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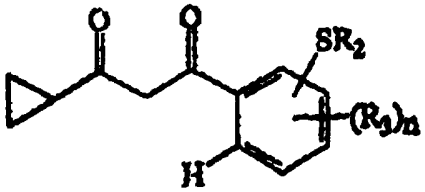
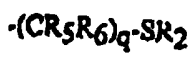


(I)



(II)

(57) Abstract

The invention relates to a process for preparing compounds of formula (I), wherein R_2 is lower alkyl; or phenyl optionally substituted by from one to five groups which may be the same or different selected from lower alkyl, lower haloalkyl, halogen and $-SR_4$; R_3 is halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, -S-alkyl, cycloalkyl having from 3 to 7 carbon atoms in the ring, alkenyl or alkynyl having from 3 to 7 carbon atoms, or $-(CR_5R_6)_q-SR_2$ wherein q is one or two; R_4 is lower alkyl; R_5 and R_6 independently represent hydrogen, lower alkyl or lower haloalkyl; and n is zero or an integer from one to three; to intermediate compounds used in preparing compounds of formula (II), and processes for preparing such compounds.

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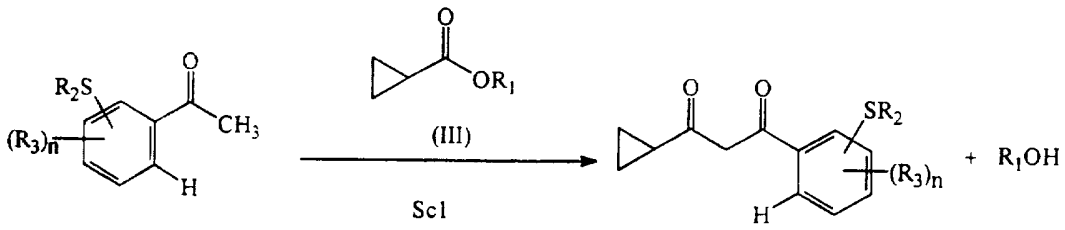
PROCESS FOR PREPARING DIKETONE COMPOUNDS

This invention relates to a process for preparing ketone compounds and the products obtained by this process. More particularly the invention relates to the preparation of intermediate compounds in the manufacture of pesticides.

Pesticidal 4-benzoylisoxazoles, particularly 5-cyclopropylisoxazole herbicides and intermediate compounds in their synthesis, are described in the literature, for example in European Patent Publication Nos. 0418175, 0487353, 0527036, 0560482, 0609798 and 0682659.

Various methods for preparing these compounds are known. It is an object of the present invention to provide improved methods for the preparation of these compounds and the intermediate compounds thereto.

According to one aspect of the invention there is provided a process for the preparation of a compound of formula (I) by the reaction of a compound of formula (II) with a compound of formula (III), according to the reaction scheme Sc1 indicated below:-



(II) (I)

wherein

R_1 is lower alkyl;

R_2 is lower alkyl; or phenyl optionally substituted by from one to five groups which may be the same or different selected from lower alkyl, lower haloalkyl, halogen and $-SR_4$;

R_3 is halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, -S-alkyl, cycloalkyl having from 3 to 7 ring carbon atoms, alkenyl or alkynyl having from 3 to 7 carbon atoms, or $-(CR_5R_6)_q-SR_2$ wherein q is one or two;

n is zero or an integer from one to three;

R_4 is lower alkyl;

and R_5 and R_6 independently represent hydrogen, lower alkyl or lower haloalkyl.

The compounds of formula (I) and a number of processes for their preparation have been described in the European Patent Applications cited above.

By the term "lower" is meant radicals comprising at least one hydrocarbon chain, it being understood that such radicals contain from one to six carbon atoms linked together in a straight- or branched-carbon chain.

Preferably R_1 and R_2 are lower alkyl (most preferably methyl).

Preferably the group $-SR_2$ occupies the 2-, 3- or 4- position of the phenyl ring (most preferably the 2-position).

Preferably n is one or two.

The reaction generally proceeds in better yield when a group R_3 is not halogen in the 2-position of the phenyl ring.

Preferably R_3 is halogen or trifluoromethyl. More preferably $(R_3)_n$ is 4-CF_3 or 3,4-dichloro.

The compounds of formula (III) above are known in the literature and their preparation has been expressly described in the prior art known to the skilled worker. Some references particularly pertinent to the preparation of this reagent may be found by the skilled worker in various sources of chemical literature, including Chemical Abstracts and information databases available to the public.

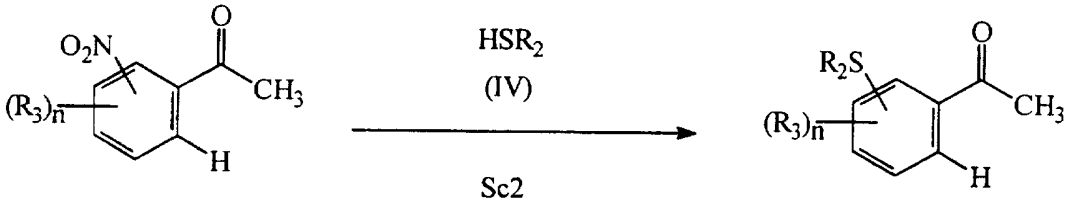
The preparation of compounds of formula (I) using compounds of formula (II) and (III) according to scheme Sc1 above may be preferably affected in a polar or apolar aprotic solvent. Examples of polar aprotic solvents include dimethyl sulphoxide, dimethyl formamide, N,N-dimethylacetamide, N-methyl pyrrolidone, a compound of formula (III); an ether compound, particularly dioxane and tetrahydrofuran; or an aromatic or aliphatic halogenated hydrocarbon, particularly chlorobenzenes. Examples of apolar aprotic solvents include aromatic or aliphatic hydrocarbons, particularly toluene and xylenes.

Generally the reaction temperature used in Sc1 above is from 0°C to the boiling point of the solvent, preferably between 0°C and 100°C. Generally the reaction takes place in the presence of a strong base which is most preferably selected from an alkoxide of an alkali or alkaline earth metal, notably sodium ethoxide, sodium methoxide, sodium or

potassium t-butoxide; and a metal hydride (notably sodium hydride).

According to a preferred variant of the process of the present invention the reaction is performed with continuous distillation of the alcohol R_1-OH formed in the course of the reaction, at atmospheric pressure or under reduced pressure (preferably from 1 to 20% below atmospheric pressure). Optionally the alcohol R_1-OH formed may be removed by the use of a suitable molecular sieve for example 4 Angstrom molecular sieve.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (II) by the reaction of a compound of formula (V) with a mercaptan of formula (IV), optionally present in the form of the thiolate, according to reaction scheme Sc2 indicated below:-



(V) (II)

wherein R_2, R_3 and n in formulae (II) and (V) have the same meanings as given before in reaction scheme Sc1. The group -NO_2 is generally present in the 2- or 4- position, preferably the 2-position of the phenyl ring.

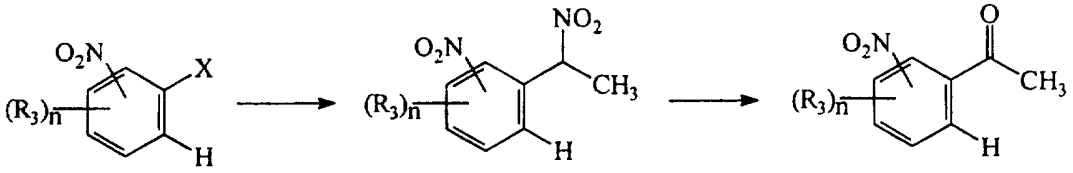
Compounds of formula HSR_2 are known in the literature and their preparations are expressly described in the prior art known to the skilled worker. The references particularly pertinent to the preparation of this reagent may be found by the skilled worker in various sources of classical chemistry including Chemical Abstracts and information databases available to the public. The salts or thiolates derived from the compound of formula (IV) may be prepared by means known to the skilled worker. These thiolates are preferably alkaline salts, particularly sodium or potassium thiolate.

The preparation of compounds of formula (II) according to scheme Sc2 from the acetophenone of formula (V) and a compound of formula (IV) is preferably performed in a solvent of the compound of formula (IV) which may be inert to the reaction conditions. Examples of other suitable solvents include sulphoxides such as dimethyl sulphoxide;

amides such as dimethyl formamide, N,N-dimethylacetamide and N-methyl pyrrolidone; ketones such as acetone and methyl isobutyl ketone; ether solvents, particularly dioxane and tetrahydrofuran; aromatic, aliphatic and cycloaliphatic hydrocarbons and halogenated or non-halogenated hydrocarbons, particularly chlorobenzene, dichloromethane and toluene. The presence of a small quantity of water is also acceptable in allowing the solubilization of the thiolate.

When the reaction according to scheme Sc2 takes place using a compound of formula (IV) in the form of the mercaptan and not in the form of a thiolate salt, the reaction is preferably affected in the presence of a base such as a hydroxide of an alkali metal or alkali earth metal (preferably sodium or potassium), or a carbonate or hydride (such as sodium hydride). The reaction may also be performed using various forms of catalyst, particularly phase transfer catalysts such as a quaternary ammonium salt, for example tetrabutylammonium bromide.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula (V) by the reaction of a compound of formula (VII) or (VI) as well as a process for the preparation of a compound of formula (VI) from a compound of formula (VII), according to the reaction scheme Sc3 indicated below:-



(VII) (VI) (V)

Sc3

wherein R_3 and n have the same meanings as in reaction schemes Sc2 and Sc1, and X represents halogen, preferably chlorine or fluorine. Preferably the group $-NO_2$ in formula (VII) is in the 2- or 4- position, most preferably in the 2- position of the phenyl ring.

These two reactions comprise together the reaction scheme Sc3 above and are generally distinct but preferably they may occur in succession. That is, the compounds of formula (V) may be prepared from the compounds of formula (VII) via an intermediate of formula (VI) which may be isolated or used in situ in the course of the reaction.

The reaction conditions for the preparation of the compound of

formula (V) from the compound of formula (VI) is known in the art and described in the literature, notably by J.G. Reid and J.M. Reny Runge in Tetrahedron Letters, Vol.31 (1990) pp 1093-1096; G.A. Olah et al, Synthesis (1980) pp 662-663; N. Kornblum et al, J.Org.Chem., Vol.47 (1982) pp 4534-38; S.Chandrasekaran et al, Synthetic Communications, Vol.17 (1987) pp 195-201.

The invention is thus also concerned with the preparation of compounds of formula (VI) from compounds of formula (VII) by the reaction of nitroethane in the presence of a base in a solvent which is selected from a compound of formula (VII), nitroethane, a solvent inert to the reaction conditions, and the base being selected from an hydroxide, a carbonate, a hydride, an alkoxide of an alkaline metal or an alkaline earth metal, and guanidine. An advantage of this aspect of the present invention is that relatively simple bases may be used in the reaction scheme Sc3.

Solvents suitable for use include nitroethane itself (used in excess compared to the quantity normally used as a reactant); aromatic or aliphatic halogenated or non-halogenated hydrocarbons, particularly chlorobenzene; aromatic or aliphatic hydrocarbons, particularly toluene and xylenes; polar aprotic solvents such as dimethyl sulphoxide, dimethyl formamide, N,N-dimethylacetamide, N-methyl pyrrolidone; acetonitrile; ether solvents, particularly dioxane and tetrahydrofuran. The presence of a small quantity of water is also acceptable in allowing the solubilization of the reaction mixture, while not reacting with the reactants themselves.

The reaction temperature is generally from 0°C to 50°C. The reaction may also be carried out in an aqueous or non-aqueous medium. Among the bases suitable for the use in this process one may cite hydroxides or carbonates of alkali metals or alkaline earth metals preferably sodium or potassium, sodium carbonate, potassium carbonate or caesium carbonate; or tetramethylguanidine. These bases may be used alone or in mixture with others. The reaction may also be conveniently performed using various types of catalyst, particularly phase transfer catalysts such as a quarternary ammonium salt, for example tetrabutylammonium bromide.

Certain intermediate compounds of formula (II) are novel and as

such constitute a further feature of the present invention, in particular 2-methylthio-4-trifluoromethylacetophenone and 3,4-dichloro-2-(methylthio)acetophenone.

The following non-limiting examples illustrate the invention.

Example 1

Preparation of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (reaction scheme Sc1).

In a reaction vessel under an inert atmosphere one adds 1.15g of sodium methoxide and 22 ml of toluene. This is heated to 80°C at a pressure of 400 mbars. A mixture of 3.3 ml of methyl cyclopropylcarboxylate and 3.8 g of 2-methylthio-4-trifluoromethylacetophenone in 6 ml of anhydrous toluene is added over 3 hours with constant distillation of methanol formed. The reaction is stirred for one hour at 80°C. The reaction is then cooled and the diketone precipitated in a mixture of 80 ml of ice water containing 0.75 ml of concentrated sulphuric acid. The organic phase is retained, washed with water and the toluene removed under reduced pressure to give 3.67 g of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione in the form of an orange powder, m.p. 64°C. Yield = 75%.

By proceeding in a similar manner way heating at a temperature of 70°C and a pressure of 230mbars) 3-(4-chloro-2-methylthiophenyl)-1-cyclopropylpropan-1,3-dione was prepared in 98% yield (purity greater than 80%). This compound was also similarly prepared wherein the reaction took place at a temperature of 70° for 6.5 hours and in the presence of 4 Angstrom molecular sieves in place of constant distillation of the methanol formed.

Example 2

Preparation of 1-cyclopropyl-3-[3,4-dichloro-2-(methylthio)phenyl]propane-1,3-dione (reaction scheme Sc1).

Sodium hydride (0.178 g, 60% oil dispersion, 0.0045 M) is suspended in tetrahydrofuran(1.8 ml), stirred and heated at reflux while a solution of a mixture of methyl cyclopropanecarboxylate (0.42 g, 0.0042M) and 3,4-dichloro-2-(methylthio)acetophenone (0.5 g, 0.0021M) in tetrahydrofuran (3 ml) is added. The mixture is stirred and heated at reflux for 3.5 hours then cooled and poured onto saturated aqueous sodium bicarbonate. The mixture is then extracted with ether, washed with brine, dried over magnesium sulphate, filtered and evaporated to give a gum which is purified by dry column flash chromatography eluted with ethyl acetate in cyclohexane to give 3-cyclopropyl-1-[3,4-dichloro-2-(methylthio)phenyl]propane-1,3-dione (0.35 g, 55%) as a yellow oil.

Example 3

Preparation of 2-methylthio-4-trifluoromethylacetophenone (reaction scheme Sc2).

To 0.15 g of 2-nitro-4-trifluoromethylacetophenone diluted in 0.5 ml of acetone is added 0.256 g of an aqueous solution of 21% wt/wt sodium thiomethoxide and the mixture is stirred for five hours at 20°C. The aqueous phase is separated then removed, 2 ml of water are added and the acetone removed under reduced pressure. The mixture is then treated with dichloromethane and the aqueous phase removed. The organic phase is washed with fresh water then the solvent is evaporated under reduce pressure to obtain 0.085 g of 2-methylthio-4-trifluoromethylacetophenone with a melting point of 71°C.

By proceeding in a similar manner 3,4-dichloro-2-(methylthio)acetophenone may be prepared, ^{1}H NMR ($CDCl_3$) 2.4(s,3H), 2.6(s,3H), 7.15(d,1H), 7.5 (d,1H).

Example 4

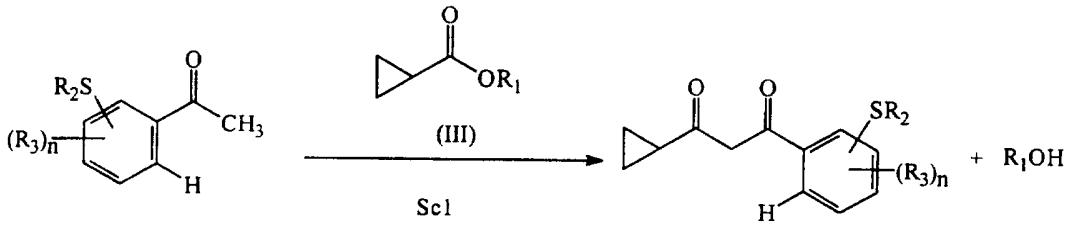
Preparation of 1-(2-nitro-4-trifluoromethylphenyl)-1-

nitroethane (Reaction Scheme Sc3).

0.87g of sodium carbonate in 5 ml of anhydrous toluene are placed in a 30 ml reaction vessel, and 0.11 g of benzyltriethylammonium chloride and 1.13 g of 4-chloro-3-nitro-benzotrifluoride and 0.38g of nitroethane are added at the same time. The mixture is stirred for 16 hours at 20°C, 10 ml of water is added and the aqueous phase is separated then acidified by a 4N solution of sulphuric acid. It is then extracted with 5 ml of methyl t-butyl ether. After removing the organic solvent 0.18 g of a mixture is obtained which is separated by column chromatography using reverse phase silica eluting with a mixture of water and acetonitrile to obtain 0.12 g of the title compound, m.p. 48°C.

CLAIMS

1. A process for the preparation of a compound of formula (I) by the reaction of a compound of formula (II) with a compound of formula (III), according to the reaction scheme indicated below:-



(II) (I)

wherein

R_1 is lower alkyl;

R_2 is lower alkyl; or phenyl optionally substituted by from one to five groups which may be the same or different selected from lower alkyl, lower haloalkyl, halogen and $-SR_4$;

R_3 is halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower haloalkoxy, -S-alkyl, cycloalkyl having from 3 to 7 carbon atoms in the ring, alkenyl or alkynyl having from 3 to 7 carbon atoms, or $-(CR_5R_6)_q-SR_2$ wherein q is one or two;

R_4 is lower alkyl;

R_5 and R_6 independently represent hydrogen, lower alkyl or lower haloalkyl;

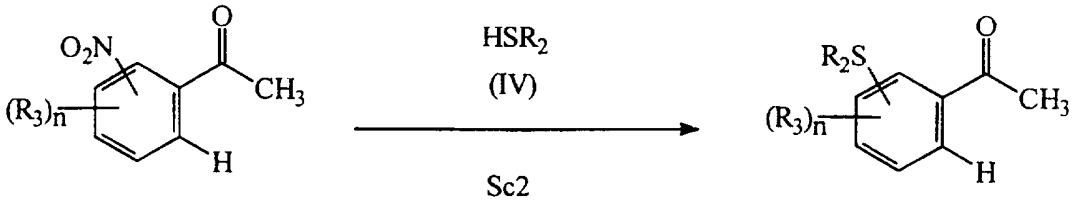
and n is zero or an integer from one to three.

2. A process according to claim 1 in which the reaction is performed in an aprotic solvent and at a temperature of from 0°C to the boiling point of the solvent, preferably between 0°C and 100°C.

3. A process according to claim 1 or 2 in the presence of a strong base, preferably an alkoxide of an alkali or alkaline earth metal or a metal hydride.

4. A process according to claim 1, 2 or 3, wherein invention the reaction is performed with continuous distillation of the alcohol R_1-OH formed in the course of the reaction, at atmospheric pressure or under reduced pressure (preferably from 1 to 20% below atmospheric pressure).

5. A process for preparing a compound of formula (II) as defined in claim 1 which comprises the reaction of a compound of formula (V) with a mercaptan HSR_2 of formula (IV) according to reaction scheme Sc2 indicated below:-



(V) (II)

wherein the radicals R_2, R_3 and n in formulae (II) and (V) are as defined in claim 1.

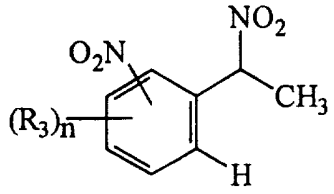
6. A process according to claim 5 using a compound of formula (IV) as solvent.

7. A process according to claim 6 wherein the compound of formula (IV) is in the form of a mercaptan, and the reaction is performed in the presence of a base.

8. A process according to claim 7 wherein the base is a hydroxide of an alkali metal or alkali earth metal, or a carbonate or hydride.

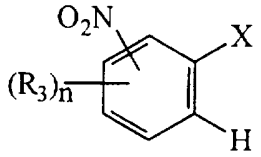
9. The process according to any one of claims 5 to 8 using a catalyst, particularly phase transfer catalysts such as the salts of quarternary ammonium.

10. A process for the preparation of a compound of formula (VI):



(VI)

wherein R_3 and n are as defined in claim 1, which comprises the reaction of a compound of formula (VII):



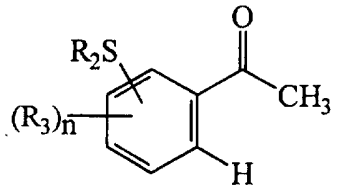
(VII)

in which R_3 and n are as defined above and X is halogen, with nitroethane, wherein the reaction is performed in the presence of a base selected from a hydroxide, a carbonate, a hydride, an alkoxide of an alkali or alkaline earth metal, and guanidine; and using a solvent selected from nitroethane and an inert solvent.

11. A process according to claim 10 wherein the reaction temperature is from 0°C to 50°C.

12. A process according to claim 10 or 11, wherein the reaction is performed in the presence of a phase transfer catalyst, preferably a salt of quarternary ammonium.

13. A compound of the formula (II):



(II)

wherein R_2, R_3 and n are as defined in claim 1.

14. The compound according to claim 13 which is 2-methylthio-4-trifluoromethylacetophenone or 3,4-dichloro-2-(methylthio)acetophenone.