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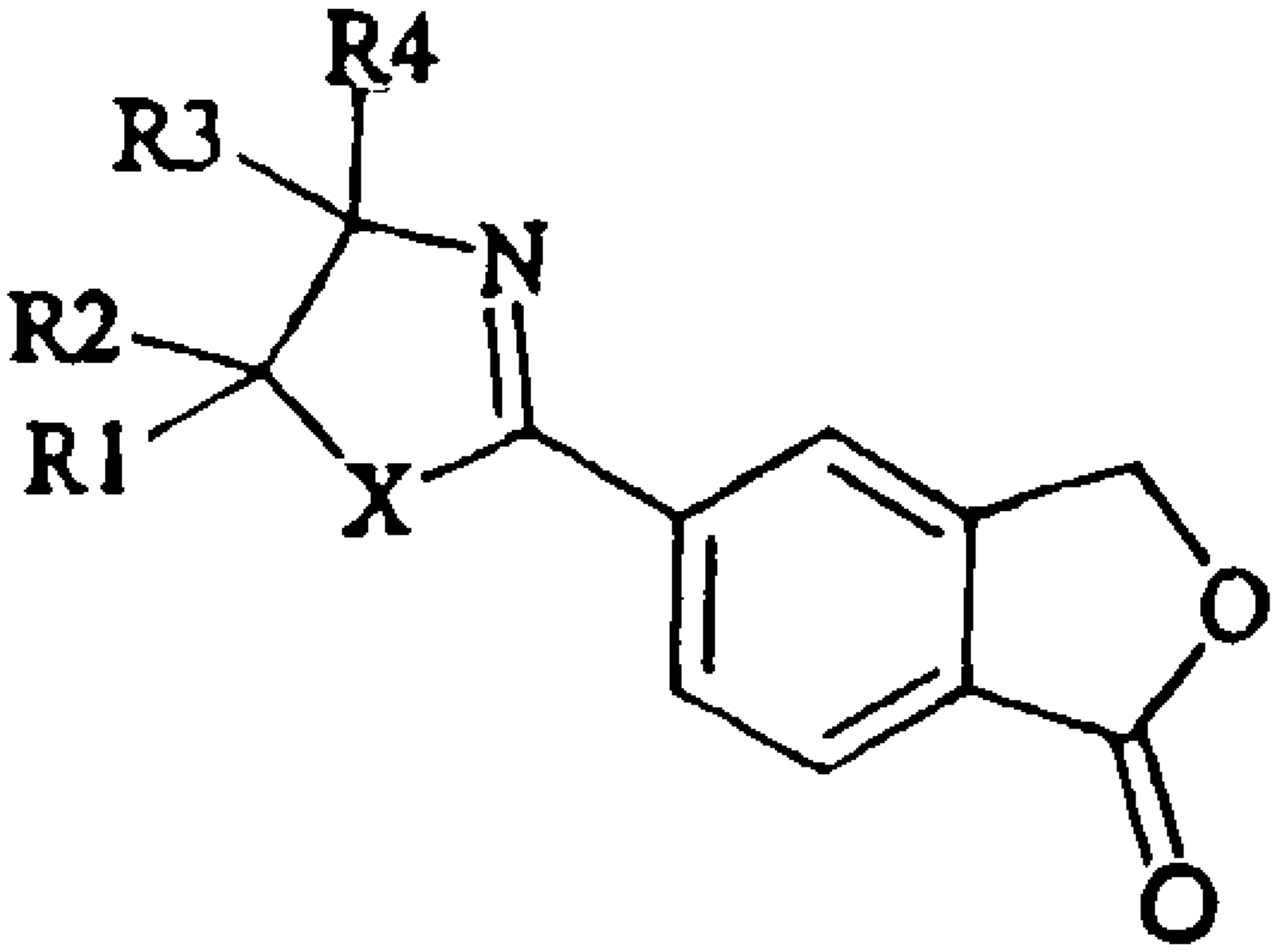
(54) Titre : PROCEDE DE PREPARATION DE 5-CYANOPHTHALIDE
(54) Title: METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE



Formula IV

(57) Abrégé/Abstract:

A method for the preparation of 5-cyanophthalide comprising treatment of a compound of formula (IV) wherein X is O or S; R^1-R^2 are each independently selected from hydrogen and C_{1-6}alkyl, or R^1 and R^2 together form a C_{2-5}alkylene chain thereby forming a spiro-ring; R^3 is selected from hydrogen and C_{1-6}alkyl, R^4 is selected from hydrogen, C_{1-6}alkyl, a carboxy group or a precursor group therefore, or R^3 and R^4 together form a C_{2-5}alkylene chain thereby forming a spiro-ring; with a dehydration agent or alternatively where X is S, thermally cleavage of the thiazoline ring or treatment with a radical initiator, such as peroxide or with light, to form 5-cyanophthalide, which is an important intermediate used in the preparation of the antidepressant drug citalopram.

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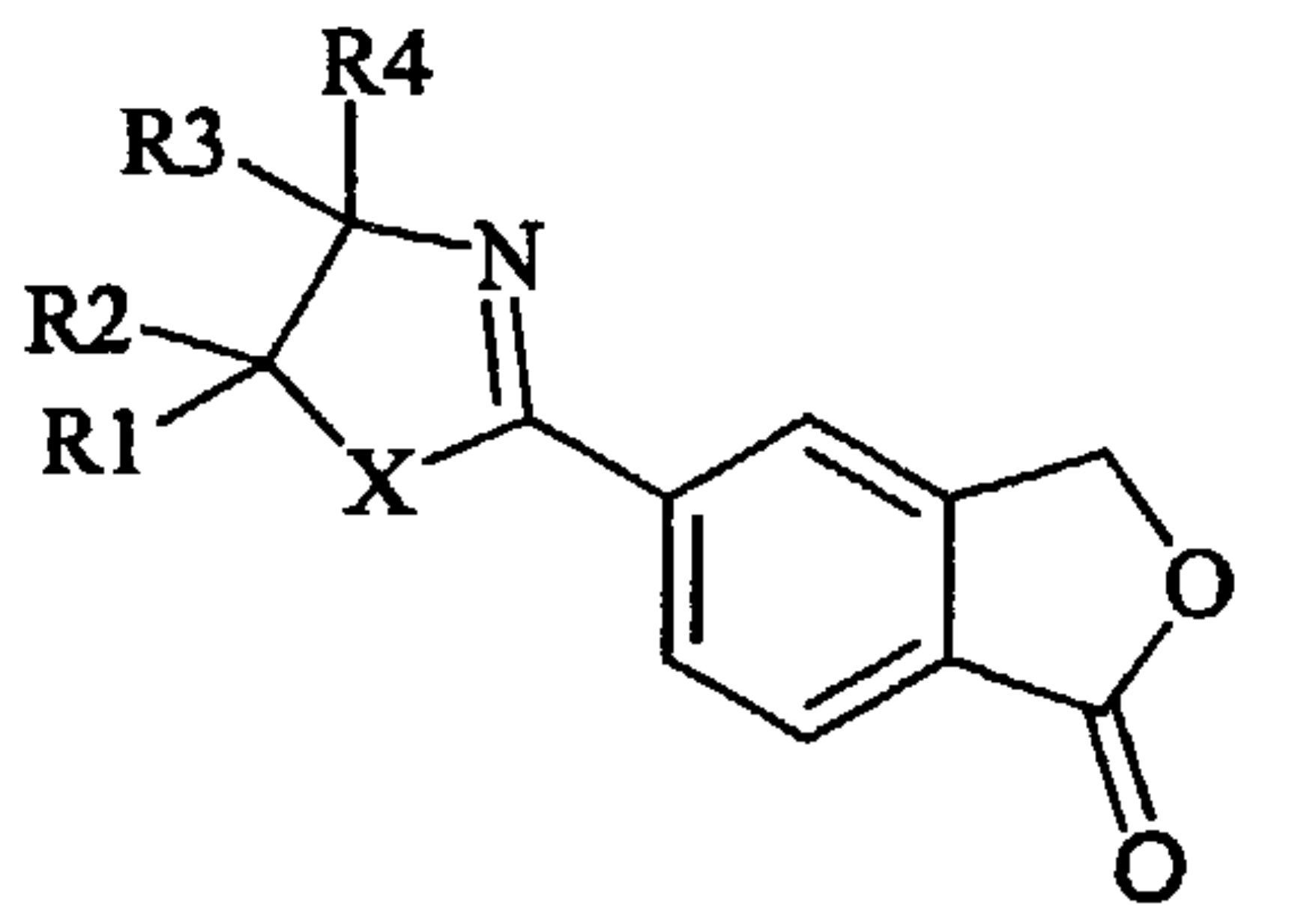
(54) **Title:** METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE



(IV)

(57) **Abstract:** A method for the preparation of 5-cyanophthalide comprising treatment of a compound of formula (IV) wherein X is O or S; R^1-R^2 are each independently selected from hydrogen and C_{1-6}alkyl, or R^1 and R^2 together form a C_{2-5}alkylene chain thereby forming a spiro-ring; R^3 is selected from hydrogen and C_{1-6}alkyl, R^4 is selected from hydrogen, C_{1-6}alkyl, a carboxy group or a precursor group therefore, or R^3 and R^4 together form a C_{2-5}alkylene chain thereby forming a spiro-ring; with a dehydration agent or alternatively where X is S, thermally cleavage of the thiazoline ring or treatment with a radical initiator, such as peroxide or with light, to form 5-cyanophthalide, which is an important intermediate used in the preparation of the antidepressant drug citalopram.

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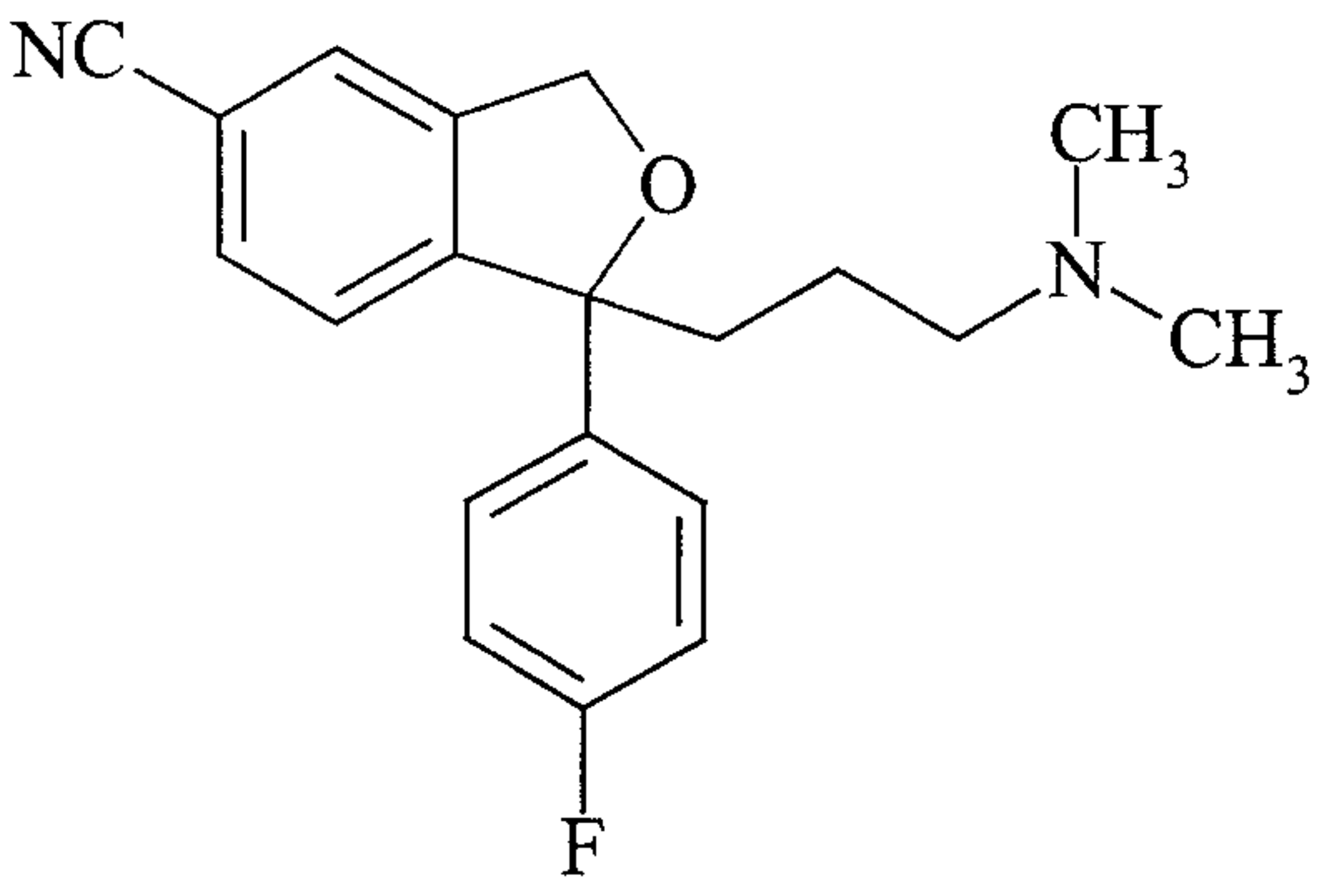
METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE

The present invention relates to a novel process for the preparation of 5-cyanophthalide which is an intermediate used for the manufacture of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention.

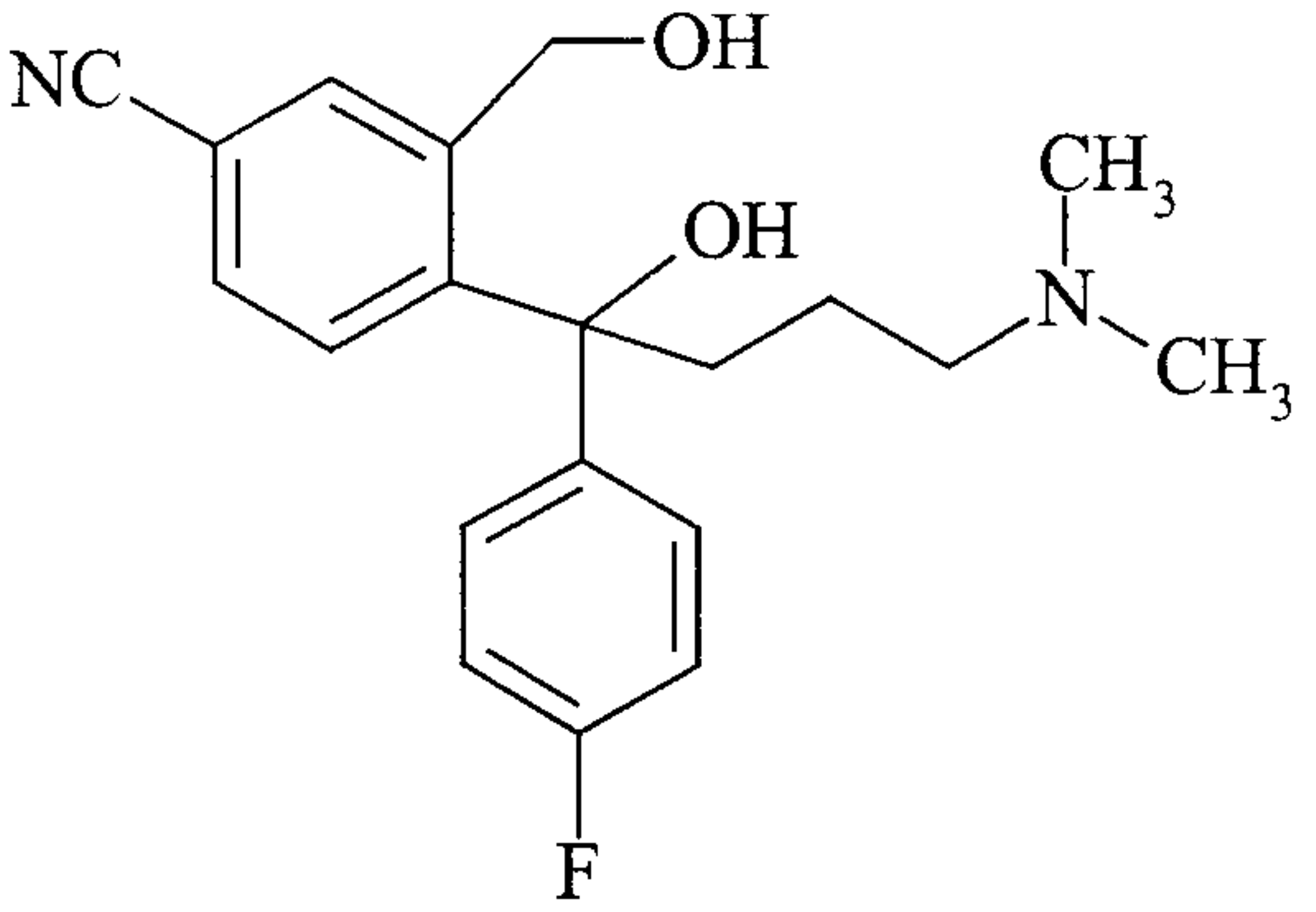
Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982,** *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486.

Citalopram is prepared by the process described in US Patent No 4,650,884, according to which 5-cyanophthalide is subjected to two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively, and the resulting compound of the formula



Formula II

is subjected to a ring closure reaction by dehydration with strong sulfuric acid.

Enantiomers of citalopram may be prepared by the method described in US Patent No 4,943,590, i.e. by separating the enantiomers of the intermediate of Formula II and performing enantioselective ring closure in order to obtain the desired enantiomer.

Thus, 5-cyanophthalide is an important intermediate for the manufacture of citalopram and it is important to produce this material in an adequate quality, by a convenient process and in a cost-effective way.

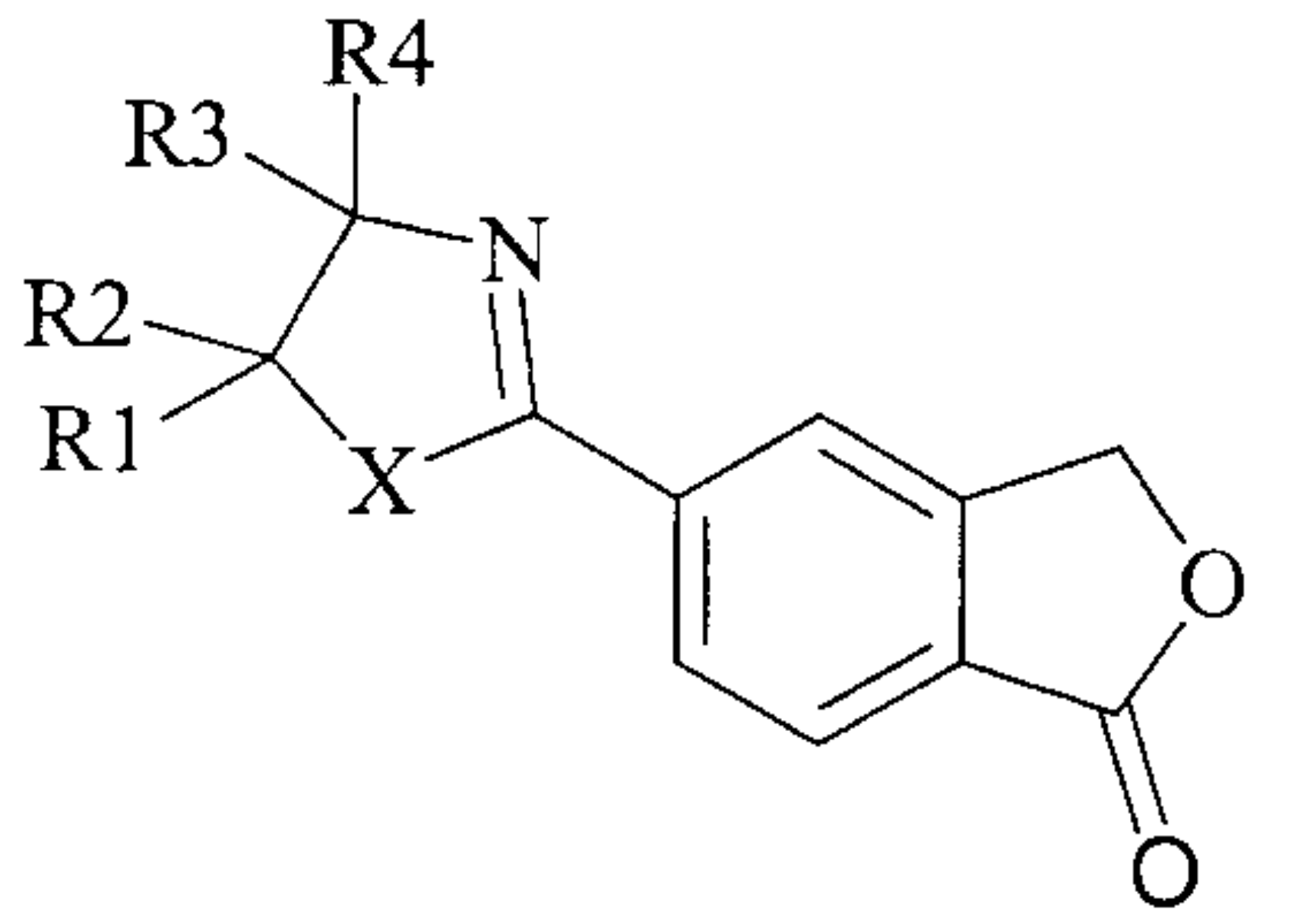
A method for the preparation of 5-cyanophthalide has previously been described in *Bull. Soc. Sci. Bretagne*, **1951**, *26*, 35 and in *Levy and Stephen, J. Chem. Soc.*, **1931**, 867. By this method 5-aminophthalide is converted to the corresponding 5-cyanophthalide by diazotation followed by reaction with CuCN. 5-Aminophthalide was obtained from 4-aminophthalimide by a two step reduction procedure.

Synthesis of certain alkyl- and phenylnitriles from acid chlorides is described in *Tetrahedron Letters*, **1982, 23**, *14*, 1505 - 1508, and in *Tetrahedron*, **1998**, *54*, 9281.

It has been found that 5-cyanophthalide may be prepared in high yields by a convenient, cost-effective procedure from the 2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline or -thiazoline intermediates of Formula IV.

Description of the invention

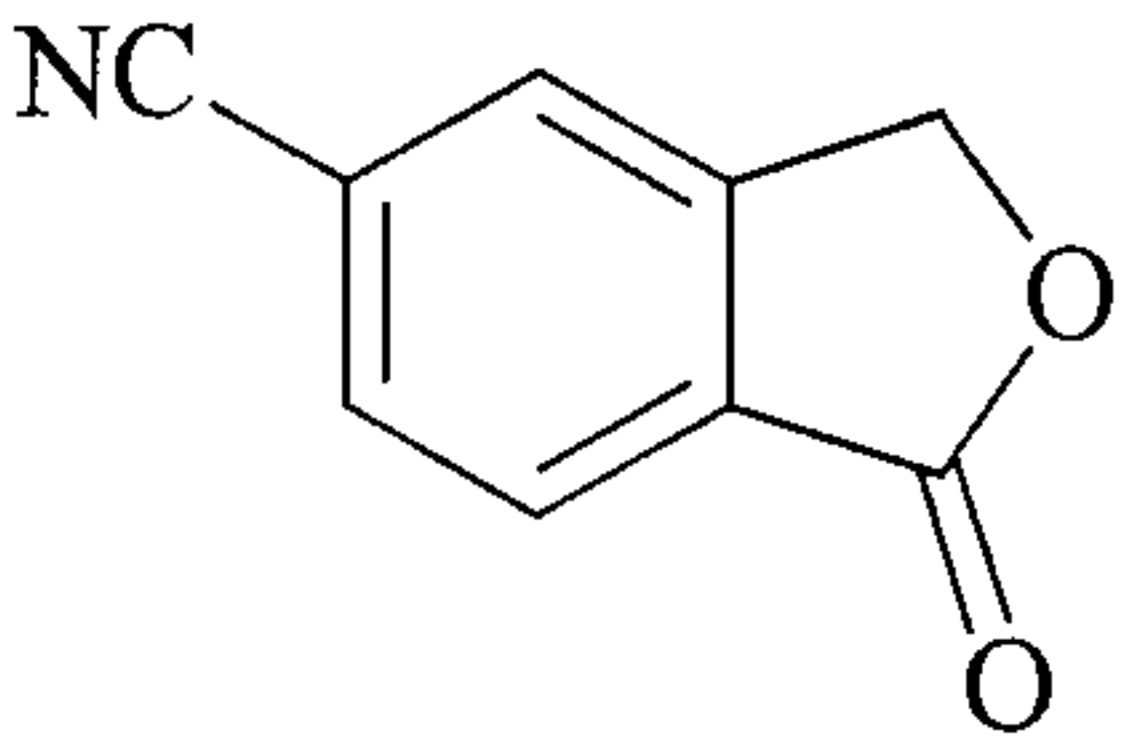
Accordingly, the present invention provides a novel method for the preparation of 5-cyanophthalide comprising treatment of a compound of Formula IV



Formula IV

wherein X is O or S;

R^1 - R^2 are each independently selected from hydrogen and C_{1-6} alkyl, or R^1 and R^2 together form a C_{2-5} alkylene chain thereby forming a spiro-ring; R^3 is selected from hydrogen and C_{1-6} alkyl, R^4 is selected from hydrogen, C_{1-6} alkyl, a carboxy group or a precursor group therefore, or R^3 and R^4 together form a C_{2-5} alkylene chain thereby forming a spiro-ring; with a dehydration agent or alternatively where X is S, thermally cleavage of the thiazoline ring or treatment with a radical initiator, such as peroxide or with light, to form 5-cyanophthalide having the formula



Formula III

The dehydration agent may be phosphoroxytrichloride, thionylchloride, phosphorpentachloride, PPA (polyphosphoric acid), and P_4O_{10}. The reaction may be carried out in the presence of an organic base, such as pyridine or a catalytic amount of a tertiary amide.

Preferably, the compound of Formula IV is treated with $SOCl_2$ as a dehydrating agent and the reaction is carried out in toluene comprising a catalytic amount of N,N-dimethylformamide.

Alternatively, the dehydration agent may be a Vilsmeier reagent, i.e. a compound which is formed by reaction of a chlorinating agent, preferably an acid chloride, e.g. phosgene, oxalyl chloride, thionyl chloride, phosphoroxychloride, phosphorpentachloride, trichloromethyl chloroformate, also briefly referred to as "diphosgene", or bis(trichloromethyl) carbonate, also briefly referred to as "triphosgene", with a tertiary amide such as N,N-dimethylformamide or a N,N-dialkylalkanamide, e.g N,N-dimethylacetamide. A classic Vilsmeyer reagent is the chloromethylenedimethyliminium chloride. The Vilsmeier reagent is preferably prepared *in situ* by adding the chlorinating agent to a mixture containing the starting oxazoline or thiazoline derivative of formula IV and the tertiary amide.

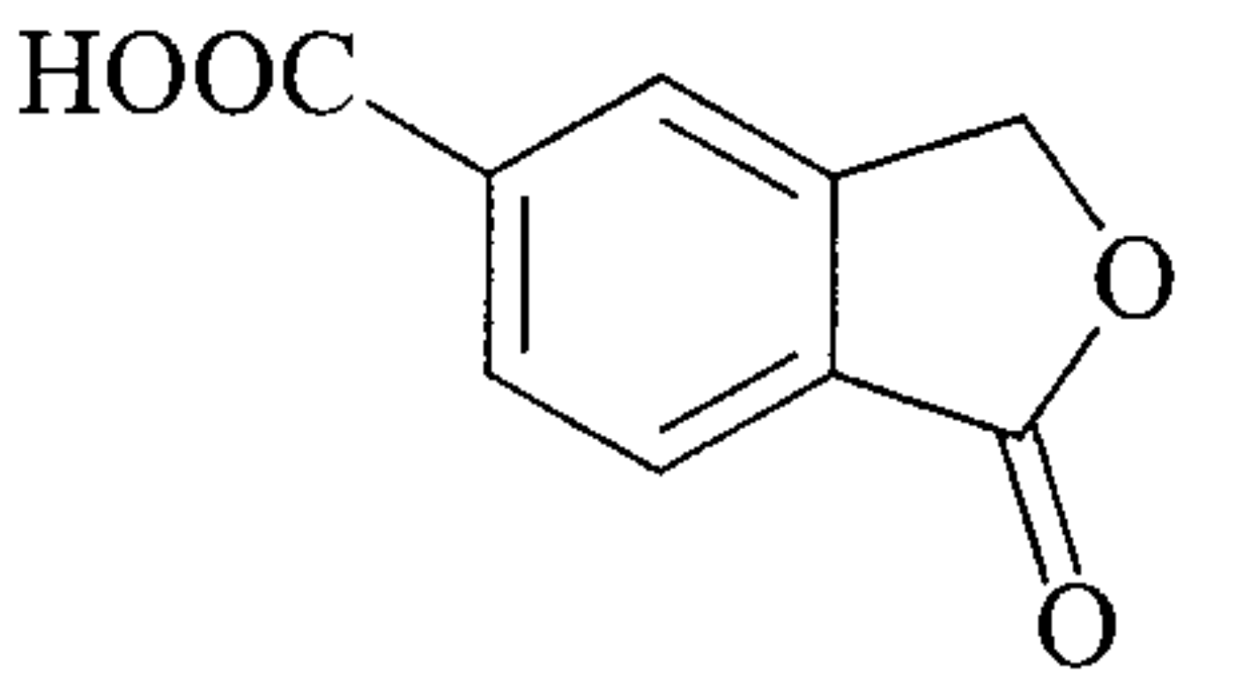
When X is S and the conversion of the thiazoline group into the cyano group is made by thermal transformation, the thermal decomposition of compound IV is preferably carried out in an anhydrous organic solvent, more preferably an aprotic polar solvent, such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide or acetonitrile. The temperature at which the thermal decomposition transforms the 2-thiazolyl group to a cyano group is between 60 °C and 140 °C. The thermal decomposition may conveniently be carried out by reflux in a suitable solvent, preferably acetonitrile. The thermal cleavage may conveniently be carried out in the presence of oxygen or an oxidation agent. Compounds of Formula IV where X is S and R^4 is a carboxy group or a precursor for a carboxy group can also be converted to citalopram by treatment with a radical initiator such as light or peroxides.

Throughout the specification and the claims, C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

Accordingly, by the process of the invention, 5-cyanophthalide is obtained in high yields and the process is much more convenient than the known process. It is a so-called robust process. The usage of CuCN is eliminated thereby minimising the amount of undesirable by-products and making an environmentally compatible process.

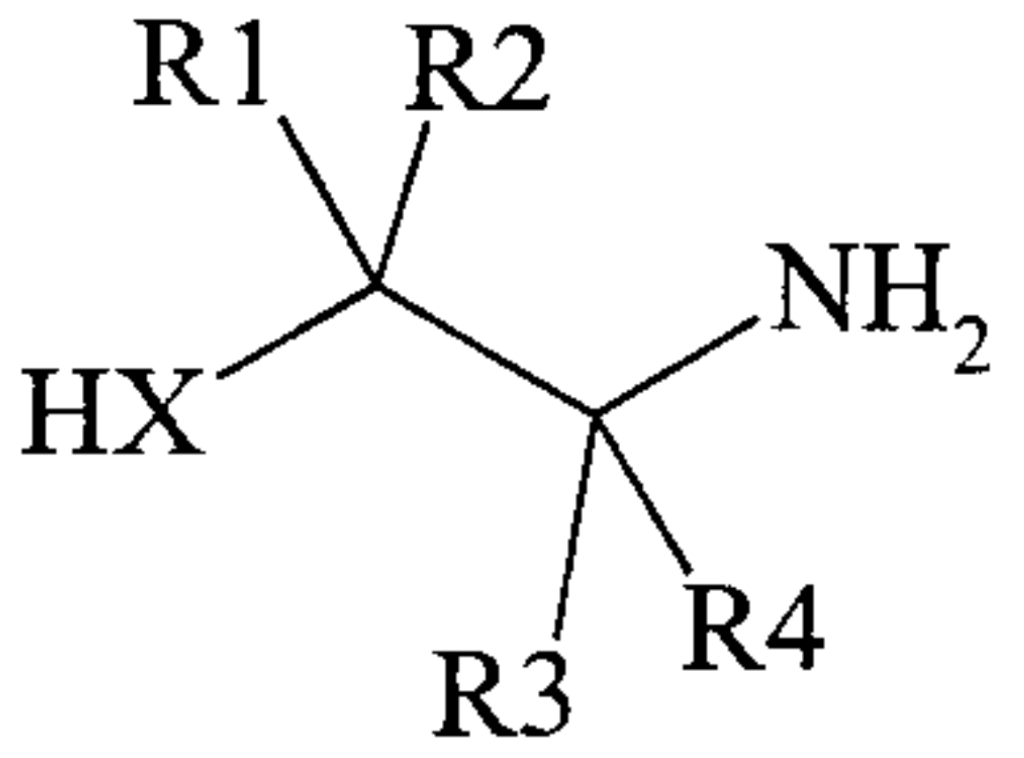
In a further aspect, the invention relates to a method for preparing the intermediate of Formula IV comprising:

a) reacting a functional derivative of 5-carboxyphthalide of Formula V



Formula V

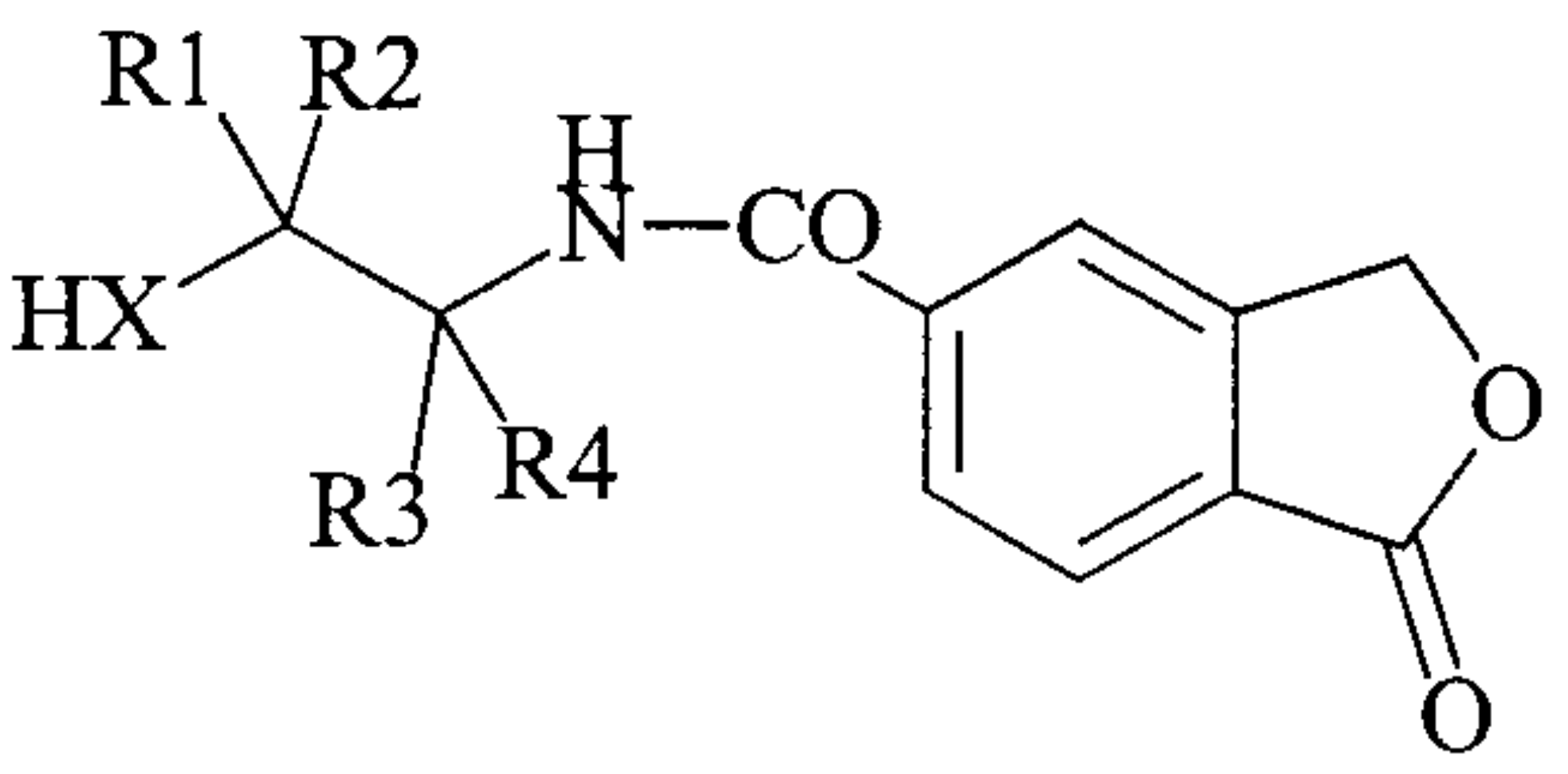
with a 2-hydroxy- or 2-mercaptoethanamine of Formula VI



Formula VI

in which X, $R^1 - R^4$ are as defined above,

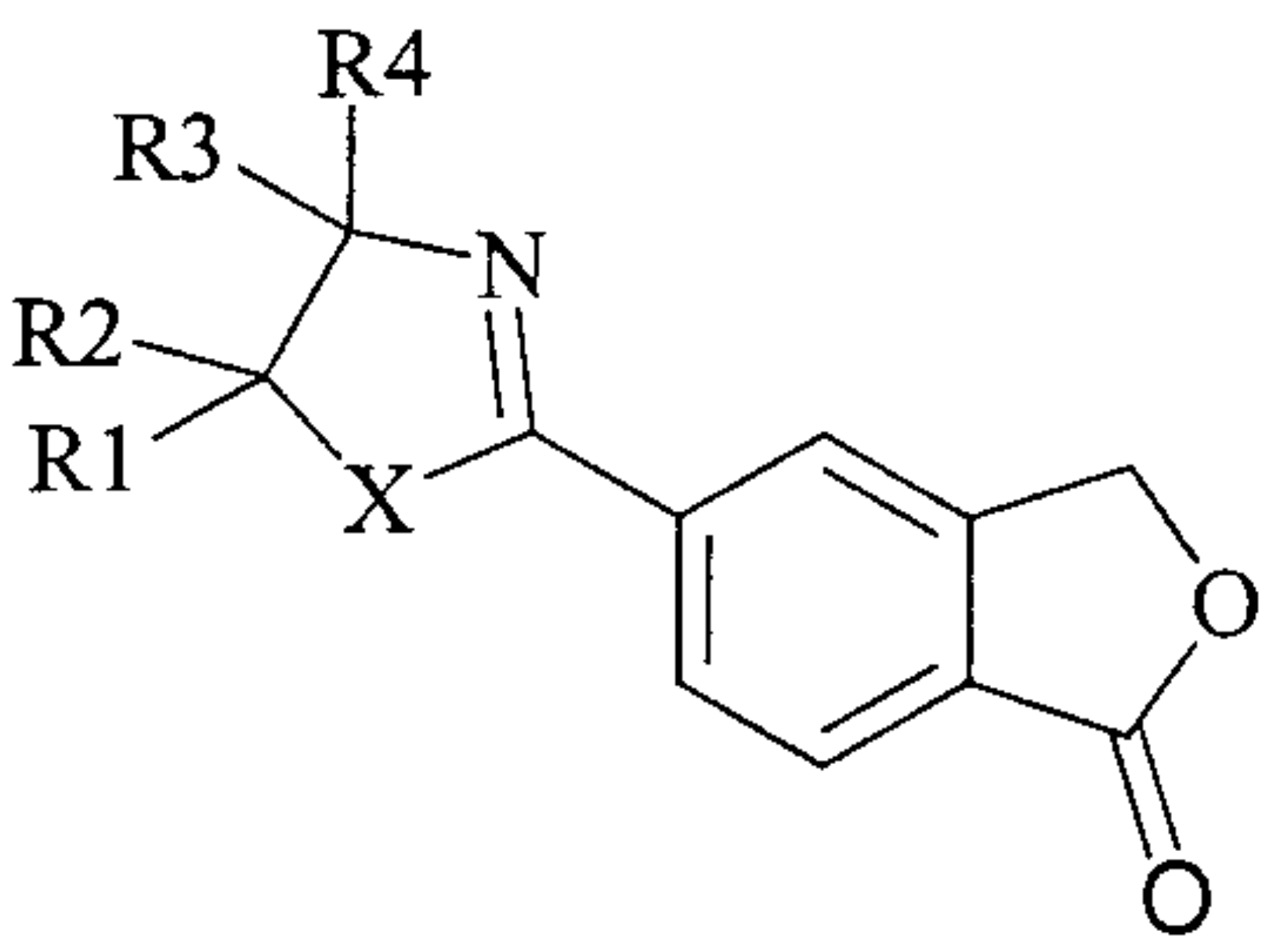
(b) submitting the amide of Formula VII thus obtained



Formula VII

in which X, $R^1 - R^4$ are as defined above, to a ring closure by dehydration;

thereby obtaining the 2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline or -thiazoline of Formula IV



Formula IV

Preferably, the functional derivative used in step a) is an ester, such as alkylester, arylester or alkylarylester derivative of 5-carboxyphthalide, or an acidhalide derivative of 5-carboxyphthalide.

Preferably, the dehydrating agent used in step b) is $SOCl_2$, $POCl_3$ and PCl_5, most preferably $SOCl_2$.

The reaction in step b) is carried out neat or in a suitable solvent, such as toluene, sulfolan or acetonitrile. Furthermore, when a solvent is used, a catalytic amount of N,N-dimethylformamide may be needed, in particular when the dehydrating agent is $SOCl_2$. Preferably, toluene is used as the solvent, if necessary in the presence of a catalytic amount of N,N-dimethylformamide.

The reaction in step b) is carried out at elevated temperature, preferably at the reflux temperature of the solvent.

The reaction time is not important and may easily be determined by a person skilled in the art.

The 5-carboxyphthalide used as a starting material may be obtained by the methods described in US patent No 3,607,884 or German patent No 2630927, i.e. by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO_3 or by electrochemical hydrogenation of trimellithic acid.

In a preferred embodiment of the process of the invention, R^3 is methyl or ethyl.

5-Cyanophthalide may be isolated in a conventional way, e.g. by addition of water, filtration and subsequent washing of the crystals. Further purification may, if desired, be performed by recrystallisation.

Accordingly, by the process of the invention, 5-cyanophthalide is obtained by the novel use of the 2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline or -thiazoline intermediates of Formula IV as reactants. Using these reactants, process conditions are much more convenient than the conditions previously described in the known process for preparing 5-cyanophthalide, especially with the use of $SOCl_2$ as a dehydrating agent.

Examples

The invention is further illustrated by the following examples.

Example 1

Preparation of 2-[[(1-oxo-1,3-dihydroisobenzofuran-5-yl)carbonyl]amino]-2-methyl-1-propanol.

5-carboxyphthalide (267g, 1.5mol) is added to thionyl chloride (950 mL) and then N,N-dimethylformamide (12 mL) is added dropwise. The mixture is heated at reflux for 1 hour and the thionyl chloride is destilled off under reduced pressure followed by successive evaporations with toluene (2 x 50 mL) to give a solid residue. The crude acid chloride is then taken up with 1000 mL of tetrahydrofuran. To a solution of 2-amino-2-methyl-1-propanol (400.5g, 4.5 mol) in tetrahydrofuran (500 mL) , cooled to +5°C, the acid chloride solution is added dropwise whilst maintaining the temperature between +5→+10°C. After the addition is completed, the cooling is removed and the mixture is stirred overnight at ambient temperature. Then the mixture is poured into deionized water (2000 mL) and the organic solvent is removed under reduced pressure at 50 °C. After cooling and stirring for 2 hours, the solid product is filtered off and washed with deionized water (2 x 100 mL). The obtained product is dried at 70 °C for 36 hours under reduced pressure. Yield: 285.3g (76%) of an off-white product having a purity (HPLC, peak area) = 90%. ^{1}H NMR (DMSO d-6, 500 MHz): 1.18 (3H,s), 1.32 (3H,s), 3.55 (2H,s), 5.45 (2H,s), 7.88 – 7.98 (3H,m), 8.07 (1H,s).

Example 2

Preparation of 4,4-dimethyl-2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline.

To thionyl chloride (130ml), cooled at –10 °C, 2-[[(1-oxo-1,3-dihydroiso -benzofuran-5-yl)carbonyl]amino]-2-methyl-1-propanol (85g, 0.34mol) is added portionwise with stirring. The temperature is maintained at –10 → -5 °C for 1.5 hours whereafter the cooling is removed and the reaction is stirred overnight at ambient temperature. It is then cooled to 0 °C and tetrahydrofuran (860 mL) is added dropwise keeping the temperature below +8 °C. The obtained suspension is kept under stirring for 2 hours at 5 °C, and then filtered and the crystals washed with tetrahydrofuran (150 mL). The wet solid is dissolved in deionized water (400 mL) and the pH is adjusted to 9.1 by the addition of 25% aqueous ammonia. The solid is filtered, washed with deionized water and dried for 14 hours at 50 °C under reduced pressure. Yield: 62.8g (80%) of a white product having a purity (HPLC, peak area) = 94%. ^{1}H NMR (DMSO d-6, 500 MHz): 1.31 (6H,s), 4.18 (2H,s), 5.44 (2H,s), 7.9 (1H,d, J=11.3Hz), 8.01 (1H,d, J=11.3Hz), 8.12 (1H,s).

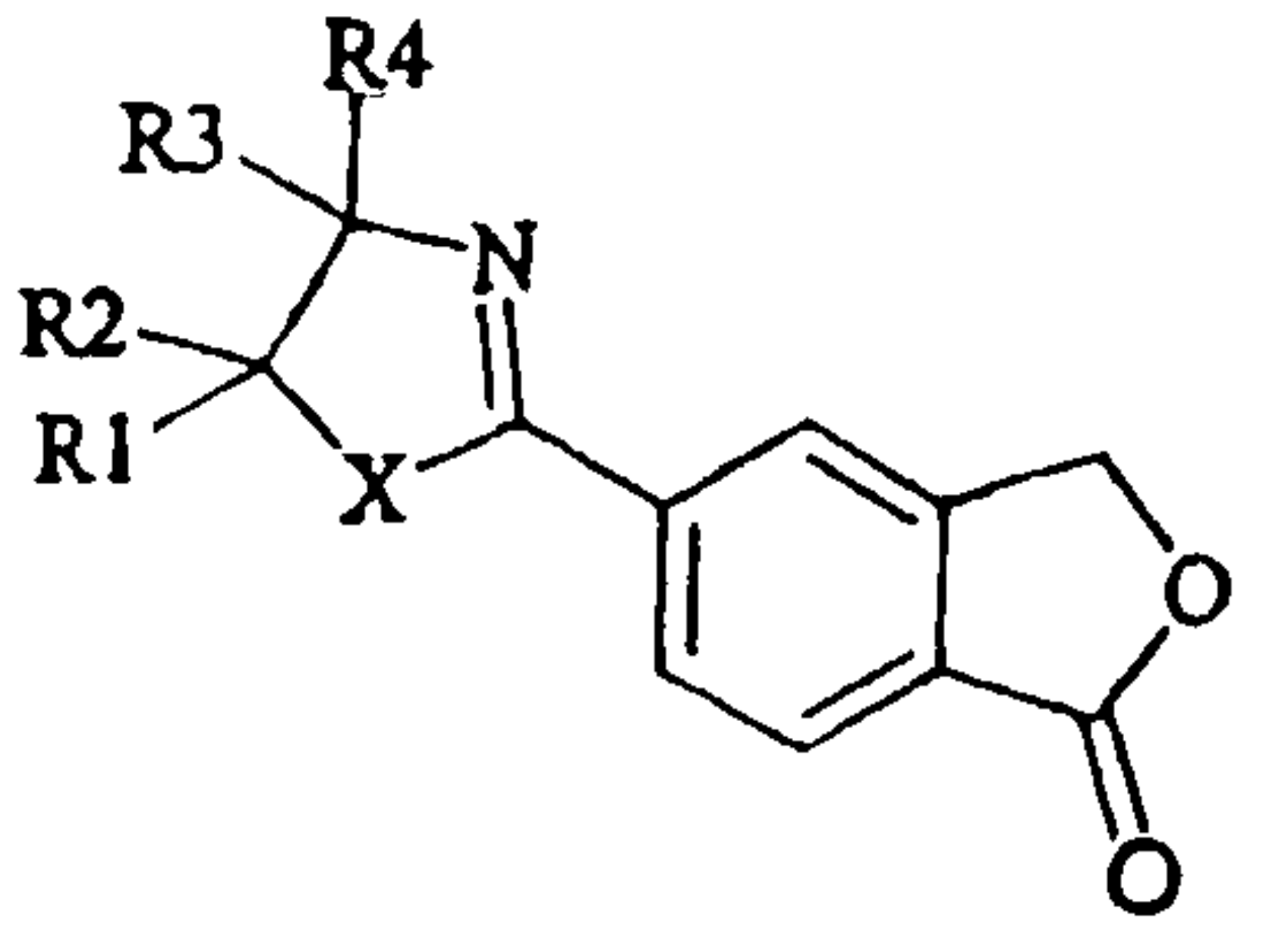
Example 3

Preparation of 5-cyanophthalide.

To a suspension of 4,4-dimethyl-2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline (23.1g, 0.1mol) in thionyl chloride (36 mL) is slowly added N,N-dimethylformamide (5ml). The solution is heated at reflux for 1 hour and then allowed to cool to room temperature over 3 hours. Then toluene (150 mL) is added and the suspension is filtered and washed with toluene (2 x 50 mL). The wet crystals are taken into deionized water (150 mL) and the pH is adjusted to 8.0 with 25% aqueous ammonia. The solid is filtered and washed with deionized water (2 x 50 mL) and dried at 60 °C under reduced pressure. Yield: 11.9g (75%) of an off-white product having a purity (HPLC, peak area) = 92%. An analytical pure sample is obtained by crystallisation from acetic acid or toluene. ^{1}H NMR (DMSO d-6, 500 MHz): 5.48 (2H,s), 8.04 (2H,s+s), 8.22 (1H,s)

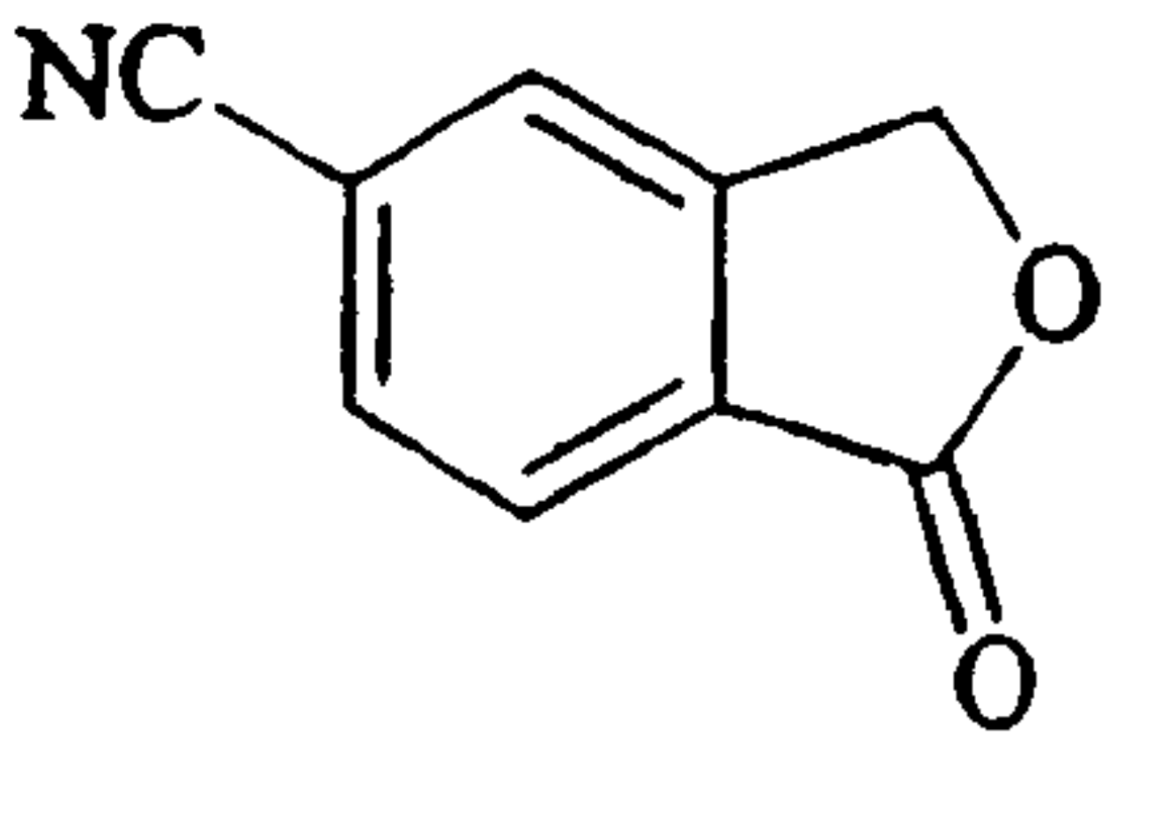
CLAIMS:

1. A method for the preparation of 5-cyanophthalide comprising treatment of a compound of Formula IV



Formula IV

wherein X is O or S;
R^1 - R^2 are each independently selected from hydrogen and C_{1-6} alkyl, or R^1 and R^2 together form a C_{2-5} alkylene chain thereby forming a spiro-ring; R^3 is selected from hydrogen and C_{1-6} alkyl, R^4 is selected from hydrogen, C_{1-6} alkyl, a carboxy group or R^3 and R^4 together form a C_{2-5} alkylene chain thereby forming a spiro-ring; with a dehydration agent or alternatively where X is S, thermally cleavage of the thiazoline ring or treatment with a radical initiator, or with light, to form 5-cyanophthalide having the formula

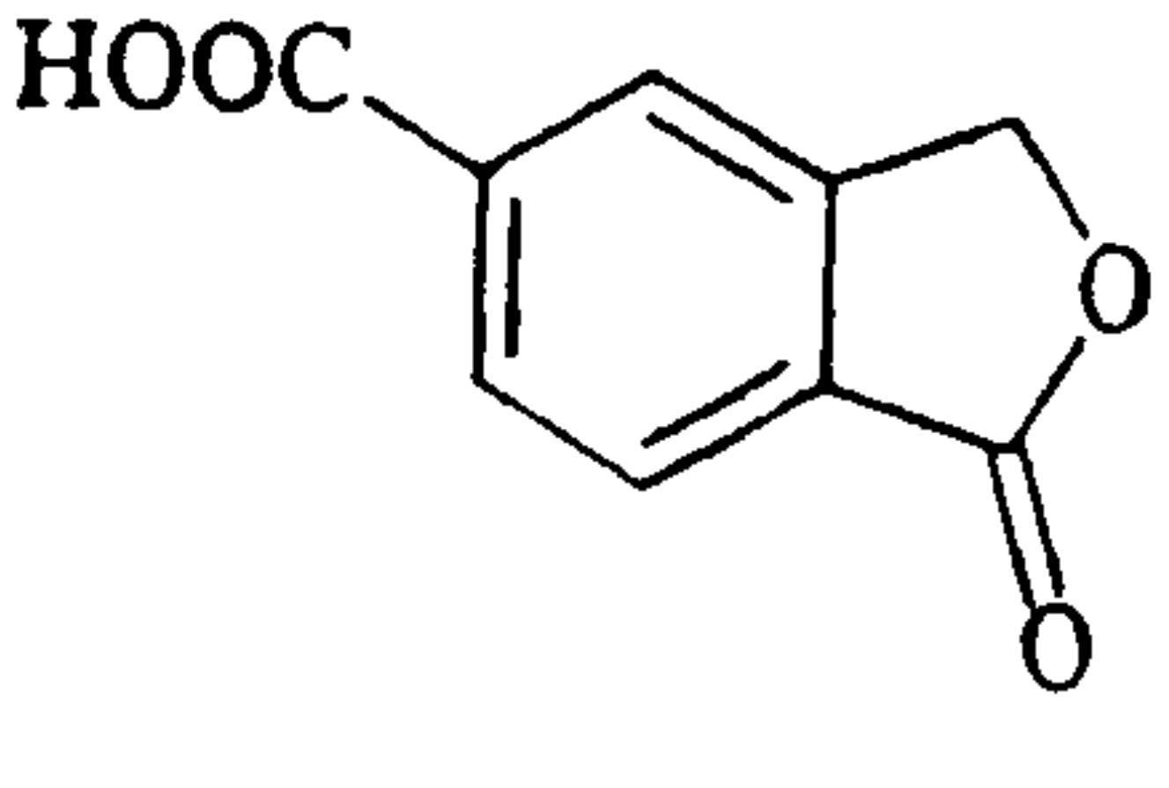


Formula III .

2. The method of claim 1 wherein the radical initiator is a peroxide.

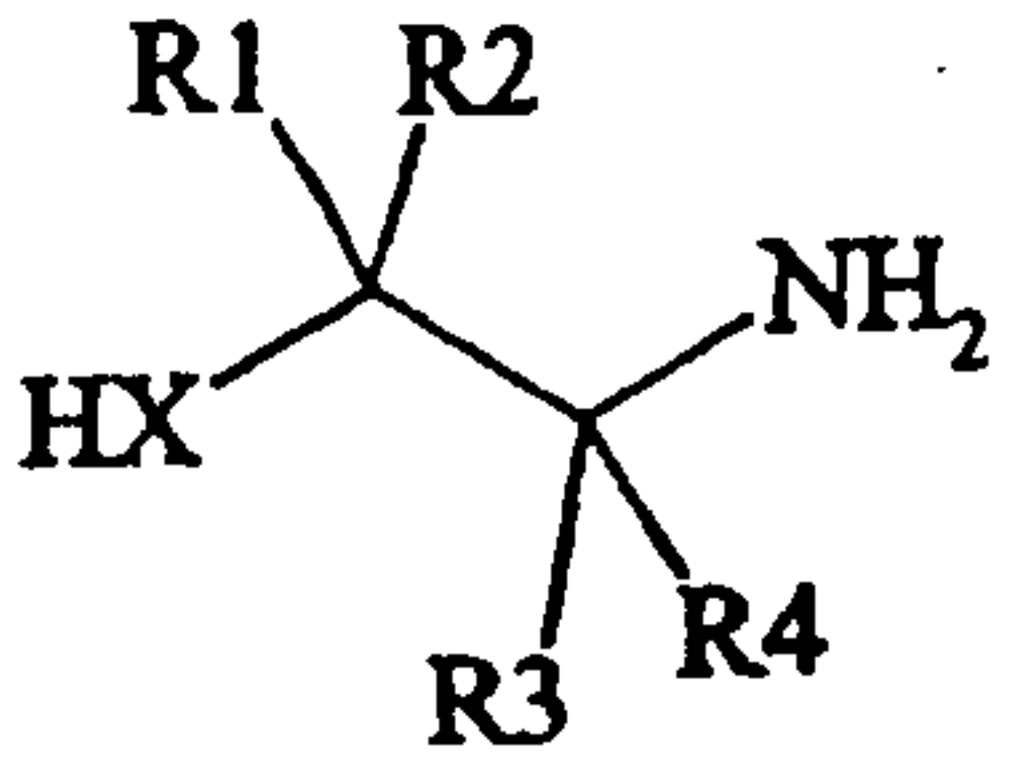
3. The method of claim 1 characterised in that the compound of Formula IV is prepared by a process comprising:

a) reacting a functional derivative of 5-carboxyphthalide of Formula V



Formula V

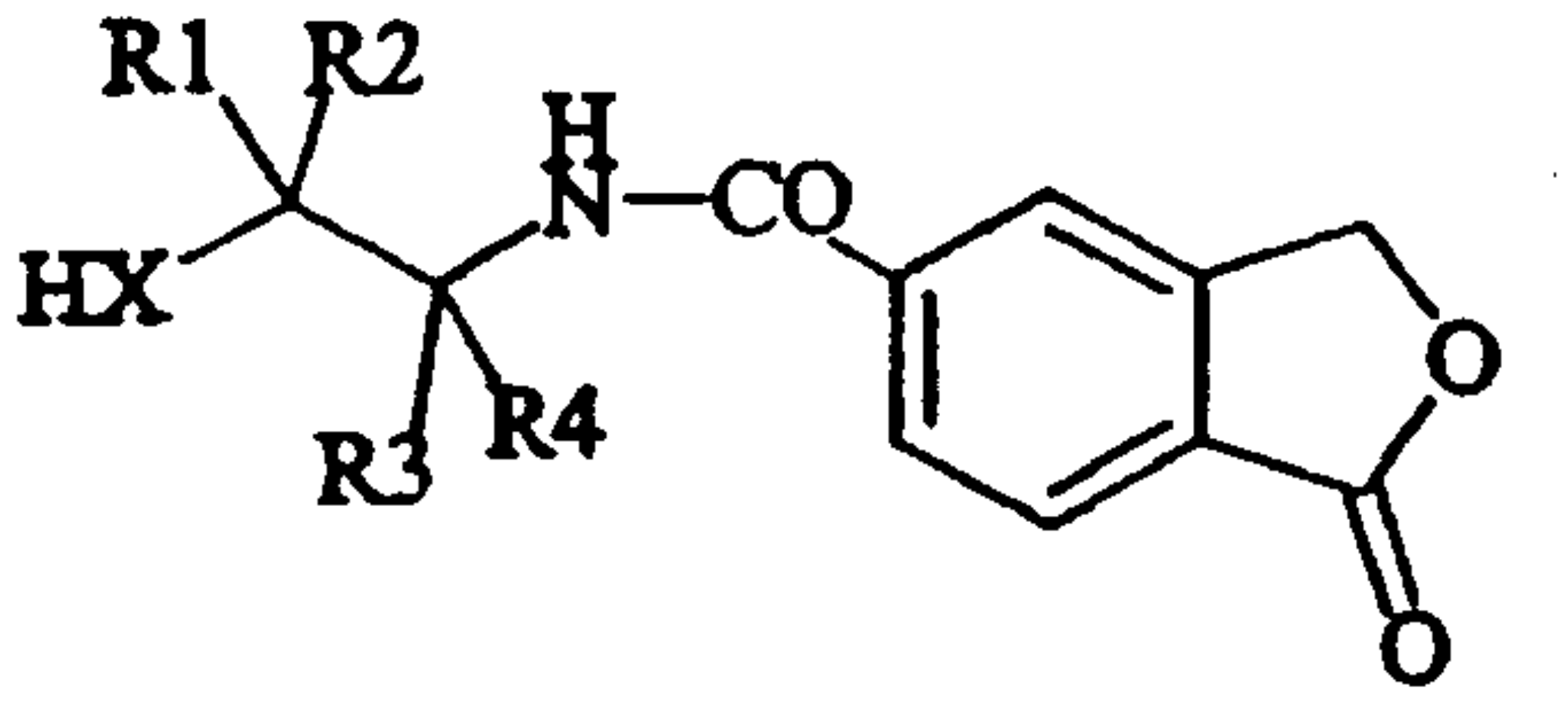
with a 2-hydroxy- or 2-mercaptoethanamine of Formula VI



Formula VI

in which X, R^1 – R^4 are as defined above,

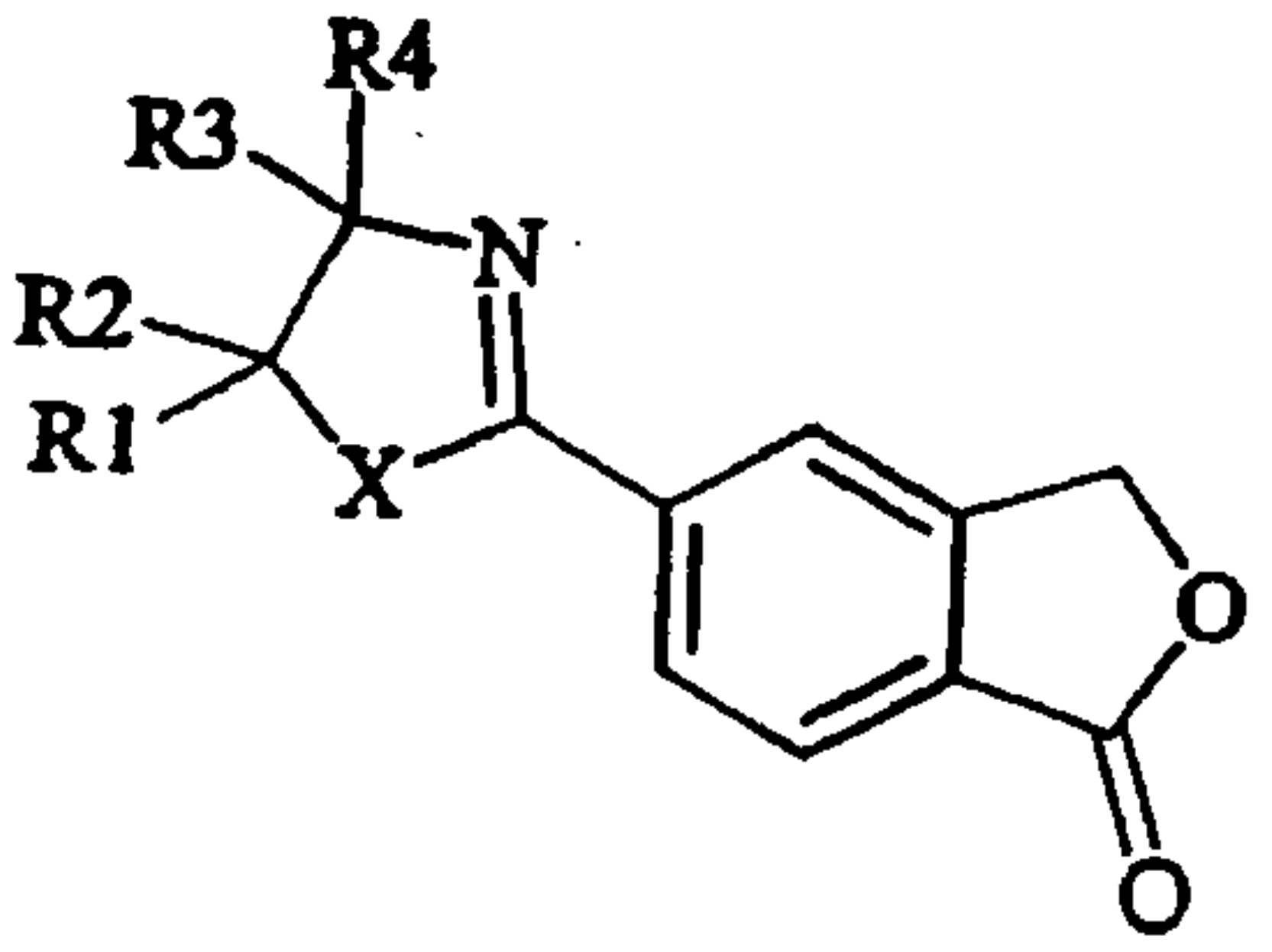
b) submitting the amide of Formula VII thus obtained



Formula VII

in which X, R^1 – R^4 are as defined above, to a ring closure by dehydration;

thereby obtaining the 2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)oxazoline or –thiazoline of formula IV



Formula IV

in which X, R^1 – R^4 are as defined above.

4. A method for the preparation of 5-cyanophthalide according to claim 1 or 3 wherein the compound of formula IV is treated with a dehydrating agent selected from phosphoroxytrichloride, thionylchloride, phosphorpentachloride, PPA (polyphosphoric acid) and P_4O_{10} or a Vilsmeier reagent, eventually in combination with an organic base or a catalytic amount of a tertiary amide.

5. The method of claim 4 wherein the organic base is pyridine.

6. The method of claim 4 wherein the compound of formula IV is treated with $SOCl_2$ as a dehydrating agent and the reaction is carried out in toluene comprising a catalytic amount of N,N-dimethylformamide.

7. A method for the preparation of 5-cyanophthalide according to claim 1 or 3 wherein the thermally cleavage of the thiazoline ring of a compound of formula IV where X is S is carried out in presence of oxygen or an oxidizing agent.

8. A method for the preparation of 5-cyanophthalide according to claim 1 or 3 wherein the thiazoline ring of a compound of formula IV where X is S and R^4 is carboxy is treated with a radical initiator.

9. A method according to claim 8 wherein the radical initiator is light or peroxides.

10. The method of any one of claims 1-9 wherein R^3 is methyl or ethyl.

11. The method of claim 3 in which the dehydrating agent used in step b) is $SOCl_2$, $POCl_3$ or PCl_5.

12. The method of claim 11 wherein the dehydrating agent is $SOCl_2$.

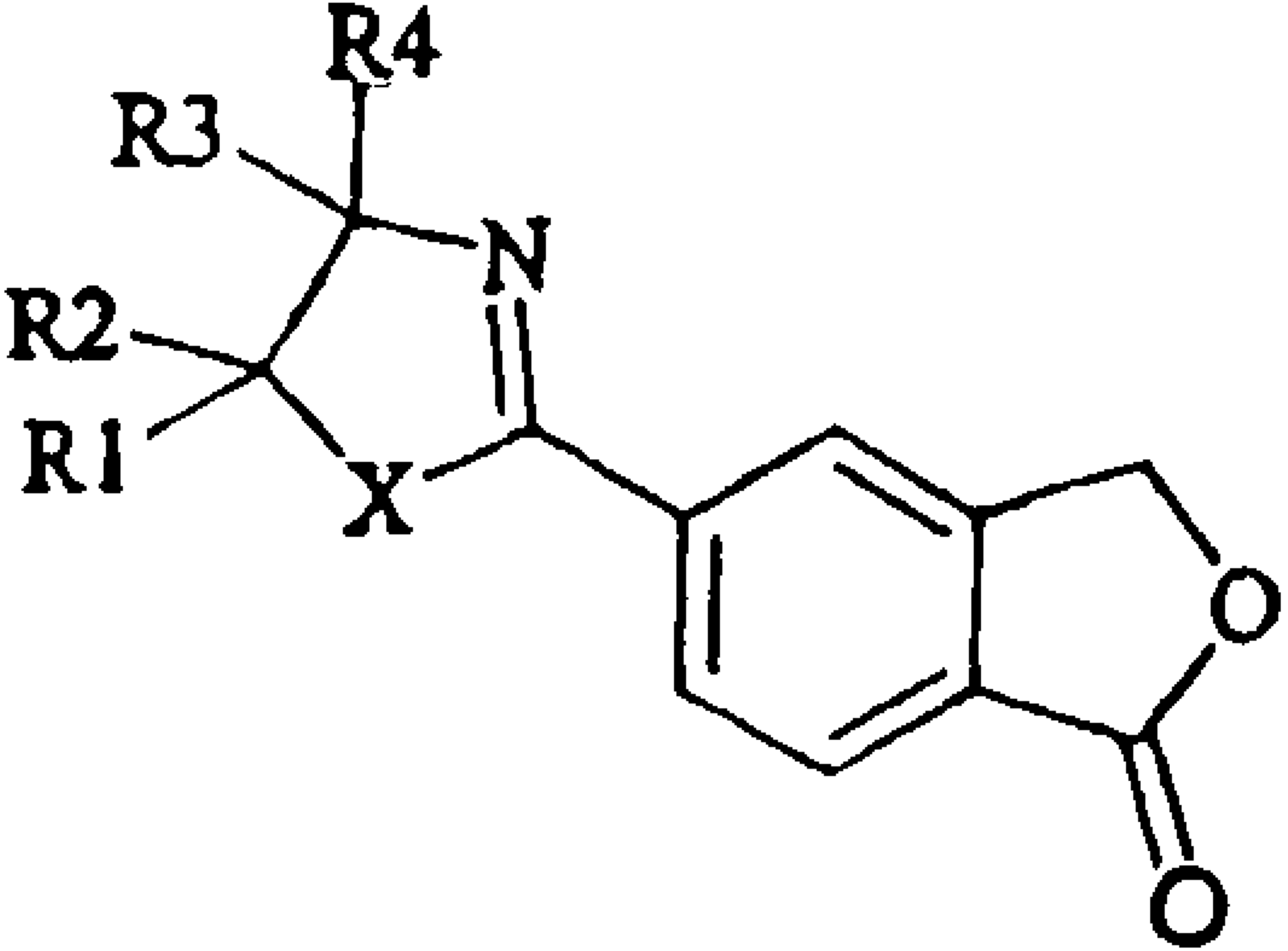
13. The method of claim 3 wherein the reaction in step b) is carried out neat or in a suitable solvent.

14. The method of claim 13 wherein R^3 is methyl or ethyl.

15. The method of claims 13 or 14 wherein the solvent is toluene, sulfolan or acetonitrile.

16. The method of claim 15 wherein the solvent is toluene.

17. The method of any one of claims 11-16 wherein the dehydrating agent used in step b) is $SOCl_2$ and the reaction is carried out in toluene comprising a catalytic amount of N,N-dimethylformamide.



Formula IV