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(54) PROCESS FOR THE PREPARATION OF PHENYL GLYOXYLIC ACID ESTER OXIMES

VERFAHREN ZUR HERSTELLUNG VON PHENYL GLYOXYL ESTER OXIME

PROCEDE DE PREPARATION D'OXIMES DE PHENYLESTER D'ACIDE GLYOXYLIQUE

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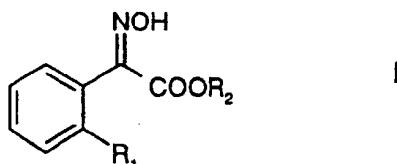
(56) References cited:
EP-A- 0 629 609 EP-A- 0 782 982
**• W F BEECH: "Preparation of aromatic aldehydes
and ketones from diazonium salts" JOURNAL
OF THE CHEMICAL SOCIETY,GB,CHEMICAL
SOCIETY. LETCHWORTH, 1954, pages
1297-1302, XP002075827 cited in the application**

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Description

[0001] The invention relates to a process for the preparation of compounds of formula I

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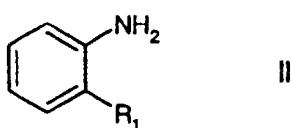
wherein:

R₁ is optionally substituted alkyl,

15 R₂ is C₁-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkyl-C₁-C₂alkyl, aryl, aryl-C₁-C₂alkyl, heterocycl, heterocycl-C₁-C₂alkyl, which groups are optionally substituted by alkyl, alkoxy, or halogen; in which process

(1) an aniline of formula II,

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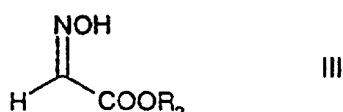


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wherein R₁ is as defined for formula I, is diazotized with an organic or inorganic nitrite or nitrous acid;

(2) the resulting diazonium salt is reacted with an oxime of formula III

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wherein R₂ is as defined for formula I, in presence of a copper(II)-salt.

[0002] The compounds of formula I are intermediates for the preparation of pesticides; e.g. EP-A-460575 and WO 95/18789.

40 [0003] Several processes for preparing compounds of formula I are known, which, however, are not always satisfying in any respect, as number of reaction steps, yields, availability of educts, safety and ecology.

For example EP-A-253213 discloses a process comprising a Grignard reaction; in EP-A-782982 a reaction with a lithium organic reagent, as butyllithium, is described.

45 [0004] These processes are not suitable for large scale production, as organometallic reactions have serious disadvantages with respect to economic, ecological and safety reasons. Other methods for preparation of compounds of formula I are therefore highly desirable.

[0005] Reactions of phenyl diazonium salts with oximes are known, e.g. J. Chem. Soc. 1954, p.1297-1302; Research Disclosure, October 1997, Vol. 402, 40221 and WO 98/50335. Reactions with glyoxylic acid oxime derivatives are not disclosed in these references.

50 [0006] Surprisingly, it has been found that compounds of formula I may be obtained directly from the corresponding anilines by reaction with a glyoxylic acid oxime derivative in yields of up to 80% and in good qualities. The method provided herewith is distinguished by ready availability of the raw materials, good technical feasibility and is economically and ecologically favorable.

55 [0007] An additional advantage of the reaction according to the invention is that compounds of formula I are obtained almost exclusively in form of their E-isomers with respect to the oxime double bond (E:Z > 95:5), which isomer is biologically more active than the Z-isomer in the corresponding final active ingredients. A separate isomerisation or isomer-purification step can therefore be avoided.

[0008] Alkyl groups are straight-chain or branched and will typically be methyl, ethyl, n-propyl, isopropyl, n-butyl,

sec-butyl, isobutyl, tert-butyl, n-amyl, tert-amyl, 1-hexyl or 3-hexyl. Halogen and halo substituents are fluoro, chloro, bromo or iodo.

Alkoxy is typically methoxy, ethoxy, propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy and tert-butyloxy. Methoxy and ethoxy are preferred.

5 Cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

Aryl is phenyl or naphthyl; phenyl is preferred.

Heterocycl stands for aromatic and non-aromatic cyclic moieties with 3 to 8 ring members of which at least one is a nitrogen, oxygen or sulfur. Heterocycl typically encompasses up to three heteroatoms where preferably at least one is nitrogen. Typical examples of heterocycl are aromatic moieties like furyl, benzofuranyl, thieryl, benzothienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, iso-indolyl, triazinyl; and non-aromatic moieties like tetrahydrofuranyl, pyrazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolinidinyl, piperidinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, and the like.

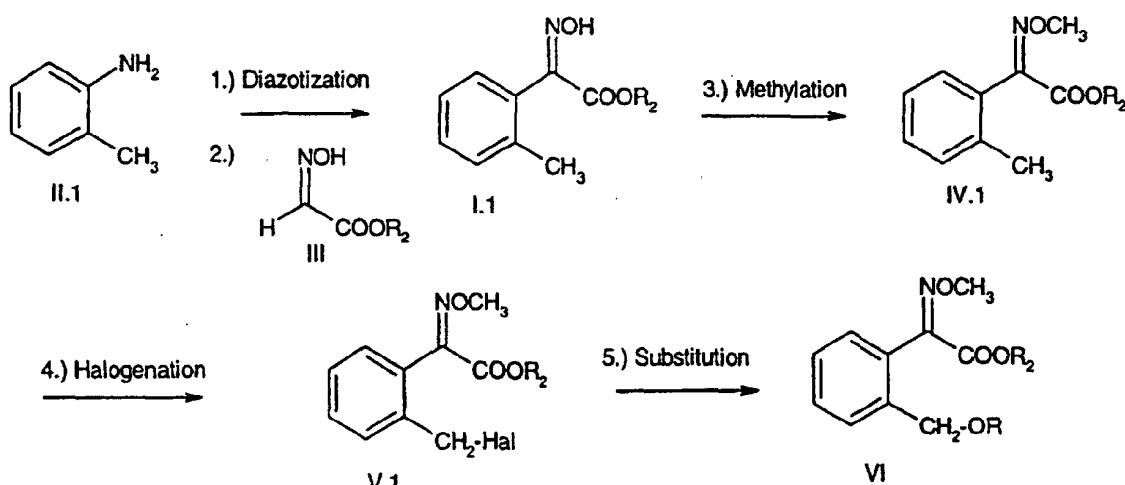
[0009] R₁ is optionally substituted alkyl, wherein the substituents have to be inert towards the reactions; suitable substituents are for example halogen, alkoxy and phenoxy.

15 R₂ is preferably C₁-C₄alkyl, most preferably ethyl or methyl.

[0010] The reaction according to the invention is particularly suitable for the preparation of compounds of formula I, wherein R₁ is methyl. In this case, the important intermediates of formula V.1 for the preparation of pesticides of formula VI may be prepared according to the following reaction scheme:

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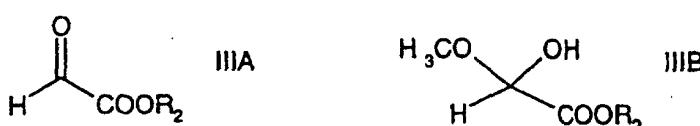


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This reaction sequence is also an object of the present invention. R represents an organic radical linked via an oxygen bridge. It encompasses the designations as e.g. disclosed in EP-A-460575 and WO 95/18789, but is not limited to such examples.

[0011] Due to its relative instability, the oxime of formula III is advantageously prepared immediately before use by reaction of the corresponding glyoxylic acid ester IIIA or its hemiacetal IIIB

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50 with hydroxylamine or a salt thereof, as the hydrochloride, the sulfate, the phosphate or the acetate, in aqueous solution and further reacted without isolating.

[0012] Compounds of formulae II, III, IIIA and IIIB are well known in the art and are partially commercially available.

[0013] The diazotation reaction is carried out in an organic solvent with an organic nitrite, e.g. an alkyl nitrite as isoamyl nitrite, or an aryl nitrite, as phenyl nitrite; or, more preferably, in aqueous solution with nitrous acid or a salt thereof, in presence of an acid. Preferred nitrites are sodium nitrite, potassium nitrite, magnesium nitrite, particularly preferred is sodium nitrite. Preferred acids are hydrochloric acid, sulfuric acid and nitrosulfuric acid; particularly preferred is sulfuric acid. Advantageous is a temperature of -10 to +30°C and a pH 0-3.

[0014] The diazonium salt is preferably reacted in the presence of a copper(II)-salt like copper acetate, CuCl₂ or CuSO₄ at -10 to +40°C, more preferably -10 to +15°C, and at pH 2-7, more preferably at pH 3-5. The amount of the copper(II)-salt is 1 to 30 mol%, more preferably 5 to 20 mol%, in relation to the aniline of formula II. The addition of a reducing agent, as a sulfite salt, e.g. sodium sulfite or potassium sulfite, may be advantageous, preferably in amounts of 1 to 20 mol%, more preferably 5 to 10 mol%, in relation to the aniline of formula II.

[0015] In a preferred mode of running the reaction step (2), an aqueous suspension of the diazonium salt is added to an aqueous solution comprising the aldoxime of formula III, the copper(II)-salt and optionally the reducing agent, maintaining a pH of 3-5 by simultaneously adding a base to the reaction mixture. It may be advantageous for working up and purification of intermediates and products to run the reaction steps (1) and (2) in presence of a hydrophobic solvent, as hydrocarbons, halogenated hydrocarbons, ethers and ketones, for example hexane, cyclohexane, methylcyclohexane, benzene, toluene, xylene, mineral oil, kerosene, methylene chloride, chloroform, ethylenechloride, chlorobenzene and dichlorobenzene.

[0016] Methylation of the oxime group is carried out for example with methyl iodide, methyl bromide, methyl chloride or dimethyl sulfate in a solvent, preferably in presence of a base.

[0017] Methods for halogenation include iodination with I₂, bromination with NBS (N-bromosuccinimide) or Br₂, chlorination with NCS (N-chlorsuccinimide) or Cl₂ or SO₂Cl₂. Particularly preferred is the bromination with NBS.

[0018] Suitable solvents are halogenated hydrocarbons, typically chlorobenzene, bromobenzene, chloroform, dichloromethane, trichloromethane, dichloroethane or trichloroethane; ethers, typically diethyl ether, tert-butylmethyl ether, glyme, diglyme, tetrahydrofuran or dioxane, as well as nitrogen containing compounds like triethylamine, piperidine, pyridine, alkylated pyridine, quinoline and isoquinoline.

[0019] The compound of formula V may be reacted with a compound of the formula HOR, wherein R is an organic radical, under basic conditions in a solvent according to known methods, to obtain the active ingredients of formula VI, which may, if desired, be transesterified or amidated according to generally known methods.

25 Preparation Examples

[0020]

(a) Preparation of 2-methyl benzene diazonium salt (solution A):

To an ice-cooled mixture of 225 g water, 35.1 g concentrated sulfuric acid (0.36 mol) and 32.0 g 2-toluidine (0.30 mol), an aqueous solution of 21.0 g sodium nitrite (0.303 mol) in 80 g water is added at 0-5 °C. The mixture is stirred for ca. 15 minutes, and the excess sodium nitrite is destroyed with 0.9 g sulfamic acid.

(b) Preparation of glyoxylic acid methylester oxime (solution B):

In a separate reactor 54.0 g glyoxylic acid methylester methylhemiacetal (0.45 mol), 150 g water, 27.0 g glacial acetic acid (0.45 mol) and 29.7 g aqueous hydroxylamine 50% (0.45 mol) are mixed for ca. 30 minutes at 0-5 °C; subsequently 15.0 g solid copper(II)sulfate (0.06 mol) and 3.78 g of sodium sulfite (0.03 mol) are added in one portion.

(c) Preparation of 2-methylphenyl glyoxylic acid methylester oxime:

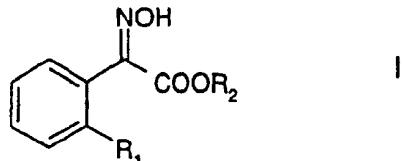
Solution A is added to solution B at 12-18 °C, maintaining the pH at 3-4 by addition of a 20% aqueous solution of sodium acetate. During the reaction a constant stream of nitrogen is evolved and the product is crystallizing from the aqueous medium. The mixture is stirred for 2 hours at ca. 20°C, the suspension is filtered and the product is washed with water and dried at 50 °C under vacuum to yield 42.8 g dark crystals, m.p. 92 °C (decomposition). ¹H-NMR (CDCl₃): 2.18 and 3.78 ppm (2 methyl groups); exclusively E-isomer (71 % of theory).

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Claims

1. A process for the preparation of a compound of formula I

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wherein:

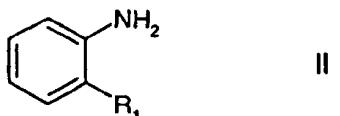
R₁ is optionally substituted alkyl,

R₂ is C₁-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkyl-C₁-C₂alkyl, aryl, aryl-C₁-C₂alkyl, heterocycl, heterocycl-C₁-C₂alkyl, which groups are optionally substituted by alkyl, alkoxy and halogen, in which process

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- (1) an aniline of formula II

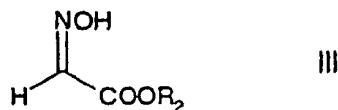
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wherein R₁ is as defined for formula I, is diazotized with an organic or inorganic nitrite or nitrous acid;

15 (2) the resulting diazonium salt is reacted with an oxime of formula III

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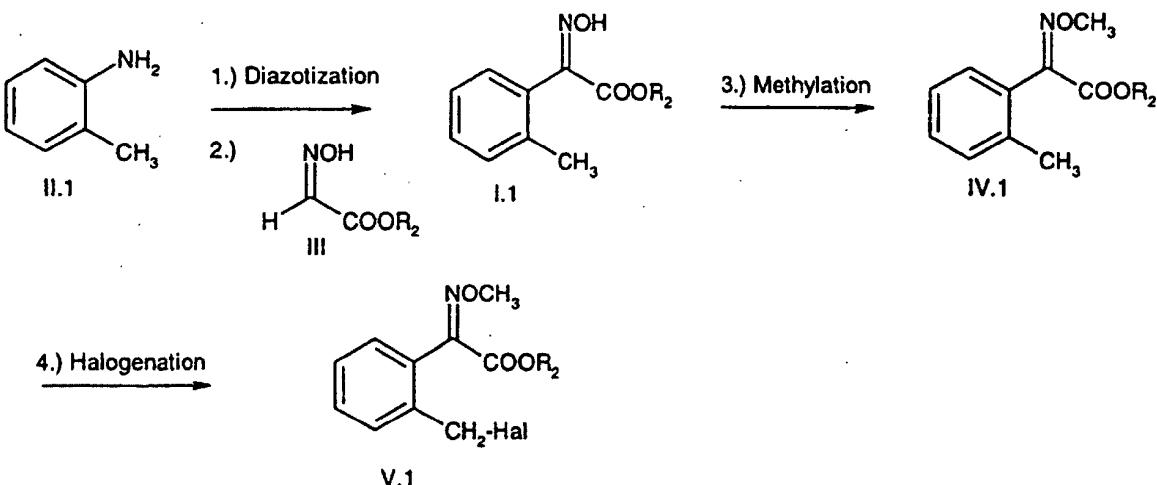


wherein R₂ is as defined for formula I, in presence of a copper(II)-salt.

- 25 2. A process according to claim 1, wherein the copper(II)-salt is CuCl₂ or CuSO₄.
- 30 3. A process according to claim 1, wherein the amount of the copper(II)-salt is 1 to 30 mol%, in relation to the compound of formula II.
- 35 4. A process according to claim 1, wherein in reaction step (2) the diazonium salt is reacted in the presence of a reducing agent.
5. A process according to claim 4, wherein the reducing agent is sodium sulfite or potassium sulfite.
- 40 6. A process according to claim 1, wherein in formulae I, II and III
R₁ is methyl and R₂ is methyl or ethyl.
- 45 7. A process for the preparation of a compound of formula V.1,

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wherein

R_2 is $C_1\text{-}C_6$ alkyl, $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkyl- $C_1\text{-}C_2$ alkyl, aryl, aryl- $C_1\text{-}C_2$ alkyl, heterocyclyl, heterocyclyl- $C_1\text{-}C_2$ alkyl, which groups are optionally substituted by alkyl, alkoxy and halogen, in which process

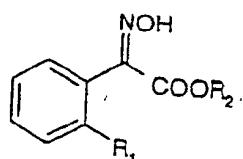
- 5 (1) the aniline of formula II.1 is diazotized with an organic or inorganic nitrite or nitrous acid;
 (2) the resulting diazonium salt is reacted with an oxime of formula III, wherein R_2 is as defined for formula I.
 1, in presence of a copper(II)-salt;
 (3) the resulting oxime of formula I.1 is methylated;
 (4) the resulting oxime ether of formula V.1 is halogenated.

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Patentansprüche

1. Verfahren zur Herstellung von Verbindungen der Formel I:

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I,

worin gilt:

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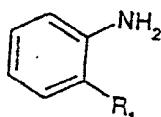
R_1 ist gegebenenfalls substituiertes Alkyl,

R_2 ist $C_{1\text{-}6}$ -Alkyl, $C_{3\text{-}6}$ -Cycloalkyl, $C_{3\text{-}6}$ -Cycloalkyl- $C_{1\text{-}2}$ alkyl, Aryl, Aryl- $C_{1\text{-}2}$ -alkyl, Heterocyclyl, Heterocyclyl- $C_{1\text{-}2}$ alkyl, welche Gruppen gegebenenfalls mit Alkyl, Alkoxy oder Halogen substituiert sind, wobei in dem Verfahren

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(1) ein Anilin der Formel II:

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II,

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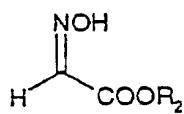
worin

R_1 wie für Formel I definiert ist, mit einem organischen oder anorganischen Nitrit oder mit salpetriger Säure diazotiert und

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(2) das entstandene Diazoniumsalz mit einem Oxim der Formel III:

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III,

worin R_2 wie für Formel I definiert ist, in der Gegenwart eines Kupfer(II)salzes umgesetzt werden.

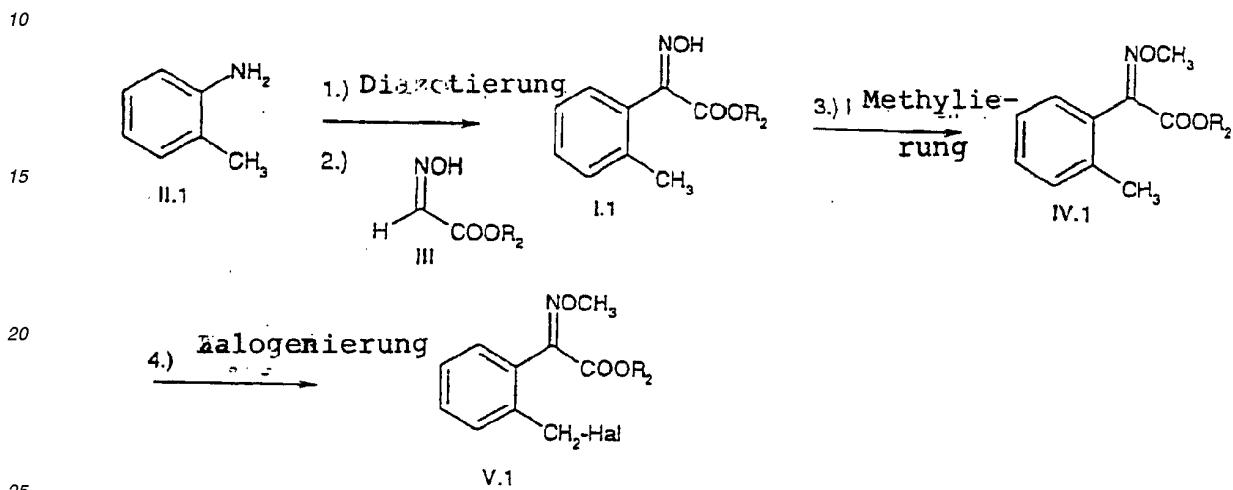
- 55 2. Verfahren gemäß Anspruch 1, worin das Kupfer(II)salz $CuCl_2$ oder $CuSO_4$ ist.
 3. Verfahren gemäß Anspruch 1, worin die Menge des Kupfer(II)salzes 1 bis 30 Mol%, bezogen auf die Verbindung der Formel II, beträgt.

4. Verfahren gemäß Anspruch 1, worin in Reaktionsstufe (2) das Diazoniumsalz in der Gegenwart eines reduzierenden Mittels zur Reaktion gebracht wird.

5. Verfahren gemäß Anspruch 4, worin das reduzierende Mittel Natrium- oder Kaliumsulfit ist.

6. Verfahren gemäß Anspruch 1, worin in den Formeln I, II und III R₁ Methyl und R₂ Methyl oder Ethyl sind.

7. Verfahren zur Herstellung einer Verbindung der Formel V.1:



worin gilt:

30 R₂ ist C₁₋₆-Alkyl, C₃₋₆-Cycloalkyl, C₃₋₆-Cycloalkyl-C₁₋₂-alkyl, Aryl, Aryl-C₁₋₂-alkyl, Heterocycl, Heterocyclyl-C₁₋₂-alkyl, welche Gruppen gegebenenfalls mit Alkyl, Alkoxy und Halogen substituiert sind, wobei in dem Verfahren

35 (1) das Anilin der Formel II.1 mit einem organischen oder anorganischen Nitrit oder mit salpetriger Säure diazotiert,

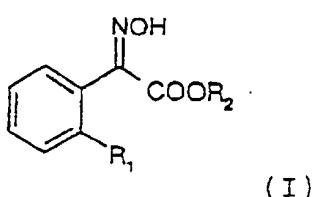
40 (2) das entstandene Diazoniumsalz mit einem Oxim der Formel III, worin R₂ wie für Formel I.1 definiert ist, in der Gegenwart eines Kupfer(II)salzes umgesetzt,

(3) das entstandene Oxim der Formel I.1 methyliert und

45 (4) der entstandene Oximether der Formel V.1 halogeniert werden.

Revendications

45 1. Procédé pour la préparation d'un composé de formule I



55 dans laquelle

R₁ est alkyle facultativement substitué ;

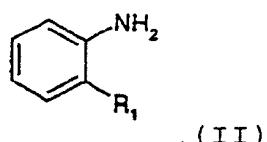
R₂ est alkyle en C_{1-C6}, cyclo(alkyle en C_{3-C5}), cyclo(alkyle en C_{3-C6})(alkyle en C_{1-C2}), aryle, aryl(alkyle en

C_1-C_2), hétérocycle, hétérocycl(alkyle en C_1-C_2), groupements qui sont facultativement substitués par alkyle, alkoxy et halogène, procédé dans lequel

5 (1) une aniline de formule II

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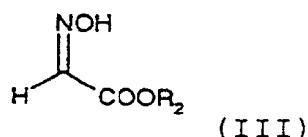
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dans laquelle R_1 est comme défini pour la formule I, est diazotée avec un nitrite organique ou inorganique ou l'acide nitreux ;

15 (2) le sel de diazonium résultant est mis à réagir avec une oxime de formule III

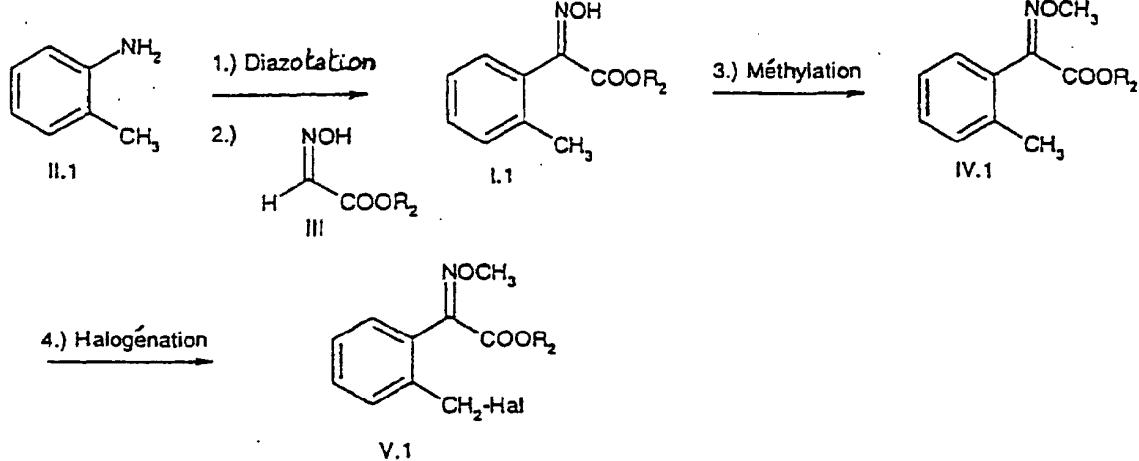
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dans laquelle R_2 est comme défini pour la formule I, en présence d'un sel de cuivre (II).

- 25 2. Procédé selon la revendication 1, dans lequel le sel de cuivre (II) est $CuCl_2$ ou $CuSO_4$.
3. Procédé selon la revendication 1, dans lequel la quantité du sel de cuivre (II) est de 1 à 30% en mole, par rapport au composé de formule II.
- 30 4. Procédé selon la revendication 1, dans lequel, dans l'étape de réaction (2), le sel de diazonium est mis à réagir en présence d'un agent réducteur.
5. Procédé selon la revendication 4, dans lequel l'agent réducteur est du sulfite de sodium ou du sulfite de potassium.
- 35 6. Procédé selon la revendication 1, dans lequel dans les formules I, II et III, R_1 est méthyle et R_2 est méthyle ou éthyle.
7. Procédé pour la préparation d'un composé de formule V.1

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où

R_2 est alkyle en C_1-C_6 , cyclo(alkyle en C_3-C_5), cyclo(alkyle en C_3-C_6)(alkyle en C_1-C_2), aryle, aryl(alkyle en C_1-C_2), hétérocycle, hétérocycl(alkyle en C_1-C_2), groupements qui sont facultativement substitués par alkyle,

alkoxy et halogène, procédé dans lequel

- 5 (1) l'aniline de formule II.1 est diazotée avec un nitrite organique ou inorganique ou l'acide nitreux ;
(2) le sel de diazonium résultant est mis à réagir avec une oxime de formule III, dans laquelle R₂ est comme
défini pour la formule I.1, en présence d'un sel de cuivre (II) ;
(3) l'oxime résultante de formule I.1 est méthylée ;
(4) l'éther d'oxime résultant de formule V.1 est halogéné.

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