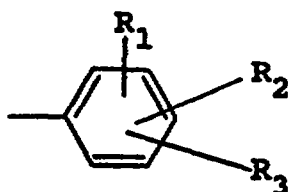


Description

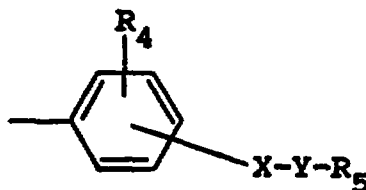
The invention concerns a new process for the preparation of 3,3-diaryl acrylic acid amides of the formula



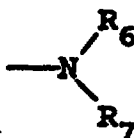
in which
A represents



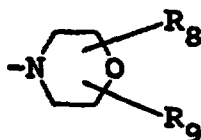
B represents



and
Q represents



or



where

R₁ represents a C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, mono- or di-(C₁₋₄ alkyl)amino, C₃₋₄ alkenyl, C₃₋₄ alkynyl, C₃₋₄ alkenyloxy, C₃₋₄ alkynyloxy or C₃₋₆ cycloalkyl group;

R₂ represents a C₁₋₄ alkyl or C₁₋₄ alkoxy group or a halogen atom;

R₃ represents a hydrogen or halogen atom;

R₄ represents a hydrogen or halogen atom or a C₁₋₄ alkyl or C₁₋₄ alkoxy group;

R₅ represents a hydrogen atom, a phenyl group optionally substituted by one or more substituents

selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, phenyl and phenoxy moieties, a C₁₋₁₂ alkyl group optionally substituted by one or more halogen atoms, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl or a C₂₋₆ alkynyl group each optionally substituted by a phenyl group, or a naphthyl or C₅₋₈ cycloalkenyl group;

-X-Y- represents a single bond or a -O-, -S(O)_p- where p is 0, 1 or 2, -N=N-, -CHR₁₀-O-, -O-CHR₁₀-, -CHR₁₀-S(O)_p-, -S(O)_p-CHR₁₀-, -C_nH_{2n}- where n is an integer from 1 to 10, -HC=CH- or -C≡C- moiety;

R₆ represents a C₁₋₄ alkyl, C₃₋₇ cycloalkyl, benzyl, C₃₋₄ alkenyl or C₃₋₄ alkynyl group;

R₇ represents a C₁₋₄ alkyl group;

R₈ represents a hydrogen atom or a C₁₋₄ alkyl or C₁₋₄ alkoxy group; and

R₉ and R₁₀ independently represent a hydrogen atom or a C₁₋₄ alkyl group.

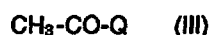
Compounds of formula I are fungicidally active and are particularly useful in the control of phytopathogenic fungi, especially *Plasmopara viticola* and *Phytophthora infestans*. Particularly preferred compounds of formula I in this respect are those in which A represents a 3,4-dimethoxyphenyl, 3-ethoxy-4-methoxyphenyl, 3-chloro-4-methoxyphenyl, 3-bromo-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-ethyl-4-methoxyphenyl, 3-propyl-4-methoxyphenyl, 3,4-dimethylphenyl, 3-amino-4-methoxyphenyl, 3,5-dichloro-4-aminophenyl or 3-methoxy-4-methylphenyl group and, of these, 3,4-dimethoxyphenyl is especially preferred. It is also preferred that Q represents a morpholino group. An especially preferred compound of formula I is 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl) acrylic acid morpholide.

Compounds of formula I form the subject of European patent applications nos. 84102012.6 and 86113835.2, published as EP 0 120 321 A1 and EP 0219756 A1 respectively, and these documents describe methods for the preparation of these compounds. Additionally, W. Chodkiewicz et al, Bull. Soc. Chim. France, 1958, pp. 1586-91 describes, inter alia, the preparation of diaryl α-ethylenic amides by condensing a diarylketone with an acetamide or N-acetyl morpholine in the presence of a strong base to form an intermediate β-hydroxyamide and then dehydrating the β-hydroxyamide by heating it in the presence of an acid, preferably a mixture of sulphuric and acetic acids, to obtain the desired diaryl α-ethylenic amide. However, it has now been surprisingly discovered that compounds of formula I can also be prepared by reacting a benzophenone with an appropriate acetamide, in a modification of a known reaction, followed, if necessary, by dehydration under alkaline conditions.

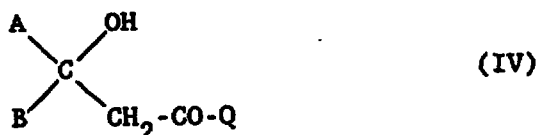
According to the present invention there is therefore provided a process for the preparation of a compound of formula I, as defined above, which comprises condensing a compound of formula



in which A and B have the meanings given above, with a compound of formula

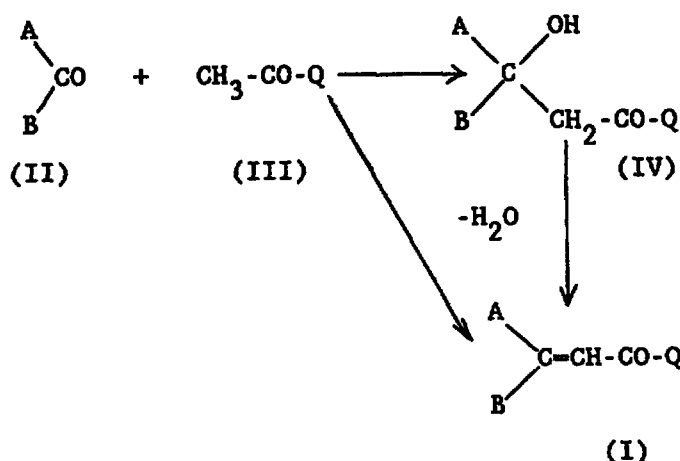


in which Q has the meaning given above, in the presence of a strong base and a solvent at a temperature from room temperature to the reflux temperature of the reaction mixture and, if an intermediate compound is formed of formula



in which A, B and Q have the meanings given above, dehydrating the intermediate compound characterised in that the intermediate compound of formula IV is dehydrated by heating in an inert solvent under alkaline conditions.

The above process can be represented by the following reaction scheme:-



In this scheme A, B and Q are as defined above. As shown in the scheme, depending on the reaction conditions and reagents used, the above reaction may proceed directly to the final product of formula I in one step or may proceed in two steps via an intermediate of formula IV. In the latter case, a separate dehydration step is required to produce the final product of formula I.

As stated above, the condensation reaction is carried out in the presence of a strong base. Suitable strong bases include alkali hydroxides, alkali carbonates, potassium tert-butyrate and tert-butyl lithium. Depending on the base used and the temperature at which the reaction is carried out, compounds of formula I are sometimes formed directly by elimination of water without the need for a separate dehydration step. (cf. W. Chodkiewicz et al, Bull. Soc. Chim. France, 1958, 1586-9).

The reactions are carried out in the presence of an inert solvent, such as toluene, benzene, diethyl ether, diisopropyl ether, diglyme, tetrahydrofuran, dimethyl formamide, acetone or ethylene chloride. Alternatively, an excess of one of the reactants may also serve as a solvent. Depending on the reactivity of the reactants, the condensation reaction may be carried out at any temperature from room temperature to the reflux temperature of the reaction mixture.

Compounds of formula II and formula III are either known compounds or can be produced from known compounds by known methods.

The process of the invention is illustrated by the following specific examples.

Example 1 (Comparative Example)

Preparation of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid morpholide

6.92g (25 mmol) 4-chloro-3',4'-dimethoxybenzophenone, 12.9g (100 mmol) N-acetylmorpholine and 11.2g (170 mmol) powdered potassium hydroxide (85%) were mixed well and allowed to stand at room temperature for 30 minutes, with occasional stirring. The viscous mass so obtained was then added to a vigorously stirred mixture of 100 ml water and 50 ml toluene. The toluene phase was dried and separated over a column containing 50g silica gel using 150 ml each of 95:5, 90:10 and 80:20 toluene-acetone mixture as eluant. The fractions with an R_f value of 0.37 (Toluene/Acetone 7:3) were evaporated in a rotary evaporator, after which 0.8 g of the title compound were obtained by trituration with a little diisopropyl ether.

By evaporating the fractions with an R_f value of 0.52, 3.4g (33.5% of theory) of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-3-hydroxypropionic acid morpholide were obtained, m.pt. 150°C. For the dehydration step, this substance was then dissolved in 10 ml glacial acetic acid by warming, 0.1 ml conc. sulphuric acid were added and the mixture was then boiled under reflux for 5 minutes. After cooling to 50°C, the mixture was stirred into 100 ml water. The oil that initially separated out solidified on further stirring. The substance was then filtered off under suction, washed with water and dried. Thin layer chromatography (TLC) indicated that the final product was substantially pure.

Yield: 2.9g (30% of theory)

Total yield: 3.7g (38% of theory), TLC - pure.

Example 2Preparation of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid morpholide

5 13.84g (50 mmol) 4-chloro-3',4'-dimethoxybenzophenone, 7.75g (60 mmol) N-acetylmorpholine, 7.29g (65 mmol) potassium tert-butyrate and 75 ml anhydrous toluene were mixed and stirred for 2 hours under nitrogen at 80 °C. The solution was then cooled, extracted with 100ml water, dried and evaporated in a rotary evaporator. 11.5g of a viscous oil were obtained, which were then heated with 50 ml diisopropyl ether whilst stirring. The oil crystallised on cooling and rubbing. The crystals were then filtered off under suction,
 10 washed with a little diisopropyl ether and dried.

Yield : 9.25g (48% of theory)

M.pt : 122-148 °C

TLC-pure, R.f. value: 0.38 in 7:3 toluene/acetone.

15 Example 3Preparation of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl) acrylic acid morpholide

5.53g (20 mmol) 4-chloro-3',4'-dimethoxybenzophenone, 3.23g (25 mmol) N-acetylmorpholine, 3.29g (50
 20 mmol) powdered potassium hydroxide (85%) and 30 ml absolute tetrahydrofuran were stirred under reflux for 5 hours under nitrogen. After cooling, the liquid paste so obtained was added to a well stirred mixture of 100 ml water and 50 ml toluene. The toluene phase was dried and separated over a column containing 50g silica gel, using 100 ml each of 95:5, 90:10 and 80:20 toluene-acetone mixture as eluant. The fractions
 25 containing a substance with an Rf-value of 0.38 (Toluene/Acetone 7:3) were then evaporated in a rotary evaporator. The oil thus obtained solidified on trituration with a little diisopropyl ether.

M.pt: 125-145 °C

Yield: 3.25g (42% of theory)

Claims

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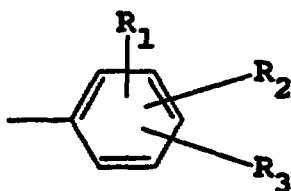
1. A process for the preparation of a compound of formula

35



40 in which
 A represents

45



50 B represents

55

**Example 2****Preparation of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid morpholide**

13.84g (50 mmol) 4-chloro-3',4'-dimethoxybenzophenone, 7.75g (60 mmol) N-acetylmorpholine, 7.29g (65 mmol) potassium tert-butyrate and 75 ml anhydrous toluene were mixed and stirred for 2 hours under nitrogen at 80°C. The solution was then cooled, extracted with 100ml water, dried and evaporated in a rotary evaporator. 11.5g of a viscous oil were obtained, which were then heated with 50 ml diisopropyl ether whilst stirring. The oil crystallised on cooling and rubbing. The crystals were then filtered off under suction, washed with a little diisopropyl ether and dried.

Yield : 9.25g (48% of theory)

M.pt : 122-148°C

TLC-pure, R.f. value: 0.38 in 7:3 toluene/acetone.

Example 3**Preparation of 3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl) acrylic acid morpholide**

5.53g (20 mmol) 4-chloro-3',4'-dimethoxybenzophenone, 3.23g (25 mmol) N-acetylmorpholine, 3.29g (50 mmol) powdered potassium hydroxide (85%) and 30 ml absolute tetrahydrofuran were stirred under reflux for 5 hours under nitrogen. After cooling, the liquid paste so obtained was added to a well stirred mixture of 100 ml water and 50 ml toluene. The toluene phase was dried and separated over a column containing 50g silica gel, using 100 ml each of 95:5, 90:10 and 80:20 toluene-acetone mixture as eluant. The fractions containing a substance with an Rf-value of 0.38 (Toluene/Acetone 7:3) were then evaporated in a rotary evaporator. The oil thus obtained solidified on trituration with a little diisopropyl ether.

M.pt: 125-145°C

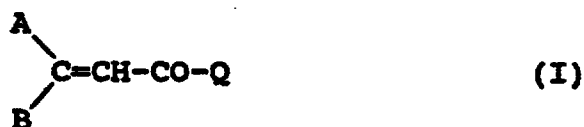
Yield: 3.25g (42% of theory)

Claims

30

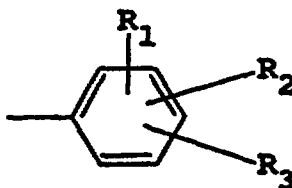
1. A process for the preparation of a compound of formula

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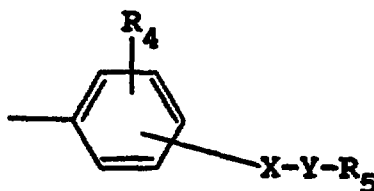
in which
A represents

45

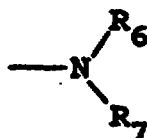


B represents

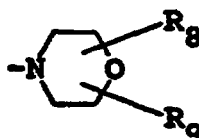
55



and
Q represents



or



where

R_1 represents a C_{1-4} alkyl, C_{1-4} alkoxy, amino, mono- or di- $(C_{1-4}$ alkyl)amino, C_{3-4} alkenyl, C_{3-4} alkynyl, C_{3-4} alkenyloxy, C_{3-4} alkynyloxy or C_{3-6} cycloalkyl group;

R_2 represents a C_{1-4} alkyl or C_{1-4} alkoxy group or a halogen atom;

R_3 represents a hydrogen or halogen atom;

R_4 represents a hydrogen or halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group;

R_5 represents a hydrogen atom, a phenyl group optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen, phenyl and phenoxy moieties, a C_{1-12} alkyl group optionally substituted by one or more halogen atoms, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl or C_{2-6} alkynyl group each optionally substituted by a phenyl group, or a naphthyl or C_{5-8} cycloalkenyl group;

-X-Y- represents a single bond or a -O-, $-S(O)_p-$ where p is 0, 1 or 2, $-N=N-$, $-CHR_{10}-O-$, $-O-CHR_{10}-$, $-CHR_{10}-S(O)_p-$, $-S(O)_p-CHR_{10}-$, $-C_nH_{2n}-$ where n is an integer from 1 to 10, $-HC=CH-$ or $-C\equiv C-$ moiety;

R_6 represents a C_{1-4} alkyl, C_{3-7} cycloalkyl, benzyl, C_{3-4} alkenyl or C_{3-4} alkynyl group;

R_7 represents a C_{1-4} alkyl group;

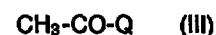
R_8 represents a hydrogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group; and

R_9 and R_{10} independently represent a hydrogen atom or a C_{1-4} alkyl group;

which comprises condensing a compound of formula

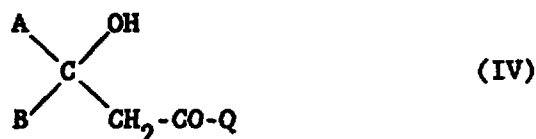


in which A and B have the meanings given above, with a compound of formula





in which Q has the meaning given above, in the presence of a strong base and a solvent at a temperature from room temperature to the reflux temperature of the reaction mixture, and, if an intermediate compound is formed of formula

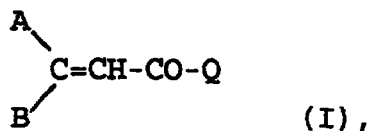


in which A, B and Q have the meanings given above, dehydrating the intermediate compound characterised in that the intermediate compound of formula IV is dehydrated by heating in an inert solvent under alkaline conditions.

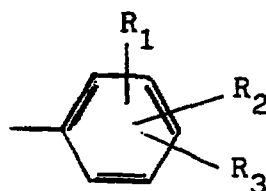
2. A process according to claim 1 in which the strong base is selected from alkali hydroxides, alkali carbonates, potassium tert-butyrate and tert-butyl lithium.
3. A process according to claim 1 in which the solvent is selected from toluene, benzene, diethylether, diisopropyl ether, diglyme, tetrahydrofuran, dimethyl formamide, acetone and ethylene chloride.

Patentansprüche

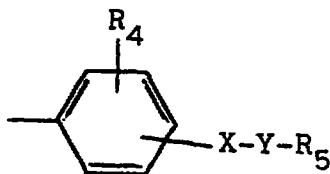
1. Verfahren zur Herstellung einer Verbindung mit der Formel



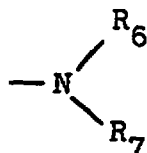
worin
A für



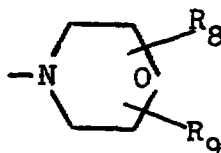
steht;
B für



steht; und
für



oder



steht, worin

R_1 eine C_{1-4} Alkyl-, C_{1-4} Alkoxy-, Amino-, Mono- oder Di- $(\text{C}_{1-4}$ -alkyl)amino-, C_{3-4} Alkenyl-, C_{3-4} Alkynyl-, C_{3-4} Alkenyloxy-, C_{3-4} Alkinyloxy oder C_{3-6} Cycloalkylgruppe darstellt;

R_2 eine C_{1-4} Alkylgruppe oder C_{1-4} Alkoxygruppe oder ein Halogenatom bedeutet;

R_3 ein Wasserstoff- oder Halogenatom bedeutet;

R_4 ein Wasserstoff- oder Halogenatom oder eine C_{1-4} Alkyl- oder C_{1-4} Alkoxygruppe bedeutet;

R_5 für ein Wasserstoffatom, eine gegebenenfalls durch einen oder mehrere, unter C_{1-4} Alkyl-, C_{1-4} Alkoxy-, Halogen-, Phenyl- und Phenoxyresten ausgewählten Substituenten substituierte Phenylgruppe, eine gegebenenfalls durch ein oder mehrere Halogenatome substituierte C_{1-12} Alkylgruppe, eine C_{3-7} Cycloalkylgruppe, eine C_{2-6} Alkenylgruppe oder eine C_{2-6} Alkynylgruppe, die jeweils gegebenenfalls durch eine Phenylgruppe substituiert sind, oder für eine Naphthylgruppe oder eine C_{5-8} Cycloalkenylgruppe steht;

$-\text{X}-\text{Y}-$ eine Einfachbindung oder einen $-\text{O}-$, $-\text{S}(\text{O})_p-$, worin p 0, 1 oder 2 ist, $-\text{N}=\text{N}-$, $-\text{CHR}_{10}-$, $-\text{O}-\text{CHR}_{10}-$, $-\text{CHR}_{10}-\text{S}(\text{O})_p-$, $-\text{S}(\text{O})_p-\text{CHR}_{10}-$, $-\text{C}_n\text{H}_{2n}-$, worin n eine ganze Zahl von 1 bis 10 ist, $-\text{HC}=\text{CH}-$ oder $-\text{C}=\text{C}-$ Rest bedeutet;

R_6 eine C_{1-4} Alkyl-, C_{3-7} Cycloalkyl-, Benzyl-, C_{3-4} Alkenyl- oder C_{3-4} Alkynylgruppe darstellt;

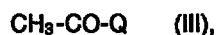
R_7 eine C_{1-4} Alkylgruppe bedeutet;

R_8 ein Wasserstoffatom oder eine C_{1-4} Alkyl- oder C_{1-4} Alkoxygruppe bedeutet; und

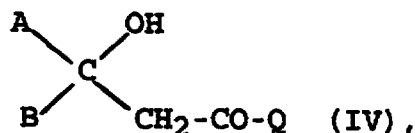
R_9 und R_{10} unabhängig voneinander ein Wasserstoffatom oder eine C_{1-4} Alkylgruppe darstellen, welches Verfahren ein Kondensieren einer Verbindung der Formel



worin A und B die oben angegebenen Bedeutungen aufweisen, mit einer Verbindung der Formel



worin Q die oben angeführte Bedeutung hat, in Gegenwart einer starken Base und eines Lösungsmittels bei einer Temperatur von Raumtemperatur bis zur Rückflußtemperatur des Reaktionsgemisches, und, falls eine Zwischenverbindung mit der Formel



5

10

worin A, B und Q die oben angeführten Bedeutungen aufweisen, gebildet wird, ein Dehydratisieren der Zwischenverbindung umfaßt, dadurch gekennzeichnet, daß die Zwischenverbindung der Formel IV durch Erwärmen in einem inerten Lösungsmittel unter alkalischen Bedingungen dehydratisiert wird.

15

2. Verfahren nach Anspruch 1, worin die starke Base unter Alkalihydroxiden, Alkalicarbonaten, Kalium-tert.butylat und tert.Butyllithium ausgewählt wird.
3. Verfahren nach Anspruch 1, worin das Lösungsmittel unter Toluol, Benzol, Diethylether, Diisopropylether, Diglyme, Tetrahydrofuran, Dimethylformamid, Aceton und Ethylenchlorid ausgewählt wird.

Revendications

1. Un procédé pour la préparation d'un composé de formule

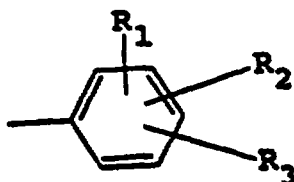
25



30 où

A représente

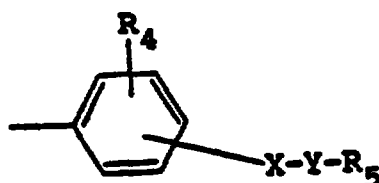
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40

B représente

45

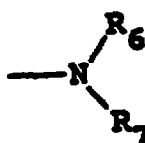


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et

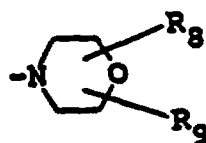
Q représente

55





ou



10 où

R_1 représente un groupe C_{1-4} alcoyle, C_{1-4} alcoxy, amino, mono- ou di- $(C_{1-4}$ alcoyl)amino, C_{3-4} alcényle, C_{3-4} alcynyle, C_{3-4} alcényloxy, C_{3-4} alcynyloxy ou C_{3-6} cycloalcoyle ;

R_2 représente un groupe C_{1-4} alcoyle ou C_{1-4} alcoxy ou un atome d'halogène ;

R_3 représente un atome d'hydrogène ou d'un halogène ;

15 R_4 représente un atome d'hydrogène ou d'un halogène ou un groupe C_{1-4} alcoyle ou C_{1-4} alcoxy ;

R_5 représente un atome d'hydrogène, un groupe phényle éventuellement substitué par un ou plusieurs substituants choisis parmi des portions C_{1-4} alcoyle, C_{1-4} alcoxy, halogène, phényle et phénoxy, un groupe C_{1-12} alcoyle éventuellement substitué par un ou plusieurs atomes d'halogènes, un groupe C_{3-7} cycloalcoyle, un groupe C_{2-6} alcényle ou C_{2-6} alcynyle, chacun éventuellement substitué par un groupe phényle, ou un groupe naphthyle ou C_{5-8} cycloalcényle ;

-X-Y- représente une liaison simple ou une portion -O-, -S(O)_p- où p est 0, 1 ou 2, -N=N-, -CHR₁₀-O-, -O-CHR₁₀-, -CHR₁₀-S(O)_p-, -S(O)_p-CHR₁₀-, -C_nH_{2n}- où n est un nombre entier de 1 à 10, -HC=CH- ou -C≡C- ;

25 R_6 représente un groupe C_{1-4} alcoyle, C_{3-7} cycloalcoyle, benzyle, C_{3-4} alcényle ou C_{3-4} alcynyle ;

R_7 représente un groupe C_{1-4} alcoyle ;

R_8 représente un atome d'hydrogène ou un groupe C_{1-4} alcoyle ou C_{1-4} alcoxy ; et

R_9 et R_{10} indépendamment représentent un atome d'hydrogène ou un groupe C_{1-4} alcoyle ;

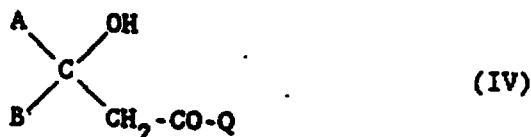
30 qui comprend la condensation d'un composé de formule



où A et B ont les significations indiquées ci-dessus, avec un composé de formule



où Q a la signification indiquée ci-dessus, en présence d'une base forte et d'un solvant à une température comprise entre la température ambiante et la température de reflux du mélange réactionnel, et, si un composé intermédiaire se forme de formule



où A, B et Q ont les significations indiquées ci-dessus, la déshydratation du composé intermédiaire, caractérisé en ce que le composé intermédiaire de formule IV est déshydraté par chauffage dans un solvant inerte dans des conditions alcalines.

2. Un procédé selon la revendication 1, dans lequel la base forte est choisie parmi les hydroxydes de métaux alcalins, les carbonates de métaux alcalins, le tert-butylate de potassium et le tert-butyllithium.



3. Un procédé selon la revendication 1, dans lequel le solvant est choisi parmi le toluène, le benzène, l'oxyde d'éthyle, l'oxyde d'isopropyle, le diglyme, le tétrahydrofuranne, le diméthyl formamide, l'acétone et le chlorure d'éthylène.

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