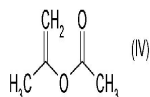
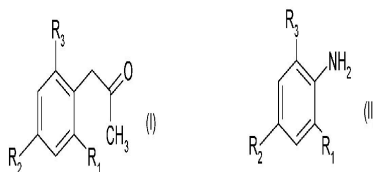


DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD FASE NACIONAL - PCT



1	Título de la Invención (200 caracteres o espacios máximos)		
PROCESO PARA LA PREPARACION DE FENILPROPANONAS SUSTITUIDAS			
2	Datos del Solicitante / Titular		
Nombre:	SYNGENTA PARTICIPATIONS AG	Dirección Electrónica:	sic@castellanosyco.co
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Identificación: ☐ CEDULA DE CIUDADANIA ☒ EMPRESA EXTRANJERA ☐ PASAPORTE ☐ CEDULA DE EXTRANJERIA ☐ NIT Número: 516861778840-			
3	Solicitantes		

Apellidos - Nombres o Razón Social		Tipo	Identificación
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4	Datos del Inventor		
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Identificación: ☐ CEDULA DE CIUDADANIA ☐ EMPRESA EXTRANJERA ☐ PASAPORTE ☐ CEDULA DE EXTRANJERIA ☐ NIT ☒ No Aplica Número: -			
5	Inventor(es)		
Apellidos - Nombres		Domicilio	
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2.	WALTER HARALD	SUIZA	
6	Datos Inventor(es)		
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Dirección			
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SYNGENTA CROP PROTECTION, MUNCHWILEN AG			
2.	SUIZA	SCHAFFHAUSEN	SCHAFFHAUSEN
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Identificación: ☒ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA ☐ EMPRESA EXTRANJERA ☐ NIT ☐ PASAPORTE Número: 39779654-			
Presentación de Poder			
Año de Radicación			
Número de Radicación			
8	Datos Solicitud: PCT / WO		
Número Solicitud:	PCT/EP2012/053371	Fecha Solicitud:	28/02/2012
Número Publicacion:	WO 2013/127441 A1	Fecha Publicacion:	06/09/2013
9	Declaraciones de prioridad	☐ SI ☒ NO	
1 2 3	(33) País de origen	Codigo del país	(31) No. Solicitud (32) Fecha _
10	Reivindicaciones		
Número reivindicaciones:		5	Pago Reivindicaciones: No
11	Reducción de tasas.		
<i>Declaro que carezco de medios económicos para presentar la solicitud de patente.</i> ☐ SI ☒ NO Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.			
☐ Micro, pequeñas y medianas empresas			

☐ Universidades públicas o privadas

☐ Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

12	Documentos Anexos
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☒ Reivindicaciones

☒ Descripción

☐ Dibujos y/o Figuras

☒ Resumen

☐ Certificado Depósito Material Biológico

☐ Uso de Conocimiento tradicional

☐ Listado de secuencias

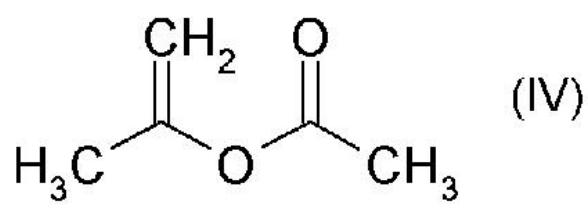
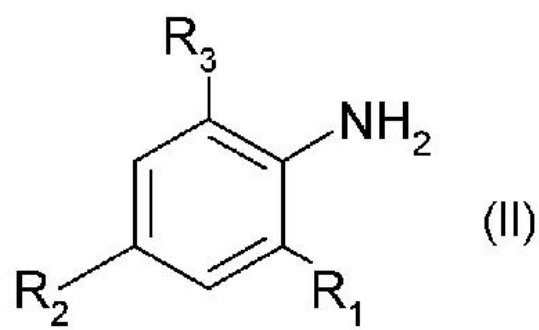
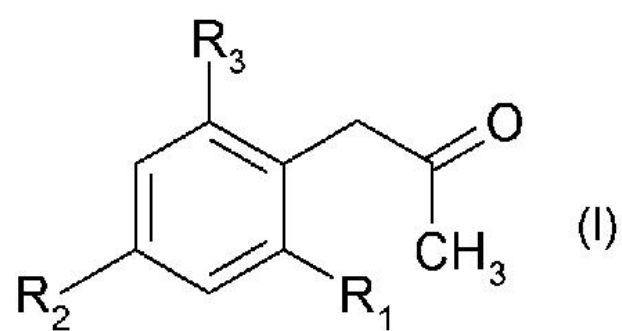
☒ Artes finales 12 x 12 cm

☒ Poderes, si fuere el caso

☐ Copia de la primera solicitud si se reivindica prioridad

☐ Traducción simple de la primera solicitud, si se reivindica prioridad

☒ Otros Anexos



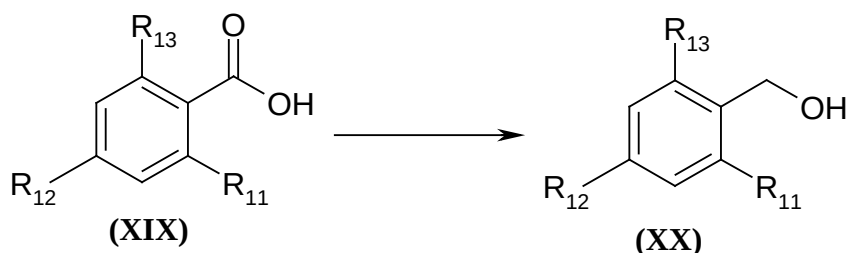
PROCESO PARA LA PREPARACIÓN DE FENILPROPANONAS SUSTITUIDAS

La presente invención se refiere a un proceso para la preparación de fenilos con sustituyentes de tipo propan-2-ona, en particular a la preparación de 1-(2,4,6-trihalofenil)propan-2-onas.

Los fenilos con sustituyentes de tipo propan-2-ona son intermedios valiosos para la preparación de pirazolcarboxamidas activas como fungicidas, tal como se ha descrito, por ejemplo, en WO 2010/063700.

Se sabe a partir del esquema 3 en la página 11 de WO 2010/063700 que se pueden preparar fenilos con sustituyentes de tipo propan-2-ona de la siguiente forma:

a) reduciendo un compuesto de fórmula XIX para obtener un compuesto de fórmula XX,



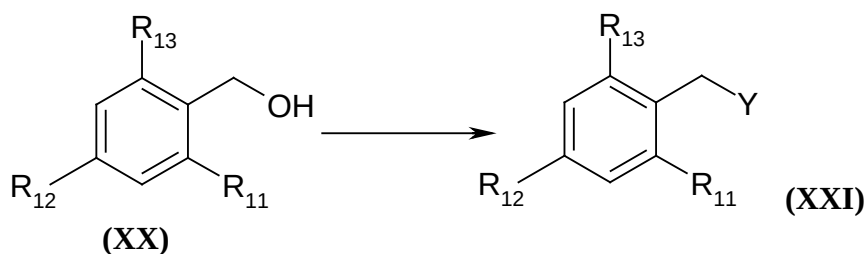
donde R₁₁ es hidrógeno, halógeno o alquilo C₁-C₆;

R₁₂ es hidrógeno, halógeno, alquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₃-C₆, (cicloalquil C₃-C₆)-(alquinilo C₃-C₆), halofenoxi, halofenil-(alquinilo C₃-C₆), C(alquil C₁-C₄)=NO-(alquilo C₁-C₄), haloalquilo C₁-C₆,

haloalcoxi C₁-C₆, haloalquenilo C₂-C₆ o haloalqueniloxi C₂-C₆; y

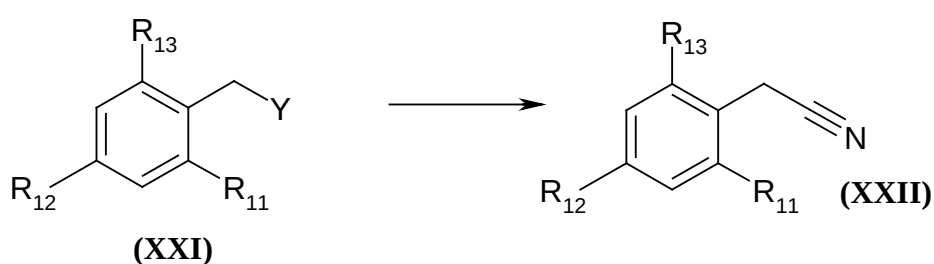
R₁₃ es hidrógeno, halógeno o alquilo C₁-C₆;

b) haciendo reaccionar el compuesto de fórmula XX para obtener un derivado bencílico activado de fórmula XXI,



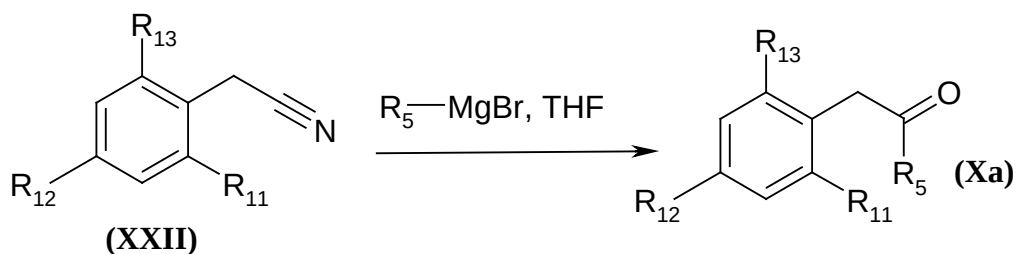
5 donde Y representa un grupo saliente tal como halógeno, mesilato o tosilato,

 c) haciendo reaccionar el compuesto de fórmula XXI para obtener un derivado nitrilado de fórmula XXII



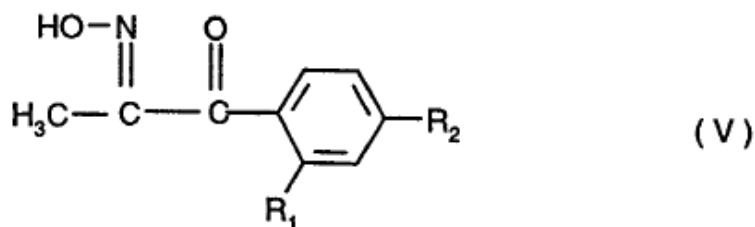
y

15 d) haciendo reaccionar el compuesto de fórmula XXII con un reactivo de Grignard de fórmula $R_5\text{-MgBr}$, donde R_5 es, por ejemplo, metilo, para obtener el fenilo con un sustituyente de tipo propan-2-ona de fórmula Xa (donde R_5 es metilo).

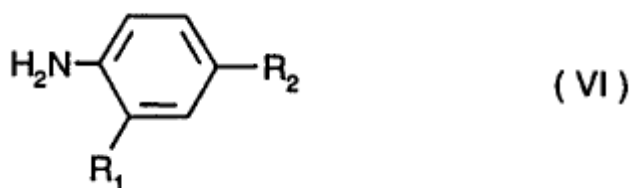


20 Una desventaja de este proceso de la técnica anterior son los elevados costos de producción debidos al número significativo de pasos de reacción, que hacen que este proceso sea poco rentable y especialmente inadecuado para una producción a gran escala.

25 El documento WO 00/34229 describe un proceso para la preparación de una cetona de fórmula V

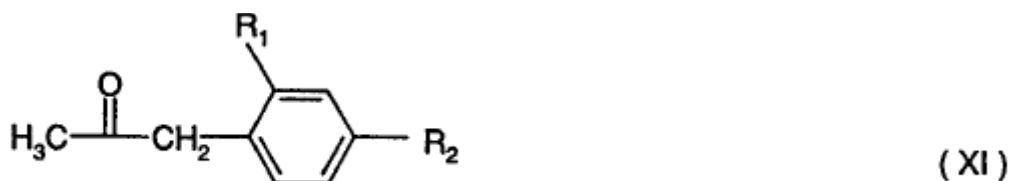


5 sometiendo a un proceso de diazotación una anilina de
fórmula VI



10 y haciendo reaccionar la sal de diazonio resultante con
un acetato de isopropenilo de fórmula X

 y haciendo reaccionar la cetona resultante de fórmula XI



15 con un nitrito orgánico en presencia de ácido
clorhídrico.

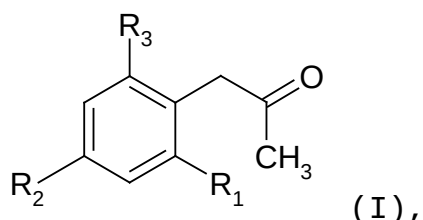
20 Una desventaja de este proceso es la acumulación de la
sal de diazonio, la cual es muy reactiva, en la mezcla de
reacción. En general, las sales de diazonio son sensibles a
agentes físicos tales como calor, luz, choque, electricidad
estática y deshidratación, que pueden provocar explosiones y
descomposiciones rápidas e incontrolables.

 Otra desventaja es que se necesitan dos equipos
diferentes para llevar a cabo las reacciones.

25 Por consiguiente, el objetivo de la presente invención
consiste en proporcionar un proceso novedoso para la
producción de

fenilos con sustituyentes de tipo propan-2-ona que no presente las desventajas del proceso conocido y que permita preparar fenilos con sustituyentes de tipo propan-2-ona con rendimientos elevados y calidad satisfactoria de forma rentable y con menos pasos de reacción.

Por lo tanto, de acuerdo con la presente invención, se proporciona un proceso para la preparación del compuesto de fórmula I



donde

R_1 es hidrógeno, halógeno o alquilo C_1-C_6 ;

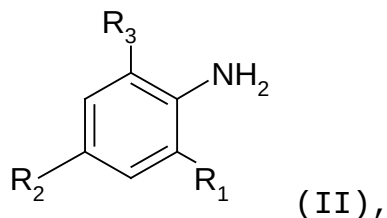
R_2 es hidrógeno, halógeno, alquilo C_1-C_6 , alquenilo C_2-C_6 , alquinilo C_3-C_6 , (cicloalquil C_3-C_6)-(alquinilo C_3-C_6), halofenoxi, halofenil-(alquinilo C_3-C_6), $C(\text{alquil } C_1-C_4)=NO-$ (alquilo C_1-C_4), haloalquilo C_1-C_6 ,

haloalcoxi C_1-C_6 , haloalquenilo C_2-C_6 o haloalqueniloxi C_2-C_6 ; y

R_3 es hidrógeno, halógeno o alquilo C_1-C_6 ;

comprendiendo el proceso

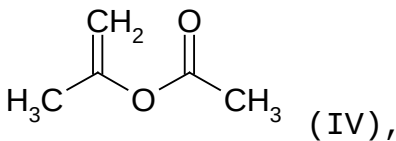
a) añadir un compuesto de fórmula II



donde R_1 , R_2 y R_3 tienen los significados que se han descrito para la fórmula I, en presencia de un disolvente orgánico inerte, a una mezcla que comprende un nitrito orgánico de fórmula III

$R_4-O-N=O$ (III),

donde R₄ es alquilo C₁-C₈, un compuesto de fórmula IV



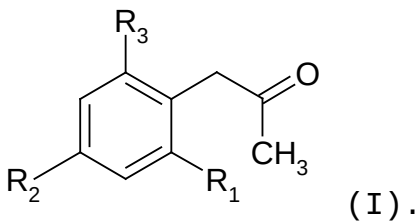
y un disolvente orgánico inerte.

El proceso de acuerdo con la invención utiliza materiales de partida fáciles de obtener y atóxicos, sin que sea necesario aislar o acumular sal de diazonio y, por consiguiente, es especialmente adecuado para la preparación a gran escala de un compuesto de fórmula I.

El proceso de acuerdo con la invención es especialmente adecuado para la producción de compuestos de fórmula I, donde al menos uno de los grupos R₁, R₂ y R₃ no es hidrógeno. El proceso de acuerdo con la invención es especialmente adecuado para la preparación de compuestos de fórmula I, donde al menos uno de los grupos R₁, R₂ y R₃ es halógeno.

Se pueden preparar otros compuestos de fórmula I de forma beneficiosa, donde todos los grupos R₁, R₂ y R₃ son halógeno, especialmente cloro. Los compuestos de fórmula I que se pueden preparar de forma beneficiosa de acuerdo con el proceso de esta invención se describen en la Tabla 1.

Tabla 1: Compuestos preferidos de fórmula I



N.º	R ₁	R ₂	R ₃
1.01	Cl	Cl	Cl
1.02	Cl	H	Cl
1.03	Cl	Cl	H
1.04	Cl	Br	Cl

1.05	Br	Br	Br
1.06	H	Cl	H
1.07	H	Br	H
1.08	H	CF ₃	H

El compuesto de fórmula V se puede preparar preferentemente mediante una reacción en un único paso añadiendo la anilina de fórmula II a una mezcla del acetato de isoprenilo de fórmula IV, un nitrito orgánico de fórmula III y un disolvente. En los compuestos preferidos de fórmula III, R₄ es alquilo C₄-C₇. Un nitrito preferido es nitrito de *tert*-butilo.

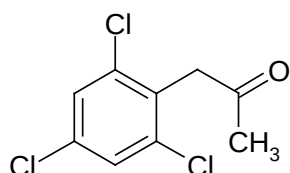
La mezcla del acetato de isoprenilo de fórmula IV, un nitrito orgánico de fórmula III y un disolvente puede contener adicionalmente un compuesto de cobre, el cual puede resultar beneficioso para aumentar el rendimiento y/o la calidad del producto. Los compuestos de cobre preferidos son CuO, CuCl₂ o CuSO₄. La cantidad de los compuestos de cobre es preferentemente de un 1-20% mol respecto a la anilina de fórmula II. Una temperatura de -10 °C a 50 °C es beneficiosa para la reacción. No se requiere el aislamiento ni la acumulación de la sal de diazonio para este paso de reacción. Preferentemente, se utiliza el mismo disolvente para la anilina de fórmula II y la mezcla del acetato de isoprenilo de fórmula IV y el nitrito orgánico de fórmula III. Los disolventes orgánicos inertes adecuados son, por ejemplo, cetonas, por ejemplo, acetona, cetona etil metílica (MEK) o nitrilos, por ejemplo, acetonitrilo. Los disolventes preferidos son acetona y acetonitrilo.

Los compuestos de fórmula II y III son conocidos o se pueden preparar de acuerdo con métodos de uso común en la técnica. Algunos compuestos de fórmula II se pueden adquirir de proveedores comerciales, p. ej., el compuesto de fórmula

II en el que R₁, R₂ y R₃ son cloro. El acetato de isoprenilo de fórmula IV se puede adquirir de proveedores comerciales.

Ejemplos de preparaciones:

Ejemplo P1: Preparación de 1-(2,4,6-triclorofenil)propan-2-ona (CAS del compuesto 1228284-86-3):

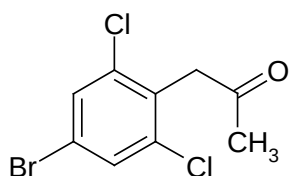


En un recipiente para sulfonación de 1.5 L dotado de agitación mecánica, embudo de refrigeración, embudo de adición y termómetro en atmósfera de nitrógeno a temperatura ambiente que contenía acetona (240 mL), se añadieron acetato de isopropenilo (66 mL, 0.60 mol), nitrito de *tert*-butilo (40 mL, 0.30 mol) y sulfato cúprico pentahidratado (2.5 g, 0.001 mol). La suspensión resultante de color azul verdoso claro se agitó durante 15 min a temperatura ambiente. Se añadió una solución de 2,4,6-tricloroanilina (40 g, 0.20 mol) disuelta en acetona (320 mL) gota a gota durante un periodo de 2 horas. Durante la adición, se observó un burbujeo, la temperatura subió hasta 30 °C y la mezcla se volvió verde. Una hora después de la adición, se obtuvo una solución de color ámbar. La mezcla se agitó durante 6 horas. La finalización de la reacción se confirmó por GC-MS. La mezcla cruda se concentró a presión reducida para eliminar la mayor parte de la acetona y el residuo se disolvió en acetato de etilo (300 mL), y se lavó con ácido clorhídrico 1 M (2 x 300 mL), agua (2 x 300 mL), una solución de carbonato de potasio (300 mL) y a continuación agua (300 mL). Los componentes acuosos básicos combinados se volvieron a extraer con acetato de etilo (150 mL). Los componentes orgánicos combinados se secaron con sulfato de sodio, y los componentes orgánicos se concentraron a presión reducida para obtener 1-(2,4,6-

triclorofenil)propan-2-ona cruda (53 g) como un aceite marrón oscuro. El crudo se disolvió nuevamente en acetato de etilo (200 mL) y se lavó con hidróxido de sodio 1 M (300 mL), ácido clorhídrico 1 M (100 mL) y agua (200 mL). Las fases orgánicas se secaron y evaporaron para obtener 49 g de 1-(2,4,6-triclorofenil)propan-2-ona cruda como un aceite marrón oscuro, que cristalizó.

^1H RMN (400 MHz, CDCl_3): δ 2.26 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.34 (s, 2H, Ar-H)

Ejemplo P2: Preparación de 1-(4-bromo-2,6-diclorofenil)propan-2-ona:

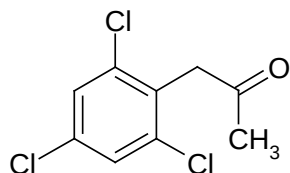


En un recipiente de tres bocas de 50 mL dotado de agitación mecánica, embudo de refrigeración, embudo de adición y termómetro en atmósfera de nitrógeno a temperatura ambiente que contenía acetonitrilo (10 mL), se añadieron óxido cuproso (1.5 g, 0.018 mol), acetato de isopropenilo (13.6 mL, 0.125 mol) y nitrito de *tert*-butilo (1.7 mL, 0.0125 mol). La suspensión roja resultante se agitó durante 15 min a temperatura ambiente. Se añadió una solución de 4-bromo-2,6-dicloroanilina (2.0 g, 0.0083 mol) disuelta en acetonitrilo (15 mL) gota a gota durante un periodo de 20 minutos. Durante la adición, se observó un burbujeo. La mezcla se agitó a 40°C durante 20 horas. La mezcla cruda roja se hizo pasar a través de celite para eliminar las partículas sólidas y se concentró a presión reducida para obtener un sólido marrón. El residuo se disolvió en diclorometano (120 mL) y se lavó con agua (2 x 50 mL) y salmuera (40 mL). Los componentes orgánicos se secaron con sulfato de sodio y se concentraron a presión

reducida para obtener 1-(4-bromo-2,6-diclorofenil)propan-2-ona cruda (2.3 g) como un aceite marrón oscuro.

^1H RMN (400 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 7.50 (s, 2H, Ar-H)

Ejemplo P3: Preparación de 1-(2,4,6-triclorofenil)propan-2-ona:



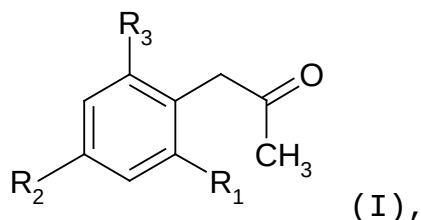
Se enfrió hasta 10 °C una mezcla de acetato de isopropenilo (12.2 g, 122 mmol), 2,4,6-tricloroanilina (16.0 g, 81.4 mmol), carbonato de potasio (100 mg, 0.7 mmol) y acetona (100 g). Se añadió nitrito de *tert*-butilo (90%, 10 g, 87.3 mmol) a lo largo de 30 minutos. La reacción se agitó durante 90 minutos más y se concentró para obtener un aceite negro. El residuo se lavó con agua y el pH se ajustó a 10.5 con una solución de hidróxido de sodio. El precipitado se filtró y se recristalizó en metanol-agua 1:1. El sólido se filtró, se lavó con metanol-agua 1:1 y se secó. Se obtuvo el producto como un material cristalino marrón oscuro (15.9 g, 70.7% de pureza, 47.3 mmol, 58% de rendimiento). Se logró una mayor purificación por recristalización en hexanos. ^1H RMN (400 MHz, CDCl_3): δ 2.23 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 7.31 (s, 2H, CH).

Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

REIVINDICACIONES

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

1. Un proceso para la preparación del compuesto de fórmula I



donde

R₁ es hidrógeno, halógeno o alquilo C₁-C₆;

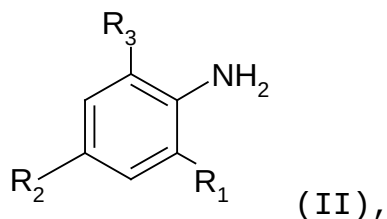
R₂ es hidrógeno, halógeno, alquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₃-C₆, (cicloalquil C₃-C₆)-(alquinilo C₃-C₆), halofenoxi, halofenil-(alquinilo C₃-C₆), C(alquil C₁-C₄)=NO-(alquilo C₁-C₄), haloalquilo C₁-C₆,

haloalcoxi C₁-C₆, haloalquenilo C₂-C₆ o haloalqueniloxi C₂-C₆;

R₃ es hidrógeno, halógeno o alquilo C₁-C₆;

comprendiendo el proceso

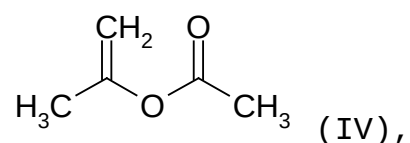
a) añadir un compuesto de fórmula II



donde R₁, R₂ y R₃ tienen los significados que se han descrito para la fórmula I, en presencia de un disolvente orgánico inerte, a una mezcla que comprende un nitrito orgánico de fórmula III

R₄-O-N=O (III),

donde R₄ es alquilo C₁-C₈, un compuesto de fórmula IV



y un disolvente orgánico inerte.

2. Un proceso de acuerdo con la reivindicación 1 para la
preparación de un compuesto de fórmula I, donde al menos uno
de los grupos R_1 , R_2 y R_3 es distinto de hidrógeno.

3. Un proceso de acuerdo con la reivindicación 1 para la
preparación de un compuesto de fórmula I, donde al menos uno
de los grupos R_1 , R_2 y R_3 es halógeno.

4. Un proceso de acuerdo con la reivindicación 1 para la
preparación de un compuesto de fórmula I, donde R_1 , R_2 y R_3
son cloro.

5. Un proceso de acuerdo con la reivindicación 1 para la
preparación de un compuesto de fórmula I, donde R es alquilo
 C_4-C_7 .

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 73529_WO_PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2012/053371	International filing date (day/month/year) 28/02/2012	(Earliest) Priority Date (day/month/year)
Applicant SYNGENTA PARTICIPATIONS AG		

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 4 sheets.

☒ 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
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ 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 No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

PROCESS FOR THE PREPARATION OF SUBSTITUTED PHENYLPROPANONES

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, 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/EP2012/053371

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07C45/51 C07C49/457
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, 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.
Y	WO 00/34229 A1 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; WADITSCHATKA RUDO) 15 June 2000 (2000-06-15) cited in the application claim 1; example 6	1-5
Y	US 2008/221198 A1 (ZHAO DALIAN [US] ET AL) 11 September 2008 (2008-09-11) paragraphs [0047] - [0048] ----- -/-	1-5



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

27 September 2012

Date of mailing of the international search report

05/10/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
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Authorized officer

Steinreiber, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/053371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI LIA ET AL: "Facile Synthesis of 1-Aryl-2-propanones from Aromatic Amine", SYNTHETIC COMMUNICATIONS,, vol. 37, no. 6, 31 December 2007 (2007-12-31), pages 985-991, XP002666726, ISSN: 0039-7911, DOI: 10.1080/00397910601163950 [retrieved on 2007-02-24] table 4 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/053371

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0034229	A1	15-06-2000	AU	1974800 A	26-06-2000
			EP	1137627 A1	04-10-2001
			JP	2002531540 A	24-09-2002
			WO	0034229 A1	15-06-2000

US 2008221198	A1	11-09-2008	AU	2006223411 A1	21-09-2006
			CA	2599710 A1	21-09-2006
			EP	1858844 A1	28-11-2007
			JP	2008533033 A	21-08-2008
			US	2008221198 A1	11-09-2008
			WO	2006099077 A1	21-09-2006

(51) International Patent Classification:

C07C 45/51 (2006.01) C07C 49/457 (2006.01)

(21) International Application Number:

PCT/EP2012/053371

(22) International Filing Date:

28 February 2012 (28.02.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(71) Applicant (for all designated States except US): SYNGENTA PARTICIPATIONS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

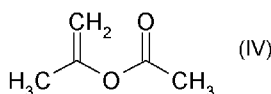
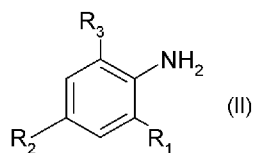
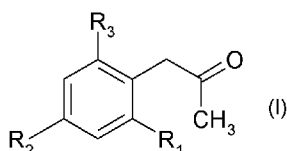
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED PHENYLPROPANONES



(57) Abstract: The invention relates to a process for the preparation of a compound of formula (I) wherein the substituents are defined as in claim 1, which process comprises adding a compound of formula (II), wherein R₁, R₂ and R₃ have the meanings as described under formula (I), in the presence of an inert organic solvent, to a mixture comprising an organic nitrite of formula (III) R₄-O-N=O, wherein R₄ is C₁-C₈alkyl, a compound of formula (IV), and an inert organic solvent.

- 1 -

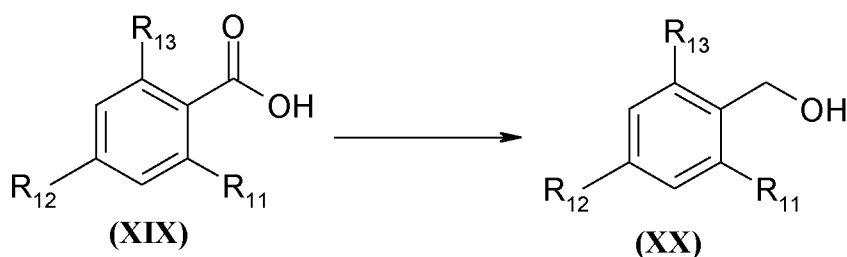
PROCESS FOR THE PREPARATION OF SUBSTITUTED PHENYLPROPANONES

The present invention relates to a process for the preparation of propane-2-one-substituted phenyls, in particular to the preparation of 1-(2,4,6-trihalo-phenyl)-propan-2-ones.

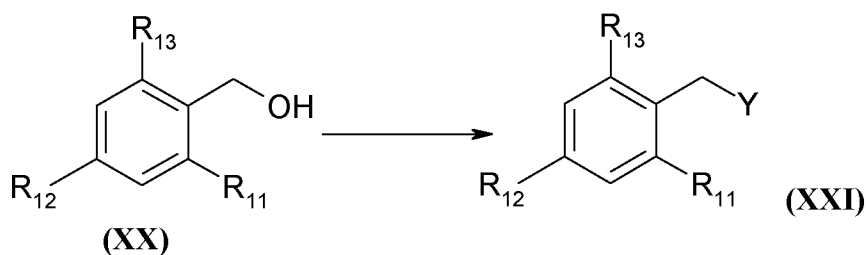
- 5 Propane-2-one-substituted phenyls are valuable intermediates for the preparation of fungicidally active pyrazole carboxamides, as described for example in WO 2010/063700.

It is known from scheme 3 on page 11 of WO 2010/063700 to prepare propane-2-one-substituted phenyls by

a) reducing a compound of formula XIX to a compound of formula XX,



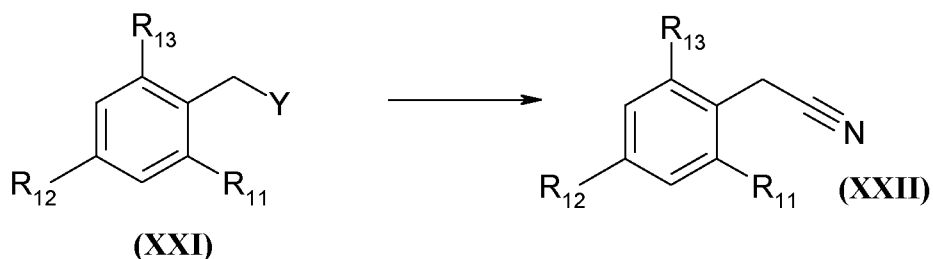
- 15 wherein R₁₁ is hydrogen, halogen or C₁-C₆alkyl;
 R₁₂ is hydrogen, halogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆alkinyl, C₃-C₆cycloalkyl-C₃-C₆alkinyl, halophenoxy, halophenyl-C₃-C₆alkinyl, C(C₁-C₄alkyl)=NO-C₁-C₄alkyl, C₁-C₆haloalkyl,
 C₁-C₆haloalkoxy, C₂-C₆haloalkenyl, or C₂-C₆haloalkenyloxy; and
 20 R₁₃ is hydrogen, halogen or C₁-C₆alkyl;
 b) reacting the compound of formula XX to an activated benzylic derivative of formula XXI,



- 25 wherein Y represents a leaving group, such as halogen, mesylate or tosylate,

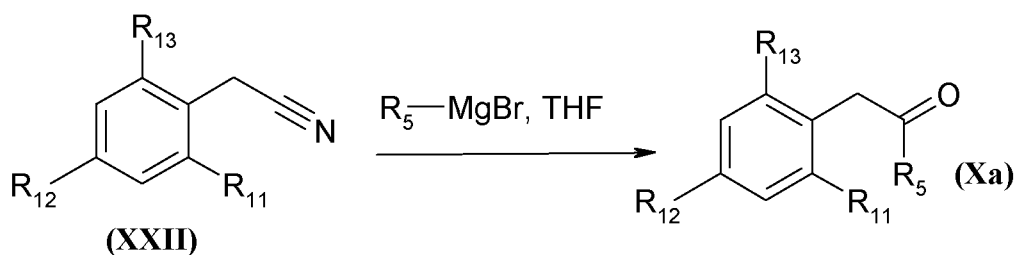
- 2 -

c) reacting the compound of formula XXI to the nitril derivative of formula XXII



and

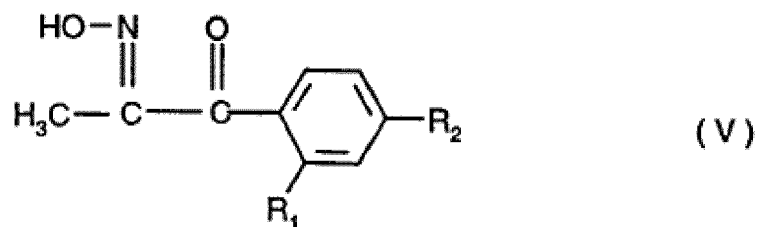
- 5 d) reacting the compound of formula XXII with a Grignard reagent of the formula $\text{R}_5\text{-MgBr}$, wherein R_5 is for example methyl, to the propane-2-one-substituted phenyl of formula Xa (wherein R_5 is methyl).



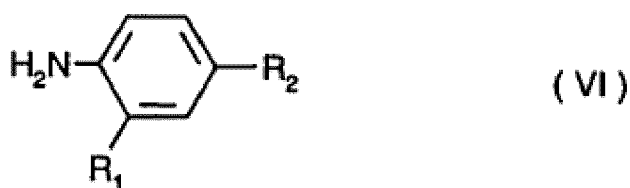
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A disadvantage of this prior art process is the high production costs caused by the significant number of reaction steps which makes this process uneconomical and especially unsuitable for a large-scale production.

- 15 WO 00/34229 describes a process for the preparation of a ketone of formula V



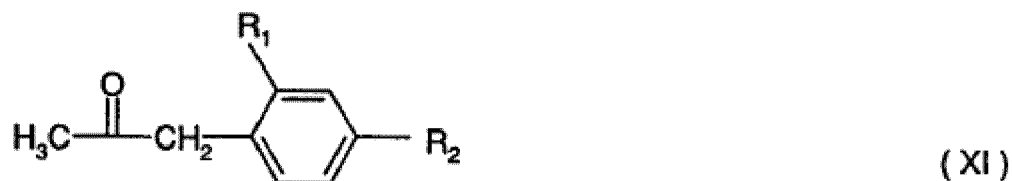
by diazotizing an aniline of formula VI



- 3 -

and reacting the resulting diazonium salt with isopropenylacetate of formula X

and reacting the resulting ketone of formula XI



5

with an organic nitrite in the presence of hydrogen chloride.

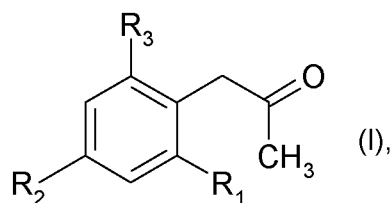
A disadvantage of this process is the accumulation of the very reactive diazonium salt in the reaction mixture. Diazonium salts in general are sensitive to physical agents such as
10 heat, light, shock, static electricity and dehydration that can lead to rapid, uncontrollable decompositions and explosions.

A further disadvantage is that 2 different equipments are needed to perform the reactions.

15 The aim of the present invention is therefore to provide a novel process for the production of
propane-2-one-substituted phenyls that avoids the disadvantages of the known process and makes it possible to prepare propane-2-one-substituted phenyls in high yields and good quality in an economically advantageous way with less reaction steps.

20

Thus, according to the present invention, there is provided a process for the preparation of the compound of formula I



wherein

25 R₁ is hydrogen, halogen or C₁-C₆alkyl;

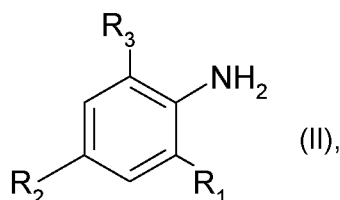
R₂ is hydrogen, halogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆alkinyl, C₃-C₆cycloalkyl-C₃-C₆alkinyl, halophenoxy, halophenyl-C₃-C₆alkinyl, C(C₁-C₄alkyl)=NO-C₁-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₂-C₆haloalkenyl or C₂-C₆haloalkenyloxy; and

- 4 -

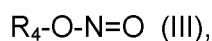
R₃ is hydrogen, halogen or C₁-C₆alkyl;

which process comprises

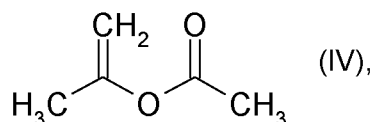
adding a compound of formula II



- 5 wherein R₁, R₂ and R₃ have the meanings as described under formula I, in the presence of an inert organic solvent, to a mixture comprising an organic nitrite of formula III



- 10 wherein R₄ is C₁-C₈alkyl, a compound of formula IV



and an inert organic solvent.

- The process according to the invention uses easily accessible and nontoxic starting
 15 material, without the need of isolation or accumulation of diazonium salt and is therefore especially suitable for the large-scale preparation of a compound of formula I.

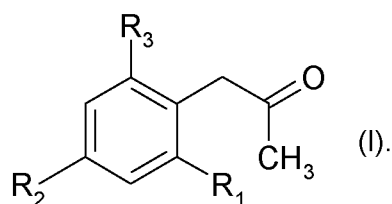
The process according to the invention is especially suitable for the production of compounds of formula I, wherein at least one of R₁, R₂ and R₃ is different from hydrogen.

- 20 The process according to the invention is especially suitable for the preparation of compounds of formula I, wherein at least one of R₁, R₂ and R₃ is halogen.

- Further compounds of formula I can be advantageously prepared, wherein R₁, R₂ and R₃ are all halogen, especially chloro. Compounds of formula I which can be advantageously
 25 prepared according to the process of this invention are described in Table 1.

Table 1: Preferred compounds of formula I

- 5 -



No.	R ₁	R ₂	R ₃
1.01	Cl	Cl	Cl
1.02	Cl	H	Cl
1.03	Cl	Cl	H
1.04	Cl	Br	Cl
1.05	Br	Br	Br
1.06	H	Cl	H
1.07	H	Br	H
1.08	H	CF ₃	H

- 5 The compound of formula V can be prepared preferably by a one pot reaction adding the aniline of formula II to a mixture of isoprenylacetate of formula IV, an organic nitrite of formula III and a solvent. In preferred compounds of formula III, R₄ is C₄-C₇alkyl. A preferred nitrite is tert-butyl nitrite.
- 10 The mixture of isoprenylacetate of formula IV, an organic nitrite of formula III and a solvent can additionally contain a copper compound which can be advantageous to increase yield and/or quality of the product. Preferred copper compounds are CuO, CuCl₂ or CuSO₄. The amount of the copper compounds is preferably is 1-20 mol% in the relation to the aniline of formula II. Advantageous for the reaction is a temperature of -10°C to 50°C. No isolation or
- 15 accumulation of the diazonium salt is required for this process step. Preferably, the same solvent is used for the aniline of formula II and the mixture of isoprenylacetate of formula IV, and the organic nitrite of formula III. Suitable inert organic solvents are for example ketones, for example acetone, methylethylketone (MEK) or nitriles, for example acetonitrile. Preferred solvents are acetone and acetonitrile.

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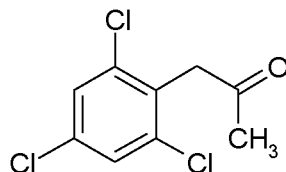
The compounds of formula II and III are either known or can be prepared according to methods well known in the art. Some compounds of formula II are commercially available,

- 6 -

e.g. the compound of formula II, wherein R₁, R₂ and R₃ is chloro. Isoprenylacetate of formula IV is commercially available.

Preparatory examples:

- 5 **Example P1:** Preparation of 1-(2,4,6-trichloro-phenyl)-propan-2-one (compound CAS1228284-86-3):

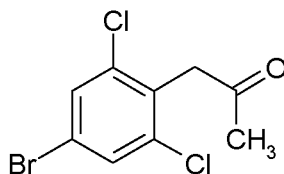


In a 1.5l sulfonation flask equipped with mechanical stirring, cooling funnel, dropping funnel and thermometer under nitrogen at ambient temperature filled with acetone (240 ml), were
10 added isopropenyl acetate (66 ml, 0.60 mol), tert-butyl nitrite (40 ml, 0.30 mol) and cupric sulfate pentahydrate (2.5 g, 0.001 mol) . The resulting light green-blue suspension is stirred for 15min at ambient temperature. A solution of 2,4,6-trichloroaniline (40 g, 0.20 mol), dissolved in acetone (320 ml) was added dropwise over a period of 2 hours. During the addition, bubbling observed, temperature rose to 30°C and the mixture turned green. 1
15 Hour after the addition, an amber solution was obtained. The mixture was stirred for 6 hours. Completion of the reaction was confirmed by GC-MS. The crude mixture was concentrated under reduce pressure to remove most of the acetone and the residue was dissolved in ethyl acetate (300 ml) and wash with 1M hydrochloric acid (2x300 ml), water (2x300 ml) potassium carbonate solution (300 ml) followed by water (300 ml). Combined
20 basic aqueous were re-extracted with of ethyl acetate (150 ml). Combined organics were dried over sodium sulfate, and the organics were concentrated under reduced pressure to give crude 1-(2,4,6-trichloro-phenyl)-propan-2-one (53g) as a dark brown oil. The crude was dissolved again in ethyl acetate (200 ml) and washed with 1M sodium hydroxide (300 ml) 1M hydrochloric acid (100 ml) and water (200 ml). The organic layers were dried and
25 evaporated to give crude 1-(2,4,6-trichloro-phenyl)-propan-2-one 49 g dark brown oil which crystallized.

¹H NMR (400MHz, CDCl₃): δ 2.26 (s,3H,CH₃), 4.05(s,2H,CH₂), 7.34 (s,2H, Ar-H)

Example P2: Preparation of 1-(4-bromo-2,6-dichloro-phenyl)-propan-2-one:

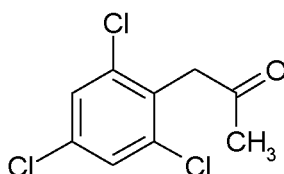
- 7 -



In a 50ml three-neck flask equipped with mechanical stirring, cooling funnel, dropping funnel and thermometer under nitrogen at ambient temperature filled with acetonitrile (10 ml), were added cuprous oxide (1.5 g, 0.018 mol), isopropenyl acetate (13.6 ml, 0.125 mol) and tert-butyl nitrite (1.7 ml, 0.0125 mol). The resulting red suspension is stirred for 15min at ambient temperature. A solution of 4-bromo-2,6-dichloroaniline (2.0 g, 0.0083 mol), dissolved in acetonitrile (15 ml) was added dropwise over a period of 20 minutes. During the addition, bubbling was observed. The mixture was stirred at 40°C for 20 hours. The red crude mixture was passed through celite to remove solid particles and concentrated under reduce pressure to give a brown solid. The residue was dissolved in dichloromethane (120 ml) and washed with water (2 x 50 ml) and brine (40 ml). Organics were dried over sodium sulfate and concentrated under reduced pressure to give crude 1-(4-bromo-2,6-dichlorophenyl)-propan-2-one (2.3g) as a dark brown oil.

¹H NMR (400MHz, CDCl₃): δ 2.25 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 7.50 (s, 2H, Ar-H)

Example P3: Preparation of 1-(2,4,6-trichloro-phenyl)-propan-2-one:

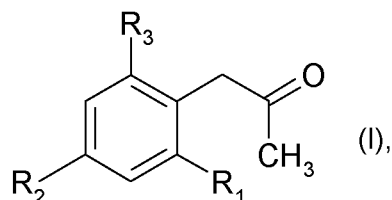


A mixture of isopropenyl acetate (12.2 g, 122 mmol), 2,4,6-trichloroaniline (16.0 g, 81.4 mmol), potassium carbonate (100 mg, 0.7 mmol), and acetone (100 g) was cooled to 10 °C. tert-Butyl nitrite (90%, 10 g, 87.3 mmol) was dosed over 30 minutes. The reaction was stirred for further 90 minutes, and it was concentrated to a black oil. The residue was triturated with water, and the pH was adjusted to 10.5 with sodium hydroxide solution. The precipitate was filtered and recrystallized from methanol–water 1:1. The solid was filtered, washed with methanol–water 1:1, and dried. The product was obtained as dark-brown crystalline material (15.9 g, 70.7% purity, 47.3 mmol, 58% yield). Further purification was achieved by recrystallization from hexanes. ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃), 4.02 (s, 2H, CH₂), 7.31 (s, 2H, CH).

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What is claimed is:

1. A process for the preparation of the compound of formula I



5 wherein

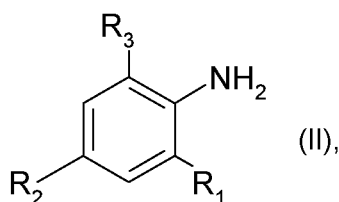
R₁ is hydrogen, halogen or C₁-C₆alkyl;

R₂ is hydrogen, halogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆alkinyl, C₃-C₆cycloalkyl-C₃-C₆alkinyl, halophenoxy, halophenyl-C₃-C₆alkinyl, C(C₁-C₄alkyl)=NO-C₁-C₄alkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₂-C₆haloalkenyl, or C₂-C₆haloalkenyloxy;

10 R₃ is hydrogen, halogen, C₁-C₆alkyl;

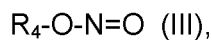
which process comprises

adding a compound of formula II

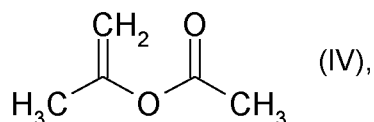


wherein R₁, R₂ and R₃ have the meanings as described under formula I, in the presence of

15 an inert organic solvent to a mixture comprising an organic nitrite of formula III



wherein R₄ is C₁-C₈alkyl, a compound of formula IV



20

and an inert organic solvent.

2. A process according to claim 1 for the preparation of a compound of formula I, wherein at least one of R₁, R₂ and R₃ is different from hydrogen.

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3. A process according to claim 1 for the preparation of a compound of formula I, wherein at least one of R₁, R₂ and R₃ is halogen.
4. A process according to claim 1 for the preparation of a compound of formula I, wherein
- 5 R₁, R₂ and R₃ are chloro.
5. A process according to claim 1 for the preparation of a compound of formula I, wherein R is C₄-C₇alkyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053371

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C45/51 C07C49/457
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

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C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, 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.
Y	WO 00/34229 A1 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; WADITSCHATKA RUDO) 15 June 2000 (2000-06-15) cited in the application claim 1; example 6	1-5
Y	US 2008/221198 A1 (ZHAO DALIAN [US] ET AL) 11 September 2008 (2008-09-11) paragraphs [0047] - [0048] ----- -/--	1-5



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

27 September 2012

Date of mailing of the international search report

05/10/2012

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

Steinreiber, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI LIA ET AL: "Facile Synthesis of 1-Aryl-2-propanones from Aromatic Amine", SYNTHETIC COMMUNICATIONS,, vol. 37, no. 6, 31 December 2007 (2007-12-31), pages 985-991, XP002666726, ISSN: 0039-7911, DOI: 10.1080/00397910601163950 [retrieved on 2007-02-24] table 4 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/053371

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0034229	A1	15-06-2000	AU	1974800 A		26-06-2000
			EP	1137627 A1		04-10-2001
			JP	2002531540 A		24-09-2002
			WO	0034229 A1		15-06-2000

US 2008221198	A1	11-09-2008	AU	2006223411 A1		21-09-2006
			CA	2599710 A1		21-09-2006
			EP	1858844 A1		28-11-2007
			JP	2008533033 A		21-08-2008
			US	2008221198 A1		11-09-2008
			WO	2006099077 A1		21-09-2006

PODER

POWER OF ATTORNEY

El (los) Gregory W. Warren
SYNGENTA PARTICIPATIONS AG

I (we) the undersigned Gregory W. Warren
Syngenta Participations AG

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Carrera 9 No. 93-09, Bogotá-Colombia para

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS A.** attorneys residing at Carrera 9 No. 93-09, Bogota- Colombia, to prosecute

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso -administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

and to obtain the protection of my (our Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos; b) Para la obtención de registros sanitarios; c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan, pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

a) Obtention of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights; b) For the obtention of Sanitary registrations; c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us; and that in all the above matters they may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Dado y firmado hoy 24 de Marzo de 2004

Given and signed this 24th March 2004

en Research Triangle Park, Carolina
del Norte 27709
por Gregory W. Warren

in Research Triangle Park, North Carolina 27709

by Gregory W. Warren *Gregory W. Warren*

(El notario debe suscribir el documento en la pagina siguiente)

(Notary shall execute on the other side)

(Se requiere legalización consular)

(Consular legalization required)

ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail acastell@impsat.net.co

COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 24 de Marzo del año 2004

compareció (eron) personalmente Gregory W. Warren a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañía denominada Certifico: Syngenta Participations AG

- a) Que es una sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de
- b) Que el domicilio de dicha Sociedad/Compañía es Basel, Suiza
- c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad /Compañía.
- d) Que el Sr. Gregory W. Warren esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

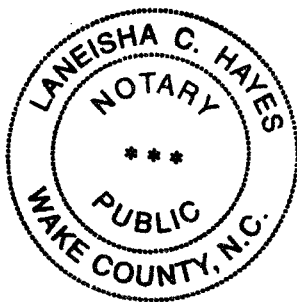
(Ciudad) REsearch Triangle Park

(Estado) Carolina del Norte 27709

Hoy del 24 de Marzo de 2004

(Notario Público) LANEISHA C. HAYES

*Los documentos debe identificarse con fecha y origen.



NOTARIAL (Corporation)

On this 24th day of March of 2004 personally appeared Gregory W. Warren whom I know to be the person(s) who signed this document as representative(s) of the Corporation /Company named Syngenta Participations AG

I certify:

- a) That Syngenta Participations AG is a corporation (Company legally constituted and in existence in accordance with the laws of Basel, Switzerland
- b) That the domicile of said Corporation/Company is Basel, Switzerland
- c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation/Company.
- d) That Mr. Gregory W. Warren is (are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*: on the 24th day of March, 2004 in Research Triangle Park, North Carolina 27709.

(City) Research Triangle Park

(State) North Carolina, 27709

this 24th day of March of the year 2004

(Notary Public)

Laneisha C. Hayes
*Documents must be identified with date and origin
3/24/04 - Research Triangle
Park, North Carolina
27709 -
Syngenta Biotech, Inc.

ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / 60 / 80 - Fax (571) 610 07 06 - e-mail acastell@impsat.net.co

XC/cm



Wake County Register of Deeds
Post Office Box 1897
Raleigh, North Carolina 27602-1897

Laura M. Riddick
Register Of Deeds

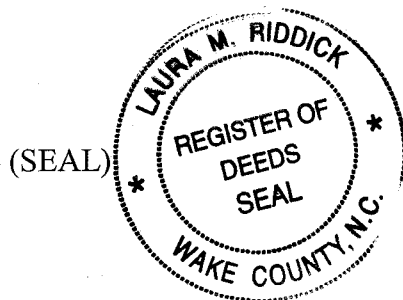
STATE OF NORTH CAROLINA

WAKE COUNTY

**CERTIFICATE OF REGISTER OF DEEDS THAT
NOTARY PUBLIC WAS ACTING NOTARY
AT TIME OF SIGNATURE**

I, LAURA M. RIDDICK, REGISTER OF DEEDS OF THE AFORESAID COUNTY AND STATE, DO HEREBY CERTIFY THAT Laneisha C. Hayes WAS, AT THE TIME OF SIGNING THE FOREGOING (OR ANNEXED) CERTIFICATE, A DULY COMMISSIONED AND QUALIFIED NOTARY PUBLIC IN AND FOR THE COUNTY OF WAKE, STATE OF NORTH CAROLINA, AND AS SUCH FULL FAITH AND CREDIT IS DUE TO HIS OFFICIAL ACTS; AND, FURTHER, THAT HIS SIGNATURE THERETO IS IN HIS OWN PROPER HANDWRITING.

IN TESTIMONY WHEREOF, I HAVE HEREUNTO SET MY HAND AND SEAL OF OFFICE THIS, THE 30TH DAY OF MARCH, 2004.



REGISTER OF DEEDS

DEPUTY / ASSISTANT

APOSTILLE
(Convention de La Haye 5 octobre 1961)

1. COUNTRY: **UNITED STATES OF AMERICA**

2. This Public Document
has been signed by CARLA N. BROWN

3. acting in the capacity of DEPUTY REGISTER OF DEEDS
~~LAURA M. RIDDICK, REGISTER OF DEEDS~~

4. bears the seal/stamp of COUNTY OF WAKE, NORTH CAROLINA

CERTIFIED

5. at Raleigh, North Carolina

6. the 1ST DAY OF APRIL, 2004

7. by Deputy Secretary of State, State of North Carolina

8. No. 8117

9. Seal/Stamp:

10. Signature



Robyn S. Moschler

-----TRADUCCION OFICIAL No. -040417-----

de un documento escrito en INGLES, el cual para su identificación
lleva el sello de la Traductora e Intérprete oficial, Res. 2755/68 y
01144/97 de Minjusticia, al igual que la presente.-----

------(Anexos a un poder otorgado por Syngenta

Participations AG)

(fdo) ilegible

3/24/04 Research Triangle Park, NC 27709

ESTADO DE CAROLINA DEL NORTE

CONDADO DE WAKE

Yo, Laura M. Riddick, Registrador de Escrituras del condado y estado
antes mencionados, certifico por medio del presente que Laneisha C.
Hayes, al momento de firmar este documento era un Notario Público
debidamente comisionado y habilitado en y para el Condado de Wake,
Estado de Carolina del Norte, y como tal debe dars plena fe y crédito a
sus actos oficiales, y además, que su firma en el mismo es de su propia
letra.

En testimonio de lo cual, he impuesto aquí mi firma y sello de oficio,
hoy día 30 de Marzo de 2004.

Laura M. Riddick, Registrador de Escrituras

Por (fdo) ilegible

DORA SUQUE DE BERNAL
TRADUCTORA E INTÉRPRETE OFICIAL
RES. 2755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

Delegado

APOSTILLA

(Convención de La Haya de octubre 5, 1961)

1. País: Estados Unidos de América
 2. Este documento público ha sido firmado por CARLA N. BROWN
 3. actuando en su carácter de Delegado del Registrador de Escrituras
 4. lleva el sello de Laura M. Riddick, Registrador de Escrituras
- Condado de Wake, Carolina del Norte

CERTIFICADO

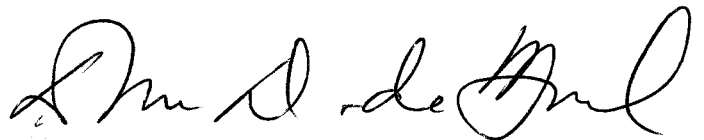
5. En Raleigh. Carolina del Norte
6. el día 1 de Abril de 2004
7. por el Secretario de Estado Delegado, Estado de Carolina del Norte
8. No. 8117
9. Sello: (sello en oblea ocre)

10. Firma

(fdo) Rodney S. Maddox

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, Abril 15, 2004



DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

MINISTERIO DE
RELACIONES EXTERIORES

2109992

Dora Duque

COLOMBIA
DOCUMENTO DE IDENTIFICACION
LAS FUNCIONES INDICADAS

TEST
2109992
Dora Duque
COLOMBIA
DOCUMENTO DE IDENTIFICACION
LAS FUNCIONES INDICADAS

TEST

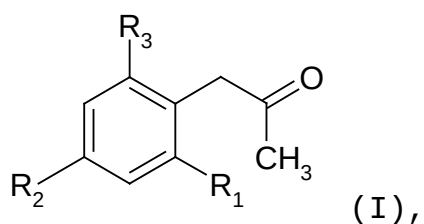
2109992

Dora Duque

COLOMBIA
DOCUMENTO DE IDENTIFICACION
LAS FUNCIONES INDICADAS

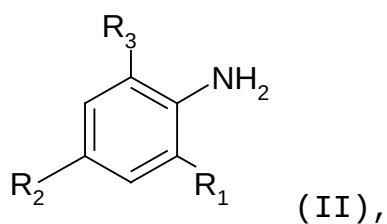
RESUMEN

La invención se refiere a un proceso para la preparación de un compuesto de fórmula I



donde

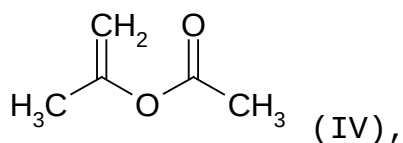
los sustituyentes se definen como en la reivindicación 1, donde el proceso comprende añadir un compuesto de fórmula II



15 donde R₁, R₂ y R₃ tienen los significados que se han descrito para la fórmula I, en presencia de un disolvente orgánico inerte, a una mezcla que comprende un nitrito orgánico de fórmula III

R₄-O-N=O,

donde R₄ es alquilo C₁-C₈, un compuesto de fórmula IV



y un disolvente orgánico inerte.