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(21) International Application Number: PCT/NL95/00359 (22) International Filing Date: 17 October 1995 (17.10.95) (30) Priority Data: 9401708 17 October 1994 (17.10.94) NL (71) Applicant (for all designated States except US): DSM N.V. [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): CASTELIJNS, Anna, Maria, Cornelia, Francisca [NL/NL]; Mergelakker 24, NL-6176 JB Beek (NL). HOGEWEG, Johanna, Margreet [NL/NL]; Vrangendael 2, NL-6137 BB Sittard (NL). VAN NISPEN, Simon, Petrus, Johannes, Maria [NL/NL]; Erenfriedstraat 8, NL-6191 SJ Beek (NL). (74) Agent: JACOBS, Monique, Sophie, Nicole; Octrooibureau DSM, P.O. Box 9, NL-6160 MA Geleen (NL).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>In English translation (filed in Dutch).</i>
(54) Title: PROCESS FOR THE PREPARATION OF 3-PHENYLPROPANAL (57) Abstract Process for the preparation of 3-phenylpropanal in which cinnamaldehyde is hydrogenated with the aid of a Pd-containing catalyst in the presence of a small amount of water. A high yield and a high selectivity are obtained in a commercially attractive process. The reaction mixture obtained can without intermediate further processing be subjected to an oxidation in which the cinnamaldehyde is oxidized to 3-phenylpropionic acid with a high degree of conversion and a high selectivity. The combination of the two process steps constitutes a simple, commercially attractive process for the preparation of 3-phenylpropionic acid using cinnamaldehyde as a starting material. 3-phenylpropionic acid can be used in particular in the preparation of pharmaceuticals such as HIV protease inhibitors.		

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PROCESS FOR THE PREPARATION OF 3-PHENYLPROPANAL

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The invention relates to a process for the preparation of 3-phenylpropanal in which cinnamaldehyde is hydrogenated with the aid of a Pd-containing catalyst.

Such a process is known from DE-A-2030031, which describes a process with which a (substituted) cinnamaldehyde is hydrogenated with the aid of a Pd/Al₂O₃ catalyst, under conditions that are essentially free of water. Good results are obtained with the hydrogenation of p-t.butyl- α -methyl cinnamaldehyde. The results obtained with the hydrogenation of non-substituted cinnamaldehyde are not reported. In general, as is for example apparent from NL-A-6613916, the yield and selectivity obtained with the hydrogenation of non-substituted cinnamaldehyde are considerably poorer than those obtained with substituted cinnamaldehydes.

The hydrogenation of (substituted) cinnamaldehyde using a Pd/C catalyst, in the presence of an aqueous basic solution of an alkali compound, i.e. in a two-phase system, is known, for example from NL-A-7703007 and NL-A-6613916. Such a two-phase system presents the advantages in this type of hydrogenation that the formation of byproducts such as cinnamic alcohol is suppressed and the yield is increased. A drawback of a two-phase system, however, is that, due to the presence of an aqueous solution, the production capacity is much lower and, moreover, an additional separation step is necessary. Such a process is hence commercially less attractive.

The invention provides a process for the

hydrogenation of cinnamaldehyde to 3-phenylpropanal with which, in a commercially attractive process, 3-phenylpropanal is obtained with a high yield and a high selectivity.

5 This is achieved according to the invention by carrying out the hydrogenation in the presence of 1-5 wt.% water, relative to the amount of cinnamaldehyde.

 With the process according to the present invention both a high production capacity and a high
10 yield and high selectivity are realised in the hydrogenation of cinnamaldehyde to 3-phenylpropanal.

 The temperature at which the process according to the invention is carried out is not critical and is usually around ambient temperature or
15 an elevated temperature, for example of between 20 and 180°C. Preferably a temperature of between 55 and 90°C is used because it seems that the highest selectivity can then be obtained. The pressure at which the process according to the invention is carried out is not
20 critical either. Usually use is made of atmospheric or an elevated pressure, for example a pressure of between 0.1 and 15 MPa. Preferably the hydrogenation is carried out at a pressure of between 0.5 and 8 MPa, in particular between 4 and 8 MPa.

25 Preferably Pd on a carrier is used as the Pd-containing catalyst, for example a Pd/C or a Pd/Al₂O₃ catalyst. The amount of catalyst to be used is not critical. Mostly use is made of between 0.01 and 2 wt.% Pd, preferably between 0.01 and 0.5 wt.% Pd, relative
30 to the amount of cinnamaldehyde.

 The selectivity of the hydrogenation can be further increased by adding an alkali salt of a weak acid to the reaction mixture. It has been found that the potassium salt in particular considerably increases
35 the selectivity. Acids with pKa values of 4 or more are suitable for use as the weak acid, for example carbonic acid or carboxylic acids, in particular acetic acid,

propionic acid and butyric acid.

The best results were obtained by adding potassium acetate.

The reaction mixture obtained after the
5 hydrogenation, which contains mainly 3-phenylpropanal, can, after the removal of the catalyst, be subjected as such, directly, to an oxidation, in which 3-phenylpropionic acid is obtained. It has been found that it is possible to convert 3-phenylpropanal into 3-phenylpropionic acid via a simple oxidation using a
10 medium containing molecular oxygen, for example air, optionally without using a solvent or a catalyst. In this way an extremely simple and commercially attractive process is obtained for the preparation of 3-phenylpropionic acid using cinnamaldehyde as a
15 starting material. To obtain a pure end product in this process it suffices to solely purify the end product - for example through distillation or crystallisation; no intermediate further processing of the hydrogenation
20 mixture is required.

The invention hence also relates to the preparation of 3-phenylpropionic acid via the hydrogenation of cinnamaldehyde to 3-phenylpropanal, followed by the oxidation of 3-phenylpropanal to 3-phenylpropionic acid.
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A route via cinnamic acid which is converted into 3-phenylpropionic acid via hydrogenation is often followed for the preparation of 3-phenylpropionic acid in the known processes. This route is technically less
30 attractive because cinnamic acid has to be isolated as a solid substance; the route is also commercially less attractive because of the higher cost price of cinnamic acid.

The oxidation is preferably carried out at an
35 elevated temperature. The temperature is preferably between 40 and 80°C. The temperature is chosen to be as high as possible to obtain the highest possible

reaction rate; however, it has been found that the selectivity of the oxidation reaction decreases at higher temperatures. Preferably the temperature is therefore chosen to be between 50 and 70°C, in particular between 55 and 65°C. The pressure at which the oxidation is carried out is not critical and is mostly between approximately atmospheric pressure and 5 MPa. Preferably the oxidation is carried out at elevated pressure, in particular between 0.2 and 2 MPa. In practice it is often simpler to retain a high oxygen concentration in the reaction mixture at an elevated pressure. For obtaining a good result in the oxidation it is of course important to ensure that the reaction mixture contains sufficient oxygen. The optimum conditions for the reaction are hence for example a suitable combination of the amount of oxygen supplied, the degree of mixing of the oxygen in the reaction mixture and the pressure at which the reaction takes place. A person skilled in the art will easily be able to determine the optimum combination for his situation.

The oxidation can optionally be carried out in the presence of a solvent that is inert under the reaction conditions. Examples of suitable solvents are water, aliphatic or aromatic hydrocarbons, in particular hexane, toluene or petroleum ether, or ethers, in particular methyl-t-butylether (MTBE). Preferably the oxidation is carried out without using a solvent, because then the production capacity is greatest and the further processing is simplest.

An oxidation catalyst may optionally also be added. Preferably, however, the oxidation is carried out without a catalyst, because then a simpler process, without catalyst removal, is obtained.

The 3-phenylpropionic acid obtained can be used as an intermediate in the preparation of a number of end products such as pharmaceuticals, in particular, after conversion into the corresponding acid chloride,

in the preparation of HIV protease inhibitors, known for example as L-735,524, as described in Tetrahedron Letters, Vol. 33, No. 3, 673-676, J. Med. Chem. 1992, 35, 1685-1701 and Chemistry & Engineering News, May 16, 5 1994, 6-7.

The invention will be further elucidated with reference to the following examples, without however being limited thereto.

10 Example I

79.5 g of cinnamaldehyde (CALD), 0.19 g of potassium acetate (PAC), 0.8 g of water and 1.86 g of 5% Pd/C (Johnson Matthey type 487; 57.2% H₂O w/w) were dosed to an inertised reactor with a volume of 160 ml, 15 fitted with a turbine stirrer and a hydrogen dosage pipe. The reactor was then brought to a pressure of 58 bar with stirring (with the aid of hydrogen), after which the temperature was raised to 60°C. The pressure was maintained at 50 bar by constantly supplying H₂ gas 20 during the reaction. After a reaction time (t) of approximately 5.5 hours virtually no more hydrogen was absorbed. The reactor contents were then cooled to room temperature, after which the reactor was made pressureless and was purged with N₂. After the removal 25 of the catalyst through filtration the reaction mixture was analysed by means of gas chromatography. The results are presented in Table 1.

Examples II-V

30 Examples II-V were carried out in the same way as described for Example I. The reaction conditions and results are shown in Table I.

Example VI

35 60 kg of cinnamaldehyde, 0.144 kg of potassium acetate and 0.6 kg of H₂O were successively introduced into an inertised Buss-loop reactor with a

volume of 50 litres. Then the circulation pump was started and 1.01 kg of 5.2% Pd/C (Johnson Matthey type 487; 54.0% H₂O) was dosed, after which the temperature was raised to 65°C, while the pressure was simultaneously raised to 50 bar with the aid of hydrogen. The pressure was kept at 50 bar by constantly supplying H₂ gas during the reaction. After approximately 3 hours virtually no more hydrogen was absorbed. The reactor contents were then cooled to room temperature, the pressure was released and the reactor was drained with the aid of N₂. After the catalyst had been removed through filtration the reaction mixture was analysed by means of gas chromatography. The results are shown in Table 1.

Examples VII-X

Examples VII-X were carried out in the same way as described for Example VI. The reaction conditions and results are shown in Table 1.

Comparative experiments 1-4

The comparative experiments 1-4 were carried out in the same way as described for Example I. The reaction conditions and results are shown in Table 1.

Example XI

The oxidation was carried out in a reactor with a volume of 200 litres, fitted with a stirrer, a gas inlet pipe and a condenser.

143.44 kg of 'crude' phenylpropanal, obtained by mixing two hydrogenation batches obtained according to the procedure described in Example VIII and one hydrogenation batch obtained according to the procedure described in Example IX, was introduced into this reactor. This crude product had the following composition: 93.0 wt.% 3-phenylpropanal, 2.6 wt.% 3-phenylpropanol and 0.9 wt.% H₂O.

Then the dosage of air at a flow rate of 73.2 m³/h (15°C/1 bar) was started, with stirring, and the pressure in the reactor was set to 5 bar. The reaction mixture was then heated to 60°C and kept at this

5 temperature. The percentage of O₂ in the off-gas was originally 15-16% and gradually increased after 4 hours' reaction. After 7.4 hours' reaction virtually no more oxygen was absorbed and the gas flow was stopped and the mixture was cooled to room temperature. The

10 reaction mixture now weighed 154.7 kg; GLC analysis showed that it had the following composition: 3.2 wt.% 3-phenylpropanal, 0.7 wt.% 3-phenylpropanol, 0.5 wt.% cinnamaldehyde; 85.1 wt.% 3-phenylpropionic acid; 0.74 wt.% ethylbenzene and 0.44 wt.% H₂O. This corresponds

15 to a degree of conversion of 3-phenylpropanal of 96.3% and a selectivity towards 3-phenylpropionic acid of 91.6%.

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TABLE 1

Exp. No.	Cat. ¹⁾	%Cat. ²⁾	%H ₂ O ³⁾ added (w/w)	%H ₂ O ³⁾ total (w/w)	%KAC ³⁾	T (°C)	p (bar)	t (hr)	degree of conv. of CALD (%)	sel. towards PPAL ^{3,4)} (%)	sel. towards PPOL ^{3,4)} (%)	sel. towards CALC ^{3,4)} (%)
I	1	1	1	2.34	0.24	60	50	5.5	100	92.3	4.3	0.7
II	1	1	0	1.34	0.24	60	50	6.75	100	85.1	5.7	0.7
III	1	1	1	2.34	0	60	50	5.0	97.6	79.8	14.5	n.b.
IV	1	1	1	2.34	0.24	30-40	50	5.66	99.7	83.7	11.9	2
V	2	1	1.57	1.57	0	22-84	40-50	1.75	99.7	85.9	11.0	n.b.
VI	3	0.774	1	1.91	0.24	65	50	3.25	99.8	91.1	5.5	0.3
VII	3	0.61	1	1.72	0.24	75	50	2.83	99.7	93.3	3.1	0.6
VIII	3	0.61	1	1.72	0.24	85	50	2.1	99.4	93.5	2.4	0.6
IX	3	0.61	1	1.72	0.24	90	50	1.73	99.5	92.9	2.8	0.5
X	3	0.61	1	1.72	0.24	85	60	1.63	99.4	94.0	3.0	0.2
1	1	1	10	11.32	0.24	60	50	5.25	99.5	80.0	17.1	0.7
2	1	1	10	11.32	0	60	50	4.33	93.8	70.0	23.2	
3	1	1	10	11.32	0.28	30-40	50	3.25	100	69.3	26.0	1.8
4	1	5	0.9	7.56	0	60	50	5.63	100	66.2	28.8	

cat-1: Johnson Matthey type 487; 57.2% H₂O (w/w); 5% Pd/Ccat-2: Degussa E213XR/D; 0% H₂O (w/w); 5% Pd/Al₂O₃cat-3: Johnson Matthey type 487; 54.0% H₂O (w/w); 5.2% Pd/C²⁾ % cat. (excl. water) relative to CALD (w/w)³⁾ relative to CALD⁴⁾ PPAL = 3-phenylpropanal

PPOL = 3-phenylpropanol

CALC = cinnamic alcohol

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C L A I M S

1. Process for the preparation of 3-phenylpropanal in which cinnamaldehyde is hydrogenated with the aid of a Pd-containing catalyst, characterised in that 1-5 wt.% water, relative to the amount of cinnamaldehyde, is present in the reaction mixture during the reaction.
2. Process according to Claim 1, characterised in that the hydrogenation is carried out in the presence of potassium acetate.
3. Process according to Claim 1 or Claim 2, characterised in that the hydrogenation is carried out at a temperature of between 55 and 90°C.
4. Process according to any one of Claims 1-3, characterised in that the hydrogenation is carried out at a pressure of between 4 and 8 MPa.
5. Process for the preparation of 3-phenylpropionic acid, characterised in that cinnamaldehyde is converted into 3-phenylpropanal according to any one of Claims 1-4, after which the 3-phenylpropanal obtained is subjected to an oxidation using a medium containing molecular oxygen.
6. Process according to Claim 5, characterised in that the oxidation takes place at a pressure between 0.2 and 2 MPa.
7. Process according to any one of Claims 5-7, characterised in that the oxidation takes place at a temperature between 50 and 70°C.
8. Process according to any one of Claims 5-7, characterised in that the oxidation is carried out in the absence of a solvent.
9. Process according to any one of Claims 5-8, characterised in that the oxidation is carried out in the absence of a catalyst.
10. Process for the preparation of a HIV protease

inhibitor, characterised in that 3-phenylpropionic acid is prepared using the process according to any one of Claims 5-9 and is then converted into the HIV protease inhibitor.

- 5 11. Use of 3-phenylpropionic acid obtained using the process according to any one of Claims 5-9 in the preparation of pharmaceuticals, in particular HIV protease inhibitors.

INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/NL 95/00359

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C45/62 C07C47/228 C07C57/30 C07C51/235

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 data base consulted during the international search (name of data base and, where practical, 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	DE,A,20 30 031 (UNIVERSAL OIL PRODUCTS) 23 December 1971 cited in the application see page 6, line 1 - line 14 see claims 1-4 ---	1-4
X	GB,A,955 421 (I.C.I.) 15 April 1964 see page 2, line 65 - line 67 see claims 1,3,4,8 -----	5-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2030031	23-12-71	US-A- 3520934	21-07-70
GB-A-955421		NONE	