(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number
WO 2005/065046 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IN2004/000370

(22) International Filing Date:
30 November 2004 (30.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

7/MUM/2004	2 January 2004 (02.01.2004)	IN
374/MUM/2004	26 March 2004 (26.03.2004)	IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— *without international search report and to be republished upon receipt of that report*

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(54) **Title:** AN EFFICIENT INDUSTRIAL PROCESS FOR 3-HYDROXY-3-(3'-SULFAMYL-4'-CHLOROPHENYL)PHTALIMIDINE

(57) **Abstract:** The oximination/cyclization of 2-(4-chlorobenzoyl)benzoic acid with hydroxylamine hydrochloride in presence of molar quantities of inorganic base in water or in alcoholic solvents to form 4-(4'-chlorophenyl)-5,6-bent-oxazine-l-one Formula (8) in high yield and purity; reduction of latter with zinc metal and acetic acid to the corresponding phtalimidine of Formula (9); followed by conversion into 2-(3'-chlorosulphonyl-4'-chlorophenyl)phtalimidine Formula (10) by reaction with chlorosulphonic acid and thionyl chloride in the absence of solvent. Amidation of compound of formula (10) was carried out with ammonia gas/solution in non.-aqueous solvent like ketones and polar aprotic solvents like dimethylformamide, to yield compound of formula (11). Oxidation of Formula (11) with hydrogen peroxide in presence of alkali results in high yield of chlorihalidone.

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An efficient industrial process for 3-hydroxy-3-(3'-sulfamyl-4'-chlorophenyl)phtalimidine

Related Applications

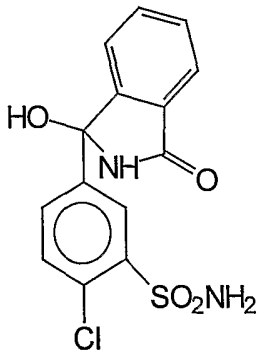
This application claims priority from Indian national applications 7/MUM/2004 filed on 2nd January 2004 and 374/MUM/2004 filed on 26th March 2004.

Field of invention

The present invention relates to an efficient process for the manufacture of chlorthalidone, a commonly used therapeutic agent in pharmaceutical applications.

Background of the invention

The chemical name of chlorthalidone is 3-hydroxy-3-(3'-sulfamyl-4'-chlorophenyl)phtalimidine and is represented by the structural formula shown below.



Chlorthalidone

Formula 1

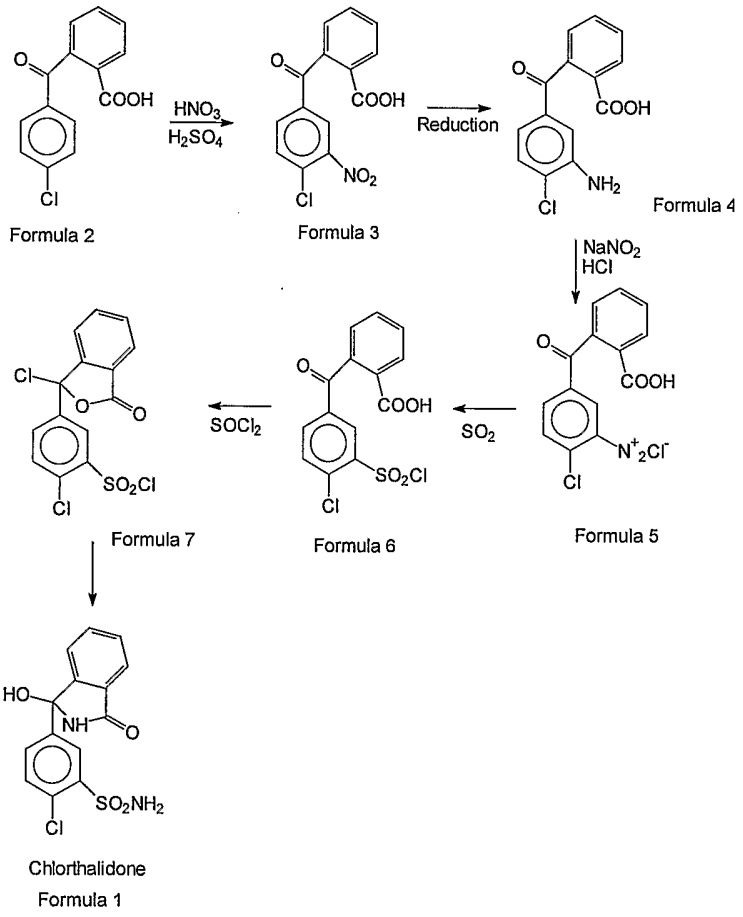
Chlorthalidone, a 'water pill,' is used to treat high blood pressure and fluid retention caused by various conditions, including heart disease. It causes the kidneys to get rid of unneeded water and salt from the body into the urine. Chlorthalidone also may be used to treat patients with diabetes insipidus and certain electrolyte disturbances and to prevent kidney stones in patients with high levels of calcium in their blood.

Chlorthalidone is a valuable pharmaceutical as it is recently used in combination with other anti-hypertensive such as atenolol, losartan potassium etc., an active medicinal combination.

Chlorthalidone, its related compounds and their methods of preparation are first disclosed in Helv. Chim. Acta 42, 1085, (1959) and also in United States patent No. 3055904 (1962). Referring to the general preparation method for chlorthalidone, the '904 patent teaches that a 2-(4'-chlorobenzoyl)benzoic acid (Formula 2) was nitrated using a nitrating mixture(H2SO4 & HNO3)to form 2-(4'-chloro-3'-nitrophenyl)benzoic acid (Formula 3), the nitro group of compound (3) was reduced to an amino derivative 2-(4'-chloro-3'-aminophenyl)benzoic acid (Formula 4) which was subsequently diazotized and decomposed with sulphur dioxide to form 2-(4'chloro-3'-sulphochorobenzoyl)benzoic acid (Formula 6). Compound 6 was treated with thionyl chloride to form the dichloride compound namely 3-chloro-3-(3'-chlorosulphonyl-4'chlorophenyl)phthalide (Formula 7) which was then treated with ammonia to form chlorthalidone as shown in scheme 1.

The above method of preparation suffers from many drawbacks as it involves numerous steps and that many of which involved usage of hazardous reagents or intermediates in the process such as sulphur dioxide – a hazardous gas, nitration involves an explosive hazard reagent & intermediate, and the diazotization & decomposition reaction. The diazotization & decomposition reactions are considered to be runaway reactions, if the precise conditions are not maintained and the maintenance of such conditions on an industrial scale is often a major concern.

Scheme 1



Many other improved processes are reported thereafter to find a suitable process, which involves fewer steps and avoids hazardous reagents or reaction steps, most desirable for industrial preparation.

In that respect, United States patent No. 4331600 disclosed an alternative process route that ameliorates some of the above disadvantages involved in the process of '904 patent.

This process involves fewer steps and eliminates the reagents/intermediates, which are considerably hazardous. This process comprises: an oxymination reaction of 2-(4'-chlorobenzoyl)benzoic acid with hydroxylamine hydrochloride in pyridine which acts as a base as well as solvent to give a benzoxazine of Formula 8; reduction of compound 8 to form phthalimidine of Formula 9; chlorosulphonation of compound (9) to form compound of Formula (10) using chlorosulphonic acid in chloroform and subsequent amidation with ammonia in aqueous media to form compound of Formula (11); oxidation of compound (11) at the 3-position of phthalimidine in presence of oxidizing agent such as permanganates, manganese dioxide, air, bromine etc. to form targeted chlorthalidone.

Among the reported processes, the process route of '600 patent is promising but involves many disadvantages from operational point of view, impurities generation, usage of environmentally unfriendly solvent like pyridine, isolation of product/intermediates from these reaction media, longer duration of reactions, poor yields and finally the incomplete or over oxidation of penultimate intermediate of chlorthalidone based on the process teachings from said patent.

Objective of the present invention

It is an objective of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art or to provide a useful alternative.

It is an object of the present invention in its preferred form to provide an improved industrial process for preparation of chlorthalidone in high yield and pharmaceutically acceptable purity by modifying the route disclosed in '600 patent.

Summary of the invention

According to the present invention there is provided a useful industrial process for preparation of chlorthalidone which involves fewer steps, common industrial solvents and conditions, easy isolation and purification's of intermediates/product, faster reactions, limiting the impurity formation and yielding high purity product in high throughput reaction conditions.

In one aspect of the present invention, there is provided an oximination/cyclization of 2-(4-chlorobenzoyl)benzoic acid with hydroxylamine hydrochloride in presence of molar quantities of inorganic bases such as sodium hydroxide in water or alcoholic solvents to form 4-(4'-chlorophenyl)-5,6-benz-oxazine-1-one (Formula 8). The reaction is faster with minimal impurity generation and the pure product is isolated by simple precipitation in high yield.

In another aspect of the present invention there is provided a process for amidation of compound of Formula 10 with ammonia in non-aqueous solvent like ketones and polar aprotic solvents like dimethyl formamide, limiting the formation of impurity of Formula 12 in the prior processes.

Yet another aspect of the present invention is the oxidation of penultimate intermediate of Formula 11 to form chlorthalidone using hydrogen peroxide in presence of alkali in a molar ratio of compound 9 : hydrogen peroxide : aqueous alkali in the range of from about 1:2.5:2.5 to about 1:3.5:3 and limits the formation of impurity of Formula 13.

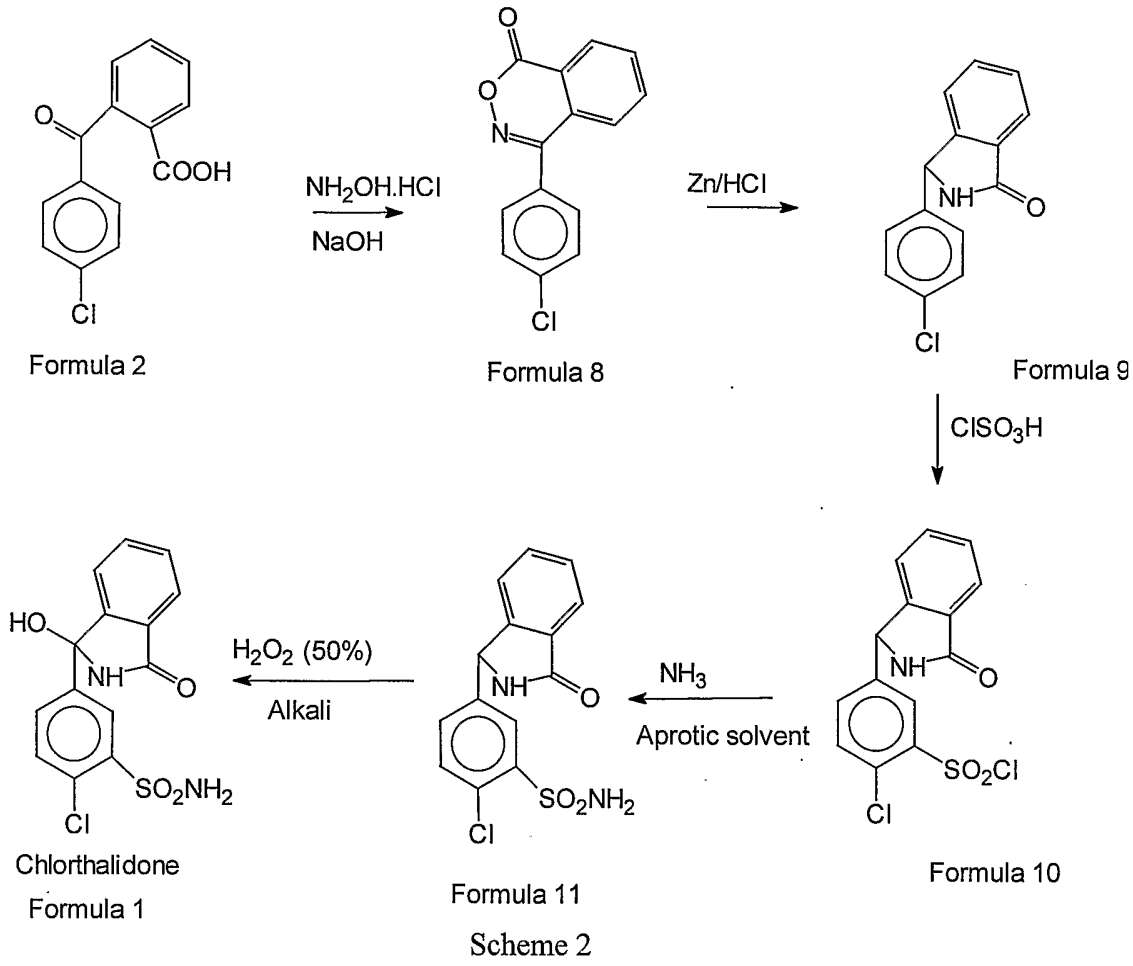
Another embodiment according to the present invention is the simple isolation of chlorthalidone from the reaction medium by neutralization, precipitation of crude chlorthalidone and single purification by crystallization from a solvent combination

such as water-methanol or water ethanol, water-ketone mixture in order to give pharmaceutical grade purity product in higher yield.

Detailed description of the invention

The present invention is directed to improve the manufacturing process of chlorthalidone, an antihypertensive and diuretic drug, by a simple, environmental friendly, using limited/minimal required amounts of hazardous chemicals. The various embodiments and alternatives are discussed herein after in detail.

In a first aspect of the present invention, a pure intermediate 4-(4'-chlorophenyl)-5,6-benz-oxazine-1-one of Formula 8 is provided by an oximination/cyclization reaction. This improved process involves an inorganic base catalyzed cyclization of a compound of Formula (2) with hydroxyl amine hydrochloride in a suitable solvent (Scheme 2). The starting material, 2-(4'-chlorobenzoyl) benzoic acid, of Formula (2) and its preparation was reported earlier for example in patents US 4500636, US 30555904, US4379092, US 3764664.



Scheme 2

In the prior art ('600 patent), this reaction was carried out in presence of pyridine base, which also acts as solvent, in a mixture of 1.25:1 proportion of pyridine and absolute ethanol. The use of pyridine in large excess results in a sticky mass when isolated by quenching with water due to the presence of pyridine. It is observed that use of molar amounts of organic bases like triethyl amine or pyridine does not lead the reaction to completion. The prior art also indicates anhydrous condition by the use of absolute ethanol (with 1: 1.25 v/v pyridine) for the reaction completion in presence of pyridine. The crude product was required to be further purified. The solvent pyridine also has disadvantages from environmental/operator hazard point of view when used in large excess as reported in the earlier processes. Moreover the isolation/purification of 4-(4'-

chlorophenyl)-5,6-benz-oxazine-1-one from pyridine and the recovery of pyridine, essential for environmental point of view, is considerably difficult.

It is, therefore, of interest to see the workability of employing an inorganic base for the complete transformation of compound of Formula (2) to Formula (8) and to employ a simple isolation procedure which is environmental friendly unlike pyridine process to get pure product.

Accordingly, it is found that an inorganic base such as potassium hydroxide or sodium hydroxide catalyzes this reaction and the reaction completes in a lesser period of time under suitable conditions. The reaction of compound of Formula 2 with hydroxylamine hydrochloride is performed in solvent selected from water, ethanol, isopropanol or their mixture thereof in any proportions. It is advantageous to perform the reaction in these solvents as the resulting 4-(4'-chlorophenyl)-5,6-benz-oxazine-1-one can be directly isolated after completion of reaction from solvent by precipitation of product, pure enough to proceed in subsequent step.

The inorganic base catalyzed transformation of Formula (2) to (8) is carried out preferably at a temperature of 75° to 100° C. The most preferable temperature range is 80° to 85° C and the reaction is completed in 4 to 7 hours.

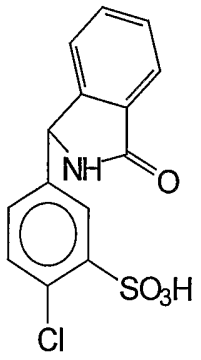
In process, according to this invention, inorganic base such as sodium or potassium hydroxides are preferably used in a molar ratio of 1.1 to 3 moles per mole of starting material of Formula (2) and most preferably in the ratio of 1.5 to 2 moles.

On completion of reaction the 4-(4'-chlorophenyl)-5,6-benz-oxazine-1-one precipitates out from these solvents, used in the present invention, upon cooling and is filtered under suction to give a compound of Formula (8) in substantially pure form.

The improved process of the invention is advantageous that it substantially reduces the impurity formation in the reaction thereby making the isolation of product from a single solvent and eliminates further purification of product, recovery and recyclability of pyridine, and handling as well as effluent problem associated with pyridine.

The intermediate of Formula 8 is then reduced with zinc metal and acetic acid to the corresponding phtalimidine of Formula (9) which is converted to 2-(3'-chlorosulphonyl-4'-chlorophenyl)phtalimidine(Formula 10) by reaction with chlorosulphonic acid and thionyl chloride in the absence of solvent.

According to the invention, there is provided an amidation process of Formula (10) to get the penultimate intermediate (Formula (11)) of chlorthalidone. The '600 patent process for amidation of 2-(3'-chlorosulphonyl-4'-chlorophenyl)phthalimidine results in partial hydrolysis of compound (10) to give an impurity of Formula(12) in 20% to 30% proportions invariably. This results in considerable yield loss and requires additional purifications in order for getting consistent purity for final product preparation.



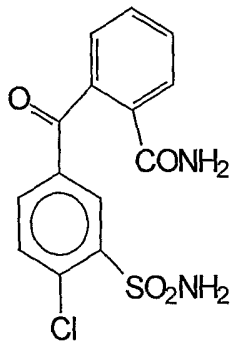
Formula12

In this aspect, according to present invention, an ammonia gas/solution is reacted with compound 10 in non-protic solvents such as ketones, chlorinated hydrocarbons like

dichloromethane, dimethylformamide, or acetonitrile. This limits the hydrolysis of compound 10 thereby formation of impurity of Formula (12). The reaction is advantageously performed at a temperature range of -10° to 10°C but preferably at a temperature of -5° to +5°C. It is preferable to use an ammonia solution in said solvents as reagent from operational point of view. The reaction completes in a time span of 2 to 4 hours, while limiting the formation of impurity (12), with an isolated yield of compound of Formula (11) in 90 to 95%.

The penultimate oxidation reaction of desoxy compound of Formula (11) is a major concern in the preparation of chlorthalidone. The '600 patent describes a number of oxidants like cromic acid, oxygen along with catalysts such as ferrous ammonium sulphate, cuprous sulphate, cobalt naphthalate, cuprous chloride etc., air with or without catalyst, permanganates, peroxides, chromates, hypochlorites are a few to name. And the reaction times vary from 0.5 hours to 72 hours or even more depending on yield required. The yields according to the examples 2(A, B, C, D) vary from 40 % and above and in some reactions the same is not determined.

As far as pharmaceuticals are concerned metal oxidation has serious limitation with respect to the removal of residual metals. It is observed that oxidants such as permanganates leads to over oxidation and breaking of the phthalimidine ring to form a compound of Formula (13) and is a serious limitation. Mild oxidants either not leads the reaction to completion or the longer duration of reaction leads to opening of phthalimidine ring to give the said impurity. Most of the general reagent described in the '600 patent is not applicable to preparation of chlorthalidone. This leads the present inventors to study various parameters such as reagent selection, reagent ratios, catalyst requirement and its amount if required, time of reaction, temp, etc. a few to name.



Formula 13

The present inventors have found that a moderately active oxidant namely hydrogen peroxide can be used where the complete oxidation of Formula 11 can be effected while formation of impurity of Formula 13 is reduced, if used in a specific combination of reagent to starting material.

According to example 2 C of '600 patent the reagent, hydrogen peroxide, was used in molar excess of 60 fold (hazardous reagent when used in excess) and the reaction mass collected after 24 hours was not isolated but only identified the product among many others using techniques such as TLC. So it was of interest to see the behaviour of reaction towards hydrogen peroxide in presence or absence of alkali and to optimize the formation of chlorthalidone.

Surprisingly it was found, according to the present invention, that a significantly lesser molar amounts of hydrogen peroxide in presence of an alkali oxidizes compound of Formula (11) exclusively to chlorthalidone at a particular ratio of reagents to starting material under specified conditions. The important results of the explorations are listed below.

Serial No	Formula 11 (mole)	Hydrogen peroxide In moles	Alkali (sodium hydroxide) (mole)	Reaction time	Temp °C	Unreacted 11	Impurity 12	% yield
1	1	1.5	1.5	*30*	50	20%	10%	NI
2	1	2.0	2.0	30	30	5%	7.8%	90%
3	1	2.5	2.5	4	25	0%	1.0%	95%
4	1	3.0	2.5	3	25	0%	1.0%	95%
5	1	3.0	3.0	3	25	.0%	1.1%	95%
6	1	4.0	4.0	3	20	0%	5.5%	84%
7	1	5.0	5.0	3	20	0%	10%	80%
8	1 mole	60	3.0	1	20	0%	60%	NI

Reaction solvent: water, NI stands for not isolated

Accordingly a molar ratio in the range of 1:2.5 to 1:3.5 of hydrogen peroxide relative to starting material (11) is essential to give complete oxidation of compound (11) and for limiting the generation of impurity of Formula 13. It is advantageous to perform the reaction in presence of alkali like sodium hydroxide for reducing the amount of hydrogen peroxide which is hazardous in large amounts.

The oxidation reaction of the present invention is carried out in solvents selected from water or a combination of water and alcoholic solvents. This organic solvent-water system is also essential for the success of the reaction as the reactants are in a homogeneous condition while reaction. The preferable solvent is water when an alkali is used in the oxidation along with hydrogen peroxide. The other solvent system used in the present invention is selected from water-methanol, water-ethanol, and water–

isopropyl alcohol, water–acetone. The preferable ratio of organic solvent-water is in the range of 10% to 50 % of organic solvent and 50% to 90 % of water.

It is also possible to use hydrogen peroxide of a different concentration such as 20%, 30% or 60% etc. Then according to the present invention, the concentration of hydrogen peroxide in the reaction is adjusted to be in the range of 2 to 5 % based on the volume of reaction medium and more preferably the amount of hydrogen peroxide in the reaction medium is from about 2.5% to about 3.5%

The present reaction is conducted at a temperature range of 20° to 30°C for better results. The most preferable amount of oxidant is in the range of 2.5 to 3.5 molar excess hydrogen peroxide relative to compound of Formula (11). Below the limit the oxidation remains incomplete and on increasing the amount on the upper limits results in over oxidation and impurity generation. The alkali preferably used in the invention is sodium hydroxide or potassium hydroxide and the preferable ratio is 2.5 to 3.5 relative to compound of Formula (11) irrespective of the amount of hydrogen peroxide used.

Further, on completion of the reaction the reaction mass is adjusted to a pH of 4.5 to 5.0 with inorganic acid preferably hydrochloric acid to precipitate the product from the reaction medium. The crude product obtained by the optimized process of the present invention is having a purity of at least 97%.

In another embodiment of the present invention, there is provided a purification method wherein the crude product is crystallized from a combination solvent to attain a purity of at least 99.9 % (based on HPLC analysis) in a single purification step. The combination solvent used is selected from the group consist of water-methanol, water-ethanol, water-acetone and water-acetonitrile and the preferable solvent is water-methanol. The dissolution is effected at a temperature range from ambient to reflux temperature. The ratio of the multiple solvent systems is in the range of 30 to 60%

organic solvent and 70 to 40% water and preferably the ratio is 50:50 organic solvent to water.

The purification involves the steps of forming a solution of crude chlorthalidone in a combination of solvents selected from water-methanol, water-ethanol, water-acetone or water-acetonitrile. The resulting solution is optionally treated with an adsorbent like charcoal and filtered to remove insolubles. The clear solution so obtained is cooled to crystallize pure chlorthalidone.

The following non-limiting specific examples presented to illustrate the best mode of carrying out the process of the present invention. The examples are not limited to the particular embodiments illustrated herein but include the permutations, which are obvious set forth in the description. There is also provided a comparative process which is carried out according to example 2C of '600 patent in order to ascertain the present inventive features.

Examples

Example-1 (4-(4'-chlorophenyl)-5,6-benz-2,3-oxazin-1-one)

In a reaction vessel, 100 gm 2-(4'-chlorobenzoyl) benzoic acid, 100gm hydroxylamine hydrochloride and 24 gm sodium hydroxide were taken. Then 600 ml isopropyl alcohol was added to the mixture. The stirred mixture was heated to 80° to 85°C and maintained at the same temperature for 6 hours. The reaction mass was cooled to room temperature (nearly 25°C) and the precipitated 4-(4'-chlorophenyl)-5,6-benz-2,3-oxazin-1-one were filtered off and dried to constant weight to give 95 gm (yield :96%) product.

Example-2: (4-(4'-chlorophenyl)-5,6-benz-2,3-oxazin-1-one)

In a reaction vessel, 100 gm 2-(4'-chlorobenzoyl)benzoic acid, 125gm hydroxylamine hydrochloride and 25 gm sodium hydroxide were taken. Then 1000 ml water was added to the mixture. The stirred mixture was heated to 85° to 90°C and maintained at the

same temperature for 6 hours. The reaction mass was cooled to room temperature (25°C) and the precipitated 4-(4'-chlorophenyl)-5,6-benz-2,3-oxazin-1-one were filtered off and dried to constant weight to give 95 gm (yield :96%) product.

Example-3: (3-(3'-chlorosulphonyl-4'chlorophenyl)phthalimidine)

In a reaction vessel, 100 gm 2-(4'-chlorobenzoyl) benzoic acid, was taken and 490 gm chlorosulphonic acid and 99.2 gm thionyl chloride were added. The reaction mixture was heated under stirring to 75° to 80°C and maintained for 4 hours. The reaction mass was cooled to 30 to 35°C. The reaction mass then quenched on to crushed ice and water mixture at temperature 0° to 5°C. The precipitated 3-(3'chlorosulphonyl-4'chlorophenyl)phthalimidine was filtered off to give 450 gm wet product.

Example–4: (3-(3'chlorosulphamyl-4'-chlorophenyl)phthalimidine)

In a reaction vessel, 450 gm wet 3-(3'-chlorosulphonyl-4'chlorophenyl)phthalimidine was taken and 1000ml acetone was added. The resulting slurry was cooled to 0° to -5°C and ammonia gas was purged slowly into the slurry while maintaining the temperature at 0° to –5°C till a pH of 10 to 11 was obtained. The reaction mass was then raised to 25°C and maintained for 3 hours. On completion of reaction, 700 ml of water was added and cooled to 0° to 5°C and adjusted the pH of the reaction mass to 7 to 8 with conc. HCl. The precipitated 3-(3'-chlorosulphamyl-4'-chlorophenyl)phthalimidine was filtered off and dried to constant weight to give 125 gm (yield :95%) product.

Example-5: (3-hydroxy-3-(3'-sulphamyl-4-chlorophenyl)phthalimidine)

In a reaction vessel, 100 gm 3-(3'-chlorosulphamyl-4'-chlorophenyl)phthalimidine was dissolved in sodium hydroxide solution (prepared by dissolving 37 gm sodium hydroxide in 1000 ml water) at a temperature of 25 to 30°C. To the dissolved solution, 65 gm of 50% hydrogen peroxide solution was added dropwise while maintaining the temperature at 20° to 25°C and maintained the reaction mass at 20 to 25 °C for 2 hours.

The pH was adjusted with 75 ml conc. HCl to precipitate the product. The precipitated 3-hydroxy-3-(3-sulphamyl-4-chlorophenyl)phthalimidine was then filtered and dried to constant weight (98 gm, yield : 94%)

Example-6: (3-hydroxy-3-(3'-sulphamyl-4-chlorophenyl)phthalimidine)
In a reaction vessel, 100 gm 3-(3'-chlorosulphamyl-4'-chlorophenyl)phthalimidine was dissolved in sodium hydroxide solution (prepared by dissolving 31 gm sodium hydroxide in 1000 ml water) at a temperature of 25 to 30°C. To the dissolved solution, 53 gm of 50% hydrogen peroxide solution was added dropwise while maintaining the temperature at 20° to 25°C and maintained the reaction mass at 20 to 25°C for 2 hours. The pH was adjusted with 70 ml conc. HCl to precipitate the product. The precipitated 3-hydroxy-3-(3-sulphamyl-4-chlorophenyl)phthalimidine was then filtered and dried to constant weight (97 gm, yield : 93%)

Example-7: (3-hydroxy-3-(3'-sulphamyl-4-chlorophenyl)phthalimidine)
In a reaction vessel, 100 gm 3-(3'-chlorosulphamyl-4'-chlorophenyl)phthalimidine was suspended in 500 ml methanol and was dissolved in sodium hydroxide solution (prepared by dissolving 37 gm sodium hydroxide in 500 ml water) at a temperature of 25 to 30°C. To the dissolved solution, 65 gm of 50% hydrogen peroxide solution was added dropwise while maintaining the temperature at 20° to 25°C and maintained the reaction mass at 20 to 25°C for 2 hours. The pH was adjusted with 75 ml conc. HCl to precipitate the product. The precipitated 3-hydroxy-3-(3-sulphamyl-4-chlorophenyl)phthalimidine was then filtered and dried to constant weight (94 gm, yield : 90%)

Example-8: Purification of chlorthalidone
In a vessel, 100gm 3-hydroxy-3-(3-sulphamyl-4-chlorophenyl) phthalimidine was suspended in 1000 ml methanol and heated the mass to reflux to obtain clear solution. 10 gm activated carbon was added to the clear solution. After Filtering the solution, the

filtrate was added to 1000ml water at 45-50°C. The mixture was cooled slowly to crystallize the product. The product was filtered, washed with 200 ml water, and dried to constant weight (90 gm). Yield: 90%, HPLC purity: 99.9%.

We claim,

1. An industrial process for the preparation of chlorthalidone of Formula (1) comprising the steps of:

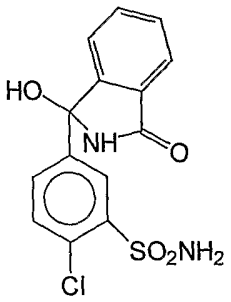
a) reacting 2-(4'-chlorobenzoyl)benzoic acid with hydroxylamine hydrochloride characterized in that, the reaction is performed in the presence of an inorganic base in a protic solvent to yield 4-(4'-chlorophenyl)-5,6-benz-oxazine-1-one (Formula 8);

b) reducing said compound of Formula (8) using zinc and acetic acid to provide phthalimidine of Formula 9;

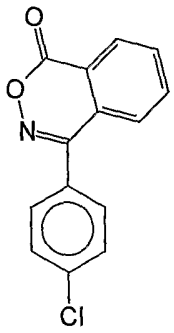
c) chlorosulphonating said phthalimidine of Formula (9) to yield a compound of Formula (10) using chlorosulphonic acid and thionyl chloride;

d) converting the sulphonylchloride functional group of said compound (10) to sulphonamide compound (11) using ammonia characterized in that, the reaction is performed in non-protic solvent.

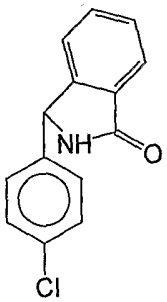
e) oxidizing the resulting compound of Formula (11) using hydrogen peroxide in the presence of alkali characterized in that, the compound (10), hydrogen peroxide, and alkali are reacted at a molar ratio of from about (1):(2.5):(2) to (1):(3.5):(3.5) in a solvent system to give chlorthalidone, in high yield.



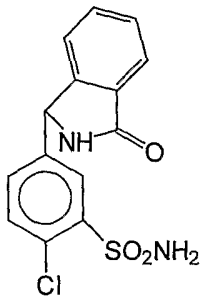
Formula 1



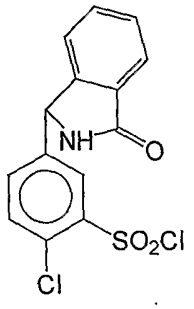
Formula 8



Formula 9



Formula 11



Formula 10

2. The process as claimed in claim 1(a), wherein said inorganic base is selected from sodium hydroxide or potassium hydroxide.

3. The process as claimed in claims1 (a) and 2, wherein said base is used in a molar ratio of 1.1 to3 moles per mole of 2-(4'-chlorobenzoyl) benzoic acid, preferably in the ratio of 1.5 to 2 moles.

4. The process as claimed in claim 1(a), wherein said solvent used is polar protic solvent.

5. The process as claimed in claims 1 (a) and 3, wherein said polar protic solvent is selected from water, ethanol, isopropyl alcohol or their mixture thereof.

6. The process as claimed in claim 1 (a) wherein said reaction is effected at a temperature ranging from 75° to 100°C.

7. The process as claimed in claim 1(a), wherein said reaction is effected at a temperature range of 80-85°C.

8. The process as claimed in claim 1 (d), wherein said non-protic solvent is selected from ketones, chlorinated benzenes like dichloromethane, dimethylformamide and acetonitrile.

9. The process as claimed in claim 1 (d) wherein said reaction is carried out at a temperature range of -10 to 10°C.

10. The process as claimed in claim 9, wherein said reaction is carried out at temperature range of -5 to 5°C.

11. The process as claimed in claim 1(e),wherein said hydrogen peroxide used in a molar ratio of 1:2.5 to 1:3.5 relative to compound of Formula (11) in presence of an alkali.

12. The process as claimed in claim 1(e) and 11, wherein said alkali is sodium hydroxide or potassium hydroxide.

13. The Process as claimed in claim 1(e), wherein said reaction is effected at a temperature ranging 20° to 30°C.

14. The process as claimed in claims 1(e), wherein said hydrogen peroxide is a 50% solution in water.

15. The process as claimed in claim 13, wherein the concentration of said hydrogen peroxide is in the range of 2 to 5 % based on the volume of reaction medium.

16. The process as claimed in claim 14, wherein the concentration of said hydrogen peroxide is in the range of 2.5 to 3.5 % based on the volume of reaction medium.

17. The process as claimed in any of the preceding claims 11 to 16, wherein said hydrogen peroxide is used in molar excess of 2.5 to 3.5 relative to compound of Formula (11)

18. The process as claimed in any of the preceding claims 11 to 17 wherein said alkali is used in a molar excess of 2 to 3.5 moles relative to starting compound of Formula (11).

19. The process as claimed in any of the preceding claims 1(e) and11 to 18 wherein said solvent is selected from water or a combination of water and organic solvent like water-methanol, water-ethanol water-isopropanol or water-acetone.

20. The process as claimed in claim 18, wherein said solvent combination of water and organic solvent is 40% to 80% of water and 60% to 20 % of organic solvent.

21. The process as claimed in claims 1 or 18 wherein the reaction is performed in water.

22. The process for preparation of chlorthalidone as claimed in claim 1 further comprising purification steps of: precipitating crude chlorthalidone by neutralizing the reaction mass produced in claim 1 using hydrochloric acid; dissolving crude chlorthalidone in a combination of solvents selected from water-methanol, water-ethanol, water-acetone or water-acetonitrile; optionally treating the said solution with an adsorbent; and crystallizing pure chlorthalidone from said solution on cooling.

23. The process as claimed in claim 22 wherein the ratio of said solvent combination is 30 to 70% of organic solvent and 70 to 30% of water and preferable ratio is 1:1.

24. The process as claimed in claims 1 or 22 wherein the crude chlorthalidone has a purity of at least 97%.

25. The process as claimed in claims 1 or 22 wherein the chlorthalidone obtained is substantially free of impurity of Formula (13) or at least less than 0.1% wt/wt.

26. An industrial process for the preparation of chlorthalidone of Formula (1) and purification of said chlorthalidone as substantially described herein with reference to the foregoing examples 1 to 8.