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(54) Title: 1S TO 1R EPIMERIZATIONS OF PYRETHROID INTERMEDIATES

(57) Abstract

This invention relates to a process for preparing certain isomers of 2,2–dimethyl–3–(2,2–disubstituted vinyl)cyclopropanecarboxylic acid or derivatives thereof. More specifically it relates to the epimerization of the 1S cyclopropanecarboxylic acid and its derivatives into the corresponding 1R isomers.

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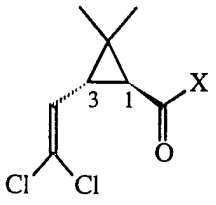
1S TO 1R EPIMERIZATIONS OF PYRETHROID INTERMEDIATES

Field of the Invention

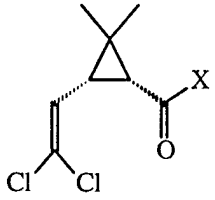
This invention relates to a process for preparing certain isomers of 2,2-dimethyl-3-(2,2-disubstitutedvinyl)cyclopropanecarboxylic acid or derivatives thereof. More specifically it relates to epimerizations of the 1S cyclopropanecarboxylic acid and its derivatives into the corresponding 1R isomers. Most specifically it relates to the epimerization of 1S-*trans* into 1R-*cis* and the epimerization of 1S-*cis* into 1R-*trans* cyclopropanecarboxylic acids and derivatives. The products of the epimerizations are useful for preparing pyrethroids that have enhanced insecticidal activity.

Background of the Invention

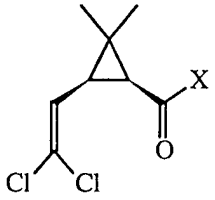
Pyrethroid esters of 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylic acid (DV acid) are important commercial insecticides. These pyrethroids are typically prepared as mixtures of isomers due to the chiral centers at positions 1 and 3 of the cyclopropane ring. The two chiral centers can lead to four possible isomers: 1S-*trans*, 1R-*cis*, 1S-*cis*, and 1R-*trans*. *Cis* and *trans* refer to the relative stereochemistry of the carboxyl and vinyl groups at cyclopropane positions 1 and 3 respectively, and 1R and 1S refer to the absolute stereochemistry at position 1. A change in absolute stereochemistry at a given position, for example from 1S to 1R in the structures below, is known as an epimerization.



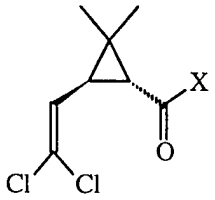
1S-*trans*
X = OH, Cl



1R-*cis*



1S-*cis*



1R-*trans*

Esterification of a *cis*:*trans* racemic mixture of DV acid chloride with either 3-phenoxybenzyl alcohol or the cyanohydrin of 3-phenoxybenzaldehyde leads to the commercially useful pyrethroids permethrin or cypermethrin, respectively. As discussed below, the different isomers in each of these pyrethroid products differ with respect to their activities in both insect and mammalian systems, and it would be useful to convert one isomer into another that is either more insecticidal and/or safer to non-target species.

Trans isomers of permethrin and cypermethrin are reported to have lower mammalian toxicity than the corresponding *cis* isomers (Nature 244, 456, 1973). Preparations of *trans* DV acid or the acid halide or lower alkyl anhydride thereof by isomerization of the corresponding *cis* DV acid derivatives are known. US Patent 4,008,268, incorporated herein by reference, describes the conversion of a 45:55 *cis*/*trans* mixture of DV acid to about 20:80 by heating the mixture to 160 - 165° C in the presence of an acid catalyst such as p-toluenesulfonic acid and either acetic anhydride or thionyl chloride. A higher percentage of the *trans* isomers can be obtained by isomerizing the *cis* DV acid halide in the presence of an aryl phosphine, as described in US Patent 4,954,651, also incorporated herein by reference. While the above methods are reported to be useful for obtaining *trans* isomers, they are not directed at obtaining a specific configuration at the 1 position of the cyclopropane ring.

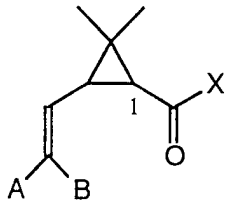
With regard to the insecticidal activity of the isomeric constituents of permethrin or cypermethrin, the isomer having the 1R configuration for either the *cis* or *trans* pyrethroid is more insecticidally active than the

corresponding isomer having the 1S configuration, with the 1R-*cis* isomer being the most potent (US Patents 5,164,411 and 4,997,970). The insecticidal potency of the 1S pyrethroid isomer is many-fold less active than the corresponding 1R isomer. The most insecticidal isomer of cypermethrin is the S-α-cyano-m-phenoxybenzyl ester of 1R-*cis* DV (the "S" in "S-α-cyano" refers to the absolute stereochemistry at the carbon to which the cyano group is attached).

The isomer having the 1R configuration is also more insecticidally potent than the 1S isomer of pyrethroid esters wherein the dichlorovinyl group is replaced by a dibromovinyl group (US Patent 4,024,163). Of the eight possible isomers of α-cyano-m-phenoxybenzyl-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate, the most insecticidal is (S)-α-cyano-m-phenoxybenzyl (1R-*cis*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate (deltamethrin). Thus, the optimum stereochemistry for insecticidal activity of 3-phenoxybenzyl or α-cyano-3-phenoxybenzyl esters of dihalovinylcyclopropylcarboxylic acids is the same when the vinyl halogens are either bromine or chlorine.

Summary of the Invention

This invention relates to a process for the epimerization of compounds represented by formula I:



I

where both A and B are chlorine or bromine, or one of A and B is chlorine and the other is trifluoromethyl; and X is selected from halogen, OH, and O_2C-alkyl. In the process, epimerization of certain 1S-*trans* dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropanecarboxylic acids and derivatives thereof

enhances the content of the corresponding 1R-*cis* isomer and epimerization of certain 1S-*cis* dimethyl-3-(2,2-disubstitutedvinyl)-cyclopropanecarboxylic acids and derivatives thereof enhances the content of the corresponding 1R-*trans* isomer.

Description of the Invention

The methods of the present invention, describing the epimerization of 1S-*trans* to 1R-*cis* and 1S-*cis* to 1R-*trans*, are directed at both the relative and absolute stereochemistry of the cyclopropane ring. The conversions described herein are stereospecific in that position 3 of the cyclopropane ring is unaffected. The 1S dimethyl-3-(2,2-disubstitutedvinyl) cyclopropanecarboxylic acids and derivatives capable of undergoing epimerization to the corresponding 1R compounds in accordance with the present process are represented by formula I above.

In the present process, the 1S-*trans* or 1S-*cis*-dimethyl-3-(2,2-disubstitutedvinyl) cyclopropanecarboxylic acid or anhydride is heated at a temperature between 140-170° C in the presence of a suitable catalyst. Suitable catalysts are protic acids such as toluenesulfonic acid, sulfuric acid or the like. The amount of catalyst used is about 1% to 10% by weight based on the weight of acid or anhydride of formula I (X is OH or O_2C-alkyl). The alkyl portion of the O_2C-alkyl group may be from one to six carbons. A preferred anhydride for isomerization is I where X is O_2CCH_3. This anhydride may be formed in situ starting with the DV acid and acetylchloride. Reaction times are typically at least about one hour to up to several hours.

If the corresponding acid halide (I, X is Cl or Br) is employed as the starting material, the epimerization process may be performed with or without solvent. The acid halide is heated at a temperature between about 140-170° C, preferably between about 145-150° C. Reaction times are typically at least about one-half hour to up to several hours, and preferably about three to four hours. The use of a Lewis acid catalyst in the mixture to

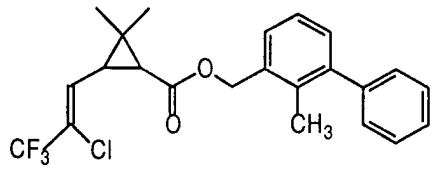
be epimerized, such as the Lewis acids described in US Patent 4,954,651, is optional. In the present process, it is preferred to carry out the epimerization process by heating the acid halide without solvent and without added catalyst.

When the 1S-*trans* DV acid chloride is heated at 145-150° C for four hours, the resulting isomeric mixture will contain about 22% of the 1R-*cis* isomer and 78% of the 1S-*trans* isomer. The 1S-*trans* DV acid chloride that is used may be present in a mixture having an isomeric content of between about 0:100 to 21:79 of 1R-*cis*:1S-*trans* isomers. After the heating, the resulting mixture may be converted directly to a pyrethroid by esterification with 3-phenoxybenzyl alcohol, with the cyanohydrin of 3-phenoxybenzaldehyde or with any other alcohol which gives an insecticidal ester with the DV acid. The resulting pyrethroid composition enriched with the 1R-*cis* DV moiety will have greater insecticidal activity than the corresponding composition having more of the 1S-*trans* DV moiety. Alternatively, the unwanted 1S-*trans* intermediate can separated from its 1R-*cis* isomer. Specific methods of separating these diastereomers have been reported in US Patents 4,024,163 and 4,261,921. Also, other methods for separating diastereomers such as the DV acid derivatives and pyrethroid isomers are known to one skilled in the art. If separated, the 1S-*trans* intermediate may be recycled in the present process for another partial epimerization.

Using the same conditions as those described above for the epimerization of the 1S-*trans* isomer, the 1S-*cis* isomer undergoes epimerization to provide an isomeric mixture containing about 77% 1R-*trans* and 23% 1S-*cis*. The 1S-*cis* isomer that is used may be present in a mixture having an isomeric content of between about 0:100 to 76:24 of 1R-*trans*:1S-*cis* isomers. The mixture may be directly converted to a pyrethroid or the 1S-*cis* isomer may be separated and recycled as discussed above.

The present process also has application in the preparation of other pyrethroids. For example, the process of the present invention is applicable

to the preparation of 1R-*cis* or 1R-*trans* enriched mixtures of cyclopropanecarboxylic acids and their derivatives represented by formula I where A or B is chlorine and the other is trifluoromethyl, which are useful in the preparation of pyrethroids such as bifenthrin shown below. The present invention is also applicable to the preparation of 1R-*cis* or 1R-*trans* enriched mixtures of cyclopropanecarboxylic acids and their derivatives represented by formula I where A or B are both bromine, which are useful in the preparation of pyrethroids such as deltamethrin discussed above.



bifenthrin

The examples below show how the epimerization process of the present invention may be carried out to provide the 1R isomer.

Example 1

1R-*cis* DV acid chloride

Thionyl chloride (1.15 g, 9 mmol) was added to 1S-*trans* 2,2-dimethyl-3-(2,2-chloroethenyl)cyclopropane-carboxylic acid (0.6 g, 3 mmol; $[\alpha]_{25°C}$ = - 36.6, $CHCl_3$) under nitrogen and the mixture was stirred at room temperature for three hours. After removing excess thionyl chloride in vacuo, the 1S-*trans* DV acid chloride product was heated in a sealed ampoule at 145-150° C for four hours. Upon cooling, an aliquot of the reaction mixture was esterified with R-(-)-2-butanol [99%, [α]D -13° (neat)]. Capillary gas chromatography of the resulting diastereomeric ester mixture revealed that the isomerization had afforded a 22:78 mixture of 1R *cis*:1S-*trans* isomers of DV acid chloride.

Example 2

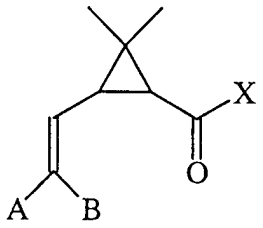
1R-*trans* DV acid chloride

Thionyl chloride (0.85 g, 7 mmol) was added to 1S-*cis* 2,2-dimethyl-3-(2,2-chloroethenyl)cyclopropane-carboxylic acid (95% 1S-*cis* and 5% 1R-*cis*;

0.5 g, 2 mmol) under nitrogen and the mixture was stirred at room temperature for two hours. After removing excess thionyl chloride in vacuo, the *cis* DV acid chloride product was heated in a sealed ampoule at 145° C for 3.5 hours. Upon cooling, an aliquot of the reaction mixture was esterified with R-(-)-2-butanol. Capillary gas chromatography of the resulting diastereomeric ester mixture revealed that the isomerization had afforded a 77:23 mixture of *trans*:*cis* isomers. The *trans* isomers were 94% 1R and 6% 1S and the *cis* isomers were 95% 1S and 5% 1R.

We claim:

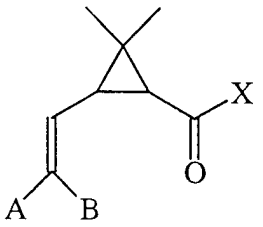
1. A process for converting a first composition of a 2-(2,2-disubstitutedvinyl)-3,3-dimethylcyclopropane carboxylic acid derivative represented by the formula



where both A and B are chlorine or bromine, or one of A and B is chlorine and the other is trifluoromethyl; and X is OH or O_2C-alkyl, to a second composition of the derivative, wherein the first composition has an isomeric content of between about 0:100 to 21:79 of 1R-*cis*:1S-*trans* isomers of the derivative and the second composition has an isomeric content of about 22:78 1R-*cis*:1S-*trans* isomers of the derivative which comprises the step of heating the first composition at a temperature between 140-170 °C in the presence of a protic acid.

2. A process according to claim 1 wherein the derivative is heated in the presence of about 1% to 10% of a protic acid.

3. A process for converting a first composition of a 2-(2,2-disubstitutedvinyl)-3,3-dimethylcyclopropane carboxylic acid derivative represented by the formula



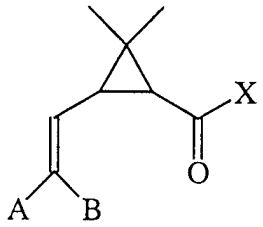
where both A and B are chlorine or bromine, or one of A and B is chlorine and the other is trifluoromethyl; and X is halogen, to a second composition of the derivative, wherein the first composition has an isomeric content of between about 0:100 to 21:79 of 1R-*cis*:1S-*trans* isomers of the

derivative and the second composition has an isomeric content of about 22:78 1R-*cis*:1S-*trans* isomers of the derivative which comprises the step of heating the first composition at a temperature between 140-170° C.

4. A process according to claim 3 wherein the heating is carried out without a solvent.

5. A process according to claim 4 wherein the heating is carried out at a temperature between 145 - 150° C.

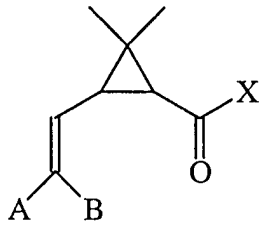
6. A process for converting a first composition of a 2-(2,2-disubstitutedvinyl)-3,3-dimethylcyclopropane carboxylic acid derivative represented by the formula



where both A and B are chlorine or bromine, or one of A and B is chlorine and the other is trifluoromethyl; and X is OH or O_2C-alkyl, to a second composition of the derivative, wherein the first composition has an isomeric content of between about 0:100 to 76:24 of 1R-*trans*:1S-*cis* isomers of the derivative and the second composition has an isomeric content of about 77:23 1R-*trans*:1S-*cis* isomers of the derivative which comprises the step of heating the first composition at a temperature range of 140-170° C in the presence of a protic acid.

7. A process according to claim 6 wherein the derivative is heated in the presence of about 1% to 10% of a protic acid.

8. A process for converting a first composition of a 2-(2,2-disubstitutedvinyl)-3,3-dimethylcyclopropane carboxylic acid derivative represented by the formula



where both A and B are chlorine or bromine, or one of A and B is chlorine and the other is trifluoromethyl; and X is halogen, to a second composition of the derivative, wherein the first composition has an isomeric content of between about 0:100 to 76:24 of 1R-*trans*:1S-*cis* isomers of the derivative and the second composition has an isomeric content of about 77:23 1R-*trans*:1S-*cis* isomers of the derivative which comprises the step of heating the first composition at a temperature range of 140-170°.

9. A process according to claim 8 wherein the heating is carried out without a solvent.

10. A process according to claim 9 wherein the heating is carried out at a temperature between 145 - 150° C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18442

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07B 55/00; C07C 51/58, 53/00, 55/00, 61/04
US CL :562/401, 506, 856, 887

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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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	NL 7507007 A (SUMITOMO CHEMICAL COMPANY KK) 17 December 1975, see entire document.	1, 2, 6, 7 --- 1-10
Y	US 3,794,680 A (MATSUI et al.) 26 February 1974, see entire document.	1-10
Y	US 3,989,750 A (NAGASE et al.) 02 November 1976, see entire document.	1-10
Y	US 4,812,264 A (SUZUKAMO et al.) 14 March 1989, See entire document.	1-10
Y	US 4,485,257 A (SUZUKAMO, et al), 27 November 1984 see entire document.	1-10
Y	US 4,898,655 (SUZUKAMO, et al) 06 Feb 1990, see entire	1-10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18442

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 49-31978 A (SUMITOMO CHEMICAL COMPANY LTD.) 27 August 1974, see entire document.	1-10
Y	JP 50-88055 A (SUMITOMO CHEMICAL COMPANY KK) 15 Jul 1975, see entire document.	1-10
Y	Chemival Abstracts, Volume 73, Number 15SUZUKI et al. Trans-Chrysanthemic Acid from cis-Chrysanthemoyl Chloride. Columbus, Ohio, 12 October 1970, page 324, column 2, abstract no. 76735, DE 2,003,065 A 13 Aug 1970, see entire abstract.	1-10