

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199888635 B2
(10) Patent No. 748503

(54) Title
Process for the preparation of 1-aryl-3-cyclopropyl-1,3-propanediones

(51)⁶ International Patent Classification(s)
C07C 045/45 C07C 323/22
C07C 319/20

(21) Application No: 199888635 (22) Application Date: 1998 .07 .03

(87) WIPO No: W099/02476

(30) Priority Data

(31) Number	(32) Date	(33) Country
9714305	1997 .07 .07	GB

(43) Publication Date : 1999 .02 .08

(43) Publication Journal Date : 1999 .03 .25

(44) Accepted Journal Date : 2002 .06 .06

(71) Applicant(s)
Rhone Poulenc Agro

(72) Inventor(s)
Didier Bernard; Michel Casado; Virginie Pevere; Alain Truchon

(74) Agent/Attorney
DAVIES COLLISON CAVE,1 Little Collins Street,MELBOURNE VIC 3000

(56) Related Art
EP 560482
EP 527037
EP 609798

OPI DATE 08/02/99 APPLN. ID 88635/98
AOJP DATE 25/03/99 PCT NUMBER PCT/EP98/04947



AU9888635

IN

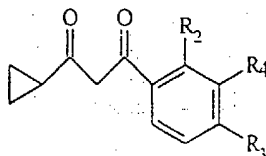
<p>(51) International Patent Classification⁶ : C07C 45/45, 319/20, 323/22</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/02476 (43) International Publication Date: 21 January 1999 (21.01.99)</p>
<p>(21) International Application Number: PCT/EP98/04947 (22) International Filing Date: 3 July 1998 (03.07.98) (30) Priority Data: 9714305.1 7 July 1997 (07.07.97) GB (71) Applicant (for all designated States except US): RHONE POULENC AGRO [FR/FR]; 14-20, rue Pierre Baizet, F-69009 Lyon (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): BERNARD, Didier [FR/FR]; 14, rue Roger Salengro, F-69009 Lyon (FR). CASADO, Michel [FR/FR]; Les Magnolias N° 14, Route de Corbas, F-69360 Saint Symphorien d'Ozon (FR). PEVERE, Virginie [FR/FR]; 37, rue Bataille, F-69008 Lyon (FR). TRUCHON, Alain [FR/FR]; 27 ter, avenue des Bruyères, F-69580 Sathonay Camp (FR). (74) Agent: BRACHOTTE, Charles, Yves; Rhône-Poulenc Agro, Boîte postale 9163, F-69263 Lyon Cedex 09 (FR).</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: PROCESS FOR THE PREPARATION OF 1-ARYL-3-CYCLOPROPYL-1,3-PROPANEDIONES</p>		
<p>(I) <chem>CC1(C)CC(=O)CC(=O)C2=CC=C(C=C2)R2R3R4</chem> (II) <chem>CC1(C)CC(=O)CC(=O)C2=CC=C(C=C2)C(=O)R1R2R3R4</chem> (III) <chem>CC1(C)CC(=O)C</chem></p>		
<p>(57) Abstract</p> <p>This invention relates to a process for the preparation of compounds of formula (I) wherein: R₂ is C₁₋₆ straight- or branched-chain alkylthio, C₁₋₆alkyl, C₁₋₆haloalkyl, CH₂SR₅, C₁₋₆alkoxy, C₁₋₆haloalkoxy, or halogen; or an N-linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-triazole ring which ring systems are optionally substituted by one or more groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or C₁₋₆ straight- or branched-chain alkylthio; R₃ is C₁₋₆ straight- or branched-chain haloalkyl, C₁₋₆ straight- or branched-chain alkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, halogen, C₁₋₆ straight- or branched-chain alkylthio or nitro; or an N-linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-triazole ring which ring systems are optionally substituted by one or more groups selected from halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or C₁₋₆ straight- or branched-chain alkylthio; R₄ is hydrogen, C₁₋₆ straight- or branched-chain haloalkyl, C₁₋₆ straight- or branched-chain alkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, halogen, C₁₋₆ straight- or branched-chain alkylthio; or a 5- or 6-membered heterocyclic ring (which may be unsaturated or partially saturated) containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulphur, optional substituted by halogen, C₁₋₆haloalkyl, C₁₋₆alkyl, C₁₋₆haloalkoxy, C₁₋₆alkoxy, SO_nR₅, nitro or cyano; or R₃ and R₄ together with the carbon atoms to which they are attached, form a 5- to 7-membered saturated or unsaturated heterocyclic ring containing up to three ring heteroatoms selected from nitrogen, oxygen and sulfur, which ring is optionally substituted by one or more groups selected from halogen, nitro, C₁₋₆ straight- or branched-chain alkylthio, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, =O and =NO-R₅; and R₅ represents C₁₋₆ straight- or branched-chain alkyl; and n represents zero, one or two; which process comprises the reaction of a compound of formula (II); wherein R₁ is C₁₋₆ straight- or branched-chain alkyl, R₂, R₃ and R₄ are as hereinbefore defined, with a compound of formula (III); in an aprotic solvent in the presence of a base.</p>		

PROCESS FOR THE PREPARATION OF 1-ARYL-3-CYCLOPROPYL-1,3-PROPANEDIONES

This invention relates to a process for preparing 1,3-diketone
5 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-
10 cyclopropylisoxazole herbicides and intermediate compounds in their
synthesis, are described in the literature. for example in European Patent
Publication Nos. 0418175, 0527036, 0560482, 0609798, 0682659 and 0527037.
Various methods for preparing these compounds are known. The
present invention seeks to provide an improved method for the
preparation of intermediate compounds in their synthesis.

15 The present invention provides a process for the preparation of a
compound of formula (I):



(I)

wherein:

20 R₂ is C₁₋₆ straight- or branched- chain alkylthio, C₁₋₆ alkyl, C₁₋₆
haloalkyl, CH₂SR₅, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or halogen; or a N-
linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-
triazole ring which ring systems are optionally substituted by one or
more groups selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆
25 straight- or branched- chain alkylthio;

R₃ is C₁₋₆ straight- or branched- chain haloalkyl, C₁₋₆ straight- or
branched- chain alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, halogen, C₁₋₆



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straight- or branched- chain alkylthio or nitro ; or a N-linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-triazole ring which ring systems are optionally substituted by one or more groups selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ straight- or branched- chain alkylthio;

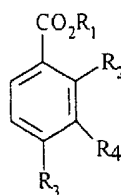
R₄ is hydrogen, C₁₋₆ straight- or branched- chain haloalkyl, C₁₋₆ straight- or branched- chain alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, halogen, C₁₋₆ straight- or branched- chain alkylthio; or a 5 or 6-membered heterocyclic ring (which may be unsaturated or partially saturated) containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulphur, optionally substituted by halogen, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkoxy, SO_nR₅, nitro or cyano;

or R₃ and R₄ together with the carbon atoms to which they are attached, form a 5 to 7 membered saturated or unsaturated heterocyclic ring containing up to three ring heteroatoms selected from nitrogen, oxygen and sulfur, which ring is optionally substituted by one or more groups selected from halogen, nitro, C₁₋₆ straight- or branched- chain alkylthio, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, =O and =NO-R⁵;

R₅ represents C₁₋₆ straight- or branched- chain alkyl; and

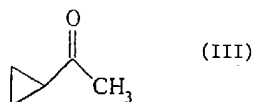
n represents zero, one or two;

which process comprises the reaction of a compound of formula (II):



(II)

wherein R₁ is C₁₋₆ straight- or branched- chain alkyl, and R₂, R₃ and R₄ are as hereinbefore defined, with a compound of formula (III):



in an aprotic solvent in the presence of a base, wherein said process
5 is performed with distillation of the alcohol R₁-OH formed, or with removal of the alcohol R₁-OH using a molecular sieve.

When R₄ represents a heterocyclic ring, preferred rings include
3-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 5-oxazolyl, 2-furyl, 3-furyl, 2-thienyl and 3-thienyl.

10 R₁ preferably represents methyl.

R₂ preferably represents methylthio or methylthiomethyl.

R₃ preferably represents trifluoromethyl or bromo.

R₄ preferably represents hydrogen.

In an especially preferred embodiment of the invention R₁
15 represents C₁₋₆ alkyl (methyl is most preferred);

R₂ represents methylthiomethyl;

R₃ represents bromo; and R₄ represents hydrogen.

In a most especially preferred embodiment of the invention R₁
represents C₁₋₆ alkyl (methyl is most preferred);

20 R₂ represents C₁₋₆ alkylthio (methylthio is most preferred);

R₃ represents C₁₋₆ haloalkyl (trifluoromethyl is most preferred);

and R₄ represents hydrogen.

Using these reaction conditions it has been found that the reaction
25 gives high yields of the desired final product.

Certain compounds of formula (I) and a number of processes for
their preparation have been described in the European Patent



Applications cited above. Compounds (II) are known or may be prepared by known methods. Compound (III) and methods for its preparation are known.

The aprotic solvents which may be used may be nonpolar or polar. Nonpolar aprotic solvents which are suitable include aromatic or aliphatic hydrocarbons, particularly toluene and xylenes (toluene is preferred); aromatic halogenated hydrocarbons (chlorobenzene is preferred) or ethers such as tert-butyl methyl ether, dioxan or tetrahydrofuran. Examples of suitable polar aprotic solvents include dimethylsulphoxide, N-methylpyrrolidinone, N,N-dimethylformamide or N,N-dimethylacetamide (dimethylsulphoxide and N-methylpyrrolidinone are preferred). Chlorobenzene and toluene are especially preferred because of the good results obtained, and cost and suitability of such solvents for large scale preparations.

Generally the reaction temperature used in the above process is from 0°C to the boiling point of the solvent, preferably from 0°C to 100°C; for non-polar solvents such as toluene or chlorobenzene a temperature of from 40°C to 90°C is especially preferred; whilst for polar aprotic solvents such as dimethylsulphoxide and N-methylpyrrolidinone chlorobenzene a temperature of from 20°C to 40°C is especially preferred.

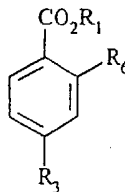
Generally the reaction takes place in the presence of a strong base which is most preferably selected from an alkoxide of an alkali or alkaline earth metal, notably sodium ethoxide, sodium methoxide, sodium or potassium t-butoxide; and a metal hydride (notably sodium hydride). Sodium methoxide is an especially preferred base for reasons of effectiveness in the reaction.

According to a preferred variant of the process of the present invention the reaction is performed with continuous distillation of the alcohol R₁-OH formed in the course of the reaction, at atmospheric pressure or under reduced pressure (preferably from 150 to 250 mbars).



Alternatively the alcohol R_1 -OH formed may be removed by the use of a suitable molecular sieve, for example a 4 Angstrom molecular sieve.

Compounds of formula (II) wherein R_2 represents C_{1-6} alkylthio; R_3 represents C_{1-6} haloalkyl and R_4 represents hydrogen may be prepared by the reaction of a compound of formula (IV):



(IV)

wherein R_1 and R_3 are as defined above and R_6 represents a halogen atom selected from fluorine, chlorine and bromine (preferably fluorine or chlorine), with an alkylthiol (or metal salt thereof) of formula R_2 -X wherein R_2 is as defined above (preferably methylthio) and X represents hydrogen or an alkali metal (preferably sodium, potassium or lithium).

Preferably the above reaction to prepare intermediates of formula (II) is performed under substantially anhydrous conditions using a polar aprotic solvent preferably N-methylpyrrolidinone, acetonitrile or dimethylsulphoxide, at a temperature of from $-20^\circ C$ to $150^\circ C$, preferably 0° to $50^\circ C$.

The following non-limiting examples illustrate the invention.

Example 1

Preparation of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (small scale).



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Sodium methoxide (3.51g, 0.065M) was added to a mixture of methyl 2-methylthio-4-trifluoromethylbenzoate (12.5g, 0.050M) and cyclopropyl methyl ketone (7ml, 0.070M) in toluene. The mixture was heated at 55-57°C for 1 hour. Methanol was distilled under reduced pressure. After cooling to 20°C the mixture was acidified and the organic phase washed (sodium bicarbonate solution and with water) and evaporated to give 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione as yellow crystals (14.03g), m.p. 64°C. A yield of 92.9% was obtained. The purity of the product was 95%.

Example 2

Preparation of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (large scale).

Sodium methoxide (64g, 1.15M) was added to a mixture of methyl 2-methylthio-4-trifluoromethylbenzoate (200g, 0.8M) in chlorobenzene (380g). The mixture was heated to 75°C and cyclopropyl methyl ketone (75g, 0.88M) added during 2 hours whilst maintaining stirring at 75°C. After 4 hours methanol was distilled under reduced pressure. the mixture cooled to 50°C, and water followed by sulphuric acid (53g of 36N) added. The organic phase was distilled under reduced pressure to give 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione as yellow crystals (240g), m.p. 58-60°C. A yield of 88% was obtained. The purity of the product was 90%.

Example 3

Preparation of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (small scale).

Sodium methoxide (0.54g, 0.01M) was added to a mixture of methyl 2-methylthio-4-trifluoromethylbenzoate (1.25g, 0.005M) and cyclopropyl methyl ketone (0.5g, 0.006M) in anhydrous N-methylpyrrolidinone and heated at 30°C for 3 hours. The cooled mixture was acidified, extracted (ether), washed (water) and evaporated to give 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (1.43g), m.p.68°C in a yield of 94%. The purity of the product was greater than 95%.

The above experiment was repeated but replacing the N-methylpyrrolidinone by dimethylsulphoxide to give the desired product in a yield of 97%. The purity of the product was greater than 95%.

Example 4

By proceeding according to the method described in Example 1 but using sodium methoxide (1.5 equivalents) and cyclopropyl methyl ketone (1.5 equivalents) and replacing the toluene by tert-butyl methyl ether, there was obtained, after 3 hours at 55°C (with distillation of methanol), a 92% yield of 1-cyclopropyl-3-(2-methylthio-4-trifluoromethylphenyl)propane-1,3-dione (purity 95%).

Example 5

By proceeding according to the method described in Example 1 but using cyclopropyl methyl ketone (1.5 equivalents) and replacing the toluene by tetrahydrofuran, there was obtained, after 5 hours at 40°C (without distillation of methanol), a 75% yield of the desired product.

Reference Example 1

Dry sodium thiomethoxide (0.385g, 0.0055M) was added to a solution of methyl 2-chloro-4-trifluoromethylbenzoate (1.19g, 0.005M) in anhydrous N-methylpyrrolidinone (10ml) at 5°C. After 3 hours the

mixture was acidified, extracted (ether), washed (water) and evaporated to give methyl 2-methylthio-4-trifluoromethylbenzoate (1.18g, 94% yield), ¹H NMR . 2.44(s,3H), 3.89(s,3H), 7.33(1H), 7.41(1H), 8.02(1H).

The reference to any prior art in this specification is not, and should not be taken
5 as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

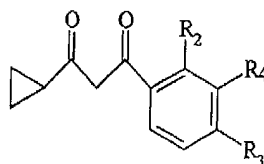
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or
10 group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

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



(I)

wherein:

R₂ is C₁₋₆ straight- or branched- chain alkylthio, C₁₋₆ alkyl, C₁₋₆ haloalkyl, CH₂SR₅, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or halogen; or a N-linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-triazole ring which ring systems are optionally substituted by one or more groups selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ straight- or branched- chain alkylthio;

R₃ is C₁₋₆ straight- or branched- chain haloalkyl, C₁₋₆ straight- or branched- chain alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, halogen, C₁₋₆ straight- or branched- chain alkylthio or nitro; or a N-linked imidazole, pyrazole, 1,2,3,4-tetrazole, 1,2,3-triazole or 1,2,4-triazole ring which ring systems are optionally substituted by one or more groups selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ straight- or branched- chain alkylthio;

R₄ is hydrogen, C₁₋₆ straight- or branched- chain haloalkyl, C₁₋₆ straight- or branched- chain alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, halogen, C₁₋₆ straight- or branched- chain alkylthio; or a 5 or 6-membered heterocyclic ring (which may be unsaturated or partially saturated) containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulphur, optionally substituted by halogen, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkoxy, SO_nR₅, nitro or cyano;

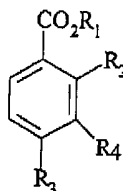


or R₃ and R₄ together with the carbon atoms to which they are attached, form a 5 to 7 membered saturated or unsaturated heterocyclic ring containing up to three ring heteroatoms selected from nitrogen, oxygen and sulfur, which ring is optionally substituted by one or more groups selected from halogen, nitro, C₁₋₆ straight- or branched- chain alkylthio, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, =O and =NO-R⁵; and

R₅ represents C₁₋₆ straight- or branched- chain alkyl; and

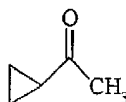
n represents zero, one or two;

which process comprises the reaction of a compound of formula (II):



(II)

wherein R₁ is C₁₋₆ straight- or branched- chain alkyl, and R₂, R₃ and R₄ are as hereinbefore defined, with a compound of formula (III):



(III)

in an aprotic solvent in the presence of a base, wherein said process is performed with distillation of the alcohol R₁-OH formed, or with removal of the alcohol R₁-OH using a molecular sieve.

2. A process according to claim 1 wherein the solvent is toluene, chlorobenzene, dimethylsulphoxide or N-methylpyrrolidinone.



3. A process according to claim 1 or 2 wherein the base is selected from alkali metal and alkaline earth metal alkoxides and metal hydrides.

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4. A process according to any one of claims 1 to 3 in which R₁ represents C₁₋₆ alkyl; R₂ represents C₁₋₆ alkylthio; R₃ represents C₁₋₆ haloalkyl and R₄ represents hydrogen.

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5. A process according to any one of claims 1 to 4 in which R₁ represents methyl; R₂ represents methylthio; R₃ represents trifluoromethyl and R₄ represents hydrogen.

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6. A process according to any one of claims 1 to 4 in which R₁ represents C₁₋₆ alkyl; R₂ represents methylthiomethyl; R₃ represents bromine and R₄ represents hydrogen.

7. A process according to claim 1 substantially as hereinbefore described in any one of Examples 1 to 5.

8. A compound of formula (I) as defined in claim 1 when prepared by a process according to any one of the preceding claims.

DATED this 5th day of April, 2002

Rhone Poulenc Agro

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicants

