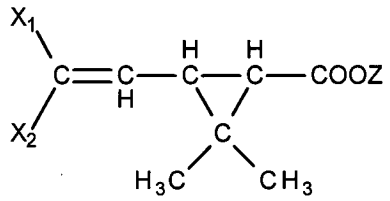
ABSTRACT

"IMPROVED PROCESS FOR THE PREPARATION OF PYRETHROIDS"

The present invention relates to a process for preparing pyrethroids of formula (I) in all stereochemical configuration as well as their mixtures

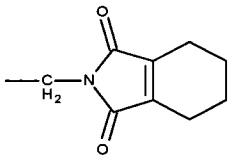


(I)

wherein

X_1 and X_2 are the same or different and are selected from hydrogen, (C_1-C_4) alkyl , (C_2-C_4) alkenyl and halogen;

Z is a group selected from:



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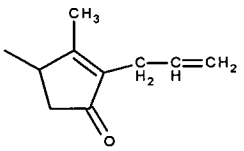

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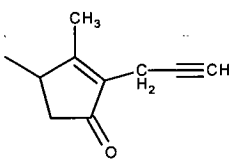

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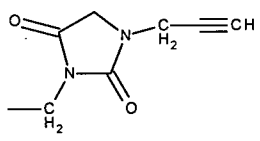

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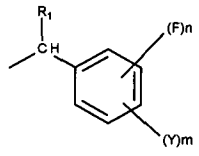
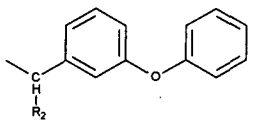


, wherein R_1 is hydrogen, methyl or –CN, n is an integer from 1 to 5, m is (5-n), Y is hydrogen, $(C_1\text{-}C_4)$alkyl or $(C_2\text{-}C_5)$alkoxy$(C_1\text{-}C_4)$alkyl

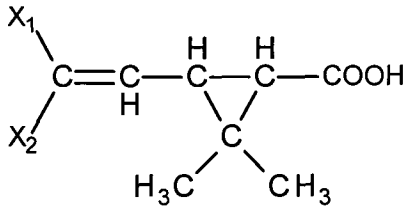
and



wherein R_2 is hydrogen, methyl or -CN

comprising the steps of:

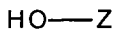
a) preparing an organic solution of an acid of formula (II)



(II)

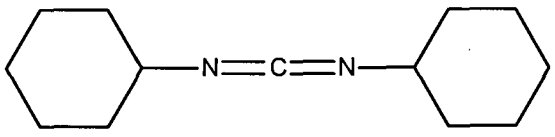
in a suitable organic solvent

b) preparing an organic solution of an alcohol of formula (III)



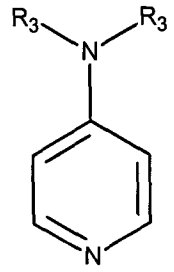
(III)

in a suitable organic solvent and in the presence of dicyclohexylcarbodiimide (DCC) of formula (IV),



(IV)

and a N,N'-dialkylpyridine catalyst of formula (V)



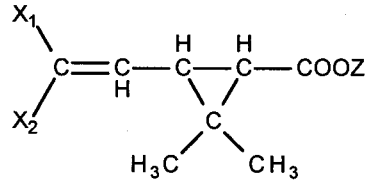
(V)

wherein R_3 is (C_1-C_4) alkyl; and

c) reacting the organic solution of step a) with the organic solution of step b) by adding the organic solution of the acid of formula (II) of step a) to the organic solution of step b) comprising the alcohol (III).

We claim

1. A process for preparing pyrethroids of formula (I) in all stereochemical configuration as well as their mixtures

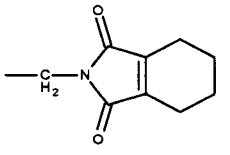


(I)

wherein

X_1 and X_2 are the same or different and are selected from hydrogen, (C_1-C_4) alkyl , (C_2-C_4) alkenyl and halogen;

Z is a group selected from:



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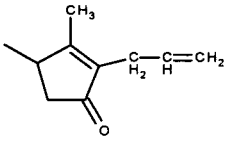

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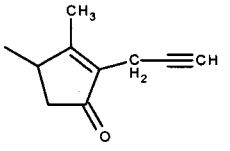

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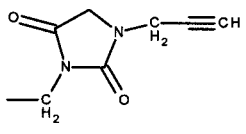

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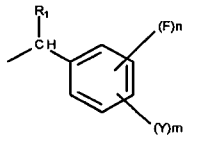
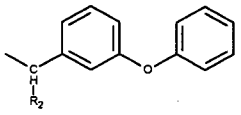


, wherein R_1 is hydrogen, methyl or –CN, n is an integer from 1 to 5, m is (5-n), Y is hydrogen, $(C_1\text{-}C_4)$alkyl or $(C_2\text{-}C_5)$alkoxy$(C_1\text{-}C_4)$alkyl

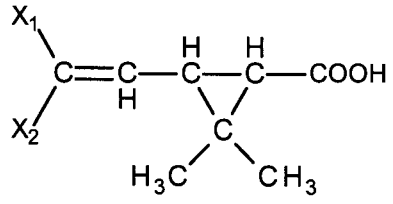
and



wherein R_2 is hydrogen, methyl or -CN

comprising the steps of:

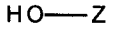
a) preparing an organic solution of an acid of formula (II)



(II)

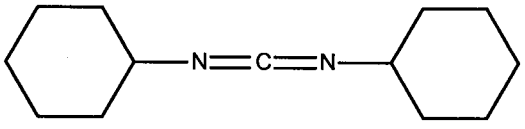
in a suitable organic solvent

b) preparing an organic solution of an alcohol of formula (III)



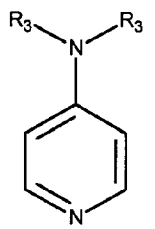
(III)

in a suitable organic solvent and in the presence of dicyclohexylcarbodiimide (DCC) of formula (IV),



(IV)

and a N,N'-dialkylpyridine catalyst of formula (V)



(V)

wherein R_3 is (C_1-C_4) alkyl; and

c) reacting the organic solution of step a) with the organic solution of step b) by adding the organic solution of the acid of formula (II) of step a) to the organic solution of step b) comprising the alcohol (III).

2. The process according to claim 1, wherein the suitable organic solvent of step a) and the organic solvent of step b) are, independently of each other, selected from the group consisting of n-pentane, n-hexane, n-heptane, diethyl ether, diisopropyl ether, tetrahydrofurane, methyl-tetrahydrofurane, dichloromethane, benzene, toluene, mesitylene and their mixtures.

3. The process according to claim 2, wherein the organic solvent of step a) and the organic solvent of step b) are equal.

4. The process according to anyone of claims 1-3, wherein the organic solvent of step a) and the organic solvent of step b) are toluene.

5. The process according to anyone of claims 1-4, wherein the ratio of the acid of formula (II) with respect to the alcohol of formula (III) is in the range from (1.5 to 1.0) eq. to (1.1 to 1.0) eq,, preferably 1.05 to 1.0 eq.

6. The process according to anyone of claims 1-5, wherein the N,N'-dialkylpyridine catalyst of formula (V) is 4-(N,N'-dimethylamino)pyridine.

7. The process according to claim 6, wherein the amount of the catalyst is preferably in the range from 0.1 to 0.01eq. with respect to the alcohol of

formula(III), preferably from 0.08 to 0.01 eq., more preferably from 0.05 to 0.01 eq.

8. The process according to anyone of claims 1-7, wherein the ratio of the amount of alcohol of formula (III) with respect to the organic solvent of step b) is the range from 1:4 to 1:7 (w/w), preferably 1:4.5 to 1:5 (w/w).

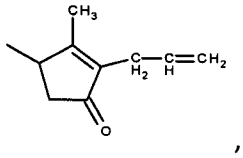
9. The process according to anyone of claims 1-8, the ratio of the amount of the acid of formula (II) with respect to the amount of the organic solvent of step a) is the range from 1:2 to 1:0.5 (w/w), preferably the ratio of 1:1 (w/w) .

10. The process according to anyone of claims 1-9, wherein the addition time of the organic solution of the acid (II) to the organic solution of the alcohol (III) is in the range from 1/240 eq/minute to 1/60 eq/minute of the acid with respect to the alcohol.

11. The process according to claim 10, wherein the addition time is between of 1/200 eq/minute to 1/90 eq/minute of the acid of formula (II) with respect to the alcohol of Formula (III).

12. The process according to anyone of claims 1-11 wherein X_1 and X_2 of Formula (I) and of Formula (II) are the same or different and are selected from hydrogen, methyl, (C_2-C_4) alkenyl , chloro and bromo.

13. The process according to anyone of claims 1-12, wherein Z of Formula (I) or of Formula (III) is preferably a group selected from:



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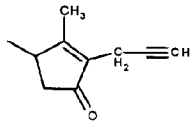

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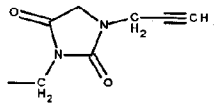

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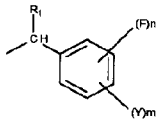
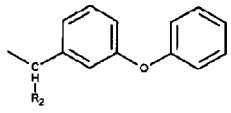


, wherein R_1 is hydrogen, n is an integer from 4 to 5, m is (5-n), Y is hydrogen or CH_3-O-CH_2-

and



wherein R_1 is hydrogen.

Dated this 5th day of February 2014

(R P BHATTACHARYA)
Reg. No. IN/PA-60
of DE PENNING & DE PENNING
Agent for the Applicants

IMPROVED PROCESS FOR THE PREPARATION OF PYRETHROIDS

Field of the invention

The present invention relates to an improved process for the preparation of pyrethroids in all stereochemical configuration as well as their mixtures.

Background and prior art

The use of N,N'-dicyclohexylcarbodiimide (DCC) as well as the modification by using 4-dimethylaminopyridine, known as Steglich esterification, in a process for preparing pyrethroids are cited in some documents.

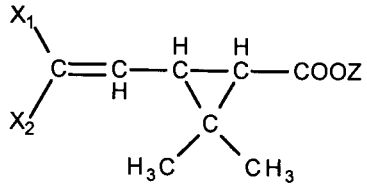
EP261033 describes the use of DCC to obtain ester derivatives of pyrethroidic acids with indol alcohols. In particular on page 4, lines 62-63 ,the preferred process of the invention consists of the reaction of the pyrethroidic acid and the suitable alcohol with DCC in the presence of 4-dimethylaminopyridine. Example 2 of the same document on page 7, lines 25-37, reports that the pyrethroidic ester is prepared by adding a solution of DCC and 4-dimethylamino pyridine in dichloromethane at 0°C to a solution of the suitable alcohol and acid in dichloromethane. After the needed purification step the yield of the pyrethroidic ester was 79.7% calculated on the basis of the alcohol (limitant reactant).

EP378025 describes the use of DCC to obtain ester derivatives of 3-ethynyl-2,2-dimethylcyclopropane-1-carboxylic acid and fluorinated derivatives of benzyl alcohol: The preparation is reported in example 1, on page 5, lines 55-57 and on page 6, lines 1-8. The preparation is carried out by adding at 0°C a solution of DCC and 4-dimethylaminopyridine in dichloromethane to a solution of the suitable alcohol and pyrethroidic acid in methylene chloride. After the necessary purification the total yield was 84.1% calculated on the basis of the alcohol (limitant reactant).

EP521780 describes the use of DCC to get ester derivatives of pyrethroidic acids and 1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl-methyl alcohol. Specifically, in Example 1 on page 8, lines 21-32, the preparation of the ester derivatives is carried out by adding at 0°C a solution of DCC in methylene chloride to a solution of the suitable alcohol and 4-dimethylaminopyridine in methylene choride and by keeping the mixture at room temperature for 16 hrs. There is still the need of having a process for preparing pyrethroids in better yield.

Brief Summary of the Invention

This object has been achieved by an improved process for preparing pyrethroids of formula (I) in all stereochemical configuration as well as their mixtures

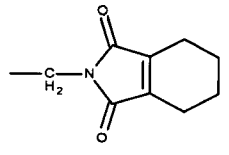


(I)

wherein

X_1 and X_2 are the same or different and are selected from hydrogen, (C_1-C_4)alkyl , (C_2-C_4)alkenyl and halogen;

Z is a group selected from:



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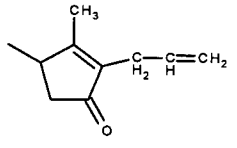

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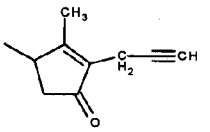

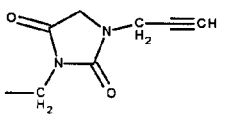

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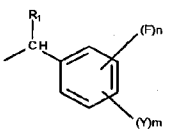
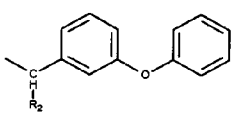


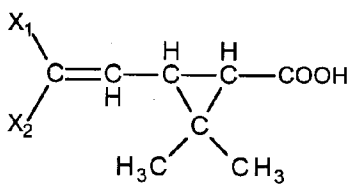
, wherein R_1 is hydrogen, methyl or –CN, n is an integer from 1 to 5, m is (5-n), Y is hydrogen, $(C_1\text{-}C_4)$alkyl or $(C_2\text{-}C_5)$alkoxy$(C_1\text{-}C_4)$alkyl and



wherein R_2 is hydrogen, methyl or -CN ,

comprising the steps of:

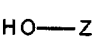
a) preparing an organic solution of an acid of formula (II)



(II)

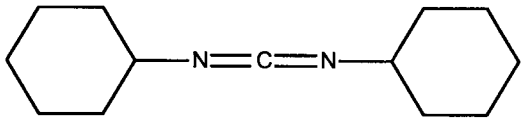
in a suitable organic solvent

b) preparing an organic solution of an alcohol of formula (III)



(III)

in a suitable organic solvent and in the presence of dicyclohexylcarbodiimide (DCC) of formula (IV),



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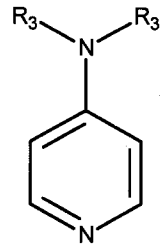
and a N,N'-dialkylpyridine catalyst of formula (V)



(V)

wherein R3 is (C_1-C_4) alkyl and

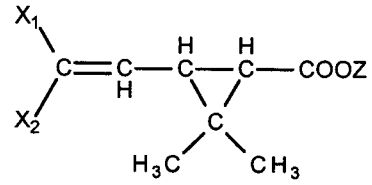
c) reacting the organic solution of step a) with the organic solution of step b) by adding the organic solution of the acid of formula (II) of step a) to the organic solution of step b) comprising the alcohol (III).

In the present invention the suitable organic solvent of step a) can be equal or different to the organic solvent of step b), being in this latter case the two organic solvents miscible each one in the other.

The process of the invention represents a substantial improvement in comparison with the processes of the prior art, allowing to get yields higher than 90% and shorter reaction times, based on the order of the addition of the reactants. Advantageously, the process of the invention allows the use of solvents with lower environmental impact, specifically when compared with chloride solvents. A further great advantage of the invention, is that no column purification is required.

Detailed description of the invention

The present invention concerns a process for preparing pyrethroids of formula (I) in all stereochemical configuration as well as their mixtures

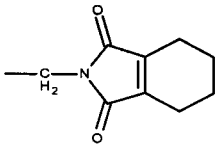


(I)

wherein

X_1 and X_2 are the same or different and are selected from hydrogen, (C_1-C_4) alkyl , (C_2-C_4) alkenyl and halogen;

Z is a group selected from:



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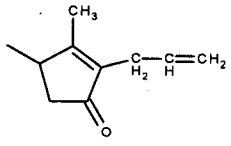

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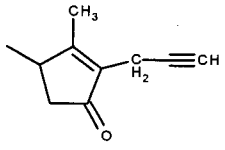

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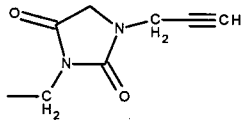

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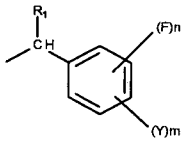
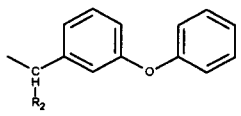


, wherein R_1 is hydrogen, methyl or –CN, n is an integer from 1 to 5, m is (5-n), Y is hydrogen, (C_1-C_4)alkyl or (C_2-C_5)alkoxy(C_1-C_4)alkyl

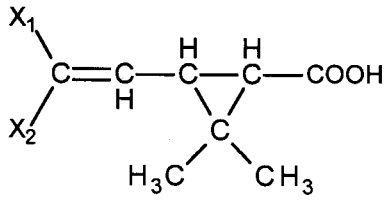
and



wherein R_2 is hydrogen, methyl or -CN

comprising the steps of:

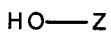
a) preparing an organic solution of an acid of formula (II)



(II)

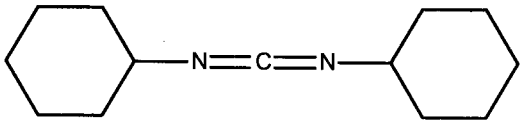
in a suitable organic solvent

b) preparing an organic solution of an alcohol of formula (III)



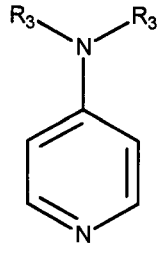
(III)

in a suitable organic solvent and in the presence of dicyclohexylcarbodiimide (DCC) of formula (IV),



(IV)

and a N,N'-dialkylpyridine catalyst of formula (V)



(V)

wherein R3 is (C_1-C_4) alkyl; and

c) reacting the organic solution of step a) with the organic solution of step b) by adding the organic solution of the acid of formula (II) of step a) to the organic solution of step b) comprising the alcohol (III).

In the present invention the suitable organic solvent of step a) can be equal or different to the organic solvent of step b), being in this latter case the two organic solvents miscible each one in the other .The organic solvent of step a) and the organic solvent of step b) are, independently preferably selected from the group consisting of n-pentane, n-hexane, n-heptane, diethyl ether, diisopropyl ether, tetrahydrofurane, methyl-tetrahydrofurane, dichloromethane, benzene, toluene, mesitylene and their mixtures.

The aromatic solvents are preferred; toluene is particularly preferred. Still more preferably the organic solvent of step a) equal to the organic solvent of step b). Advantageously the reaction is carried out by firstly preparing the organic solution of the acid of formula (II) and then adding it to the organic solution comprising the alcohol of formula (III), DCC and the catalyst of formula (V).

The ratio of DCC versus the acid of formula (II) is from 1.2 to 0.95 eq. , preferably from 1.1 to 0.95 eq., more preferably from 1.02 to 0.95 eq.

The ratio of the acid of formula (II) versus the alcohol of formula (III) is preferably in the range from (1.5 to 1.0) eq. to (1.1 to 1.0) eq., more preferably 1.05 to 1.0 eq. Advantageously, in the preferred and more preferred embodiments the purity of the final compound is higher.

The preferred catalyst of formula (V) is 4-(N,N'-dimethylamino)pyridine and the amount of the catalyst is preferably in the range from 0.1 to 0.01eq. with respect to the alcohol of formula(III), more preferably from 0.08 to 0.01 eq., still more preferably from 0.05 to 0.01 eq.

The ratio of the amount of alcohol of formula (III) with respect to the organic solvent of step b) can range from 1:4 to 1:7 (w/w). A range from 1:4.5 to 1:5 is preferred.

The ratio of the amount of the acid of formula (II) with respect to the amount of the organic solvent of step a) can range from 1:2 to 1:0.5 (w/w). The ratio of 1:1 is preferred .

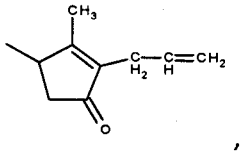
The addition time of the organic solution of the acid (II) to the organic solution of the alcohol (III) can preferably vary in the range from 1/240 eq/minute to 1/60 eq/minute of the acid with respect to the eq. of the alcohol. An addition time between of 1/240 eq/minute to 1/90 eq/minute of the acid of formula (II) with respect to the alcohol of formula (III) is more preferred.

Advantageously, in the preferred and more preferred embodiments the purity of the final compound is higher.

The reaction step during the addition of the acid (II) solution to the solution of the alcohol (III) is preferably carried out in the temperature range from -10°C to 20°C; being the range from 0°C to 5°C more preferred .

After the addition, the reaction step is preferably carried out from 20°C to 60°C depending on the organic solvents used during the reaction. The temperature between 15°C and 25°C is more preferred.

X_1 and X_2 of Formula (I) and of Formula (II) are the same or different and are preferably selected from hydrogen, methyl, (C_2-C_4)alkenyl , chloro and bromo.
Z of Formula (I) or of Formula (III) is preferably a group selected from:



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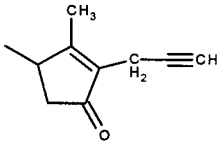

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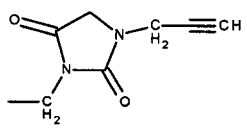
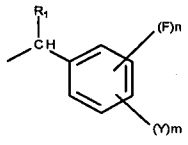
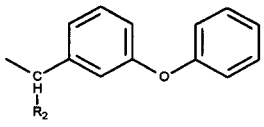


and



, wherein R_1 is hydrogen, n is an integer from 4 to 5, m is (5-n), Y is hydrogen or CH_3-O-CH_2-

or a group



wherein R_1 is hydrogen.

The present invention is illustrated by way of examples, which, however, should not be construed to limit the scope of the invention.

Example 1 (Synthesis of d-Allethrin**)**

In a three necked bottom flask with a stirrer, 20.0 g (0.127 moles) of racemic allethrolone (title 97.1% w/w) , 27.2 g (0.131 moles) of dicyclohexylcarbodiimide, 0.31 g (2.5 mmoles) of 4-(N,N'-dimethylamino) pyridine were dissolved in 90 g of toluene under stirring and nitrogen atmosphere.

The solution was cooled to 0°-5°C and added at 1/180eq per minute with a solution of 22.0 g(0.131 moles) of d-trans/cis (80/20) chrysanthemic acid in 19 g of toluene.

After the addition the mixture was heated to room temperature 20°C) and stirred for further 2 hrs under nitrogen.

The mixture was then filtered and the organic solution washed in sequence with 30 ml of water ,with 30 ml of basic water (pH10) and with 30 ml of water.

The solvent was evaporated under vacuum (40°C/1.8 mbar), thus obtaining 38.3 g of d-allethrin (title 96% w/w) as a colorless oil (yield 95.9%).

Example 2 (Synthesis of d-phenothrin)

Following the same procedure as in Example 1, d-phenothrin was prepared starting from a solution of 25.6 g (0.128 moles) of 3-phenoxybenzylalcohol, 27.2 g (0.131 moles) of dicyclohexylcarbodiimide, 0.31 g (2.5 mmoles) of 4-(N,N'-dimethylamino) pyridine in 90 g of toluene. The solution was cooled to 0°-5°C and added at 1/180eq/minute with a solution of 22.0 g(0.131 moles) of d-trans/cis (80/20) chrysanthemic acid in 19 g of toluene

After the addition the mixture was heated to room temperature (20°C) and stirred for further 2 hrs under nitrogen.

After the work up of the reaction, the solvent was evaporated under vacuum (40°C/1.8 mbar) thus obtaining 42.5 g of d-phenothrin (title 98% w/w) as a colorless oil (yield 97.1%).