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TITLE OF INVENTION
54 METHOD FOR PRODUCING 2-CHLOROMETHYLPHENYL ACETIC ACID DERIVATIVES

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57 Abstract (not more than 150 words) and figure of the drawings to which the abstract refers, are attached.	Number of sheets	17
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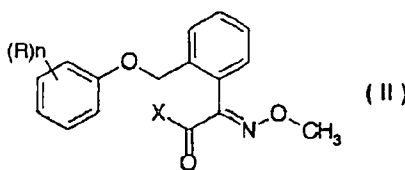
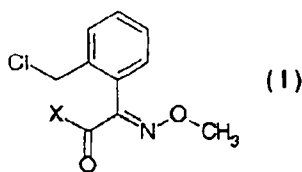
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— mit internationalem Recherchenbericht

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHOD FOR PRODUCING 2-CHLOROMETHYL-PHENYL ACETIC ACID DERIVATIVES

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON 2-CHLORMETHYL-PHENYLESSIGSÄUREDERIVATEN



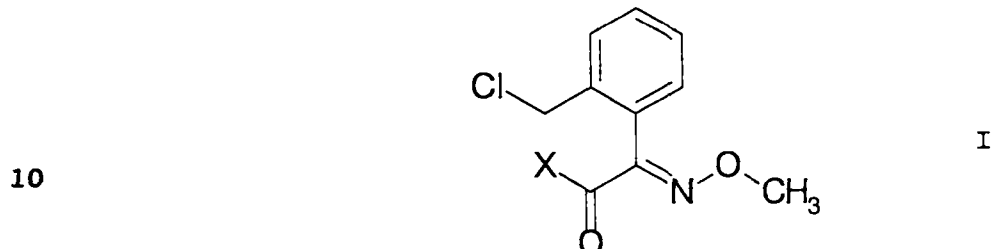
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(57) Abstract: The invention relates to a method for producing 2-chloromethylphenyl acetic acid derivatives of formula (I), in which X represents C₁-C₄ alkoxy or methylamino, by cleaving the ether bonds in compounds of formula (II), in which R represents C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₂ alkyl halide, C₁-C₄ alkylcarbonyl, C₁-C₄ alkylcarbonyloxy, halogen, nitro or cyano, and X has the above-mentioned meaning. The inventive method is characterized in that the transformation takes place in the presence of hydrogen chloride and of an inert solvent, and in that a catalyst selected from the group comprised of: iron, indium or halogenides, oxides or triflates thereof is added to the reaction mixture.

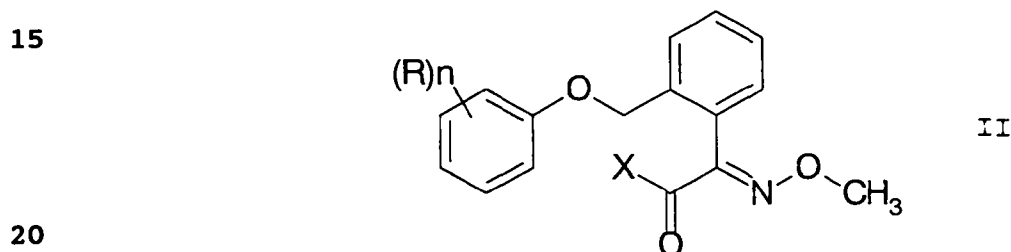
(57) Zusammenfassung: Verfahren zur Herstellung von 2-Chlormethyl-phenylessigsäurederivaten der Formel (I), in der X für C₁-C₄-Alkoxy oder Methylamino steht, durch Etherspaltung von Verbindungen der Formel (II), in der R C₁-C₄-Alkyl, C₁-C₄-Alkoxy, C₁-C₂-Halogenalkyl, C₁-C₄-Alkylcarbonyl, C₁-C₄-Alkylcarbonyloxy, Halogen, Nitro oder Cyano bedeutet und X die obengenannte Bedeutung besitzt, dadurch gekennzeichnet, dass die Umsetzung in Gegenwart von Chlorwasserstoff und einem inerten Lösungsmittel stattfindet, und dem Reaktionsgemisch ein Katalysator ausgewählt aus der Gruppe: Eisen, Indium oder deren Halogenide, Oxide oder Triflate zugesetzt wird.

Preparation of 2-(chloromethyl)phenylacetic acid derivatives

The present invention relates to a process for preparing
 5 2-(chloromethyl)phenylacetic acid derivatives of the formula I,



where X is C₁-C₄-alkoxy or methylamino, by ether cleavage of
 15 compounds of the formula II,



where R is C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₂-haloalkyl,
 C₁-C₄-alkylcarbonyl, C₁-C₄-alkylcarbonyloxy, halogen, nitro or
 cyano and X is as defined above.

25 J. Chem. Research (S) 232-3 (1985) and J. Org. Chem. 64, 4545
 (1981) disclose methods for cleaving benzyl ethers in the
 presence of specific Lewis acids such as sodium iodide/boron
 trifluoride or iron(III) chloride on silica. The Lewis acids are
 used in greater than stoichiometric quantities, which makes the
 30 process uneconomical.

Synlett (10), 1575-6 (1999) describes a process for cleaving
 4-nitrobenzyl ethers in the presence of indium and aqueous
 ammonium chloride. Indium is used in an excess of more than 8
 35 equivalents based on the ether to be cleaved.

A process for preparing 2-(chloromethyl)phenyl acetic acid
 derivatives of the formula I by cleaving the appropriate benzyl
 ethers II is described in WO-A 97/21686. This involves admixing
 40 the benzyl ether II with an excess of two or more mol equivalents
 of boron trichloride.

The prior art processes use greater than stoichiometric
 quantities of Lewis acids. The handling of Lewis acids used is
 45 additionally problematic and the majority thereof are highly
 corrosive.

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A need exists to provide a catalytic process for preparing 2-(chloromethyl)phenylacetic acid derivatives of the formula I from the appropriate benzyl ethers in high yield and selectivity which does not have the abovementioned disadvantages. Care also had to be taken that the benzyl ether II was cleaved with high selectivity, i.e. that the methoxyiminophenyglyoxylic acid unit in the target compound I was retained.

We have found that this need is fulfilled by carrying out the ether cleavage in the presence of hydrogen chloride and an inert solvent, and adding a catalyst to the reaction mixture selected from the group consisting of iron, indium and halides, oxides and triflates thereof.

The hydrogen chloride is generally passed into the reaction mixture in gaseous form. However, it is also possible to condense in the hydrogen chloride. In general, the hydrogen chloride is used in a molar ratio relative to the benzyl ether of from 1 to 25, preferably from 1 to 10 and more preferably from 3 to 5 mol equivalents.

Useful catalysts include Lewis acids selected from the group consisting of iron, indium and halides, oxides and triflates thereof. Preferred catalysts are iron and indium(III) chloride and also in particular iron(III) oxide and iron(III) chloride. The catalyst is used in a concentration of from 0.001 to 0.5 and preferably from 0.01 to 0.2 mol equivalents.

Useful solvents include aromatic (halogenated) hydrocarbons, e.g. benzene, toluene, xylene, chlorobenzene, dichlorobenzene, bromobenzene and benzotrifluoride; aliphatic (halogenated) hydrocarbons, e.g. pentane, heptane, dichloromethane, chloroform, 1,2-dichloroethane and carbon tetrachloride; cycloaliphatic hydrocarbons, e.g. cyclohexane and cyclopentane; ethers, e.g. dimethoxyethane, diethyl ether and di-isopropyl ether; and esters, e.g. ethyl acetate and butyl acetate. Mixtures of these solvents may also be used.

Preferred solvents are aromatic (halogenated) hydrocarbons and aliphatic (halogenated) hydrocarbons.

It may possibly be advantageous to add Lewis bases, e.g. pyridine, N,N-dimethylaniline or ethanethiol and/or further auxiliaries such as trimethylsilyl chloride, to the reaction mixture.

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It may also be advantageous to work in a biphasic system in the presence of a phase transfer catalyst, e.g. tetrabutylammonium chloride, tetrahexylammonium chloride, tetrabutylphosphonium chloride, bis(triphenylphosphoranylidene)ammonium chloride, 5 trimethylbenzylammonium chloride, triethylbenzylammonium chloride or triphenylbenzylammonium chloride.

The reaction temperature is customarily from 0 to 100°C and preferably from 30 to 70°C. The reaction pressure is customarily 10 from 0 to 6 bar. Preference is given to carrying out the reaction under atmospheric pressure.

It is also advantageous to perform the ether cleavage under a protective gas atmosphere.

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Useful starting materials for the ether cleavage include the benzyl ethers II mentioned at the outset. They are accessible by literature methods (EP-A 253 213, EP-A 254 426, EP-A 398 692 or EP-A 477 631). In particular, the crop protection agents 20 currently on the market are suitable, for example methyl 2-methoxyimino-2-[(2-methylphenyloxymethyl)phenyl] acetate (Kresoxim-methyl, EP-A 253 213).

After the ether cleavage, the reaction mixture is generally 25 worked up by extraction. Catalyst impurities may be removed, for example, by extraction using aqueous mineral acid such as hydrochloric acid. The phenol cleavage product may advantageously be removed by extraction using aqueous alkali such as sodium hydroxide.

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The 2-(chloromethyl)phenylacetic acid derivative obtained may be further processed directly, dissolved in the inert solvent, or as a melt after distillative removal of the solvent.

35 The crude product can be further purified by recrystallization in alcohols such as methanol, ethanol, n-butanol or mixtures thereof or mixtures of alcohols and dimethylformamide. The crude product can also be purified by melt crystallization.

40 Process examples

Inventive Example 1

7.5 g (24 mmol) of kresoxim-methyl were dissolved in 150 ml of 45 chlorobenzene. 0.32 g (2.4 mmol) of iron(III) chloride were then added and 2.6 g (72 mmol) of hydrogen chloride were gassed in within 1 h, during the heating phase to 50°C. The reaction mixture

was held at 50°C for a further 2 hours with stirring and the conversion was then monitored by means of HPLC. After the reaction had ended, the reaction solution was cooled and admixed with 10 ml of methanol. The reaction mixture was extracted, first
5 with hydrochloric acid and then with sodium hydroxide. The organic phase was washed to neutrality and then freed of solvent. The yield of methyl
2-methoxyimino-2-[(2-chloromethyl)phenyl]acetate was 75%.

10 Inventive Example 2

7.5 g (24 mmol) of kresoxim-methyl were dissolved in 150 ml of toluene. 0.53 g (2.4 mmol) of indium(III) chloride were then added and 2.6 g (72 mmol) of hydrogen chloride were gassed in
15 within 1 h, during the heating phase to 40°C. The reaction mixture was held at 40°C for a further 4 hours with stirring and then worked up as in inventive example 1. The yield of methyl
2-methoxyimino-2-[(2-chloromethyl)phenyl]acetate was 80%.

20 Inventive Example 3

The ether cleavage of inventive example 1 was repeated in 150 ml of 1,2-dichloroethane. 4.1 g (112 mmol) of hydrogen chloride were gassed in within 1 h, during the heating phase to 100°C, and the
25 reaction mixture was held at 100°C for a further 5 hours. The yield of product of value was 80%.

Comparative Example 4

30 7.5 g (24 mmol) of kresoxim-methyl were dissolved in 150 ml of toluene. 0.32 g (2.4 mmol) of aluminum chloride were then added and 2.6 g (72 mmol) of hydrogen chloride were gassed in within 1 h, during the heating phase to 100°C. The reaction mixture was held at 100°C for a further 2 hours with stirring and then worked
35 up as in inventive example 1. The yield of product of value was 30%.

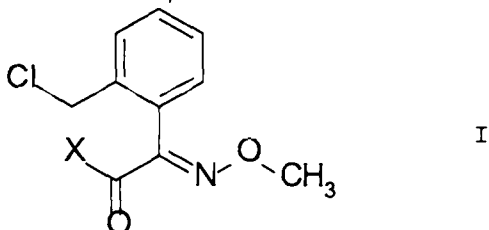
Comparative Example 5

40 7.5 g (24 mmol) of kresoxim-methyl were dissolved in 150 ml of 1,2-dichloroethane. 0.63 g (2.4 mmol) of tin tetrachloride were then added and 2.6 g (72 mmol) of hydrogen chloride were gassed in within 1 h, during the heating phase to 85°C. The reaction mixture was held at 85°C for a further 4 hours with stirring and
45 then worked up as in Inventive Example 1. The yield of product of value was 30%.

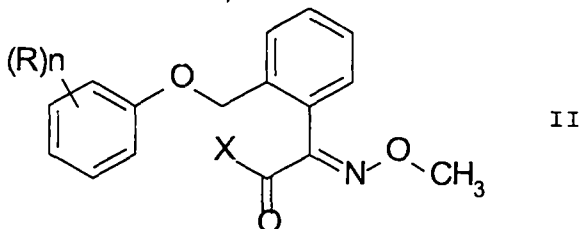
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We claim:

1. A process for preparing 2-(chloromethyl)phenylacetic acid derivatives of the formula I,



where X is C₁-C₄-alkoxy or methylamino, by ether cleavage of compounds of the formula II,



where R is C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, C₁-C₄-alkylcarbonyl, C₁-C₄-alkylcarbonyloxy, halogen, nitro or cyano and X is as defined above, which comprises carrying out the reaction in the presence of hydrogen chloride and an inert solvent, and adding a catalyst to the reaction mixture selected from the group consisting of iron, indium and halides, oxides and triflates thereof.

2. A process as claimed in claim 1, wherein the catalyst used is iron(III) chloride.
3. A process as claimed in claim 1 or 2, wherein the catalyst is used in a concentration of from 0.001 to 0.5 mol equivalents.
4. A process as claimed in any one of claims 1 to 3, wherein from 1 to 25 mol equivalents of hydrogen chloride are used.
5. A process as claimed in any one of claims 1 to 4, wherein the inert solvent used is an aromatic or aliphatic, optionally halogenated hydrocarbon.
6. A process according to the invention for preparing a compound of the formula I, substantially as hereinbefore described or exemplified.
7. A process for preparing a compound of the formula I including any new and inventive integer or combination of integers, substantially as herein described.

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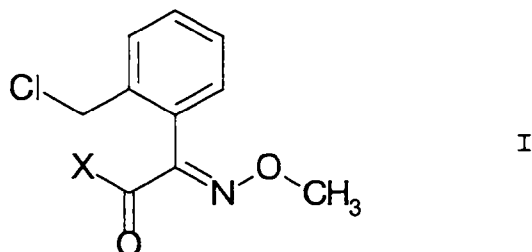
Preparation of 2-(chloromethyl)phenylacetic acid derivatives

Abstract

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A process for preparing 2-(chloromethyl)phenylacetic acid derivatives of the formula I,

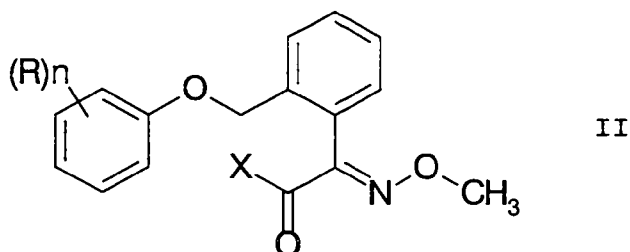
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where X is C₁-C₄-alkoxy or methylamino, by ether cleavage of compounds of the formula II,

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where R is C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, C₁-C₄-alkylcarbonyl, C₁-C₄-alkylcarbonyloxy, halogen, nitro or cyano and X is as defined above comprises carrying out the reaction in the presence of hydrogen chloride and an inert solvent, and adding a catalyst to the reaction mixture selected from the group consisting of iron, indium and halides, oxides and triflates thereof.

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