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(54) Titre : PROCEDE DE PREPARATION DE DICHLORURE D'ACIDE 5-AMINO-2,4,6-TRIIODO-ISOPHTALIQUE PAR CHLORATION A L'AIDE DE CHLORURE DE THIONYLE EN PRESENCE D'UN CATALYSEUR
 (54) Title: PROCESS FOR THE PREPARATION OF 5-AMINO-2,4,6-TRIIODOISOPHTHALIC ACID DICHLORIDE BY CHLORINATION WITH THIONYL CHLORIDE IN THE PRESENCE OF A CATALYST

(57) **Abrégé/Abstract:**

A process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride in the presence of a suitable solvent characterized in that the reaction is carried out in the presence of catalytic amounts of a tetraalkylammonium salt of the formula (I): $R_1R_2R_3R_4NX$ wherein X is halogen, mesylate or tosylate; R_1 , R_2 , R_3 and R_4 , the same or different, are C_1 - C_{20} alkyl groups so that the total number of carbon atoms of the groups R_1 , R_2 , R_3 and R_4 is higher than 16. The 5-amino-2,4,6-triiodoisophthalic acid dichloride obtained according to the process of the present invention is useful as intermediate in the synthesis of iodinated contrast media.



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<p>(21) International Application Number: PCT/EP96/02009</p> <p>(22) International Filing Date: 10 May 1996 (10.05.96)</p> <p>(30) Priority Data: MI95A001004 18 May 1995 (18.05.95) IT</p> <p>(71) Applicant: ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I-36100 Vicenza (IT).</p> <p>(72) Inventors: VILLA, Marco; Viale Lunigiana, 10, I-20125 Milano (IT). POZZOLI, Claudio; Viale Libertà, 87, I-20052 Monza (IT). RUSSO, Laura; Via Ojetti, 9, I-20151 Milano (IT). CASTALDI, Graziano; Via Livia Gallina, 5, I-28072 Briona (IT).</p> <p>(74) Agent: LONGONI, Alessandra; Zambon Group S.p.A., Corp. Patent & Trademark Dept., Via Lillo del Duca, 10, I-20091 Bresso (IT).</p>		<p>(81) Designated States: AT, AU, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, NO, PT, SE.</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PROCESS FOR THE PREPARATION OF 5-AMINO-2,4,6-TRIIODOISOPHTHALIC ACID DICHLORIDE BY CHLORINATION WITH THIONYL CHLORIDE IN THE PRESENCE OF A CATALYST</p>		
<p>(57) Abstract</p> <p>A process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride in the presence of a suitable solvent characterized in that the reaction is carried out in the presence of catalytic amounts of a tetraalkylammonium salt of the formula (I): $R_1R_2R_3R_4NX$ wherein X is halogen, mesylate or tosylate; R_1, R_2, R_3 and R_4, the same or different, are C_1-C_{20} alkyl groups so that the total number of carbon atoms of the groups R_1, R_2, R_3 and R_4 is higher than 16. The 5-amino-2,4,6-triiodoisophthalic acid dichloride obtained according to the process of the present invention is useful as intermediate in the synthesis of iodinated contrast media.</p>		

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"Process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination with thionyl chloride in the presence of a catalyst"

5 The present invention relates to a process for the preparation of an intermediate useful in the synthesis of organic compounds and, more particularly, it relates to a process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride.

5-Amino-2,4,6-triiodoisophthalic acid dichloride is a known compound useful for the preparation of iodinated contrast media among which we can cite Iopamidol (British patent no. 10 1,472,050 - Savac AG), Iohexol (U.S. patent No. 4,250,113 - Nyegaard & Co.) and Ioversol (European patent application no. 0 083 964 - Mallinckrodt Inc.).

Several examples of synthesis of 5-amino-2,4,6-triiodoisophthalic acid dichloride are reported in the literature and all of them foresee the chlorination of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride.

15 In particular, we can cite the syntheses described in the already mentioned British patent no. 1,472,050, in the Belgian patent no. 852,418 (Mallinckrodt Inc.) and in the U.S.A. patent no. 3,655,752 (Sterling Drug Inc.) which use a large excess of thionyl chloride and which require a long and cumbersome work-up, difficulty suitable from the industrial view-point, even though sometimes they allow to obtain the desired dichloride with high yields.

20 Also the synthesis described in the European patent application no. 0 118 347 (Guerbet S.A.) foresees the use of thionyl chloride in excess but in the presence of catalytic amounts of N,N-dimethylformamide. The yields are high but, also in this case, the work-up needs the removal of the excess thionyl chloride by evaporation.

The use of solvents such as ethyl acetate, as described in the International patent applications 25 no. WO 91/09007 (Mallinckrodt Inc.) and no. WO 93/10825 (Mallinckrodt Inc.) or in the already cited European patent application no. 0 083 964, does not allow to obtain the desired dichloride with satisfactory yields.

The European patent application no. 0 026 281 (Bracco Industria Chimica S.p.A.) describes the preparation of 5-methylamino-2,4,6-triiodoisophthalic acid dichloride by reaction with 30 thionyl chloride in the presence of small amounts of quinoline, without reporting the yields yet. The International patent publication No. WO1996/016927 published June 6, 1996 in the

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name of the same Applicant, describes a process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination with thionyl chloride characterized in that the reaction is carried out in the presence of a salt of a tertiary amine or of a quaternary ammonium in a molar ratio from 1:1 to 1:2 with respect to 5-amino-2,4,6-triiodoisophthalic acid.

The use of catalytic amounts of benzyltriethylammonium chloride or betaine in the preparation of acid chlorides has been described in Synthesis, June 1991, pages 441-442.

We have now found that, by using a tetraalkylammonium salt of formula



wherein X is halogen, mesylate or tosylate; R_1 , R_2 , R_3 and R_4 , the same or different, are C_1 - C_{20} alkyl groups so that the total number of carbon atoms of the groups R_1 , R_2 , R_3 and R_4 is higher than 16;

the chlorination reaction of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride occurs with high yields and with the same degree of purity even if in the presence of catalytic amounts of said tetraalkylammonium salt.

Therefore, object of the present invention is a process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride in the presence of a suitable solvent characterized in that the reaction is carried out in the presence of catalytic amounts of a tetraalkylammonium salt of formula



wherein X is halogen, mesylate or tosylate; R_1 , R_2 , R_3 and R_4 , the same or different, are C_1 - C_{20} alkyl groups so that the total number of carbon atoms of the groups R_1 , R_2 , R_3 and R_4 is higher than 16.

The 5-amino-2,4,6-triiodoisophthalic acid dichloride obtained according to the process object of the present invention is useful as intermediate in the synthesis of iodinated contrast media.

The amount of thionyl chloride used in the process object of the present invention is generally between 2 and 6 moles with respect to 5-amino-2,4,6-triiodoisophthalic acid.

Preferably, from 3 to 4 moles of thionyl chloride for mole of 5-amino-2,4,6-triiodoisophthalic acid are used.

For catalytic amount of tetraalkylammonium salt of formula I a molar amount from 0.3 to 10% with respect to 5-amino-2,4,6-triiodoisophthalic acid is intended.

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Preferably, a molar amount of compound of formula I from 1 to 5% is used.

The compounds of formula I which can be used in the process object of the present invention are preferably compounds wherein X is chlorine, bromine, mesylate or tosylate; R₁, R₂, R₃,
5 R₄, the same or different, are C₁-C₂₀ alkyl groups so that the total number of carbon atoms is from 25 to 38.

Specific examples of preferred compounds of formula I are trioctylmethylammonium, methyl-trialkyl(C₈-C₁₀)ammonium, dioctadecyldimethylammonium and tridodecylmethylammonium chlorides, bromides, mesylates or tosylates, which can be optionally prepared in situ from the
10 corresponding tertiary amine and from the suitable alkyl chloride, bromide, mesylate or tosylate.

For practical and economical reasons trioctylmethylammonium chloride, commercialized as Aliquat 336[®] (registered trademark of Henkel Corporation), and methyltrialkyl-(C₈-C₁₀)ammonium chloride, commercialized as Adogen 446[®] (registered trademark of
15 Ashland Chemical Co.) are preferably used.

Suitable solvents are ethyl acetate, toluene, methylene chloride, 1,2-dichloroethane, isopropyl acetate and mixture thereof.

Preferably, toluene is used.

The reaction temperature is not a critical parameter and it can range from 20°C to the reflux
20 temperature.

Preferably, the chlorination process object of the present invention is carried out at warm at a temperature from 60°C to 90°C.

A preferred practical embodiment of the present invention is the following.

A catalytic amount of a tetraalkylammonium salt of formula I is added to a suspension of 5-
25 amino-2,4,6-triiodoisophthalic acid in a suitable solvent.

After heating to the reaction temperature, thionyl chloride is added dropwise to the suspension.

The resultant solution is kept at the reaction temperature for some hours.

At the end of the reaction, the mixture is cooled at room temperature and water is added observing the precipitation of a crystalline product.

30 By simple filtration and washing, 5-amino-2,4,6-triiodoisophthalic acid dichloride is obtained in pure form.

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The characterizing feature of the present invention is the presence of a tetraalkylammonium salt as catalyst.

As far as we know, there are no examples of preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by reaction with thionyl chloride in the presence of a tetraalkylammonium salt as a catalyst in the literature.

The use of this kind of catalyst allows to achieve a number of advantages with respect to the prior art, such as extremely high yields and decrease in the amount of thionyl chloride to be used, but mainly a significant decrease of reaction by-products which make difficult the isolation of 5-amino-2,4,6-triiodoisophthalic acid dichloride with a degree of purity suitable for the use as intermediate in the synthesis of iodinated contrast media.

The improvement of the reaction yields and the decrease of the impurities with respect to the reactions for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride described in the literature is proved by the comparison between the results obtained in example 10, wherein the procedure described in the British patent no. 1,472,050 was used, and in example 11, wherein the procedure described in the International patent application no. WO 91/09007 was used, and the results obtained in examples 1-9 and 12-13, according to the process object of the present invention.

It is worth underlining that the substantial absence of by-products in the reaction for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride according to the process object of the present invention does not result exclusively in an improvement of the overall yield of the process with respect to the known methods, but allows also the isolation of the desired product by simple treatment with water of the reaction mixture.

Furthermore, by using catalytic amounts of tetraalkylammonium salt it is possible to carry out the reaction with an amount of thionyl chloride only slightly in excess with respect to the stoichiometric amount without lowering the reaction yield yet.

It is clear to the man skilled in the art the advantage deriving from the possibility of carrying out the process for the synthesis of an intermediate with high yields, high purity, through extremely simple work-up, without the need of removing thionyl chloride by evaporation or repeating purification procedures for the isolation of the desired product in pure form.

As already underlined, contrary to what described for the known processes for the preparation

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of 5-amino-2,4,6-triiodoisophthalic acid dichloride, the isolation of the pure product is carried out by simple treatment of the reaction mixture with water.

On the base of our knowledge, a mechanism able to explain the unexpected advantages deriving from the use of a tetraalkylammonium salt as catalyst according to the process of the present invention cannot be hypothesized.

In this connection, however, it is worth noting that the use of quinoline or of a tetraalkylammonium salt having a total number of carbon atoms lower than or equal to 16, such as for example benzyltriethylammonium chloride, as catalysts in the reaction between thionyl chloride and 5-amino-2,4,6-triiodoisophthalic acid does not allow to obtain the desired product with a suitable degree of purity (see example 14).

In order to better illustrate the present invention, the following examples are now given.

Example 1

In a 500 ml reactor equipped with magnetic stirrer, thermometer and reflux condenser with florentine flask, 5-amino-2,4,6-triiodoisophthalic acid (KF=3.44%; 150 g; 0.259 moles) and toluene (173 g) were charged under inert atmosphere.

After azeotropic distillation of water, the mixture was cooled at 85°C and Aliquat 336[®] (5.25 g; 0.013 moles) was added.

By keeping under stirring, thionyl chloride 97% (111.6 g; 0.91 moles) was added dropwise in 3 hours.

At the end of the addition, the reaction mixture was kept at 85°C for 4 hours.

After cooling at room temperature water (16.4 g) was added dropwise.

After addition of a seed of 5-amino-2,4,6-triiodoisophthalic acid dichloride, the mixture was kept under stirring for about 16 hours, the solid filtered and triturated with toluene (30 g) and then dried in oven under vacuum (40°C - 30 mmHg) for about 18 hours obtaining 5-amino-2,4,6-triiodoisophthalic acid dichloride (141 g; 88% yield) with 96.5% titre.

Examples 2-11

By working as described in example 1 the experiments 2-9 reported in the table were carried out.

Experiments 10 and 11 were carried out by using the procedures described in the British patent no. 1,472,050 and in the International patent application no. WO 91/09007, respectively.

Table

Example	Solvent	Concentration(a)	Catalyst(b) (% mole)	Temperature (°C)	Time (hours)	Yield (titre)	Impurity (HPLC area %)
2	toluene	600	5 %	85	4	90.6% (97.7%)	2.1
3	ethyl acetate	300	10 %	75	24	78.5% (98.3%)	1.1
4	toluene	300	10 %	85	4	80 %	1.9
5	toluene	1200	5 %	85	4	92 % (95 %)	2.4
6	toluene	1200	1 %	85	4	90 % (96.5%)	3.0
7	toluene	600	2.5%	85	4	87 % (99 %)	2.2
8	toluene	1000	2.5%	85	4	90.6% (98.5%)	2.5
9	toluene:methylene chloride=1:1	1000	5 %	60	4	87 %	3.5
10(c)	-----	-----	-----	72	6	71.6 %	>18
11(c)	ethyl acetate	600	-----	75	20	60 %	> 5

(a) concentrations expressed as grams of 5-amino-2,4,6-triiodoisophthalic acid/liters of solvent

(b) Aliquat 336® - percentage expressed with respect to molar amount of 5-amino-2,4,6-triiodoisophthalic acid

(c) Comparative examples

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Example 12

In a 500 ml reactor equipped with magnetic stirrer, thermometer and reflux condenser with florentine flask, 5-amino-2,4,6-triiodoisophthalic acid (KF=2.96%; 100 g; 0.173 moles) and
5 toluene (100 g) were charged under inert atmosphere.

After azeotropic distillation of water, the mixture was cooled at 70°C and Aliquat 336[®] (2.5 g; 0.006 moles) was added.

By keeping the reaction mixture under stirring at 70°C, thionyl chloride (74.5 g; 0.626 moles) was added dropwise in 16 hours.

10 At the end of the addition, the reaction mixture was kept at 70°C for 4 hours.

After cooling at room temperature water (300 g) was slowly added.

After addition of a seed of 5-amino-2,4,6-triiodoisophthalic acid dichloride, the mixture was kept under stirring for about 16 hours, the solid filtered and triturated with dichloromethane and then dried in oven under vacuum for about 18 hours obtaining 5-amino-2,4,6-
15 triiodoisophthalic acid dichloride (97.9 g; 90% yield) with 98% titre.

Example 13

In a 100 ml reactor equipped with magnetic stirrer, thermometer and reflux condenser with florentine flask, 5-amino-2,4,6-triiodoisophthalic acid (KF=2.96%; 30 g; 52.08 mmoles) and toluene (55 g) were charged under inert atmosphere.

20 After azeotropic distillation of water, the mixture was cooled at 85°C and Adogen 446[®] (2.5 g; 5.1 mmoles) was added.

By keeping under stirring, thionyl chloride 97% (22.1 g; 180.2 mmoles) was added dropwise in 3 hours.

At the end of the addition, the reaction mixture was kept at 85°C for 4 hours.

25 After cooling at room temperature water (4 g) was slowly added.

After addition of a seed of 5-amino-2,4,6-triiodoisophthalic acid dichloride, the mixture was kept under stirring for about 16 hours, the solid filtered and triturated with toluene and then dried in oven under vacuum for about 18 hours obtaining 5-amino-2,4,6-triiodoisophthalic acid dichloride (28.5 g; 89% yield) with 97% titre.

30

Comparative Example 14

In a 100 ml reactor equipped with magnetic stirrer, thermometer and reflux condenser with

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florentine flask, 5-amino-2,4,6-triiodoisophthalic acid (KF=1%; 13.84 g; 24.5 mmoles), 1,2-dichloroethane (45 ml) and benzyltriethylammonium chloride (0.009 g; 0.038 mmoles) were charged under inert atmosphere.

5 Thionyl chloride (10.62 g; 89.24 mmoles) was added to the reaction mixture under reflux.

At the end of the addition, the reaction mixture was kept under reflux for 18 hours.

After cooling at room temperature water (2 g) was slowly added.

After addition of a seed of 5-amino-2,4,6-triiodoisophthalic acid dichloride, the mixture was kept under stirring for about 16 hours, the solid filtered and triturated with dichloromethane

10 and then dried in oven under vacuum for about 18 hours obtaining 5-amino-2,4,6-triiodoisophthalic acid dichloride (10.8 g; 61% yield) with 82.5% titre.

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Claims

1) A process for the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride by chlorination of 5-amino-2,4,6-triiodoisophthalic acid with thionyl chloride in the presence of a suitable solvent characterized in that the reaction is carried out in the presence of catalytic amounts of a tetraalkylammonium salt of formula



wherein X is halogen, mesylate or tosylate; R_1 , R_2 , R_3 and R_4 , the same or different, are C_1 - C_{20} alkyl groups so that the total number of carbon atoms of the groups R_1 , R_2 , R_3 and R_4 is higher than 16.

2) A process according to claim 1 wherein the amount of thionyl chloride is from 3 to 4 moles with respect to 5-amino-2,4,6-triiodoisophthalic acid.

3) A process according to claim 1 wherein the tetraalkylammonium salt of formula I is used in a molar amount from 0.3 to 10% with respect to 5-amino-2,4,6-triiodoisophthalic acid.

4) A process according to claim 3 wherein the molar amount of tetraalkylammonium salt is between 1 and 5%.

5) A process according to claim 1 wherein a tetraalkylammonium salt of formula I wherein X is chlorine, bromine, mesylate or tosylate; R_1 , R_2 , R_3 , and R_4 , the same or different, are C_1 - C_{20} alkyl groups so that the total number of carbon atoms is between 25 and 38 is used.

6) A process according to claim 5 wherein the tetraalkylammonium salt of formula I is selected among trioctylmethylammonium, methyltrialkyl(C_8 - C_{10})ammonium, dioctadecyldimethylammonium and tridodecylmethylammonium chlorides, bromides, mesylates or tosylates.

7) A process according to claim 6 wherein trioctylmethylammonium chloride or methyltrialkyl(C_8 - C_{10})ammonium chloride is used.

8) A process according to claim 1 wherein the solvent is selected among ethyl acetate, toluene, methylene chloride, 1,2-dichloroethane, isopropyl acetate and mixture thereof.

9) A process according to claim 8 wherein the solvent is toluene.

10) A process for the preparation of iopamidol, iohexol or ioversol comprising the preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride according to claim 1.