FORM 1 SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 602998

APPLICATION FOR A STANDARD PATENT

Pfizer Inc., of 235 East 42nd Street, New York, New York, 10017, UNITED STATES OF AMERICA, hereby apply for the grant of a standard patent for an invention entitled:

Process for the Preparation of Meso 2,5-dihaloadipates

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
082703	US	7 August 1987

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this FOURTH day of AUGUST 1988

Pfizer Inc.

By: M.J. Anderson

Registered Patent Attorney

ACCEPTED AND AMENDMENTS

10-8-88

TO: THE COMMISSIONER OF PATENTS
OUR REF: 63200
CS&F CODE: 60030

01517

RINT OF RECEIPT
NT OF RECEIPT 5845/2

RINT OF RECEIPT
01517 05/08/88

COMMONWEALTH OF AUSTRALIA
THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

AUSTRALIA CONVENTION STANDARD & PETTY PATENT DECLARATION

In support of the Convention Application made for a patent for an invention entitled:

PC7248

Title of Invention: PROCESS FOR THE PREPARATION OF MESO 2,5-DIHALOADIPATES

Full name(s) and address(es) of Declarant(s)

I/We Allen J. Spiegel on behalf of PFIZER INC.

of 235 East 42nd Street, New York, New York, United States of America

do solemnly and sincerely declare as follows:-

Full name(s) of Applicant(s)

1. I ~~am/We are the applicant(s) for the patent~~

(or, in the case of an application by a body corporate)

1. I am/~~We are~~ authorised by PFIZER INC.

the applicant~~(s)~~ for the patent to make this declaration on its/~~their~~ behalf.

2. The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made

Basic Country(ies): in the United States of America

Priority Date(s): on August 7, 1987

Basic Applicant(s): by Brian T. O'Neill and Harry A. Watson, Jr.

3. ~~I am/We are the actual inventor(s) of the invention referred to in the basic application(s).~~

Full name(s) and address(es) of inventor(s)

(or where a person other than the inventor is the applicant)

3. Brian T. O'Neill and Harry A. Watson, Jr. respectively of 1528 Essex Road, Westbrook; 694 Eastern Point Road, Groton, both of the State of Connecticut;

of United States of America

(respectively)

~~is~~/are the actual inventor(s) of the invention and the facts upon which the applicant~~(s)~~ is/~~are~~ entitled to make the application are as follows:

Set out how Applicant(s) derive title from actual inventor(s) e.g. The Applicant(s) is/are the assignee(s) of the invention from the inventor(s)

The Applicant Company is the assignee of the said invention from the actual inventors by virtue of an assignment dated July 24, 1987

4. The basic application~~(s)~~ referred to in paragraph 2 of this Declaration ~~was/were~~ was the first application~~(s)~~ made in a Convention country in respect of the invention~~(s)~~ the subject of the application.

Declared at New York, New York, this 14th day of June 1988

PFIZER INC.

.....
Signature of Declarant(s)
ALLEN J. SPIEGEL
ASSISTANT DIRECTOR FOR FOREIGN PATENTS

FP4

To: The Commissioner of Patents

1/81

(12) PATENT ABRIDGMENT (11) Document No. AU-B-20516/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 602998

(54) Title
PROCESS FOR THE PREPARATION OF MESO 2,5-DIHALOADIPATES

International Patent Classification(s)
(51)* C07C 067/52 C07C 069/63

(21) Application No. : 20516/88 (22) Application Date : 05.08.88

(30) Priority Data

(31) Number (32) Date (33) Country
082703 07.08.87 US UNITED STATES OF AMERICA

(43) Publication Date : 09.02.89

(44) Publication Date of Accepted Application : 01.11.90

(71) Applicant(s)
PFIZER INC.

(72) Inventor(s)
BRIAN T. O'NEILL; HARRY A. WATSON JR.

(74) Attorney or Agent
SPRUSON & FERGUSON, GPO Box 3898, SYDNEY NSW 2001

(57) Claim

1. A process for the preparation of the meso dialkyl 2,5-dihaloadipate from a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate comprising

(a) halogenating an adipoyl monohalide under conditions wherein a mixture of racemic and meso-dihalo adipoyl halides are formed, said conditions also resulting in the formation of an acidic hydrogen halide,

(b) esterifying said mixture of resultant dihalo adipoyl halides under conditions resulting in the formation of a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate, said conditions also resulting in the formation of an acidic hydrogen halide.

(c) allowing the mixture of (b) to remain in contact with the acidic hydrogen halide produced in steps (a) and (b) for a sufficient period of time to allow spontaneous crystallization of said meso ester, and acidic hydrogen halide epimerizing said racemic ester to said meso ester,

(d) removing the meso diester thus produced from the equilibrium mixture of (c) by crystallization, whereby said crystallization of the meso diester drives the equilibrium of the mixture towards formation of the meso diester.

S & F Ref: 63200

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

602998

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

This document contains the amendments made under Section 49 and is correct for printing.

Priority:

Related Art:

Name and Address of Applicant: Pfizer Inc.
235 East 42nd Street
New York New York 10017
UNITED STATES OF AMERICA

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Process for the Preparation of Meso 2,5-dihaloadipates

The following statement is a full description of this invention, including the best method of performing it known to me/us

P.C. 7248

PROCESS FOR THE PREPARATION OF MESO 2,5-DIHALOADIPATES

Abstract

The present process produces the meso dialkyl 2,5-dihaloadipate from a mixture of the racemic dialkyl 2,5-dihaloadipate and meso 2,5-dihaloadipate. In the disclosed process, a 2,5-dihaloadipoyl halide is formed under conditions which result in the formation of an acidic compound. The 2,5-dihaloadipoyl halide is then esterified under conditions wherein the ester of the dihaloadipoyl halide is allowed to remain in contact with the acidic compound, thus allowing the racemic diester to epimerize in the presence of the acidic compound to the meso form and then the meso diester spontaneously crystallizes. In the last stage, the meso diester produced is removed.

P.C. 7248

PROCESS FOR THE PREPARATION OF MESO 2,5-DIHALOADIPATES

Dihaloadipates are important intermediates in the formation of many compounds having pharmaceutical, herbicidal and other attributes. In particular, the esterified derivatives of meso-2,5-dihaloadipates are useful intermediates in the synthesis of heterocycles such as disubstituted pyrrolidines and diazabicyclo-octanes.

A number of methods directed to the synthesis of the meso compounds have been reported.

For instance, an article by Willstatter appearing in Chem. Ber., 35, 2065,1902 reports the synthesis of the diethylester of meso dibromoadipate with very little experimental detail.

In later articles appearing in J. Chem. Soc., 273, 1909 and J. Chem. Soc. 951, 1921, the bromination of the adipoyl halide and latter esterification to yield the diethyl ester resulted in yields of the desired product of 28% and 40%, respectively. The above two references disclose the improved formation of the meso-ester only after high temperature vacuum distillation.

An analogous process affording a 60% yield of the methyl ester of the dihalo adipoyl halide is reported in J. Org. Chem., 26, 2750, 1961. The method reported in this reference also required careful fractionation.

An article appearing in J. Amer. Chem. Soc. 64, 2696, (1942), discloses the preparation of meso methyl dibromoadipate in a 70% yield by (a) a first crop crystallization of 50% of pure meso and (b) fractional distillation of the resulting mother liquor to obtain

the remaining 20% of the pure meso compound. These authors report that the diethyl ester was obtained in an overall yield of 46%.

Thus, there remains a need for a process affording the pure meso-2,5-dibromoadipate without resort to careful fractionation or long reaction times.

The present invention is directed to a process for the preparation of the meso dialkyl 2,5-dihaloadipate from a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate comprising

(a) halogenating an adipoyl halide under conditions wherein a mixture of racemic and meso-dihalo adipoyl halides are formed, said conditions also resulting in the formation of an acidic compound,

(b) esterifying said mixture of resultant dihalo adipoyl halides under conditions resulting in the formation of a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate, said conditions also resulting in the formation of an acidic compound,

(c) allowing the mixture of (b) to remain in contact with the acidic compound produced in steps (a) and (b) for a sufficient period of time to allow spontaneous crystallization of said meso diester, said acidic compound serving to epimerize said racemic dialkyl 2,5-dihaloadipate to said meso dialkyl, 2,5-dihaloadipate,

(d) removing the meso dialkyl 2,5-dihaloadipate thus produced from the equilibrium mixture of (c) by crystallization, whereby said crystallization of the meso dialkyl 2,5-dihaloadipate drives the equilibrium of the mixture towards formation of the meso dialkyl 2,5-dihaloadipate.

Preferred dialkyl 2,5-dihaloadipates which can be produced by the above process are C_1-C_3 alkyl diesters,

with especially preferred alkyl diesters being the dimethyl and diethyl esters.

Another preferred diester which can be produced by the above process is the dibenzyl ester.

Preferred acidic compounds which epimerize the mixture of the racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate are hydrogen bromide and hydrogen chloride.

A preferred adipoyl halide which is halogenated in step (a) is adipoyl chloride with a preferred halogenation being the bromination of the adipoyl chloride to produce a dibromoadipoyl halide.

An especially preferred compound produced by the process of the present invention is meso diethyl 2,5-dibromoadipate.

The adipoyl halides which are halogenated in step (a) of the present invention are items of commerce and may be obtained from a variety of sources, for example, Aldrich Chemical Company.

The halogenation reaction is conducted at a temperature of from about 70°C to about 100°C, preferably about 75°C to about 85°C, with one method being to heat the adipoyl halide to this temperature and then add the halogen to the heated adipoyl halide in the presence of light. The adipoyl halide can be adipoyl chloride, adipoyl fluoride, adipoyl bromide or adipoyl iodide with an especially preferred adipoyl halide being adipoyl chloride.

The halogen used in the halogenation reaction can be chlorine or bromine, with bromine being an especially preferred halogen.

The halogenation reaction of step (a) of the present invention is conducted under conditions wherein

a mixture of racemic and meso-dihaloadipoyl halides is formed. Additionally, an acidic compound is formed. The acidic compound formed is a hydrogen halide. For instance if the adipoyl halide is adipoyl chloride and the halogen is bromine, the reaction mixture contains hydrogen bromide.

In the present invention, it has now been surprisingly found that if the acidic compound is not removed, the presence of the acidic compound drives the epimerization of the racemic diester to the meso diester, a reaction to be discussed in more detail below.

In step (b) of the present invention, the resultant mixture of dihaloadipoyl halides of step (a) is esterified. In this step, the reaction mixture also contains a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate and in addition, contains an acidic compound. The esterification reaction is carried out under conventional conditions for such reactions, i.e. using a C_1-C_3 alcohol at a temperature of about 10°C to about 25°C. C_1-C_3 alcohols which can be used in the esterification reaction are methanol and ethanol. If the alcohol used in step (b) is ethanol, then the acidic compound generated is hydrogen chloride.

Since the acidic compounds generated in steps (a) and (b) of the present process have not been removed, they function in the esterification step in a similar manner, that is, the presence of the acidic compounds spontaneously epimerizes the racemic dialkyl 2,5-dihaloadipate to the meso diester, as described in step (c) of the present process.

In step (d) of the present process, the meso dialkyl 2,5-dihaloadipate is removed by crystallization, thereby driving the equilibrium of the mixture towards formation of the meso dialkyl ester. Since the removal of the meso dialkyl ester shifts the equilibrium between the racemic dialkyl ester and meso dialkyl

ester away from the thermodynamic equilibrium, the epimerization continues in an effort to maintain the thermodynamic equilibrium. Removal of the meso dialkyl ester is accomplished by conventional means, i.e., filtering, washing, etc.

Having described the invention in general terms, reference is now made to specific examples thereof. It is to be understood that these examples are not to be construed as limiting the invention, the scope of which is determined by the appended claims.

~~Having described the invention in general terms~~ reference is now made to specific examples thereof. It is to be understood that these examples are not to be construed as limiting the invention, the scope of which ~~is determined by the appended claims.~~

Example 1

Bromination of Adipoyl Chloride

A two liter four neck round bottom flask was assembled on a steam bath. The flask was equipped with a thermometer, paddle-stirrer, dropping funnel and reflux condenser. The top of the reflux condenser was vented into a scrubber system. A sun lamp was positioned two to three inches from the side wall of the flask.

The above described two liter flask was charged with 200 g(1.093 mole) of 98% adipoyl chloride. The sun lamp was turned on and the stirred oil was heated to 75-85°C. Once at 75-85°C , 374.3 g(2.342 mole) of liquid bromine was added dropwise over five hours and fifteen minutes. After this addition was complete the reaction was kept at 75-85°C for another one hour and forty-five minutes. Thin-layer chromatography at this point indicated incomplete reaction. An additional 78g (.488 mole) of bromine was added over 45 minutes, followed by 30 minutes of heating at 75°C to 85°C. Thin-layer chromatography then showed complete reac-

tion. The heating was stopped and the sun lamp was removed. The dropping funnel was replaced with a nitrogen inlet and the condenser was removed. Nitrogen was blown through the flask venting through the scrubber system. It took approximately one hour to purge the bromine color from the flask. The crude oil was used in the following step as is.

Example 2

Preparation of Diethyl-meso-dibromoadipate

A two liter three neck round bottom flask was equipped with paddle stirrer and thermometer, then immersed in an ice water bath. The flask was charged with 650 ml 2B ethanol. Crude dibromo adipoyl chloride (1.093 mole) was added to this stirred 2B ethanol, not allowing the internal temperature to exceed 25°C. This addition took forty-five minutes and the resulting suspension was stirred at room temperature for sixteen hours, then at 5°C for thirty minutes. The suspension was filtered and the moist cake was reslurried briefly in 250 ml fresh 2B ethanol at 10-15°C. This suspension was filtered and the white solid was washed with a minimal amount of 10-15°C 2B ethanol. This first crop was dried at 30°C in a vacuum oven to yield 205 g(52.1%) of white crystalline solid melting point 64-66°C.

All the clear yellow ethanol mother liquors from the above were combined and stripped to a 600 ml volume. After standing three days at room temperature, crystals had precipitated from solution. This mixture was stirred for one hour at 5-10°C, then filtered.

The moist cake was restirred in 150 ml 2B ethanol at 5-10°C, then filtered and dried at 30°C in a vacuum oven. This second crop of white crystalline solid weighed 92g(23.4%) and melted at 64-66°C.

The claims defining the invention are as follows:

1. A process for the preparation of the meso dialkyl 2,5-dihaloadipate from a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate comprising

(a) halogenating an adipoyl monohalide under conditions wherein a mixture of racemic and meso-dihalo adipoyl halides are formed, said conditions also resulting in the formation of an acidic hydrogen halide,

(b) esterifying said mixture of resultant dihalo adipoyl halides under conditions resulting in the formation of a mixture of racemic dialkyl 2,5-dihaloadipate and meso dialkyl 2,5-dihaloadipate, said conditions also resulting in the formation of an acidic hydrogen halide.

(c) allowing the mixture of (b) to remain in contact with the acidic hydrogen halide produced in steps (a) and (b) for a sufficient period of time to allow spontaneous crystallization of said meso ester, and acidic hydrogen halide epimerizing said racemic ester to said meso ester,

(d) removing the meso diester thus produced from the equilibrium mixture of (c) by crystallization, whereby said crystallization of the meso diester drives the equilibrium of the mixture towards formation of the meso diester.

2. The process of claim 1 wherein said dialkyl 2,5-dihaloadipate is a C_1-C_3 ester.

3. The process of claim 2 wherein said dialkyl 2,5-dihaloadipate is the dimethyl ester.

4. The process of claim 2 wherein said dialkyl 2,5-dihaloadipate is the diethyl ester.

5. The process of claim 1 wherein said acidic compound generated in step (a) is hydrogen bromide.

6. The process of claim 1 wherein said acidic compound generated in step (b) is hydrogen chloride.

7. The process of claim 1 wherein said adipoyl halide is adipoyl chloride.

8. The process of claim 1 wherein said dihaloadipate is a dibromoadipate.

9. The process of claim 1 wherein said meso dialkyl 2,5-dihaloadipate is meso diethyl 2,5-dibromoadipate.

10. A process for the preparation of the meso dialkyl 2,5-dihaloadipate substantially as hereinbefore described with reference to any one of the examples.

11. The product ~~of~~ when made by the process of any one of claims 1 to 10.

DATED this THIRD day of AUGUST 1988
Pfizer Inc.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON