Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-98496

54. **TÍTULO** "SÍNTESIS DE PIRROL-2-CARBONITRILOS"

51. **CLASIFICACIÓN INTERNACIONAL** C07D 207/416 · C07B 43/08
A61K 31/275

71. **SOLICITANTE** WYETH

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74. **APODERADO** ALVARO CORREA ORDOÑEZ.
T.P. 20.281

22. **BOGOTÁ, D. C.,** Septiembre 29, 2006

(FORMA P-10)

S.S

PETITORIO

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-098496- -00000-0000
Fec: 2006-09-29 16:00:15 Dep: 2020 NUECREACIONE Radicación
Tra: 11 PATENTEYM
Eve: 376 FASENACIONALI
Act: 411 PRESENTACION Folios: 45

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

30-10-06

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capítulo I. [ ] Capítulo II.

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C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

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C.E. [ ] Otro [ ]

Cual

Número 79.143.366 de Usaquén TP 20.281

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Nacionalidad o Domicilio: Estadounidenses

(5) PCT (85)

Solicitud Internacional No. PCT/US2005/010468 Fecha 28/03/2005

Publicación Internacional No. WO 2005/097743 Fecha 20/10/2005

(6) Título (54) SÍNTESIS DE PIRROL-2-CARBONITRILOS

(7) Clasificación Internacional (51) C07D 207/416; C07B 43/08

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	30/03/2004	60/557,807
	US	22/03/2005	11/086,061

(9) Comprobante de pago No. 6-64866 **Fecha** 24-AGO-2006

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud .. 00052
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [ ] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Reporte de Búsqueda Internacional, Opinión Escrita, Notificación de presentación de documento de Prioridad y Extractos.

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-096496- -00000-0000
Fec: 2006-09-29 16:00:15 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYM
Eva: 378 FASENACIONALI
Act: 411 PRESENTACION .. Folios: 45

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 64,066
FECHA : AGOSTO 24 DE 2006

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
[redacted]BECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	49367693	24/08/2006	65,767,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2005 (20.10.2005)

PCT

(10) International Publication Number
WO 2005/097743 A1

(51) International Patent Classification[7]: C07D 207/416, C07B 43/08

(21) International Application Number:
PCT/US2005/010468

(22) International Filing Date: 28 March 2005 (28.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/557,807	30 March 2004 (30.03.2004)	US
11/086,061	22 March 2005 (22.03.2005)	US

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

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

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/097743 A1

(54) Title: SYNTHESIS OF PYRROLE-2-CARBONITRILES

(57) Abstract: The instant invention concerns processes for the production of pyrrole-2-carbonitriles such as 1-methylpyrrole-2-carbonitrile. Such processes preferably comprise the steps of reacting a pyrrole with chlorosulfonyl isocyanate in the presence of a solvent and contacting the resulting product with a molar excess of an amide such as N,N-dimethylformamide. The product of this contacting step is then contacted with a molar excess of an organic base to produce a precipitate and a solution phase. The precipitate is then separated from the solution phase and the corresponding pyrrole-2-carbonitrile is isolated from the resulting solution phase.

SYNTHESIS OF PYRROLE-2-CARBONITRILES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. 60/557,807, filed on March 30, 2004, the disclosure of which is incorporated by reference herein in its entireties. This application corresponds to U.S. Application No. _____ filed on March 22, 2005.

FIELD OF THE INVENTION

[0002] The present invention is in the field of synthesis and isolation of pyrrole-2-carbonitriles such as 1-methylpyrole-2-carbonitrile.

BACKGROUND OF THE INVENTION

[0003] Pyrrole-2-carbonitriles are useful as intermediates in the production of chemical compounds, including pharmaceutical and insecticide compositions. See, for example, U.S. Patent Nos. 6,492,402 (directed to thrombin inhibitors) and 5,204,332 (directed to pyrrole carbonitrile insecticidal, acaricidal and molluscicidal agents).

[0004] Barnett, *et al.*, *J. Can. Chem.* 1980, 58, 409, teaches a synthetic process for 1-methylpyrrole-2-carbonitrile involving the reaction of 1-methylpyrrole with chlorosulfonyl isocyanate in dichloromethane in a first step. In Barnett's process, the product of the first step was reacted with DMF, and the reaction mixture was then poured into ice-cold 4M HCl. Following product workup and vacuum distillation, 1-methylpyrrole-2-carbonitile was said to be obtained in 58% yield.

[0005] Other synthetic methods for 1-methylpyrrole-2-carbonitrile from 1-methylpyrrole are said to include reaction with methanolic cyanide solution under anoidic

oxidation conditions (*J. Am. Chem. Soc.* 1977, 99, 6111), reaction with excess 1,4-dicyanobenzene as a photosensitizer in the presence of methanolic cyanide solution (*J. Chem. Soc., Chem. Commun.* 1978, 1108), reaction of trimethylsilyl cyanide in a tetraphenylphorphine-sensitized photooxidation at -70 °C (*J. Am. Chem. Soc.* 1985, 107, 5279), and reaction with freshly prepared $Ph_3P(SCN)_2$ at -40 °C (*J. Chem. Soc., Perkin Trans. I* 1980, 1132). Another synthetic process starts with 2-pyrrolecarboxaldehyde (*Can. J. Chem.* 1959, 37, 2053 and *J. Chem. Soc., Chem. Commun.* 1972, 1226). Yet another process uses 2-pyrrolecarboxaldehyde as the starting material (*J. Prakt. Chem.* 1994, 336, 467 and *Tetrahedron Lett.* 1993, 34, 141). Such processes often require tedious aqueous workup and repetitive extractions with ether, methylene chloride, or some other suitable solvent. Some procedures require the use of chromatography in the isolation/purification step.

SUMMARY OF THE INVENTION

[0006] In some aspects, the instant invention concerns a process for the production of pyrrole-2-carbonitriles such as 1-methylpyrrole-2-carbonitrile. A pyrrole is reacted with chlorosulfonyl isocyanate in the presence of a solvent that is substantially unreactive with chlorosulfonyl isocyanate and contacting the resulting product with a molar excess (preferably at least about 2.0 molar equivalents) of an N,N-dialkylformamide. This product is then contacted with a molar excess (preferably at least about 2.0 molar equivalents) of an organic base to produce a precipitate and a solution phase. The precipitate is then separated from the solution phase and the corresponding pyrrole-2-carbonitrile is isolated from the resulting solution phase. In some embodiments, water is added to the solution phase prior to isolating the pyrrole-2-carbonitrile. In certain embodiments, the pyrrole-2-carbonitrile is isolated by distillation.

[0007] In some embodiments, the solvent is toluene or acetonitrile. In certain of these embodiments, it is preferred that the solvent comprises toluene.

[0008] In other preferred embodiments, the N,N-dialkylformamide is N,N-dimethylformamide (DMF).

[0009] In certain embodiments, the base is a tertiary amine or an aromatic amine. In some preferred embodiments, the base is triethylamine.

[0010] In yet other embodiments, reaction of the pyrrole and the chlorosulfonyl isocyanate is performed at a temperature at or below about 0 °C. In certain embodiments 0.1 to 0.4 molar equivalents of water per equivalent of the solvent is added to effect dilution. In certain preferred embodiments, the isolated solution phase is concentrated prior to its subsequent dilution and distillation.

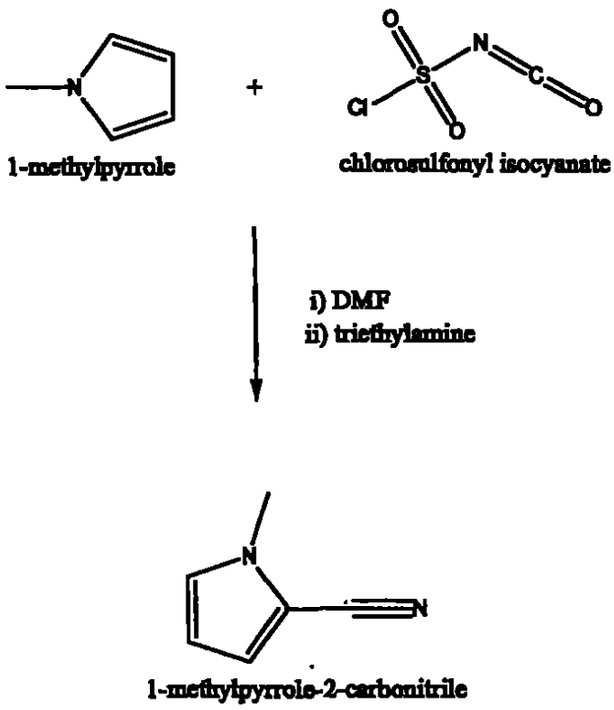
[0011] In other aspects, the invention also concerns products that are made by the processes of the instant invention.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0012] The instant invention relates to methods of producing pyrrole-2-carbonitriles, particularly 1-methylpyrrole-2-carbonitrile and preferably with improved isolated yields. In preferred embodiments, the methods of the invention involve reacting a pyrrole such as 1-methylpyrrole with chlorosulfonyl isocyanate. In certain embodiments, the molar ratio of pyrrole to chlorosulfonyl isocyanate is from about 0.9:1 to about 1.1:1, preferably approximately 1:1. It is also preferred that the reaction be preformed at or below about 0 °C. The product of this reaction is then contacted with N,N-dialkylformamide, followed by the addition of an organic base.

[0013] The synthesis of 1-methylpyrrole-2-carbonitrile from 1-methylpyrrole is illustrated in Scheme I.

Scheme I



[0014] Although we do not intend to be bound by any particular theory or mechanism of operation, the N,N-dialkylformamide (such as N,N-dimethylformamide (DMF)) is believed to

serve as a catalyst for the reaction. It is preferred that two equivalents of DMF be used in the instant process. During the reaction, DMF·HCl and DMF·SO_3 complexes are believed to be formed. By using a molar excess of DMF (preferably at least two equivalents), it is believed that one can avoid emission of the gaseous by-products HCl and SO_3.

[0015] Alkyl groups in N,N-dialkylformamides include aliphatic hydrocarbon chains having one to six, preferably one to four, and more preferably one to three carbon atoms, and includes, but is not limited to, straight and branched chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl. N,N-dialkylformamides also include cyclic compositions, e.g., where the cyclic group can have 5-7 ring members, such as six including N-formylpiperidine and N-formylmorpholine.

[0016] Organic bases useful in the instant invention include, but are not limited to, tertiary amines and aromatic amines. Tertiary amines include, but are not limited to, trimethylamine, triethylamine, tripropylamine, 1-methylpiperidine, 1,4-dimethylpiperazine, and N,N-diisopropylethylamine (Hunig's Base). Aromatic amines include, but are not limited to, pyridine, 2-picoline, 2,6-lutidine, quinoline, 5,6,7,8-tetrahydroquinoline. In some embodiments, triethylamine is preferred.

[0017] Solvents useful in the instant invention are those that are substantially unreactive with chlorosulfonyl isocyanate. These solvents include aliphatic hydrocarbons (such as heptane), aromatic hydrocarbons (such as toluene), chlorinated hydrocarbons (such as methylene chloride), chlorobenzene, dialkyl ethers (such as diisopropyl ether) and alkyl nitriles (such as acetonitrile). In some embodiments, toluene or acetonitrile are preferred. In other embodiments, toluene is preferred.

[0018] The pyrrole moiety is generally sensitive to acids and will form tar in their presence. In the instant process, the use of a molar excess of a base such as triethylamine (Et_3N) (preferably at least two equivalents), is believed to effect precipitation of a relatively pure, solid salt (*e.g.*, $Et_3N·SO_3$) that can be removed by filtration. The filtrate (containing, *e.g.*, $Et_3N·HCl$) can be worked up by aqueous extraction. Applicants have found that the triethylamine treatment increased the 31-41 % yield reported by Barnett, *et al., J. Can. Chem.* 1980, 58, 409 to 65-76%.

[0019] Applicants have found that although one can distill the solution phase that is isolated following treatment with the organic base, in some embodiments, it is preferred to first add at least some water thereto, particularly when the distillation is performed at atmospheric pressure. While not wanting to be bound by theory, it is believed the addition of water breaks, for example, the toluene-nitrile complex. The addition of water has been found to allow

separation of toluene from the product at a temperature of less than 85 °C. In certain embodiments, 0.1 to 0.4 molar equivalent of water per equivalent of solvent is used.

[0020] This invention can be further illustrated by the following examples of the preferred embodiments thereof, although it will be understood that these examples are included only for illustration and comparison to the existing art, and are not intended to limit the scope of the invention unless specifically indicated.

Example 1

[0021] A 5 liter flask was charged with acetonitrile (2.0 L) and 1-methylpyrrole (83 g, 3.5 mol). Chlorosulfonyl isocyanate (495 g, 3.5 mol) was added dropwise maintaining so as to maintain the reaction temperature at -6 to 0 °C. It should be noted that chlorosulfonyl isocyanate is corrosive and reacts violently with water. After stirring for 15 min., N,N-dimethylformamide (DMF, 511 g, 7.0 mol) was added at -4 to 0 °C followed by triethylamine (707 g, 7.0 mol) and the stirring was continued at 10 °C. The resulting white precipitate was filtered and washed with acetonitrile (200 mL). The filtrate was concentrated under reduced pressure. Water (4.0 L) was added to the residue, phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with brine (3 x 500 mL). The organic phase was concentrated under vacuum and the residue was distilled using a Vigreux column at approximately 4 mm Hg/ 70 ± 10 °C to give 1-methylpyrrole-2-carbonitrile (282 g, 76% yield).

Example 2

[0022] Starting with 47.0 g of 1-methylpyrrole, the reaction was conducted in a manner generally analogous to Example 1 except that the acetonitrile was replaced with toluene. After addition of chlorosulfonyl isocyanate, two layers were formed. Upon cooling to 0 to 5 °C, the bottom layer solidified. The hygroscopic solids were collected by filtration and washed with toluene. Concentration of the filtrates gave 325 mL of a toluene solution containing (as determined by 1H NMR) 0.55 mol of 1-methylpyrrole-2-carbonitrile (58.3 g, 95 % yield).

Example 3

[0023] A crude solution of 1-methylpyrrole-2-carbonitrile in toluene, produced as in Example 2, was washed with brine containing sodium hydroxide to remove traces of acids. The separated organic layer (673 g) was atmospherically distilled (head temperature 110-115 °C) to remove the bulk of the toluene. Water was added (255 mL total) and the distillation was

continued until the head temperature started to increase to above 86 °C. The pot residue (290 g), containing some water, was fractionally distilled under reduced pressure to give 1-methylpyrrole-2-carbonitrile (217 g).

[0024] All patents, patent applications, and other publications that appear in this application are incorporated herein in their entirety.

What is Claimed:

1. A process for preparing a pyrrole-2-carbonitrile comprising:

(a) reacting a pyrrole with chlorosulfonyl isocyanate in the presence of a solvent;

(b) contacting the product of step (a) with a molar excess of an N,N-dialkylformamide;

(c) contacting the product of step (b) with a molar excess of an organic base resulting in the production of a precipitate and a solution phase;

(d) separating the precipitate from the solution phase; and

(e) isolating a pyrrole-2-carbonitrile from the solution phase of step (d).

2. The process of claim 1 wherein at least about 2.0 molar equivalents of an N,N-dialkylformamide are used in step (b).

3. The process of claim 1 wherein said organic base is a tertiary amine or an aromatic amine.

4. The process of claim 3 wherein at least 2.0 molar equivalents of a tertiary amine or aromatic amine are used in step (c).

5. A process according to any one of claims 1 to 4 wherein the pyrrole-2-carbonitrile is isolated by distillation.

6. A process according to any one of claims 1 to 5 wherein the pyrrole is 1-methylpyrrole.

7. A process according to any one of claims 1 to 6 wherein the solvent is toluene or acetonitrile.

8. A process according to any one of claims 1 to 6 wherein the solvent is toluene.

9. A process according to any one of claims 3 to 8 wherein the tertiary amine is triethylamine.

10. A process according to any one of claims 3 to 8 wherein the aromatic amine is pyridine.

11. A process according to any one of claims 1 to 10 wherein the N,N-dialkylformamide is N,N-dimethylformamide, N-formylpiperidine or N-formylmorpholine.

12. A process according to any one of claims 1 to 10 wherein the N,N-dialkylformamide is N,N-dimethylformamide.

13. A process according to any one of claims 1 to 12 wherein the molar ratio of the pyrrole to chlorosulfonyl isocyanate is from 0.9:1 to 1.1:1.

14. A process according to claim 5 wherein water is added to the solution phase prior to distilling the pyrrole-2-carbonitrile from the solution phase of step (d).

15. A process according to claim 14 wherein 0.1 to 0.4 molar equivalent of water per equivalent of solvent is utilized.

16. A process according to claim 15 wherein the solution phase of step (d) is concentrated prior to the addition of water in step (e).

17. A process according to any one of claims 1 to 16 wherein step (a) is performed at a temperature at or below about 0 °C.

18. A product that is produced by the process of any one of claims 1 to 17.

PATENT COOPERATION TREATY

PCT/US2005/010468

RECEIVED

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From the INTERNATIONAL BUREAU

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To:

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ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing *(day/month/year)* 10 August 2005 (10.08.2005)	
Applicant's or agent's file reference WYNC-1668 (AM 100968)	IMPORTANT NOTIFICATION
International application No. PCT/US2005/010468	International filing date *(day/month/year)* 28 March 2005 (28.03.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 30 March 2004 (30.03.2004)

Applicant

WYETH et al

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 March 2004 (30.03.2004)	60/557,807	US	25 April 2005 (25.04.2005)
22 March 2005 (22.03.2005)	11/086,061	US	01 August 2005 (01.08.2005)

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SÍNTESIS DE PIRROL-2-CARBONITRILOS

REFERENCIA CRUZADA CON SOLICITUDES RELACIONADAS

[0001] Esta solicitud reivindica prioridad de la Solicitud Estadounidense No. 60/557.807, presentada el 30 de marzo de 2004, cuyo contenido se incorpora aquí como referencia en su totalidad. Esta solicitud corresponde a la Solicitud Estadounidense No. _____ presentada el 22 de marzo de 2005.

CAMPO DE LA INVENCIÓN

[0002] La presente invención pertenece al campo de la síntesis y aislamiento de pirrol-2-carbonitrilos tal como el 1-metilpirrol-2-carbonitrilo.

ANTECEDENTES DE LA INVENCIÓN

[0003] Los pirrol-2-carbonitrilos son útiles como intermedios en la producción de compuestos químicos, incluyendo composiciones farmacéuticas y insecticidas. Ver, por ejemplo, las patentes estadounidenses Nos. 6.492.402 (dirigida a inhibidores de trombina) y 5.204.332 (dirigida a agentes insecticidas, acaricidas y molucicidas de pirrol carbonitrilo).

[0004] Barnett, et al., *J. Can. Chem.* **1980**, 58, 409, enseña un proceso sintético para el 1-metilpirrol-2-

carbonitrilo que involucra la reacción de 1-metilpirrol con isocianato de clorosulfonilo en diclorometano en una primera etapa. En el proceso de Barnett, el producto de la primera etapa se hace reaccionar con DMF, y la mezcla de reacción es entonces vertida en HCl al 4M enfriado con hielo. Luego de trabajar el producto y destilación en vacío, se dice que se obtuvo 1-metilpirrol-2-carbonitrilo con un rendimiento de 58%.

[0005] Otros métodos sintéticos para obtener el 1-metilpirrol-2-carbonitrilo a partir de 1-metilpirrol se dice que incluyen la reacción con solución de cianuro metanólico bajo condiciones de oxidación anoídica (*J. Am. Chem. Soc.* **1977**, 99, 6111), reacción con 1,4-dicianobenceno como un fotosensibilizador en la presencia de la solución de cianuro metanólico (*J. Chem. Soc., Chem. Commun.* **1978**, 1108), reacción con cianuro de trimetilsililo en una fotooxidación sensibilizada con tetrafenilforfina a -70° C (*J. Am. Chem. Soc.* **1985**, 107, 5279), y la reacción con Ph3P(SCN)2 preparado fresco a -40° C (*J. Chem. Soc., Perkin Trans. I* **1980**, 1132). Otro proceso sintético inicia con 2-pirrolcarboxaldehido (*can. J. Chem.* **1959**, 37, 2053 y *J. Chem. Soc., Chem. Commun.* **1972**, 1226). Todavía otro proceso usa 2-pirrolcarboxaldehido como material de partida (*J. Prakt. Chem.* **1994**, 336, 467 y *Tetrahedron Lett.* **1993**, 34, 141). Tales procesos requieren frecuentemente un trabajo acuoso tedioso y extracciones repetitivas con éter, cloruro de metileno, u otros disolventes adecuados. Algunos

procedimientos requieren el uso de cromatografía en la etapa de aislamiento/purificación.

RESUMEN DE LA INVENCIÓN

[0006] En algunos aspectos, la presente invención se relaciona con un proceso para la producción de pirrol-2-carbonitrilos tal como el 1-metilpirrol-2-carbonitrilo. Un pirrol se hace reaccionar con isocianato de clorosulfonilo en la presencia de un disolvente que sustancialmente no reacciona con el isocianato de clorosulfonilo y se pone en contacto el producto resultante con un exceso molar (preferiblemente por lo menos 2 equivalentes molares) de una N,N-dialkilformamida. Este producto se pone entonces en contacto con un exceso molar (preferiblemente por lo menos 2 equivalentes molares) de una base orgánica para producir un precipitado y una fase de solución. El precipitado es entonces separado de la fase de solución y el pirrol-2-carbonitrilo correspondiente es aislado de la fase de solución resultante. En algunas modalidades, se agrega agua a la fase d solución antes de aislar el pirrol-2-carbonitrilo. En ciertas modalidades, pirrol-2-carbonitrilo es aislado por destilación.

[0007] En algunas modalidades, el disolvente es tolueno o acetonitrilo. En algunas de estas modalidades, lo preferido es que el disolvente comprenda tolueno.

[0008] En otras modalidades preferidas, el N,N-dialkilformamida es N,N-dimetilformamida (DMF).

[0009] En ciertas modalidades, la base es una amina terciaria o una amina aromática. En algunas modalidades preferidas, la base es trietilamina.

[0010] En todavía otras modalidades, la reacción del pirrol y el isocianato de clorosulfonilo se lleva a cabo a una temperatura de o por debajo de 0° C. En ciertas modalidades se agrega 0,1 a 0,4 equivalentes molares de agua por equivalente del disolvente para efectuar la dilución. En ciertas modalidades preferidas, la fase de solución aislada es concentrada antes de su subsiguiente dilución y destilación.

[0011] En otros aspectos, la invención también se relaciona con productos fabricados por medio de los procesos de la presente invención.

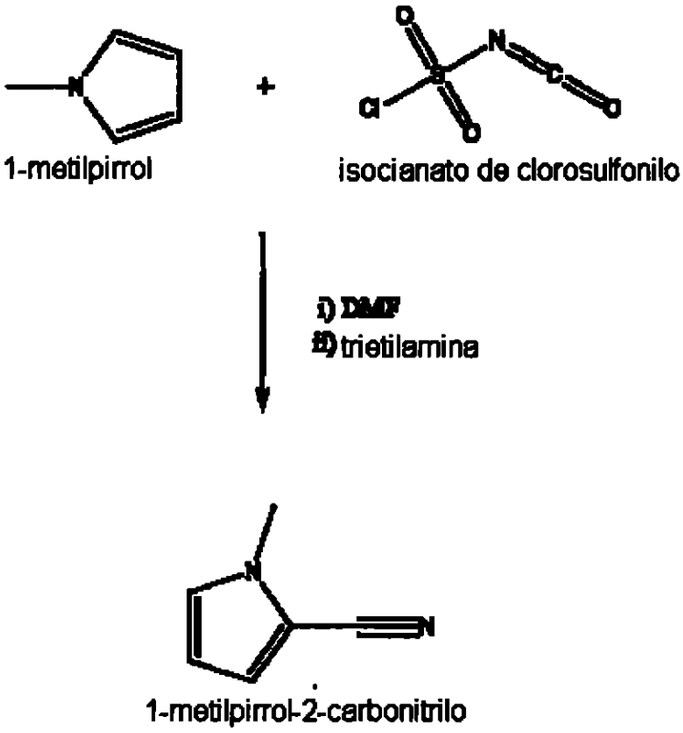
DESCRIPCIÓN DETALLADA DE LAS MODALIDADES ILUSTRATIVAS

[0012] La presente invención se relaciona con procesos para la producción de pirrol-2-carbonitrilos tales como 1-metilpirrol-2-carbonitrilo y preferiblemente con rendimientos aislados mejorados. En las modalidades preferidas, los métodos de la invención involucran hacer reaccionar un pirrol tal como 1-metilpirrol con isocianato de clorosulfonilo. En ciertas modalidades la proporción molar

del pirrol respecto del isocianato de clorosulfonilo está entre cerca de 0,9:1 a cerca de 1,1:1, preferiblemente aproximadamente 1:1. También se prefiere que la reacción se lleve a cabo a o por debajo de 0° C. El producto de esta reacción se pone entonces en contacto con N,N-dialkilformamida, seguido por la adición de una base orgánica.

[0013] La síntesis de 1-metilpirrol-2-carbonitrilo a partir de 1-metilpirrol se ilustra en el esquema I.

Esquema I



[0014] Aunque no queremos apegarnos a ninguna teoría en particular o mecanismo de operación, la N,N-dialkilformamida (tal como N,N-dimetilformamida (DMF)) se cree que sirve como un catalizador para la reacción. Se

prefiere usar dos equivalentes de DMF en el presente proceso. Durante la reacción, se cree que se forman complejos de DMF.HCl y DMF.SO_3. Al usar un exceso molar de DMF (preferiblemente por lo menos dos equivalentes), se cree que se puede evitar la emisión de productos intermedios gaseosos de HCl y SO_3.

[0015] Los grupos alquilo en las N,N-dialkilformamidas incluyen cadenas alifáticas de hidrocarbonos que tienen de uno a seis, preferiblemente de uno a cuatro, y más preferiblemente de uno a tres átomos de carbono, e incluye, sin limitarse, cadenas rectas y ramificadas tales como metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, t-butilo, n-pentilo, isopentilo, neo-pentilo, n-hexilo, e isohexilo. Las N,N-dialkilformamidas también incluyen composiciones cíclicas, por ejemplo, en donde el grupo cíclico puede tener 5 a 7 miembros de anillo, tal como seis incluyendo N-formilpiperidina y N-formilmorfolina.

[0016] Las bases orgánicas útiles en la presente invención incluyen, sin limitarse, aminas terciarias y aminas aromáticas. Las aminas terciarias incluyen, sin limitarse, trimetilamina, trietilamina, tripropilamina, 1-metilpiperidina, 1,4-dimetilpiperazina, y N,N-diisopropiletilamina (Base de Hunig). Las aminas aromáticas incluyen, sin limitarse a, piridina, 2-picolina,2,6-lutidina, quinolina, 5,6,7,8-tetrahidroquinolina. En algunas modalidades, se prefiere la trietilamina.

[0017] Los disolventes útiles en la presente invención son aquellos que sustancialmente no reaccionan con el isocianato de clorosulfonilo. Estos disolventes incluyen hidrocarburos alifáticos (tal como el heptano), hidrocarburos aromáticos (tal como el tolueno), hidrocarburos clorados (tal como cloruro de metileno), clorobenceno, dialquil éteres (tal como diisopropil éter) y alquilnitrilos (tal como acetonitrilo). En algunas modalidades, se prefiere el tolueno y el acetonitrilo. En otras modalidades, el tolueno es el preferido.

[0018] La parte pirrol es generalmente sensible a los ácidos y formará alquitrán en su presencia. En el presente proceso, el uso de un exceso molar de una base tal como trietilamina (Et_3N) (preferiblemente por lo menos 2 equivalentes), se cree que efectúa la precipitación de una sal sólida relativamente pura (por ejemplo, $Et_3N \cdot SO_3$) la cual puede removerse por filtración. El filtrado (que contiene, por ejemplo, $Et_3N \cdot HCl$) puede ser trabajado por extracción acuosa. Los solicitantes han encontrado que el tratamiento con trietilamina incrementó el rendimiento de 31 a 41 % reportado por Barnett, et al., *J. Can. Chem.* **1980**, 58, 409 a 65-76 %.

[0019] Los solicitantes han encontrado que aunque uno puede destilar la fase de solución que es aislada luego del tratamiento con la base orgánica, en algunas modalidades, se prefiere agregar primero algo de agua a esta, particularmente

cuando la destilación es llevada a cabo a presión atmosférica. Aunque no se desea amarrase a una teoría, se cree que la adición de agua rompe, por ejemplo, el complejo tolueno-nitrilo. Se ha encontrado que la adición de agua permite la separación del tolueno del producto a una temperatura menor a 85 ° C. En ciertas modalidades, se ha usado 0,1 a 0,4 equivalentes molares de agua por equivalente del disolvente.

[0020] Esta invención será ilustrada adicionalmente por los siguientes ejemplos de las modalidades preferidas de la misma, aunque debe entenderse que estos ejemplos se incluyen solo como ilustración y comparación respecto del estado de la técnica, y no tienen el propósito de limitar el alcance de la invención a menos que específicamente se indique.

Ejemplo 1

[0021] Un frasco de 5 L fue cargado con acetonitrilo (2.0 L) y 1-metilpirrol (83g, 3,5 moles). Se agregó isocianato de clorosulfonilo (495g, 3,5 moles) gota a gota para mantener la temperatura de reacción en -6 ° C. Debe notarse que el isocianato de clorosulfonilo es corrosivo y reacciona violentamente con el agua. Después de agitar durante 15 minutos, se agregó N,N-dimetilformamida (DMF, 522g, 7,0 moles) entre -4° C a 0° C seguido por trietilamina (707g, 7,0 moles) y se continuó la agitación a 100° C. El precipitado blanco resultante fue filtrado y lavado con

acetonitrilo (200 mL). El filtrado fue concentrado bajo presión reducida. Se agregó agua (4,0 L) al residuo, las fases fueron separadas y la fase acuosa fue extraída con acetato de etilo (2 x 200 mL). Las fases orgánicas combinadas fueron lavadas con salmuera (3 x 500 mL). La fase orgánica fue concentrada bajo vacío y el residuo fue destilado usando una columna Vigreux en aproximadamente 4 mm Hg/70 ± 10 0° C para dar 1-metilpirrol-2-carbonitrilo (282g, 76% de rendimiento).

Ejemplo 2

[0022] Iniciando con 47,0g de 1-metilpirrol, la reacción se condujo de una manera generalmente análoga al ejemplo 1 excepto porque el acetonitrilo se reemplazó por tolueno. Después de la adición de isocianato de clorosulfonilo, se formaron dos capas. Luego de enfriar entre 0 a 5 ° C, la capa inferior se solidificó. Se recolectaron los sólidos higroscópicos por filtración y se lavaron con tolueno. La concentración de los filtrados dio 325 mL de una solución de tolueno que contiene (según se determinó por 1H NMR) 0,55 moles de 1-metilpirrol-2-carbonitrilo (58,3 g, rendimiento 95%).

Ejemplo 3

[0023] Una solución cruda de 1-metilpirrol-2-carbonitrilo en tolueno, producida según el ejemplo 2, fue lavada con salmuera que contenía hidróxido de sodio para

remover la trazas de ácidos. La capa orgánica separada (673g) fue destilada atmosféricamente (cabeza de temperatura 110 a 115 ° C) para remover la masa de tolueno. Se agregó agua (225 mL total) y la destilación continuó hasta que la cabeza de temperatura empezó a incrementarse por encima de 86 ° C. El residuo del pote (290 g), que contenía algo de agua, fue destilado fraccionadamente bajo presión reducida para dar 1-metilpirrol-2-carbonitrilo (217 g).

[0024] Todas las patentes, solicitudes de patente, y otras publicaciones que aparecen mencionadas en esta solicitud son incorporadas a esta en su totalidad.

Lo que se reivindica es:

1. Un proceso para preparar un pirrol-2-carbonitrilo que comprende:

   (a) Hacer reaccionar un pirrol con isocianato de clorosulfonilo en la presencia de un disolvente;

   (b) Poner en contacto el producto de la etapa (a) con un exceso molar de una N,N-dialkilformamida;

   (c) Poner en contacto el producto de la etapa (b) con un exceso molar de una base orgánica resultando en la producción de un precipitado y una fase de solución;

   (d) Separar el precipitado de la fase de solución; y

   (e) Aislar un pirrol-2-carbonitrilo de la fase de solución de la etapa (d).

2. Un proceso de la reivindicación 1 en donde por lo menos cerca de 2 equivalentes molares de una N,N-dialkilformamida son usados en la etapa (b).
3. Un proceso de la reivindicación 1 en donde dicha base orgánica es una amina terciaria o una amina aromática.
4. El proceso de la reivindicación 3 en donde por lo menos cerca de 2 equivalentes molares de una amina terciaria o una amina aromática son usados en la etapa (c).

5. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 4 en donde el pirrol-2-carbonitrilo es aislado por destilación.

6. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 5 en donde el pirrol es 1-metilpirrol.

7. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 6 en donde el disolvente es tolueno o acetonitrilo.

8. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 6 en donde el disolvente es tolueno.

9. Un proceso de acuerdo con una cualquiera de las reivindicaciones 3 a 8 en donde la amina terciaria es trietilamina.

10. Un proceso de acuerdo con una cualquiera de las reivindicaciones 3 a 8 en donde la amina aromática es piridina.

11. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en donde la N,N-dialkilformamida es N,N-dimetilformamida,N-formilpiperidina y N-formilmorfolina.

12. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en donde la N,N-dialkilformamida es N,N-dimetilformamida.

13. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en donde la proporción molar del pirrol respecto del isocianato de clorosulfonilo está entre 0,9:1 a 1,1:1.

14. Un proceso de acuerdo con la reivindicación 5 en donde se utiliza 0,1 a 0,4 equivalentes molares de agua por equivalente del disolvente.

15. Un proceso de acuerdo con la reivindicación 14 en donde se utiliza 0,1 a 0,4 equivalentes molares de agua por equivalente del disolvente.

16. Un proceso de acuerdo con la reivindicación 15 en donde la fase de solución de la etapa (d) es concentrada antes de la adición de agua en la etapa (e).

17. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 16 en donde la etapa (a) se lleva a cabo a una temperatura de o por debajo de 0° C.

18. Un producto que es producido por el proceso de una cualquiera de las reivindicaciones 1 a 17.

SÍNTESIS DE PIRROL-2-CARBONITRILOS

Resumen: La presente invención se relaciona con procesos para la producción de pirrol-2-carbonitrilos tales como 1-metilpirrol-2-carbonitrilo. Tales procesos comprenden preferiblemente las etapas de hacer reaccionar un pirrol con isocianato de clorosulfonilo en la presencia de un disolvente y poner en contacto el producto resultante con un exceso molar de una amida tal como N,N-dimetilformamida. El producto de esta etapa de poner en contacto, se pone ahora en contacto con un exceso molar de una base orgánica para producir un precipitado y una fase de solución. El precipitado es entonces separado de la fase de solución y el pirrol-2-carbonitrilo correspondiente es aislado de la fase de solución resultante.

PATENT COOPERATION TREATY

JL/JAH 28

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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To:
WOODCOCK WASHBURN LLP
Attn. Lucci, Joseph
46th Floor
One Liberty Place
Philadelphia, PA 19103
UNITED STATES OF AMERICA

RECEIVED
AUG 0 3 2005
Woodcock Washburn

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference WYNC-1668 (AM100968) Milowsky RECEIVED	Date of mailing (day/month/year) 29/07/2005
International application No. PCT/US2005/010468 AUG 0 3 2005	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant WYETH DOCKET DEPT WWKMN	International filing date (day/month/year) 28/03/2005

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41–22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Federico Bonomelli

Form PCT/ISA/220 (January 2004)

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VN 9/8/05

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
WYNC-1668		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/010468	28/03/2005	30/03/2004
Applicant		
WYETH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [ ] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US2005/010468 00032

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/416 C07B43/08

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)
IPC 7 C07D C07B

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN 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.
Y	BARNETT, GRAHAM H. ET AL: "Pyrrole chemistry. XXI. Synthetic approaches to cyanopyrroles" CANADIAN JOURNAL OF CHEMISTRY , 58(4), 409-11 CODEN: CJCHAG; ISSN: 0008-4042, 1980, XP008049778	1-17
X	the whole document	18
Y	LOADER, CHARLES E. ET AL: "Pyrrole chemistry. XXIII. The cyanation of substituted pyrroles with chlorosulfonyl isocyanate (CSI). New syntheses of pyrrole-3-carbonitriles" CANADIAN JOURNAL OF CHEMISTRY, vol. 59, 1981, pages 2673-2676, XP008049785	1-17
X	the whole document	18

-/--

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in 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 document 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
18 July 2005	29/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gavrilîu, D

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VORBRÜGGEN HELMUT: "REAKTIVE ISOCYANATE I. DIE DIREKTE EINFUEHRUNG VON NITRIL-GRUPPEN IN UNGESATTIGTE SYSTEME. EINE EINFACHE UMWANDLUNG VON CARBONSÄUREN IN IHRE NITRILE" TETRAHEDRON LETTERS, vol. 9, no. 13, 1968, pages 1631-1634, XP002336475 the whole document	1-17

1

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/010468	28.03.2005	30.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D207/416, C07B43/08

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Gavriliu, D Telephone No. +49 89 2399-8274

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/010468

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/010468

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents:**

D1: BARNETT, GRAHAM H. ET AL: "Pyrrole chemistry. XXI. Synthetic approaches to cyanopyrroles" CANADIAN JOURNAL OF CHEMISTRY , 58(4), 409-11 CODEN: CJCHAG; ISSN: 0008-4042, 1980, XP008049778

D2: LOADER, CHARLES E. ET AL: "Pyrrole chemistry. XXIII. The cyanation of substituted pyrroles with chlorosulfonyl isocyanate (CSI). New syntheses of pyrrole-3-carbonitriles" CANADIAN JOURNAL OF CHEMISTRY, vol. 59, 1981, pages 2673-2676, XP008049785

D3: VORBRÜGGEN HELMUT: "REAKTIVE ISOCYANATE I. DIE DIREKTE EINFUEHRUNG VON NITRIL-GRUPPEN IN UNGESATTIGTE SYSTEME. EINE EINFACHE UMWANDLUNG VON CARBONSÄUREN IN IHRE NITRILE" TETRAHEDRON LETTERS, vol. 9, no. 13, 1968, pages 1631-1634, XP002336475

2. **Novelty** (Article 33(1) and 33(2) PCT)

The subject-matter of the present application relates to pyrrole-2-carbonitrile derivatives (Claim 18) as well as to a process for preparing the above-mentioned compounds (Claim 1-17).

The processes claimed by the Claims 1-17 differ from the D1-D2 processes on the account of the step (c) (see present Claim 1) and from the D3 processes on the account of step (b). Consequently, the novelty for the subject-matter claimed by the present Claims 1-17 is acknowledged.

Claim 18 relates to pyrrole-2-carbonitriles, which are prepared through the present process. Such a claim cannot be allowable under Article 33(1) and 33(3)PCT, as the documents D1 and D2 already disclose pyrrole-2-carbonitriles. The fact that a pyrrole-2-carbonitrile is prepared according to the present claimed process (a novel one) does not imply that the obtained product is novel. 1-Methyl-2-cyano-pyrrole as disclosed in the present application is identical as 1-Methyl-2-cyano-pyrrole disclosed in D1. The subject-matter of the claim 18 is not considered to be

novel.

3. **Inventive step** (Article 33(1) and 33(3)PCT

The present application discloses a process for preparing pyrrole-2-carbonitriles starting from a pyrrole and using the steps (a) to (e) (see present Claim 1).

D1, which is regarding as being the closest prior art, discloses also a process for preparing pyrrole-2-carbonitriles starting from pyrroles. The processes disclosed for preparing pyrrole-2-carbonitrile, 1-methylpyrrole-2-carbonitrile or 1-ethylpyrrole-2-carbonitrile (see D1 page 411) use also as reagent the corresponding pyrroles, chlorosulfonyl isocyanate(CSI) and the DMF in excess. The main difference between the present process and the D1 process is the use in the present step (c) of a molar excess of an organic base instead of pouring the reaction mixture onto ice.

The technical problem of the present application may therefore be regarded as a provision of further process for the synthesis of pyrrole-2-carbonitriles.

D2 discloses a process for preparing pyrrole-2-carbonitriles through the reaction between a pyrrole and CSI in the presence of acetonitrile and DMF. After the synthesis reaction has been performed, the mixture was poured onto aqueous basic solution (NaOH) (see page 2675-right column).

D3 discloses the use of triethylamine and CSI for the syntheses of carbonitrile derivatives (see table from page 1633 of D3).

Since D1 discloses a process for the synthesis of pyrrole-2 carbonitriles which differs from the present one only through the use of an excess of an organic base and D2-D3 discloses the use of a base (an organic one in the case of D3) for the same type of syntheses, the skilled person would have expected that the same qualitative effect be maintained in such similar processes. Moreover, the yields for the synthesis of pyrrole-2-carbonitrile according to D1 is 58% (see page 411 left column)and according to D2 is 73%(in Do is used the same solvent as in the present case-acetonitrile), values which are comparable with the present ones. Consequently, no inventive step can be acknowledged for the subject-matter claimed by the present Claims 1-17 in the absence of comparative tests showing

an unexpected or improved characteristic of the present process over the closest prior art process.

Re Item VIII
Certain observations on the international application

It is clear from the present examples and in view of the prior art processes that the rapport between the pyrrole and chlorosulfonyl isocyanate is an essential feature for the syntheses of the pyrrole-2-carbonitrile derivatives according to the present invention.

Since independent claim 1 does not contain this feature (present in the depending Claim 13) it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essentials to the definition of the invention.

JJ/JAP JPW

PCT/US2005/010468

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

RECEIVED

JUN 01 2005

DOCKET DEPT WWKMN

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

Copy sent to client

Date 6/1/05

To:

RECEIVED

JUN 01 2005

Woodcock Washburn

LUCCI, Joseph
Woodcock Washburn LLP
46th Floor
One Liberty Place
Philadelphia, PA 19103
United States of America

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
23 May 2005 (23.05.2005)	
Applicant's or agent's file reference	**International application No.**
WYNC-1668 AM100968	PCT/US2005/010468

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

WYETH (for all designated States except US)
HELOM, Jean, Louise et al (for US)

International filing date	:	28 March 2005 (28.03.2005)
Priority date(s) claimed	:	30 March 2004 (30.03.2004) 22 March 2005 (22.03.2005)
Date of receipt of the record copy by the International Bureau	:	25 April 2005 (25.04.2005)
List of designated Offices	:	

AP :BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IS,IT,LT,LU,MC,NL,PL,PT,RO,SE,SI,SK,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NA,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,SM,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer:

Tewfik BENYAHIA

Telephone No. (41-22) 338 8458

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
23 May 2005 (23.05.2005)	
Applicant's or agent's file reference	**International application No.**
WYNC-1668	PCT/US2005/010468

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - see updated important information (as of April 2002)
- requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

ANNEX TO FORM PCT/IB/301

International application No.
PCT/US2005/010468

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the **"national phase"** must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at http://www.wipo.int/pct/en/index.html.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

folio 94 y 95
Tarjetas temáticas

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

00043

(21) N° de solicitud: 06 – 98496	(51) Int Cl: C07D 207/416; C07B 43/08
22) Fecha de solicitud: 29/09/06	(71)Solicitante(s) WYETH
(30) Prioridad (31) *No.* 32) *Fecha* (33) *País* 60/557,807 30/03/2004 US 11/086,061 22/03/2005 US	(72) Inventor(es) HELOM, Jean Louise Otros
	(74) Apoderado: ALVARO CORREA ORDOÑEZ
(85) Fecha límite inicio fase nacional: 30/10/2006 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 28/03/2005 No. de solicitud PCT/US2005/010488	(87) Publicación Internacional Fecha: 20/10/2005 N° publicación: WO 2005/097743

(54) Título: SÍNTESIS DE PIRROL-2-CARBONITRILOS

Reivindicación(es):

1. Un proceso para preparar un pirrol-2-carbonitrilo que comprende:

   (a) Hacer reaccionar un pirrol con isocianato de clorosulfonilo en la presencia de un disolvente;
   (b) Poner en contacto el producto de la etapa (a) con un exceso molar de una N,N-dialkilformamida;
   (c) Poner en contacto el producto de la etapa (b) con un exceso molar de una base orgánica resultando en la producción de un precipitado y una fase de solución;
   (d) Separar el precipitado de la fase de solución; y
   (e) Aislar un pirrol-2-carbonitrilo de la fase de solución de la etapa (d).

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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ( ) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Descripción de la invención.	( )	( )
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: _____

46

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO

REFERENCIA	Radicación No.	06 98496
	Solicitud internacional	PCT/US2005/010468
	Fecha inicio fase nacional	30/10/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13584

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 24 NOV. 2006
aalvarado