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(54) Title: PROCESS FOR THE PREPARATION OF IOPAMIDOL

(57) Abstract: The present invention provides a process for the preparation of a compound of Formula (II) wherein the process comprises: (i) reacting a compound of Formula (I) with pyridine and 2-acetyloxypropanoyl chloride (APC) to give a compound of Formula (II), wherein the compound of Formula (I) has the following structure.



WO 2022/002953 A1

PROCESS FOR THE PREPARATION OF IOPAMIDOL

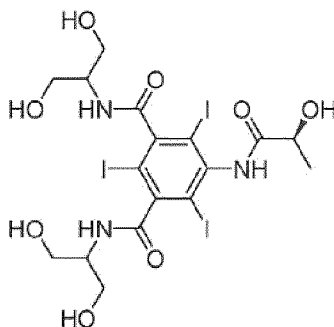
Technical Field of the Invention

5 The present invention concerns X-ray contrast agents and in particular methods to manufacture iodinated X-ray contrast agents. The methods of the present invention provide certain advantages over known such methods.

Description of Related Art

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The use of iopamidol as a contrast agent (e.g. in X-ray imaging) is well established. Iopamidol has the following structure and is referred to here as a compound of Formula (III):



15

The manufacture of iopamidol involves the production of the compound of Formula (III) followed by the preparation of a formulation for use as a contrast agent. The chemical compound is usually made in a multistep synthesis and then purified before being used in the formulation. In each of the synthesis steps it is important to optimize the yield and minimize the production of impurities. For steps in which expensive reagents are used, it is particularly important to optimize usage of those reagents. The iodination reagents are expensive and thus the triiodination of the aromatic ring is an important step, generally performed at a late stage in the overall synthesis. In this step it is especially important to obtain a high yield with few impurities and minimal wastage of the iodination agent.

25

Iopamidol has previously been manufactured by processes such as that depicted in the reaction scheme in Figure 1. Such a process is described, for example, in WO 02/44132 A1. This process has the disadvantage that it requires the use of solvents such as N,N-dimethylacetamide (DMAc) and hazardous and corrosive chemicals such as SOCl₂.

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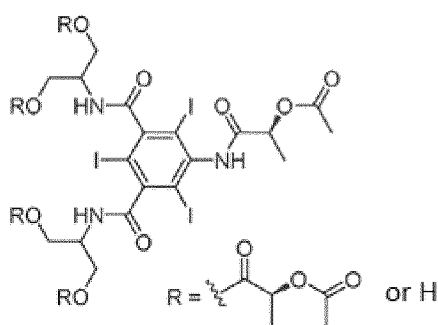
Iopamidol has also previously been manufactured by the process depicted in the reaction scheme in Figure 2. In this reaction scheme, an alkyl ester of 5-nitroisophthalic acid is first reacted with 2-amino-1,3-propanediol (serinol) to give the compound 5-amino-N,N'-bis(1,3-dihydroxypropan-2-yl)isophthalamide (also known as 1,3-ABA). 1,3-ABA is then iodinated using iodine monochloride. The free hydroxyl groups in the resulting compound are protected in several different ways, e.g. with acetone to give an acetal, with acid anhydride to give an ester or with an alkyl or aryl phosphoric acid to give a phosphate ester. The protected intermediate is then N-acylated with 2-acetyloxypropanoyl chloride (APC), deprotected and hydrolysed to give iopamidol.

There is a need for an improved process for the production of iopamidol. The process of the invention meets this need.

The present invention provides advantages over the above processes for producing iopamidol. For example, the process of the present invention may be carried out in solvents that are easily accessible, non-restricted and more environmentally friendly than those previously used. In addition, the process of the present invention may be carried out in fewer process steps than previous processes, which provides significant costs savings. In particular, compared to the reaction scheme shown in Figure 2, the process of the present invention avoids the need for a protection step before reacting with APC.

Summary of the Invention

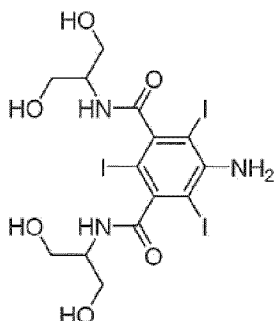
In one aspect the present invention provides a process for the preparation of a compound of Formula (II):



Formula (II);

wherein the process comprises:

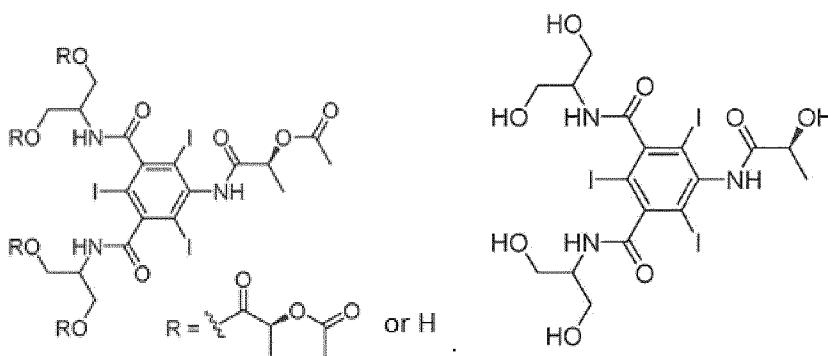
(i) reacting a compound of Formula (I) with pyridine and 2-acetyloxypropanoyl chloride (APC) to give a compound of Formula (II), wherein the compound of Formula (I) has the following structure:



Formula (I).

In another aspect the present invention provides a compound or a formulation produced
5 by the process of the invention.

The present invention also provides for use of a compound of Formula (II) as an
intermediate in a process for the production of iopamidol of Formula (III):



10 Formula (II)

Formula (III).

The present invention has advantages compared to prior methods. The use of OH-
protecting groups is avoided, which would introduce an additional protecting step, and
potentially an additional deprotecting step in the reaction sequence. The use of high
15 boiling solvents like DMAc or DMF, which are under strict restrictions by the REACH
Directive, is also avoided, which in turn inhibits the formation of certain impurities.
Furthermore, the process gives short reaction times without the use of expensive and
toxic catalysts like DMAP, etc.

20 **Brief Description of the Figures**

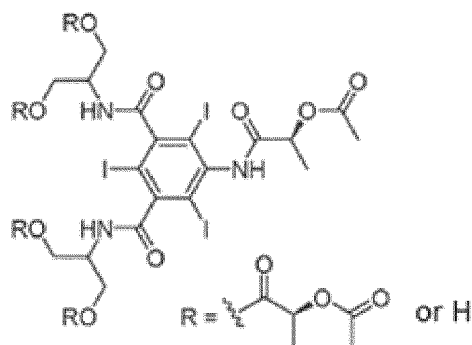
Figures 1 and 2 depict previous methods for the manufacture of iopamidol.

Figure 3 shows a reaction scheme with steps that may be performed in the process of the present invention.

Detailed Description of the Preferred Embodiments

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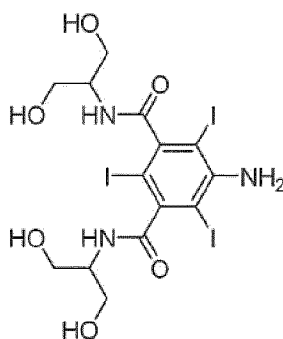
The present invention relates to a process for the preparation of a compound of Formula (II):



Formula (II);

10

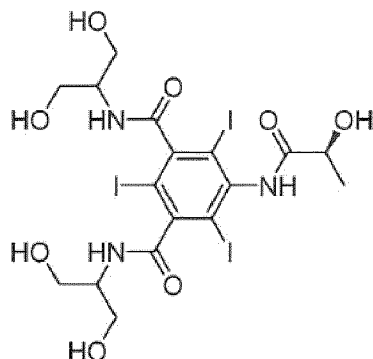
wherein the process comprises: (i) reacting a compound of Formula (I) with pyridine and 2-acetyloxypropanoyl chloride (APC) to give a compound of Formula (II), wherein the compound of Formula (I) has the following structure:



Formula (I).

15

The process may further comprise the step of (ii) reacting the compound of Formula (II) with a hydrolysis agent to give a compound of Formula (III):

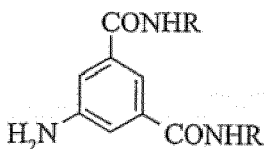


Formula (III), i.e. iopamidol.

A reaction scheme showing steps that may be performed in the process of the present invention is set out in Figure 3.

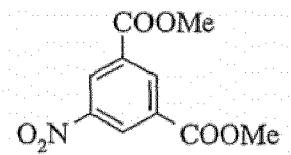
The starting compounds of the process of the invention may be made in any suitable way.

For example, N,N'-substituted 5-amino-1,3-benzenedicarboxamides (e.g. shown below as a compound of Formula (IV)) is known as an intermediate in the synthesis of iopamidol. These compounds may be used to prepare a compound of Formula (I) by iodination. In the formula below, R represents a 1,3-dihydroxy-2-propyl group (R = -CH(CH₂OH)₂) or a 2,3-dihydroxy-1-propyl group (R = -CH₂CH(OH)CH₂(OH)).



Formula (IV)

Compounds of Formula (IV) may be prepared starting from 5-nitro-1,3-benzenedicarboxylic acid dimethyl ester (shown below as a compound of Formula (V)), e.g. by amidation of the ester groups with 2-amino-1,3-dihydroxypropane (commonly known as serinol) or with 1-amino-2,3-dihydroxypropane (commonly known as isoserinol), followed by reduction of the 5-nitro group of the obtained N,N'-bis-substituted 5-nitro-1,3-benzenedicarboxamides. Alternatively, the reduction reaction step may be performed first, followed by the amidation reaction step.



Formula (V)

The amidation reaction in such processes is typically carried out with at least stoichiometric amounts of serinol or isoserinol (i.e. at least two moles of serinol or
5 isoserinol per mol of 5-nitro-1,3-benzenedicarboxylic acid dimethyl ester), in the presence of a protic organic solvent, such as a lower alkanol, and at a temperature of from about 65°C to about 150°C. Further details on such processes are provided in WO 02/44125 A1 and in WO 00/29372 A1.

10 N,N'-substituted 5-amino-1,3-benzenedicarboxamides (e.g. a compound of Formula (IV)) may also be prepared as described in WO 00/29372. For example, a di-lower-alkyl 5-nitroisophthalate may be reacted with at least two molar equivalents of a compound of the formula RNH₂ (e.g., where R is CH₂CH(OH)CH₂OH or CH(CH₂OH)₂) in a solvent comprising a lower-aliphatic alcohol containing a basic catalyst to obtain a solution
15 containing 5-nitro-N,N'-bis(R)isophthalamide and, without isolating the latter, catalytically hydrogenating said solution to obtain a solution of 5-amino-N,N'-bis(R)-isophthalamide.

Further details on the process of the present invention are provided below. Any of the features provided below may be taken in combination with any other feature(s) provided
20 below.

In the process, the compound of Formula (I) is reacted with pyridine and APC in step (i) in a solvent. The solvent in step (i) may be any suitable solvent, such as an aprotic solvent. The solvent in step (i) may be at least one of toluene, tetrahydrofuran (THF), acetonitrile,
25 diethyl ether, methylethylketone, diglyme, glyme, dioxane, methylene chloride, chloroform, ethyl acetate, benzene, diisopropyl ether and acetone. The solvent in step (i) may be at least one of toluene, THF and acetonitrile. The solvent in step (i) may be acetonitrile.

Step (i) of the process may be carried out at any suitable temperature. For example,
30 step (i) may be carried out at a temperature of: from 5°C to 75°C, from 15°C to 65°C, from 15°C to 50°C, from 15°C to 30°C, from 40°C to 60°C or from 20°C to 30°C.

In step (i) of the process, the APC may be added to a mixture of the compound of at least the compound of Formula (I) and pyridine. In step (i) of the process, the APC may be
35 added to the mixture of at least the compound of Formula (I) and pyridine over a period of 0 to 10 hours, 0.5 to 6 hours or 1 to 3 hours. The APC may be added in a first amount, followed by cooling and subsequent addition of APC in a second amount, where the first

and second amounts may be the same or different. When the cooling takes place, it may be to a temperature of from 10 to 40°C or to ambient temperature.

5 Pyridine has three important functions. Firstly, pyridine's main function is to work as a base as HCl is generated during the reaction. Free HCl will cause degradation of the compound of Formula (II). Secondly, pyridine is a co-solvent in the reaction. The compound of Formula (II) is difficult to dissolve with most organic solvents, including acetonitrile, but is soluble in pyridine. And thirdly, pyridine works as a catalyst in the reaction. As APC is added to the reaction mixture, it will first react with pyridine, forming
10 an acyl pyridinium complex. The acyl pyridinium complex will then react with free hydroxyl- (OH) and amine (NH₂) groups in the compound of Formula (I), eventually giving the compound of Formula (II).

15 After the addition of the APC, the resulting reaction mixture may be maintained at a temperature of: from 5°C to 75°C, from 5°C to 70°C, from 5°C to 95°C, from 15°C to 75°C, from 15°C to 65°C, from 15°C to 60°C, from 15°C to 50°C, from 15°C to 30°C, from 40°C to 60°C, from 20°C to 40°C or from 20°C to 30°C. The resulting reaction mixture may be maintained at any of these temperatures for up to 24 hours or for 2 to 12 hours.

20 The compound of Formula (II) produced in step (i) of the process may be reacted in step (ii) of the process without being isolated. In particular, it is not necessary to purify the compound of Formula (II) produced in step (i) before further reaction.

25 Step (ii) of the process may be carried out at any suitable temperature. For example, step (ii) may be carried out at a temperature of: from 5°C to 95°C, from 5°C to 70°C, from 15°C to 75°C, from 15°C to 60°C, from 15°C to 50°C, from 40°C to 60°C or from 20°C to 40°C.

30 Step (ii) of the process may be carried out in acidic or basic conditions. When carried out under acidic conditions, any suitable acid may be used. For example, sulphuric acid and/or hydrochloric acid may be used as the hydrolysis agent.

35 In the process, the hydrolysis agent may be used with water in step (ii) to control the pH between 12 and 14. The hydrolysis agent may be used with water in step (ii) to control the pH between 12.8 and 13.7 or between 13 and 13.6 or at approximately 13.5.

The hydrolysis agent in step (ii) may be an aqueous base or a basic ion exchange resin. The hydrolysis agent in step (ii) may be aqueous NaOH, aqueous KOH or ammonia and/or combinations thereof. In particular, the hydrolysis agent in step (ii) may be aqueous NaOH.

5

The compound of Formula (III) may be purified. It is desirable that the compound of Formula (III) be purified to give a purity of at least 90%, at least 95% or at least 99.8%. The purification may be achieved using any suitable method of purification. One or more of the following purification methods may be used in any combination: desalination (e.g.,
10 electro dialysis or ion exchange resins), distillation, one or more columns (e.g. using Amberlite XAD1600N), evaporation of water, crystallization. For example, the compound of Formula (III) may be purified in accordance with the methods described in US 2011/017673 A1.

15

The compound of Formula (III) may be used to prepare a formulation, e.g. for use as a contrast agent. The formulation may be prepared by dissolving the formulation in a solvent (e.g. water). This allows the formulation to be injected into a subject.

20

In addition to the solvent, the formulation may further include one or more of a buffer, a complexing agent and a pH adjuster. The buffer may be tromethamine. The complexing agent may be calcium disodium EDTA. The pH adjuster may be hydrochloric acid and/or sodium hydroxide. The formulation may include a compound of Formula (III), water, tromethamine, calcium disodium EDTA and hydrochloric acid and/or sodium hydroxide.

25

The present invention also relates to a compound and/or formulation produced by the process described according to the invention. The present invention also relates to the use of a compound and/or formulation produced by the process of the invention. In particular, the compound and/or formulation may be used as a contrast agent (e.g. in a subject).

30

The present invention also relates to the use of a compound of Formula (II) as an intermediate in a process for the production of iopamidol.

Examples

35

The present invention is described with reference to the following examples.

Example 1

5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (30.0 g; 42.6 mmol), acetonitrile (93.0 g) and pyridine (18.5 g; 234 mmol) were added to a reactor with magnetic stirring. The reaction medium was heated to 67°C and (S)-2-acetyloxypropanoyl chloride (22.0 ml; 174 mmol) was added over a period of 60 minutes. The reaction mixture was cooled down to 35°C and an additional amount of (S)-2-acetyloxypropanoyl chloride (9.2 ml; 72.7 mmol) was added over a period of 60 minutes and was then left while stirring for another 18 hours. Water (150 ml) was added followed by careful addition of 50 % NaOH (54.4 g; 680 mmol). The pH was then adjusted to 13.5 using additional amounts of 50 % NaOH and stirred for 45 min. The reaction mixture was neutralized to pH 7.0 using 35 % HCl and the organic solvent was distilled off under reduced pressure to give iopamidol with 91.6 % HPLC purity. The iopamidol product can be further purified using conventional purification methods.

15

Example 2

5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (30.1 g; 42.7 mmol), acetonitrile (93.0 g) and pyridine (20.4 g; 258 mmol) were added to a reactor with magnetic stirring. The temperature of the reactor was set to 67.5°C and (S)-2-acetyloxypropanoyl chloride (31.2 ml; 246 mmol) was added over a period of 60 minutes. 4 hours after the addition, the reactor was cooled down to ambient temperature and water (150 ml) was added followed by careful addition of 50 % NaOH (54.4 g; 680 mmol). The pH was then adjusted to 13.5 using additional amounts of 50 % NaOH and stirred for 30 min. The reaction mixture was neutralized to pH 6.5 using 35 % HCl and the organic solvent was distilled off under reduced pressure to give iopamidol with 91.2 % purity. The iopamidol product can be further purified using conventional purification methods.

25

Example 3

30

5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (30.0 g; 42.6 mmol), acetonitrile (93.0 g) and pyridine (18.5 g; 234 mmol) were added to a reactor with magnetic stirring. The temperature of the reactor was set to 60°C and (S)-2-acetyloxypropanoyl chloride (30.6 ml; 242 mmol) was added over a period of 60 minutes. 5 hours after the addition, the reactor was cooled down to ambient temperature and water (150 ml) was added followed by careful addition of 50 % NaOH (53.2 g; 665 mmol). The pH was then adjusted to 13.5 using additional amounts of 50 % NaOH and stirred for

35

30 min. The reaction mixture was neutralized to pH 7.0 using 35 % HCl and the organic solvent was distilled off under reduced pressure to give iopamidol with 92.5 % purity. The iopamidol product can be further purified using conventional purification methods.

5 **Example 4**

5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (40.0 g; 56.7 mmol), acetonitrile (124 g) and pyridine (20.7 g; 262 mmol) were added to a reactor with magnetic stirring. The temperature of the reactor was set to 25°C and (*S*)-2-acetyloxypropanoyl chloride (43.5 ml; 344 mmol) was added over a period of 30 min. The reaction mixture was stirred at 25°C over a period of 23 hours and water (100 ml) was added. 50 % NaOH (76.0 g; 950 mmol) was slowly added to the reaction mixture giving a pH of 11.7. The pH was then adjusted to 13.6 by careful addition of more 50 % NaOH. After stirring for 30 minutes, the pH was adjusted to 6.9 using 35 % HCl and the organic solvent was distilled off under reduced pressure. The crude product was desalinated using electro dialysis and ion exchange resins (Purolite PPC150 and Purolite A847), and further purified by passing the solution through a column with Amberlite XAD1600N, followed by evaporation of water to give iopamidol with 98.2 % purity.

20 **Example 5**

5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (3.53 g; 5.00 mmol), toluene (8.67 g) and pyridine (2.38 g; 30.0 mmol) were added to a round-bottom flask with magnetic stirring. (*S*)-2-acetyloxypropanoyl chloride (4.04 ml; 31.9 mmol) was added over a period of 60 min and the reaction mixture was left stirring at ambient temperature over a period of 18 hours. Water (40 ml) and methanol (40 ml) were added and the pH was adjusted to and maintained at 13.5 by the addition of 25 % NaOH. After stirring for 30 minutes, the reaction mixture was neutralized to pH 7 with acetic acid and concentrated under reduced pressure to give iopamidol with 57 % HPLC purity as a dark brown residue. The iopamidol product can be further purified using conventional purification methods.

Example 6

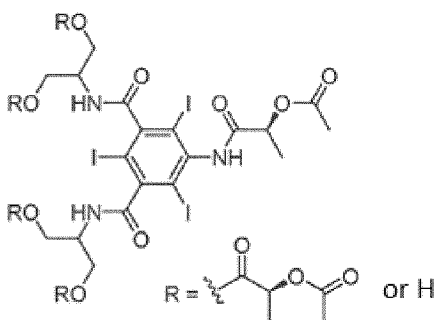
35 5-amino-*N,N'*-bis(1,3-dihydroxypropan-2-yl)-2,4,6-triiodoisophthalamide (3.53 g; 5.00 mmol), THF (8.88 g) and pyridine (2.38 g; 30.0 mmol) were added to a round-bottom flask with magnetic stirring. (*S*)-2-acetyloxypropanoyl chloride (4.04 ml; 31.9 mmol) was added

over a period of 60 min and the reaction mixture was left stirring at ambient temperature over a period of 18 hours. Water (50 ml) and methanol (20 ml) were added and the pH was adjusted to and maintained at 13.5 by the addition of 25 % NaOH. After stirring for 30 minutes, the reaction mixture was neutralized to pH 7 with acetic acid and concentrated under reduced pressure to give iopamidol with 74 % HPLC purity as a yellow residue. The iopamidol product can be further purified using conventional purification methods.

It will be understood by a person skilled in the art that the Examples, as usual, have been performed on a laboratory scale and that the conditions used may be adapted when putting the invention into practice on an industrial scale.

Claims

1. A process for the preparation of a compound of Formula (II):

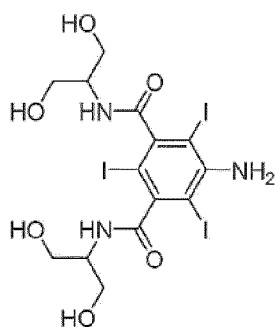


5

Formula (II);

wherein the process comprises:

- (i) reacting a compound of Formula (I) with pyridine and 2-acetyloxypropanoyl chloride (APC) to give a compound of Formula (II), wherein the compound of Formula (I) has the following structure:



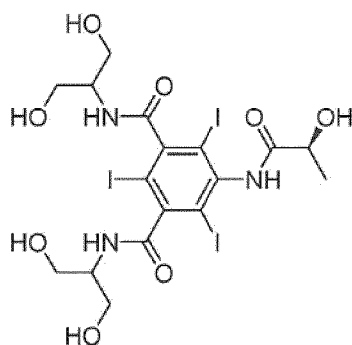
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Formula (I).

2. The process of claim 1, wherein the process further comprises:

- (ii) reacting the compound of Formula (II) with a hydrolysis agent to give a compound of Formula (III):

15



Formula (III).

3. The process of claim 1 or claim 2, wherein the compound of Formula (I) is reacted with pyridine and APC in step (i) in a solvent, preferably wherein the solvent is an aprotic solvent.
- 5 4. The process of any preceding claim, wherein the solvent in step (i) is:
- (i) toluene, THF, acetonitrile, diethyl ether, methylethylketone, diglyme, glyme, dioxane, methylene chloride, chloroform, ethyl acetate, benzene, diisopropyl ether or acetone and/or combinations thereof; or
 - (ii) toluene, THF or acetonitrile and/or combinations thereof; or
 - 10 (iii) acetonitrile.
5. The process of any of claims 2 to 4, wherein the hydrolysis agent is used with water in step (ii) to control the pH: (i) between 12 and 14; or (ii) between 12.8 and 13.7; or (iii) at approximately 13.5.
- 15 6. The process of any of claims 2 to 5, wherein the hydrolysis agent in step (ii) is:
- (a) an aqueous base or a basic ion exchange resin; or
 - (b) aqueous NaOH, aqueous KOH or ammonia and/or combinations thereof; or
 - (c) aqueous NaOH.
- 20 7. The process of any preceding claim, wherein step (i) is carried out at a temperature of:
- (a) from 5°C to 75°C; or
 - (b) from 15°C to 65°C; or
 - 25 (c) from 15°C to 50°C; or
 - (d) from 15°C to 30°C; or
 - (e) from 40°C to 60°C; or
 - (f) from 20°C to 30°C.
- 30 8. The process of any of claims 2 to 7, wherein step (ii) is carried out at a temperature of:
- (a) from 5°C to 95°C; or
 - (b) from 5°C to 70°C; or
 - (c) from 15°C to 75°C; or
 - 35 (d) from 15°C to 60°C; or
 - (e) from 15°C to 50°C; or
 - (f) from 40°C to 60°C; or

(g) from 20°C to 40°C.

9. The process of any preceding claim, wherein in step (i) the APC is added to the mixture of at least the compound of Formula (I) and pyridine:

5 (i) over a period of 0 to 10 hours, preferably 0.5 to 6 hours, more preferably 1 to 3 hours; and/or

(ii) in a first amount, followed by cooling and subsequent addition of APC in a second amount, where the first and second amounts may be the same or different, preferably wherein the cooling is to a temperature of from 10°C to 40°C, more preferably
10 wherein the cooling is to ambient temperature.

10. The process of claim 8 or claim 9, wherein after the addition of the APC, the resulting reaction mixture is maintained at a temperature as defined in claim 7 and/or claim 10, preferably for up to 24 hours, more preferably for 2 to 12 hours.

15 11. The process of any of claims 2 to 10, wherein the compound of Formula (II) produced in step (i) is reacted in step (ii) without being isolated.

12. The process of any of claims 2 to 11, wherein the compound of Formula (III) is
20 purified, preferably wherein the purification includes one or more of: desalination, resin treatment, distillation and crystallization.

13. The process of any of claims 2 to 12, wherein the compound of Formula (III) is dissolved in a solvent to produce a formulation, preferably wherein:

25 (i) the formulation further comprises a solvent, preferably wherein the solvent is water; and/or

(ii) the formulation further comprises a buffer, preferably wherein the buffer is tromethamine; and/or

(iii) the formulation further comprises a complexing agent, preferably wherein the
30 complexing agent is calcium disodium EDTA; and/or

(iv) the formulation further comprises a pH adjuster, preferably wherein the pH adjuster is hydrochloric acid or sodium hydroxide.

14. A compound:

35 (i) produced by the process of any of claims 1 to 11 or a formulation produced by the process of claim 13; or

(ii) produced by the process of any of claims 2 to 12 or a formulation produced by the process of claim 13 for use as a contrast agent, preferably wherein the compound is used in a subject as a contrast agent.

- 5 15. Use of a compound of Formula (II) as an intermediate in a process for the production of iopamidol of Formula (III):

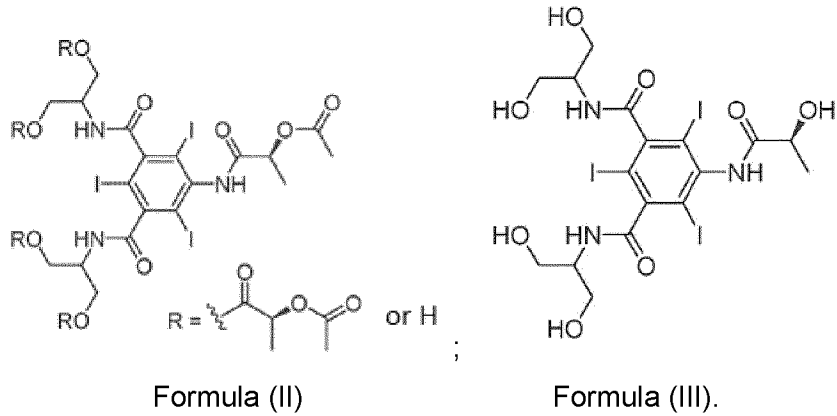


FIGURE 1

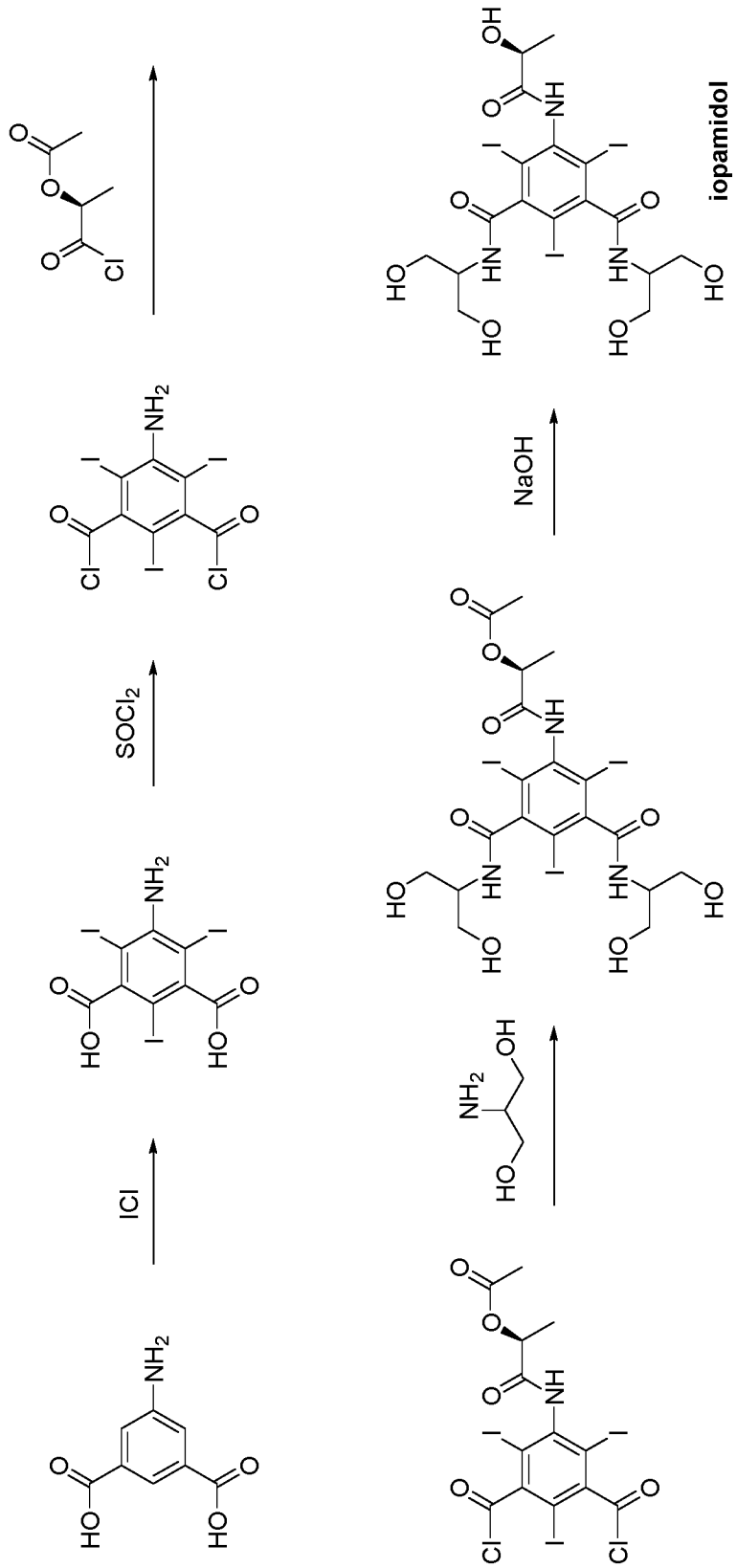


FIGURE 2

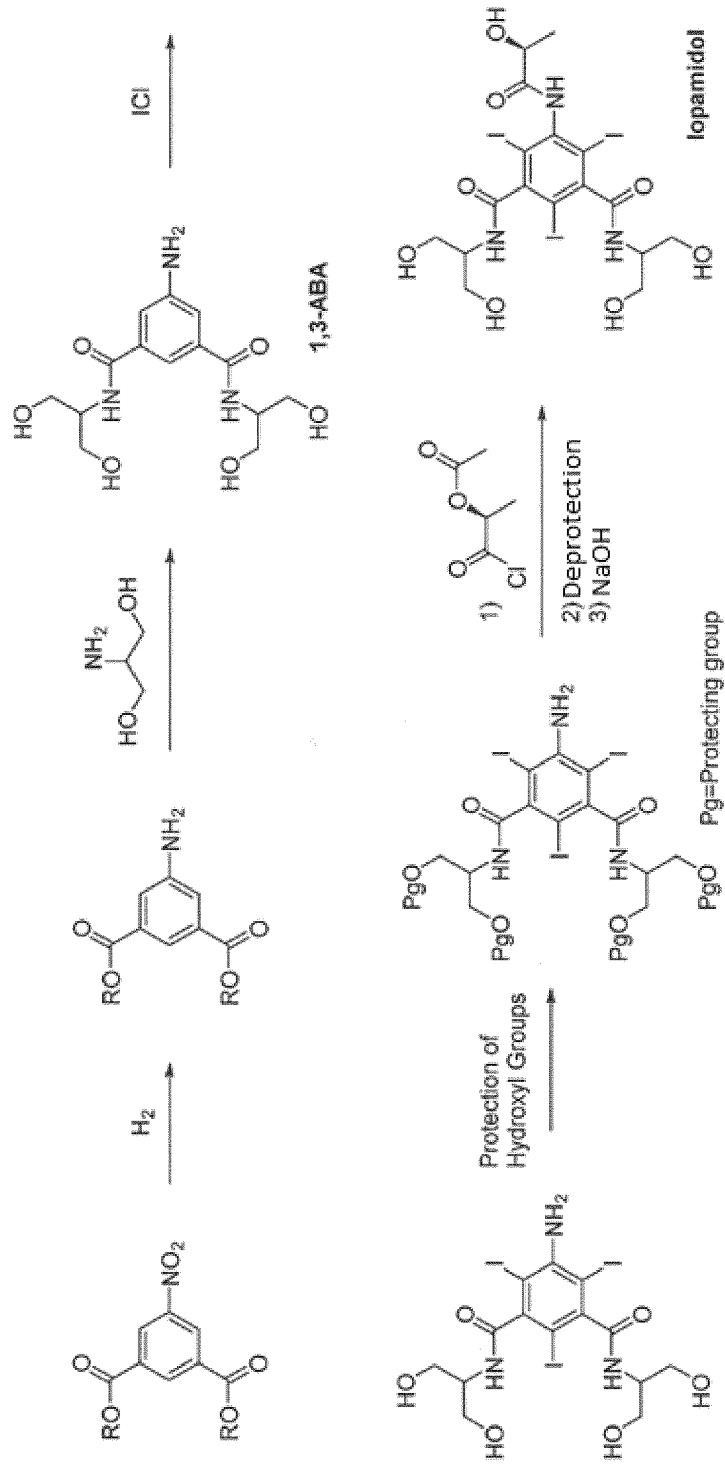
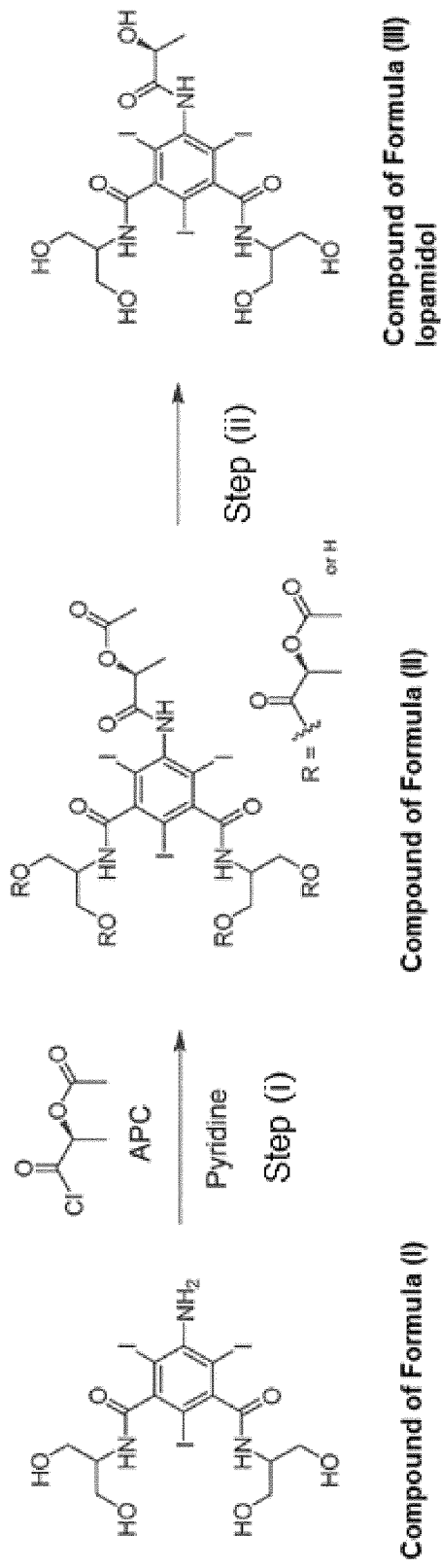


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/067871

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C237/46 C07C231/02
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07C
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/44132 A1 (BRACCO IMAGING SPA [IT]; ANELLI PIER LUCIO [IT] ET AL.) 6 June 2002 (2002-06-06) cited in the application claim 1 -----	1-15

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 1 October 2021	Date of mailing of the international search report 11/10/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Menchaca, Roberto
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2021/067871

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