

Description

The present invention relates to a process for the preparation of 3,3-diarylacrylic acid amides.

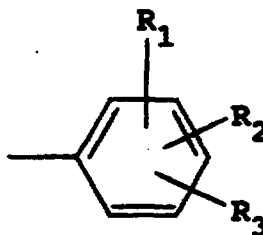
EP 0 120 321 A1, EP 0 208 999 A1 and EP 0 219 756 A1 disclose certain 3,3-diarylacrylic acid amides and various methods for the preparation of such compounds. These compounds exhibit fungicidal activity and are particularly suitable for the control of phytopathogenic fungi. EP 0 294 907 discloses a different method for the preparation of such compounds which involves the reaction of a benzophenone with an appropriate acetamide, preferably in the presence of a strong base such as potassium tert-butyrate, an alkali metal hydroxide or carbonate, or tert-butyl lithium. However, the latter method generally gives yields of less than 50%.

It has now been found that a surprising yield increase to levels in excess of 90% can be obtained if a sodium tertiary alcoholate is used as the base in the method of EP 0 294 907. According to the present invention there is therefore provided a process for the preparation of a 3,3-diarylacrylic acid amide of general formula I

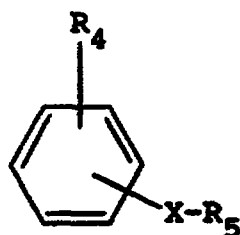


wherein

A represents



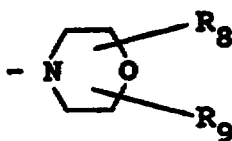
B represents



Q represents

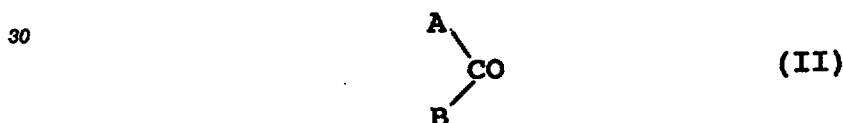


or



in which

- 10 R_1 is C_1-4 -alkyl, C_1-4 -alkoxy, NH_2 , NHC_1-4 -alkyl, $N(C_1-4$ -alkyl) $_2$, C_3-4 -alkenyl, C_3-4 -alkynyl, C_3-4 -alkenyloxy, C_3-4 -alkynyloxy, or C_3-6 -cycloalkyl;
 R_2 is C_1-4 -alkyl, C_1-4 -alkoxy or halogen;
 R_3 is hydrogen or halogen;
 R_4 is hydrogen, halogen, C_1-4 -alkyl or C_1-4 -alkoxy;
15 R_5 is hydrogen, a phenyl group optionally substituted by one or more substituents selected from C_1-4 -alkyl, C_1-4 -alkoxy and halogen moieties, a C_1-12 alkyl group optionally substituted by one or more halogen atoms, a C_3-7 -cycloalkyl, phenylphenyl, or phenoxyphenyl 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 is a single bond, $-O-$, $-S(O)_p-$, $-N=N-$, $-CHR_9O-$, $-OCHR_9-$, $CHR_9S(O)_p-$, $-S(O)_pCHR_9-$, $-(CH_2)_n-$,
20 $-HC=CH-$, or $-C\equiv C-$;
 R_6 is C_1-4 -alkyl, C_3-7 -cycloalkyl, benzyl, C_3-4 -alkenyl or C_3-4 -alkynyl;
 R_7 is C_1-4 alkyl;
 R_8 is hydrogen, C_1-4 -alkyl or C_1-4 -alkoxy;
 R_9 is hydrogen or C_1-4 -alkyl;
25 p is 0, 1 or 2; and
 n is an integer from 1 to 10
by reacting a benzophenone of formula II



35 in which A and B have the meanings given above, with an acetamide of formula III



40 in which Q has the meaning given above, in the presence of a base characterised in that the base employed is a sodium tertiary alcoholate which is present in excess, the acetamide of formula III is present in excess, an inert solvent is employed and the reaction temperature is in the range from 10° to $150^\circ C$.

The alcoholate may be derived from any tertiary alcohol but good results have been obtained with a compound of formula IV



wherein each R is independently an alkyl group of 1 to 4 carbon atoms. Preferably two of the groups R are methyl groups and the remaining R is a methyl, ethyl, propyl or butyl group. Excellent results in terms of yield of compounds of formula I have been obtained with alcoholates derived from amyl alcohol and butyl alcohol. The alcoholate may be prepared in situ or added as such and may be prepared by known methods
50 e.g. by the reaction of sodium hydride with the tertiary alcohol in the presence of an inert solvent such as toluene.

The process according to the invention is carried out in the presence of inert solvents such as toluene, benzene, diethyl ether, diglyme, tetrahydrofuran, N,N-dimethyl formamide. Also an excess of one reaction
55 component may serve as solvent. According to the reactivity of the components, the reaction may be carried out with cooling, at room temperature, or at elevated temperature up to the reflux temperature of the reaction mixture. Generally, the reaction takes place at a temperature in the range from 10° to $150^\circ C$.

A 1.5-2-fold excess of the sodium tertiary alcoholate is preferred. Excess acetamide can be recovered and fed into the reaction again.

The process according to the invention may be used to prepare all the compounds of general formula I but it is particularly useful for compounds of formula I wherein

in group A:

R₁ is C₁₋₄-alkoxy, C₁₋₄-alkyl, or amino

R₂ is C₁₋₄-alkoxy, C₁₋₄-alkyl or halogen

R₃ is hydrogen or halogen

in group B:

R₄ is hydrogen or halogen

R₅ is hydrogen, phenyl or halophenyl

X is a single bond or -O-

and Q represents a morpholine group wherein R₈ and R₉ are both hydrogen. The halogen or halo-substituent may be a fluorine, chlorine, bromine or iodine atom but is preferably a chlorine or bromine atom.

In the group A the substitution in the phenyl ring is preferably in the 3 and 4 positions or in the 3, 4 and 5 positions, particularly preferred examples of such substitution being 3,4-dimethoxy, 3-ethoxy-4-methoxy, 3-chloro-4-methoxy, 3-bromo-4-methoxy, 3-methyl-4-methoxy, 3-ethyl-4-methoxy, 3-propyl-4-methoxy, 3,4-dimethyl, 3-amino-4-methoxy, 3,5-dichloro-4-amino and 3-methoxy-4-methyl. Of these, 3,4-dimethoxy substitution of the phenyl ring is especially preferred.

The process according to the invention is further illustrated by the following Examples.

Example 1

3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid morpholide

4-Chloro-3',4'-dimethoxy benzophenone (6.92 g, 25 mmol), sodium tert.-amylate (5.50 g, 50 mmol), acetyl morpholine (23.90 g, 185 mmol), and anhydrous toluene (50 ml) were stirred under reflux for 8 hours. After cooling, the solution was washed twice with water, dried, and the toluene distilled off on a rotary evaporator. The viscous residue was stirred at 50°C with diisopropyl ether (40 ml), whereupon the substance solidified. After it had cooled to room temperature, the crude product was crushed, filtered by suction, washed with diisopropyl ether (2 x 5 ml) and dried.
Yield: 8.1 g = 83.5% of theoretical Tlc-pure product.

Example 2

3-[4-(4-Chlorophenoxy)phenyl]-3-(3,4-dimethoxyphenyl)acrylic acid morpholide

Sodium hydride (with 20% of paraffin oil; 2.25 g, 75 mmol) was stirred under reflux with absolute toluene (50 ml) and tert.-amyl alcohol (7.25 g, 82.5 mmol) was added dropwise within 30 minutes. When the solution had cooled to 100°C, 4-(4-chlorophenoxy)-3', 4'-dimethoxy benzophenone (9.22 g 25 mmol) and acetyl morpholine (16.17 g, 125 mmol) were added and the mixture was stirred under reflux for 8 hours.

After cooling to room temperature the solution was washed with water (2 x 100 ml), dried and applied onto a column packed with silica gel (50 g). The products were eluted with toluene (200 ml) and toluene-acetone mixtures (200 ml each; 90:10, 80:20, 70:30). The fractions containing the substance with an R_f-value of 0.47 (toluene-acetone 70:30) were combined and concentrated on a rotary evaporator. Crude yield: 11 g of viscous oil which contains toluene. This oil was stirred with diisopropyl ether (30 ml), whereupon the desired compound slowly crystallised.

Yield: 8.7 g = 72.5% of theoretical

mp.: 115 - 127°C

Isomer ratio E/Z: 45/55.

Example 3

3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid morpholide

Sodium hydride (with 20% of paraffin oil; 3.0 g, 100 mol) was stirred with absolute toluene (70 ml) and a solution of tert.-butanol (8.15 g, 110 mmol) in absolute toluene (30 ml) was added dropwise. After the solution had cleared, 4-chloro-3',4'-dimethoxy benzophenone (13.84 g, 50 mmol) and acetyl morpholine

(19.37 g, 150 mmol) were added and the reaction mixture was refluxed for 8 hours with stirring. When the solution had cooled to room temperature, it was washed twice with water, dried and concentrated on a rotary evaporator. Thereby 24.9 g of viscous oil were obtained which crystallised slowly upon stirring in diisopropyl ether (50 ml). Recrystallisation from isopropanol/diisopropyl ether.

Yield: 18.0 g = 92.8% of theoretical
mp. : 123 - 145 °C.

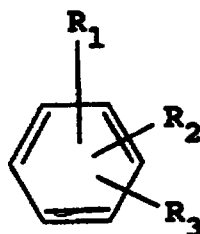
Claims

1. A process for the preparation of a 3,3-diaryl acrylic acid amide of general formula I

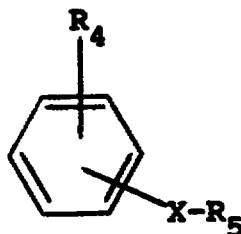


wherein

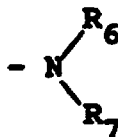
A represents



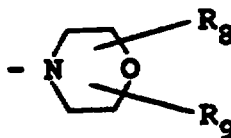
B represents



Q represents



or



in which

R₁ is C₁₋₄-alkyl, C₁₋₄-alkoxy, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, C₃₋₄-alkenyl, C₃₋₄-alkynyl,



(19.37 g, 150 mmol) were added and the reaction mixture was refluxed for 8 hours with stirring. When the solution had cooled to room temperature, it was washed twice with water, dried and concentrated on a rotary evaporator. Thereby 24.9 g of viscous oil were obtained which crystallised slowly upon stirring in diisopropyl ether (50 ml). Recrystallisation from isopropanol/diisopropyl ether.

Yield: 18.0 g = 92.8% of theoretical
mp. : 123 - 145 °C.

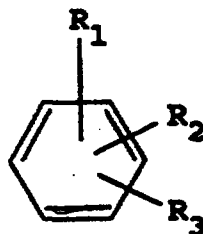
Claims

1. A process for the preparation of a 3,3-diaryl acrylic acid amide of general formula I

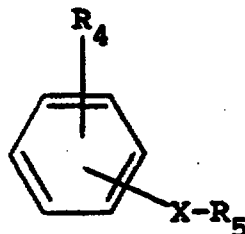


wherein

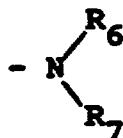
A represents



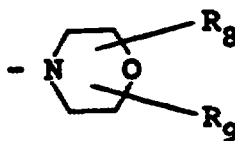
B represents



Q represents



or



in which

R₁ is C₁₋₄-alkyl, C₁₋₄-alkoxy, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, C₃₋₄-alkenyl, C₃₋₄-alkynyl,



C₃₋₄ alkenyloxy, C₃₋₄-alkynyloxy, or C₃₋₆-cycloalkyl;

R₂ is C₁₋₄-alkyl, C₁₋₄-alkoxy or halogen;

R₃ is hydrogen or halogen;

R₄ is hydrogen, halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R₅ is hydrogen, a phenyl group optionally substituted by one or more substituents selected from C₁₋₄-alkyl, C₁₋₄-alkoxy and halogen moieties, a C₁₋₁₂ alkyl group optionally substituted by one or more halogen atoms, a C₃₋₇-cycloalkyl, phenylphenyl, or phenoxyphenyl group, a C₂₋₆-alkenyl or C₂₋₆-alkynyl group each optionally-substituted by a phenyl group, or a naphthyl or C₅₋₈-cycloalkenyl group;

X is a single bond, -O-, -S(O)_p-, -N=N-, -CHR₃O-, -OCHR₃-, -CHR₃S(O)_p-, -S(O)_pCHR₃-(CH₂)_n-, -HC=CH-, or -C≡C-;

R₆ is C₁₋₄-alkyl, C₃₋₇-cycloalkyl, benzyl, C₃₋₄-alkenyl or C₃₋₄-alkynyl;

R₇ is C₁₋₄ alkyl;

R₈ is hydrogen, C₁₋₄-alkyl or C₁₋₄-alkoxy;

R₉ is hydrogen or C₁₋₄-alkyl;

p is 0, 1 or 2; and

n is an integer from 1 to 10

by reacting a benzophenone of formula II



in which A and B have the meanings given above, with an acetamide of formula III



in which Q has the meaning given above, in the presence of a base characterised in that the base employed is a sodium tertiary alcoholate which is present in excess, the acetamide of formula III is present in excess, an inert solvent is employed and the reaction temperature is in the range from 10° to 150° C.

2. A process according to claim 1 characterised in that the sodium tertiary alcoholate is derived from an alcohol of general formula IV

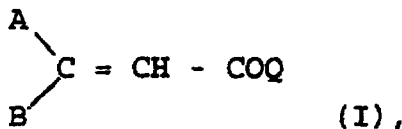


wherein each R is independently an alkyl group of 1 to 4 carbon atoms.

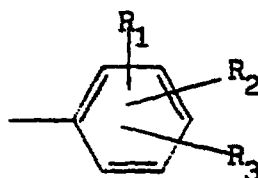
3. A process according to claim 1 or 2 characterised in that the sodium tertiary alcoholate is derived from amyl alcohol or butyl alcohol.

Patentansprüche

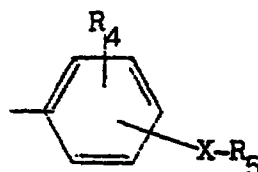
1. Verfahren zur Herstellung eines 3,3-Diarylacrylsäureamids mit der allgemeinen Formel I



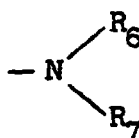
worin A für



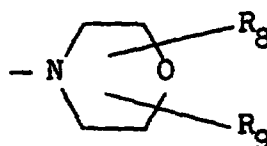
steht, B für



steht, Q für



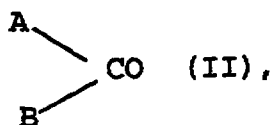
oder



steht, worin

- R_1 die Bedeutung C_1-4 Alkyl, C_1-4 Alkoxy, NH_2 , NHC_1-4 Alkyl, $N(C_1-4$ Alkyl) $_2$, C_3-4 Alkenyl, C_3-4 Alkynyl, C_3-4 Alkenyloxy, C_3-4 Alkinyloxy oder C_3-6 Cycloalkyl hat;
- R_2 für C_1-4 Alkyl, C_1-4 Alkoxy oder Halogen steht;
- R_3 Wasserstoff oder Halogen bedeutet;
- R_4 Wasserstoff, Halogen, C_1-4 Alkyl oder C_1-4 Alkoxy bedeutet;
- R_5 für Wasserstoff, eine gegebenenfalls durch einen oder mehrere, unter C_1-4 Alkyl-, C_1-4 Alkoxy- und Halogenresten ausgewählte Substituenten substituierte Phenylgruppe, eine gegebenenfalls durch ein oder mehrere Halogenatome substituierte C_1-12 Alkylgruppe, eine C_3-7 Cycloalkyl-, Phenylphenyl- oder Phenoxyphenylgruppe, eine C_2-6 Alkenylgruppe oder C_2-6 Alkynylgruppe, die jeweils gegebenenfalls durch eine Phenylgruppe substituiert sind, oder für eine Naphthylgruppe oder C_5-8 Cycloalkenylgruppe steht;
- X eine einfache Bindung, $-O-$, $-S(O)_p-$, $-N=N-$, $-CHR_9O-$, $-OCHR_9-$, $-CHR_9S(O)_p-$, $-S(O)_pCHR_9-$, $-(CH_2)_n-$, $-HC=CH-$ oder $-C\equiv C-$ bedeutet;
- R_6 für C_1-4 Alkyl, C_3-7 Cycloalkyl, Benzyl, C_3-4 Alkenyl oder C_3-4 Alkynyl steht;
- R_7 für C_1-4 Alkyl steht;
- R_8 Wasserstoff, C_1-4 Alkyl oder C_1-4 Alkoxy bedeutet;
- R_9 Wasserstoff oder C_1-4 Alkyl darstellt;
- p den Wert 0, 1 oder 2 hat; und
- n eine ganze Zahl von 1 bis 10 darstellt,

durch Umsetzen eines Benzophenons der Formel II



worin A und B die oben angegebenen Bedeutungen aufweisen, mit einem Acetamid der Formel III



worin Q die oben angeführte Bedeutung aufweist, in Gegenwart einer Base, dadurch gekennzeichnet, daß die verwendete Base ein Natrium-tert.alkoholat ist, das im Überschuß vorliegt, das Acetamid der Formel III im Überschuß zugegen ist, ein inertes Lösungsmittel verwendet wird und die Reaktionstemperatur im Bereich von 10 °C bis 50 °C liegt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Natrium-tert.alkoholat von einem Alkohol mit der allgemeinen Formel IV



abgeleitet ist, worin jeder Rest R unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Natrium-tert.alkoholat von Amylalkohol oder Butylalkohol abgeleitet ist.

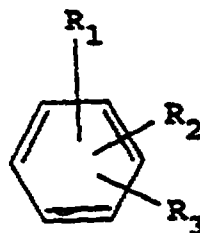
Revendications

1. Un procédé pour la préparation d'un amide d'acide 3,3-diarylacrylique de formule générale I

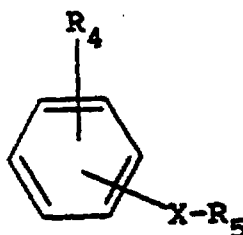


où

A représente

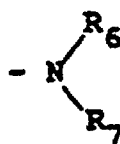


B représente

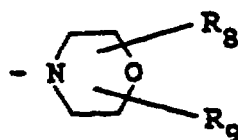




Q représente



ou



où

R_1 est un groupe C_{1-4} alcoyle, C_{1-4} alcoxy, NH_2 , NHC_{1-4} alcoyle, $\text{N}(\text{C}_{1-4}$ alcoyle) $_2$, C_{3-4} alcényle, C_{3-4} alcynyle, C_{3-4} alcényloxy, C_{3-4} alcynyloxy ou C_{3-6} cycloalcoyle ;

R_2 est un groupe C_{1-4} alcoyle, C_{1-4} alcoxy ou un halogène ;

R_3 est l'hydrogène ou un halogène ;

R_4 est l'hydrogène, un halogène ou un groupe C_{1-4} alcoyle ou C_{1-4} alcoxy ;

R_5 est l'hydrogène, un groupe phényle éventuellement substitué par un ou plusieurs substituants choisis parmi des portions C_{1-4} alcoyle, C_{1-4} alcoxy et halogène, un groupe C_{1-12} alcoyle éventuellement substitué par un ou plusieurs atomes d'halogènes, un groupe C_{3-7} cycloalcoyle, phénylphényle ou phénoxyphényle, 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 est une liaison simple, $-\text{O}-$, $-\text{S}(\text{O})_p-$, $-\text{N}=\text{N}-$, $-\text{CHR}_9\text{O}-$, $-\text{CCHR}_9-$, $-\text{CHR}_9\text{S}(\text{O})_p-$, $-\text{S}(\text{O})_p\text{CHR}_9-$, $-(\text{CH}_2)_n-$, $-\text{HC}=\text{CH}-$ ou $-\text{C}\equiv\text{C}-$;

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

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

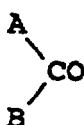
R_8 est l'hydrogène ou un groupe C_{1-4} alcoyle ou C_{1-4} alcoxy ;

R_9 est l'hydrogène ou un groupe C_{1-4} alcoyle ;

p est 0, 1 ou 2 ; et

n est un nombre entier de 1 à 10

par réaction d'une benzophénone de formule II



(II)

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

CH_3COQ (III)

où Q a la signification indiquée ci-dessus, en présence d'une base, caractérisé en ce que la base utilisée est un alcoolate tertiaire de sodium qui est présent en excès, l'acétamide de formule III est présent en excès, on utilise un solvant inerte et la température de réaction est comprise entre 10° et 150°C .

2. Un procédé selon la revendication 1, caractérisé en ce que l'alcoolate tertiaire de sodium est dérivé d'un alcool de formule générale IV

$(\text{R})_3\text{C}-\text{OH}$ (IV)



où chaque R est indépendamment un groupe alcoyle de 1 à 4 atomes de carbone.

3. Un procédé selon la revendication 1 ou 2, caractérisé en ce que l'alcoolate tertiaire de sodium est dérivé de l'alcool amylique ou de l'alcool butylique.

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