b) are not isolated. The compound of formula (4) is subjected to hydrolysis, methoxyimination and esterification, *in situ*, to obtain compound of formula (5).

In another embodiment of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5) (wherein R is Hydrogen) i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using sodium bromate in combination with sodium bisulfite ($NaBrO_3$ / NaHSOa) in biphasic medium of water immiscible "ester class of organic solvents" such as ethyl acetate, n-butyl acetate, isopropyl acetate etc and water in presence of light (UV or ordinary).



(Formula 5a)



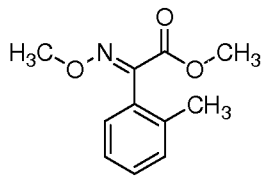
Intermediate (I)

ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

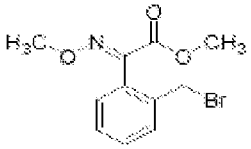
In another embodiment of the present invention bromination reaction, carried out using sodium bromate in combination with sodium bisulfite (NaBrCb / NaHSCb) in biphasic medium of water immiscible "ester class of organic solvents" such as ethyl acetate, *n*-butyl acetate, isopropyl acetate etc and water in presence of UV or ordinary light, results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

In another embodiment of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5) (wherein R is Hydrogen) i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a), to obtain Intermediate (I) using *N*-bromosuccinimide in combination with AIBN or benzoyl peroxide in an organic solvent such as acetonitrile, ethyl acetate, dichloromethane, chloroform, chlorobenzene etc.



(Formula 5a)



Intermediate (I)

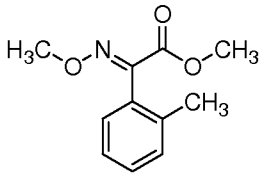
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

In another embodiment of the present invention acetonitrile, ethyl acetate, dichloromethane, chloroform, chlorobenzene etc is used as a solvent during bromination of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) using *N*-bromosuccinimide in combination with AIBN or benzoyl peroxide to obtain

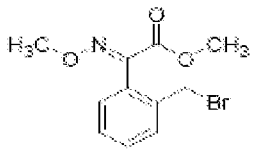
Intermediate (I) giving higher yield as compared to the yield obtained by the use of other solvent such as DCM, EDC, CTC, ethyl acetate, chlorobenzene etc.

In another embodiment of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5) (wherein R is Hydrogen) i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, etc in combination with sulphuric acid and hydrogen peroxide (LiBr, NaBr or KBr/ H_2SO_4 / H_2O_2) in halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)



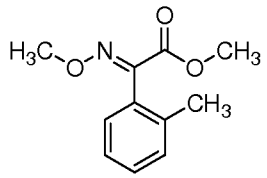
Intermediate (I)

ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

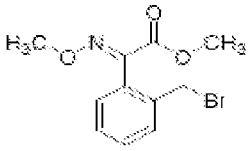
In another embodiment of the present invention bromination reaction, carried out using alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, etc in combination with sulphuric acid and hydrogen peroxide (NaBr (KBr) / H_2SO_4 / H_2O_2) in halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light, results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

In another embodiment of the present invention there is provided an improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5) (wherein R is Hydrogen) i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) to obtain Intermediate (I) using bromine in biphasic medium comprising water and one of the halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)



Intermediate (I)

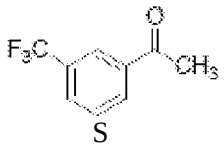
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in using any of the "ether class of organic solvents" such as diethyl ether, *di-n*-propyl ether, di-isopropyl ether, methyl *tert-butyl* ether, etc.

In another embodiment of the present invention bromination reaction, carried out using bromine in biphasic medium comprising water and one of the halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light, results in higher conversion of compound of formula (5a) into Intermediate (I) giving higher yield and purity than any other process reported in the literature.

In another embodiment of the present invention, the crude Intermediate (I) is purified by recrystallization in diisopropyl ether.

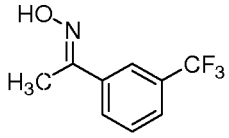
In another embodiment of the present invention there is provided a process for the preparation of Intermediate (II) which comprises the steps of:

i. Reacting a compound of formula (6):



Formula (6)

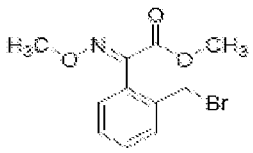
with hydroxylamine hydrochloride and methanol in the presence of sodium hydroxide to obtain Intermediate (II).



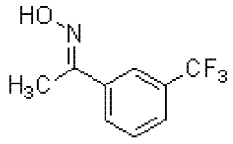
Intermediate-II

In yet another embodiment of the present invention there is provided an improved process for the preparation of Trifloxystrobin, compound of formula (I) having purity more than 98%, which comprises the steps of:

i. Reacting intermediate (II) with intermediate (I) as obtained by the process of the present invention in the presence of base in an organic solvent;

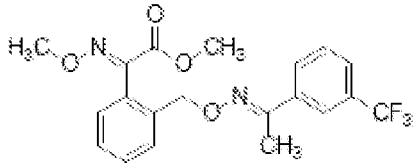


Intermediate (I)



Intermediate II

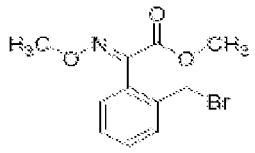
ii. Purifying the product i.e. Trifloxystrobin, compound of the formula (I) by recrystallization in an organic solvent.



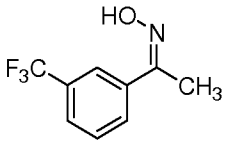
Formula (I)

In further embodiment of the present invention there is provided an improved process for preparation of substantially pure Trifloxystrobin, compound of formula (I), which comprises the steps of

i) condensation of Intermediate (I) and Intermediate (II) in organic solvent using alkali metal carbonate.



Intermediate (I)

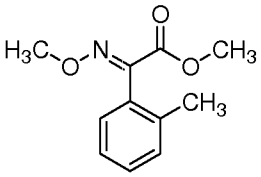


Intermediate (II)

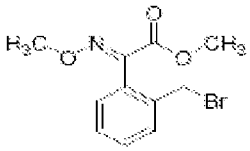
ii) Purification of crude Trifloxystrobin, compound of formula (I), obtained in step (i) by recrystallization in organic solvent.

iii) Recovery of excess base for reuse in subsequent batch.

iv) Recovery of alkali metal bromide, by-product formed in the reaction, for reuse in bromination of compound of formula (5a) to obtain Intermediate (I)



(Formula 5a)



Intermediate (I)

In another embodiment of the present invention base used in the step of condensation of Intermediate (I) and Intermediate (II) is selected from the group consisting of inorganic base or organic base.

Inorganic base includes alkali metal carbonate, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate or alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide or alkali metal hydride, such as sodium hydride, potassium hydride or potassium ieri-butoxide or sodium amide.

Organic base includes triethylamine, di-isopropylethyl amine, *N*-methylmorpholine, piperidine, pyridine etc.

In another embodiment of the present invention an organic solvent used in the step of condensation of Intermediate (I) and Intermediate (II) is selected from the group consisting of "ketone class of organic solvents" such as acetone, methyl isobutyl ketone, etc or polar aprotic solvents such as dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide, *N*-methylpyrrolidine, etc or cyclic and acyclic ethers such as tetrahydrofuran, dioxane, dimethoxyethane, etc or "ester class of organic solvents" such as ethyl acetate, ft-butyl acetate, isopropyl acetate, isobutyl acetate, etc or acetonitrile.

In another embodiment of the present invention organic solvent used in the step of purifying the product i.e. Trifloxystrobin, compound of formula (I) is selected from the group consisting of methanol, ethanol, isopropanol, n-propanol, w-butanol, acetonitrile, ethyl acetate, diethyl ether, diisopropyl ether, methyl isobutyl ether etc.

In a preferred embodiment of the present invention for the synthesis of Trifloxystrobin, compound of formula (I), wherein Intermediate (I) is condensed with Intermediate (II) using alkali metal carbonate in MIBK at 115 °C. The excess alkali metal carbonate is recovered and reused in the subsequent batch. In the course of the reaction, alkali metal bromide is formed as a byproduct which is recovered and reused for the bromination of compound of formula (5a) to obtain Intermediate (I).

In another embodiment of the present invention Trifloxystrobin, compound of formula (I) is obtained with purity more than 98%

Batch wise data of o-toluic acid methyl ester formed during synthesis of compound of formula (4); wherein R is hydrogen.

Batch No	**Batch Size**	**% of oxo-o-tolylacetic acid methyl ester [compound of formula (4)] by HPLC**	**% of o-toluic acid methyl ester by HPLC (by-product)**
1	100 g	60.0 %	38.0 %
2	100 g	70.0 %	24.0 %
3	100 g	55.0 %	37.0 %

Batch wise data of selective hydrolysis of oxo-o-tolylacetic acid methyl ester; compound of formula (4); wherein R is hydrogen.

Batch No	Batch Size	% of oxo-*o*-tolylacetic acid in aqueous layer [compound of formula (4a); wherein R is hydrogen] by HPLC.	% of *o*-toluic acid methyl ester in organic layer by HPLC (by-product)
1	100 g	90.0 %	91.0 %
2	100 g	98.0 %	80.0 %
3	100 g	96.0 %	87.0 %

Batch wise data of recovery of o-toluic acid; compound of formula (1), wherein R is hydrogen.

Batch No	Batch Size	Weight of product (output)	Weight of recovered *o*-toluic acid	Yield w/w	Yield (%)	Purity of recovered *o*-toluic acid by HPLC
1	100 g	52.0 g	25.0 g	0.69	45.6 %	99.3 %
2	100 g	61.0 g	16.0 g	0.72	47.7%	99.2 %
3	100 g	55.0 g	21.0 g	0.69	45.8%	99.7 %

Batch wise data of ratio of Z-and E-methoxyimino-o-tolylacetic acid; compound of formula (4b); wherein R is hydrogen.

Batch No.	Batch Size	Ratio of *Z*- and *E*- isomers of methoxyimino-*o*-tolylacetic acid compound of formula (4b) by HPLC
1	100 g	45:55
2	100 g	50:50
3	100 g	49:50

Batch wise data of ratio of Z-and E-methoxyimino-o-tolylacetic acid methyl ester compound of formula (5); wherein R is hydrogen.

Batch No	Batch Size	Weight of *E*-methoxyimino-*o*-tolylacetic acid methyl ester compound of formula (5)	% of Z-and fi-methoxyimino-o-tolylacetic acid methyl ester compound of formula (5)	
			Z-isomer	fi-isomer
1	100 g	52.0	0.8 %	99.0 %
2	100 g	61.0	0.48 %	99.5 %
3	100 g	55.0	0.63 %	99.37 %

Batch wise data of 2-methylphenoxybenzoic acid methyl ester formed during synthesis of compound of formula (4); wherein R is 2-methylphenoxy-

Batch No.	Batch Size	% of oxo-(2-*o*-tolyloxymethylphenyl)acetic acid methyl ester [compound of formula (4)] by HPLC	% of 2-methylphenoxybenzoic acid methyl ester by HPLC (by product)
1	100 g	58.27%	18.95%
2	100 g	61.19%	17.20%
3	100 g	68.64%	14.86%

Batch wise data of oxo-(2-o-tolyloxymethylphenyl) acetic acid sodium salt formed during synthesis of compound of formula (4a); wherein R is 2-methylphenoxy-

Batch No.	Batch Size	% of oxo-(2-*o*-tolyloxymethylphenyl)acetic acid in aqueous layer [compound of formula (4a)] by HPLC	% of 2-methylphenoxybenzoic acid methyl ester by HPLC (by product)
1	100 g	85.45%	68.57%
2	100 g	91.92%	46.96%
3	100 g	97.24%	65.16%

Batch wise data of recovery of 2-methylphenoxybenzoic acid; compound of formula (1), wherein R is 2-methylphenoxy-

Batch No.	Batch Size	Weight of product (output)	Weight of recovered 2-methylphenoxy benzoic acid	Yield (w/w)	Yield (%)	Purity of recovered 2-methyl phenoxy benzoic acid by HPLC
1	100 g	52.58 g	13.7 g	0.81	52.6%	97.1 %
2	100 g	57.5 g	13.1 g	0.85	57.5%	97.3 %
3	100 g	61.0 g	10.4 g	0.80	61.0%	97.7 %

Batch wise data of ratio of Z- and E-methoxyimino-(2-o-tolyloxymethylphenyl) acetic acid compound of formula (4b); wherein R is 2-methylphenoxy-

Batch No.	Batch Size	Ratio of *Z*- and *E*-isomer of methoxyimino-(2-*o*-tolyloxymethylphenyl)acetic acid (4b) by HPLC
1	100 g	42 : 58
2	100 g	43 : 57
3	100 g	46: 54

Batch wise data of ratio of Z- and j?-methoxyimino-(2-o-tolyloxymethylphenyl)acetic acid methyl ester compound of formula (5); wherein R is 2-methylphenoxy-

Batch No.	Batch Size	Weight of *E*-methoxyimino-(2-*o*-tolyloxymethylphenyl)acetic acid methyl ester (5b)	% of *Z*- and *E*-methoxyimino-(2-*o*-tolyloxymethylphenyl)acetic acid methyl ester (5b)	
			Z–isomer	*E*-isomer
1	100 g	52.6 g	0.34 %	99.66%
2	100 g	57.5 g	0.16 %	99.84%
3	100 g	55.0 g	0.63 %	99.37%

Batch wise data regarding yield and purity of Intermediate (I) formed by using NBS-AIBN / C¾CN

Batch No	Batch Size	Weight of product (output)	Yield w/w	Yield (%)	Purity of Intermediate (I) by HPLC (% Area)
1	10.0 g	10.4 g	1.04	78.7	96.60
2	10.0 g	10.5 g	1.05	79.5	96.13

Batch wise data regarding yield and purity of Intermediate (I) formed by using (NaBrCb / NaHSOa)

Batch No	Batch Size	Weight of product (output)	Yield w/w	Yield (%)	Purity of Intermediate (I) by HPLC (% Area)
1	25 g	24.5 g	0.98	71.3	98.01
2	25 g	24.3 g	0.972	70.7	97.5
3	25 g	24.4 g	0.976	71.0	98.23

Batch wise data regarding yield and purity of Intermediate (I) formed by using Br_2/H_2Q

Batch No.	Batch size	Weight of product (output)	Yield w/w	Yield (%)	Purity of Intermediate (I) by HPLC (% Area)
1	1.0 g	1.0 g	1.0	72.3	98.0

Batch wise data regarding yield and purity of Intermediate (I) formed by using KBr/H?SQ4 /Peroxide e.g. H?Q2_benzoyl peroxide

Batch No.	Batch size	Weight of product (output)	Yield w/w	Yield (%)	Purity of Intermediate (I) by HPLC (% Area)
1	1.0 kg	0.916 kg	0.916	66.6	96.54

2	1.0 kg	0.948 kg	0.948	68.9	96.78
3	1.0 kg	1.02 kg	1.02	74.2	95.6

Batch wise data regarding yield and purity of Intermediate (I) formed by using recovered KBr (formed as a by-product during synthesis of Trifloxystrobin)

Batch No.	**Batch size**	**Weight of product (output)**	**Yield w/w**	**Yield (%)**	**Purity of Intermediate (I) by HPLC (% Area)**
1	1.0 g	1.0 g	1.0	72.3	98.3

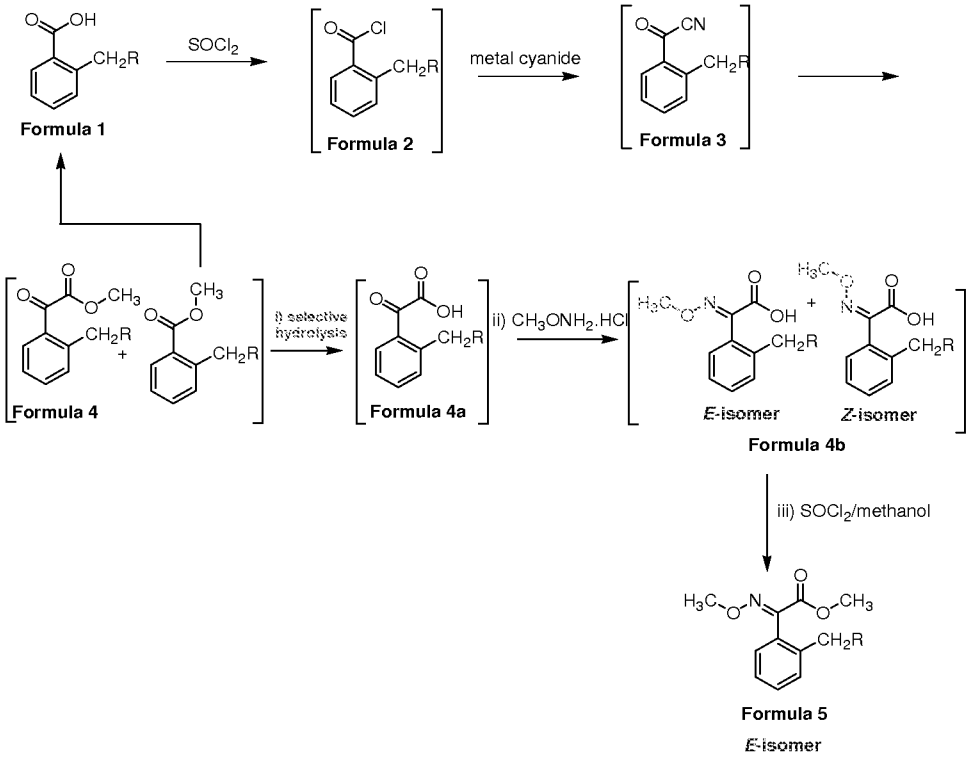
Batch wise data regarding yield and purity of Intermediate (II)

Batch No	**Batch Size**	**Weight product (output)**	**Yield w/w**	**Yield (%)**	**Purity of Intermediate of formula (II) by HPLC (% Area)**
1	1.0 kg	0.944 kg	0.944	88.2	99.75
2	1.0 kg	0.992 kg	0.992	92.7	99.37
3	1.0 kg	0.976 kg	0.976	91.2	99.4

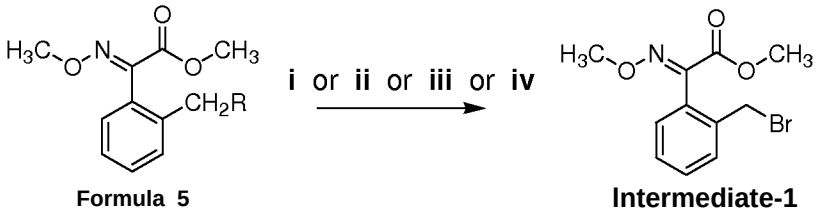
Batch wise data regarding yield and purity of compound of formula (I).

Batch No	**Batch Size**	**Weight product (output)**	**Yield w/w**	**Yield (%)**	**Purity of compound of formula (I) by HPLC (% Area)**	**Impurity of the formula 7 (%)**
1	0.94 kg	1.04 kg	1.1	78	99.58	0.25
2	0.99 kg	1.05 kg	1.06	76.5	99.54	0.28

Synthesis for preparation of compound of formula (5) can be represented as shown in scheme (I) as follows:

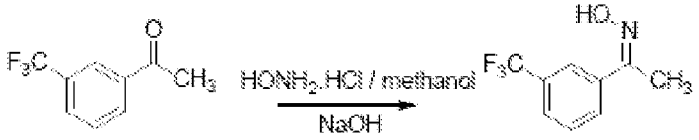


Synthesis for preparation of Intermediate (I) from *E*-isomer of compound of formula (5); wherein R is H can be represented as shown in scheme (II) as follows:



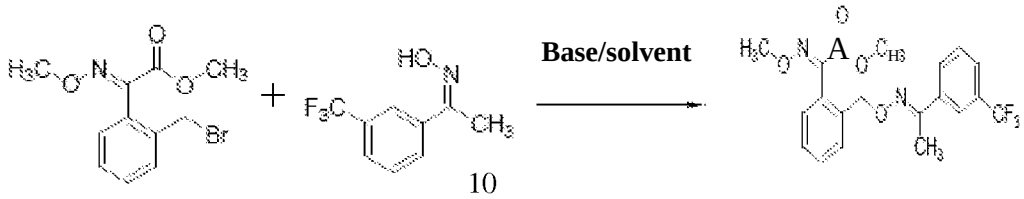
i = NBS / AIBN or benzoyl peroxide
ii = $NaBrO_3$ / $NaHSO_3$, UV or ordinary light
iii = Br_2 / H_2O , UV or ordinary light
iv = alkali metal bromide / H_2SO_4 / H_2O_2, UV or ordinary light

Synthesis for preparation of Intermediate of formula (II) can be represented in scheme (III) as follows:



Formula (6) **Intermediate (II)**

Synthesis for preparation of compound of formula (I) i.e. Trifloxystrobin can be represented in Scheme (IV) as follows:



Intermediate (I) **Intermediate (II)** **Formula (I) (Trifloxystrobin)**

The following examples are meant to illustrate the present invention. The examples are presented to exemplify the invention and are not to be considered as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of compound of formula (2); wherein R is H

o-Toluic acid (100.0 g) was added in xylene (450.0 ml) at ambient temperature. To the slurry was added DMF (9.1 g). To the reaction mass was added thionyl chloride (100 g). The reaction mass was heated at 50 °C for 1.0 hr. The reaction mass was cooled to room temperature after removing excess thionyl chloride. This reaction mass contains o-toluoyl chloride, compound of formula (2).

Example 2: Preparation of compound of formula (3); wherein R is H

Reaction mass obtained in example 1 was added drop wise into the biphasic mixture of xylene (-550.0 ml) and water (100.0 ml) containing sodium cyanide (16.0 g) and TBAB (1.0 g), under stirring below 20 °C. While the addition was continued, solution of sodium cyanide (30.0 g) in water (200.0 ml) was added simultaneously into the reaction mass. The reaction mass was stirred for 2.0 hrs at room temperature. The organic layer was separated, washed with water (3 x 200 ml), dried over sodium sulphate and cooled to -5 to 0 °C. This organic layer contains 2-oxo-o-tolylacetonitrile, compound of formula (3).

Example 3: Preparation of compound of formula (4); wherein R is H

Into the reaction mass obtained in example 2 was purged dry hydrogen chloride gas at -5 to 0 °C. After 1.0 hr, methanol (90.0 ml) was added into the reaction mass under stirring. Dry hydrogen chloride gas was purged into the reaction mass for 6.0 hrs. Methanol (60.0 ml) was added into the reaction mass at 15-20 °C. The reaction mass then heated to 40-45°C and to it was added sulfuric acid (140.0 g) maintaining the temperature between 40-45 °C. The reaction mass was stirred for 3.0 hrs. Methanol (90.0 ml) was then added into the reaction mass and stirred for 5.0 hrs at 60-65 °C. The reaction mass was cooled to 40 °C. Water (200.0 ml) was added into the reaction mass and stirred for 10.0 min. Organic layer was separated, which contains a mixture of oxo-o-tolylacetic acid methyl ester, compound of formula (4) and o-toluic acid methyl ester.

Example 4: Preparation of compound of formula (5); wherein R is H i.e. compound of formula (5a).

To the organic layer obtained in example 3 was added TBAB (1.0 g), solution of sodium hydroxide (20.0 g) in water (200.0 ml) and stirred at 45 °C for 2.0 hrs. The organic layer containing o-toluic acid methyl ester was separated and preserved to recover o-toluic acid. To the aqueous layer, which contains oxo-o-tolylacetic acid, compound of formula (4a),

was added solution of methoxyamine hydrochloride (45.0 g) in water (50.0 ml) and stirred for 1.0 hr at room temperature. DCM (200.0 ml) was added into the reaction mass and stirred for 2.0 hrs. To the reaction mass was added cone. HC1 and stirred for 10 min. Organic layer was separated. Aqueous layer was extracted with DCM (100.0 ml). The organic layers were combined and dried. This combined organic layer contains a -50:50 mixture of *E*- and Z-isomers of methoxyimino-o-tolylacetic acid, compound of formula (4b). To it was added DMF (5.0 g) followed by thionyl chloride (120.0 g) at room temperature. The reaction mass was heated at 40-45 °C for 8.0 hrs and then concentrated to obtain gummy mass. To this gummy mass was added methanol (150.0 ml). The reaction mixture was heated at 60-65 °C for 1.0 hr, cooled to 5-10 °C and filtered. The white solid was washed with methanol (50.0 ml) and dried to obtain (E)-mefhoxyimino-o-tolylacetic acid methyl ester, compound of formula **(5a)** (61.0 g, 53.4%) having 99.5% HPLC purity.

Example 5: Procedure to recover compound of formula (1); wherein R is H

To the xylene organic layer containing o-toluic acid methyl ester, from example 4, was added solution of sodium hydroxide (20.0 g) in water (200.0 ml). The reaction mixture was heated to 85-90 °C for 5-6 hrs and cooled to 25-30 °C. The aqueous layer was separated and cooled to 10-15 °C. The pH of the aqueous layer was adjusted to 2 using cone. HC1. The white solid obtained was filtered and washed with water (100.0 ml), o-Toluic acid (1) so obtained was dried at 45-50 °C (25.0 g). Purity: 98% by HPLC.

Example 6: Preparation of (2-bromomethylphenyl)methoxyiminoacetic acid methyl ester (Intermediate-I).

Method-A: Methoxyimino-o-tolylacetic acid methyl ester, compound of formula **(5a),** (10.0 g) was dissolved in acetonitrile (100.0 ml). To the clear solution was added NBS (11.17 g) and AIBN (0.48 g) at room temperature. The reaction mass was heated to 60 °C for 6.0 hrs and then concentrated to remove acetonitrile. To the crude product obtained was added diisopropyl ether (50.0 ml) and stirred to get clear solution. The solution was

washed with 10% aqueous sodium bisulfite solution (2 x 25 ml) followed by water (25.0 ml). The organic layer was dried over anhydrous sodium sulphate and cooled to -5 °C and filtered. The solid was washed with chilled diisopropyl ether (10.0 ml) and dried to obtain (2-bromomethylphenyl) methoxyiminoacetic acid methyl ester (Intermediate-I) as a white solid (10.5 g, 76%) having purity more than 95% by HPLC.

Method-B: Sodium bromate (3.3 g) was dissolved in water (16.0 ml). To the clear solution was added solution of methoxyimino-o-tolylacetic acid methyl ester, compound of formula (5a), (3.0 g) in ethyl acetate (10.0 ml) and stirred at room temperature. To the biphasic clear solution was added solution of sodium bisulfite (2.3 g) in water (10.0 ml) maintaining temperature between 30-40 °C over a period of 15 min. The reaction mass was stirred for 8.0 hrs at room temperature while it was exposed to UV light. Organic layer was separated and washed with 10% aqueous sodium bisulfite solution (2 x 3 ml) followed by water (5 ml). It was dried and concentrated to remove ethyl acetate. The crude product obtained was purified by recrystallization in diisopropyl ether to obtain (2-bromomethylphenyl) methoxyiminoacetic acid methyl ester (Intermediate-I) as a white solid (3.0 g, 72.3%) having purity more than 95% by HPLC.

Method-C: Bromine (1.0 g) was added in water (3.0 ml). To the bromine solution was added solution of methoxyimino-o-tolylacetic acid methyl ester, compound of formula (5a), (1.0 g) in dichloromethane (7.0 ml) and stirred at room temperature. The reaction mass was stirred for 4.0 hrs at room temperature while it was exposed to UV light. Organic layer was separated and washed with 10% aqueous sodium bisulfite solution (2 x 3 ml) followed by water (5 ml). It was dried and concentrated to remove dichloromethane. The crude product obtained was purified by recrystallization in diisopropyl ether to obtain (2-bromomethylphenyl) methoxyiminoacetic acid methyl ester (Intermediate-I) as a white solid (1.0 g, 72.3%) having purity more than 95% by HPLC.

Method-D: To the clear solution of methoxyimino-o-tolylacetic acid methyl ester, compound of formula **(5a),** (1.0 g) in dichloromethane (8.0 ml) was added solution potassium bromide (0.86 g) in water (1.0 ml) followed by hydrogen peroxide (30%, 0.76 ml) at room temperature. To the reaction mixture was added concentrated sulfuric acid

(0.43 ml) over a period of 5 minutes at room temperature. The reaction mass was stirred for 6.0 hrs at room temperature while it was exposed to UV light. Organic layer was separated and washed with 10% aqueous sodium bisulfite solution (2 x 3 ml) followed by water (5 ml). It was dried and concentrated to remove dichloromethane. The crude product obtained was purified by recrystallization in diisopropyl ether to obtain (2-bromomethylphenyl) methoxyiminoacetic acid methyl ester (Intermediate-I) as a white solid (1.0 g, 72.3%) having purity more than 95% by HPLC.

Example 7: Preparation of l-(3-trifluoromethylphenyl)ethanone oxime (Intermediate-II).

3-Trifluoromethylacetophenone (100.0 g) was dissolved in methanol (500.0 ml). To the solution was added hydroxylamine hydrochloride (37.0 g) at room temperature. To the reaction mass was added solution of sodium hydroxide (32.0 g) in water (150.0 ml) slowly over a period of 1.0 hr at room temperature and stirred for 10.0 hrs. Methanol was distilled off to obtain gummy product which was dissolved in ethyl acetate (500.0 ml). The solution was washed with water (150.0 ml). Organic layer was separated, dried over anhydrous sodium sulphate and concentrated to afford l-(3-trifluoromethylphenyl) ethanone oxime (Intermediate-II) as a white solid (94.5 g, 87%) having purity more than 98%.

Example 8: Preparation of Trifloxystrobin i.e. compound of formula (I)

(2-Bromomethylphenyl)methoxyiminoacetic acid methyl ester (Intermediate-I) (10.0 g) was dissolved in methyl isobutyl ketone (100.0 ml). To the solution was added Intermediate-II (6.5 g) followed by potassium carbonate (24.12 g) at room temperature. The reaction mixture was heated to 115 °C for 12.0 hrs. The reaction mixture was cooled to room temperature and filtered to remove potassium bromide by-product and excess potassium carbonate. The solid obtained after filtration was washed with methyl isobutyl ketone (10.0 ml) and preserved to be used to make Trifloxystrobin in subsequent batch. The filtrate was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate and concentrated under vacuum to obtain crude product. The crude product was

recrystallized from methanol to obtain pure Trifloxystrobin product as an off-white solid (9.3 g, 65.5%) having purity more than 98%.

Example 9: Preparation of Trifloxystrobin i.e. compound of formula (I) using potassium carbonate recovered from Example 8.

(2-Bromomethylphenyl)methoxyiminoacetic acid methyl ester (Intermediate-I) (10.0 g) was dissolved in methyl isobutyl ketone (100.0 ml). To the solution was added Intermediate-II (6.5 g) followed by potassium carbonate (recovered from Example 8) (33.16 g) at room temperature. The reaction mixture was heated to 115 °C for 12.0 hrs. The reaction mixture was cooled to room temperature and filtered to remove potassium bromide by-product and excess potassium carbonate. The solid obtained after filtration was washed with methyl isobutyl ketone (10.0 ml) and preserved to be used in bromination of compound 5a as a brominating agent. The filtrate was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate and concentrated under vacuum to obtain crude product. The crude product was recrystallized from methanol to obtain pure Trifloxystrobin product as an off-white solid (9.3 g, 65.5%) having purity more than 98%.

Example 10: Preparation of (2-bromomethylphenyl)methoxyiminoacetic acid methyl ester (Intermediate-I) using potassium bromide by-product recovered from Example 8 or Example 9.

The solid isolated after filtration in Example 8 or Example 9 (3.76 g) was dissolved in water (4.0 ml). The solution was added into the solution of methoxyimino-o-tolylacetic acid methyl ester, compound of formula (5a), (1.0 g) in dichloromethane (8.0 ml). To the reaction mixture was added hydrogen peroxide (30%, 0.76 ml) at room temperature. To the reaction mixture was added concentrated sulfuric acid (0.43 ml) over a period of 5 minutes at room temperature. The reaction mass was stirred for 6.0 hrs at room temperature while it was exposed to UV light. Organic layer was separated and washed with 10% aqueous sodium bisulfite solution (2 x 3 ml) followed by water (5 ml). It was dried and concentrated to remove dichloromethane. The crude product obtained was purified by recrystallization in diisopropyl ether to obtain (2-

bromomethylphenyl)methoxyiminoacetic acid methyl ester (Intermediate-I) as a white solid (1.0 g, 72.3%) having purity more than 98%.

Example 11: Preparation of compound of formula (2); wherein R is 2-methylphenoxy-

2-o-Tolyloxymefhylbenzoic acid (58.0 g) was dissolved in xylene (150.0 ml) at ambient temperature. To the clear solution was added DMF (3.0 g). To the reaction mass was added thionyl chloride (32.5 g) over a period of 4.0 hrs. The reaction mass was heated at 50 °C for 4.0 hrs and the distilled to remove about 50.0 ml of xylene. The reaction mass was cooled to room temperature. This reaction mass contains compound of formula (2) in xylene.

Example 12: Preparation of compound of formula (3); wherein R is 2-methylphenoxy-

Reaction mass obtained in example 9 was added drop wise into the biphasic mixture of xylene (200.0 ml) and water (35.0 ml) containing sodium cyanide (5.0 g) and TBAB (0.15 g), under stirring below 10 °C over a period of 4.0 hrs. While the addition was continued, solution of sodium cyanide (10.0 g) in water (70.0 ml) was added simultaneously into the reaction mass. The reaction mass was stirred for 2.0 hrs at room temperature. The organic layer was separated, washed with water (3 x 75 ml), dried over sodium sulphate and cooled to -5 to 0 °C. This organic layer contains, compound of formula (3).

Example 13: Preparation of compound of formula (4); wherein R is 2-methylphenoxy-

Into the reaction mass obtained in example 10 was purged dry hydrogen chloride gas at -5 to 0 °C. After 2.0 hr, while continuing dry hydrogen chloride gas purging, methanol (21.2 ml) was added into the reaction mass under stirring over a period of 10 hrs. Dry hydrogen chloride gas was purged into the reaction mass for another 10 hrs. Methanol (30.0 ml) was added into the reaction mass at 15-20 °C. The reaction mass then heated to 40-45 °C

and to it was added sulfuric acid (45.0 g) maintaining the temperature between 40-45 °C. The reaction mass was stirred for 3.0 hr. Methanol (30.0 ml) was added into the reaction mass over a period of 1.0 hr and stirred for 10.0 hrs at 60-65 °C. The reaction mass was cooled to 40 °C. Water (20.0 ml) was added into the reaction mass and stirred for 10 min. Organic layer was separated which contains a of mixture of oxo-(2-o-tolyloxymethylphenyl)acetic acid methyl ester; compound of formula (4), and 2-o-tolyloxymethylbenzoic acid methyl ester.

Example 14: Preparation of compound of formula (5b); wherein R is 2-methylphenoxy-.

To the organic layer obtained in example 12 was added TBAB (0.14 g), solution of sodium hydroxide (15.8 g) in water (132.0 ml) and stirred at 45 °C for 1.0 hr. The organic layer containing 2-o-tolyloxymefhylbenzoic acid methyl ester was separated and preserved to recover 2-o-tolyloxymethylbenzoic acid, compound of formula (1). To the Aqueous layer containing 2-o-tolyloxymethylbenzoic acid methyl ester, compound of formula (4a), was added solution of methoxyamine hydrochloride (14.5 g) in water (25.0 ml) and stirred for 1.0 hr at room temperature. DCM (35.0 ml) was added into the reaction mass and stirred for 1.0 hr. Organic layer was separated. Aqueous layer was extracted with DCM (40.0 ml). The organic layers were combined and dried. This combined organic layer contains a -50:50 mixture of *E*- and Z-isomers of methoxyimino-(2-o-tolyloxymethylphenyl)acetic acid, compound of formula (4b) wherein R is 2-methylphenoxy. To this organic layer was added DMF (0.7 ml) followed by thionyl chloride (26.3 g) at room temperature. The reaction mass was heated at 40-45 °C for 8.0 hrs and then concentrated to obtain gummy mass. To this gummy mass was added methanol (100.0 ml) over a period of 1.0 hr. The reaction mixture was heated at 60-65 °C for 1.0 hr, cooled to 10 °C and filtered. The white solid was washed with methanol (30 ml) and dried to obtain Kresoxim-methyl, compound of formula (5b), (42.5 g, 82.2%) having more than 96% HPLC purity.

Example 15: Recovery of Kresoxim acid, compound of formula (1); wherein R is 2-methylphenoxy-.

To the xylene organic layer containing 2-o-tolyloxymefhylbenzoic acid methyl ester, from example 12, was added solution of sodium hydroxide (7.0 g) in water (50.0 ml). The reaction mixture was heated to 95-100 °C for 2-3 hrs and cooled to 25-30 °C. The aqueous layer was separated and cooled to 10-15 °C. The pH of the aqueous layer was adjusted to 4 using sulphuric acid. The solid obtained was filtered and washed with water (100.0 ml). 2-o-Tolyloxymethylbenzoic acid (1) so obtained was dried at 45-50 °C (18.0 g). Purity- 98% by HPLC.

Comparative data:

Table 1: Comparison of percentage of Z-isomer of compound of formula 5(a) obtained by the process of the present invention vis-a-vis acknowledge prior art (US5334577 and US2010298593).

Table: 1

Preparation of methyl-2-methoxyimino 2 - (2'-methyl) phenylacetate (5a) as disclosed in	**Z-isomer (%)**	**fi-isomer (%)**	**Separation by**
US5334577	NA	NA	Recrystallization or chromatography
US2010298593	25	75	Recrystallization in hexane
Present invention	0.48	99.5	Exclusively *E*-isomer was synthesized without employing recrystallization or chromatography methods.

Table 2: Comparison of percentage of Z-isomer of compound of formula 5(b) i.e. Kresoxim-methyl obtained by the process of the present invention vis-a-vis acknowledge prior art US5221762).

Table: 2

Preparation of methyl (α*E*)-α-(methoxyimino)-2-[(2-methylphenoxy)-methyl]phenylacetate; compound of formula (5b) i.e Kresoxim-methyl as disclosed in	***Z*-isomer (%)**	***E*-isomer (%)**	**Separation by**
US5221762	-NA-	-NA-	-NA-
Present invention	0.16	99.84	Exclusively *E*-isomer was synthesized without employing recrystallization or chromatography methods

Table 3: Comparison of percentage yield of Intermediate (I) obtained by the process of the present invention vis-a-vis US5334577.

Table: 3

Preparation of Intermediate (I) as disclosed in	**Solvent**	**Brominating agent**	**Purification**	**Yield (%)**
US5334577	Carbon tetrachloride ($CC1_4$)	Bromine in presence of Hg vapour lamp	Column chromatography	46 %
Present invention.	Acetonitrile (CH_3CN)	N-Bromosuccinimide / AIBN	Recrystallization in ether	76%
Present invention.	Ethyl acetate-water	Sodium bromate / sodium bisulfite ($NaBr0_3$ /	Recrystallization in ether	75%

		$NaHSO_3$)		
Present invention.	dichloromethane and water	Bromine	Recrystallization in ether	72.3%
Present invention.	dichloromethane	Alkali metal bromide / H_2SO_4 / H_2O_2)	Recrystallization in ether	72.3%
Present invention.	dichloromethane	Alkali metal bromide (recovered) / H_2SO_4 / H_2O_2)	Recrystallization in ether	72.3%

Table 4: Comparison of percentage yiekl of compound of formula (I) i.e Trifloxystrobin obtained by the process of the present invention vis-a-vis US6407100.

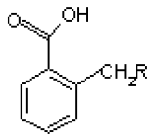
Table: 4

Preparation of compound of formula (I) i.e Trifloxystrobin as disclosed in	Yield (%)
US6407100	-NA-
Present invention.	78

CLAIMS

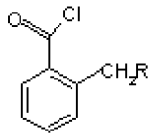
1. An improved process for the preparation of compound of formula (5) which comprises the steps of:

i. Reacting a compound of formula (1):



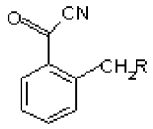
Formula (1)

with thionyl chloride in the presence of dimethylformamide in an organic solvent to obtain compound of formula (2);



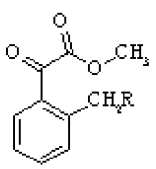
Formula (2)

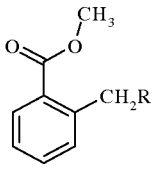
ii. Converting compound of formula (2) to compound of formula (3) by using metal cyanide in water and an organic solvent;



Formula (3)

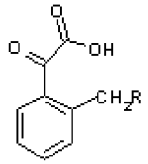
iii. Converting compound of formula (3) to compound of formula (4) and alpha-substituted-o-toluic acid methyl ester, a by-product, by using dry HC1, sulphuric acid and methanol in an organic solvent;





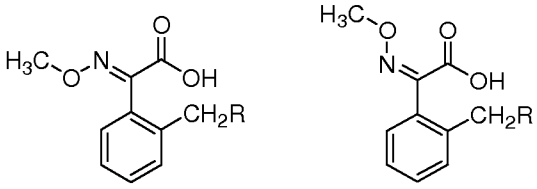
Formula (4) **alpha-substituted-0-toluic acid methyl ester**

iv. Selective hydrolysis of compound of formula (4) containing alpha-substituted-o-toluic acid methyl ester with alkali metal hydroxide in the presence of water and an organic solvent to obtain compound of formula (4a);



Formula (4a)

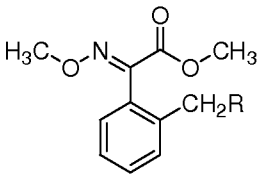
v. Methoxyimination of compound of formula (4a) by using methoxyamine hydrochloride in solvents of class chlorinated hydrocarbons such as dichloromethane, dichloroethane, etc to obtain compound of formula (4b) which is a mixture of E-isomer and Z-isomer;



E-isomer Z-isomer

Formula (4b)

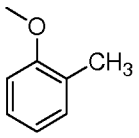
vi. Esterification of compound of formula (4b) using thionyl chloride in the presence of methanol to obtain exclusively E-isomer of compound of formula (5).



Formula (5)

Wherein R is H

or



2-methylphenoxy i.e. Kresoxim-methyl

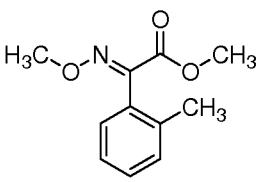
2. The process for the preparation of compound of formula (5) according to claim 1 wherein the metal cyanide used in step (ii) is sodium cyanide, potassium cyanide, cuprous cyanide, etc.

3. The process for the preparation of compound of formula (5) according to claim 1 wherein the alkali metal hydroxide used in step (iv) is sodium hydroxide.

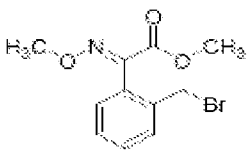
4. The process for the preparation of compound of formula (5) according to claim 1 wherein the organic solvent used in step (i) to step (iv) is selected from toluene, xylene, mesitylene, chlorobenzene, 1,2-dichlorobenzene, etc.

5. An improved process for the preparation of Intermediate (I) from the E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula 5(a) which comprises the steps of:

i. Bromination of compound of formula (5a) as obtained by the process according to claim 1 to obtain Intermediate (I) using sodium bromate in combination with sodium bisulfite (NaBrCb / NaHSCb) in biphasic medium of water immiscible "ester class of organic solvents" such as ethyl acetate, n-butyl acetate, isopropyl acetate etc and water in presence of UV or ordinary light.



(Formula 5a)

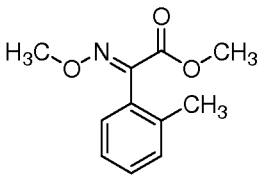


Intermediate (I)

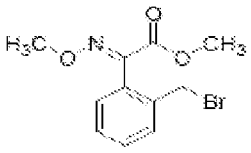
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

6. An improved process for the preparation of Intermediate (I) from the E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) as obtained in claim 1 which comprises the steps of:

i. Bromination of compound of formula (5a) as obtained by the process according to claim 1 to obtain Intermediate (I) using *N*-bromosuccinimide in combination with AIBN or benzoyl peroxide in an organic solvent such as acetonitrile, ethyl acetate, dichloromethane, chloroform, chlorobenzene etc;



(Formula 5a)

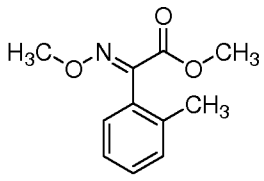


Intermediate (I)

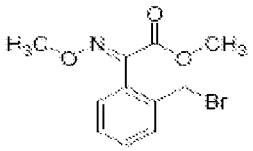
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

7. An improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) as obtained by the process according to claim 1 to obtain Intermediate (I) using bromine in biphasic medium comprising water and one of the halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)

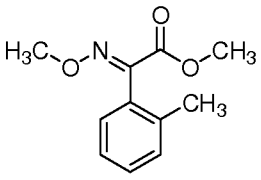


Intermediate (I)

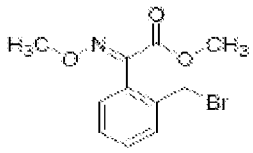
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization using any of the "ether class of organic solvents" such as diethyl ether, *di-n-*propyl ether, di-isopropyl ether, methyl *tert-butyl* ether, etc.

8. An improved process for the preparation of Intermediate (I) from E-isomer of compound of formula (5), wherein R is Hydrogen i.e. compound of formula (5a) which comprises the steps of:

i. Bromination of compound of formula (5a) as obtained by the process according to claim 1 to obtain Intermediate (I) using alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, etc in combination with sulphuric acid and hydrogen peroxide (LiBr, NaBr or KBr / H_2S0_4 / H_20_2) in halogenated solvent such as dichloromethane, chloroform, dichloroethane, etc in presence of UV or ordinary light.



(Formula 5a)

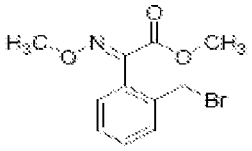


Intermediate (I)

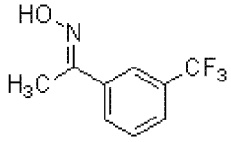
ii. Purification of crude Intermediate (I) obtained in step (i) by recrystallization in "ether class of organic solvents" such as diethyl ether, di-n-propyl ether, di-isopropyl ether, methyl teri-butyl ether, etc.

9. An improved process for the preparation of Trifloxystrobin, compound of formula (I) having purity more than 98%, which comprises the steps of:

i. Reacting intermediate **(II)** with intermediate **(I)** as obtained by the process according to claim 5 or claim 6 or claim 7 or claim 8 in the presence of base in an organic solvent;

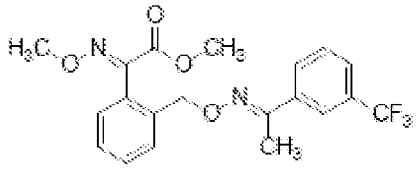


Intermediate (I)



Intermediate II

ii. Purifying the product i.e. Trifloxystrobin, compound of the formula **(I)** by recrystallization in an organic solvent.



Formula (I)

10. The process for the preparation of compound of formula **(I)** according to claim 9 wherein the organic solvent used in step (i) is selected from the group consisting of "ketone class of organic solvents" such as acetone, methyl isobutyl ketone, etc or polar aprotic solvents such as dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide, *N*-methylpyrrolidine, etc or cyclic and acyclic ethers such as tetrahydrofuran, dioxane, dimethoxyethane, etc or "ester class of organic solvents" such as ethyl acetate, n-butyl acetate, isopropyl acetate, isobutyl acetate, etc or acetonitrile.

11. The process for the preparation of compound of formula **(I)** according to claim 9 wherein the base used in step (i) is selected from the group consisting of inorganic or organic base.

12. The process for the preparation of compound of formula **(I)** according to claim 11 wherein the inorganic base is selected from the group consisting of alkali metal carbonate, such as lithium carbonate, sodium carbonate, potassium carbonate,

cesium carbonate; alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide; alkali metal hydride, such as sodium hydride, potassium hydride or potassium teri-butoxide or sodium amide.

13. The process for the preparation of compound of formula (I) according to claim 11 wherein the organic base is selected from the group consisting of triethylamine, di-isopropylethyl amine, *N*-methylmorpholine, piperidine or pyridine.

14. The process for the preparation of compound of formula (I) according to claim 9 wherein the organic solvent used in step (ii) is selected from the group consisting of methanol, ethanol, isopropanol, n-propanol, n-butanol, acetonitrile, ethyl acetate, diethyl ether, diisopropyl ether or isobutyl ether, methyl teri-butyl ether etc.

15. The process for the preparation of compound of formula (5) according to claim 1, wherein the alpha-substituted-o-toluic acid methyl ester obtained in step (iii), is subjected to hydrolysis using sodium hydroxide to recover and recycle compound of formula (1).

16. The process for the preparation of Trifloxystrobin, compound of formula (I), according to claim 9 and claim 12, wherein excess base is recovered and reused to make Trifloxystrobin, compound of formula (I).

17. The process for the preparation of Trifloxystrobin, compound of formula (I) according to claim 9, wherein the by-product i.e. alkali metal bromide formed is recovered and reused for the bromination of compound of formula (5a) to obtain Intermediate (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/052565

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C249/08 C07C249/12
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)
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 221 762 A (WINGERT HORST [DE] ET AL) 22 June 1993 (1993-06-22) cited in the application examples 2, 5, 6	1-17
A	HWANG, I-C-: "Synthesis and SAR of Methoxyimino acetate and Methoxyimino acetamide Derivatives as Strobiluri n Analogues", BULL. KOREAN SOC, vol. 30, no. 7, 2009, pages 1475-1480, XP008163218, the whole document	1-17

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

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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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
24 June 2013	02/07/2013

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/052565

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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