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HERBICIDE INTERMEDIATE o-NITROPHENYL CYCLOPROPYL
KETONE AND A METHOD FOR THE PREPARATION THEREOF

5 The crop-selective, herbicidal agent 1-{{o-(cyclopropylcarbonyl)phenyl}sulfamoyl}-3-(4,6-dimethoxy-2-pyrimidinyl)urea is described in U.S. Patent 5,009,699. This unique sulfamoyl urea derivative demonstrates a superior margin of safety toward crop plants, especially rice plants, while concomitantly controlling troublesome broadleaf weeds and sedges.

10 The present invention relates to o-nitrophenyl cyclopropyl ketone, a key intermediate in the manufacture of the crop-selective herbicidal agent 1-{{o-(cyclopropylcarbonyl)phenyl}sulfamoyl}-3-(4,6-dimethoxy-2-pyrimidinyl)urea, a method for the preparation thereof, and a method for the preparation of o-aminophenyl cyclopropyl ketone.

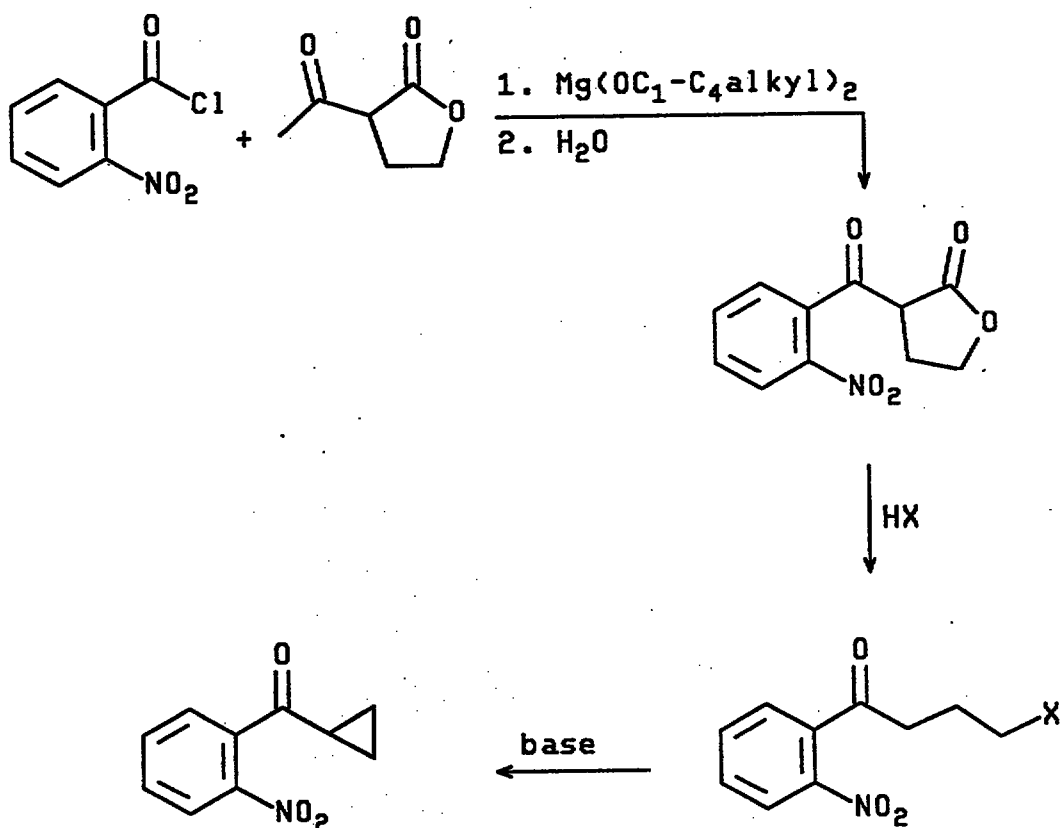
15 Advantageously, this key intermediate, o-nitrophenyl cyclopropyl ketone, may be prepared in an efficient and integrated process from readily available starting materials, dihydro-3-acetyl-2(3H)-furanone and o-nitrobenzoyl halide. In accordance with the method of invention dihydro-3-acetyl-2(3H)-furanone is reacted with about 0.5-1.0 molar equivalents of magnesium C₁-C₄alkoxide at about 0°-25°C to form an intermediate, the intermediate is reacted with at least one molar equivalent of o-nitrobenzoyl halide in the presence of a solvent at about 15°-35°C to form a second intermediate, the second intermediate is heated in the

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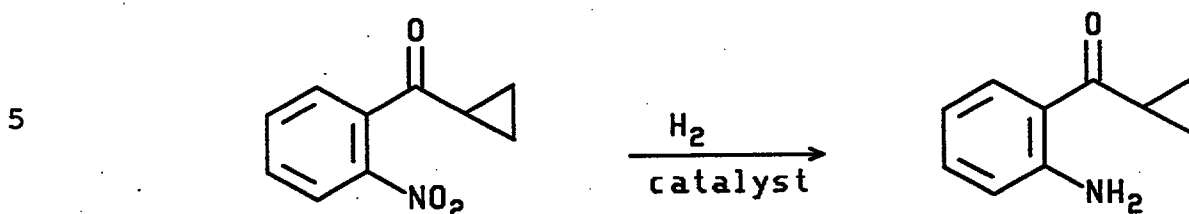
presence of water to form dihydro-3-(*o*-nitrobenzoyl)-2-(3H)-furanone, the furanone is reacted with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone and the butyrophenone is cyclized in the presence of a base to give *o*-nitrophenyl cyclopropyl ketone. The reaction sequence using *o*-nitrobenzoyl chloride as the *o*-nitrobenzoyl halide starting material is illustrated in Flow Diagram I wherein X designates halogen.

FLOW DIAGRAM I



Beneficially, the *o*-nitrophenyl cyclopropyl ketone may be reduced in the presence of hydrogen and a catalyst to give *o*-aminophenyl cyclopropyl ketone. The reaction is shown in Flow Diagram II.

FLOW DIAGRAM II



10 Solvents suitable for use in the method of
the invention are those solvents which are immiscible
in water such as aromatic hydrocarbons, dialkyl ethers,
halogenated alkanes and the like, preferably aromatic
hydrocarbons. When such solvents are used, for example
15 toluene, xylene, etc., the reaction steps may be inte-
grated such that the reaction products may be carried
on to the subsequent steps as a solution in the organic
phase without time-consuming and potentially wasteful
isolation procedures. Among the magnesium alkoxides
which may be used in the inventive method are magnesium
20 C₁-C₄ alkoxides preferably those which are readily
available such as magnesium methoxide or magnesium
ethoxide. Similarly, the *o*-nitrobenzoyl halides and
hydrogen halides which may be employed in the inventive
method include those most commonly available such as
25 chlorides or bromides.

Among the bases suitable for use in the
cyclization step of the inventive method are those
having a pK_a greater than, or equal to, 10, such as
organic amines, alkali metal carbonates or alkali metal
30 hydroxides, preferably alkali metal hydroxides such as
sodium hydroxide and potassium hydroxide. Hydro-
genation catalysts include those well-known in the art
such as platinum on carbon or palladium on carbon.

The rate of the decarboxylation/halogenation step is directly related to the concentration of the reagents, i.e. the more concentrated the organic solvent solution of dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone and the more concentrated the hydrogen halide solution, the faster the reaction rate. Therefore, increased concentration of reactants yields increased reaction rate and productivity.

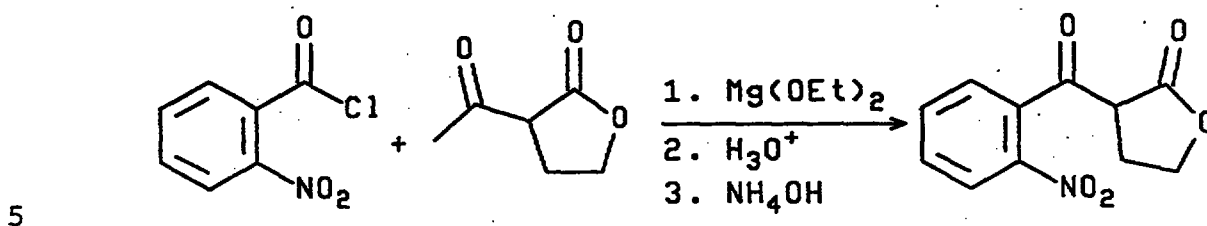
It is a feature of this invention that the individual preparative steps may be integrated by the use of a single, suitable, water-immiscible solvent such as toluene. The advantages of this feature include the elimination of costly, potentially wasteful and time-consuming isolation procedures.

The invention is further illustrated in the Examples set forth below and is not to be deemed limited thereby, except as defined in the claims.

The terms TLC, HPLC and LC designate thin layer chromatography, high performance liquid chromatography and liquid chromatography, respectively. The terms ¹HNMR and ¹³CNMR designate proton and carbon-13 nuclear magnetic resonance, respectively. All parts are parts by weight unless otherwise noted.

EXAMPLE 1

Preparation and isolation of dihydro-3-(o-nitro-benzoyl)-2(3H)-furanone



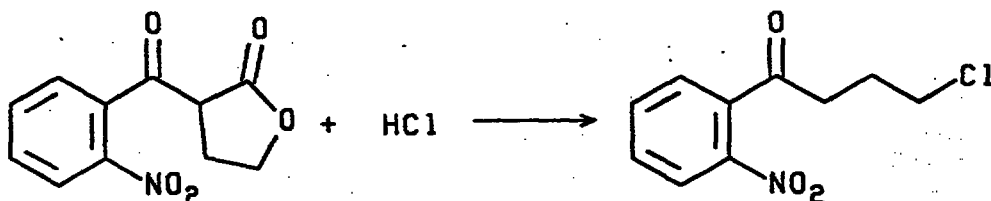
10 A mixture of $\text{Mg}(\text{OEt})_2$ (30.9 g, 0.27 mole) in toluene is treated with dihydro-3-acetyl-2(3H)-furanone (77 g, 0.55 mole) at $5^\circ\text{--}10^\circ\text{C}$, stirred for 1 hour at $25^\circ\text{--}30^\circ\text{C}$, treated with a solution of o-nitrobenzoyl chloride (92.8 g, 0.50 mole) in toluene at $30^\circ\text{--}35^\circ\text{C}$, stirred at $25^\circ\text{--}35^\circ\text{C}$ for 1-2 hours, heated at 60°C for 1 hour, cooled to 30°C , treated with water and 96% H_2SO_4 (15 g) and stirred for 0.5 hour. The phases are

15 separated and the aqueous phase is extracted with ethyl acetate. The organic phases are combined, treated with aqueous NH_4OH , stirred for 5-10 minutes and separated. The organic phase is further extracted with aqueous

20 NH_4OH . The aqueous phases are combined and acidified to pH 5.5 with 96% H_2SO_4 at $14^\circ\text{--}20^\circ\text{C}$. The resultant precipitate is removed by filtration to give the title product as a white solid, 91.3 g, (77.7% yield), 85-90% pure by NMR analysis, identified by ^1H and ^{13}C NMR.

EXAMPLE 2

Preparation and isolation of 4-chloro-2'-nitrobutyrophenone

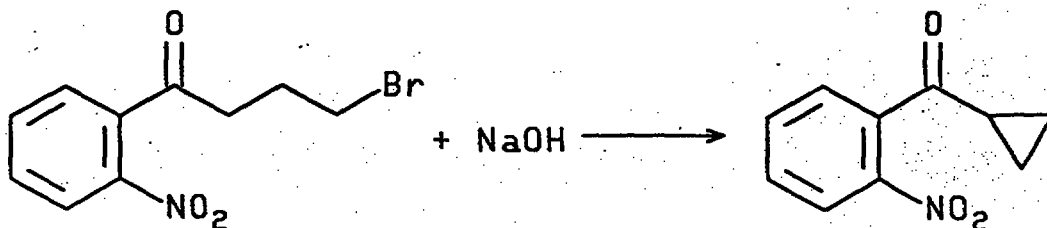


10 A mixture of dihydro-3-(*o*-nitrobenzoyl)-2(3H)-furanone (2.0 g, 8.5 mmole) in 10 g of 37% HCl solution is stirred at 70°C until reaction is complete by TLC, cooled to room temperature and extracted with toluene. The organic extracts are combined and concentrated in vacuo to give the title product as a golden oil, 1.84 g (95% yield), 99% pure by HPLC analysis, identified by ¹HNMR.

15 Using essentially the same procedure and employing 48% HBr, 4-bromo-2'-nitrobutyrophenone is obtained as a brown solid, identified by ¹HNMR and HPLC analysis.

EXAMPLE 3

Preparation and isolation of *o*-nitrophenyl cyclopropyl ketone

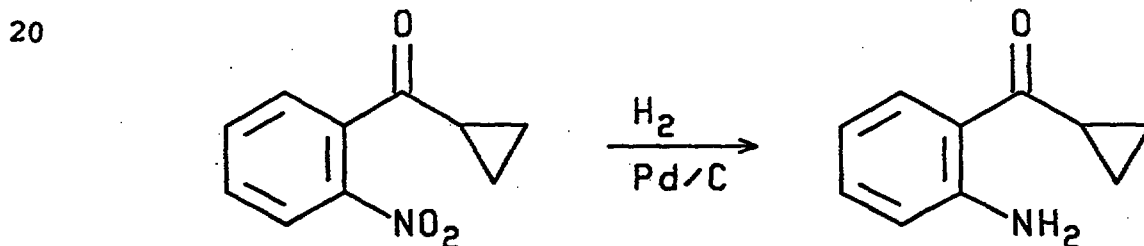


A stirred mixture of 4-bromo-2'-nitrobutyrophenone (3.44 g, 0.013 mole) and NaOH (0.76 g, 0.019 mole) in water is heated at reflux temperature until reaction is complete by TLC, cooled to room temperature and extracted with diethyl ether. The ether extracts are combined, dried over Na₂SO₄ and concentrated in vacuo to give a dark brown liquid residue. The residue is taken up in diethyl ether, filtered through silica gel and concentrated in vacuo to give the title product as a yellow oil, identified by ¹HNMR.

Using essentially the same procedure but employing 4-chloro-2'-nitrobutyrophenone as the starting material, the title product is obtained as a yellow oil in 98% yield and 99% purity by HPLC analysis, identified by ¹HNMR.

EXAMPLE 4

Preparation of o-aminophenyl cyclopropyl ketone

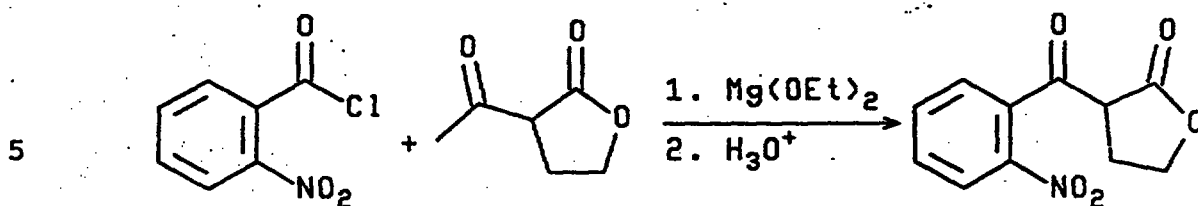


A mixture of o-nitrophenyl cyclopropyl ketone (100 mg, 0.52 mmole) and a catalytic amount of 10% Pd on carbon in methanol is stirred under hydrogen at atmospheric pressure until reaction is complete by TLC. The reaction mixture is filtered and the filtrate is concentrated in vacuo to give a bright yellow oil. The oil is flash chromatographed to give the title product as an off-white crystalline solid, 72 mg (85% yield), identified by ¹HNMR.

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EXAMPLE 5

Preparation of dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone (Integrated step 1)



10 A mixture of $\text{Mg}(\text{OEt})_2$ (63 g, 0.55 mole) in toluene, under N_2 , is treated with dihydro-3-acetyl-2(3H)-furanone (141 g, 1.10 mole) at $7^\circ\text{--}10^\circ\text{C}$ over a 15 minute period and stirred at $25^\circ\text{--}30^\circ\text{C}$ for 2 hours. The resultant reaction mixture is treated with a solution of o-nitrobenzoyl chloride (185.7 g, 1.0 mole) in toluene at $25^\circ\text{--}35^\circ\text{C}$ over a 45 minute period, stirred at ambient temperatures for 1.75 hours, treated with 400 mL H_2O and heated at $60^\circ\text{--}75^\circ$ until reaction is complete by LC analysis. The resultant reaction mixture is cooled to room temperature and the phases are separated to give the title product as a toluene solution, 875 g, 18% desired product by LC analysis (67% yield). The product solution is used as is in Example 6.

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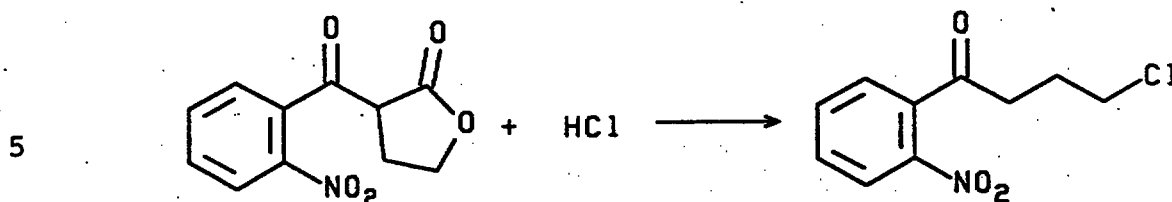
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EXAMPLE 6

Preparation of 4-chloro-2'-nitrobutyrophenone
(Integrated step 2)

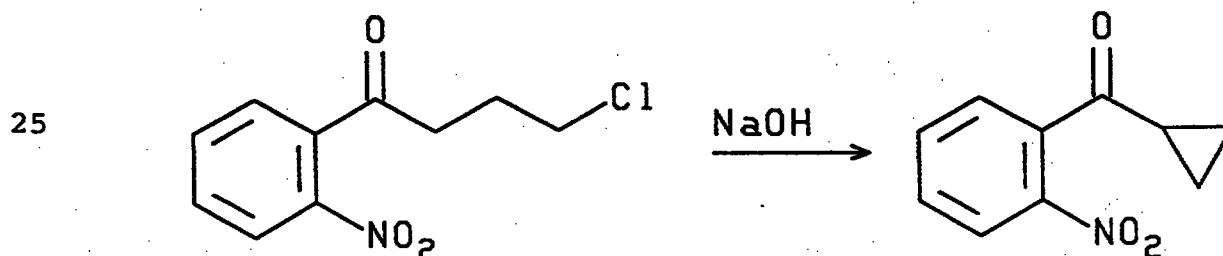


10 The 18% solution of dihydro-3-(o-nitrobenzoyl)-2(3H)furanone in toluene obtained in Example 5 (450 g, 0.34 mole furanone) is treated, with stirring, with 37% HCl (48 g, 0.60 mole HCl), heated at reflux temperature for 6-11 hours, until reaction is complete by LC analysis, cooled to 35°-45°C and allowed to settle. The phases are separated to give the title product as a toluene solution, 425 g. The product solution is used as is in Example 7.

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EXAMPLE 7

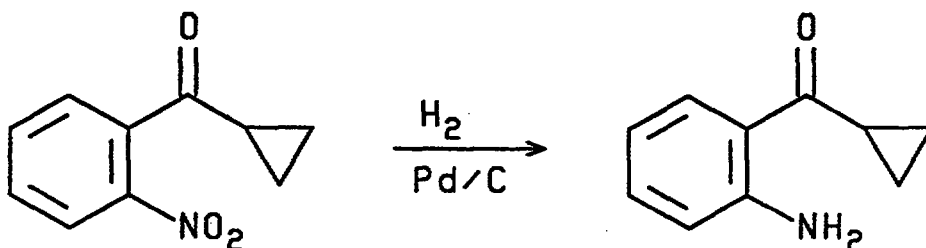
20 **Preparation of o-nitrophenyl cyclopropyl ketone**
(Integrated step 3)



30 The 13.8% toluene solution of 4-chloro-2'-nitrobutyrophenone obtained in Example 6 is treated,



with stirring, first with 90 mL water and second with 50% NaOH (48 g, 0.6 mole NaOH). The resultant reaction mixture is allowed to exotherm, then is heated at 85°-90°C for 2-3 hours, cooled to room temperature and allowed to settle. The phases are separated and the organic phase is washed with water. The aqueous phases are combined and washed with toluene. The organic phases are combined and concentrated in vacuo to give the title product as a toluene solution, 235 g, 23.6% title product by LC analysis (91% yield from furanone). The product solution is used as is in Example 8.

EXAMPLE 8**Preparation of o-aminophenyl cyclopropyl ketone**
(Integrated step 4)

A mixture of the 23.6% toluene solution of o-nitrophenyl cyclopropyl ketone obtained in Example 7 (232.3 g, 0.286 mole ketone) and 2.86 g of 5% Pd/C catalyst is placed under H₂ at 32-56 psig in a Parr hydrogenator. The hydrogen uptake is monitored and when the reaction is complete, the reaction mixture is filtered and concentrated in vacuo to give the title product, 39.5 g, 86.3% pure by HPLC analysis (73.9% yield).



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WHAT IS CLAIMED IS:

1. o-Nitrophenyl cyclopropyl ketone.
2. A method for the preparation of o-nitrophenyl cyclopropyl ketone which is characterized by reacting dihydro-3-acetyl-2(3H)-furanone with about 0.50-1.0 molar equivalents of magnesium C₁-C₄alkoxide at about 0°-25°C to form an intermediate, reacting said intermediate with at least one molar equivalent of o-nitrobenzoyl halide in the presence of a solvent at about 15°-35°C to form a second intermediate, heating the second intermediate in the presence of water to form dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone, reacting the furanone with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone and cyclizing the butyrophenone in the presence of a base to give o-nitrophenyl cyclopropyl ketone.
3. The method according to claim 2 wherein the solvent is an aromatic hydrocarbon, the magnesium C₁-C₄alkoxide is magnesium methoxide or magnesium ethoxide, the hydrogen halide is hydrogen chloride or hydrogen bromide, and the base is an alkali metal hydroxide.
4. The method according to claim 3 wherein the solvent is toluene and the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.
5. A method for the preparation of o-aminophenyl cyclopropyl ketone which is characterized by reacting dihydro-3-acetyl-2(3H)-furanone with about 0.50-1.0 molar equivalents of magnesium C₁-C₄alkoxide at about 0°-25°C to form an intermediate, reacting said intermediate with at least one molar equivalent of



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o-nitrobenzoyl halide in the presence of a solvent at about 15°-35°C to form a second intermediate, heating the second intermediate in the presence of water to form dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone, reacting the furanone with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone, cyclizing the butyrophenone in the presence of a base to give o-nitrophenyl cyclopropyl ketone and hydrogenating the nitrophenyl ketone in the presence of a catalyst to give o-aminophenyl cyclopropyl ketone.

6. The method according to claim 5 wherein the solvent is an aromatic hydrocarbon and the base is an alkali metal hydroxide.

7. The method according to claim 6 wherein the solvent is toluene and the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.

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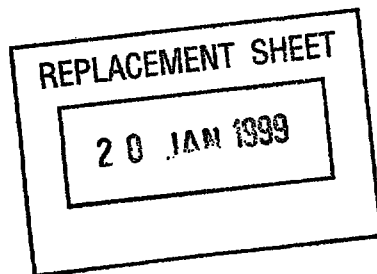
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HERBICIDE INTERMEDIATE O-NITROPHENYL CYCLOPROPYL KETONE
AND A METHOD FOR THE PREPARATION THEREOF

5 The crop-selective, herbicidal agent 1-([o-
(cyclopropylcarbonyl)phenyl]sulfamoyl)-3-(4,6-dime-
thoxy-2-pyrimidinyl)urea is described in U.S. Patent
5,009,699. This unique sulfamoyl urea derivative
demonstrates a superior margin of safety toward crop
plants, especially rice plants, while concomitantly
10 controlling troublesome broadleaf weeds and sedges.

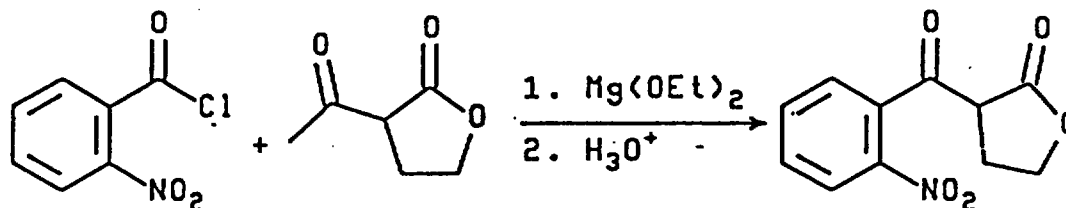
 The present invention relates to o-nitro-
phenyl cyclopropyl ketone, a key intermediate in the
manufacture of the crop-selective herbicidal agent
1-([o-(cyclopropylcarbonyl)phenyl]sulfamoyl)-3-(4,6-di-
15 methoxy-2-pyrimidinyl)urea, a method for the prepara-
tion thereof, and a method for the preparation of
o-aminophenyl cyclopropyl ketone.

 Advantageously, this key intermediate,
o-nitrophenyl cyclopropyl ketone, may be prepared in an
20 efficient and integrated process from readily available
starting materials, dihydro-3-acetyl-2(3H)-furanone and
o-nitrobenzoyl halide. In accordance with the method
of invention dihydro-3-acetyl-2(3H)-furanone is reacted
with 0.5-1.0 molar equivalents of magnesium
25 C₁-C₄alkoxide at 0°-25°C to form an intermediate,
the intermediate is reacted with at least one molar
equivalent of o-nitrobenzoyl halide in the presence of
a solvent at 15°-35°C to form a second interme-
diate, the second intermediate is heated in the



EXAMPLE 5

Preparation of dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone (Integrated step 1)



10 A mixture of $\text{Mg}(\text{OEt})_2$ (63 g, 0.55 mole) in toluene, under N_2 , is treated with dihydro-3-acetyl-2(3H)-furanone (141 g, 1.10 mole) at $7^\circ\text{--}10^\circ\text{C}$ over a 15 minute period and stirred at $25^\circ\text{--}30^\circ\text{C}$ for 2 hours. The resultant reaction mixture is treated with a solution of o-nitrobenzoyl chloride (185.7 g, 1.0 mole) in

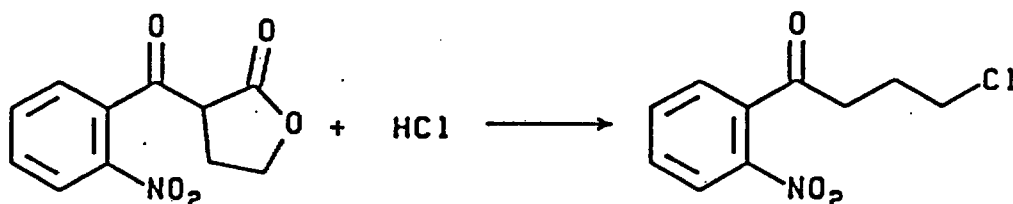
15 toluene at $25^\circ\text{--}35^\circ\text{C}$ over a 45 minute period, stirred at ambient temperatures for 1.75 hours, treated with 400 mL H_2O and heated at $60^\circ\text{--}75^\circ$ until reaction is complete by LC analysis. The resultant reaction mixture is

20 cooled to room temperature and the phases are separated to give the title product as a toluene solution, 875 g, 18% desired product by LC analysis (67% yield). The product solution is used as it is in Example 6.

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EXAMPLE 6

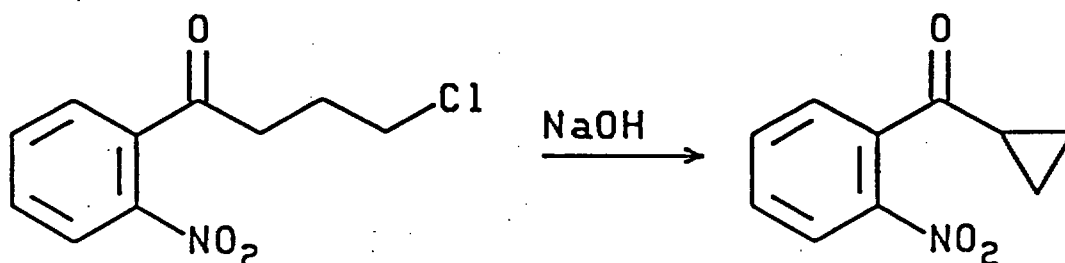
Preparation of 4-chloro-2'-nitrobutyrophenone
(Integrated step 2)



10 The 18% solution of dihydro-3-(*o*-nitrobenzoyl)-2(3H)furanone in toluene obtained in Example 5 (450 g, 0.34 mole furanone) is treated, with stirring, with 37% HCl (48 g, 0.60 mole HCl), heated at reflux temperature for 6-11 hours, until reaction is complete by LC analysis, cooled to 35°-45°C and allowed to settle. The phases are separated to give the title product as a toluene solution, 425 g. The product solution is used as it is in Example 7.

EXAMPLE 7

20 Preparation of *o*-nitrophenyl cyclopropyl ketone
(Integrated step 3)



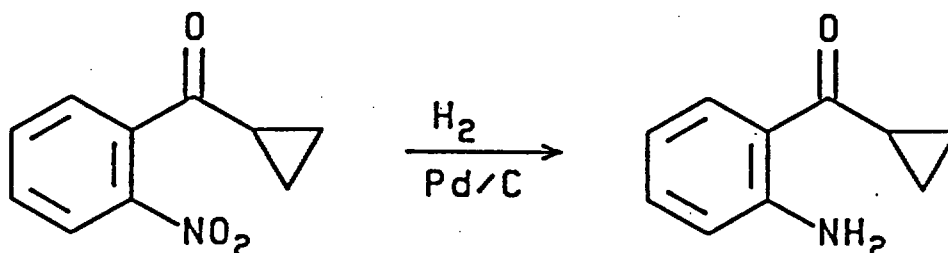
30 The 13.8% toluene solution of 4-chloro-2'-nitrobutyrophenone obtained in Example 6 is treated,

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with stirring, first with 90 mL water and second with
50% NaOH (48 g, 0.6 mole NaOH). The resultant reaction
mixture is allowed to exotherm, then is heated at
85°-90°C for 2-3 hours, cooled to room temperature and
5 allowed to settle. The phases are separated and the
organic phase is washed with water. The aqueous phases
are combined and washed with toluene. The organic
phases are combined and concentrated in vacuo to give
the title product as a toluene solution, 235 g, 23.6%
10 title product by LC analysis (91% yield from furanone).
The product solution is used as it is in Example 8.

EXAMPLE 8

Preparation of o-aminophenyl cyclopropyl ketone
15 (Integrated step 4)



A mixture of the 23.6% toluene solution of
o-nitrophenyl cyclopropyl ketone obtained in Example 7
(232.3 g, 0.286 mole ketone) and 2.86 g of 5% Pd/C
25 catalyst is placed under H₂ at 32-56 psig in a Parr
hydrogenator. The hydrogen uptake is monitored and
when the reaction is complete, the reaction mixture is
filtered and concentrated in vacuo to give the title
product, 39.5 g, 86.3% pure by HPLC analysis (73.9%
30 yield).



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CLAIMS

1. o-Nitrophenyl cyclopropyl ketone.
2. A method for the preparation of o-nitrophenyl cyclopropyl ketone which is characterized by reacting dihydro-3-acetyl-2(3H)-furanone with 0.50-1.0 molar equivalents of magnesium C₁-C₄alkoxide at 0°-25°C to form an intermediate, reacting said intermediate with at least one molar equivalent of o-nitrobenzoyl halide in the presence of a solvent at 15°-35°C to form a second intermediate, heating the second intermediate in the presence of water to form dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone, reacting the furanone with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone and cyclizing the butyrophenone in the presence of a base to give o-nitrophenyl cyclopropyl ketone.
3. The method according to claim 2 wherein the solvent is an aromatic hydrocarbon, the magnesium C₁-C₄alkoxide is magnesium methoxide or magnesium ethoxide, the hydrogen halide is hydrogen chloride or hydrogen bromide, and the base is an alkali metal hydroxide.
4. The method according to claim 3 wherein the solvent is toluene and the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.
5. A method for the preparation of o-aminophenyl cyclopropyl ketone which is characterized by reacting dihydro-3-acetyl-2(3H)-furanone with 0.50-1.0 molar equivalents of magnesium C₁-C₄alkoxide at 0°-25°C to form an intermediate, reacting said intermediate with at least one molar equivalent of



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o-nitrobenzoyl halide in the presence of a solvent at 15°-35°C to form a second intermediate, heating the second intermediate in the presence of water to form dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone, reacting the furanone with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone, cyclizing the butyrophenone in the presence of a base to give o-nitrophenyl cyclopropyl ketone and hydrogenating the nitrophenyl ketone in the presence of a catalyst to give o-aminophenyl cyclopropyl ketone.

6. The method according to claim 5 wherein the solvent is an aromatic hydrocarbon and the base is an alkali metal hydroxide.

7. The method according to claim 6 wherein the solvent is toluene and the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.

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HERBICIDE INTERMEDIATE o-NITROPHENYL CYCLOPROPYL
KETONE AND A METHOD FOR THE PREPARATION THEREOF

ABSTRACT OF THE INVENTION

There is provided o-nitrophenyl cyclopropyl ketone, a key intermediate in the manufacture of the crop-selective, herbicidal agent 1-([o-(cyclopropyl-carbonyl)phenyl]sulfamoyl)-3-(4,6-dimethoxy-2-pyrimidinyl)urea and a method for the preparation of said ketone from dihydro-3-acetyl-2(3H)-furanone and o-nitrobenzoyl halide.