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A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 08 008.499

TÍTULO SOLICITADO: PROCEDIMIENTO PARA LA PREPARACIÓN DE
COMPUESTOS DE 1-[CIANO(4-
HIDROXIFENIL)METIL]CICLOHEXANOL.

PUBLICACIÓN: Gaceta 600 de 30/01/2009, N° de publicación 1396.

PRIORIDAD: CH 01101/05 de 29/06/2005.

SOLICITANTE: WYETH.

APODERADO: EMILIO FERRERO.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

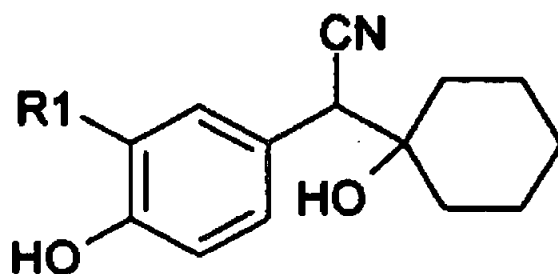
JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 27 de Septiembre de 2007, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

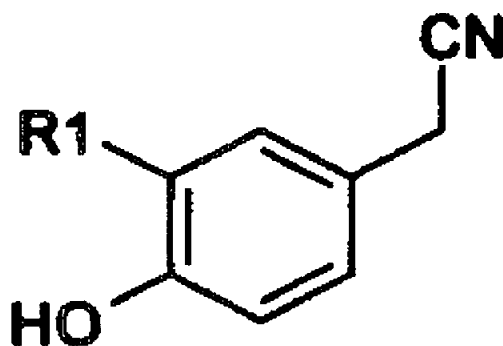
Comedidamente me permito presentar los argumentos anunciados en la oposición respetiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los

artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

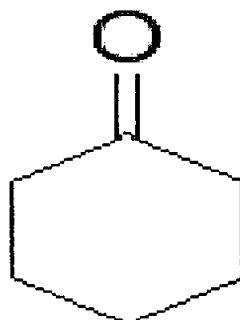
La solicitud colombiana en trámite reivindica un procedimiento para la preparación de compuestos de 1-[ciano(fenil)metil]ciclohexanol de la fórmula general (I)



caracterizado porque se hace reaccionar un compuesto de la fórmula general (II):



con ciclohexanona,



en donde la reacción se lleva a cabo en presencia de una base orgánica o inorgánica y esta base orgánica o inorgánica está presente en al menos una cantidad equimolar respecto de la cantidad de compuesto de la fórmula general (II) en la mezcla de reacción.

Dicho proceso, como cualquier persona medianamente versada en la materia reconoce, se sustenta en la formación de un carbanión estable (debido a la resonancia del triple enlace del grupo ciano) en el carbono alfa del compuesto de formula (II) a través de la base orgánica y/o inorgánica, que debe ser lo suficientemente fuerte para quitarle un protón a dicho compuesto de formula (II); para que posteriormente este carbanión formado, reaccione sobre el carbón que sustenta el grupo carbonilo de la ciclohexanona (debido a que este tiene una carga parcial δ^+) y de esta manera, a través de una adición nucleofílica del carbanión sobre dicho carbono del carbonilo, se forme el compuestos de formula (I). Teniendo en cuenta esto, se puede demostrar que esta misma estrategia sintética ya se había utilizado con anterioridad para la obtención de compuestos análogos y/o muy similares a los reivindicados por la solicitud colombiana en trámite, veamos:

La patente Europea EP 0112669 publicada el 07 de Diciembre de 1983 y titulada "PHENETHYLAMINE DERIVATIVES AND INTERMEDIATES THEREFOR" revela:

Example 1

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol
p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to -70°C . under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below -50°C . and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below -50°C . for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below -50°C . the temperature was allowed to rise to 0°C . and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. $125-127^{\circ}\text{C}$.).

Como se puede apreciar en este ejemplo, es clara la anterioridad en el uso de la misma estrategia sintética utilizada en la solicitud colombiana en cuestión, es decir

la obtención de un derivado de 1-[ciano(fenil)metil]ciclohexanol] a través de la formación de un carbocatión en un compuesto del mismo tipo de compuesto que el compuesto de la formula (II) con una base fuerte para posteriormente reaccionar con ciclohexanona y así formar dicho derivado de 1-[ciano(fenil)metil]ciclohexanol]. Si bien es cierto que dichos compuestos y condiciones de reacción, como por ejemplo la base utilizada no son los mismos, es indiscutible que la esencia del proceso de síntesis es la misma.

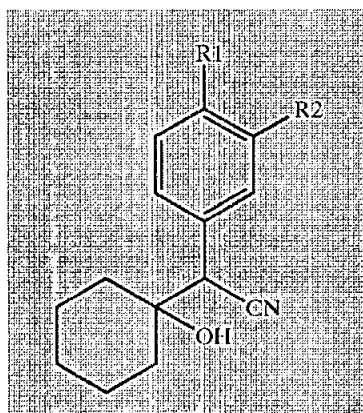
En el mismo sentido, la patente americana US 2002/0120164 publicada el 29 de Agosto de 2002 y titulada "PROCESS FOR THE PREPARATION OF 1-[CIANO(ARYL)METHYL]CYCLOHEXANOL" revela:

[0001] The present invention relates to a process for the preparation of 1-[(cyano)aryl methyl] cyclohexanol of the general formula 1 from arylacetonitriles of the general formula 3. More particularly the present invention relates to the preparation of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol of the formula 1b wherein R₁=OMe, R₂=H which is a key intermediate for the preparation of Venlafaxine of the general formula 2b wherein R₁=OMe and R₂=H and salts thereof which are well known antidepressants of the central nervous system.

1 a-d

(...)

1. A process for the preparation of 1-[(cyano) aryl methyl] cyclohexanol of the general formula 1 (1a-d), by reacting cyclohexanone with the carbanions of an aryl acetonitrile of the general formula 3 (3a-d),



1 a-d

(...)

using a base at temperature in the range of 0-15° for a time period in the range of 15 minutes to 120 minutes, isolating the compound of formula 1 and purifying the compound of formula 1a-d by crystallisation.

2. A process as claimed in claim 1 wherein the base selected from the group consisting of powdered sodium hydroxide, powdered potassium hydroxide, 10% aqueous sodium hydroxide solution, 10% aqueous potassium hydroxide solution and 50% sodium hydroxide solution.

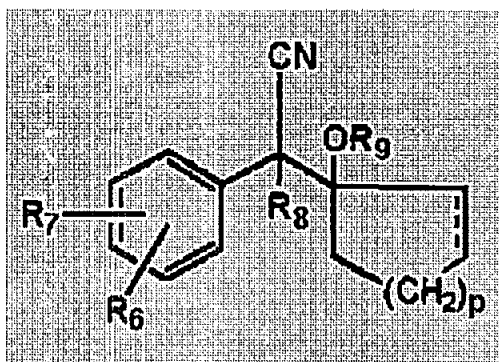
En esta anterioridad se hace mucho mas evidente el uso de esta estrategia sintética, en especial porque como se puede apreciar, se hace mención explícita de la formación del carbanión, así como la mención de algunas de las mismas bases fuertes utilizadas en la solicitud colombiana, tales como hidróxido de sodio o hidróxido de potasio. También se menciona explícitamente la posterior reacción del carbanión con ciclohexanona.

Finalmente la publicación internacional WO 03/000652 publicada el 03 de Enero de 2003 y titulada "PROCESS FOR PREPARATION OF CYCLOHEXANOL DERIVATIVES" revela:

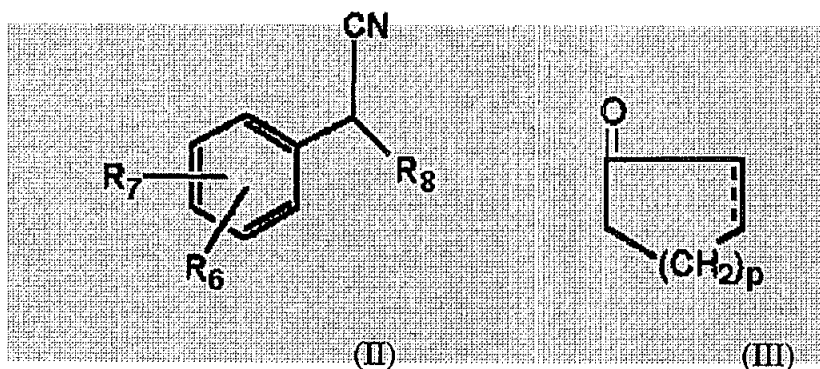
[01] The present invention relates to a process for preparation of cyclohexanol derivatives such as 1-[cyano (4-methoxyphenyl)methyl] cyclohexanol.

(...)

1. A process for preparation of cyclohexanol derivatives of formula I



comprising reacting a compound of formula II with a compound of formula III,



in the presence of a non-organometallic base catalyst represented by formula IV or V, in the presence or absence of a reaction solvent:

Como se puede apreciar, tanto los compuestos utilizados en el proceso de síntesis como las condiciones bajo las cuales se lleva a cabo la reacción coinciden fundamentalmente en lo descrito anteriormente (la formación de un carbanión en el carbono alfa del compuesto de formula II catalizado por una base fuerte, y la posterior adición de dicho carbanión un carbono que sustenta el carbonilo) en donde además se menciona explícitamente la obtención de compuestos derivados de 1-[ciano(fenil)metil]ciclohexanol], el uso de ciclohexanona (compuesto de formula III cuando $p=2$) y la adición opcional de un solvente al proceso. Con esto queda en evidencia la absoluta carencia tanto de novedad como de nivel inventivo del proceso reivindicado por la solicitud colombiana en trámite.

En conclusión el proceso de obtención reivindicado por la solicitud colombiana en trámite, carece irrefutablemente tanto de novedad como de nivel inventivo, primero que todo, porque utiliza una estrategia sintética descrita ampliamente y con anterioridad en el estado de la técnica, para obtener los mismos tipos de compuestos, y en segundo lugar, porque varios de los reactivos y condiciones específicas que se utilizan en dicho proceso, ya se había utilizado dentro de la misma estrategia sintética que se ha expuesto.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

II. ANEXOS.

- ❖ La publicación internacional WO 03/000652 publicada el 03 de Enero de 2003 y titulada "PROCESS FOR PREPARATION OF CYCLOHEXANOL DERIVATIVES" pagina 1 y capítulo reivindicatorio.
- ❖ La patente Europea EP 0112669 publicada el 07 de Diciembre de 1983 y titulada "PHENETHYLAMINE DERIVATIVES AND INTERMEDIATES THEREFOR" página 18.
- ❖ La patente americana US 2002/0120164 publicada el 29 de Agosto de 2002 y titulada "PROCESS FOR THE PREPARATION OF 1-[CIANO(ARYL)METHYL]CYCLOHEXANOL".

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000652 A1

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- (21) International Application Number: **PCI/US02/19753**
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- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
10-2001-35889 22 June 2001 (22.06.2001) KR
- (71) Applicant (for all designated States except US): **WYETH A Corporation of the State of Delaware, USA [US/US];**
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- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KIM, Keun-Sik** [KR/KR]; Jung-ang Heights Apt. 5-1403, 583 Dundook-dong, Yeosu-si, Jeollanam-do 550-760 (KR). **KIM, Kwang-il** [KR/KR]; Jangmi Apt. 210-401, Hak-dong, Yeosu-si, Jeollanam-do 555-010 (KR). **LEE, Sung-Woo** [KR/KR]; Hanryeo Jugong Apt. 109-1302, Dundook-dong, Yeosu-si, Jeollanam-do 550-761 (KR). **PARK, Jin-Soo** [KR/KR]; Jung-and Heights Apt. 1-112, 583 Dundook-dong, Yeosu-si, Jeollanam-do 550-760 (KR). **CHAI, Ki-Byung** [KR/KR]; Geumho Town Apt. 1-405, 353 Soho-dong, Yeosu-si, Jeollanam-do 555-0600 (KR).
- (74) Agents: **BARRETT, Rebecca, R. et al.**; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 (US).
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Declaration under Rule 4.17:**
— of inventorship (Rule 4.17(iv)) for US only
- 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 03/000652 A1

(54) Title: **PROCESS FOR PREPARATION OF CYCLOHEXANOL DERIVATIVES**

(57) Abstract: A process for the preparation of cyclohexanol derivatives of formula (I) by reacting a compound of formula (II) with a compound of formula (III) in the presence of a base catalyst of formula (IV) or (V). In the above formula, R₁-R₉, A, B, X and p have the meanings given in the specification.

PROCESS FOR PREPARATION OF CYCLOHEXANOL DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

[01] The present invention relates to a process for preparation of cyclohexanol derivatives such as 1-[cyano (4-methoxyphenyl)methyl] cyclohexanol.

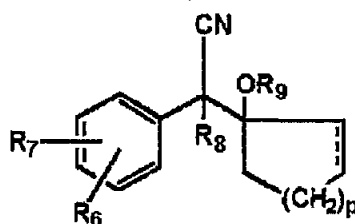
Background of the Related Art

[02] Cyclohexanol derivatives such as 1-[cyano(4-methoxyphenyl)methyl] cyclohexanol are useful intermediates for making compounds like venlafaxine which have anti-depressant effects by inhibiting re-uptake of neurotransmitters, norepinephrine and serotonin. As disclosed in U.S. Patent No. 4,535,186, cyclohexanol derivatives can be produced by reaction of a cycloalkanone or cycloalkenone with an appropriately substituted (ortho or para) phenylacetonitrile anion.

[03] The preparation method disclosed in the US '186 patent involves the use of an organometallic base such as n-butyl lithium in order to induce phenylacetonitrile anion in the reaction. The organometallic base is expensive, has to be used in an amount of at least one equivalent of the reactant at a low temperature below -50°C , is characteristically susceptible to water in air with the risk of fire or explosion, and provides a low production yield of less than 50 percent. Therefore, organometallic bases are considered impractical for industrial scale synthesis.

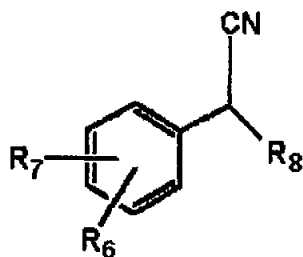
WHAT IS CLAIMED IS:

1. A process for preparation of cyclohexanol derivatives of formula I

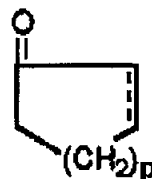


(I)

wherein R₆ and R₇ are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₇-C₉ aralkoxy, C₂-C₇ alkanoyloxy, C₁-C₆ alkylmercapto, halo or trifluoromethyl; R₈ is hydrogen or C₁-C₆ alkyl; p is one of the integers 0, 1, 2, 3 or 4; and R₉ is hydrogen or C₁-C₆ alkyl; comprising reacting a compound of formula II with a compound of formula III,

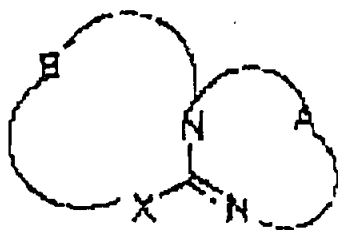


(II)

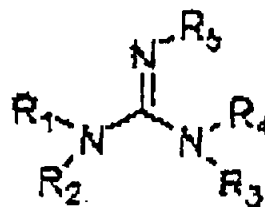


(III)

in the presence of a non-organometallic base catalyst represented by formula IV or V, in the presence or absence of a reaction solvent:



(IV)



(V)

wherein A is $-(CH_2)_n-$ where n is an integer from 2 to 4; B is $-(CH_2)_m-$ where m is an integer from 2 to 5; X is CH_2 , O, NH or NR' , where R' is a C_1 - C_4 alkyl or acyl, or an alkyl supporting polymer; and each of R_1 to R_4 is independently hydrogen, an alkyl, a cycloalkyl or an alkyl or cycloalkyl supporting polymer and all of R_1 to R_4 are not hydrogen, and R_5 is an alkyl, a cycloalkyl or an alkyl or cycloalkyl supporting polymer, and where R_9 is an alkyl, alkyl group is introduced by alkylation.

2. The process of claim 1, wherein the compound of formula II is p-methoxyphenylacetonitrile.
3. The process of claim 1, wherein the compound of formula III is cyclohexanone.
4. The process according to any one of claims 1 to 3, wherein the non-organometallic base catalyst is a mixture of catalysts selected from one or more amidines or guanidines of formula (IV) or (V).
5. The process according to any one of claims 1 to 4, wherein the base catalyst is either homogeneous or immobilized on a polymer support.

6. The process according to any one of claims 1 to 5, wherein the non-organometallic base is selected from the group consisting of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), 1,5-diazabicyclo[4,3,0]non-5-ene (DBN), 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene (MTBD), tetra methyl guanidine (TMG) and N'-butyl-N'',N''-dicyclohexylguanidine.
7. The process according to any one of claims 1 to 6, wherein the amount of the non-organometallic base used is in the range from about 0.005 to about 0.5 equivalents relative to one equivalent of the compound of formula II.
8. The process according to any one of claims 1 to 7, wherein no solvent is used.
9. The process according to any one of claims 1 to 8, wherein the reaction temperature is in the range of about -20 to 80°C.
10. The process of claim 9, wherein the reaction temperature is in the range of about 10 to 30 °C
11. The process according to any one of claims 1 to 10, wherein the compounds of formulas II and III and the base catalysts are used in equivalent ratios of 1 : 1 ~ 1.5 : 0.005 ~ 0.5.

12

EUROPEAN PATENT APPLICATION

21 Application number: **83307435.4**

22 Date of filing: **07.12.83**

51 Int. Cl.³: **C 07 C 93/14, C 07 C 93/24,**
C 07 C 91/23, C 07 C 121/75,
C 07 C 103/76, A 61 K 31/135,
A 61 K 31/22

30 Priority: **13.12.82 US 448032**
19.04.83 US 488594
18.06.83 GB 8316646
26.10.83 US 545701

43 Date of publication of application: **04.07.84**
Bulletin 84/27

84 Designated Contracting States: **AT BE CH DE FR IT LI**
LU NL SE

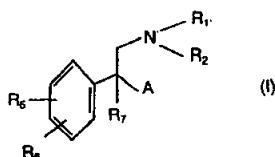
71 Applicant: **AMERICAN HOME PRODUCTS**
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72 Inventor: **Husbands, George Edward Morris,**
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Inventor: **Muth, Eric Anthony, 1447 Patterson Lane, West**
Chester Pennsylvania (US)

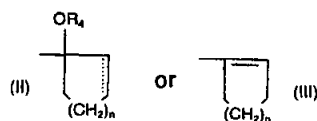
74 Representative: **Porter, Graham Ronald et al, C/O John**
Wyeth & Brother Limited Huntercombe Lane South
Taplow, Maidenhead Berkshire, SL5 0PH (GB)

64 **Phenethylamine derivatives and intermediates therefor.**

67 Novel phenethylamine derivatives are central nervous system antidepressants. The compounds are those having the formula

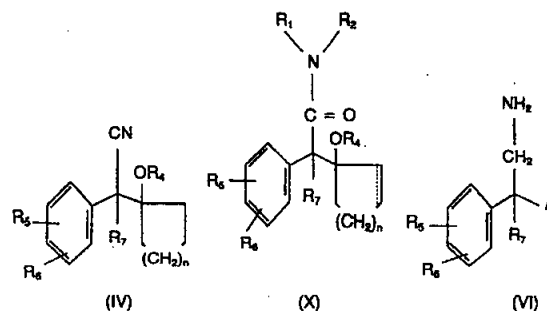


where A is



where the dotted line represents optional unsaturation;

R₁ and R₂ are, independently, hydrogen or C₁-C₆ alkyl;
R₃ is C₁-C₆ alkyl;
R₄ is hydrogen, C₁-C₄ alkyl, formyl or C₂-C₇ alkanolyl;
R₅ and R₆ are hydrogen or defined substituents and n is 0, 1, 2, 3, or 4 and their pharmaceutically acceptable salts. Novel intermediates for the preparation of these compounds include those of the formulae



Example 11-[Cyano(p-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to -70°C . under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below -50°C . and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below -50°C . for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below -50°C . the temperature was allowed to rise to 0°C . and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. $125-127^{\circ}\text{C}$.).

Mass Spectral Analysis: Molecular weight 245 $[(M + 1)^+]$ by C.I.M.S.]

N.M.R. Analysis: δ 7.32, 6.95; (4H quartet, p-substituted aromatic) 3.8 (3H singlet, $\text{O}-\text{CH}_3$); 3.76 (1H, singlet, $\text{CH}-\text{CN}$); 1.56 (10H, multiplet, aliphatic cyclohexyl)ppm.

Example 21-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium on alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm).

Mass Spectral Analysis: Molecular weight 249 $(M+1)^+$ by C.I.M.S.

Thin Layer Chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

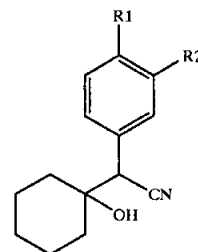


US 20020120164A1

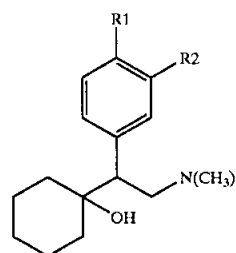
15

(19) **United States**(12) **Patent Application Publication**
Chavan et al.(10) **Pub. No.: US 2002/0120164 A1**(43) **Pub. Date: Aug. 29, 2002**(54) **PROCESS FOR THE PREPARATION OF**
1-[CYANO(ARYL)METHYL]
CYCLOHEXANOL(75) **Inventors:** Subhash Prataprao Chavan,
Maharashtra (IN); Subhash Krishnaji
Kamat, Maharashtra (IN); Latha
Sivadasan, Maharashtra (IN);
Kamalam Balakrishnan, Maharashtra
(IN); Dushant Anandrao Khobragade,
Maharashtra (IN); Ravindranathan
Thottapillil, Maharashtra (IN);
Mukund Keshao Gurjar, Maharashtra
(IN); Uttam Ramrao Kalkote,
Maharashtra (IN)**Correspondence Address:**
DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022 (US)(73) **Assignee: COUNCIL OF SCIENTIFIC AND**
INDUSTRIAL RESEARCH(21) **Appl. No.: 09/796,084**(22) **Filed: Feb. 28, 2001****Publication Classification**(51) **Int. Cl.⁷ C07C 253/30**(52) **U.S. Cl. 558/371**(57) **ABSTRACT**

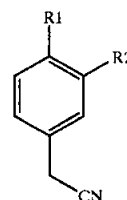
A process for the preparation of 1-[(cyano) aryl methyl] cyclohexanol of the general formula 1 (1a-d) by reacting cyclohexanone with the carbanions of an aryl acetonitrile of the general formula 3 (3a-d),



1 a-d



2 a-d



3 a-d

a) R1=H, R2=H

b) R1=OMe R2=H

c) R1=OMe R2=OMe

d) R1=OMe R2=cyclopentyloxy

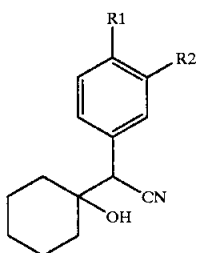
using a base, isolating the compound of formula 1 and purifying the compound of formula 1a-d by crystallisation is disclosed.

PROCESS FOR THE PREPARATION OF 1-[CYANO(ARYL)METHYL] CYCLOHEXANOL

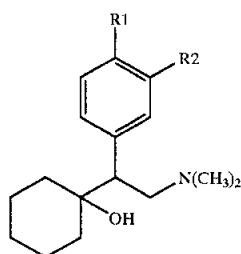
FIELD OF THE INVENTION

[0001] The present invention relates to a process for the preparation of 1-[(cyano)arylmethyl] cyclohexanol of the general formula 1 from arylacetonitriles of the general formula 3. More particularly the present invention relates to the preparation of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol of the formula 1b wherein R₁=OMe, R₂=H which is a key intermediate for the preparation of Venlafaxine of the general formula 2b wherein R₁=OMe and R₂=H and salts thereof which are well known antidepressants of the central nervous system.

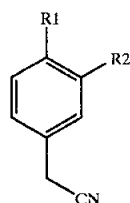
1 a-d



2 a-d



3 a-d



[0002] a) R₁=H, R₂=H

[0003] b) R₁=OMe R₂=H

[0004] c) R₁=OMe R₂=OMe

[0005] d) R₁=OMe R₂=cyclopentyloxy

BACKGROUND OF THE INVENTION

[0006] In the prior art [Husbands et al. U.S. Pat. No. 4,535,186 (1985) and EP 0112669B] various 2-aryl-(1-hydroxycyclohexyl)-acetonitriles having formula (1) were prepared with <50% yield by the condensation of arylacetonitriles having formula (3) with cyclohexanone using n-butyl lithium as the base at -70° C. [Sauvetre et al. Tetrahedron 34 2135 (1978)].

[0007] UK Patent No GB 2 227 743 A (1990) of Peter Gerald Shepherd discloses the condensation of compounds

having formula 3 with cyclohexanone using lithium diisopropylamide in hydrocarbon solvents like hexane, toluene or cyclohexane at ambient temperature thereby improving the yield to 79%.

[0008] The use of butyllithium causes great inconvenience in large-scale preparation since butyllithium is very hazardous. The need for setting up plants for operating at very low temperatures combined with the high cost of butyllithium make this method unacceptable for industrial preparations.

OBJECTS OF THE INVENTION

[0009] The main object of the present invention is to provide a simple and convenient method of preparation of compounds having formula 1(a-d).

[0010] It is another object of the invention to provide a process that avoids the use of expensive and hazardous reagents like n-butyl lithium, lithiumdiisopropylamide.

[0011] It is still another object of the invention to provide a process that avoids the use of dry solvents like THF and diethyl ether that are expensive and hazardous.

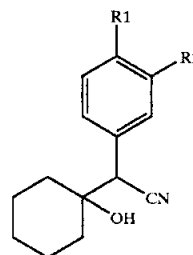
[0012] It is yet another objective of the invention to provide a process that does not require elaborate work up or purification processes like chromatography for the isolation of products.

[0013] It is a further object of the invention to provide a process by which near quantitative yields of the product are obtained. It is another object of the invention to provide a process which is simple, easy to handle, inexpensive and non-hazardous so that large-scale production is possible.

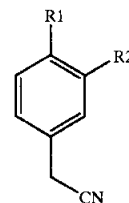
SUMMARY OF THE INVENTION

[0014] Accordingly, the present invention relates to a process for the preparation of 1-(cyano)arylmethyl] cyclohexanol of the general formula 1(1a-d), said process comprising reacting cyclohexanone with the carbanions of an aryl acetonitrile of the general formula 3 (3a-d),

1 a-d



3 a-d



[0015] a) R1=H, R2=H

[0016] b) R1=OMe R2=H

[0017] c) R1=OMe R2=OMe

[0018] d) R1=OMe R2=cyclopentyloxy

[0019] using a base, at temperature in the range of 0-15° for a time period in the range of 15 minutes to 120 minutes, isolating the compound of formula 1 and purifying the compound of formula I(a-d) by crystallisation.

[0020] In one embodiment of the invention the base used is selected from the group consisting of powdered sodium hydroxide, powdered potassium hydroxide, 10% aqueous sodium hydroxide solution, 10% aqueous potassium hydroxide solution and 50% sodium hydroxide solution.

[0021] In another embodiment of the invention the quantity of base used is in the range of 0.25 mole to 1 mole.

[0022] In a further embodiment of the invention the quantity of base used is 0.5 mole.

[0023] In another embodiment of the invention, the reaction is carried out in the presence of or absence of a phase transfer catalyst.

[0024] In another embodiment of the present invention, the phase transfer catalyst used is selected from the group consisting of tetrabutylammonium hydrogensulphate, tetrabutylammonium bromide, tetrabutylammonium chloride, and tetrabutylammonium iodide or benzyltriethyl ammonium chloride.

[0025] In still another embodiment of the present invention, the aryl acetonitrile of formula 3 used is selected from the group consisting of phenylacetonitrile, 4-methoxyphenylacetonitrile, 3,4-dimethoxy phenylacetonitrile or 3-cyclopentyloxy, 4-methoxyphenylacetonitrile.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The process of the present invention is described by the following examples, which are illustrative only and should not be construed as limit to the scope of the reaction in any manner.

EXAMPLE 1

[0027] Phenylacetonitrile 3a (11.7 parts, 0.1 moles) was placed in a beaker and cooled to 0° C. Powdered potassium hydroxide (0.28 parts, 0.05 moles catalytic quantity) and tetrabutylammonium iodide (0.37 parts, 0.01 moles) was added and mixed thoroughly. After 5 minutes, cyclohexanone (9.8 parts, 0.1 moles) was added slowly at 0° C. The mixture on stirring vigorously for 15 minutes solidified suddenly. Water (100 parts) was added at this stage and the reaction mixture stirred for an hour to complete the reaction. The product- 1-cyano [(aryl) methyl] cyclohexanol 1a was filtered by suction, washed with water (3x100 parts) and dried to constant weight. 18.7 parts, (87%). Crystallized from ethyl acetate pet ether to yield shining white crystals Mp. 101-2° C. NMR (200 MHz., CDCl₃) δ 7.4(s, 5H, aromatic); 3.80 (s, 1H CH CN); 1.59 (m, 10H cyclohexyl); 1.24 (br s, 1H). M+215

EXAMPLE 2

[0028] 4-Methoxyphenylacetonitrile 3b (147 parts, 1 mole) was cooled to 0° C., and stirred vigorously with a solution of 10% aqueous sodium hydroxide solution (100 parts, 0.25 mol). Tetrabutyl ammonium hydrogen sulphate (4.0 parts, 0.1 mol) was added in one lot while stirring. The reaction was warmed to 15° C. after which, cyclohexanone (100 parts 1.02 mol) was added rapidly in 10 minutes taking care to keep the temperature of the reaction below 15° C. A thick smooth solid separates. At this stage the solid was crushed to fine pieces and water (1000 parts) was added to facilitate stirring. Stirring was continued for 2 hrs. When the reaction was over, (monitored by tlc) the solid was filtered, washed free of alkali and dried to constant weight. Yield 162 parts (97.6%). The product 1-cyano [(4-methoxyphenyl) methyl]-cyclohexanol 1b was crystallized from ethylacetate pet. ether to obtain shining white needles of >99% purity on HPLC M.p 125-6° C. (litt. mp 123-5°). NMR (CDCl₃) δ 7.32, 6.95 (4H, q, p-substituted aromatic), 3.8 (3H, s-OCH₃); 3.76 (1H, s, CH CN 1.56 (10H, m, aliphatic cyclohexyl); M+245

EXAMPLE 3

[0029] 3,4-Dimethoxyphenylacetonitrile 3c (0.885 parts, 0.005 moles) was cooled to 15° C. in a beaker and stirred vigorously with powdered sodium hydroxide (0.100 parts 0.25 mol). Trimethylbenzylammonium chloride (0.028 parts, 0.003 moles) was added to this mixture followed by cyclohexanone (0.5 parts, 0.005 moles). Stirring was continued for 2 hrs and the reaction was left overnight at 0° C. Water (5 ml) was added after which the solid that separated was filtered, washed with water and dried 0.976 parts (71%). The product 1-cyano [(3,4-dimethoxyphenyl) methyl] acetonitrile 1c was crystallised from ethylacetate to fine needles. Mp. 134-5° C. NMR: (CDCl₃) δ 6.85 (m, 3H, aromatic). 3.87(s, 3H O CH₃); 3.86(s, 3H O CH₃); 3.69(s, 1H, CH CN); 1.59 (m, 10H, cyclohexyl) 1.24 (bs, 1H, OH); M+275

EXAMPLE 4

[0030] 3-cyclopentyloxy, 4-methoxy phenylacetonitrile 3d (0.3 parts, 0.00129 mols) was cooled to 0° C. and stirred with a 50% solution of sodium hydroxide (0.1 part, 0.00125 moles) and tetrabutylammoniumhydrogensulphate (0.044 parts, 0.000129 mol). Cyclohexanone (0.129 parts 0.0013 moles) was added after 10 minutes and stirring continued for 2 hours to ensure completion of the reaction. The product 1-cyano-[(3-cyclopentyloxy, 4methoxyphenyl) methyl] cyclohexanol 1d was isolated by filtration, washing and drying as a low melting solid. NMR (CDCl₃) δ (6.8 (m, 3H, aromatic); 4.75 (br. S, 1H, O—CH—); 3.6 (s 3H, OMe); 3.59 (s, 1H CH—CN); 1.5-2 (m, 18H cyclopentyl and cyclohexyl). M+329

EXAMPLE 5

[0031] 4-Methoxyphenylacetonitrile 1b (1.47 parts, 0.1 mol) was cooled to 0° C. and stirred with powdered sodium hydroxide (0.02 parts 0.05 mol). Tetrabutylammoniumiodide (0.036 parts 0.01 mol) was added to this mixture and condensed with cyclohexanone (0.98 parts, 0.1 mol) as described above. The product 1b was isolated by filtration, washing and drying of the solid obtained after stirring the reaction mixture for 10 minutes. (2.2 parts, 89.7%)

EXAMPLE 6

[0032] 4-Methoxyphenylacetonitrile 1b (1.47 parts, 0.1 mol) was cooled to 0° C. and stirred with powdered sodium hydroxide (0.100 parts, 0.025 mol) without any phase transfer catalyst. When the reaction became thick, cyclohexanone (0.98 parts, 0.1 mol) was added and the reaction stirred for another 10 minutes till solid separated. The product 1b was isolated as described above. (1.91 part, 78%)

[0033] The advantages of the present invention are as follows:

[0034] The present invention avoids the use of expensive and hazardous reagents like n-butyl lithium, lithiumdiisopropylamide.

[0035] The present invention also avoids the use of dry solvents like THF and diethyl ether, which are also expensive and hazardous. The present method can be conducted in water or even under solvent free conditions.

[0036] The present invention does not involve elaborate work up or purification processes like chromatography for the isolation of products.

[0037] The present invention avoids the inconvenience of carrying out reactions at very low temperatures.

[0038] The present invention does not require the use of inert atmosphere.

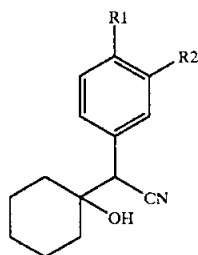
[0039] The present invention describes a process by which near quantitative yields of the product are obtained.

[0040] The present invention describes a process, which is simple, easy to handle, and non-hazardous so that large-scale production is possible.

[0041] The present invention presents a very convenient method of preparation of 1 through a simple short and cost effective process.

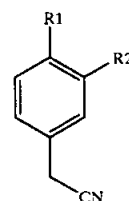
We claim:

1. A process for the preparation of 1-[(cyano) aryl methyl] cyclohexanol of the general formula 1 (1a-d), by reacting cyclohexanone with the carbanions of an aryl acetonitrile of the general formula 3 (3a-d),



1a-d

-continued



3a-d

a) R1=H, R2=H

b) R1=OMe R2=H

c) R1=OMe R2=OMe

d) R1=OMe R2=cyclopentyloxy

using a base at temperature in the range of 0-15° for a time period in the range of 15 minutes to 120 minutes, isolating the compound of formula 1 and purifying the compound of formula 1a-d by crystallisation.

2. A process as claimed in claim 1 wherein the base selected form the group consisting of powdered sodium hydroxide, powdered potassium hydroxide, 10% aqueous sodium hydroxide solution, 10% aqueous potassium hydroxide solution and 50% sodium hydroxide solution.

3. A process as claimed in claim 1 wherein the base used is in an amount in the range of 0.25 mole to 1 mole.

4. A process as claimed in claim 3 wherein the quantity of base used is 0.5 mole.

5. A process as claimed in claim 1 wherein the reaction is carried out in the presence of or absence of a phase transfer catalyst.

6. A process as claimed in claim 5 wherein the phase transfer catalyst used is selected from the group consisting of tetrabutylammonium hydrogensulphate, tetrabutylammonium bromide, tetrabutylammonium chloride, and tetrabutylammonium iodide or benzyltriethyl ammonium chloride.

8. A process as claimed in claim 1 wherein the aryl acetonitrile of formula 3 used is selected from the group consisting of phenylacetonitrile, 4-methoxyphenylacetonitrile, 3,4-dimethoxy phenylacetonitrile or 3-cyclopentyloxy, 4-methoxy phenylacetonitrile.

9. A process as claimed in claim 1 wherein the solvent used is water.

10 A process as claimed in claim 1 wherein the base is used in a catalytic amount.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 9866

ASUNTO:

Radicación PCT N°	08-8499
Trámite	011
Evento	379
Actuación	440
Folios	024

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

28 AGO. 2009

El anterior oficio fue notificado por fijación en lista de fecha, _____.

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