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(54) Title: PREPARATION OF MIXTURES OF CYPERMETHRIN OR CYFLUTHRIN ISOMERS ENRICHED IN MORE ACTIVE SPECIES (57) Abstract <p>This application discloses a process for the preparation of an (R,S)-(cyano)(3-phenoxyphenyl)methyl or (R,S)-(cyano)(4-fluoro-3-phenoxyphenyl)methyl <i>cis/trans</i>-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate enriched in the more insecticidal <i>c₂</i> and <i>t₂</i> isomers by the addition of (R,S)-α-hydroxy-3-phenoxyphenylacetonitrile or (R,S)-α-hydroxy-4-fluoro-3-phenoxyphenylacetonitrile to the <i>cis/trans</i> acid chloride in refluxing heptanes in an inert atmosphere. The reaction mixture is then washed with aqueous base and the ester recovered.</p>		

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PREPARATION OF MIXTURES OF CYPERMETHRIN OR
CYFLUTHRIN ISOMERS ENRICHED IN MORE ACTIVE SPECIES

This invention relates to an improvement in a chemical process. In particular, it relates to an improved esterification process that results in enantiomerically enriched (R,S)-(cyano)(3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) or (R,S)-(cyano)(4-fluoro-3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cyfluthrin). It also relates to the preparation of similarly enriched mixtures of diastereomers. This process improvement requires the esterification of a substituted-cyclopropanecarbonyl chloride with an appropriate cyanohydrin without an acid acceptor being present. The product ester is enriched in the more insecticidally active enantiomers or diastereomers compared to the product produced by the same reaction with an acid acceptor present.

Both cypermethrin (U.S. Patent 4,024,163) and cyfluthrin (U.S. Patent 4,218,469) are well-known pyrethroid insecticides and are articles of commerce in many countries. Each may contain eight isomers.

For racemic cypermethrin the eight isomers are designated I-VIII as follows:

cis isomers

I = (S)-(cyano)(3-phenoxyphenyl)methyl 1R,cis-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
(abbreviated 1R,cis S)

II = (R)-(cyano)(3-phenoxyphenyl)methyl 1S,cis-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
(abbreviated 1S,cis R)

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III = (S)-(cyano)(3-phenoxyphenyl)methyl 1S,cis-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
(abbreviated 1S,cis S)

IV = (R)-(cyano)(3-phenoxyphenyl)methyl 1R,cis-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
5 (abbreviated 1R,cis R)

trans isomers

V = (1R,trans S), the trans isomer of I
VI = (1S,trans R), the trans isomer of II
VII = (1S,trans S), the trans isomer of III
10 VIII = (1R,trans R), the trans isomer of IV

The designations 1R,cis; 1R,trans; 1S,cis; and 1S,trans refer to the spatial relationship of the hydrogen atoms at the 1 and 3 positions of the cyclopropane ring, and the single letter designations R and S
15 refer to the spatial configuration of the cyano group on the alpha carbon of the alcohol portion of the molecule.

The same designations are applied to the corresponding isomers of cyfluthrin.

It is well known that the most insecticidally active
20 isomers are I and V. It is also well known that the enantiomer pairs I/II, referred to as the c_2 enantiomer pair, and V/VI, referred to as the t_2 enantiomer pair, are more insecticidally active than the enantiomer pairs, III/IV, referred to as the c_1 enantiomer pair,
25 and VII/VIII, referred to as the t_1 enantiomer pair.

It is extremely difficult and commercially impractical to separate the more active isomers from the complex mixture of isomers produced in the usual synthesis of pyrethroids. Consequently, substantial
30 effort has been devoted to methods for increasing the proportion of active isomers in products consisting of mixtures of isomers, for example, by converting less active isomers in such mixtures to more active isomers. Such processes are disclosed in U.S. Patents 4,427,598
35 and 4,782,174, inter alia.

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While the increased processing costs incurred in such isomer enrichment techniques may be justified for some pesticidal applications, an esterification process which would lead directly to a mixture enriched in the more active isomers would be highly desirable, both for the increased insecticidal activity of the esterification product itself and as an enhanced feed stock for conversion.

In accordance with the present invention the reaction of an α -hydroxyphenoxyphenylacetonitrile with a solution of the appropriate cyclopropanecarbonyl chloride in the absence of an acid acceptor gives a product enriched in the more active isomers over the product obtained when an acid acceptor is present. The conventional process for reacting an acid chloride with an alcohol calls for the presence of a stoichiometric amount of an acid acceptor, usually pyridine or another tertiary amine, to react with the hydrogen chloride liberated in the reaction.

More recently Japanese Kokai 60-202843, (Sumitomo Chemical Industries KK), has described a process for preparing esters, including pyrethroid esters, from acid halides and alcohols while omitting the acid acceptor. This is accomplished either by running the reaction under reduced pressure to draw off the hydrogen halide gas or by sparging the reaction mixture with an inert gas, nitrogen or helium, and removing the hydrogen halide by entrainment in the gas stream. Example 9 of the Kokai makes (S)- α -cyano-3-phenoxybenzyl (1R,cis)-2,2-dimethyl-3-(2,2-dibromovinyl)cyclopropane-1-carboxylate from (S)- α -hydroxy-3-phenoxyphenylacetonitrile. Although this reference teaches the esterification in the absence of an acid acceptor, it does not and could not teach the advantageous effect on the c_1/c_2 or t_1/t_2 ratio of applying this process to

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cypermethrin or cyfluthrin mixtures, since only one isomer was produced.

Also, while the Kokai prefers either a vacuum of 500 mm of mercury or less or a inert gas flow in excess of 5
5 times the volume of hydrogen chloride liberated in the reaction, the present process requires only that the process be carried out under an inert gas. The most practical approach is to have a gentle flow of inert gas carrying the hydrogen chloride to a scrubber (to avoid
10 the pollution that would be caused by venting the hydrogen chloride to the atmosphere), but as will be shown, the beneficial effect on isomer ratios is obtained even if the reaction is run in a vessel simply flushed with an inert gas.

15 In the process of this invention essentially equimolar amounts of α -hydroxy-3-phenoxyphenylacetonitrile (or its 4-fluoro analog) and cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride are reacted in a hydrocarbon solvent at reflux
20 without an acid acceptor being present. In the preparation of cypermethrin this process typically produces product having c_1/c_2 and t_1/t_2 isomer ratios of 48/52. The nearly identical process utilizing the same reactants in the presence of an acid acceptor, for
25 example, pyridine, yields cypermethrin typically having c_1/c_2 and t_1/t_2 ratios of 55/45. Thus, the amounts of c_2 and t_2 enantiomer pairs are increased relative to the c_1 and t_1 pairs, resulting in cypermethrin having correspondingly increased insecticidal activity.

30 It will be noted that the reactions with and without acid acceptor are run at different temperatures. The reason for this is that when pyridine is present the reaction must be run at lower temperatures, since at high temperatures the pyridine attacks the cyanohydrin,
35 causing a reduction in yield. When pyridine is absent,

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the reaction must be run at higher temperatures, preferably reflux for the preferred mixed heptanes solvent, to drive off the hydrogen chloride produced. Thus a comparison at the same temperature would not be
5 meaningful.

The only process variable that appears to be at all critical is the temperature of the reaction, which should be high enough to drive off the hydrogen chloride formed, but not high enough to degrade either the
10 reactants or the product. Temperature is preferably controlled by choosing a solvent that refluxes in the range of about 75 to 115°C. The nature of the hydrocarbon solvent appears not to be critical, both aromatic and aliphatic solvents having been used effectively.
15 Neither is reaction time critical, within limits that will be readily apparent to the chemist. The rate of addition of cyanohydrin to refluxing solution of acid chloride must be such that the reaction does not get out of control, and the completion of the reaction can be
20 followed by cessation of the evolution of hydrogen chloride.

The following Examples are given to further illustrate the process of the invention.

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EXAMPLE 1

PRIOR ART PROCESS

PREPARATION OF (R,S)-(CYANO) (3-PHENOXYPHENYL) METHYL
CIS/TRANS-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-
CYCLOPROPANECARBOXYLATE IN THE PRESENCE OF PYRIDINE
30 AS AN ACID ACCEPTOR

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In a stirred flask under nitrogen were placed 61.1 g (0.252 mole) of (R,S)- α -cyano-3-phenoxyphenylacetonitrile (93% purity), 22.3 g (0.280 mole) of pyridine, and 500 ml of toluene. While the temperature of the

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reaction was held between 35°C and 43°C, a solution of 61.6 g (0.253 mole) of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride (93.7% purity) in 50 ml of toluene was added dropwise over a period of 100 minutes. The reaction mixture was stirred for two hours, and then an additional 1.89 g (0.008 mole) of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride (93% purity) was added. The reaction mixture was stirred for an additional 138 minutes before 75 ml of water was added to quench the reaction. The aqueous phase was separated and discarded, and the organic phase was washed in succession with 75 ml portions of 2N hydrochloric acid, a 10% solution of sodium carbonate in water, and pure water. After separation of the final wash, the solvent was removed from the organic phase under reduced pressure, leaving a liquid residue weighing 109.0 g. Analysis of this residue by liquid chromatography showed that 89.3% was (R,S)-(cyano)(3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. The cis/trans composition was 48.8/51.2, and the c_1/c_2 and t_1/t_2 enantiomer pair compositions were 55.9/44.1 and 56.7/43.3, respectively. The yield of product was 92.8%, based on the amount of α -hydroxy-3-phenoxyphenyl-acetonitrile used in the reaction.

EXAMPLE 2

PREPARATION OF (R,S)-(CYANO)(3-PHENOXYPHENYL)METHYL
CIS/TRANS-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-
CYCLOPROPANECARBOXYLATE WITHOUT AN ACID
ACCEPTOR PRESENT

In a stirred flask were placed 733.2 g (1.505 moles) of a solution containing 46.7% of cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl

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chloride and 175 ml of mixed heptanes. A nitrogen atmosphere was maintained over the solution, which was heated to reflux. Dropwise, 354.1 g (1.462 moles) of (R,S)- α -hydroxy-3-phenoxyphenylacetonitrile (93% purity) was added to the refluxing solution over a 104 minute period. When the addition was complete, the reaction mixture was heated at reflux for one hour, then cooled and quenched with 375 ml of a 10% solution of sodium carbonate in water. After stirring for thirty minutes, the aqueous phase was separated from the organic reaction mixture and the organic phase was washed with 375 ml of water. Following separation from the aqueous wash, the solvent was removed from the organic phase under reduced pressure. A liquid residue weighing 631.1 g remained. Analysis of this residue by liquid chromatography showed that 92.4% of its composition was (R,S)-(cyano)(3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. The cis/trans composition was 53.2/46.8, and the c_1/c_2 and t_1/t_2 enantiomer pair compositions were 48.2/51.8 and 47.9/52.1, respectively. The yield of product was 95.8%, based on the amount of α -hydroxy-3-phenoxyphenylacetonitrile used in the reaction.

EXAMPLE 3

PREPARATION OF (R,S)-(CYANO)(3-PHENOXYPHENYL)METHYL CIS/TRANS-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-CYCLOPROPANECARBOXYLATE WITHOUT AN ACID ACCEPTOR PRESENT AND WITH AN ARGON SPARGE

In a flask were placed 68.1 g (0.200 mole) of cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride (66.8% purity) and 100 mL of heptanes. An argon sparge was placed below the surface of the liquid, and a flow of argon was maintained

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throughout the reaction period. The reaction mixture was heated to reflux, and 49.2 g (0.203 mole) of R,S- α -hydroxy-3-phenoxyphenylacetonitrile (93% purity) was added dropwise over a 110 minute period. Heating at reflux was continued for an additional hour after completion of addition. The temperature of the reaction mixture was reduced to 60°C, and 55 mL of a 10% aqueous solution of sodium carbonate was added to it. The mixture was stirred vigorously for 30 minutes, after which the aqueous phase was separated and discarded. Distilled water was then added to the reaction mixture, and this mixture was then stirred at 50°C for 30 minutes. The phases were separated, and the solvent for the organic phase was evaporated under reduced pressure, leaving a residue weighing 87.2 g. Analysis of this residue by liquid chromatography revealed that 90.5% of its composition was (R,S)-(cyano)(3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. The cis/trans composition of this product was 51.4/48.6, and the c_1/c_2 and t_1/t_2 enantiomer pair compositions were 48.6/51.4 and 48.4/51.6, respectively. The yield of product was 94.8%, based on the amount of cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride used in the reaction.

EXAMPLE 4

PREPARATION OF (R,S)-(CYANO)(3-PHENOXYPHENYL)METHYL
CIS/TRANS-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-
CYCLOPROPANECARBOXYLATE WITHOUT AN ACID ACCEPTOR
PRESENT AND WITHOUT INERT GAS FLOW

A flask was flushed with nitrogen before 170.2 g (0.500 mole) of cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride (66.8% purity) and

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185 ml of heptanes were placed in it. No additional nitrogen was introduced into the reaction mixture after heating of the flask commenced. The reaction mixture was stirred vigorously. After vigorous reflux was established, 122.0 g (0.504 mole) of (R,S)- α -cyano-3-phenoxyphenylacetonitrile (93% purity) was added dropwise to the reaction mixture during a 130 minute period. Upon completion of addition, heating was continued for an additional 70 minutes after which the reaction mixture was cooled to 75°C, and 125 mL of a 10% aqueous solution of sodium carbonate was added. This mixture was stirred at 45-50°C for 30 minutes after which the aqueous phase was separated and discarded. Distilled water (125 mL) was added to the reaction mixture, and the mixture was stirred at 45-50°C for 30 minutes. The phases were then separated and the solvent removed from the organic phase under reduced pressure, leaving a residue weighing 215.1 g. Analysis of this residue by liquid chromatography revealed that 92.5% of its composition was (R,S)-(cyano)(3-phenoxyphenyl)methyl cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. The cis/trans composition of this produce was 51.8/48.2, and the c_1/c_2 and t_1/t_2 enantiomer pair compositions were 48.9/51.1 and 47.8/52.2, respectively. The yield of product was 95.6% based on the amount of cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride used in the reaction.

The foregoing Examples have all produced eight isomer mixtures of cypermethrin. The process is equally applicable to reactions in which the acid chloride is predominantly cis or predominantly trans and to the production of enhanced isomer mixtures of cyfluthrin. Table 1 shows typical reactions of cis-(>90% cis), cis/trans-, or trans-3-(2,2-dichloroethenyl)-2,2-

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dimethylcyclopropanecarbonyl chloride (>90% trans) with
racemic or (S)- α -hydroxy-3-phenoxyphenylacetonitrile or
racemic α -hydroxy-(4-fluoro-3-phenoxyphenyl)-
acetonitrile. In all cases the cis/trans ratio of the
5 starting material is preserved in the ester product;
only the c_1/c_2 and t_1/t_2 ratios are altered. Yields of
93-97% are usually obtained and do not reflect any
dependency on one reactant or the other being present in
a slight excess. In all cases the reactions were
10 carried out under inert gas, either argon or nitrogen,
usually with a slight flow of gas over the surface of
the reaction mixture, less frequently with sparging.
There is no indication that the manner of maintaining an
inert atmosphere in the reaction vessel is in the least
15 critical.

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TABLE I

Ex.	DVAC ^a (moles)	Cyanohydrin ^b (moles)	Solvent		Time			Product		Product Analysis			
			Type	Amount (ml)	Temp. (°C)	Addition (min)	Heat- ing (min)	Weight (g)	Pyrethroid (%)	Yield ^c (%)	cis/trans ^d	c1/c2 ^e	t1/t2 ^f
5	0.503	0.501	heptanes	245	102-105	90	45	212.1	93.3	94.9	51.3/48.7	48.1/51.9	48.2/51.8
6	0.200	0.205	heptanes/ toluene	100/10	100-101	75	60	87.1	90.8	95.0	5.4/95.6	47.7/52.3	48.3/51.7
7	0.093	0.090	heptanes	45	100-101	90	60	35.9	91.7	87.9	4.9/95.1	49.7/50.3	49.4/50.6
8	0.200	0.204	"	75	100-102	85	75	89.1	90.5	96.8	51.1/48.9	48.2/51.8	48.3/51.7
9	0.500	0.504	"	185	98-102	110	0	213.4	92.1	94.4	51.5/48.5	48.3/51.7	47.9/52.1
10	0.500	0.503	"	185	101-102	115	30	216.4	90.3	93.9	51.5/48.5	48.5/51.5	47.7/52.3
11	3.534	3.506	"	820	95-97	139	44	1494.4	92.8	95.0	52.1/47.9	48.2/51.8	48.3/51.7
12	0.452	0.434	heptanes	235	108-110	360	0	186.9	91.2	94.3	95.9/4.1	47.7/52.3	48.6/51.4
13	0.506	0.505 ^h	toluene	100	109-111	140	60	235.0	86.7	96.9	52.3/47.7	47.4/52.6	47.5/52.5
14	0.505	0.500 ^h	heptanes	120	100-104	96	98	213.9	96.8	99.5	50.4/49.6	49.0/51.0	48.7/51.3
15	0.505	0.482 ^h	heptanes	245	99-102	125	60	215.9	88.8	95.5	52.5/47.5	49.3/50.7	48.8/51.2
16	0.2508	0.250 ^h	toluene	550	40-45	75	120	113.6	87.3	95.3	49.5/50.5	52.2/47.8	52.0/48.0
17	0.200	0.206 ^h	heptanes	45	101-104	110	134	89.8	84.8	91.5	98.7/1.3	49.0/51.0	46.2/53.8
18	0.250	0.289 ⁱ	heptanes	30	101-105	107	60	125.6	81.3	94.1	53.5/46.5	47.7/52.3	48.0/52.0
19	0.2758	0.289 ⁱ	toluene	550	36-37	90	183	132.2	78.8	87.3	55.4/44.6	54.6/45.4	54.8/45.2

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Footnotes to Table of Experiments

- 5 a. 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropylcarbonyl chloride
- b. α -Hydroxy-3-phenoxyphenylacetonitrile
- 10 c. Based on the reactant (DVAC or cyanohydrin) introduced into the reaction in smaller molar amount.
- d. Ratio of cis- and trans-cyclopropyl moieties present.
- 15 e. $c_1 = 1S, \underline{cis} S$ and $1R, \underline{cis} R$ enantiomer pair of isomers
 $c_2 = 1R, \underline{cis} S$ and $1S, \underline{cis} R$ enantiomer pair of isomers
- 20 f. $t_1 = 1S, \underline{trans} S$ and $1R, \underline{trans} R$ enantiomer pair of isomers
 $t_2 = 1R, \underline{trans} S$ and $1S, \underline{trans} R$ enantiomer pair of isomers
- 25 g. More than 1 molar equivalent of pyridine present during the reaction to serve as an acid acceptor.
- h. (S)- α -hydroxy-3-phenoxyphenylacetonitrile
 $c_1 = 1S, \underline{cis} S$
30 $c_2 = 1R, \underline{cis} S$
 $t_1 = 1S, \underline{trans} S$
 $t_2 = 1R, \underline{trans} S$
- i. α -hydroxy-4-fluoro-3-phenoxyphenylacetonitrile
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While the change from about 56/44 c_1/c_2 and t_1/t_2 may seem relatively modest, the resulting increase in insecticidal activity is consistent, providing a more effective product without the high cost of sophisticated separation techniques. This increase in activity is illustrated in Table II in which the test insect is the economically important tobacco budworm.

TABLE II
Foliar LC_{50} (ppm) - Tobacco Budworm

	<u>Acid</u> <u>Acceptor</u> (Example 1)	<u>No Acid</u> <u>Acceptor</u> (Example 5)
$c_1/c_2:t_1/t_2$	55.9/44.1:56.7/43.3	48.1/51.9:48.2/51.8
Test 1	8.4	6.5
Test 2	18.7	12.3
Test 3	12.5	11.0
Average	13.2	9.9

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Claims:

1. A process for the preparation of a mixture of isomers of cypermethrin or cyfluthrin enriched in the more insecticidally active isomers characterized by reacting the appropriate α -hydroxy-3-phenoxyphenyl-acetonitrile with a solution of the 3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarbonyl chloride in a hydrocarbon solvent at a temperature of 75 to 115°C in an inert atmosphere, no acid acceptor being present in the reaction mixture, washing the reaction mixture with aqueous base, and recovering the product.

2. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-cis/trans configuration.

3. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-cis configuration.

4. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-trans configuration.

5. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-cis/trans configuration.

6. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-cis configuration.

7. The process of claim 1 characterized in that the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-trans configuration.

AMENDED CLAIMS

[received by the International Bureau on 09 April 1991 (09.04.91);
original claim 1 amended; other claims unchanged (2 pages)]

1. In the process for the preparation of a mixture of isomers of cypermethrin or cyfluthrin by reacting α -hydroxy-3-phenoxyphenylacetonitrile or its 4-fluoro analog with a solution of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonyl chloride, the improvement that comprises increasing the concentration of the c_2 or t_2 isomers or both relative to the c_1 or t_1 isomers by carrying out the reaction at atmospheric pressure in an inert atmosphere by adding, at a rate such that the reaction does not get out of control, the acetonitrile to a refluxing solution of the acid chloride in a hydrocarbon solvent boiling in the range of about 75 to 115°C, no acid acceptor being present in the reaction mixture, washing the reaction mixture with aqueous base, and recovering the product.

2. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-cis/trans configuration.

3. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-cis configuration.

4. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the R,S configuration and the acid chloride has the R,S-trans configuration.

5. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-cis/trans configuration.

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6. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-cis configuration.

5 7. The process of claim 1 in which the α -hydroxy-3-phenoxyphenylacetonitrile has the S configuration and the acid chloride has the R,S-trans configuration.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/05578

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): C07C 253/30		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
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U.S.	558/407	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁶		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁵	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	US, A, 2,769,835 (KOSMIN et al.) 06 November 1956 Note column 1, lines 67-68.	1-7
Y	US, A, 3,078,306 (SCHICKH et al.) 19 February 1963; Note column 2, lines 60-62.	1-7
Y	US, A, 3,082,236 (MAGELI et al.) 19 March 1963 Note column 2, line 48.	1-7
Y	US, A, 4,536,345 (MARTEL et al.) 20 August 1985 Note column 5, lines 8 and ff.	1-7
Y	JP, A, 60-202843 (SUMIMOTO) 14 October 1985	1-7
Y	Preparative Organic Chemistry, Weygand/Hilgetag; Edited by Hilgetag-Martini, John Wiley & Sons, N.Y.-London-Sydney-Toronto, (1972), page 378, lines 30-31-32	1-7
Y	The Merck Index, Eleventh Edition (1989), Compound Number 2764 and 2775, Published by Merck and Co., Inc., Rahway, N.Y.	1-7
<p>¹⁵ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²		Date of Mailing of this International Search Report ²
15 January 1991		20 FEB 1991
International Searching Authority ¹		Signature of Authorized Officer ²⁰
ISA/US		<i>Joseph Paul Brust</i> Joseph Paul Brust