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(54) Title: HERBICIDE INTERMEDIATE O-NITROPHENYL CYCLOPROPYL KETONE AND A METHOD FOR THE PREPARATION THEREOF

(57) Abrégé/Abstract:
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.

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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-pyri-midinyl)urea and a method for the preparation of said ketone from dihydro-3-acetyl-2(3H)-furanone and o-nitrobenzoyl halide.

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

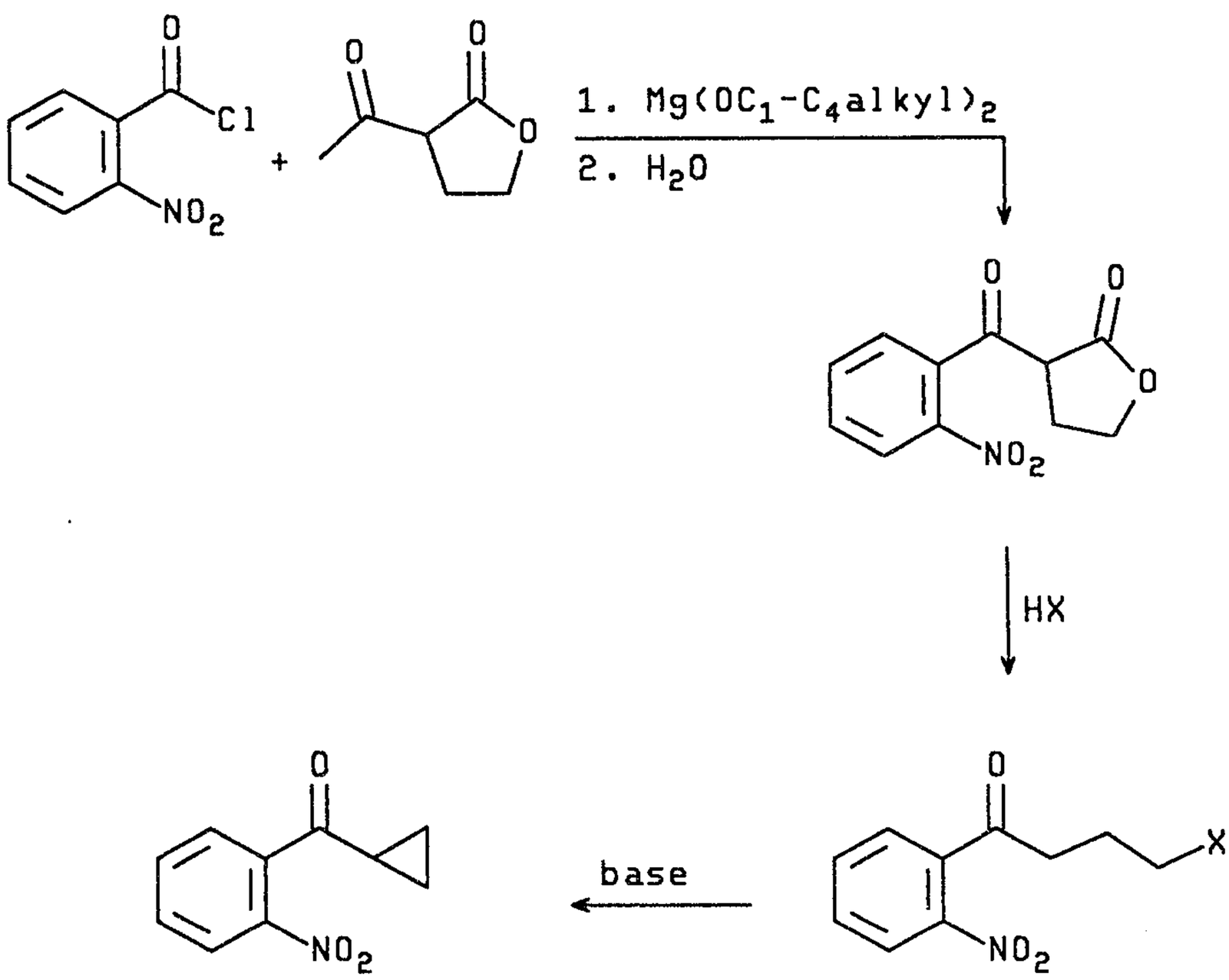
The crop-selective, herbicidal agent 1-{[o-(cyclopropylcarbonyl)phenyl]sulfamoyl}-3-(4,6-dimethoxy-2-pyrimidinyl)urea is described in U.S. Patent 5,009,699. This unique sulfamoyl urea derivative demonstrates a superior margin of safety toward crop plants, especially rice plants, while concomitantly controlling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

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.

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 C_1-C_4alkoxide 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

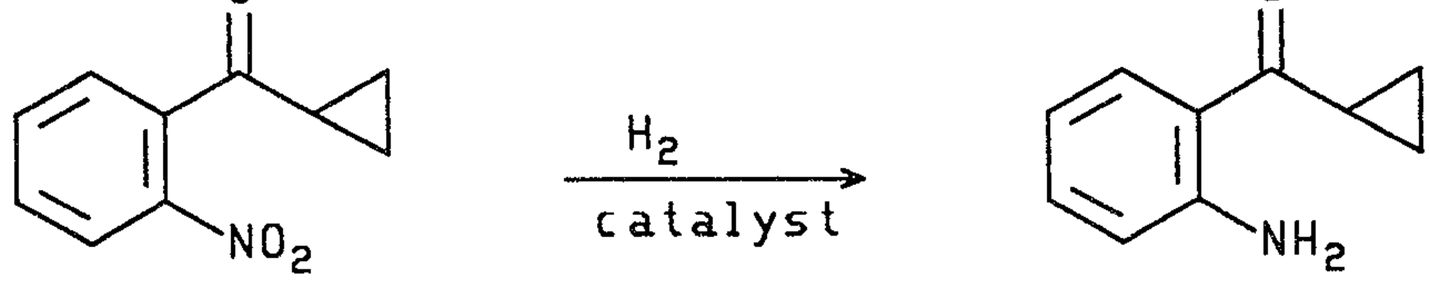
presence of water to form dihydro-3-(o-nitrobenzoyl)-2-(3H)-furanone, the furanone is reacted with a hydrogen halide to form 4-halo-2'-nitrobutyrophenone and the butyrophenone is cyclized in the presence of a base to give o-nitrophenyl cyclopropyl ketone. The reaction sequence using o-nitrobenzoyl chloride 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



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 toluene, xylene, etc., the reaction steps may be integrated 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 C_1-C_4 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 chlorides or bromides.

Among the bases suitable for use in the cyclization step of the inventive method are those having a pKa greater than, or equal to, 10, such as organic amines, alkali metal carbonates or alkali metal hydroxides, preferably alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. Hydrogenation 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.

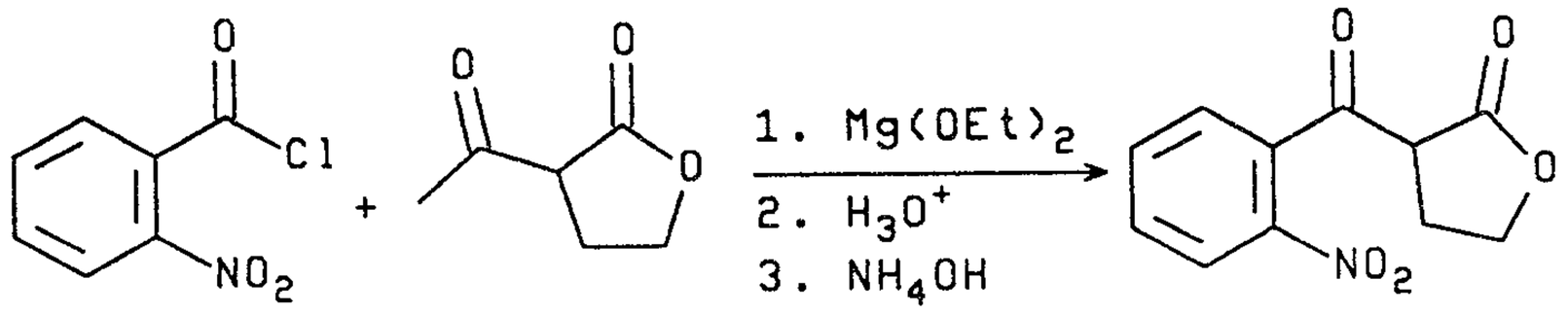
It is a feature of this invention that the individual preparative steps may be integrated by the use of a single, suitable, water-immiscible solvent such as toluene. The advantages of this feature include the elimination of costly, potentially wasteful and time-consuming isolation procedures.

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 ^{1}HNMR and ^{13}CNMR designate proton and carbon-13 nuclear magnetic resonance, respectively. All parts are parts by weight unless otherwise noted.

EXAMPLE 1

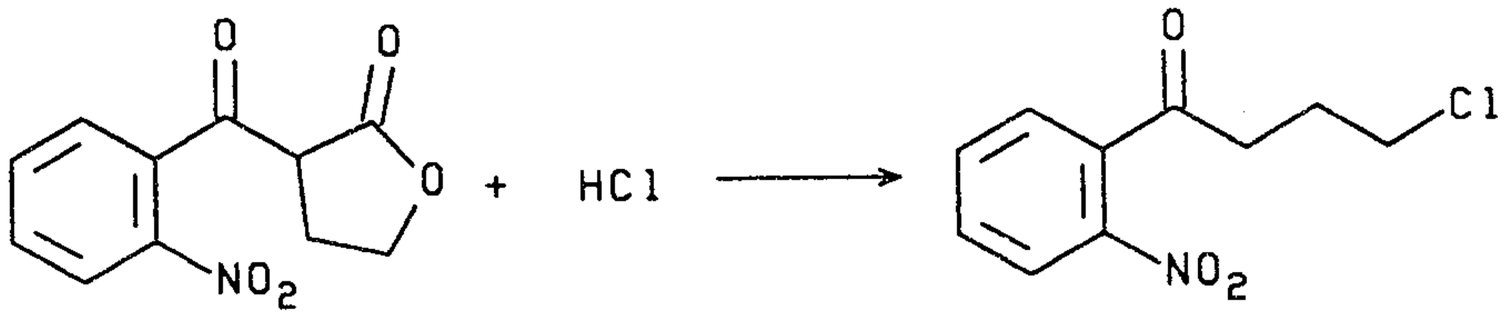
Preparation and isolation of dihydro-3-(o-nitrobenzoyl-2(3H)-furanone



A mixture of $Mg(OEt)_2$ (30.9 g, 0.27 mole) in toluene is treated with dihydro-3-acetyl-2(3H)-furanone (77 g, 0.55 mole) at 5°-10°C, stirred for 1 hour at 25°-30°C, treated with a solution of o-nitrobenzoyl chloride (92.8 g, 0.50 mole) in toluene at 30°-35°C, stirred at 25°-35°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 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 NH_4OH. The aqueous phases are combined and acidified to pH 5.5 with 96% H_2SO_4 at 14°-20°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}CNMR.

EXAMPLE 2

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

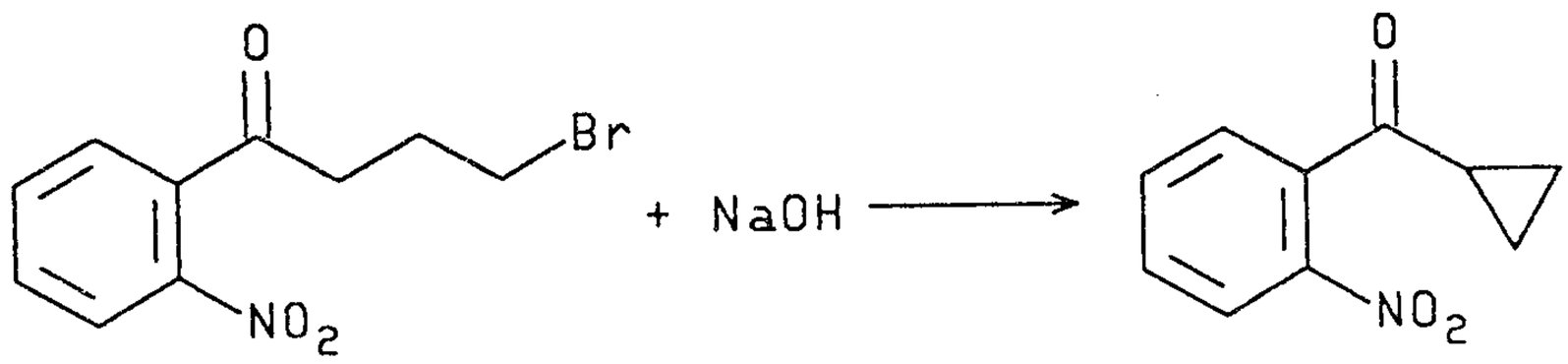


A mixture of dihydro-3-(o-nitrobezoyl-2(3H)-furanone (2.0 g, 8.5 mmole) in 10 g of 37% HCl solution is stirred at 70°C until reaction is complete by TLC, cooled to room temperature and extracted with toluene. The organic extracts are combined and concentrated *in vacuo* to give the title product as a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

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

EXAMPLE 3

Preparation and isolation of o-nitrophenyl cyclopropyl ketone

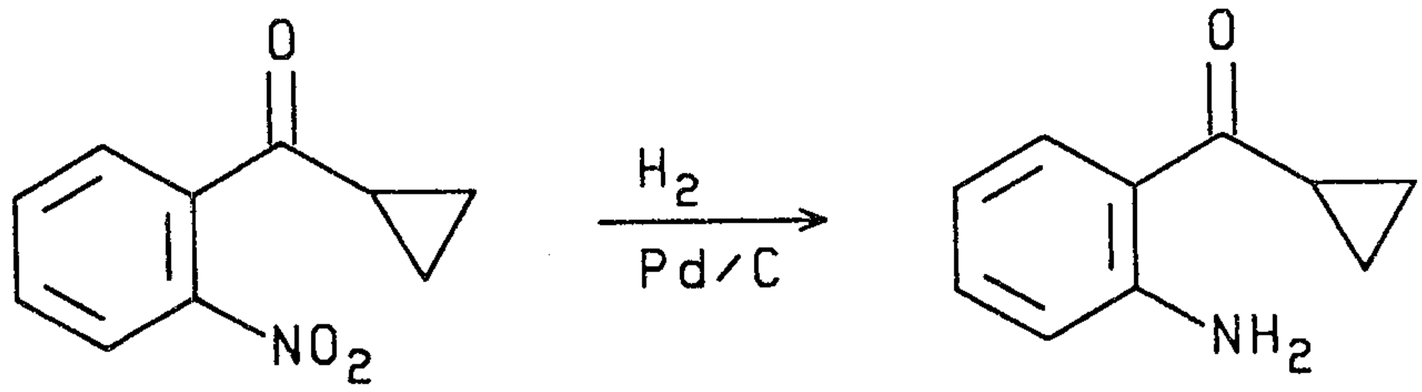


A stirred mixture of 4-bromo-2′-nitrobutyrophenone (3.44 g, 0.013 mole) and NaOH (0.76 g, 0.019 mole) in water is heated at reflux temperature until reaction is complete by TLC, cooled to room temperature and extracted with diethyl ether. The ether extracts are combined, dried over Na_2SO_4 and concentrated *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 ^{1}HNMR.

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 ^{1}HNMR.

EXAMPLE 4

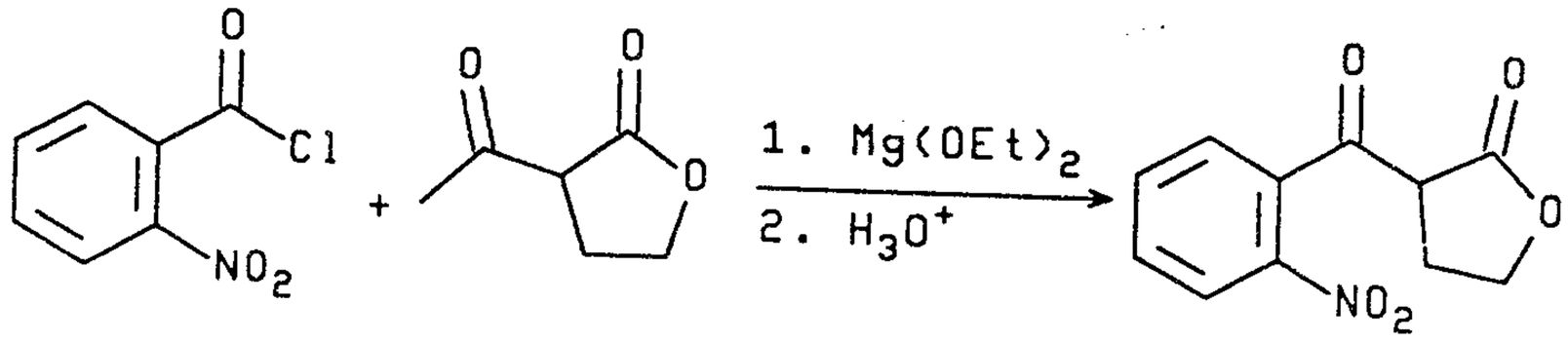
Preparation of o-aminophenyl cyclopropyl ketone



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 ^{1}HNMR.

EXAMPLE 5

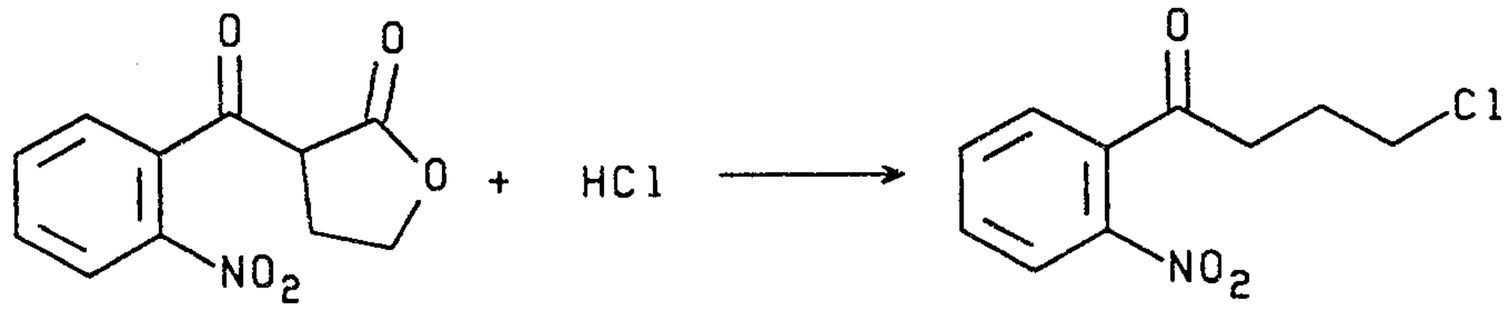
Preparation of dihydro-3-(o-nitrobenzoyl)-2(3H)-furanone (Integrated step 1)



A mixture of $Mg(OEt)_2$ (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°-10°C over a 15 minute period and stirred at 25°-30°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°-35°C over a 45 minute period, stirred at ambient temperatures for 1.75 hours, treated with 400 mL H_2O and heated at 60°-75° 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.

EXAMPLE 6

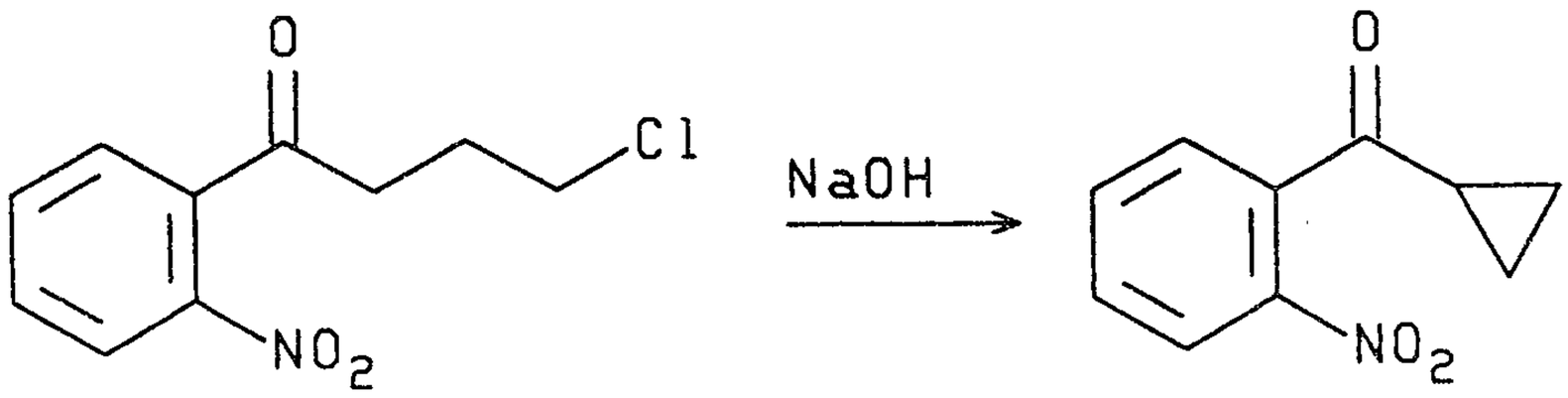
Preparation of 4-chloro-2'-nitrobutyrophenone (Integrated step 2)



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.

EXAMPLE 7

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

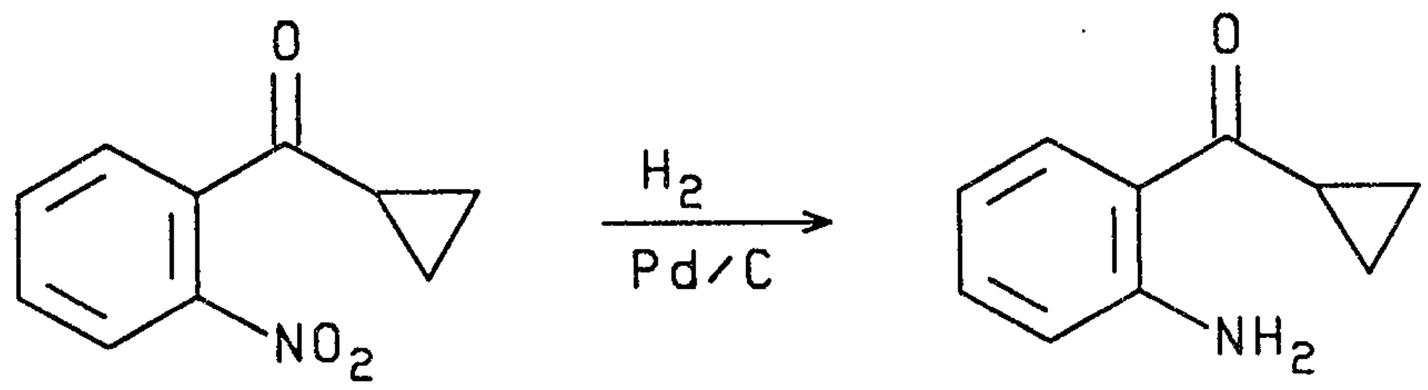


The 13.8% toluene solution of 4-chloro-2'-nitrobutyrophenone obtained in Example 6 is treated,

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 H_2 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).

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 C_1-C_4alkoxide 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 C_1-C_4alkoxide 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 C_1-C_4alkoxide 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, 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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