654898

SPRUSON & FERGUSON

AUSTRALIA

PATENTS ACT 1990

PATENT REQUEST: STANDARD PATENT

I/We, the Applicant(s)/Nominated Person(s) specified below, request I/We be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] Applicant(s)/Nominated Person(s):

F Hoffmann-La Roche AG, of 124 Grenzacherstrasse, CH-4002, Basel, SWITZERLAND

[54] Invention Title:

Process for the Manufacture of Aldehydes

[72] Inventor(s):

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Details of Basic Application(s):

[31] Appl'n No(s):	**[33] Country:**	**[32] Application Date:**
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F Hoffmann-La Roche AG

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Registered Patent Attorney

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Australia

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NOTICE OF ENTITLEMENT

I, Daniel Meier

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being authorised by the Applicant(s)/Nominated Person(s) in respect of an application entitled:

Process for the manufacture of aldehydes

state the following:-

1. The Applicant(s)/Nominated Person(s) has/have, for the following reasons, gained entitlement from the actual inventor(s):-

[X] The Applicant is the assignee of the invention from the inventor(s)

[ ] The inventor(s) have assigned the invention to Hoffmann-La Roche Inc., Nutley, USA, who have reassigned all their rights for Australia to the Applicant

2a.* The Applicant(s)/Nominated Person(s) is/are the applicant(s) of the basic application(s) listed* on the Patent Request/* ~~in the Declaration under Article 8 of the PCT.~~

~~2b.* The Applicant(s)/Nominated Person(s) is/are entitled to rely on the basic application(s) listed* on the Patent Request/* in the Declaration under Article 8 of the PCT as follows:~~

3.* The basic application(s) listed* on the Patent Request/* ~~in the Declaration under Article 8 of the PCT~~ is/are the applications first made in a Convention Country in respect of the invention.

DATED this 8th day of February, 1993.

Daniel Meier

Daniel Meier

* Delete if not applicable

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 654898

(54) Title
PROCESS FOR THE MANUFACTURE OF ALDEHYDES

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(57) 1 mol of 1,2-butylene oxide and 23.5 g of Pd/C (5% Pd) were added to a solution to a solution of 0.5 mol of 3-phenyl-2(S)-phthalimidopropionyl chloride in 1200 ml of toluene. The suspension was hydrogenated at room temperature and atmospheric pressure while stirring vigorously for 17 hours, whereby 11.3 l of hydrogen were taken up. Thereafter, the suspension was filtered over a filter aid and the residue was washed with toluene. The filtrate and washings were combined and treated while stirring with a solution of 0.5 mol of sodium pyrosulphite in 1 l of water. After stirring at room temperature for 4.5 hours the phases were separated. The aqueous phase was washed with 500 ml of toluene. The toluene phases were washed with 350 ml of water. The combined aqueous phases were treated with 1400 ml of toluene and 420 ml of 3N sulphuric acid and stirred at 60° for 6 hours. Thereafter, the phases were separated and the aqueous phase was extracted with 500 ml of toluene. The toluene phases were washed with water, combined, dried over $MgSO_4$ and evaporated. There were obtained 97.8 g (70%) of (S)-α-benzyl-1,3-dioxo-2-isoindolineacetaldehyde as a white solid, melting point 115-117°, $[\alpha]_D^{20}$ -200° (1% in ethyl acetate).

It has now been found that the catalytic hydrogenation of carboxylic acid chlorides to aldehydes can be carried out advantageously in the presence of alkylene oxides.

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CLAIM

1. A process for the manufacture of aldehydes, which process comprises catalytically reducing a carboxylic acid halide with hydrogen in the presence of an alkylene oxide.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: Process for the Manufacture of Aldehydes

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

The manufacture of aldehydes by the catalytic hydrogenation of carboxylic acid halides, especially chlorides, is known as the Rosenmund reaction. Hydrogen halide (chloride) which results in this reduction poses problems in the use of the reaction. Thus, on the one hand, the resulting hydrogen halide reduces the yield of the desired aldehyde, insofar as this is acid-labile, or makes the reaction wholly unsuitable for the manufacture of such aldehydes. On the other hand, on safety grounds and taking into consideration the corrosive properties of the hydrogen halide, particular technical measures can be required in the removal of the hydrogen halide from the reaction mixture, e.g. in a hydrogen stream.

The neutralization of the hydrogen halide by the addition of conventional bases gives poor yields when carboxylic acid halides which are base-labile have to be used.

It has now been found that the catalytic hydrogenation of carboxylic acid chlorides to aldehydes can be carried out advantageously in the presence of alkylene oxides.

The process in accordance with the invention is especially suitable for the manufacture of acid-labile or base-labile aldehydes such as α-aminoaldehydes. Further examples of acid-labile aldehydes are aldehydes which contain acid-labile groups such as carbamate groups, e.g. 2-trimethylsilylethyl carbamate, tert.butyl carbamate and 1-methyl-1-(4-biphenylyl)ethyl carbamate groups; or aminoacetal groups such as N-methoxymethylamino, pivaloyloxymethylamino or N-tetrahydropyranylamino; or phosphinamido groups such as N-diphenylphosphinylamino.

The invention is accordingly concerned with a process for the manufacture of aldehydes by the catalytic reduction of carboxylic acid chlorides with hydrogen in the presence of an alkylene oxide.

The reduction is preferably carried out in the presence of C_{2-6}-alkylene oxides, especially butylene oxide, propylene oxide or ethylene oxide.

The process in accordance with the invention is conveniently carried out in the presence of an inert organic solvent. Examples of such solvents are hydrocarbons such as petroleum ether or toluene; or halogenated hydrocarbons such as methylene chloride. Moreover, the process in accordance with the invention can be carried out under the reaction conditions which are known per se for the Rosenmund reaction. Preferably, the reduction is carried out at room temperature and normal pressure. As the catalyst there can be used usual noble metal catalysts, especially palladium, conveniently on carriers such as $BaSO_4$ or charcoal. The use of palladium on charcoal, e.g. 5% Pd on charcoal, is preferred. The aldehyde formed can be separated from the reaction mixture obtained after the hydrogenation in a manner known per se, e.g. by extraction.

The invention is illustrated in more detail by the following Examples.

Example 1

1 mol of 1,2-butylene oxide and 23.5 g of Pd/C (5% Pd) were added to a solution to a solution of 0.5 mol of 3-phenyl-2(S)-phthalimidopropionyl chloride in 1200 ml of toluene. The suspension was hydrogenated at room temperature and atmospheric pressure while stirring vigorously for 17 hours, whereby 11.3 l of hydrogen were taken up. Thereafter, the suspension was filtered over a filter aid and the residue was washed with toluene. The filtrate and washings were combined and treated while stirring with a solution of 0.5 mol of sodium pyrosulphite in 1 l of water. After stirring at room temperature for 4.5 hours the phases were separated. The aqueous phase was washed with 500 ml of toluene. The toluene phases were washed with 350 ml of water. The combined aqueous phases were treated with

1400 ml of toluene and 420 ml of 3N sulphuric acid and stirred at 60° for 6 hours. Thereafter, the phases were separated and the aqueous phase was extracted with 500 ml of toluene. The toluene phases were washed with water, combined, dried over $MgSO_4$ and evaporated. There were obtained 97.8 g (70%) of (S)-α-benzyl-1,3-dioxo-2-isoindolineacetaldehyde as a white solid, melting point 115-117°, $[\alpha]_D^{20}$ -200° (1% in ethyl acetate).

Example 2

3-Cyclohexyl-2-(tert.-butoxycarbonylamino)propionaldehyde can be obtained from 2-tert.-butoxycarbonylamino-3-cyclohexylpropionyl chloride in analogy to Example 1.

Example 3

N-Phthaloyl-leucinal can be obtained from N-phthaloyl-leucyl chloride in analogy to Example 1.

Example 4

1-tert.-Butoxycarbonyl-pyrrolidine-2-carbaldehyde can be obtained from 1-tert.-butoxycarbonyl-pyrrolidine-2-carbonyl chloride in analogy to Example 1.

The claims defining the invention are as follows:-

1. A process for the manufacture of aldehydes, which process comprises catalytically reducing a carboxylic acid halide with hydrogen in the presence of an alkylene oxide.

2. A process according to claim 1, wherein the alkylene oxide is butylene oxide, propylene oxide or ethylene oxide.

3. A process according to claim 1 or 2 for the manufacture of acid-labile or base-labile aldehydes, especially of α-aminoaldehydes.

4. A process for the manufacture of aldehydes substantially as hereinbefore described with reference to any one of the Examples.

5. Aldehydes produced by the process of any one of claims 1 to 4.

Dated 25 February, 1993
F Hoffmann-La Roche AG

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

Abstract

A process for the manufacture of aldehydes by the catalytic reduction of carboxylic acid halides with hydrogen in the presence of an alkylene oxide.