Title: PROCESS FOR THE PREPARATION OF ACECLOFENAC

Abstract

Compounds of formula (I), wherein R\(^1\), R\(^2\) and R\(^3\) are independently selected from lower alkyl groups Ci−C\(_4\) or hydrogen, are particularly useful intermediates in producing Aceclofenac. The compounds are prepared by reacting Diclofenac acid with triethylamine, disopropylamine or ammonia in a solvent at a temperature of from 20 °C to 60 °C. The compounds of formula (I) are reacted with an appropriate α-haloacetic acid ester to form acetates which are deprotected to form Aceclofenac. Other α-Arylpropanoic Acid NSAID's may be prepared analogously.
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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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PROCESS FOR THE PREPARATION OF ACECLOFENAC

Introduction

The invention relates to a process for preparing non-steroidal anti-inflammatory drugs, to intermediates used in the process, and processes for preparing such intermediates.

Aceclofenac (formula III) is one example of a non-steroidal anti-inflammatory drug (NSAID) with properties similar to Diclofenac. The gastrointestinal tolerability of Aceclofenac is better than that of Diclofenac and other NSAIDs and it has a faster onset of action (Drugs Vol. 52(1), 113-124 [1996]).

![Chemical Structure](image)

EP-A-119932 describes a process for preparing Aceclofenac by hydrogenation of benzyl-2-[(2,6-dichlorophenyl)amine] phenylacetoxyacetate with a palladium catalyst over a long period of time at severe reaction conditions. The 2-[(2,6-dichlorophenyl)amine] phenylacetoxyacetate is prepared by dissolving the corresponding phenylacetoacetate in DMF and reacting with benzyl bromoacetate.

ES-A-2020146 describes the preparation of Aceclofenac by treating corresponding esters with iodine trimethylsilane which is prepared from chloromethylsilane and anhydrous sodium iodide in an inert atmosphere. Acetonitrile is used as the solvent.
CH-A-682747 describes a process for preparing Aceclofenac by acid hydrolysis of a 2-tetrahydropyryl or 4-methoxy-4-tetrahydropyryl ester. The esters are prepared by reacting the corresponding acetic acid with a corresponding haloacetate.

CA-A-2111169 describes phenylacetic acid derivatives and their salts. Sodium diclofenac is dissolved in DMF under a nitrogen atmosphere, the temperature is raised and tert.-butyl chloroacetate is added to yield tert.-butyl (2-(2,6-dichloroaniline)phenyl) acetoxyacetate.

There are a number of problems with conventional processes for preparing Aceclofenac. The yield of at least some of the steps is low, the reaction time is relatively high, hazardous reaction conditions and/or solvents are required and/or the use of dipolar aprotic solvents such as DMF causes difficulties in purification of the final product.

There is therefore a need for an improved process for preparing Aceclofenac which will overcome at least some of these problems and thereby provide a process which is economic and viable on a commercial scale.

Statements of Invention
The invention provides a compound of formula I

![Chemical structure](image)
wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from lower alkyl groups (C<sub>1</sub>-C<sub>4</sub>) or hydrogen.

Preferably R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from one or more of ethyl and isopropyl.

The invention also provides a process for preparing a compound of formula I by reacting 2-[(2,6-Dichlorophenyl)amine] phenylacetic Acid (Diclofenac Acid) with an appropriate amine of the formula NR<sup>1</sup>R<sup>2</sup>R<sup>3</sup> wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above.

The reaction may be carried out in a solvent selected from toluene, THF, acetone, MEK, MIBK, acetonitrile or a chlorinated solvent.

The formation of adduct I is carried out at a temperature of from 0º to 100ºC, preferably from 20º to 60ºC.

The amine may be triethylamine, diisopropylethylamine, or ammonia.

The invention also provides a process for preparing a compound of the formula II.

![Chemical Structure](image)

by reacting a compound of formula I as defined above with an appropriate α-haloacetic acid ester, especially tert.-butyl-bromoacetate. In this case the
substituent $R^4$ is preferably tert.-butyl and the compound is tert.-butyl-2-[(2,6-dichlorophenyl) amine] phenylacetoxyacetate of the formula:-

![Chemical structure](image)

5

The invention further provides a process for preparing a compound of formula II as defined above with a deprotecting agent, especially formic acid or trifluoroacetic acid.

The invention also provides Aceclofenac whenever prepared by a process of the invention and/or using an intermediate of the invention.

**Detailed description of the invention**

We have found that compounds of the general formula I are synthetically very useful compounds, especially as intermediates for producing 2-[(2,6-Dichlorophenyl)-amine]phenylacetoxyacetic acid (Aceclofenac).
Reaction Scheme

\[
\begin{align*}
\text{Compound I can be obtained in a simple process by reacting 2-[(2,6-Dichlorophenyl)amine]phenylacetic Acid (Diclofenac Acid) with an amine NR}^{1}R^{2}R^{3}. \text{ It was found that a variety of amines are suitable for the formation of adduct I. R}^{1}, R^{2} \text{ and } R^{3} \text{ can independently be lower alkyl groups (C}_{1}-C_{3}) \text{ or hydrogen, preferably ethyl and isopropyl. The solvents are toluene, THF, acetone, MEK, MIBK, acetonitrile or a chlorinated solvent and the adduct formation is carried out under very mild conditions of } 0^\circ\text{-}100^\circ\text{C, preferably } 20\text{-}60^\circ\text{C.}
\end{align*}
\]

The ammonium salts of formula I can be reacted without isolation and purification directly with various α-haloacetic acid esters to give compounds of type II. The halogen substituent X can be Cl or Br, preferably Br. Group R^4 is a
lower alkyl substituent C₁-C₄, preferably tert.-butyl. The reaction step is carried out in a temperature range of 20°-100°C, preferably 20°-60°C.

For the conversion of a compound of type II wherein R₄ is tert.-butyl into 2-[(2,6-Dichlorophenyl)amine]phenylacetoxyacetic Acid (Aceclofenac), formic acid and trifluoroacetic acid are suitable. The reaction can be carried out under very mild conditions 0°-100°C, preferably 20°-60°C.

The procedure for the preparation of 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid (Aceclofenac) is a major improvement compared to known methods as the process is very simple. The reaction sequence can be carried out in either separate reaction steps or in a one pot process. The reaction time is relatively short and the reaction process is carried out without the use of heavy metal catalysts and hydrogen and/or difficult solvents. The product is obtained in high overall yield in very high purity under extremely mild reaction conditions.

Example 1

Preparation of tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate (method 1).

200 g (0.675 mol) of 2-[(2,6-dichlorophenyl)amine]phenylacetic Acid were suspended in 800 ml of toluene at room temperature. 94 ml (0.675 mol) of triethylamine were added and the mixture was stirred until a clear solution was obtained. 109 ml (0.675 mol) of tert.-Butyl-bromoacetate were added. The mixture was heated to 40-60°C. After a reaction time of 3-4 hours 400 ml of water were added and the mixture was basified with 30% sodium hydroxide solution. The phases were separated and the organic layer was washed with water. The organic solvent was removed and the crude material purified with Petroleum Ether. Yield 76%.
\(^1\)H-NMR spectrum as attached (figure 1).

IR spectrum as attached (figure 2).

Microanalysis.
calc.: C 58.54, H 5.12, N 3.41;
found: C 58.70, H 5.32, N 3.30.

**Example 2**

Preparation of tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate (method 2).

100 g (0.338 mol) of 2-[(2,6-Dichlorophenyl)amine]phenylacetic Acid were suspended in 300 ml of THF at room temperature. 58 ml (0.338 mol) of diisopropylethylamine were added and the mixture was stirred until a clear solution was obtained. 55 ml (0.338 mol) of tert.-Butyl-bromoacetate were added. The mixture was heated to 40-60°C. After a reaction time of 3-4 hours the mixture was basified with 30% sodium hydroxide solution. The phases were separated and the organic layer dried over sodium sulphate. The organic solvent was removed and the crude material purified with Petroleum Ether. Yield 64%.

**Example 3**

Preparation of Ammonium-2-[(2,6-dichlorophenyl)amine]phenylacetate.

100 g (0.338 mol) of 2-[(2,6-Dichlorophenyl)amine]phenylacetic Acid were added to 300 ml of aqueous ammonia (25-30%). The mixture was heated to reflux and then cooled to room temperature to precipitate the product. The solid was filtered off and dried under vacuum. Yield 96 g (90%).
Example 4

Preparation of 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid from tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate (method 1).

260 g (0.634 mol) of tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate were dissolved in 260 ml of formic acid. The mixture was stirred for 10-60 min, preferably 10-30 min at 20-80°C, preferably 50-60°C. The mixture was cooled and diluted with water to precipitate the product 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid. The crude material was recrystallised. Yield 204 g (91%).

Melting point 145°-149°C.

¹H-NMR spectrum as attached (figure 3).

¹³C-NMR spectrum as attached (figure 4).

IR spectrum as attached (figure 5).

Microanalysis:
calc.: C 54.26, H 3.67, N 3.95.
found: C 54.40, H 3.69, N 3.88.
Example 5

Preparation of 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid from tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate (method 2).

10 g (0.024 mol) of tert.-Butyl-2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetate were stirred in 50 ml of a 1:1 mixture of trifluoroacetic acid and dichloromethane at a temperature of 0-30°C, preferably 15-20°C for 10-70 min, preferably 20-40 min. The solvent was removed and the product 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid precipitated by adding water. The crude material was recrystallised. Yield 79%.

Example 6

Preparation of 2-[(2,6-dichlorophenyl)amine]phenylacetoxyacetic Acid in a one pot process.

800 g (2.70 mol) of 2-[(2,6-Dichlorophenyl)amine]phenylacetic Acid were suspended in 3.2 litres of toluene at room temperature. 273 g (2.70 mol) of triethylamine were added and the mixture stirred until a clear solution was obtained. 480 ml (2.96 mol) of tert.-Butyl-bromoacetate were added. The mixture was heated to 40-60°C. After a reaction time of 3-4 hours the mixture was basified with 30% sodium hydroxide solution. The phases were separated and the organic layer was washed with water. The organic solvent was removed and 1.4 litres of formic acid were added. The mixture was stirred at 50-60°C, cooled to room temperature after approximately 30 min and diluted with water. The product was filtered off and purified with toluene. Overall yield 832 g (87%).
It is anticipated that the invention may be applied to other α-Arylpropanoic Acid NSAID's. Analogous intermediates of structures I, II, and III above are also provided. The reaction scheme is analogous to that given above for Aceclofenac.

Some examples of α-Arylpropanoic Acid NSAID's to which the invention can be applied include the following:

- Naproxen
- Ibuprofen
- Ketoprofen
- Flurbiprofen
- Fenoprofen
- Indaproxen
- Carprofen
- Pelubiprofen

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.
Claims

1. A compound of formula I

\[
\text{\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\text{\textsmaller{\textbf{(I)}}}};
\node (B) at (-1.5,1) {\text{\textsmaller{\textbf{Cl}}}};
\node (C) at (-1.5,-1) {\text{\textsmaller{\textbf{Cl}}}};
\node (D) at (0,2) {\text{\textsmaller{\textbf{O}}}};
\node (E) at (0,1) {\text{\textsmaller{\textbf{O}}}};
\node (F) at (1,0) {\text{\textsmaller{\textbf{R}_1}}};
\node (G) at (2,0) {\text{\textsmaller{\textbf{R}_2}}};
\node (H) at (3,0) {\text{\textsmaller{\textbf{R}_3}}};
\node (J) at (0,0) {\text{\textsmaller{\textbf{NH}}}};
\node (K) at (0,1) {\text{\textsmaller{\textbf{HN}}}};
\node (L) at (0,2) {\text{\textsmaller{\textbf{\oplus}}}};
\draw (A) -- (B);
\draw (A) -- (C);
\draw (A) -- (D);
\draw (A) -- (E);
\draw (A) -- (F);
\draw (A) -- (G);
\draw (A) -- (H);
\draw (A) -- (J);
\draw (A) -- (K);
\draw (A) -- (L);
\end{tikzpicture}
\end{center}}
\]

wherein $R^1$, $R^2$ and $R^3$ are independently selected from lower alkyl groups ($C_1$-$C_4$) or hydrogen.

2. A compound as claimed in claim 1 wherein $R^1$, $R^2$ and $R^3$ are independently selected from one or more of ethyl and isopropyl.

3. A process for preparing a compound of formula I as defined in claim 1 by reacting 2-[(2,6-Dichlorophenyl)amine]phenylacetic Acid (Diclofenac Acid) with an appropriate amine of the formula $NR^1R^2R^3$ wherein $R^1$, $R^2$ and $R^3$ are as defined in claim 1.

4. A process as claimed in claim 3 wherein the reaction is carried out in a solvent selected from toluene, THF, acetone, MEK, MIBK, acetonitrile or a chlorinated solvent.
5. A process as claimed in claim 3 or 4 wherein the adduct formation is carried out at a temperature of from 0 to 100°C, preferably from 20 to 60°C.

6. A process as claimed in any of claims 3 to 5 wherein the amine is triethylamine.

7. A process as claimed in any of claims 3 to 5 wherein the amine is diisopropylethylamine.

8. A process as claimed in any of claims 3 to 5 wherein the amine is ammonia.

9. A compound of formula I as defined in claim 1 whenever made by a process as claimed in any of claims 3 to 8.

10. A process for preparing a compound of the formula II

\[
\text{wherein } R^4 \text{ is lower alkyl}
\]

by reacting a compound of formula I as defined in claim 1 with an appropriate \(\alpha\)-haloacetic acid ester.

11. A process as claimed in claim 10 wherein the halo group is Cl or Br.
12. A process as claimed in claim 10 or 11 wherein the halo group is Br.

13. A process as claimed in any of claims 10 to 12 wherein the \(\alpha\)-haloacetic acid ester is tert.-Butyl-bromoacetate.

14. A process as claimed in any of claims 10 to 13 wherein \(R^4\) is tert. Butyl.

15. A process as claimed in any of claims 10 to 14 wherein the reaction is carried out at a temperature of from 0 to 100°C, preferably 20 to 60°C.

16. A compound of formula II as defined in claim 10 whenever made by a process as claimed in any of claims 10 to 15.

17. A process for preparing Aceclofenac by treating a compound of formula II as defined in claim 10 or 16 with a deprotecting agent.

18. A process as claimed in claim 17 wherein the deprotecting agent is formic acid.

19. A process as claimed in claim 17 wherein the deprotecting agent is trifluoroacetic acid.

20. A process for preparing Aceclofenac substantially as hereinbefore described with reference to the examples.

21. Aceclofenac whenever prepared by a process as claimed in any of claims 3 to 15 or claims 17 to 20.

22. A process for preparing a compound of formula I as defined in claim 1 substantially as hereinbefore described with reference to the examples.
23. A process for preparing a compound of formula II as defined in claim 10 substantially as hereinbefore described with reference to the examples.

24. A compound of the formula

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{O} \\
\text{H} & \quad \text{N} \quad \text{R}^1 \\
\text{R}^2 & \quad \text{R}^3
\end{align*}
\]

wherein R-COOH is an \(\alpha\)-Arylpropanoic Acid NSAID.

25. A compound of the formula

\[
\begin{align*}
\text{R} & \quad \text{OR}^4 \\
\text{O} & \quad \text{O} \quad \text{OR}^4
\end{align*}
\]

wherein R-COOH is an \(\alpha\)-Arylpropanoic Acid NSAID and \(\text{R}^4\) is \(\text{C}_1\) to \(\text{C}_4\) alkyl.

26. A process for preparing a chain extended \(\alpha\)-Arylpropanoic Acid with an appropriate amine of the formula \(\text{NR}^1\text{R}^2\text{R}^3\) wherein \(\text{R}^1\), \(\text{R}^2\) and \(\text{R}^3\) are as defined in claim 1.
*Acquisition*
OBNUC 1H
OBFRQ  270.05 MHz
EXMOD SGNON
IRFIN  5400.0 Hz
SCANS  8
POINT  32768
ACQTM  4.096 sec
PD    5.000 sec
PW1    4.5 us
TEMP   20.0 c
SLVNT CD3OD

*Fft*
RESOL  0.24 Hz
BF     0.12 Hz

*Plot*
XE     3377.0790 Hz
XS    -451.8937 Hz
YG     3.19

Fig. 3
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6  C07C227/18  C07C229/42

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6  C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>EP 0 428 352 A (BETA LAB SA) 22 May 1991 see claim 1</td>
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<td>X</td>
<td>EP 0 600 395 A (SS PHARMACEUTICAL CO) 8 June 1994 see claim 2</td>
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<td>A</td>
<td>WO 92 16492 A (DU PONT) 1 October 1992 see example 19</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search: 19 July 1999

Date of mailing of the international search report: 30.07.99

Name and mailing address of the ISA:

European Patent Office, P.B. 5816 Patentlaan 2, NL - 2280 HV Rijswijk, Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Janus, S
### INTERNATIONAL SEARCH REPORT

**Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. [x] Claims Nos.: 24-26 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   
   see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
Claims Nos.: 24-26

The term "alpha-arylp propaneic acid NSAID" included in these claims covers such a wide range of compounds that a lack of clarity within the meaning of Art. 6 PCT arises to such an extent as to render a meaningful search of said claims impossible. Consequently, no search report can be established for these claims.
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