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(54) Title: PROCESS FOR MANUFACTURING (TRIMETHYL)PLATINUM IODIDE

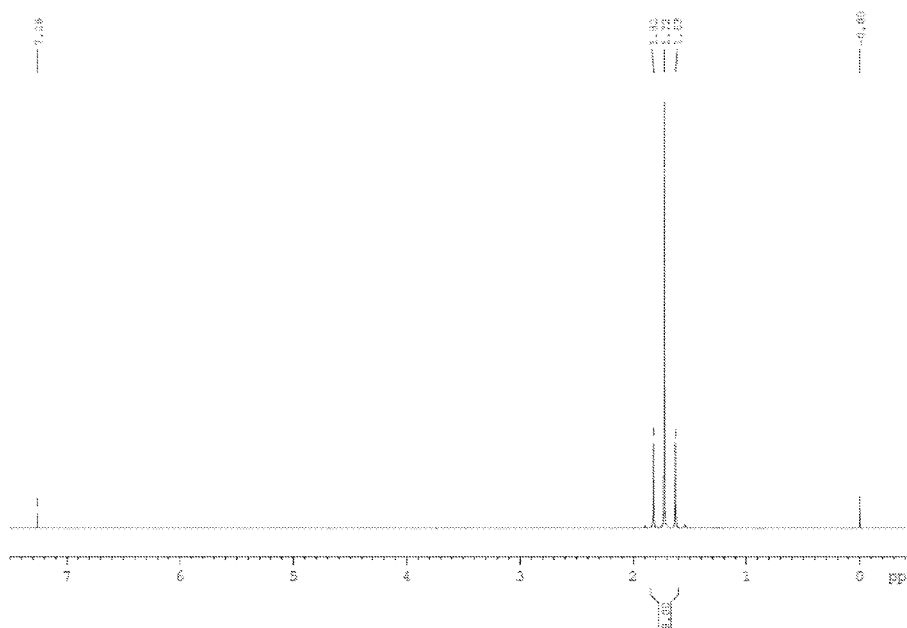


Figure 1.

(57) Abstract: The invention relates to a process for the manufacture of (trimethyl)platinum iodide by the reaction between potassium hexachloroplatinate (K_2PtCl_6) and methyllithium (MeLi) followed by quenching with iodine (I_2).



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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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Process for manufacturing (trimethyl)platinum iodideTechnical field

The present invention relates to the manufacture of (trimethyl)platinum iodide.

Background art

The complex (trimethyl)platinum iodide $[\text{PtMe}_3\text{I}]_4$ also known as iodo(trimethyl)platinum, is used as an intermediate in the synthesis of (trimethyl)methylcyclopentadienyl platinum ($\text{Pt}(\text{MeCp})\text{Me}_3$). The latter complex has several applications including as a siloxane curing catalyst and a source of platinum in chemical vapor deposition. Several routes to $[\text{PtMe}_3\text{I}]_4$ have been described previously.

The article "Improved Isolation Procedure for the Preparation of iodo(trimethyl)platinum (IV)" (*Inorganic Chemistry*, Vol. 14, No. 8, 1975, p2020) describes the production of $[\text{PtMe}_3\text{I}]_4$ in 80-81% yield from potassium chloroplatinate (K_2PtCl_6) and methylmagnesium iodide (MeMgI). While this procedure may be possible on a small scale, MeMgI is prohibitively expensive to use at scale.

The article " ^{195}Pt NMR Study of (η^5 -Cyclopentadienyl)trialkylplatinum(IV) Complexes" (*Magnetic Resonance in Chemistry*, vol 30, 481-489 (1992)) describes the production of $[\text{PtMe}_3\text{I}]_4$ from K_2PtCl_6 and methyllithium (MeLi). The mixture is quenched by the addition of 1,2-dibromoethane, presumably forming bromo(trimethyl)platinum (IV) in situ, which is then treated with a saturated solution of potassium iodide in hydrochloric acid in order to substitute iodine into the intermediate complex. The reported yield is 89%. This reference also describes the preparation of $\text{Pt}(\text{MeCp})\text{Me}_3$ by treating $[\text{PtMe}_3\text{I}]_4$ with methylcyclopentadienyl sodium. The same procedure is used in Example 1 of US 6 809 212 B2 (Praxair Technology, Inc) to prepare $[\text{PtMe}_3\text{I}]_4$ with a reported yield of 80%. The downsides of this procedure are that (i) 1,2-dibromoethane is toxic and hazardous to use at scale; (ii) the use of 1,2-dibromoethane results in the release of ethylene gas which is hazardous, and (iii) the requirement to exchange bromide for iodide in a separate step also adds complexity to the process.

WO2021/186087A1 (Umicore AG & Co. KG) describes a process for producing (trimethyl)platinum iodide by reacting together a platinum (II) or platinum (IV) compound, at least one methyl Grignard compound of formula MeMgX where $\text{X} = \text{Cl}, \text{Br}$ or I , and

iodomethane, with the molar ratio of Pt : MeMgX : iodomethane being between 1 : 4 : 4 and 1 : 6 : 6. The reaction is carried out in an aprotic polar solvent "SA" comprising an ether compound "SE" and a halogenated hydrocarbon compound "SH". The examples are carried out using a mixed solvent of CH₂Cl₂ and diethyl ether. A disadvantage of this method is the requirement to use a halogenated hydrocarbon solvent.

There is a need for an alternative process for producing [PtMe₃I]₄ which does not involve 1,2-dibromoethane, does not require the use of a halogenated solvent, and which is straightforward to implement at scale. The present invention addresses this problem.

Summary of the invention

US 6 809 212 B2 suggests that a variety of quenchers which can be used to quench the MeLi used in the reaction, namely: alkyl halides, ketones, alcohols, water, mineral acids, organic acids, carboxylic acids. Specific examples of quenchers are 1-bromo-2-chloroethane, 1-bromo-2-fluoroethane, iodomethane and 1,2-dibromoethane. Despite this statement, the present inventors found that when using oxygen-containing quenching agents the platinum was typically reduced to Pt(0) and resulted in a complex sludge-like mixture.

The present inventors have surprisingly found that modifying the procedure reported in *Magnetic Resonance in Chemistry*, vol 30, 481-489 (1992) and US 6 809 212 B2 by quenching using iodine (I₂) solves the above mentioned problems. The iodine reacts with the intermediate formed between K₂PtCl₆ and MeLi to produce [PtMe₃I]₄ directly without the need for a subsequent step of treating the residue with potassium iodide.

Several existing syntheses of the complex (trimethyl)platinum iodide have reported a yellow-coloured solid, which yellow colour has been attributed to iodine impurities (see WO2021/186087 and references cited therein). It is therefore surprising that it is possible to produce a clean product despite using I₂ to quench the reaction.

In a first aspect the invention relates to a process for the manufacture of (trimethyl)platinum iodide comprising the steps of:

- (i) adding a dispersion containing ≥ 3 molar equivalents of methyllithium (MeLi) in an organic solvent to a dispersion of potassium hexachloroplatinate (K₂PtCl₆) in an organic solvent;
- (ii) allowing the K₂PtCl₆ and MeLi to react;
- (iii) quenching the mixture from step (ii) with a source of iodine (I₂);

(iv) acidifying the mixture from step (iii) with an aqueous solution to provide a crude mixture containing (trimethyl)platinum iodide.

The term “dispersion” encompasses slurries and solutions, unless stated otherwise.

This process gives good yields of product (70-85%) and avoids the use of toxic 1,2-dibromoethane.

Description of the Figures

Figure 1 is the ^1H NMR spectrum (CDCl_3) of the $[\text{PtMe}_3\text{I}]_4$ product prepared in Example 4.

Detailed description

The process requires the addition of ≥ 3 molar equivalents of MeLi relative to the equivalents of K_2PtCl_6 . It is preferred that ≥ 6 molar equivalents of MeLi are added to ensure complete conversion of the K_2PtCl_6 . Typically the process uses 6 to 10 molar equivalents of MeLi in step (i), and in a preferred embodiment 7 to 9 equivalents of MeLi are added, most preferably 8 molar equivalents of MeLi are added.

The K_2PtCl_6 may be dispersed in any suitable organic solvent. Preferred solvents are organic solvents containing an ether unit. A preferred solvent is tetrahydrofuran (THF).

The MeLi may be dissolved in any suitable organic solvent. Preferred solvents are organic solvents containing an ether unit, such as diethyl ether (Et_2O) or diethoxymethane (DEM). DEM is preferred over Et_2O because the former has a higher boiling point, and is safer to use at scale.

It is preferred that the temperature of the mixture is maintained between 0 to 20 °C during the addition of MeLi, preferably between 0 to 15 °C, preferably between 2.5 to 15 °C.

In step (ii) the MeLi and K_2PtCl_6 are allowed to react. Step (ii) is preferably carried out while maintaining the temperature of the mixture at 0 to 15 °C, preferably at 2.5 to 15 °C, such as 5 to 15 °C. A duration of 60 to 180 minutes is normally suitable, with a duration of 120 minutes being preferred.

In step (iii) the mixture from step (ii) is quenched with a source of iodine (I_2). The source of iodine is preferably a dispersion of I_2 in an organic solvent, preferably a solution of I_2 in THF. It is preferred that at least 3 molar equivalents of I_2 are added relative to the amount of K_2PtCl_6 , preferably 3 to 5 equivalents, typically 3 to 4 equivalents. In a preferred embodiment approximately 3.5 equivalents are added. Step (iii) is preferably carried out while maintaining the temperature of the reaction at 5 to 15 °C, typically around 7.5 °C.

Once the reaction with I_2 is complete the mixture is acidified (step (iv)) by addition of an aqueous solution, preferably a HCl/NaCl brine solution.

Lithium salts can be removed by washing the organics with aqueous solution as will be known to those skilled in the art.

The crude (trimethyl)platinum iodide product may be purified by any means known to those skilled in the art. A preferred procedure involves distilling the mixture of (trimethyl)platinum iodide in organic solvent until the residue has reached approximately 10% of its original volume. Precipitation of the product can be achieved by the addition of acetone. The solid can be isolated by filtration. Typical yields are 70-85%.

The process may include a subsequent step of converting the (trimethyl)platinum iodide into another platinum complex by substituting the iodide ligand with an organic ligand. In a preferred embodiment the process includes a step of substituting the iodide ligand with a substituted or unsubstituted cyclopentadienyl ligand, for example by treatment with a salt of the desired substituted or unsubstituted cyclopentadienyl ligand. The (trimethyl)platinum iodide may be converted to $(Pt(MeCp)Me_3)$ by techniques described elsewhere in the literature e.g. by reaction with methylcyclopentadienyl sodium.

Examples

Example 1 (K_2PtCl_6 in THF, MeLi in DEM)

A slurry of potassium hexachloroplatinate (K_2PtCl_6) and anhydrous THF was cooled to 10 °C with stirring. A solution of MeLi (8 equivalents relative to K_2PtCl_6) in diethoxymethane (DEM) was added to the K_2PtCl_6 /THF slurry over a period of ~ 100 mins while maintaining the temperature at 7.5 to 10.5 °C. Once addition was complete stirring was maintained for ~ 120 mins. After this time a solution of I_2 (3.4 equivalents relative to K_2PtCl_6) in THF was added over a period of ~ 30 mins while maintaining the temperature at 7.5 to 10.5 °C. On completion

the mixture was stirred at 10 °C for ~ 60 mins. The mixture was acidified by addition of a HCl/NaCl brine solution over a period of ~ 15 mins while maintaining a temperature of 10 to 20 °C. Lithium salts were removed by washing the organics with water followed by two washes with brine.

The organic layer was distilled until the residual distillation volume was ~ 10% of the original volume, at which point solid formation was observed. Approximately 2.5 times the volume of acetone was added relative to the residual distillation volume. The solid was isolated over a fritted adapter with a medium frit. Any bypass seen in the mother liquor was recycled over the frit until all of the solid had been collected. The solid was washed with approximately 8 times the residual distillation volume, spread across three aliquots, to aid in removing impurities and colour in the product. The frit was then dried to constant weight to give an off-white coloured solid. The yield of $[\text{PtMe}_3\text{I}]_4$ was 70-85%. The ^1H NMR spectrum of the product in CDCl_3 matched that shown in Figure 1. Elemental analysis $\text{PtC}_3\text{H}_9\text{I}$ requires C, 9.82; H 2.47; found C, 10.14; H, 2.06.

Example 2 (K_2PtCl_6 in THF, MeLi in Et_2O)

A slurry of potassium hexachloroplatinate (K_2PtCl_6) and anhydrous THF was cooled to 5 °C with stirring. A solution of MeLi (8 equivalents relative to K_2PtCl_6) in diethylether (Et_2O) was added to the K_2PtCl_6 /THF slurry over a period of ~ 80 mins while maintaining the temperature at 5.0 to 8.0 °C. Once addition was complete stirring was maintained for ~ 100 mins. After this time the reaction mixture was cooled to 2 °C and a solution of I_2 (3.4 equivalents relative to K_2PtCl_6) in THF was added over a period of ~ 60 mins while maintaining the temperature at 2.0 to 5.0 °C. On completion the mixture was stirred at 2 °C for ~ 16 hours. The mixture was acidified by addition of a HCl/NaCl brine solution over a period of ~ 15 mins while maintaining a temperature of 10 to 20 °C. Lithium salts were removed by washing the organics with water followed by two washes with brine.

The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The isolated solid was washed with 50 mL acetone to remove impurities and colour in the product, filtered, and the frit was then dried to constant weight to give an off-white coloured solid. The yield of $[\text{PtMe}_3\text{I}]_4$ was 76%. The ^1H NMR spectrum of the product in CDCl_3 matched that shown in Figure 1.

Example 3 (K_2PtCl_6 in THF, MeLi in DEM)

Potassium hexachloroplatinate (K_2PtCl_6) was dissolved in anhydrous THF and the slurry was cooled to 5 °C with stirring. A solution of MeLi (8 equivalents relative to K_2PtCl_6) in diethoxymethane (DEM) was added to the K_2PtCl_6 /THF mixture over a period of ~ 100 mins while maintaining the temperature at 5.0 to 8.0 °C. Once addition was complete stirring was maintained for ~ 120 mins. After this time the reaction mixture was cooled to 2 °C and a solution of I_2 (3.4 equivalents relative to K_2PtCl_6) in THF was added over a period of ~ 60 mins while maintaining the temperature at 2.0 to 5.0 °C. On completion the mixture was stirred at 2 °C for ~ 16 hours. The mixture was acidified by addition of a HCl/NaCl brine solution over a period of ~ 50 mins while maintaining a temperature of 5 to 8 °C. Following this, the reaction temperature was increased to 20 °C and lithium salts were removed by washing the organics with water followed by two washes with brine.

The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The isolated solid was washed with 150 mL acetone to remove impurities and colour in the product, filtered, and the frit was then dried to constant weight to give an off-white coloured solid. The yield of $[PtMe_3I]_4$ was 83%. The 1H NMR spectrum of the product in $CDCl_3$ matched that shown in Figure 1.

Example 4 (K_2PtCl_6 in THF, MeLi in DEM – scaled procedure)

Potassium hexachloroplatinate (K_2PtCl_6) was transferred into a flexible isolator and slurried in anhydrous THF. The slurry was transferred from the flexible isolator into a 30 L reactor which had been previously degassed. The slurry was cooled to 10 °C with agitation. A solution of MeLi (8 equivalents relative to K_2PtCl_6) in diethoxymethane (DEM) was transferred into the slurry over a period of 100 to 120 minutes while maintaining a temperature between 7.5 to 12.5 °C. Once the MeLi addition was completed the solution was allowed to agitate for ~120 minutes. After this reaction period, a solution of I_2 (3.2 equivalents relative to K_2PtCl_6) in anhydrous THF was added over a period of 30-45 minutes while maintaining a temperature of 7.5 to 12.5 °C. Once the addition was completed the solution was allowed to agitate at 10°C for ~60 minutes. The solution was acidified by adding HCl/NaCl brine solution over a period of ~15 minutes while maintaining the solution temperature under 20 °C. Lithium salts were removed by washing the organics with water followed by two washes of brine solution.

The organic solution was then distilled until ~10% of the starting volume remained, at this volume solid formation was observed. Approximately 1.75 times the volume of acetone was used relative to the residual distillation volume. The solid was isolated over a fritted adapter with a medium Frit. Any bypass seen in the mother liquor was recycled over the frit until all

solid had been collected. The solid was washed with ~1.25 times the residual distillation volume, spread across three aliquots, to aid in removing impurities and color in the product. If color in the rinse liquors were still present, an optional 1.25 times the residual distillation volume of acetone was available to remove any additional color.

The frit was then dried to constant weight to give an off-white to white colored product. The yield of $[\text{PtMe}_3\text{I}]_4$ was ~75%. The ^1H NMR spectrum of the product in CDCl_3 is show in Figure 1. Elemental Analysis of $\text{PtC}_3\text{H}_9\text{I}$ requires C: 9.82; H: 2.47; found C: 10.08; H: 2.39.

Claims

1. A process for the manufacture of (trimethyl)platinum iodide comprising the steps of:
 - (i) adding a dispersion containing ≥ 3 molar equivalents of methyllithium (MeLi) in an organic solvent to a dispersion of potassium hexachloroplatinate (K_2PtCl_6) in an organic solvent;
 - (ii) allowing the K_2PtCl_6 and MeLi to react;
 - (iii) quenching the mixture from step (ii) with a source of iodine (I_2);
 - (iv) acidifying the mixture from step (iii) with an aqueous solution to provide a crude mixture containing (trimethyl)platinum iodide.
2. A process as claimed in claim 1, wherein 6 to 10 molar equivalents of MeLi are added in step (i).
3. A process as claimed in claim 1 or claim 2, wherein the dispersion of K_2PtCl_6 in an organic solvent in step (i) is a slurry of K_2PtCl_6 in tetrahydrofuran.
4. A process as claimed in any of claims 1 to 3, wherein the dispersion of MeLi in an organic solvent in step (i) is a solution of MeLi in diethoxymethane or a solution of MeLi in diethylether.
5. A process as claimed in any of claims 1 to 4, wherein during step (i) the temperature is maintained at between 0 to 15 °C during the addition.
6. A process as claimed in any of claims 1 to 5, wherein during step (ii) the temperature of the mixture is maintained at between 0 to 15 °C.
7. A process as claimed in any of claims 1 to 6, wherein the source of iodine is a solution of I_2 in an organic solvent.
8. A process as claimed in any of claims 1 to 7, wherein the source of iodine is a solution of I_2 in tetrahydrofuran.
9. A process as claimed in any of claims 1 to 8, wherein 3 to 4 molar equivalents of I_2 are added in step (iii).

10. A process as claimed in any of claims 1 to 9, wherein the process includes a step (v) of treating the crude (trimethyl)platinum iodide product with acetone and isolating (trimethyl)platinum iodide by filtration.
11. A process as claimed in any of claims 1 to 10, comprising a subsequent step of substituting the iodide ligand within the (trimethyl)platinum iodide with an organic ligand.
12. A process as claimed in any of claims 1 to 11, comprising a subsequent step of substituting the iodide ligand within the (trimethyl)platinum iodide with a substituted or unsubstituted cyclopentadienyl ligand.
13. A process as claimed in any of claims 1 to 12, comprising a subsequent step of substituting the iodide ligand within the (trimethyl)platinum iodide with a methylcyclopentadienyl ligand.

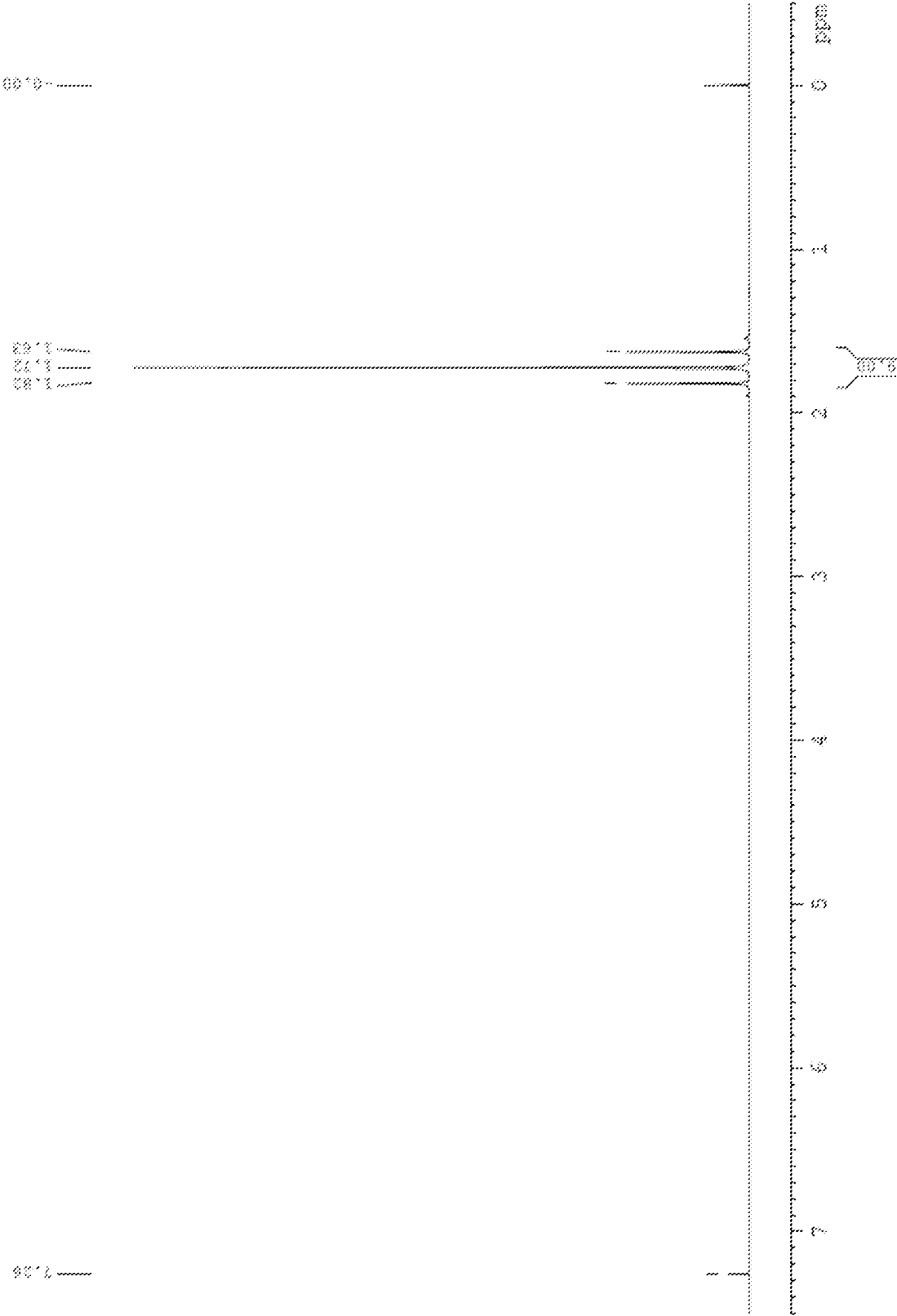


Figure 1.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07F15/00 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) C07F		
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, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/010158 A1 (MEIERE SCOTT HOUSTON [US] ET AL) 15 January 2004 (2004-01-15) example 4 paragraph [0065] pages 6-7 -----	1-13
☐ 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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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		Date of mailing of the international search report
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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 Bourghida, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004010158 A1	15-01-2004	AU 2003275973 A1	31-12-2003
		US 2004010158 A1	15-01-2004
		WO 03106011 A2	24-12-2003
