



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-002341- -00002-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 140

FORMULARIO UNICO DE OPOSICION
2000-12

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OPOSICION A:

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Diseño Industrial

☐ Esquema de Trazado para Circuitos Integrados

☐ Marcas de Productos o Servicios

☐ Marca Colectiva

☐ Marca de Certificación

☐ Lema Comercial

2

SOLICITUD PUBLICADA

Número del expediente: 08 002.341

Solicitante: NOVARTIS AG

Apoderado: CARLOS R. OLARTE

Título de la nueva creación o denominación del signo:
SALES METALICAS DE 2'-(1H-TETRAZOL-5-IL)-1,1'-BIFENIL-4-CARBOXALDEHÍDO.

Gaceta: 590 de 31 de Marzo de 2008, número de publicación 191.

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 300 466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: 621.26.31 E-mail: info@reyes-abogados.com Fax: 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) 16 y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia).

Justificación: VER ANEXO

5

Comprobante de pago No. 08-50.765 (Oposición) Fecha Junio 24 de 2008
08-50.768 (Prórroga) Fecha Junio 24 de 2008

6

Anexos:

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Comprobante de pago de la tasa

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Poderes, si fuere el caso

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Pruebas de los fundamentos de la oposición

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Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas

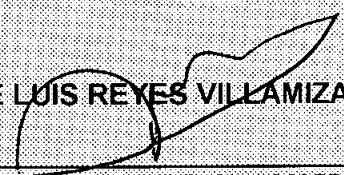
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Documentos que acrediten el legítimo interés, si fuere el caso

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Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR
FIRMA: 

C.C.No. 79.152.473 T.P. No. 44655

REYES & REYES

A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 08-002-341

TÍTULO SOLICITADO: SALES METALICAS DE 2'-(1H-TETRAZOL-5-IL)-1,1'-BIFENIL-4-CARBOXALDEHÍDO.

PUBLICACIÓN: Gaceta 590 de 31 de Marzo de 2008, N° de publicación 191.

PRIORIDAD: GB 0514206.2 de 11/07/2005

SOLICITANTE: NOVARTIS AG

APODERADO: CARLOS R. OLARTE

TRÁMITE: PRESENTACIÓN DE OPOSICION

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.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **08 002.341**, por no cumplir con lo dispuesto por los artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud en curso, que se refiere a un proceso de síntesis de agentes para bajar la presión arterial, tales como Valsartan y novedosos intermediarios que se involucran en esta síntesis, carece por completo de los requisitos fundamentales para otorgársele el privilegio de patente de invención, tal y como lo demuestran los siguientes argumentos:

- 3.1. Cualquier persona medianamente versada en la materia, reconoce que la primera definición de ácido y base fue acuñada en la década de 1880 por Savane Arrhenius quien los definió como sustancias que pueden donar protones (H^+) o iones hidróxido (OH^-) respectivamente. Una definición mas general fue propuesta en 1923 por Johannes Brönsted y Thomas Lowry quienes enunciaron que una sustancia ácida es aquella que puede donar H^+ , y definieron a una base como una sustancia que puede aceptar protones. Finalmente, una definición mas completa de ácidos y bases fue propuesta por Gilbert Lewis quien describió que un ácido es una sustancia que puede aceptar un par de electrones y una base es aquella que puede donar ese par. Así mismo las reacciones entre ácidos y bases (denominadas reacciones de neutralización) son reacciones descritas ampliamente y conforman un conjunto de reacciones sencillas cuyos resultados están sujetos a los valores de pK_a que manejen los reactivos correspondientes, reactivos que se pueden clasificar como ácidos fuertes y débiles, y bases fuertes o débiles.

De igual manera, también es ampliamente sabido que, las sales son compuestos que están formados por un metal (catión) más un radical (anión), que se obtiene de la disociación de los ácidos, es decir, cuando se rompe el enlace covalente liberando protones (H^+), el radical adquiere la carga negativa según el número de protones liberado, luego, el metal se une al radical por medio de enlace iónico.

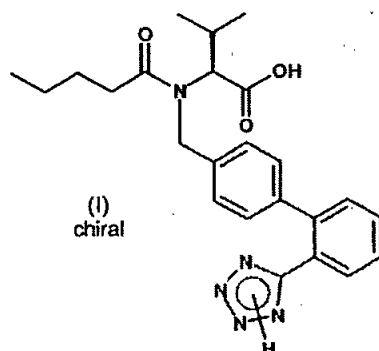
En el caso de la solicitud colombiana en trámite, la reacción entre la solución del compuesto de fórmula (I) (anión) con el material que proporciona cationes de la reivindicación 1, se ajustan a las características ampliamente conocidas de este tipo de reacciones ácido-base, por lo cual, el método de obtención de sales del intermediario de dicha solicitud en trámite carece irrefutablemente de nivel inventivo.

- 3.2. Por su parte, la publicación internacional WO 2004/026847 publicada el 01 de abril de 2004 y titulada "PROCESS FOR THE MANUFACTURE OF VALSARTAN" revela:

The present invention relates to a process for the manufacture of an angiotensin receptor blocker (ARB; also called angiotension II receptor antagonist or AT_1 receptor antagonist) and salts thereof, to novel intermediates and process steps. ARBs can, for example, be used for the treatment of hypertension and related diseases and conditions. (...)

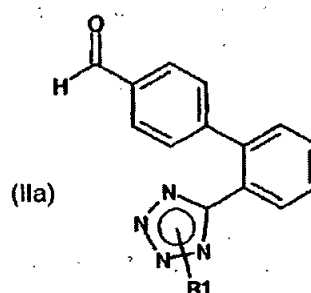
The formation of the tetrazole ring is a critical step in the manufacture of these compounds. Methods for the manufacture of ARBs having this structural feature include the formation of said tetrazole ring by starting from corresponding cyano derivatives that react with HN_3 or a suitable alkali metal salt thereof such as sodium azide or with an organotin azide such as tributyltin azide or with a silyl azide. The use of azides for forming the tetrazol ring system requires a sophisticated system to run the reaction in a safe way during an up-scaled production process. Accordingly, an objective is to develop alternative process variants that exclude the use of azides in the last steps of the production of corresponding ARBs. (...)

The present invention relates to a process for the manufacture of the compound of formula (I)

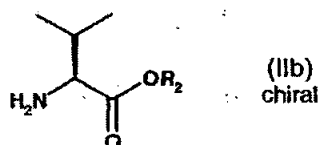


(...)

(a) reacting a compound of formula (II a)

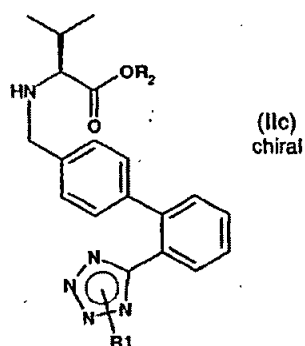


or a salt thereof, wherein R₁ is hydrogen or a tetrazole protecting group, with a compound of formula

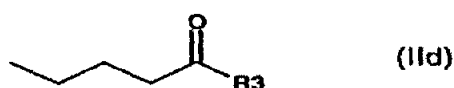


or a salt thereof, wherein R₂ represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination; and

(b) acylating a resulting compound of formula (II c)



or a salt thereof with a compound of formula (II d)



(...)

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10°C to about $+200^{\circ}\text{C}$, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

(...)

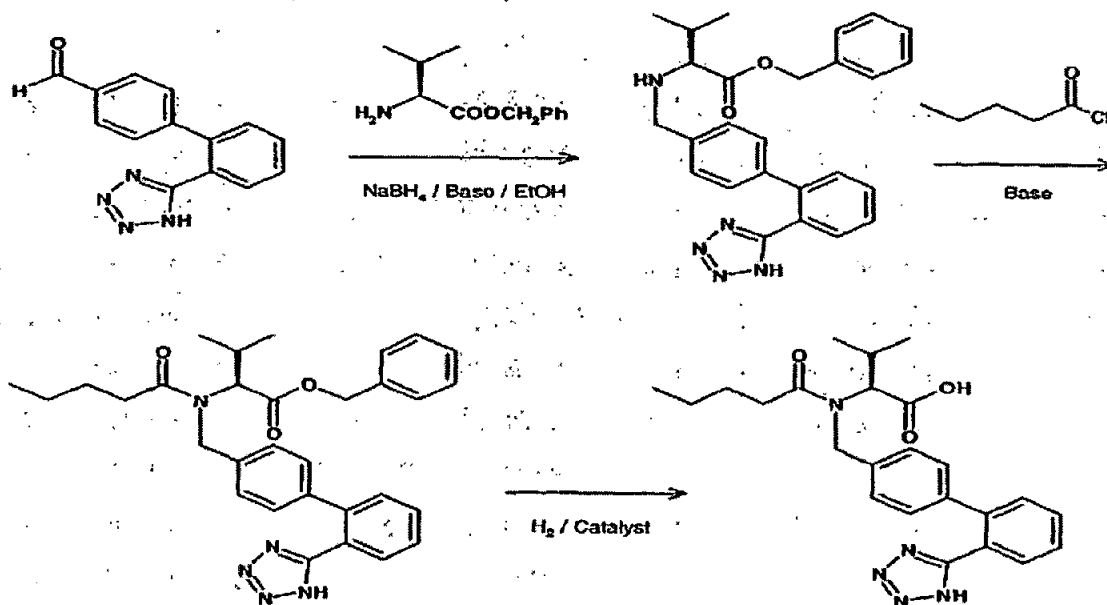
Step (a):

In reaction Step (a), the reductive amination is carried out in the presence of a reducing agent. A suitable reducing agent is a borohydride, which may also be in a complexed form, or hydrogen or a hydrogen donor both in the presence of a hydrogenation catalyst. Furthermore, a reducing agent is a suitable selenide or a silane.

(...)

Example 2:

This example can be illustrated by means of the following reaction scheme:



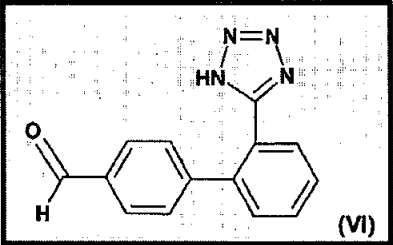
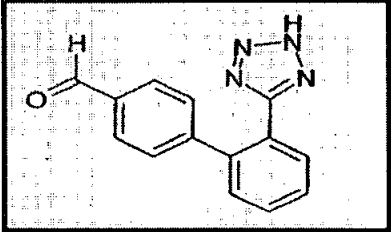
En esta anterioridad, se revela claramente tanto los mismos intermediarios utilizados por la solicitud colombiana en trámite para la obtención de Valsartan, así como se ven involucrados los mismos tipos de reacciones, especificando además lo referido a diversas condiciones de reacción y diferentes reactivos que pueden ser aplicables al caso.

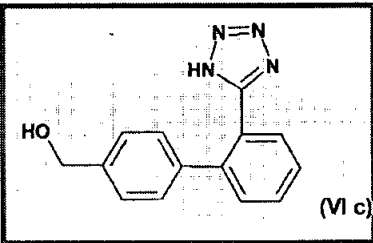
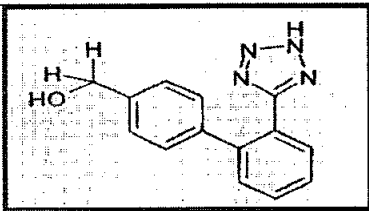
También es importante destacar que si bien es cierto no se demuestra detalladamente la obtención de las sales del compuesto (IIa) de la anterioridad en mención, si se hace mención de manera general a las sales de dicho compuesto (ver recuadro rosado más arriba), además, es bastante claro para cualquier persona medianamente versada en la materia cómo se forma una sal.

En consecuencia, todo lo consignado hasta el momento permite desvirtuar de manera irrefutable, al menos el nivel inventivo del proceso de síntesis consignado en el capítulo reivindicatorio de dicha solicitud colombiana en discusión.

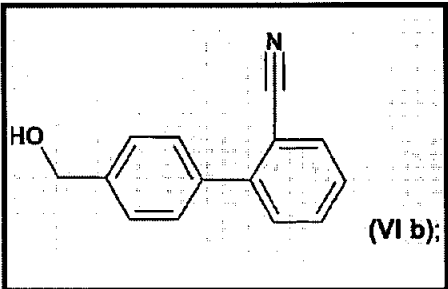
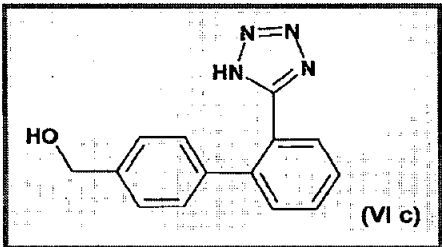
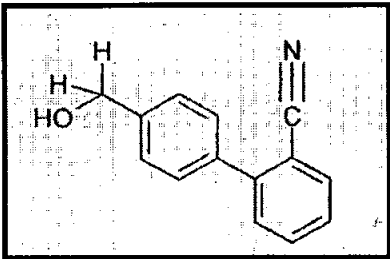
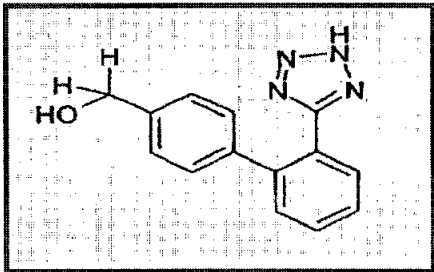
3.3. La publicación internacional WO 2005/014602 publicada el 17 de febrero de 2005 y titulada “PROCESS FOR THE PREPARATION OF TETRAZOLE DERIVATIVES FROM ORGANO BORON AND ORGANO ALUMINIUM AZIDES” revela un método para preparar tetrazoles sustituidos mediante distintas reacciones, los cuales son útiles como bloqueadores del receptor de angiotensina (ARBs).

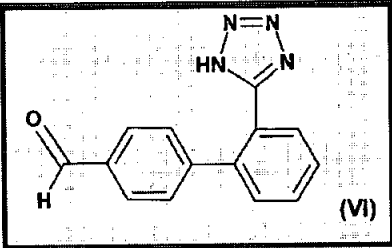
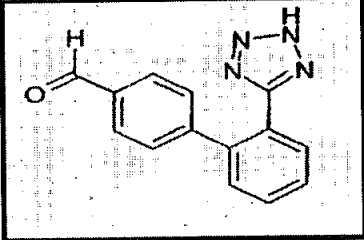
La reivindicación 9 de la solicitud colombiana en trámite carece de novedad y nivel inventivo si se tiene en cuenta que la WO 05/014602 en mención revela:

WO 05/014602	CO 08-002-341
Rv 6: Fabricación del compuesto de fórmula (VI)  que comprende la oxidación del compuesto de fórmula (VI c);	Rv 9: Fabricar un compuesto de fórmula (I)  mediante la oxidación de un compuesto hidroximetilo de fórmula (II):

WO 05/014602	CO 08-002-341
 (VI c) y posterior aislamiento del compuesto resultante (VI)	 hasta un compuesto de fórmula (I)

La reivindicación 10 de la solicitud colombiana en trámite carece de novedad y nivel inventivo si se tiene en cuenta que la WO 05/014602 en mención revela:

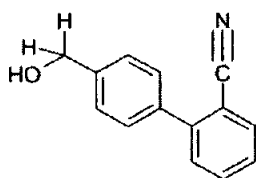
WO 05/014602	CO 08-002-341
Rv 5: Proceso para la fabricación del compuesto de fórmula (VI) mediante la reacción de un compuesto de fórmula (Vb)  (VI b): con una azida de fórmula: (R1) (R2)-M-N3 (IIb) M= Boro, Aluminio Resultando en un compuesto de fórmula (VI c);  (VI c) el cual se oxida y permite obtener el compuesto de fórmula (VI)	Rv 10: Un proceso según la Rv 9 el cual comprende además formar un compuesto de fórmula (II) como se da en la Rv9, mediante la reacción de un cianuro de fórmula (III)  con una azida de fórmula: (R1) (R2)-M-N3 M= Boro, Aluminio Para dar un compuesto de fórmula (II)  que se oxida y permite obtener el compuesto de fórmula (I)

WO 05/014602	CO 08-002-341
 (VI)	

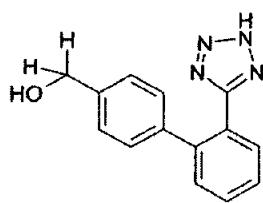
Esta anterioridad revela de manera muy clara la obtención de los mismos intermediarios del proceso de síntesis de la solicitud colombiana, específicamente en lo que se refiere al intermediario de fórmula (I), el intermediario de fórmula (II) y la reacción tipo cicloadición [2+3] entre los compuestos de fórmula (III) y una azida de fórmula (R1)(R2)-M-N₃, con lo cual, se desvirtúa en estos puntos la novedad y si esto no fuera posible, entonces es claro que la solicitud en trámite carece de nivel inventivo puesto que se emplean dichos intermediarios en la obtención de compuestos relacionados a Valsartan y se mencionan los mismos tipos de reacción entre dichos intermediarios, específicamente en lo que se refiere a la oxidación de un alcohol primario del mismo tipo que el del compuesto de fórmula (III) y la obtención del anillo de tetrazol a partir de un compuesto de nitrilo y una azida.

3.4. Para terminar y en forma muy general, el proceso de obtención de Valsartan que describe la solicitud colombiana en trámite, puede resumirse en:

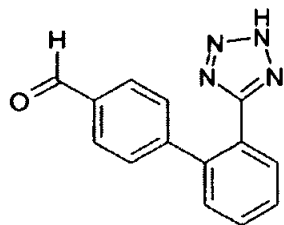
* Una primera reacción (**que llamaremos reacción A**) entre el compuesto de fórmula (III)



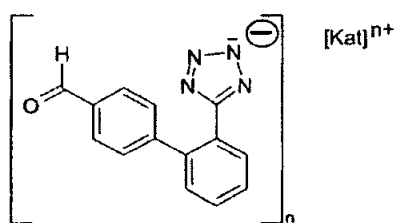
y un compuesto tipo azida de la fórmula (R1)(R2)-M-N₃, que da como resultado un compuesto de fórmula (II)



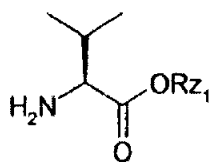
que posteriormente se oxida (la llamaremos **Reacción B**) a un compuesto de fórmula (I)



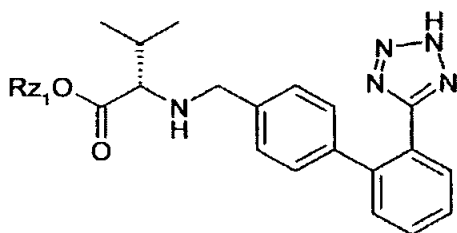
del cual se forma la sal de la fórmula (IA)



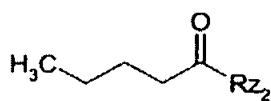
(**Reacción C**), para después reaccionar con el compuesto de fórmula (IV)



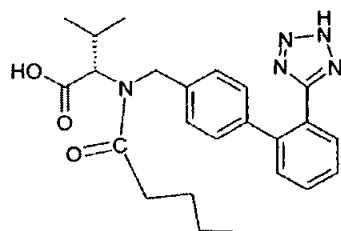
(**Reacción D**) para obtener así el compuesto de fórmula (V)



que, posteriormente reacciona con el compuesto de fórmula (VI)



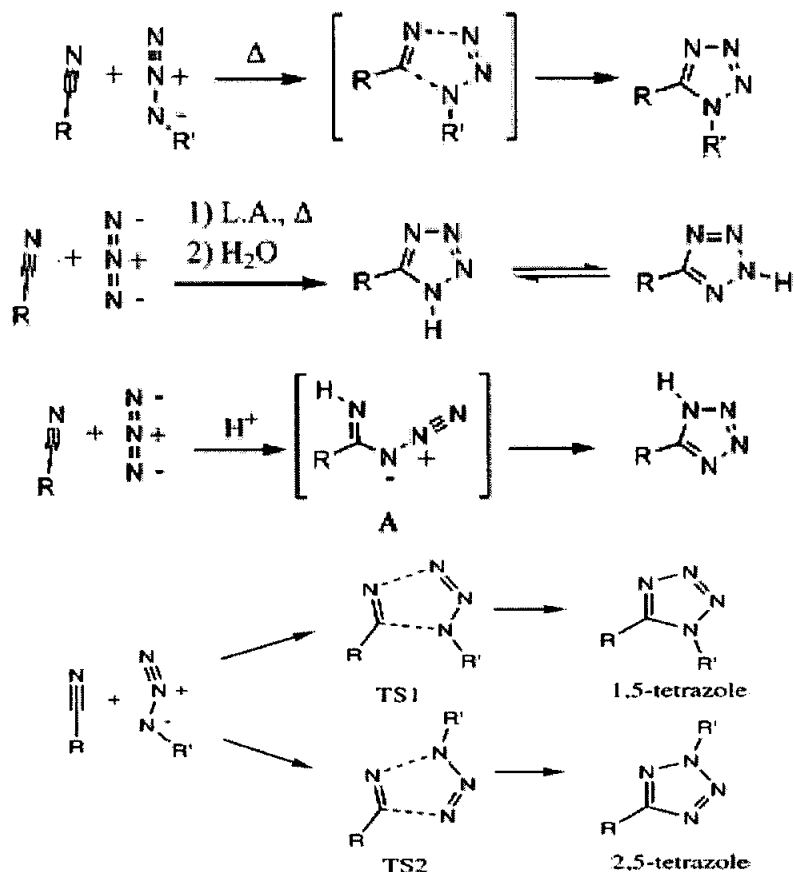
(**Reacción E**); para finalmente obtener el compuesto de fórmula (VII)



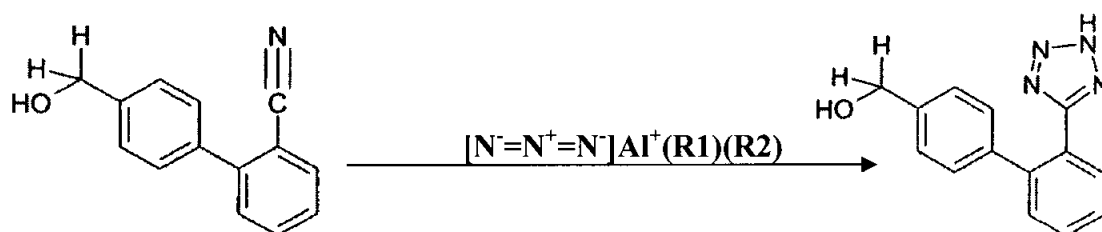
(Valsartan).

Todas estas reacciones son reacciones sencillas descritas en el estado de la técnica y reconocidas por cualquier persona medianamente versada en la materia y/o dedicada a la síntesis química.

Por ejemplo la **reacción A** es un clásico y reconocido método de reacción de cicloadición [2 + 3] entre un compuesto orgánico de tipo azida ($R-N_3$) y un compuesto orgánico de tipo nitrilo ($R-CN$) de la forma:



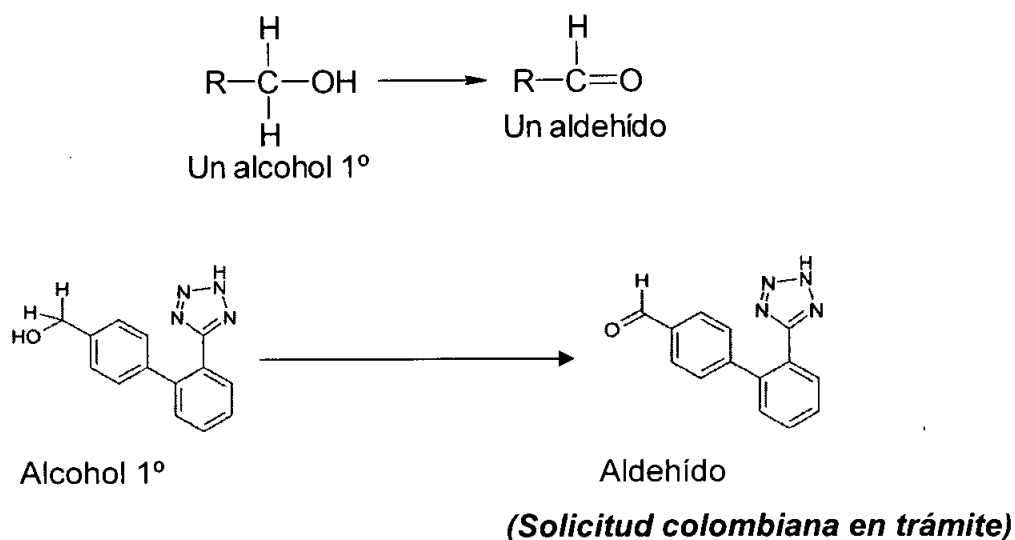
Que como se puede apreciar claramente, es el mismo tipo de reacción que se tiene en la **reacción A** descrita en la solicitud colombiana:



Las características fundamentales, tales como las condiciones óptimas de reacción, los mecanismos de reacción y las variantes, como la estereoquímica resultante y los posibles isómeros que pueden resultar de la reacción entre los diversos compuestos azídicos y nitrílicos para formar tetrazoles, se encuentran ampliamente documentadas en publicaciones de

carácter científico tales como "Novel Synthesis of 5-Substituted-Tetrazoles¹"; "Why Is Tetrazole Formation by Addition of Azide to Organic Nitriles Catalyzed by Zinc(II) Salts²?" y "Mechanisms of Tetrazole Formation by Addition of Azide to Nitriles³"

Por su parte la **reacción B** es una simple y común reacción de oxidación de alcoholes, que como cualquier persona medianamente versada en la materia reconoce, implica la pérdida de uno o más hidrógenos del carbono que sustenta el grupo hidroxilo. El tipo de producto que se genera depende del número de estos hidrógenos que tiene el alcohol, es decir, si es primario secundario o terciario; un alcohol primario como en el caso del compuesto de fórmula (II) de la solicitud colombiana contiene dos hidrógenos de este tipo, de modo que puede perder uno de ellos para dar un aldehído:



Agentes oxidantes empleados para este tipo de reacciones siempre han estado disponibles para el químico orgánico; al igual que con todos los métodos sintéticos, el interés de este tipo de reacciones se centra en el desarrollo de reactivos altamente selectivos que operen sólo sobre un grupo funcional de una molécula compleja sin afectar a otros grupos funcionales que pudieran estar presentes.

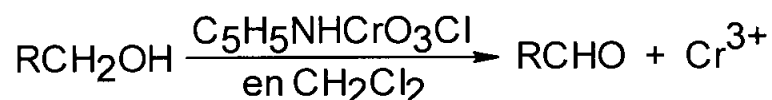
¹ KOGURO K. ; OGA T. ; MITSUI S. ; ORITA R. ; Synthesis ISSN 0039-7881 CODEN SYNTBF; 1998, no6, pp. 910-914 [5 page(s) (article)] INIST-CNRS, Cote INIST : 14694, 35400007661649.0210.

² Fahmi Himo, Zachary P. Demko, Louis Noodleman, and K. Barry Sharpless. J. AM. CHEM. SOC. 2003, 125, 9983-9987.

³ Fahmi Himo, Zachary P. Demko, Louis Noodleman, and K. Barry Sharpless. J. AM. CHEM. SOC. 2002, 124, 12210-12216.

Es así que, de los numerosos reactivos que se pueden utilizar para oxidar alcoholes, podemos considerar los más comunes aquellos que contienen Mn (VI) o Cr (VI), entre estos, el manganeso heptavalente en la forma de permanganato de potasio, KMnO_4 ; también se utiliza mucho el cromo hexavalente, en particular el ácido crómico $\text{K}_2\text{Cr}_2\text{O}_7$, CrO_3 en ácido acético glacial, CrO_3 en piridina, etc.

La oxidación de alcoholes a aldehído o cetona se logra utilizando Cr(VI) en una de las formas descritas antes, pero dado que los aldehídos resultantes de la oxidación de alcoholes primarios son susceptibles a una mayor oxidación (o sea tienden a oxidarse hasta ácidos carboxílicos), la conversión de un alcohol primario en aldehído puede ser complicada. Uno de los mejores y más convenientes reactivos para este propósito es el clorocromato de piridonio ($\text{C}_5\text{H}_5\text{NH}^+\text{CrO}_3^-$), que se obtiene por reacción entre ácido crómico y cloruro de piridinio, el cual da muy buenos rendimientos en la oxidación de alcoholes primarios a aldehídos:



Otros oxidantes como permanganato o dicromato producen sobre-oxidación del alcohol a ácido carboxílico y el complejo de cromo con piridina en un medio ausente de agua permite detener la oxidación en el aldehído.

Este tipo de reacciones de oxidación se encuentran ampliamente descritas en publicaciones de carácter científico tales como "Fast and Selective Oxidation of Primary Alcohols to Aldehydes or to Carboxylic Acids and of Secondary Alcohols to Ketones Mediated by Oxoammonium Salts under Two-Phase Conditions"⁴ y "Readily Accessible 12-14' Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones"⁵.

En cuanto a la **reacción C** debemos decir que, se resume a una simple y conocida reacción del tipo ácido-base en donde el compuesto de fórmula (I) responde como donador de un protón frente a la adición de una sal básica

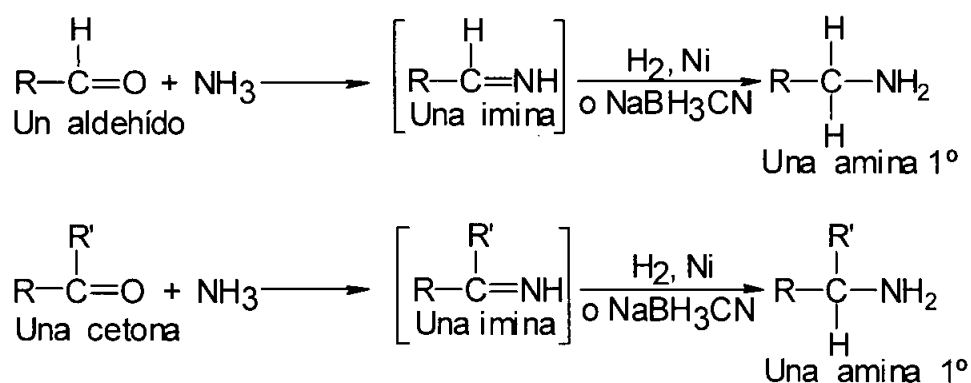
⁴ Pier Lucio Anelli, Carlo Biffi, Fernando Montanari, and Silvio Quici. J. Org. Chem. 1987,52,2559-2562.

⁵ Pier Lucio Anelli, Carlo Biffi, Fernando Montanari, and Silvio Quici. J. Org. Chem. 1983,48,4155-4156

lo suficientemente fuerte como para desprotonar el nitrógeno correspondiente al anillo de tetrazol de dicho compuesto de fórmula (I); esto resume la selección de las sales mencionadas por la solicitud en trámite a la verificación de sus correspondientes valores de pKa que aseguren que el equilibrio ácido-base se desplace hacia la forma desprotonada del anillo de tetrazol del compuesto de fórmula (IA), como cualquier persona medianamente versada en la materia tendría en cuenta.

La **reacción D** por su parte, corresponde a una reacción ampliamente conocida en el estado de la técnica, y denominada Aminación Reductiva^{6,7,8}; de tal manera que cualquier persona medianamente versada en la materia sabe que, muchos aldehídos (RCHO) y cetonas (R₂CO) se convierten en aminas por aminación reductiva, que es en si una reducción en presencia de amoníaco o aminas.

La aminación reductiva es un método de síntesis de aminas que permite obtener una amina 1°, 2°, 3° dependiendo de si parte de amoníaco o de una amina; esta reducción se logra catalíticamente o usando cianoborohidruro de sodio, NaBH₃CN y la reacción comprende la reducción de un compuesto intermediario (una imina, RCH=NH o R₂C=NH) que contiene un doble enlace carbono-nitrógeno:



⁶ T.W. Graham Solomons Fundamentos de Química Orgánica Traducción de Sanginez Franchini, Maria Segunda Edición México, Editorial Limusa, 1998 1215 p.

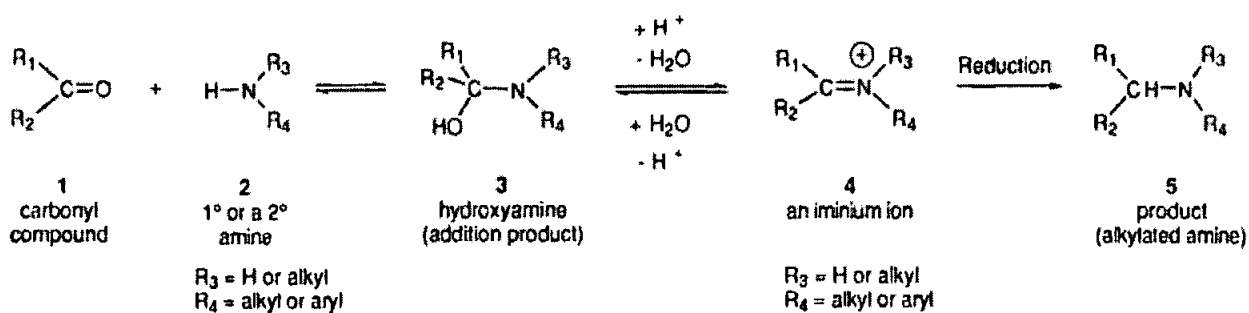
⁷ L.G. Wade Jr. Química Orgánica Traducción de Montaña Pedrero Ángel Manuel Quinta Edición España, Editorial Pearson Prentice Hall, 2006 1220 p.

⁸ <http://www.chem.ucalgary.ca/courses/351/Carey/Ch22/ch22-2-1-1.html>

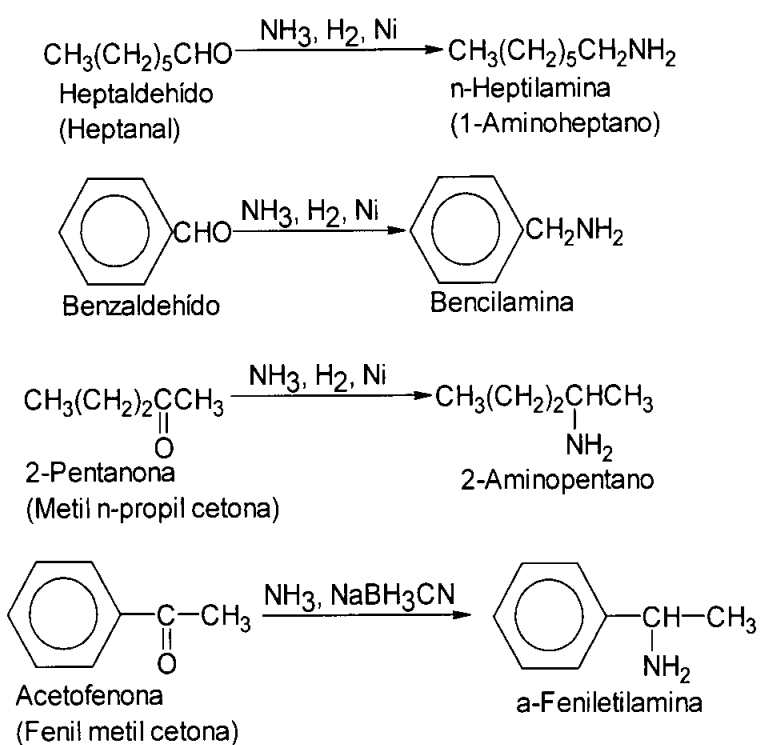
<http://webpages.ull.es/users/agalindo/LECCION15.pdf>

<http://dta.uta.cl/quimica/profesor/astudillo/Capitulos/capitulo26.htm>

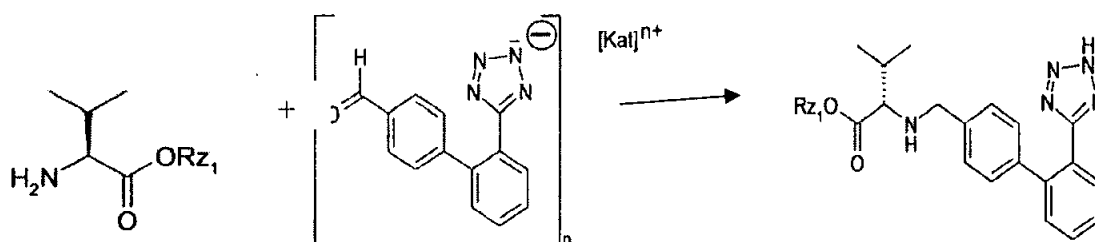
<http://webmail.fq.edu.uy/~organica/org101/teo22.pdf>



Es importante resaltar que la aminación reductiva se ha usado con éxito en una amplia variedad de aldehídos y cetonas alifáticas y aromáticas; por ejemplo:



Como se puede observar, este es el mismo caso en la reacción que se presenta en la solicitud colombiana en trámite:

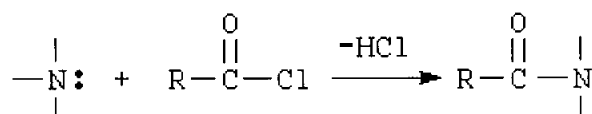
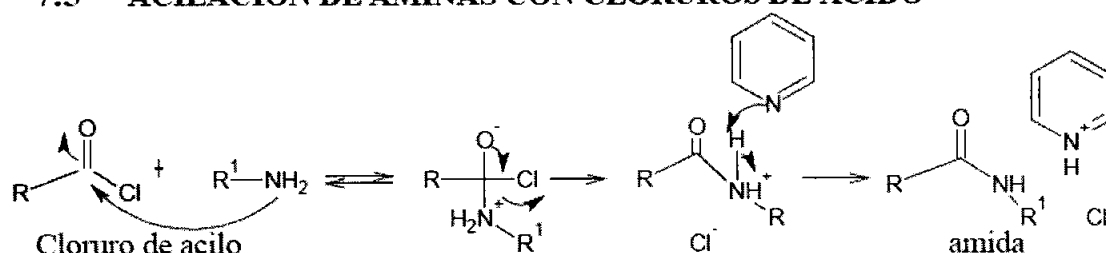


Las características fundamentales de este tipo de reacciones, tales como el mecanismo de acción, tipo de reactivos, tipos de productos, condiciones de reacción, aplicaciones y demás, se encuentran ampliamente descritas en

publicaciones de carácter científico tales como "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures"⁹; "Sodium borohydride on wet clay: Solvent-free reductive amination of carbonyl compounds using microwaves"¹⁰ e "Improved Procedures For The Conjugation Of Oligosaccharides To Protein By Reductive Amination"¹¹.

Por ultimo, la **reacción E** corresponde a una acilación convencional entre un grupo amino secundario y un compuesto con un "grupo activador" nucleófilo como pueden ser los haluros de ácido:

7.5 ACILACION DE AMINAS CON CLORUROS DE ÁCIDO



En donde, las aminas primarias y secundarias reaccionan con estos haluros de ácido para formar amidas las cuales generalmente no experimentan acilación posterior y se estabilizan por resonancia.

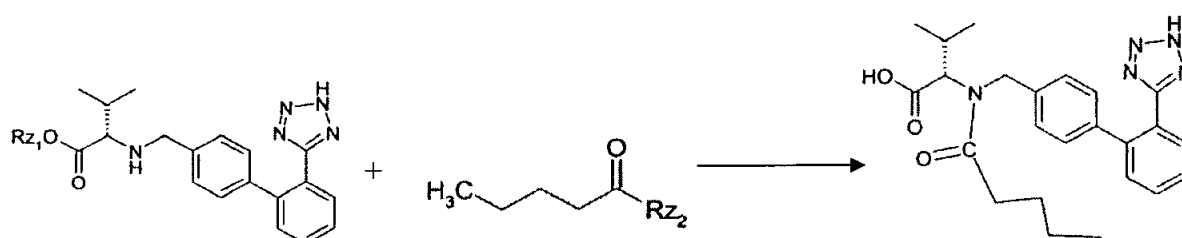
El mecanismo de acción de estas reacciones se reduce a la adición nucleofílica del nitrógeno de la amina sobre el carbono que sustenta el grupo carbonilo en el aldehído o la cetona, con la posterior pérdida de un ión haluro y un protón, que puede ser facilitada por la adición de piridina en el medio de reacción:

Como se puede observar, a este tipo de reacciones corresponde la mencionada por la solicitud colombiana en trámite:

⁹ Ahmed F. Abdel-Magid,* Kenneth G. Carson, Bruce D. Harris, Cynthia A. Maryanoff, and Rekha D. Shah. J. Org. Chem. 1996, 61, 3849-3862.

¹⁰ Rajender S. Varma, a and Rajender Dahiyab. Tetrahedron Volume 54, Issue 23, 4 June 1998, Pages 6293-6298.

¹¹ Roy R, Katzenellenbogen E, Jennings HJ. Can J Biochem Cell Biol. 1984 May;62(5):270-5.



En conclusión, se puede apreciar que cada uno de los pasos que componen el proceso de síntesis reivindicado por la solicitud colombiana en trámite corresponden a reacciones sencillas, reconocidas por cualquier persona medianamente versada en la materia y ampliamente descritas en el estado de la técnica; con lo cual queda evidentemente desvirtuado el nivel inventivo de dicha solicitud.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación internacional WO 2004/026847 publicada el 01 de abril de 2004 y titulada "PROCESS FOR THE MANUFACTURE OF VALSARTAN" paginas 1 a 5, 6, 25 a 27 y capitulo reivindicatorio.
- La publicación internacional WO 2005/014602 publicada el 17 de febrero de 2005 y titulada "PROCESS FOR THE PREPARATION OF TETRAZOLE DERIVATIVES FROM ORGANO BORON AND ORGANO ALUMINIUM AZIDES" capitulo reivindicatorio.
- Abstracts de todos los artículos científicos mencionados en el numeral 3.1 del acápite de la oposición.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

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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 2004/026847 A1

(54) Title: PROCESS FOR THE MANUFACTURE OF VALSARTAN

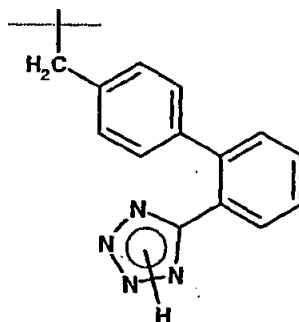
(57) Abstract: The present invention relates to a process for the manufacture of Valsartan, an angiotensin receptor blocker (ARB; also called angiotension II receptor antagonist or AT₁ receptor antagonist) and salts thereof, to novel intermediates and process steps.

PROCESS FOR THE MANUFACTURE OF VALSARTAN

The present invention relates to a process for the manufacture of an angiotensin receptor blocker (ARB; also called angiotension II receptor antagonist or AT₁ receptor antagonist) and salts thereof, to novel intermediates and process steps. ARBs can, for example, be used for the treatment of hypertension and related diseases and conditions.

The class of ARBs comprises compounds having different structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), and tasosartan (cf. EP539086), or, in each case, a pharmaceutically acceptable salt thereof.

All of these ARBs comprise the following common structural element:



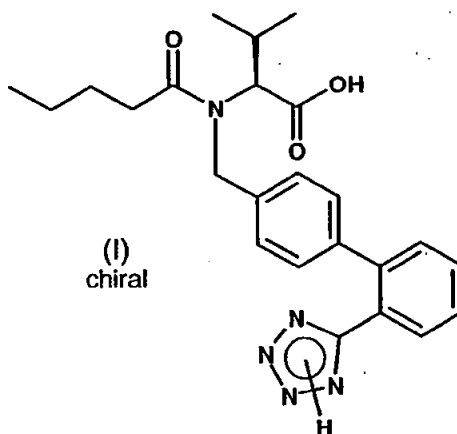
The formation of the tetrazole ring is a critical step in the manufacture of these compounds. Methods for the manufacture of ARBs having this structural feature include the formation of said tetrazole ring by starting from corresponding cyano derivatives that react with HN₃ or a suitable alkali metal salt thereof such as sodium azide or with an organotin azide such as tributyltin azide or with a silyl azide. The use of azides for forming the tetrazole ring system requires a sophisticated system to run the reaction in a safe way during an up-scaled production process. Accordingly, an objective is to develop alternative process variants that exclude the use of azides in the last steps of the production of corresponding ARBs.

The objective of the present invention is to provide a synthesis of compounds of formula (I) that (1) does not require a process step where an azide is used, (2) results in high yields, (3)

minimises pollution of the environment e.g. by essentially avoiding organotin compounds, (4) is economically attractive by using less reaction steps in the reaction sequence for the manufacture of compounds of formula (I), (5) affords enantiomerically pure target products and products of high crystallisability. In addition, as the tetrazole ring system is formed at an earlier stage of the reaction sequence, (6) the risk of contamination of the final product (and late intermediates) with trace amounts of tin components is much lower. Normally, the tetrazole ring is formed by reacting a corresponding cyano derivative with an organotin compound such as tributyl tin azide. For ecological reasons, the heavy metal tin and especially organotin compounds are to be handled with special care. Furthermore, (7) another objective of the present invention is to provide a process that can be carried out on a larger scale and can thus be used for a corresponding production process and to avoid e.g. racemisation and thus separation of any enantiomers.

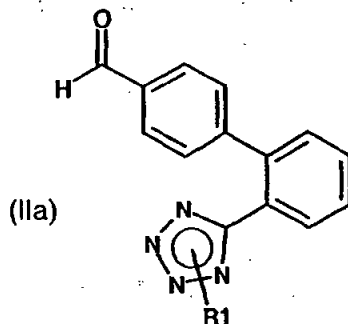
It has surprisingly been found that the process according to the present invention meets the above objectives.

The present invention relates to a process for the manufacture of the compound of formula (I)

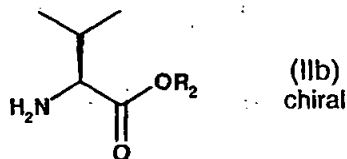


or a salt thereof, comprising

(a) reacting a compound of formula (II a)

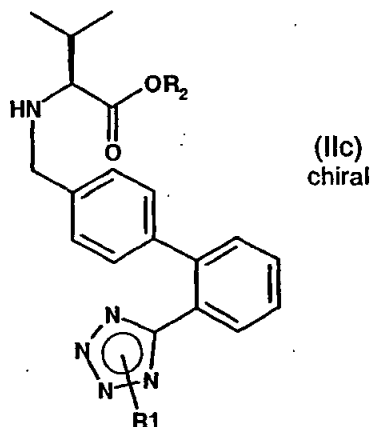


or a salt thereof, wherein R_1 is hydrogen or a tetrazole protecting group, with a compound of formula



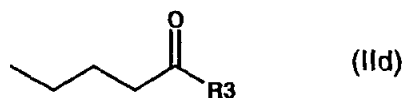
or a salt thereof, wherein R_2 represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination; and

(b) acylating a resulting compound of formula (II c)



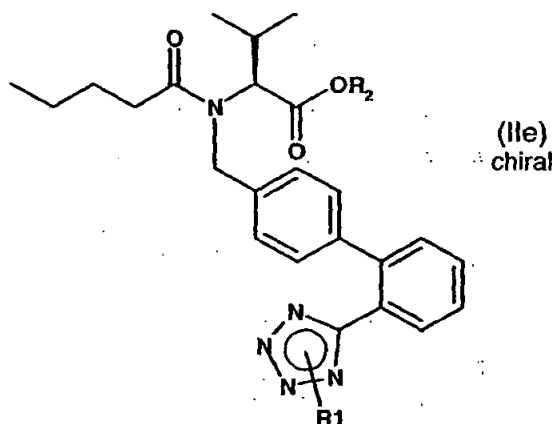
or a salt thereof with a compound of formula (II d)

- 4 -



wherein R_3 is an activating group; and,

(c) if R_1 and/or R_2 are different from hydrogen, removing the protecting group(s) in a resulting compound of formula (II e)



or a salt thereof; and

(d) isolating a resulting compound of formula (I) or a salt thereof; and, if desired, converting a resulting free acid of formula (I) into a salt thereof or converting a resulting salt of a compound of formula (I) into the free acid of formula (I) or converting a resulting salt of a compound of formula (I) into a different salt.

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10°C to about $+200^{\circ}\text{C}$, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Compounds of formulae (II a), (II b), (II c) and (II e), wherein either or both of R_1 and R_2 are hydrogen can form salts with bases, as both the unprotected tetrazole ring and the

unprotected carboxy group have acidic properties, while compounds of formulae (II b) and (IIc) can also form salts with acids.

A corresponding tetrazole protection group (R_1) is selected from those known in the art. Especially, R_1 is selected from the group consisting of tert-C₄-C₇-alkyl such as tert-butyl; C₁-C₂-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl or trityl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of tert-C₁-C₇-alkyl, hydroxy, C₁-C₇-alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and trifluoromethyl (CF₃); picolinyl; piperonyl; cumyl; allyl; cinnamoyl; fluorenyl; silyl such as tri-C₁-C₄-alkyl-silyl, for example, trimethyl-silyl, triethylsilyl or tert-butyl-dimethyl-silyl, or di-C₁-C₄-alkyl-phenyl-silyl, for example, dimethyl-phenyl-silyl; C₁-C₇-alkyl-sulphonyl; arylsulphonyl such as phenylsulphonyl wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C₁-C₇-alkyl, hydroxy, C₁-C₇-alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and CF₃; C₂-C₈-alkanoyl such as acetyl or valeroyl; and esterified carboxy such as C₁-C₇-alkoxy-carbonyl, for example, methoxy-, ethoxy- or tert-butyloxy-carbonyl; and allyloxycarbonyl. Examples of preferred protective groups which may be mentioned are tert-butyl, benzyl, p-methoxybenzyl, 2-phenyl-2-propyl, diphenylmethyl, di(p-methoxyphenyl)methyl, trityl, (p-methoxyphenyl)diphenylmethyl; diphenyl(4-pyridyl)methyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 2-tetrahydropyranyl, allyl, trimethylsilyl and triethylsilyl.

A corresponding carboxy protecting group (R_2) is selected from those known in the art. Especially, R_2 is selected from the group consisting of C₁-C₇-alkyl such as methyl, ethyl or a tert-C₄-C₇-alkyl, especially tert-butyl; C₁-C₂-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C₁-C₇-alkyl, hydroxy, C₁-C₇-alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and CF₃; picolinyl; piperonyl; allyl; cinnamyl; tetrahydrofuranyl; tetrahydropyranyl; methoxyethoxy-methyl, and benzyloxymethyl. A preferred example of protective groups which may be mentioned is benzyl.

The activating group R_3 is, for example, an activating group that is being used in the field of peptides, such as halogen such as chlorine, fluorine or bromine; C₁-C₇-alkylthio such as

26

methyl-thio, ethyl-thio or tert-butyl-thio; pyridyl-thio such as 2-pyridyl-thio; imidazolyl such as 1-imidazolyl; benzthiazolyl-oxy such as benzthiazolyl-2-oxy-; benzotriazol-oxy such as benzotriazolyl-1-oxy-; C₂-C₈-alkanoyloxy, such as butyroyloxy or pivaloyloxy; or 2,5-dioxo-pyrrolidinyl-1-oxy. Examples of an activating group which may be mentioned are ???

The general terms used hereinbefore and hereinafter have the following meanings, unless defined otherwise:

C₁-C₇-Alkyl is for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl residue. C₁-C₄-alkyl, especially methyl, ethyl or tert-butyl is preferred.

C₁-C₇-Alkoxy is for example methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy, or heptyloxy residue. C₁-C₄-alkoxy is preferred. Especially preferred is methoxy, ethoxy and tert-butoxy.

C₂-C₈-Alkanoyl in C₂-C₈alkanoyl-oxy is in particular acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C₂-C₅Alkanoyl is preferred. Especially preferred is acetyl or pivaloyl.

Halogen is in particular chlorine, fluorine or bromine, and in a broader sense includes iodine. Chlorine is preferred.

Step (a):

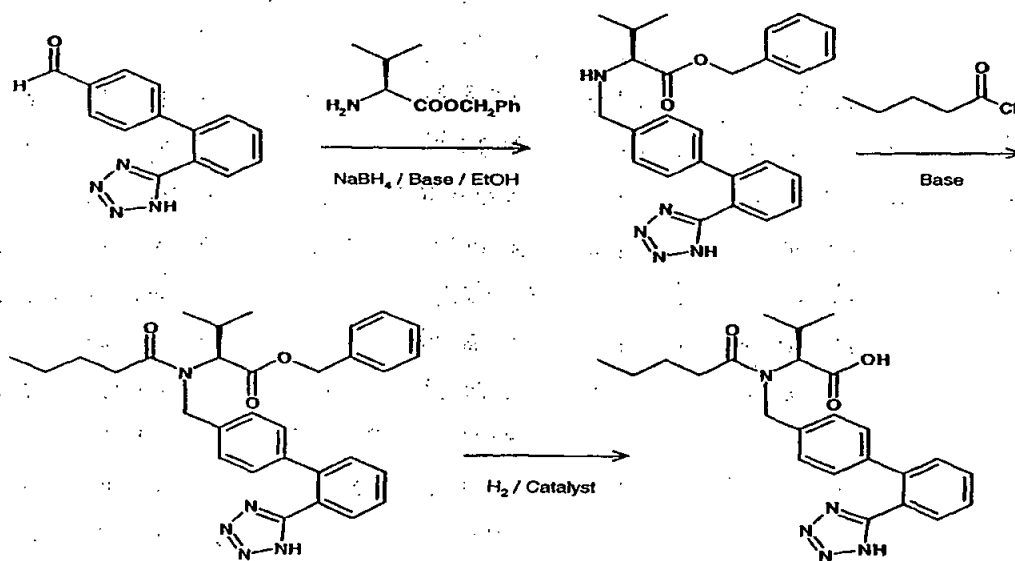
In reaction Step (a), the reductive amination is carried out in the presence of a reducing agent. A suitable reducing agent is a borohydride, which may also be in a complexed form, or hydrogen or a hydrogen donor both in the presence of a hydrogenation catalyst. Furthermore, a reducing agent is a suitable selenide or a silane.

A suitable borohydride or a complexed borohydride is, for example, an alkali metal borohydride such as sodium borohydride or lithium borohydride; an earth alkali metal borohydride such as calcium borohydride; an alkali metal cyanoborohydride, such as sodium cyanoborohydride or lithium cyanoborohydride, an alkali metal tri-(C₁-C₇-alkoxy)-borohydride such as sodium trimethoxy-ethoxy-borohydride; a tetra-C₁-C₇-alkylammonium-

g) and water (1.5 g) over 61 min. After stirring for 30 min. valerylchloride (5.3 g; 43.5 mmol) is added over 8 min., followed by slow addition over 30 min. of a mixture (4.3 g) of pyridine (3.4 g) and water (0.9 g). After each addition of pyridine the pH is controlled by sampling (hydrolyzed with water). The pH of the samples should always be below 2.5. The reaction is stirred for 25 min., then water (25.6 g) is added over 30 min. The mixture is stirred for another 30 min., then warmed to 23°C over 30 min. and stirred for another 2 hours. Adjustment of pH, remove of organic solvents by distillation, further work-up and crystallization is done as described in the example 1 c) above.

Example 2:

This example can be illustrated by means of the following reaction scheme:



a) Preparation of (S)-3-Methyl-2-([2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino)-butyric acid benzylester

L-Valin-benzylester tosylate (6.38 g, 16.8 mmol) in toluene (40 ml) is extracted with a solution of sodiumcarbonate (2.36 g, 22.0 mmol) in water (40 ml). The organic phase (contains L-valin benzylester free base is separated, and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (4.13 g, 16.0 mmol) and tri-n-propyl-amine (3.20 ml, 16.8 mmol) are added at room temperature. The resulting solution is evaporated at 50°C in vacuo (water is removed azeotropically). The residual oil (containing the intermediate imine is dissolved in absolute ethanol (40 ml), and sodium borohydride (0.68 g, 17.6 mmol) is added in portions within 10

minutes (min.) at 0-5°C. The resulting solution is stirred for 30 min at 0-5°C. After completion of the reaction, the reaction mixture is quenched with water (10 ml) and adjusted to pH 6-7 by addition of hydrochloric acid 2 M (16 ml, 32 mmol) at RT. Ethanol is distilled off from the reaction mixture at 50° in vacuo and the residual aqueous mixture extracted with toluene (60 ml). The organic phase is concentrated at 50°C in vacuo to approximately 50 % of the original volume by distillation (water and ethanol are azeotropically removed). The resulting concentrate (35 ml) containing (S)-3-methyl-2-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino]-butyric acid benzylester is used as it is as starting material for the subsequent acylation step.

b) Preparation of (S)-3-Methyl-2-{2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid benzylester

The solution of (S)-3-methyl-2-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino]-butyric acid benzylester (approximately 7.0 g, 16.0 mmol) in toluene (35 ml) from the previous step is diluted with toluene (35 ml). The clear solution is cooled to 0-5°C under anhydrous conditions, and N-ethyl-diisopropylamine (6.1 ml, 35.2 mol) and valeroylchloride (4.1 ml, 33.6 mmol) are added at this temperature. The reaction mixture is heated to 50°C within 30 min and agitated at 50°C for approximately 1 h and – after completion of the reaction – quenched by addition of methanol (10 ml) at 50°C. The clear solution is stirred for approximately 30 min at 50°C and finally cooled to RT. Water (30 ml) is added and the resulting two-phase system is adjusted to pH 2 by addition of hydrochloric acid 2.0 M (approximately 11 ml, 22 mmol). The organic phase is separated, extracted with water (30 ml) and concentrated at 50°C in vacuo to approximately 50 % of the original volume by distillation (water and methanol are azeotropically removed). The resulting concentrate in toluene (40 ml) is seeded at 40°C in order to start the crystallization and agitated at this temperature for approximately 1 hour (h). The suspension is gradually cooled to 0°C within 6-10 h. The solid is separated by filtration, washed with cold toluene (30 ml) and dried in vacuo at 50°C to give (S)-3-methyl-2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino)-butyric acid benzylester.

Melting point: 115 - 116°C

Enantiomeric excess (by HPLC): ee > 99.8 %

c) Preparation of (S)-3-Methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid

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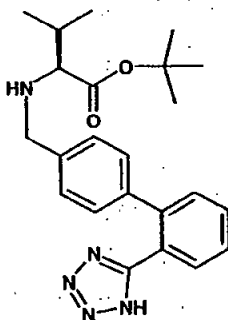
A solution of (S)-3-Methyl-2-[pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino]-butyric acid benzylester (10.6 g; 20.0 mmol) in Ethylacetate (43 ml) is hydrogenated at 4 bar / 50°C in presence of a wet palladium on charcoal catalyst 5% (1.12 g, containing 50 % water). After completion of the reaction (cease of hydrogen consumption) the catalyst is removed by filtration and the filtrate is concentrated at 45°C in vacuo (water is azeotropically removed). The crystallization of the product is initiated at 45°C and – after addition of cyclohexan (102 ml) – completed by cooling to –5°C. The solid is collected by filtration, and after drying at 50°C, (S)-3-methyl-2-[pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino]-butyric acid is received as a white powder.

Melting point: 108-110°C.

Enantiomeric excess (by HPLC): ee > 99.5 %.

Example 3:

a) Preparation of (S)-3-Methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid tert-butylester



To a suspension of L-valine tert-butylester hydrochloride (419.4 mg; 2 mmol) in 5 ml of isopropylacetate is added sodium carbonate (265 mg; 2.5 mmol) in 5 ml of water. After complete dissolution, the two phases are separated immediately. The aqueous layer is washed once with 4ml of isopropylacetate. The combined organic layers are washed with 5 mL of water. The colourless organic is dried over sodium sulfate, filtered, evaporated in vacuum and dried in high vacuum to give a colourless oil. The oil is dissolved in 4 ml of methanol. After addition of the 2'-(1H-tetrazol-2-yl)-biphenyl-4-carbaldehyde (515 mg; 2mmol) and triethylamine (0.278 ml; 2 mmol), the yellow solution is stirred for 5 minutes before evaporation in vacuum to give a yellow oil. After dissolution in 4 ml ethanol the solution is cooled to 0°C. Sodiumborohydride (78 mg; 2 mmol) is added in 4 portions with stirring until the imine dissapeared (HPLC). The slightly yellow solution is acidified from pH

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(54) Title: PROCESS FOR THE PREPARATION OF TETRAZOLE DERIVATIVES FROM ORGANO BORON AND ORGANO ALUMINIUM AZIDES

(57) Abstract: The present invention relates to a method for preparing substituted tetrazoles, compounds obtained according to this method, new reactants and new tetrazole derivatives.

PROCESS FOR THE PREPARATION OF TETRAZOLE DERIVATIVES FROM ORGANO BORON AND ORGANO ALUMINIUM AZIDES

The invention relates to a method for preparing substituted tetrazoles, compounds obtained according to this method, new reactants and new tetrazole derivatives.

Tetrazoles are structural elements, for example, of pharmaceuticals or agricultural compositions, foaming agents, automotive inflators, and the like. Especially mentioned are the class of so-called angiotensin II receptor antagonists also designated nowadays as angiotension receptor blockers (ARBs) that can be used e.g. for the treatment of hypertension and congestive heart failure. Most of said ARBs comprise as structural element a 5-tetrazole group.

It is known in the art that tetrazole derivatives can be prepared by reacting various nitriles with organic azides in relatively good yields. Representatives of corresponding azides are, for example, organo-tin azides which have some toxic profile. They have to be handled with special care in production processes, cause ecological problems and require a significant amount of additional process work to recycle them from the wastewater thereby additionally increasing the production costs. Tetrazole forming methods which use trialkylammonium azides or tetraalkylammonium azides may form volatile sublimates in the reaction reactors at higher temperatures which have the risk of explosion and are therefore not easy to handle in large scale production.

There is a strong need to develop process variants, new reagents and intermediates that avoid the above-mentioned disadvantages. Especially, a lot of effort has been made to substitute corresponding organo-tin azides with alternative agents which are viable alternatives in the production of tetrazoles with sufficiently high yields.

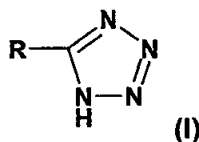
It has surprisingly been found that organo boron azides and organo aluminium azides can be used as alternatives to corresponding organo-tin compounds. Said boron and aluminium compounds are available in considerably large scales and are relatively inexpensive, especially corresponding aluminium compounds that are produced for the polymer industry (e.g. Ziegler-Natta catalysis). It has surprisingly turned out that high yields of tetrazoles can be achieved when using these organo azides to be used according to the present invention. Furthermore, as the corresponding boron and aluminium azides are not known to be toxic,

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their use does not require special care when recycling the waste water and moreover the dialkylmetal azides can be produced in a large scale at low costs and mild conditions. Even though, corresponding dialkyl boron and dialkyl aluminium azides have these advantages, they have not been described in the literature to be used in [2+3]cycloadditions with nitriles to form tetrazoles. What is known from the literature is that e.g. di-organyl aluminium azides can be used to open epoxides and also to form acyl-azides from esters. However, the use of di-organyl boron or di-organyl aluminium azides, respectively, to form tetrazoles with nitriles is fully surprising.

The present invention relates to the use of organo boron and organo aluminium azides, especially as defined below, for the manufacture of tetrazole derivatives.

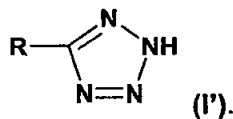
The present invention relates to a process for the manufacture of a tetrazole of formula



or a tautomer or a salt thereof, wherein R represents an organic residue; comprising

- (i) reacting a compound of formula **R-CN (II a)** with an azide of formula **(R₁)(R₂)M-N₃ (II b)**, wherein R has the meaning as defined above; R₁ and R₂, independently of another, represent an organic residue such as an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or a heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted; and M is boron or aluminium; and
- (ii) isolating the resulting compound of formula (I).

A tautomer of a compound of formula (I) is a compound of formula



A salt of a compound of formulae (I) or (I'), if the compounds of formulae (I) or (I') have, for example, at least one basic centre, can be an acid addition salt. This is formed, for example, with a strong inorganic acid, with a strong organic carboxylic acid, or with an organic sulfonic acid. A corresponding acid addition salt can also be formed, if desired, with any additionally present basic centre. If the compounds of formulae (I) or (I') have at least one acid group (for example COOH or 5-tetrazolyl) a salt with a base can be formed. A suitable salt with bases is, for example, metal salts, or a salt with ammonia or an organic amine. A corresponding internal salt may furthermore be formed.

The general definitions used above and below of the corresponding residues, unless otherwise defined below, have the following meanings:

An organic residue is, for example; an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of one another, being unsubstituted or substituted.

An aliphatic residue is, for example, alkyl, alkenyl or secondarily alkynyl, each of which can be interrupted by NH, substituted NH, O, or S; and each of which can be unsubstituted or substituted, for example, mono-, di- or tri-substituted.

Alkyl is, for example, C₁-C₂₀-alkyl, in particular C₁-C₁₀-alkyl. C₁-C₈-alkyl is preferred, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl.

Alkenyl is, for example, C₃-C₂₀-alkenyl, in particular C₃-C₁₀-alkenyl. Preferred is C₃-C₅-alkenyl; for example, 2-propenyl or 2- or 3-butenyl. Alkenyl is likewise C₂-C₂₀-alkenyl, in particular C₂-C₁₀-alkenyl. Preferred is C₂-C₅-alkenyl.

Alkynyl is, for example, C₃-C₂₀alkynyl, in particular C₃-C₁₀alkynyl. Preferred is C₃-C₅alkynyl such as propargyl. Alkynyl is likewise C₂-C₂₀alkynyl, in particular C₂-C₁₀alkynyl. Preferred is C₂-C₅alkynyl.

Alkyl, alkenyl or alkynyl that can be interrupted by NH, substituted NH, O or S is in particular C₁-C₂₀-alkoxy- C₁-C₂₀-alkyl, -C₃-C₂₀-alkenyl or - C₃-C₂₀-alkynyl, or C₃-C₂₀-alkenyloxy- C₁-C₂₀-

alkyl, -C₃-C₂₀-alkenyl or -C₃-C₂₀-alkynyl, for example, C₁-C₁₀-alkoxy-C₁-C₁₀-alkyl, -C₃-C₁₀-alkenyl or -C₃-C₁₀-alkynyl, or C₃-C₁₀-alkenyloxy-C₁-C₁₀-alkyl, -C₃-C₁₀-alkenyl or -C₃-C₁₀-alkynyl. Preferred is C₁-C₇-alkoxy-C₁-C₇-alkyl, -C₃-C₇-alkenyl or -C₃-C₇-alkynyl, or C₃-C₇-alkenyloxy-C₁-C₇-alkyl, -C₃-C₇-alkenyl or -C₃-C₇-alkynyl.

Substituted NH is, for example, NH which is substituted by C₁-C₈-alkyl such as methyl, ethyl or propyl, phenyl-C₁-C₈-alkyl such as benzyl or 2-phenethyl, or by acyl, such as C₂-C₈-alkyl-alkanoyl, phenyl-C₂-C₈-alkanoyl, benzoyl, C₁-C₈-alkanesulfonyl or benzenesulfonyl.

An alicyclic residue is, for example, mono-, bi- or polycyclic. Preferred is cycloalkyl and secondarily cycloalkenyl, each of which can also be substituted.

Cycloalkyl in particular C₃-C₈cycloalkyl. Preferred is cyclopentyl and cyclohexyl.

Cycloalkenyl is in particular C₃-C₇cycloalkenyl and is preferably cyclopent-2- and -3-enyl, or cyclohex-2- and -3-enyl.

A heteroalicyclic residue is, for example, an alicyclic residue, wherein at least one carbon atom is replaced by a heteroatom, e.g. NH, substituted NH, O, or S, each of which can also be substituted.

An alicyclic aliphatic residue is, for example, alkyl, alkenyl or alkynyl that is substituted by cycloalkyl or by cycloalkenyl. Preferred is C₁-C₈-alkyl, C₂-C₈-alkenyl or C₂-C₈-alkynyl each of which is substituted by C₃-C₈-cycloalkyl or by C₃-C₈-cycloalkenyl, especially cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, or cyclohexenyl-methyl.

A heterocyclic aliphatic residue is, for example, C₁-C₈-alkyl, C₂-C₈-alkenyl or C₂-C₈-alkynyl each of which substituted by C₃-C₈cycloalkyl or by C₃-C₈-cycloalkenyl wherein one carbon atom of C₃-C₈cycloalkyl or by C₃-C₈-cycloalkenyl, respectively, is replaced by NH, substituted NH, O, or S, especially piperidino-methyl or -ethyl.

A carbocyclic aromatic residue is, for example, a mono- or polycyclic (such as bicyclic) or benzoannellated carbocyclic residue, such as phenyl, naphthyl, but also biphenyl, each of which can also be substituted.

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A heterocyclic aromatic residue is, for example, 5- or 6-membered and monocyclic radical which has up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom, each of which can also be substituted. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl.

An araliphatic residue is, for example, C₁-C₈-alkyl, C₂-C₈-alkenyl or C₂-C₈-alkynyl each of which is substituted by phenyl or by naphthyl, especially benzyl, 2-phenethyl or 2-phenylethenyl.

A heteroaraliphatic residue, is for example, C₁-C₈-alkyl, C₂-C₈-alkenyl or C₂-C₈-alkynyl each of which is substituted by pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl, especially pyridylmethyl.

Alkyl, alkenyl, or alkynyl can also be substituted, for example, by a substituent selected from the group consisting e.g. of an alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen, amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

Alicyclic or heteroalicyclic residues can also be substituted, for example, by one or more, e.g. two or three, substituents selected from the group consisting e.g. of an aliphatic residue, alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

An alicyclic-aliphatic residue, a heteroalicyclic-aliphatic residue, an araliphatic residue or a heteroaraliphatic residue, each residue (e.g. in both the alicyclic and the aliphatic moiety),

independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents in both structural elements, for example, selected from the group consisting of an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic aromatic residue, a heterocyclic aromatic residue; an araliphatic residue; an heteroaraliphatic residue, halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

A carbocyclic or a heterocyclic aromatic residue can also be substituted, for example, by one or more, e.g. two or three, substituents selected from the group consisting e.g. of an aliphatic residue, alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

Substituents of an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, can likewise be acetalized formyl.

Halogen is in particular halogen of atomic number not more than 53, such as fluorine, chlorine, bromine and iodine.

Substituted mercapto is, for example, substituted by an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

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Etherified hydroxy is, for example, hydroxy etherified by an aliphatic, an alicyclic, heteroalicyclic, an araliphatic, a heteroaryl-aliphatic, a carbocyclic aromatic or heteroaromatic alcohol, each of which can also be substituted.

Esterified carboxy is, for example, carboxy which is esterified by an alcohol which is derived from an aliphatic or araliphatic hydrocarbon radical, such as alkyl, phenyl-alkyl, alkenyl and secondarily alkynyl, and which may be interrupted by -O-, such as alkoxy-alkyl, -alkenyl and -alkynyl. Examples which may be mentioned are C₁-C₇alkoxy-, phenyl-C₁-C₇alkoxy-, C₂-C₇alkenyloxy- and C₁-C₇alkoxy-C₁-C₇alkoxy-carbonyl.

Amidated carboxyl is, for example, carbamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by an aliphatic or araliphatic hydrocarbon radical or disubstituted by a divalent aliphatic hydrocarbon radical which may be interrupted by O or may be condensed at two adjacent carbon atoms with a benzene ring, in particular alkylene or lower alkyleneoxy-alkylene. Examples of appropriately substituted amino groups which may be mentioned are C₁-C₇alkyl-, C₂-C₇alkenyl-, C₂-C₇alkynyl-, phenyl-C₁-C₇alkyl-, phenyl-C₂-C₇alkenyl-, phenyl-C₂-C₇alkynyl-, di-C₁-C₇alkyl-, N- C₁-C₇alkyl-N-phenyl-C₁-C₇alkyl- and diphenyl-C₁-C₇alkylamino and also quinol-1-yl, isoquinol-2-yl, C₁-C₇alkylene- and C₁-C₇alkyleneoxy-C₁-C₇alkylene-amino.

Alkylene is, for example, C₁-C₁₀alkylene, in particular, C₁-C₇alkylene, for example methylene, ethylene, or 1,5-pentylene. Corresponding alkylene may also be branched.

Substituted amino has the meanings indicated in connection with substituted carbamoyl and is furthermore acylamino, such as C₂-C₈-alkanoyl-, phenyl-C₂-C₅-alkanoyl-, benzoyl-, C₁-C₈-alkanesulfonyl- or benzenesulfonylamino.

Acetalised formyl is, for example, di-alkoxymethyl or oxy-alkyleneoxymethylene. Most preferred is branched oxy-alkylene-oxy-methylene wherein the alkylene group is branched such as oxy-2,3-butylene-oxy-methylene or oxy-2,3-di-methyl-2,3-butylene-oxy-methylene.

Alkanoyl is, for example, C₂-C₁₀alkanoyl and is in particular C₂-C₇alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C₂-C₅alkanoyl is preferred.

Haloalkylsulfamoyl is in particular halo-C₁-C₁₀alkanesulfamoyl and is in particular C₂-C₇alkanesulfamoyl, for example, trifluoromethane-, difluoromethane-, 1,1,2-trifluoroethane- or heptafluoropropanesulfamoyl. Halo-C₁-C₄alkanesulfamoyl is preferred.

Pyrrrolyl is, for example, 2- or 3-pyrrrolyl. Pyrazolyl is 3- or 4-pyrazolyl. Imidazolyl is 2- or 4-imidazolyl. Triazolyl is, for example, 1,3,5-1H-triazol-2-yl or 1,3,4-triazol-2-yl. Tetrazolyl is, for example, 1,2,3,4-tetrazol-5-yl, furyl is 2- or 3-furyl and thienyl is 2- or 3-thienyl, while suitable pyridyl is 2-, 3- or 4-pyridyl or corresponding N-oxido-pyridyl.

Alkoxy is, for example, C₁-C₂₀alkoxy, in particular C₁-C₁₀alkoxy. Preferred is C₁-C₇alkoxy, most preferred C₁-C₄alkoxy such as methoxy, ethoxy, n-propyloxy or tert-butyloxy.

Substituents of residues as mentioned above and below should preferably not comprise those substituents that interfere with the reactants.

Preferred R is selected from the group consisting of phenyl or of pyridyl each of which is unsubstituted or substituted by a substituent selected from the group consisting of halogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxyl, hydroxyl-C₁-C₇alkyl, halo-C₁-C₇alkyl such as CF₃, formyl, di-C₁-C₇alkoxy-methyl, and C₂-C₇alkylene-methyl; of C₃-C₇cycloalkyl; of C₃-C₇cycloalkenyl; of biphenyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxyl, hydroxyl-C₁-C₇alkyl, halo-C₁-C₇alkyl such as CF₃, formyl, di-C₁-C₇alkoxy-methyl, and C₂-C₇alkylene-methyl, for example 4'-C₁-C₄alkyl-biphenyl-2-yl, 4'-hydroxy-C₁-C₄alkyl-biphenyl-2-yl, 4'-halo-C₁-C₄alkyl-biphenyl-2-yl, 4'-formyl-biphenyl-2-yl, 4-di-C₁-C₄alkoxy-methyl, or C₂-C₅alkylene-methyl; of C₁-C₇alkyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, of phenyl; of phenylsulphonyl, of

phenylsulphinyl, and of phenylmercapto, phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxyl, hydroxyl-C₁-C₇alkyl, and halo-C₁-C₇alkyl such as CF₃; of carboxy, and of N-phenyl-N-C₁-C₇alkyl-amino phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxyl, hydroxyl-C₁-C₇alkyl, and halo-C₁-C₇alkyl such as CF₃; and of C₂-C₇alkenyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, of phenyl; of carboxy, and of N-phenyl-N-C₁-C₇alkyl-amino phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C₁-C₇alkyl, C₁-C₇alkoxy, hydroxyl, hydroxyl-C₁-C₇alkyl, and halo-C₁-C₇alkyl such as CF₃.

Specifically preferred R is selected from the group consisting of halophenyl such as 2-, 4-chlorophenyl, 2-fluorophenyl; of hydroxyphenyl such as 2-hydroxyphenyl; of CF₃-phenyl such as 2-CF₃-phenyl; of halo-pyridyl such as 2-chloro-5-pyridyl; of hydroxy-pyridyl such as 2-hydroxy-5-pyridyl; of biphenyl that is substituted by C₁-C₄alkyl, halo-C₁-C₄alkyl, hydroxyl-C₁-C₄alkyl, or formyl; of phenyl-C₂-C₄alkenyl; of 1-carboxy-2-phenyl-C₂-C₄alkenyl, such as 4'-methyl-biphenyl-2-yl, 4'-bromomethyl-biphenyl-2-yl, 4'-formyl-biphenyl-2-yl, or 4-hydroxymethyl-biphenyl-2-yl; of carboxy-C₁-C₄alkyl, for example, carboxy-methyl; of phenylsulphonyl-C₁-C₄alkyl such as phenylsulphonyl-methyl; of phenylmercapto-C₁-C₄alkyl such as phenylmercaptomethyl; of C₃-C₆-cycloalkyl such as cyclopropyl or cyclobutyl; of C₃-C₆-cycloalkenyl such as 1-cyclohexenyl; and of N-phenyl-N'-C₁-C₄alkyl-amino-C₁-C₄alkyl such as 2-(N-phenyl-N'-methyl-amino)-methyl.

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example, in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Preferably, a compound of formula (II a) is used, wherein substituents of variable R do not interfere during the reaction with a compound of formula (II b).

A compound of formula (II a) is preferably a corresponding compound, wherein R is as defined above.

A preferred azide of formula $(R_1)(R_2)M-N_3$ (II b) is a corresponding compound, wherein M is aluminium or boron, R_1 and R_2 , independently of one another, is C_1 - C_8 -alkyl such as methyl, ethyl, propyl, diisobutyl, tert-butyl or n-octyl; C_3 - C_7 -alkenyl such as allyl or crotyl, C_3 - C_7 -cycloalkyl such as cyclohexyl; phenyl- C_1 - C_4 -alkyl such as benzyl or 2-phenethyl; phenyl- C_3 - C_5 -alkenyl such as cinnamyl, or C_3 - C_8 -cycloalkyl- C_1 - C_8 -alkyl such as cyclopropylmethyl or cyclohexylmethyl. Likewise, R_1 and R_2 , independently of one another, is phenyl- C_2 - C_5 -alkenyl.

Especially preferred azides are those as mentioned in the Examples.

The molar ratio of an azide of formula (II b) and a nitrile of formula (II a) is in a range from 5 to 1, preferably, from 3 to 1, most preferably, from 1,8 to 1 or from 1,2 to 1.

An inert solvent, diluent or mixture thereof should be selected which means that it cannot react with the starting material or intermediates. A suitable solvent is, for example, selected from the group consisting of aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an C_5 - C_{10} -alkane e.g. heptane, a cycloalkane such as cyclohexane; and alkylated C_3 - C_7 -cycloalkane such as methyl-cyclohexane or 1,3-dimethyl-cyclohexane, an alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene; a halogenated aromatic solvent such as chlorobenzene, o-, m- or p-chlorotoluene, dichlorobenzene, and trifluoromethylbenzene which may be further substituted e.g. by C_1 - C_7 -alkyl or C_1 - C_7 -alkoxy; and a halogenated hydrocarbon, for example, a halogenated aromatic compound, such as chlorobenzene. A further solvent may be an ether, such as tetrahydrofuran. Furthermore, a suitable solvent, diluent or mixture thereof should have a boiling point that is high enough to be used under the reaction conditions.

Preferred solvents or diluents are aliphatic hydrocarbons, for example, C₆-C₉alkanes such as heptane or n-octane; aromatic hydrocarbons, for example, phenyl substituted by C₁-C₄alkyl such as toluene or xylene, or mixtures thereof.

The reaction temperature is preferred in the temperature range of from room temperature to the boiling point of the solvent, diluent or mixture thereof, for example, a reaction temperature range is from about 20°C to about 170°C, preferably, from about 60°C to about 130°C or to about 140°C, depending on the reactivity and combination of the reactants. A person skilled in the art is fully enabled to select corresponding suitable solvent and diluent systems and reaction conditions adapted to the choice of the solvent system and reactants.

The reaction is most preferably carried out under anhydrous conditions.

In a preferred embodiment of the present invention, the invention is carried out in a temperature range of from 80°C to 120°C, preferably between 90°C and 110°C.

The isolation step is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (I), (IV), (IV c), (V), (VI), (VII), or (VII'), respectively, or a tautomer or salt thereof, from the reaction mixture or by chromatography of the reaction mixture, such as by crystallizing the resulting compound from the reaction mixture – if desired or necessary after work-up, especially by extraction - or by chromatography of the reaction mixture. Reference in this context is also made to the working examples.

Compounds of formula (II a) are either known or can be prepared using methods known in the art.

Preferred are compounds of formula (II a), wherein R represents a carbocyclic or heterocyclic residues.

The present invention likewise relates to a compound of formula (II b). Preferred compounds of formula (II b) are those, wherein R₁ and R₂, independently of one another, are C₁-C₁₀alkyl, C₃-C₈alkenyl, C₃-C₈-cycloalkyl, alkylated C₃-C₈-cycloalkyl or ar-C₁-C₅alkyl,

especially methyl, ethyl, isopropyl, butyl, isobutyl, octyl, allyl, cyclopropyl, cyclopentyl, cyclohexyl, methyl-cyclohexyl, or benzyl.

Azides of formula (II b) can be prepared, for example, by reacting a compound of formula $(R_1)(R_2)M-X$ (II c), wherein M is aluminium or boron, R_1 and R_2 have the meanings as defined above and X is a leaving group e.g. halogen, such as fluoride, chloride, bromide or iodide; or a sulphonate, such as an alkane sulfonate e.g. methanesulphonate; a halogenated alkane sulfonate e.g. trifluoromethansulfonate, an aromatic sulphonate e.g. tosylate; with an azide, preferably an alkaline metal azide, such as a lithium, sodium or potassium azide.

The formation of an azide of formula (II b) is carried out, in particular, in the presence of an inert solvent or diluent or a mixture thereof, in a temperature range of 0°C to 120°C. The reaction is most preferably carried out under anhydrous conditions.

Preferred azides comprise compounds of formula (II b), wherein R_1 and R_2 , independently of one another, represent C_1 - C_8 -alkyl such as ethyl, iso-propyl, n-propyl, n-butyl, sec-butyl, tert-butyl or n-octyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_8 -alkyl or aryl- C_1 - C_8 -alkyl such as benzyl or 2 phenethyl; and M is boron or aluminium. Corresponding representatives are dimethyl aluminium azide, diethyl aluminium azide, diisopropyl aluminium azide, dipropyl aluminium azide, diisobutyl aluminium azide, dibutyl aluminium azide, dicyclohexyl aluminium azide, diethyl boron azide, diisopropyl boron azide, dipropyl boron azide, diisobutyl boron azide, dibutyl boron azide or dicyclohexyl boron azide, furthermore diaryl boron azide such as diphenyl boron azide.

It might be that, dependent on the kind of substituents, reactive substituents could also react with the azide. For example, an aromatic hydroxy group or a benzylic hydroxyl group may react with an azide of formula (II b), however, the resulting hydroxy function masked by a metal or by an organo metal group can be split with e.g. an acid resulting in a compound of formula (I); accordingly, in this situation, a higher amount of a compound of formula (II a) needs to be used. An ester group might form an acyl-azide with a compound of formula (II b), while an epoxy ring structure might be opened with an compound of formula (II b). However, the person skilled in the art would be able to either directly anticipate that starting compounds with specific reactive substituents could not be used, as these substituents might react with the azide instead of the cyano function, or the person skilled in the art

would, when corresponding side reactions are realized, protect corresponding reactive groups and later on split-off the corresponding protecting groups by using conventional methods known per se.

The process of the present invention likewise comprises protecting reactive substituents of compounds of formulae (II a) and (II b) and, after formation of the tetrazole ring, splitting-off the corresponding protective group(s), especially by using conventional methods known per se e.g. by the person skilled in the pertinent art who is familiar with protecting and de-protecting functional groups.

In a preferred embodiment of the present invention, before the reaction of a compound of formula (II a) with a compound of formula (II b), a compound of formula (II a) wherein R comprises a reactive group that can be protected against the reagent of formula (II b) can be protected. Then a resulting protected compound is reacted as described herein with a compound of formula (II b) and from a resulting compound the protecting groups is split off resulting in a compound of formula (I) or a tautomere thereof. This principle can likewise be applied to the manufacture of a compound of formulae (IV), (V), (VI), respectively.

In a preferred embodiment of this variant, OH groups, such as aromatic e.g. phenolic or benzylic OH groups, can be either masked or protected, respectively. A corresponding OH group can be masked, for example, by treatment with a compound of formula (II d) $M'(R_3)_n$ wherein M' represents a suitable element of groups 1a, 2a, 3a, and 4 a of the Periodic Table of Elements, especially an element selected from the group consisting of Li, Na, K, Mg, Ca, B, Al, and Si; R_3 , independently of one another, is hydrogen, a leaving group such as halogen e.g. chlorine or bromine, NH_2 , alkyl such as C_1 - C_8 -alkyl, cycloalkyl such as C_3 - C_7 -cycloalkyl e.g. cyclopropyl or cyclohexyl, carbocyclic aryl such as phenyl or substituted phenyl, carbocyclic aryl-alkyl such as phenyl- C_1 - C_4 -alkyl e.g. benzyl or 1- or 2-phenethyl, C_1 - C_8 -alkoxy such as methoxy, ethoxy, isopropoxy, tert-butoxy, n-octyloxy, and the index "n" corresponds to the valence of the element M'. R_3 can only represent one leaving group such as halogen.

A preferred compound of formula (II d) comprises corresponding alkaline metal hydride or amide such as NaH, KH, $NaNH_2$, KNH_2 , CaH_2 and MgH_2 , a corresponding alkaline metal

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organyl, for example, M'-C₁-C₈-alkyl such as isobutyl-Li, butyl-Li, isobutyl-Li, tert-butyl-Li, n-hexyl-Li, n-hexyl-Li.

A preferred compound of formula (II d) comprises a corresponding alkaline metal alcoholate such as sodium or potassium C₁-C₅-alkanolate.

A preferred compound of formula (II d) comprises a corresponding C₁-C₈-alkyl, C₃-C₇-cycloalkyl, phenyl or substituted phenyl organyl formed with B or Al such as trimethyl-Al, triethyl-Al, or a corresponding C₁-C₈-alkoxy organyl formed with B or Al such as trimethoxy-B, triethoxy-B, triisopropoxy-B, tri-butyloxy-B and tri-n-butyloxy-B.

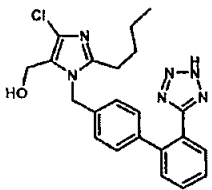
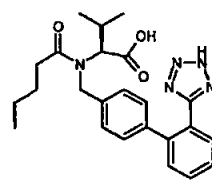
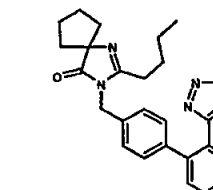
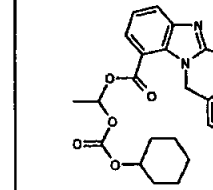
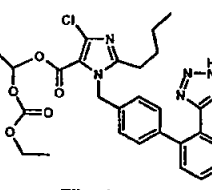
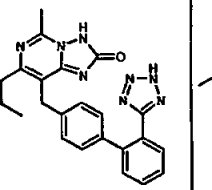
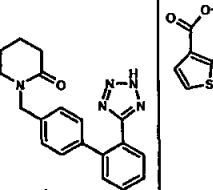
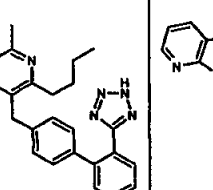
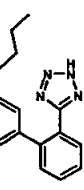
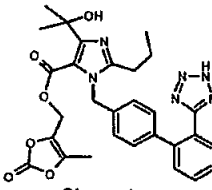
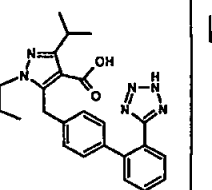
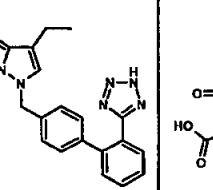
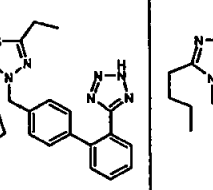
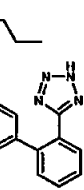
A preferred compound of formula (II d) comprises a corresponding halide of C₁-C₈-alkyl, phenyl-C₁-C₄-alkyl, C₃-C₇-cycloalkyl, phenyl or substituted phenyl organyl formed with Si such as trimethyl-Si-chloride, triethyl-Si-chloride, tribenzyl-Si-chloride, tert-buty-diphenyl-B-chloride, and triphenyl-Si-chloride.

Most preferred is LiH, but also trimethyl-Al and triethyl-Al.

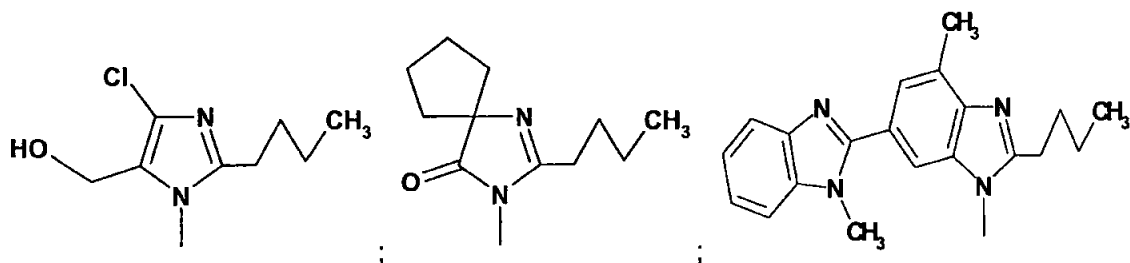
A reactive group of a compound of formula (II a), for example, a corresponding OH group, can also be protected, for example, by a suitable OH protecting group.

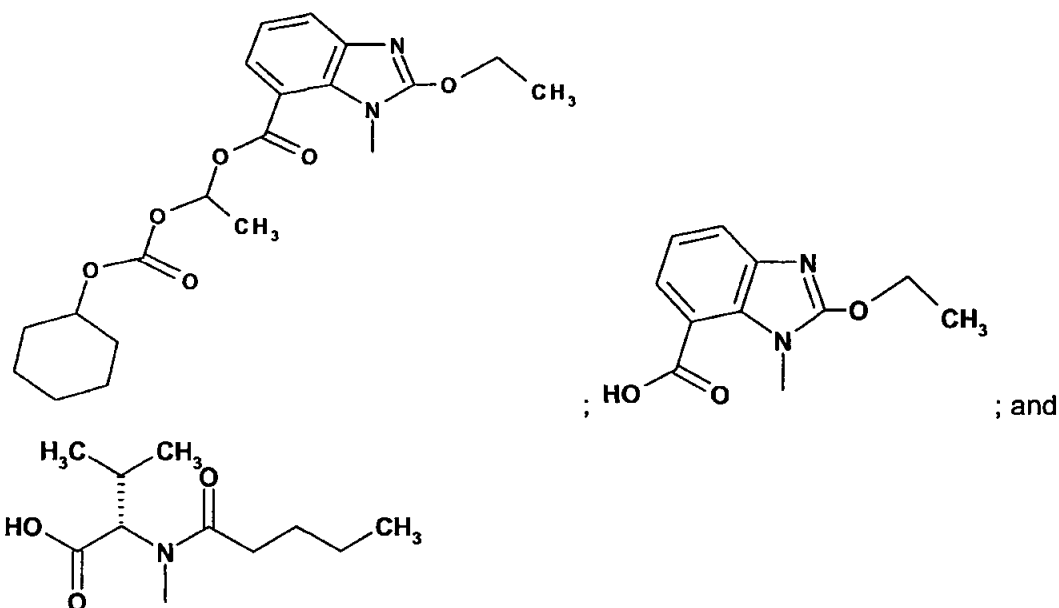
Most angiotensin II receptor antagonists have two essential structural elements, the so-called "core element" and the "pharmacophore element".

Examples for corresponding angiotensin II receptor antagonists can be taken from following table:

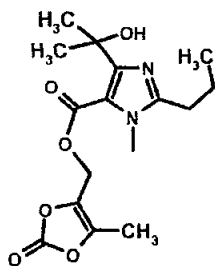
 Losartan (MSD)	 Valsartan (Novartis)	 Irbesartan (Sanofi, BMS)	 Candesartan-Cilexetil (Takeda)	
 Elosartan (Hafslund, Nycomed)	 Risperartan (BMS)	 Tasosartan (Wyeth-Ayerst)	 Milfasartan (Lusofarmaco, Menarini)	 FK-739 (Fujisawa)
 Olmesartan (Sankyo, Recordati)	 UR-7247 (Urfach)	 YM-358 (Yamanouchi)	 KRH-94 (Kissel)	 SC-52458 (Searle)

The core part of angiotensin II receptor antagonists comprises e.g. core elements derived from above table, for example, following structural elements:

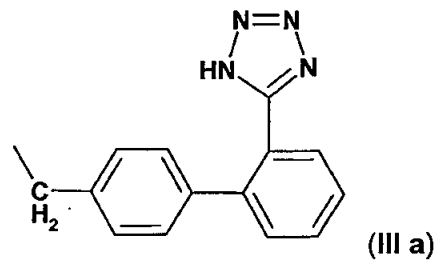




A further preferred core part of an angiotensin II receptor antagonist has following structure:

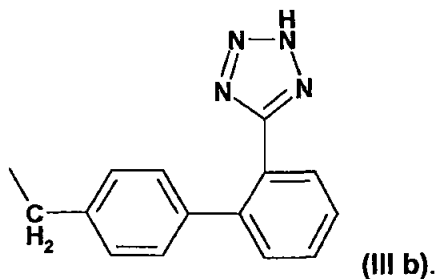


The pharmacophore element of corresponding angiotensin II receptor antagonists is represented by formula

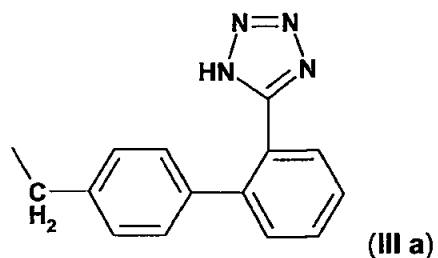


or is a tautomeric form thereof.

A tautomeric form of the side chain of formula (III a) is represented by formula (III b)

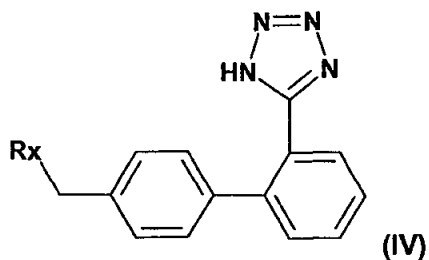


The present invention likewise relates to a process for the manufacture of said angiotensin II receptor antagonists having as structural feature side the chain of formula (III a) is represented by formula



or a tautomeric form thereof, especially of . angiotensin II receptor antagonists as shown in above table.

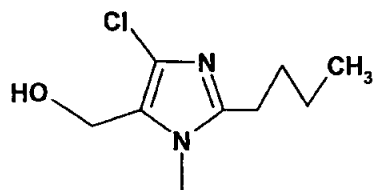
The present invention likewise relates to a process for the manufacture of said angiotensin II receptor antagonists having as structural feature a tetrazol ring, e.g. of formula (IV),



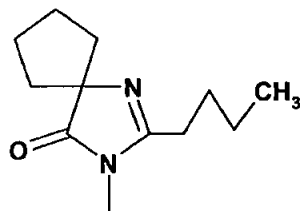
or a tautomeric form thereof, wherein Rx represents a structural element corresponding to the relevant "core elements" derived from the above table, especially a structural element selected from the group consisting of

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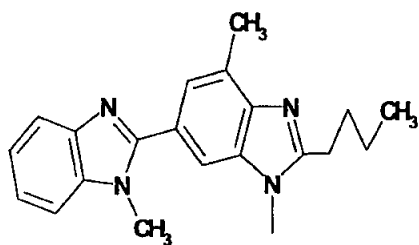
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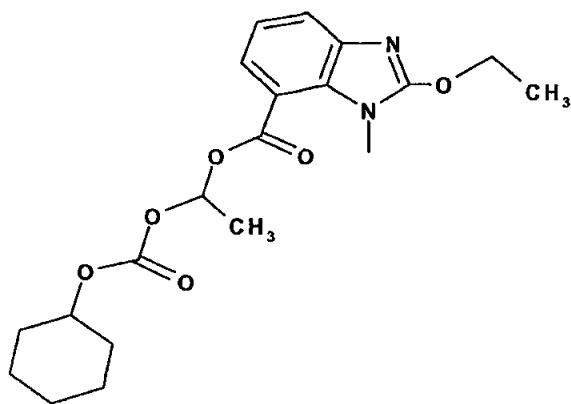
(derived from losartan - cf. EP 253310);



(derived from irbesartan - cf. EP 454511);



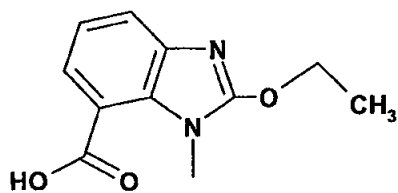
(derived from UR-7247);



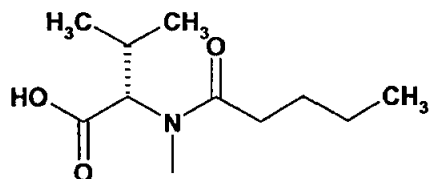
(derived from candesartan-cilexetil- EP

459136);

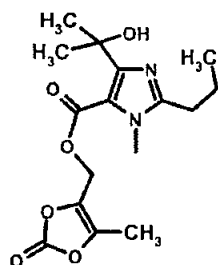
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(derived from candesartan); and



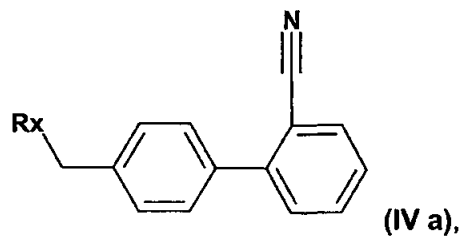
(derived from valsartan - cf. EP 443983);



(derived from olmesartan - cf. EP 503785)

or, in each case, a salt thereof.

This process is characterized by reacting a compound of formula (IV a)

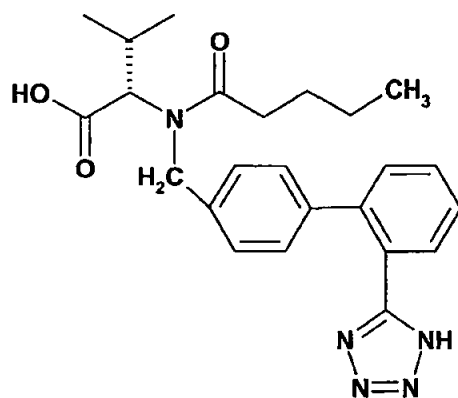


wherein Rx has the meanings as given above,

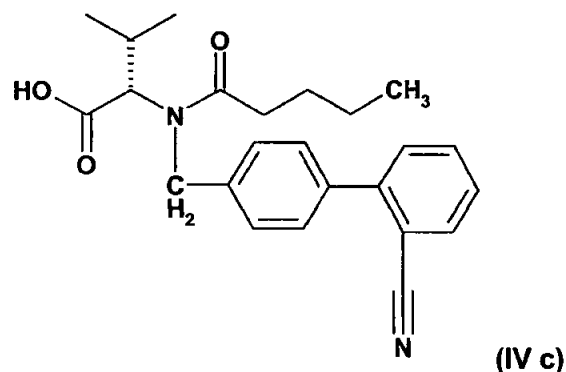
with a compound of formula $(R_1)(R_2)M-N_3$ (II b'), wherein R_1 and R_2 , independently of one another, represent an organic residue; and isolating the resulting compound of formula (IV).

A preferred angiotensin II receptor antagonist is the compound of formula

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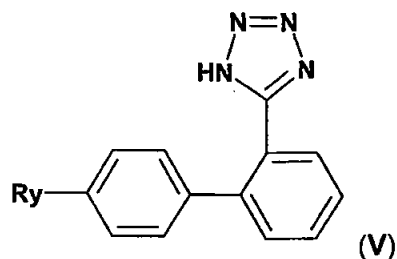
A preferred variant of the process according to the present invention for the manufacture of a compound of formula (IV b) is characterized by reacting a compound of formula (IV c)



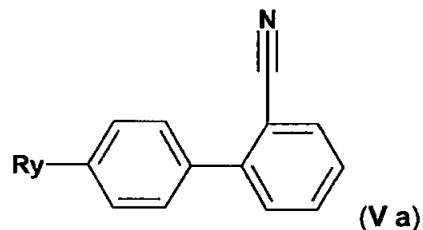
or an ester thereof with an azide of formula $(R_1)(R_2)M-N_3$ (IIb), wherein R_1 and R_2 , independently of each other, have the meanings as defined above, and isolating the compound of formula (IV b).

An ester of a compound of formula (IV c) is, for example, an ester derived from an aliphatic, araliphatic, cycloaliphatic, cycloaliphatic-aliphatic or aromatic alcohol. Preferred is a C_1 - C_7 alkyl ester or a aryl- C_1 - C_2 -alkyl ester, most preferred a benzylester thereof.

A preferred embodiment of the present invention is a process for the manufacture of a compound of formula



a tautomeric form thereof wherein Ry represents C₁-C₈-alkyl such as methyl; C₁-C₈-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, or an acetal of formyl; and X₁ being in a benzylic position, comprising reacting a compound of formula (IV a)

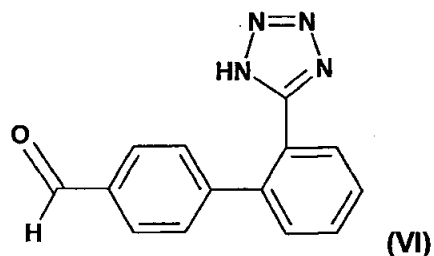


with a compound of formula (R₁)(R₂)-M-N₃ (II b), wherein R₁ and R₂, independently of one another, represent an organic residue; and isolating the resulting compound of formula (V).

An acetal of a formyl group is, for example, the corresponding di-C₁-C₈alkoxymethyl such as dimethoxy- or diethoxy-methyl, or methylene-oxy-C₂-C₆-alkylene-oxy such as methyleneoxy-ethyleneoxy.

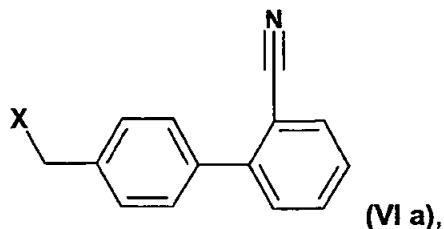
The present invention likewise relates to the above reaction. Furthermore, the present invention relates to the compounds of formula (V) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (V) whenever obtained according to above reaction.

A variant of the process for the manufacture of the compound of formula (V) is a process for the manufacture of a compound of formula (VI)

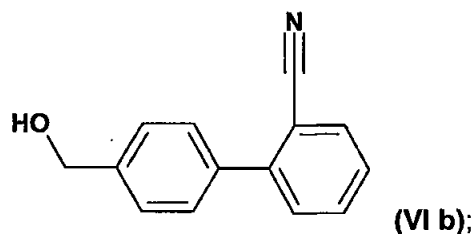


or a tautomer or salt thereof, comprising

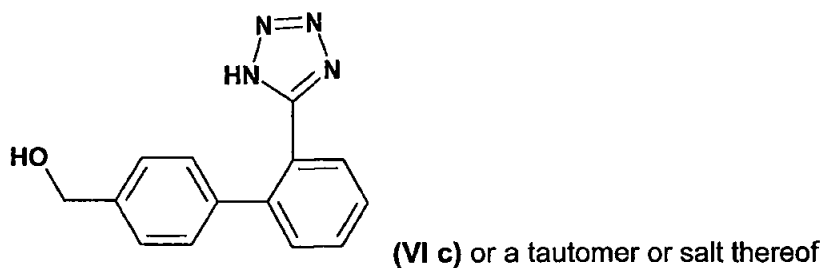
(a) treating a compound of formula (VI a)



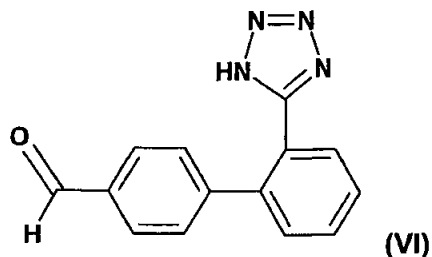
wherein X represents a leaving group, first with a nucleophilic agent and then with a "solvolytic" base resulting in a compound of formula (VI b)



(b) reacting a compound of formula (V b) with an azide of formula $(R_1)(R_2)M-N_3$ (II b), wherein the variables R_1 and R_2 , independently of one another, have the meanings as defined above; resulting in a compound of formula (VI c)



(c) oxidizing a compound of formula (VI c) or a tautomer or salt thereof resulting in a compound of formula (VI)



or a tautomer or salt thereof; and

(d) isolating the compound of formula (VI) or a tautomer or salt thereof.

The present invention relates to each of reaction steps (a) to (c) and to the product obtained according to the complete reaction sequence, but also according to each of reaction steps (a) to (c).

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Step (a) is carried out, for example, in the presence of a base, e.g. first a nucleophilic agent followed by treatment with a saponifying base.

A suitable nucleophilic agent is, for example, an alkaline metal salt of a C₂-C₁₀-alkanecarboxylic acid, especially of a C₂-C₅-alkanecarboxylic acid, an araliphatic carboxylic acid or an aromatic carboxylic acid, or aliphatic ammonium acetates, especially tetra-C₁-C₇-alkyl-ammonium acetates. Examples comprise e.g. lithium acetate, sodium acetate, potassium acetate, and tetraethylammonium acetate.

Suitable saponifying bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), the last two bases preferably in the presence of water.

Suitable saponifying bases are preferably used in the presence of water. At least stoichiometric amounts of water is used, especially a molar excess of water is preferred.

Likewise, in a specially preferred embodiment Step (a) is carried out in the presence of a phase transfer catalyst, for example, those known in the art. Suitable phase transfer catalysts comprise tri-C₁-C₈-alkyl-ar-C₁-C₅alkyl-ammonium halides such as corresponding chlorides or bromides, tetra-C₁-C₈-alkyl-ammonium halides such as corresponding chlorides or bromides, di-C₁-C₈-alkyl-diar-C₁-C₅alkyl-ammonium halides such as corresponding chlorides or bromides. Examples are tetrabutyl ammonium bromide or triethylbenzylammonium chloride.

More than one mol equivalent of a base is normally used, preferably from 1.1 to 1.5 equivalents.

An inert solvent or a mixture of solvents is used. Suitable solvents comprise e.g. hydrocarbons such as heptane, octane, toluene or xylene, a halogenated hydrocarbons such as methylenechloride, 1,2-dichloroethane, chlorobenzene, fluorobenzene or trifluorobenzene.

The reaction temperature is, for example, from 0°C to the boiling point of the solvent, preferably from 0°C to 130°C, more preferably from 40°C to 80°C.

The present invention relates to the reaction Step (a). This reaction step comprises two separate steps and it is surprising that the yield is nearly quantitative (> 99% by weight theory). The present invention also relates to compounds of formula (VI b) whenever obtained according to process Step (a).

Step (b): The molar ratio of an azide of formula (II b) and a nitrile of formula (VI b) is in a range from 5 to 1, preferably, from 3 to 1, most preferably, from 1,8 to 1 or from 1,2 to 1.

An inert solvent, diluent or mixture thereof should be selected which means that it cannot react with the starting material or intermediates. A suitable solvent is, for example, selected from the group consisting of aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an C₅-C₁₀-alkane e.g. heptane, a cycloalkane such as cyclohexane; an alkylated C₃-C₇cycloalkane such as methyl-cyclohexane or 1,3-dimethyl-cyclohexane, an alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene; a halogenated

aromatic solvent such as chlorobenzene, chlorotoluene, dichlorobenzene, and trifluoromethylbenzene; a halogenated hydrocarbon, for example, a halogenated aromatic compound, such as chlorobenzene. Furthermore, a suitable solvent, diluent or mixture thereof should have a boiling point that is high enough to be used under the reaction conditions.

Preferred solvents or diluents are aliphatic hydrocarbons, for example, C₆-C₉alkanes such as heptane; aromatic hydrocarbons, for example, phenyl substituted by C₁-C₄alkyl such as toluene or xylene, or mixtures thereof.

The reaction temperature is preferred in the temperature range of from room temperature to the boiling point of the solvent, diluent or mixture thereof, for example, a reaction temperature range is from about 20°C to about 170°C, preferably, from about 60°C to about 130°C, depending on the reactivity and combination of the reactants. A person skilled in the art is fully enabled to select corresponding suitable solvent and diluent systems and reaction conditions adapted to the choice of the solvent system and reactants.

The reaction is most preferably carried out under anhydrous conditions.

In a preferred embodiment of the present invention, the invention is carried out in a temperature range of from 80 to 120°C, preferably between 90 and 110°C.

The present invention likewise relates to reaction Step (b). Furthermore, the present invention relates to the compounds of formula (VI c) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (VI c) whenever obtained according to process Step (b).

Step (c): The oxidation is carried out in the presence of a suitable oxidizing agent.

A suitable oxidizing agent is for example, an alkali metal hypochlorite such as lithium or sodium or potassium hypochlorite, calcium hypochlorite, "a Tempo" or an analogue (cf. Fluka) thereof or an oxidizing agent selected from the group consisting of HNO₂, HNO₃ or corresponding anhydrides thereof, and peroxodisulfates.

When using e.g. an alkali metal hypochlorite as oxidizing agent, the oxidation is carried out, for example, in an inert solvent, e.g. a solvent that is inert against oxidation, such as a lower alkanecarboxylic acid, for example acetic acid, a heterocyclic aromatic, for example pyridine, a halogenated hydrocarbon, alkane nitrile, for example, acetonitrile, or water or a mixture thereof, if necessary with cooling or warming, for example from about 0° to about 50°C, for example, at room temperature. In a preferred variant, the reaction is carried out in an aqueous medium and in the presence of a base. A suitable base is, among others, an alkaline carbonate, such as potassium carbonate.

When using oxidizing agents such as HNO_2 , HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, especially nitric acid, in a preferred variant an alkylated aromatic hydrocarbon such as toluene or xylene may be used as solvent. In a preferred variant of the oxidization with as HNO_2 , HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, the reaction is preferably carried out in a temperature range from about 0°C to room temperature or to 60°C. Surprisingly, no oxidation of the solvent is observed; i.e. the methyl groups in toluene or xylene are resistant to oxidation. Accordingly, the use of oxidizing agents such as HNO_2 , HNO_3 or corresponding anhydrides thereof, or peroxodisulfates is likewise a subject matter of the present invention as is reaction Step c), especially when using as oxidizing agents such as HNO_2 , HNO_3 or corresponding anhydrides thereof, or peroxodisulfates in the an alkylated aromatic hydrocarbon solvent, especially in toluene and xylene. In another preferred variant, HNO_3 is used in water free form or in an aqueous solution from about 40% to about 95%, preferably from 40 to 65 %.

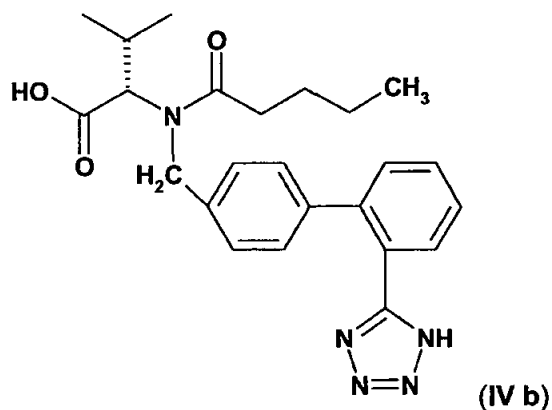
The use of oxidizing agents such as HNO_2 , HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, especially nitric acid, provides surprising results. For example, the corresponding oxidization to an aldehyde is effected without further oxidizing the aldehyde function to the carboxy group. Accordingly, the use of said oxidizing agents is likewise a subject matter of the present invention.

The present invention also relates to compounds of formula (VI) whenever obtained according to process Step (c).

Step (d): The isolation step of a compound of formula (VI) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula

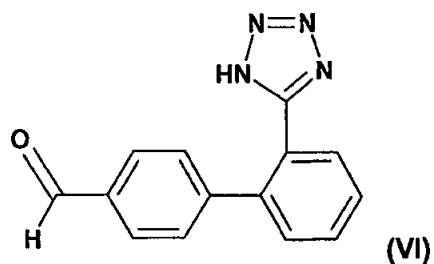
(VI) from the reaction mixture – if desired or necessary after work-up, especially by extraction - or by chromatography of the reaction mixture.

The present invention furthermore relates to a process for the manufacture of the compound of formula (IV b)

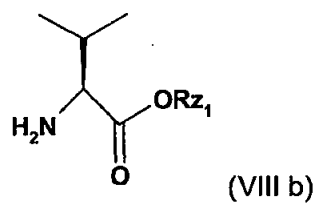


or a tautomer thereof or a salt thereof, comprising

(a') reacting a compound of formula (VI)

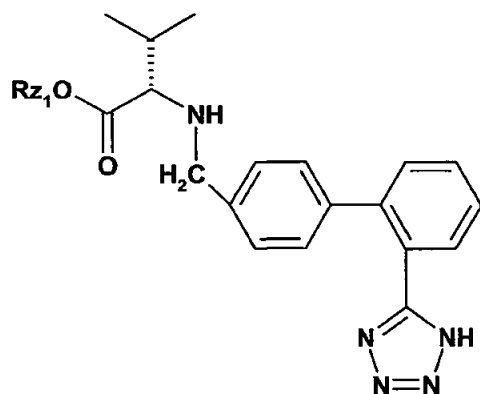


or a tautomer or salt thereof or a salt thereof, wherein the tetrazole ring is unprotected or protected by a tetrazole protecting group, with a compound of formula (VIII b)



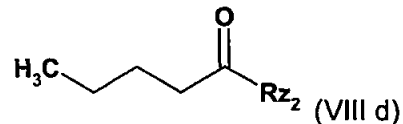
or a salt thereof, wherein R_{z1} represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination; and

(b') acylating a resulting compound of formula (VIII c)



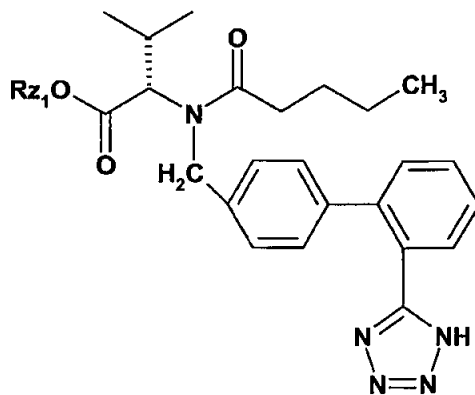
(VIII c), or a tautomer thereof or a salt thereof,

with a compound of formula (VIII d), wherein R_{z1} represents hydrogen or a carboxy protecting group and wherein the tetrazole ring is unprotected or protected by a tetrazole protecting group, with a compound of formula (VIII d)



wherein R_{z2} is an activating group; and, and,

(c') if R_{z1} is different from hydrogen, and/or the tetrazole ring is protected by a protecting group, removing the protecting group(s) in a resulting compound of formula (VIII e)



(VIII e) or a tautomer or a salt thereof; and

(d') isolating a resulting compound of formula (IV b) or a salt thereof; and, if desired, converting a resulting free acid of formula (IV b) into a salt thereof or converting a resulting salt of a compound of formula (IV b) into the free acid of formula (IV b) or converting a resulting salt of a compound of formula (IV b) into a different salt.

The present invention likewise relates to a process for the manufacture of a compound of formula (IV b) or a tautomer or a salt thereof comprising the reaction sequence comprising the full sequence comprising steps (a) to (c) for the manufacture of a compound of formula (VI) and then subsequent steps (a') to (d') for the manufacture of a compound of formula (IV b).

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10°C to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Compounds of formulae (VIII a), (VIII b), (VIII c) and (VIII e), wherein either or both of R₁ and R₂ are hydrogen can form salts with bases, as both the unprotected tetrazole ring and the unprotected carboxy group have acidic properties, while compounds of formulae (VIII b) and (VIII c) can also form salts with acids.

A corresponding tetrazole protection group is selected from those known in the art. Especially, the tetrazole protecting group is selected from the group consisting of tert-C₄-C₇-alkyl such as tert-butyl; C₁-C₂-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl or trityl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of tert-C₁-C₇-alkyl, hydroxy, C₁-C₇alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and trifluoromethyl (CF₃); picolinyl; piperonyl; cumyl; allyl; cinnamoyl; fluorenyl; silyl such as tri-C₁-C₄-alkyl-silyl, for example, trimethyl-silyl, triethylsilyl or tert-butyl-dimethyl-silyl, or di-C₁-C₄-alkyl-phenyl-silyl, for example, dimethyl-phenyl-silyl; C₁-C₇-alkyl-sulphonyl; arylsulphonyl such as phenylsulphonyl wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C₁-C₇-alkyl, hydroxy, C₁-C₇-alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and CF₃; C₂-C₈-alkanoyl such as acetyl or valeroyl; and esterified carboxy such as C₁-C₇-alkoxy-carbonyl, for example, methoxy-, ethoxy- or tert-butyloxy-carbonyl; and allyloxycarbonyl. Examples of preferred

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protective groups which may be mentioned are tert-butyl, benzyl, p-methoxybenzyl, 2-phenyl-2-propyl, diphenylmethyl, di(p-methoxyphenyl)methyl, trityl, (p-methoxyphenyl)diphenylmethyl, diphenyl(4-pyridyl)methyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 2-tetrahydropyranyl, allyl, trimethylsilyl and triethylsilyl.

A corresponding carboxy protecting group (R_{21}) is selected from those known in the art. Especially, R_{21} is selected from the group consisting of C_1 - C_7 -alkyl such as methyl, ethyl or a tert- C_4 - C_7 -alkyl, especially tert-butyl; C_1 - C_2 -alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C_1 - C_7 -alkyl, hydroxy, C_1 - C_7 -alkoxy, C_2 - C_8 -alkanoyl-oxy, halogen, nitro, cyano, and CF_3 ; picolinyl; piperonyl; allyl; cinnamyl; tetrahydrofuranyl; tetrahydropyranyl; methoxyethoxy-methyl, and benzyloxymethyl. A preferred example of protective groups which may be mentioned is benzyl.

The activating group R_{22} is, for example, an activating group that is being used in the field of peptides, such as halogen such as chlorine, fluorine or bromine; C_1 - C_7 -alkylthio such as methyl-thio, ethyl-thio or tert-butyl-thio; pyridyl-thio such as 2-pyridyl-thio; imidazolyl such as 1-imidazolyl; benzthiazolyl-oxy such as benzthiazolyl-2-oxy-; benzotriazol-oxy such as benzotriazolyl-1-oxy-; C_2 - C_8 -alkanoyloxy, such as butyroyloxy or pivaloyloxy; or 2,5-dioxo-pyrrolidinyl-1-oxy. Examples of an activating group which may be mentioned are ???

Step (a'):

In reaction Step (a'), the reductive amination is carried out in the presence of a reducing agent. A suitable reducing agent is a borohydride, which may also be in a complexed form, or hydrogen or a hydrogen donor both in the presence of a hydrogenation catalyst. Furthermore, a reducing agent is a suitable selenide or a silane.

A suitable borohydride or a complexed borohydride is, for example, an alkali metal borohydride such as sodium borohydride or lithium borohydride; an earth alkali metal borohydride such as calcium borohydride; an alkali metal cyanoborohydride, such as sodium cyanoborohydride or lithium cyanoborohydride, an alkali metal tri- $(C_1$ - C_7 -alkoxy)-borohydride such as sodium trimethoxy-ethoxy-borohydride; a tetra- C_1 - C_7 -alkylammonium-

(cyano)borohydride such as tetrabutylammonium-borohydride or tetrabutylammonium-cyanoborohydride.

A suitable catalyst for the reductive amination with hydrogen or a hydrogen donor is, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium, platinum or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate, for example, platinum on carbon. The hydrogenation with hydrogen or a hydrogen donor may preferably be carried out at pressures between 1 and about 100 atmosphere and at room temperature between about -80° to about 200°C, in particular between room temperature and about 100°C.

A preferred hydrogen donor is, for example, a system comprising 2-propanol and, if desired, a base, or, most preferably, formic acid or a salt thereof, e.g. an alkali metal, or tri-C₁-C₇-alkyl-ammonium salt thereof, for example, the sodium or the potassium salt thereof, if desired, in the presence of a tertiary amine, such as triethylamine. Further hydrogen donors comprise other alcohols such as ethanol, 2-methoxyethanol, benzyl alcohol, benzhydrol, pentan-2-ol, 1,2-ethandiol, 2,3-butandiol or cyclohexandiol, hydrazine, cyclohexene, cyclohexadiene, indane, tetralin, indoline, tetrahydroquinoline, hydroquinone, hypophosphinic acid or a suitable salt thereof such as the sodium salt thereof, sodium tetrahydroborate, sugars, ascorbic acid, limonene, or silanes. The hydrogen donor may also be used as solvent, especially 2-propanol or formic acid.

A suitable selenide is, for example, selenophenol which is unsubstituted or substituted. Suitable substituents comprise, for example, one, two or three substituents selected from e.g. halo, trifluoromethyl, trifluoromethoxy, C₁-C₇-alkyl, C₁-C₇-alkoxy, nitro, cyano, hydroxyl, C₂-C₁₂-alkanoyl, C₁-C₁₂-alkanoyloxy, and carboxy. Those silanes are preferred that are completely soluble in the reaction medium and that may moreover produce organic soluble by-products. Especially preferred are tri-C₁-C₇-alkyl-silanes, especially triethylsilane and triisopropyl-silane. Preferred are commercially available selenides.

A suitable silane is, for example, silane which is trisubstituted by a substituent selected from the group consisting of C₁-C₁₂-alkyl, especially C₁-C₇-alkyl, and C₂-C₃₀-acyl, especially C₁-C₈-acyl. Preferred are commercially available silanes.

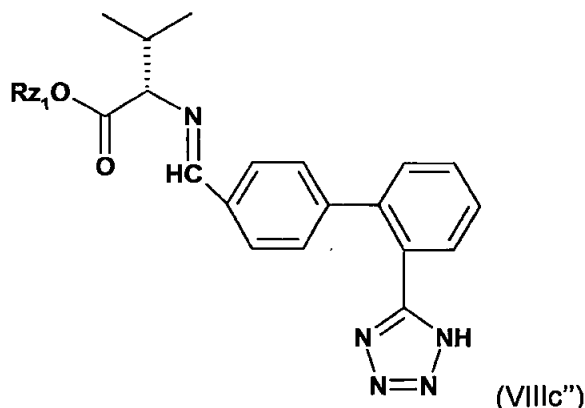
The reductive amination is preferably carried out under acidic, neutral or preferably under basic conditions. A suitable base comprises, for example, an alkali metal hydroxide or carbonate, such as sodium hydroxide, potassium hydroxide or potassium carbonate. Furthermore, an amine base can be used, for example, tri-C₁-C₇-alkylamine, such as triethylamine, tri-n-propylamine, tri-butylamine or ethyl-diisopropylamine, a piperidine, such as N-methylpiperidine, or a morpholine, such as N-methyl-morpholine. Preferred bases include lithium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium hydrogencarbonate and potassium carbonate. Especially preferred is sodium hydroxide, sodium carbonate or tri-n-propylamine.

The reductive amination is carried out in a suitable inert solvent or a mixture of solvents including water. Inert solvents conventionally do not react with the corresponding starting materials of formulae (VIII a) and (VIII b). If an alkali metal borohydride such as sodium borohydride or lithium borohydride; an earth alkali metal borohydride such as calcium borohydride; an alkali metal cyanoborohydride, such as sodium cyanoborohydride or lithium cyanoborohydride, is used as reducing agent, for example, a polar solvent, for example, an alcohol such as methanol, ethanol, isopropanol or 2-methoxyethanol, or glyme, is preferred. If an alkali metal tri-(C₁-C₇-alkoxy)-borohydride such as sodium trimethoxy-ethoxy-borohydride; a tetra-C₁-C₇-alkylammonium-(cyano)borohydride such as tetrabutylammonium-borohydride or tetrabutylammonium-cyanoborohydride, is used as reducing agent, for example, hydrocarbons, such as toluene, esters such as ethylacetate or isopropylacetate, ethers such as tetrahydrofuran or tert-butylmethylether are preferred. If hydrogen or a hydrogen donor is used as reducing system, each in the presence of a hydrogenation catalyst, a polar solvent is preferred. The reductive amination can also be carried out e.g. in a mixture of an organic solvent with water, both mono- and biphasic. In a biphasic system a phase transfer catalyst such as tetrabutylammoniumhalide, e.g. bromide, or benzyltrimethylammonium halide, e.g. chloride, may be added.

If R₂₁ represent a protecting group and the tetrazole ring is protected and if the compound of formula (VIII b) is a free base, the presence of a base is not required. If, however, R₂₁ is hydrogen and the tetrazole ring is protected by a protecting group, not more than a molar equivalent of a base may be added. In order to avoid racemisation, the reaction is preferably carried out by using less than an equimolar amount of a base. If R₂₁ is hydrogen and the tetrazole ring is not protected, no racemisation is observed even if the reaction is

carried out with equal or more than one equivalent of base under mild conditions, preferably at temperatures between -10°C and 20°C.

The reaction of a compound of formula (VIII a) with a compound of formula (VIII b) results in an intermediately formed imine (Schiff base) of formula (VIII c'')



or a tautomer or a salt thereof, wherein R_{z1} has the meaning as given above and wherein the tetrazole ring is unprotected or protected by a tetrazole protecting group that can, under certain reaction conditions, be isolated or that can be subjected to the reduction without isolation.

The reductive amination is a two-step reaction, the formation of an imine by removing water, followed by the reduction step. The removal is an equilibrium reaction, which can be directed to the formation of an imine by continuously eliminating the water, for example, by azeotropic removal. Furthermore, a water scavenger may be used to remove or inactivate free water which may be effected by a physical process such as absorption or adsorption or by a chemical reaction. A suitable water scavenger includes without limitation anhydrides of organic acid, aluminosilicates such as molecular sieves, other zeolites, finely divided silica gel, finely divided alumina, anhydrides of inorganic acids such as phosphoric anhydride (P_2O_5), inorganic sulfates such as calcium sulfate, sodium sulfate, and magnesium sulfate, and other inorganic salts such as calcium chloride.

If Step (a') is carried out via first manufacturing and isolating a compound of formula (VIII c''), a compound of formula (VIII a) is reacted with a compound of formula (VIII b), maybe in the presence of a base, if R_{z1} is hydrogen and the tetrazole ring is not protected.. Compounds of

formula (VIII c'') can then be converted into corresponding compounds of formula (VIII c') by reducing the compounds of formula (VIII c'') with a corresponding reducing agent as mentioned above.

The intermediate imine of formula (VIII c'') can, for example, be isolated by removal of the solvent, e.g. by distillation, especially by azeotropic removal of water.

In a preferred variant, the reductive amination is carried out without isolating a compound of formula (VIII c').

The reductive amination is most preferably carried out without removal of free water, especially, if R_{z1} is hydrogen and the tetrazole ring is not protected and with a base such as sodium hydroxide, a solvent such as methanol and a reducing reagent such as sodium borohydride.

In view of the imine structural element, compounds of formula (VIII c'') comprise both the corresponding E and the corresponding Z isomer thereof. Preferred is the E isomer.

The present invention likewise relates to compounds of formula (II c') wherein R_1 is hydrogen or a tetrazole protecting group and wherein R_2 is hydrogen or a carboxy protecting group. Corresponding compounds can be used as intermediates for the manufacture of the compound of formula (I). Preferred are compounds of formula (II c'), wherein at least one of R_1 and R_2 represents hydrogen or both of R_1 and R_2 represent hydrogen.

The compounds of formulae (VIII a) and (VIII b) are partially known and can be prepared according to methods known per se.

Step (a') is preferably carried out under mild conditions, especially in a temperature range of about -10°C to about room temperature, preferable in a range of about -5°C and $+5^{\circ}\text{C}$.

Step (b'):

In reaction Step (b'), the acylation is carried out, for example, in absence or in presence of a suitable base.

Suitable bases are, for example, alkali metal hydroxides or carbonates, morpholine or piperidine amines, unsubstituted or substituted pyridines, anilines, naphthalene amines, tri-C₁-C₇-alkylamines, basic heterocycles or tetra-C₁-C₇-alkylammonium hydroxides. Examples, which may be mentioned, include sodium hydroxide, potassium carbonate, triethylamine, tri-propyl-amine, tri-butyl-amine or ethyldiisopropylamine, N-methyl-morpholine or N-methyl-piperidine, dimethyl-aniline or dimethylamino-naphthalene, a lutidine, a collidine, or benzyltrimethylammonium hydroxide. A preferred base is a tri-C₁-C₄-alkylamine such as ethyl-diisopropyl-amine or is pyridine.

The acylation is carried out in a suitable inert solvent or in a mixture of solvents. The person skilled in the art is fully enabled to select a suitable solvent or solvent system. For example, an aromatic hydrocarbon such as toluene, an ester such as ethylacetate or a mixture of ethylacetate and water, a halogenated hydrocarbon such as methylene chloride, a nitrile such as acetonitrile or propionitrile, an ether such as tetrahydrofuran or dioxane, 1,2-dimethoxy-ethane, amide such as dimethylformamide, or a hydrocarbon, such as toluene, is used as solvent.

During the acylation of a compound of formula (VIII c), if R₂ is hydrogen, the carboxyl-group might also be acylated forming a mixed anhydride. This intermediate is strongly prone to racemisation, mainly under basic conditions. Racemisation however can be avoided by first adding the compound of formula (VIII d), especially the halide, to the compound of formula (VIIIc) in a suitable inert solvent (e.g. dimethoxyethane, tetrahydrofuran or acetonitril), then slowly adding a sub-stoichiometric amount of the base, especially pyridine, in relation to the compound of formula (VIII d). Small amounts of water in the reaction mixture, preferably two equivalents, may additionally suppress racemisation.

The reaction can also be carried out by simultaneous or alternative addition of a compound of formula (VIII d) and a base such as pyridine keeping the reaction mixture acidic at all times.

If R_{z1} represents a protecting group and the tetrazole ring is unprotected or protected by a protecting group, for example, two equivalents of both a compound of formula (VIII d), e.g. the corresponding halide thereof, and a base, e.g. ethyl-diisopropyl-amine or tri-n-propylamine are added to a corresponding compound of formula (VIII c) dissolved in a suitable solvent, e.g. toluene. No racemisation is observed.

If the tetrazole ring is unprotected and R_{z1} is a protecting group, the tetrazole ring might also be acylated. When, however, the reaction mixture is quenched, for example with water or an alcohol such as methanol, the corresponding compound can be obtained wherein the tetrazole ring is unprotected.

Compounds of formula (VIII d) are known or can be manufactured according to methods known per se.

Step (c'):

The removal of the protecting groups, both the tetrazole and carboxy protecting group, can be carried out according to methods known per se in the art.

For example, a benzyloxy ester can be converted into the corresponding acid especially by hydrogenation in the presence of a suitable hydrogenation catalyst. A suitable catalyst comprises, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 atm. and at room temperature between about -80° to about 200°C, in particular between room temperature and about 100°C.

The removal of a trityl or tert-butyl group, respectively, can be achieved by treating corresponding protected compounds with an acid, especially under mild conditions.

Step (d'):

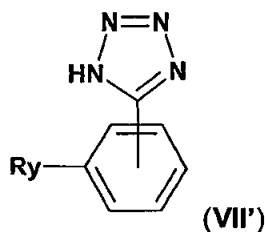
The isolation Step (d') of a compound of formula (IV b) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (IV b) from the reaction mixture – if desired or necessary after work-up, especially by extraction - or by chromatography of the reaction mixture.

The conversion of an acid of formula (IV b) into a salt is carried out in a manner known per se. Thus, for example, a salt with a base of compounds of the formula (IV b) is obtained by treating the acid form with a base. Salts with a base can, on the other hand, be converted into the acid (free compound) in a customary manner, and salts with a base can be converted, for example, by treating with a suitable acid agent.

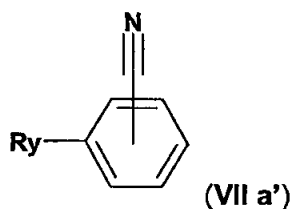
Accordingly, variable R comprises the meanings of variables Rx, Ry and also represents formyl as well as the core elements corresponding to angiotensin II receptor antagonists, especially those that are listed in the above table.

Another embodiment of the present invention is the use of a compound of formulae (VI a), (VI b), or (VI c) for the manufacture of a compound of formula (IV a), especially (IV b) or tautomer or a salt thereof, by carrying out corresponding reaction steps as described hereinbefore and hereinafter.

A further preferred embodiment of the present invention is a process for the manufacture of a compound of formula

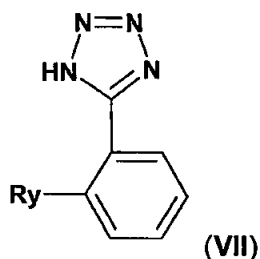


a tautomeric form thereof, wherein R_y represents C₁-C₈-alkyl such as methyl; C₁-C₈-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, or an acetal of formyl; comprising reacting a compound of formula (VII a')

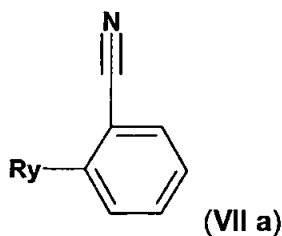


with a compound of formula $(R_1)(R_2)M-N_3$ (II b), wherein R_1 and R_2 , independently of one another, represent an organic residue; and isolating the resulting compound of formula (VII').

A further preferred embodiment of the present invention is a process for the manufacture of a compound of formula



a tautomeric form thereof, wherein R_y represents C_1 - C_8 -alkyl such as methyl; C_1 - C_8 -alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (VII a)



with a compound of formula $(R_1)(R_2)M-N_3$ (II b), wherein R_1 and R_2 , independently of one another, represent an organic residue; and isolating the resulting compound of formula (VII).

The present invention likewise relates to the above reaction. Furthermore, the present invention relates to the compounds of formula (VII) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (VII) whenever obtained according to above reaction.

The isolation step of a compound of formulae (VI) or (VII) or (VII'), respectively, is carried out according to conventional isolation methods, such as by crystallizing the resulting compound

of formula (VI)) or (VII), respectively, from the reaction mixture or by chromatography of the reaction mixture.

The conversion of an acid into a salt is carried out in a manner known per se. Thus, for example, a salt with a base is obtained by treating the acid form with a base. Salts with a base can, on the other hand, be converted into the acid (free compound) in a customary manner, and salts with a base can be converted, for example, by treating with a suitable acid agent.

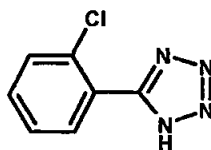
The present invention likewise relates to a compound of formulae (I), (IV), (IV b), (V), (VI), (VII), (VII') or a tautomer or salt thereof in a form being completely free of tin.

The present invention likewise relates to the use of a compound of formula (II b) in a process for the manufacture of a compound of formulae (I), (IV), (IV b), (V), (VI), (VII), (VII') or a tautomer or salt thereof, especially in a form being completely free of tin.

The invention relates to the compounds obtained according any process of the present invention.

The examples outline specific embodiments of the present invention, but are not to limit the scope of the invention.

Example 1: 5-(2-Chlorophenyl)-1H-tetrazole



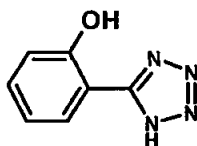
20 mmol (1.3 g) of sodium azide are charged to a 25 ml flask under argon atmosphere followed by slow addition (via syringe) of 11 ml of a solution of diethyl aluminium chloride (1.8 molar in toluene), 20 mmol, at 0 °C under stirring. The suspension is stirred over night at room temperature. Then 2.06 g (15 mmol) solid 2-chloro-benzonitrile are added and the mixture is heated at external temperature of 90 °C for 9 hours. After this time the conversion was 91.5 % (HPLC). For complete conversion (> 99.5 %, HPLC) the reaction mixture is kept for additional 6 hours at 90 °C. For work up the reaction mixture was quenched at 0 °C

under stirring on 20 ml HCl (6N) which contains 2.6 g of NaNO₂ to destroy excess hydrazoic acid. The thick white precipitate which is formed (product) is stirred at 0 °C for additional 1 hour and then filtered and dried over night at 50 °C to give the white crystalline product.

m.p. 173 - 175 °C

Tlc: R_F-value: 0.48, toluene : EtOAc : AcOH (20 : 20 : 1); SiO₂ -plates.

Example 2: 5-(2-Hydroxyphenyl)-1H-tetrazole



Method A:

286 mg of granular sodium azide (4.4 mmol) are added to a cold solution of diethyl aluminium chloride (4.4 mmol, 1M in toluene) and the mixture is stirred at room temperature for 4 hours (h).

A solution of 2-hydroxybenzonitrile (4 mmol, 476 mg) in 3 ml of toluene, cooled at 0°C, is treated with 2.2 ml of triethyl aluminium (4 mmol, 1.8 M in toluene). The mixture reaction is warmed to room temperature and stirred for 1 hour. The mixture is cooled to 0°C, treated with the solution of diethyl aluminium azide, gradually warmed to 85°C and stirred over two days. The reaction mixture is cooled to -10°C and treated drop wise with 7 ml of HCl 6 N. 10 ml of ethyl acetate are added and the mixture is extracted once with 10 ml of water, once with 10 ml of NaCl saturated. The combined aqueous layers are extracted three times with 10 ml of ethyl acetate. The combined organic phases are dried over Na₂SO₄. The solvent is removed to give the crude product.

Method B:

260 mg of granular sodium azide (4 mmol) is added to a cold solution of diethyl aluminium chloride (4 mmol, 1.8 M in toluene) diluted with 10 ml of toluene, and the mixture is stirred at room temperature for 4 hours. The stirred solution is cooled at 0°C and 238 mg of 2-hydroxybenzonitrile (2 mmol) are added. The reaction mixture is warmed to 80°C and stirred over night. After 20 hours the conversions was 83 %. Then the temperature is increased to 100°C and stirred 12 hours. At a conversion of around 90% the reaction is worked up. The

reaction mixture is cooled to 0°C and treated drop wise with 7 ml of HCl 6 M, 5 ml of water, 10 ml of ethyl acetate, 8 ml of saturated NaCl (sat.) and extracted. The organic phase is reextracted twice with 20 ml of water. The combined aqueous layers are extracted twice with 20 ml of ethyl acetate. The combining organic phases are dried over Na₂SO₄. The solvent is removed to give the crude product. The crude product is crystallized from ethyl acetate to give the pure product.

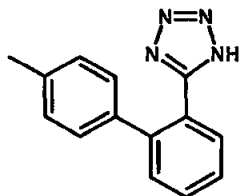
m.p.: 220 – 222 ° C,

Tlc: R_f – value: 0.46, toluene : EtOAc : AcOH (20 : 20 : 1).

HPLC:

Hewlett Packard, solvents. H₃PO₄, acetonitrile/water; flow: 2 ml/min; injection: 5.0 µl; wavelength 220 nm, 40 °C. Column: Merck, Chromolith Performance, RP-18e 100-4.6 mm; Ret. Time: 4.12 min.

Example 3a: 5-(4'-methylbiphenyl-2-yl)-1H-tetrazole



A 20 ml flask is dried under argon and then charged with 7 ml of diisobutylaluminium fluoride (1 molar in hexane) followed by 5 ml of toluene and 455 mg of NaN₃ (7 mmol). After stirring the suspension for 4 hours at room temperature 966 mg of solid ortho-tolylbenzonitrile (OTBN) is added at 0 ° C in one portion. The suspension is warmed up to 130 °C (ext. temp.) with an internal temperature of 100 °C. After 44 h at 130 °C (ext. temp.) the conversion is > 93 %. The reaction mixture was quenched in hydrochloric acid (6 molar). After addition of 10 ml of toluene the layers are separated, the organic layer is washed twice with 20 ml of water, dried over sodium sulfate and evaporated to give a crystalline residue of the product.

Physicochemical data see example 3b.

Example 3b: 5-(4'-methylbiphenyl-2-yl)-1H-tetrazole

Same reaction as in example 3a was carried out, but with diethylaluminium azide at higher concentration and higher temperatur:

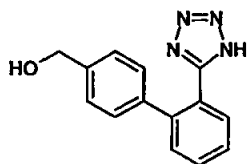
Under similar conditions with diethylaluminium azide (prepared from diethylaluminium chloride and NaN_3) in toluene and OTBN a conversion of 98.5 % was obtained after 40 hours at internal temperature of ca. 110 °C (reflux), external temperature 135 °C.

A dry 50 ml flask is charged with 5 ml toluene and 1.3 g (20 mmol) of dry solid sodium azide. The stirred suspension is cooled to 0 °C and 11 ml of a 1.8 molar solution of diethylaluminium chloride (20 mmol) is added via syringe during 10 minutes. The suspension is stirred for 4 to 6 hours or over night at room temperature. Then the suspension is cooled to 0 °C and a solution of o-tolylbenzonitrile (2.1 g, 11 mmol) in 5 ml toluene is added dropwise during 5 minutes. The stirred suspension is heated up to reflux and after 7 hours a conversion of 54.5 % (HPLC) is obtained. After refluxing over night (17 h) a conversion of 92 % is observed. After 40 h the conversion is > 98.5 %. Thereafter the reaction is quenched by dropping the reaction mixture to cold 2 N hydrochloric acid (50 ml) under stirring to give a white precipitate which is dissolved by addition of 20 ml of acetonitrile to give a clear biphasic solution. The product is extracted with 50 ml of isopropyl acetate. The organic phase is treated with aqueous potassium carbonate solution (pH 10) until all product is dissolved in the aqueous layer as the potassium salt. Then the basic aqueous phase is adjusted to pH 1-2 by addition of ca. 90 ml of 2N HCl. The product is extracted twice with 50 ml of isopropyl acetate and the organic phase is evaporated under reduced pressure to give after drying in vacuum the very pure, white crystalline product.

m.p.: 150 – 152 ° C; (Ref. substance: DiPharma sample: m.p. 149-151 °C)

Tlc: R_f -value: 0.56, (Toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2 -plate (Merck KgaA)

Example 4 a: 5-(4'-Hydroxymethylbiphenyl-2-yl)-1H-tetrazole



[2'-(2H-Tetrazol-5-yl)-
biphenyl-4-yl]-methanol

- 43 -

1.235 g of granular sodium azide (19 mmol) are added to a cold solution of diisobutyl aluminium chloride (19 mmol, 1.8M in toluene) diluted in 5 ml of toluene and the mixture is stirred at room temperature over the night to give diisobutyl aluminium azide.

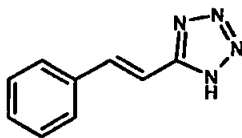
2.1 g of 4'-hydroxymethyl-biphenyl-2-carbonitrile (10 mmol), are treated, in a drop wise manner at 0 °C with 5.52 ml of triethyl aluminium (10 mmol, 1.8M in toluene). The reaction mixture is stirred for 5 minutes. After that, the clear colourless reaction mixture is added to the solution of diisobutyl aluminium azide (19 mmol), gradually warmed to an internal temperature of about 100°C and stirred over the night (conversion 95.7%). For the work up the reaction mixture is cooled to 0°C and added dropwise to a solution of 30 ml of HCl (2 N) containing 1.38g of NaNO₂ (20 mmol) (cooled to 0°C). 40 ml of iso-propyl acetate are added and the mixture is extracted once with 15 ml of HCl 2N, once with 20 ml of water. The combining aqueous layers are extracted twice with 10 ml of isopropyl acetate. The organic phase is extracted three times with 15 ml portions of an aqueous solution of K₂CO₃ (10%). The aqueous phase is washed once with 15 ml of isopropyl acetate. HCl (2 N) is added to the aqueous phase to adjust the pH to 2, and the solution is extracted three times with 20 ml portion of isopropyl acetate. The combining organic phase is washed once with 20 ml of water and the solvent is removed to give the crude product. The crude product is crystallized from ethyl acetate and isopropyl ether to give the pure product.

m.p.: 137 – 139 ° C;

Tlc: R_f-value: 0.21, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO₂- plates (Merck KgaA)
Catalog -Nr. 1.05628.0001)

Example 4 b: The reaction as in Example can also be carried out with diethyl aluminium azide at higher concentration and higher temperature.

Example 5: Synthesis of 5-((E)-Styryl-2H-tetrazole



Procedure:

To a 50 ml, three necked round bottomed flask, 10 ml of a solution of diisobutyl aluminium fluoride (10 mmol, 1 M in hexane), diluted in 10 ml of toluene, are added. NaN₃ is added to

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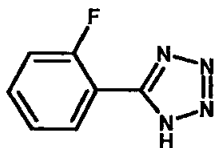
- 44 -

the solution (650 mg, 10 mmol), and the mixture is stirred at room temperature for 4h. The stirred solution is cooled at 0°C with an ice-bath. 0.62 ml of cinnamionitrile (5 mmol) diluted in 3 ml of toluene are added, the mixture is warmed to 90°C (i.t.) and stirred over the night. The temperature is increased to 105°C (i.t.) and stirred over the night. After a total time of 70 hours (no complete conversion) the reaction was quenched. The mixture is cooled to -10°C and treated drop wise with 8 ml of HCl (6N) (pH1). The aqueous phase is extracted with 10 ml of ethyl acetate. The organic phase is washed twice with 10 ml portion of NaCl sat. and then extracted twice with 10 ml portion of KHCO₃. The water phase is washed twice with 10 ml portion of ethyl acetate and then treated with HCl to pH 1-2 and extracted three times with ethyl acetate. The organic phase is dried over Na₂SO₄ and the solvent removed in vacuum to give after drying the title product.

m.p.: 158 – 160 °C

Tlc: Rf-value: 0.46 (Toluene : EtOAc : AcOH (20 : 20 :1))

Example 6: 5-(2-Fluorophenyl)-1H-tetrazole,

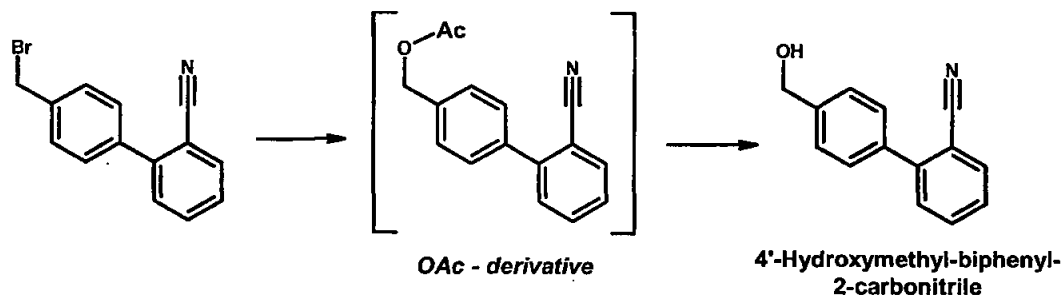


20 mmol (1.3 g) of sodium azide are charged to a 25 ml flask under argon atmosphere followed by slow addition (via syringe) of 11 ml of a solution of diethyl aluminium chloride (1.8 molar in toluene), 20 mmol, at 0 °C under stirring. The suspension is stirred over night at room temperature. Then 1.8 g (1.2 ml), (15 mmol), 2-fluoro-benzonitrile are added and the mixture is heated at external temperature of 90 °C for 7 hours. After this time the conversion was complete (HPLC). Work up: The reaction mixture is quenched on 20 ml HCl (2 molar) containing 20 mmol NaNO₂ at 0 °C to destroy hydrazoic acid which is formed from excess azide. The precipitate which is formed is dissolved by addition of 20 ml acetonitrile to give a clear biphasic solution. The aqueous phase is extracted twice with each 10 ml ethyl acetate. The combined organic phases are extracted with 15 ml of an aqueous solution (10 %) of potassium carbonate and adjusted to pH 10. The organic phase is extracted twice with 10 ml of water. The combined aqueous basic phases are neutralized with 2 N HCl and the pH is adjusted to pH 1-2. The product is extracted with ethyl acetate. The ethyl acetate is evaporated under reduced pressure to give a crystalline residue which is further dried in vacuo at 50 °C to give a white crystalline solid.

m.p.: 158 – 160 °C.

Tlc: R_f –value: 0.48 (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO₂ - plates

Example 7: 4'-Hydroxymethyl-biphenyl-2-carbonitrile



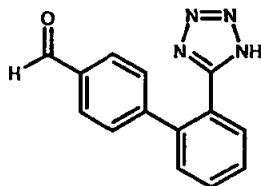
One pot PTC preparation of 4'-hydroxymethyl-biphenyl-2-carbonitrile from 4'-bromomethyl-biphenyl-2-carbonitrile without isolation of the intermediate OAc (O-acetyl) derivative.

A 750 ml flask is charged with 54.4 g (0.2 mol) of 4'-bromomethyl-biphenyl-2-carbonitrile and 250 ml of toluene. To this suspension is added a solution of 30 g (0.3 mol) of potassium acetate in 15 ml of water. The heterogeneous mixture is heated up to an internal temperature of 90 °C to become a clear biphasic solution. After 12 hours at an internal temperature of 90 °C the conversion to the OAc derivative is complete. The biphasic mixture is cooled down to internal temperature of about 50 °C followed by addition of 150 ml NaOH (2N). The mixture is heated up to an internal temperature of ca. 70 °C (extern. temp. 80 °C). After 5 hours at this temperature the PTC saponification is complete (100 % conversion, HPLC). Additional 150 ml toluene is added and the warm reaction solution (ca. 50 °C) is washed three times with 50 ml of hot water until the pH is around 7. The toluene phase is evaporated under reduced pressure and the resulting crystalline residue is dried at 50 °C over 24 hours in vacuum to give the white crystalline product with 98 % purity (HPLC) and a water content of 0.23 %.

m.p.: 118-120 °C

Tlc: : R_f –value: 0.45, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO₂ - plate

Example 8 a: 5-(4'-Formyl-biphenyl-2-yl)-1H-tetrazole or
2'-(2H-Tetrazol-5-yl)-biphenyl-4-carbaldehyd



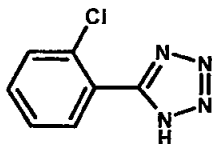
1.01 g (4 mmol) of 5-(4'-hydroxymethylbiphenyl-2-yl)-1H-tetrazole is dissolved in 7 ml of a 10 % aqueous solution of potassium carbonate. To the stirred solution is added an aqueous solution (ca. 8 %) of sodium hypochlorite (eau de Labarraque) at room temperature. After 40 min. a conversion of 50 % to the aldehyde is observed. After 3.5 hours additional 1.5 ml sodium hypochlorite is added at room temperature. After a total reaction time of 7 hours a conversion of > 93 % is observed. Stirring over night at 0 °C improves the conversion to 97 %. The reaction mixture is quenched with 20 % aqueous sodium hydrogen sulfite solution (5 ml) under stirring for 1 hour to destroy excess hypochlorite. Then 2-methyl-2-butene (1.5 ml) is added and the product is precipitated by carefully dropping 10 ml of 6 N HCl at 0 °C to the mixture under stirring. The product is extracted with ethyl acetate and the solvent is evaporated to dryness to give the solid product.

m.p.: 184 – 186 °C

Tlc: R_f-value: 0.31, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO₂ – plate.

Example 8 b: Compound (VI c), 5-(4'-hydroxymethylbiphenyl-2-yl)-1H-tetrazole, 504 mg (2 mmol) is suspended in a mixture of 2 ml of toluene and 1 ml of dichloromethane. The suspension is cooled to 0 °C and 0.42 ml of nitric acid (ca. 6 mmol), (65 %, d = 1.4) is added in one portion at 0 °C under stirring which results in a clear slightly yellow solution. The ice bath is removed and stirring is continued at room temperature for ca. 1 h. After 1 h the product (VI) is crystallizing directly from the reaction mixture. The slurry is cooled to 0 °C for 1 h and then filtered to give after drying in vacuum 400 mg of pure aldehyde (VI).

Example 9: 5-(2-Chlorophenyl)-1H-tetrazole (with dibutylboron azide)



A dry 25 ml flask is charged with 10 ml (10 mmol) of a heptane solution of dibutyl boryl triflate (1 molar) under Argon. To this solution is added 650 mg (10 mmol) of sodium azide.

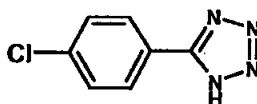
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The suspension is stirred over night at room temperature to give a dibutylboron azide. To the suspension is added 1.0 g (7.7 mmol) 2-chlorobenzo nitrile as a solid in one portion. The reaction mixture is heated up to 130 ° C external temperature. After 5 hours the conversion to the desired product is only 5 %. Additional 5 ml of toluene is added and refluxing is continued over night. After 24 hours the conversion is 27 %. After additional 24 h refluxing at 130 ° C (ext. temp.) the conversion is 35 % (HPLC). The reaction is stopped by carefully quenching the yellow suspension on 6 N HCl. The product is extracted to the water phase with 2 x 10 ml of potassium carbonate solution. The water layer is adjusted to pH 1 with 6N HCl and the product is extracted with ethyl acetate. The solvent is evaporated to dryness to give an off-white solid residue.

Tlc: R_f -value: 0.48, toluene : EtOAc : AcOH (20 : 20 : 1); SiO_2 -plate.

Example 10:

5-(4-Chlorophenyl)-1H-tetrazole



Procedure:

292 mg of granular sodium azide (4.5 mmol) are added to a cold solution of diethyl aluminum chloride (4.5 mmol, 1.8 M in toluene) diluted in 2.5 ml of toluene, and the mixture is stirred at room temperature for 4h. 473 mg of 4-Chlorobenzonitrile are added to the stirred solution, and the reaction mixture is heated up to 135°C (e.t.) and stirred over the night. Complete conversion is observed by HPLC. 5 ml of toluene are added to the mixture, then the solution is added drop wise to a cold solution of HCl 6N. 10 ml of ethyl acetate are added and the solution extracted. The aqueous phase is washed twice with 10 ml portion of ethyl acetate. The combined organic phases are washed with 10 ml portion of HCl 2N and finally with 10 ml of water. The solvent is removed and the product is dried in vacuum at 60°C over the night to give the product.

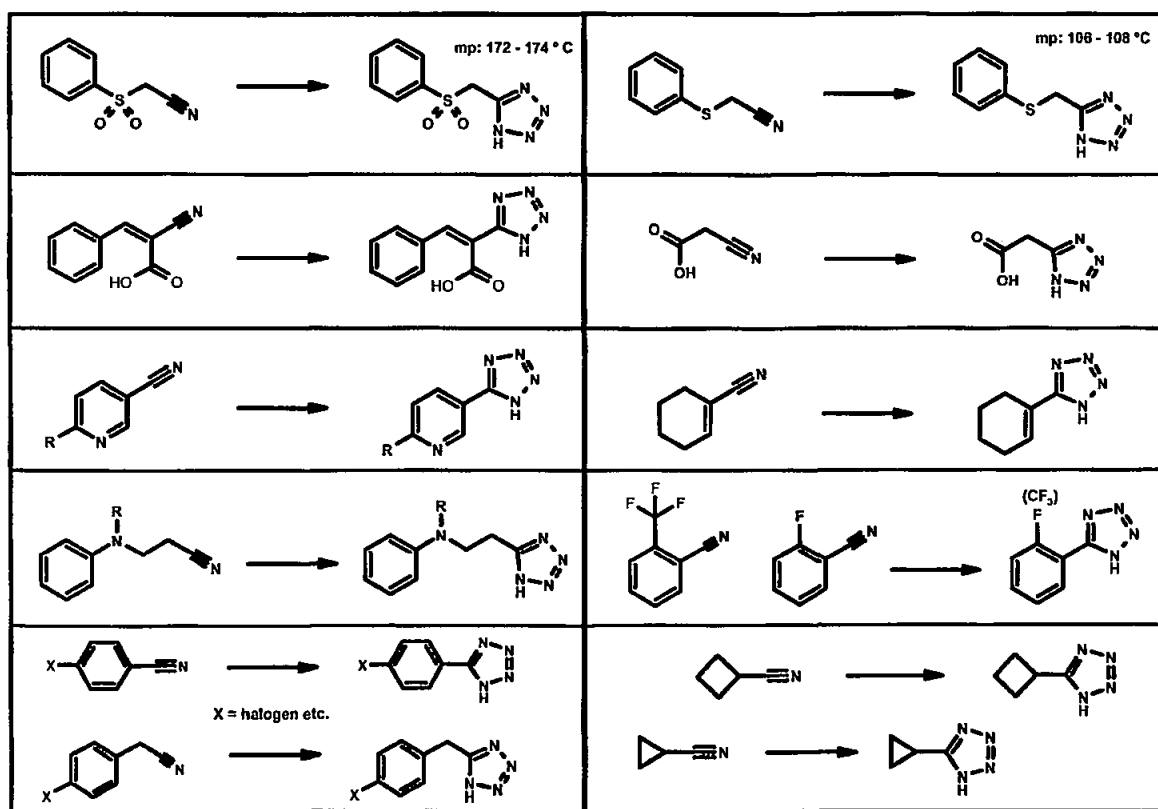
m.p.: 255 – 257 °C

Tlc: R_f -value: 0.40, toluene : EtOAc : AcOH (20 : 20 : 1); SiO_2 -plate.

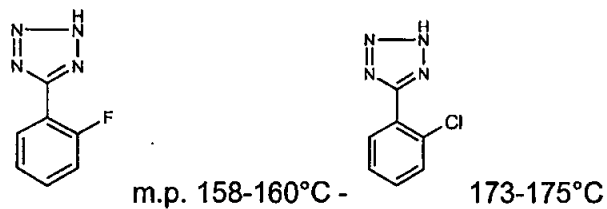
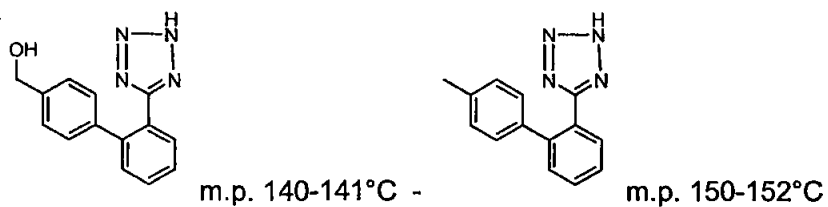
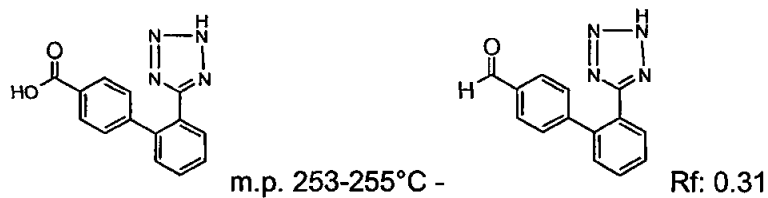
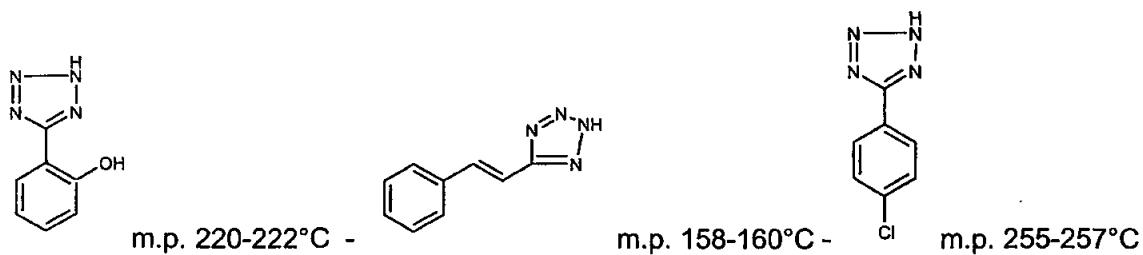
HPLC: Hewlett Packard, solvents. H_3PO_4 , acetonitrile/water; flow: 2 ml/min; injection: 5.0 μl ; wavelength 220 nm, 40 °C; flow: 2 ml/min; injection: 5.0 μl ; Column: Merck, Chromolith Performance RP-18e 100-4.6 mm. Rt. Time: 6.184 min

Examples 11 a) to 11 l):

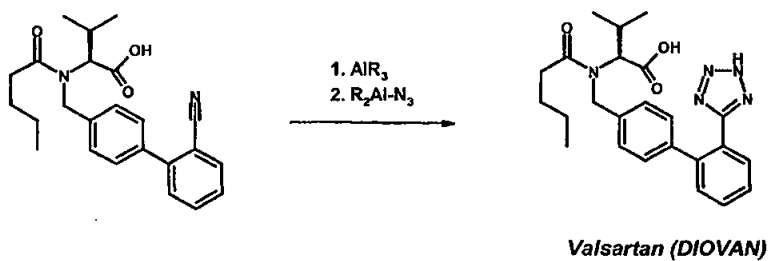
The following table (Examples 11 a) to 11 l) should further illustrate the present invention. When applying the method of the present invention, tetrazole compounds of formula (I) are obtainable starting from nitrile compounds of formula (II a):



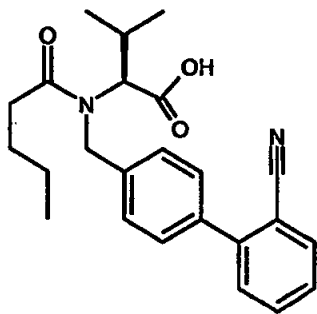
Using the technology as described above, especially as described in the examples, following compounds can be obtained:



Example 12:



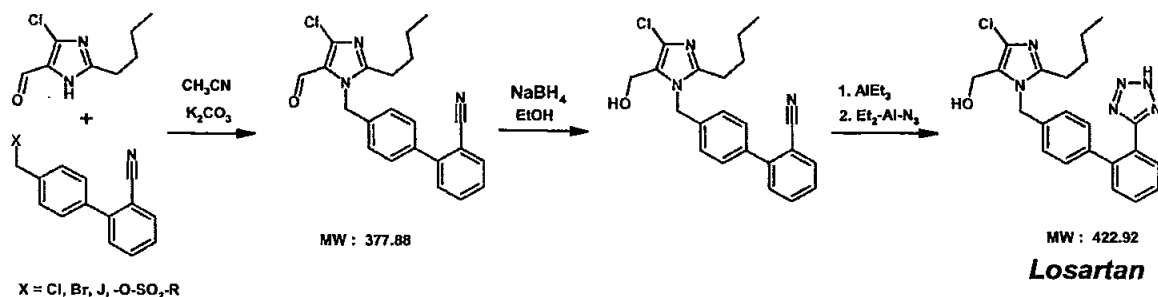
A suspension of 5 mmol of formula



1.96 g 5 mmol), in 5 ml of toluene and 2.7 ml of a 1.8 molar solution of triethyl aluminium in dry toluene are slowly combined at 0° C. The separately prepared diisobutyl-Al-azid (7 mmol) in toluene is added to the suspension and finally the mixture is heated to an internal temperature of ca. 110 °C over night. HPLC control shows after 14 h ca. 50 % conversion. Another portion of diisobutyl aluminium azid (4 mmol) is added and heating at reflux temperature at 130 °C is continued for further 12 hours. HPLC shows a conversion of ca. 77 % to the desired product (Valsartan DS) and ca. 23% of starting material. After cooling down to room temperature the reaction mixture was quenched onto a mixture of an aqueous solution of 50 mmol of NaNO₂ in 40 ml of 2N hydrochloric acid. Additional 20 ml of 2N HCl is added under stirring to dissolve precipitated aluminium hydroxide. Finally the product is isolated from the aqueous phase by extraction with i-propyl acetate. The combined organic phases (toluene/i-PrOAc) are washed with 30 ml of water and evaporated to dryness in vacuum to give crude oily valsartan which contained still ca. 23 % of starting material. The product can be purified by careful extraction with KHCO₃ from the organic phase to the aqueous phase as the bis potassium salt and subsequent adjustment with hydrochloric acid and back extraction to i-propyl acetate.

Example 13:

**Losartan via Diethyl-Al-Azid - Cycloaddition
3 Step Syntheses ex Br-OTBN**



Reaction Step 1: Disclosed in

- 1) K. Srinivas et al., Synthesis, 2004, (4), 506
- 2) R. D. Larsen et al., J. Org. Chem., 59, 6391 (1994)
- 3) T. Kato & Y. Shida, EP 578125 A1 (19940112)

Reaction Step 2. Reduction of the aldehyde with NaBH₄ to form the corresponding alcohol:

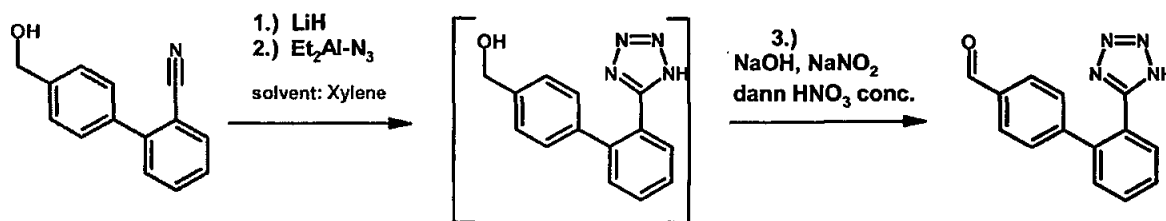
3.78 g (10 mmol) of "5-formyl-imidazol-1-ylmethyl-biphenyl-2-carbonitrile" are suspended in 50 ml of ethanol. To this suspension is added in 2 portions 152 mg (4 mmol) of NaBH₄ under stirring at 10 °C. After stirring for 2-3 hours the reaction is quenched by addition of 10 ml 2N HCl. The reaction mixture is concentrated in vacuum and finally diluted with 25 ml of water. The aqueous phase is extracted 3 times with 30 ml of ethyl acetate. The organic phases are combined and evaporated to dryness to give an almost white solid residue which is dried in vacuum. The crude "alcohol" is used in the next step without further purification.

Reaction Step 3. Example for "in-situ-protection" with AlEt₃ and subsequent cycloaddition with diethyl-Al-azide and working up to LOSARTAN.

1.9 g (5 mmol) of the „hydroxymethyl-imidazol-1-ylmethyl biphenylcarbonitrile" from the previous step is suspended in 10 ml of dry toluene under argon. To this suspension is added at room temperature under stirring 2.8 ml of a 1.8 molar solution of AlEt₃ in toluene. Stirring of the suspension was continued for additional 3 hours. Then a solution of 10 mmol diethyl aluminium azide in toluene, which is prepared in a separate flask, is added via syringe. (This 10 mmol of Et₂Al-N₃ was prepared by stirring 10 mmol of Et₂AlCl and 10 mmol

of NaN_3 in toluene at room temperature over night to give a white suspension of NaCl , but the diethyl aluminium azide is dissolved in toluene). The reaction mixture is heated to reflux ($\sim 111^\circ\text{C}$), external temperature ca. 140°C . conversion is controlled by HPLC analysis. After refluxing for 24 hours the reaction mixture was cooled to room temperature and finally quenched on an aqueous solution of 40 mmol of NaNO_2 in 40 ml of 2N hydrochloric acid. Then additional 20 ml of 2N HCl is added under stirring to dissolve the precipitated Aluminium hydroxide. Finally the product was isolated from the aqueous phase by extraction with ethyl acetate. The combined organic phases (toluene/EtOAc) are washed 2 times with 25 ml of water and evaporated to dryness in vacuum to give crude Losartan. The crude Losartan can be purified by crystallization from CH_3CN or CH_3CN /water mixtures, according to literature; (J.O.C., 59, 6391 (1994)).

Example 14:

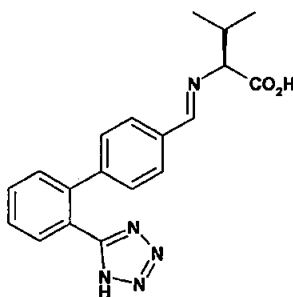


16.74 g (80 mmol) of the "4-hydroxymethyl-biphenyl-2-carbonitrile" is suspended in 100 ml of dry xylene (isomer mixture) under argon. To this suspension is added at room temperature under stirring 0.636g (80 mmol) of lithium hydride. The suspension is stirred for an additional 4 hours at 120°C external temperature and a solution of 160 mmol diethylaluminium azide in toluene (which is prepared separately by stirring 160 mmol of diethylaluminium chloride and 160 mmol of sodium azide in xylene [isomer mixture] at room temperature overnight) is added via syringe. The reaction mixture is heated to reflux ($\sim 120^\circ\text{C}$), external temperature ca. 140°C . Conversion is controlled by HPLC analysis. After refluxing for 24 hours the reaction mixture is cooled to room temperature and finally quenched with a solution of 300mmol of sodium nitrite and of 15% sodium hydroxide (240 mmol). Finally 95 ml of conc. HCl is added under stirring. To the resulting suspension is added at room temperature under stirring 31g (320 mmol) of 65% nitric acid. The suspension is stirred for an additional 6 hours at 60°C external temperature (internal

Temperature = 55°C). Finally the product is isolated by filtration. The crude 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde is obtained..

Example 15:

a) Preparation of 3-methyl-2{[1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-meth-(E/Z)-ylidene]-amino}-butyric acid

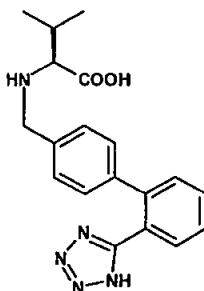


Aqueous sodium hydroxide solution 30% (4.2 ml; 31.5 mmol) is added to a stirred suspension of L-Valine (2.43 g; 20.8 mmol) and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (5 g; 19.6 mmol), in water (20 ml) at room temperature, until pH 11 is reached. The resulting solution is stirred at room temperature for 15 minutes. The clear solution is evaporated at 60°C in vacuo, and remaining water is azeotropically removed with 10 ml 1-butanol.

¹H NMR (CD₃OD, 300MHz):

δ= 8.21 (CH=N, s), 7.67 (C₆H₅-CH, d), 7.40-7.60 (4 C₆H₅-CH, m), 7.18 (C₆H₅-CH, d), 3.42 (CH, d), 2.31 (CH, m), 0.98 (CH₃, d), 0.82 (CH₃, d).

b1) Preparation of (S)-3-Methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid



Aqueous sodium hydroxide solution 2.0 M (approximately 100 ml; 200 mmol) is added to a stirred suspension of L-Valin (11.8 g; 100 mmol) and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (25.1 g; 100 mmol) in water (100 ml) at room temperature, until pH 11 is reached. The resulting clear solution is evaporated at 60°C in vacuo, and remaining water is azeotropically removed with 1-butanol. The residue (imine as a solid foam) is dissolved in absolute ethanol (300 ml), and sodium borohydride (3.78 g; 100 mmol) is added in portions to the solution at 0-5°C. The reaction mixture is stirred for 30 min at 0-5°C, and, if the reaction is complete (HPLC), quenched by addition of water (100 ml) and hydrochloric acid 2.0 M (80 ml; 160 mmol). The organic solvent (ethanol) is stripped off from the clear solution (pH 7) at 50°C in vacuo. The remaining aqueous concentrate is adjusted to pH 2 by slow addition of hydrochloric acid 2.0 M (approximately 70 ml; 140 mmol) at 40°C. During the addition the desired product precipitates. It is collected by filtration, washed with water and dried in vacuo. The crude product is suspended in methanol at 50°C, and the slurry is cooled to room temperature. (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid is collected by filtration and then dried in vacuo.

b2) Alternatively, (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid can be prepared e.g. as follows:

Aqueous sodium hydroxide solution 10 M (approximately 41 ml; 410 mmol) is added to a stirred suspension of L-Valine (24.8 g; 210 mmol) and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (50 g; 200 mmol) in water (200 ml) at room temperature, until pH 11 is reached. The resulting clear solution is evaporated at 60°C in vacuo, and remaining water is azeotropically removed with 1-butanol. The residue (imine as a solid foam) is dissolved in methanol (600 ml), and sodium borohydride (3.13 g; 80 mmol) is added in portions to the solution at 0-5°C. The reaction mixture is stirred for 30 min at 0-5°C, and, if the reaction is complete (HPLC), quenched by addition of water (300 ml) and hydrochloric acid 2.0 M (160 ml; 320 mmol). The organic solvent (methanol) is stripped off from the clear solution (pH 7) at 50°C in vacuo. The remaining aqueous concentrate is adjusted to pH 2 by slow addition of hydrochloric acid 2.0 M (approximately 90 ml) at 40°C. During the addition the desired product precipitates. It is collected by filtration, washed with water and dried in vacuo. The crude product is suspended in methanol at 50°C, and stirred for a few minutes. Then the slurry is cooled to

room temperature. (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid is collected by filtration and then dried in vacuo.

Enantiomeric excess (by HPLC): ee > 99.9 %

b3) Alternatively, (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid can be prepared e.g. as follows:

Sodium hydroxide (1.71g; 41.89 mmol) is added in portions to a stirred suspension of L-Valine (2.48 g; 21 mmol) in 15 ml methanol. The mixture is stirred at room temperature for 30 minutes. Then 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (5 g; 20 mmol) is added. The mixture becomes a clear solution after a few minutes. The mixture is then cooled to -5°C and sodium borohydride (0.315 g; 8 mmol) is added in portions to the solution. The temperature is maintained between 0-5°C during the addition. The resulting mixture is stirred for 2 hours at 0°C - the reaction completion is followed by HPLC - then quenched by addition of water (10 ml) and hydrochloric acid 37% (5.3 g) until pH is between 2-2.5. Further work-up and crystallisation are done according to example 1 b2).

Enantiomeric excess (by HPLC): ee > 99.9 %

b4) Alternatively, (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid can be prepared e.g. as follows:

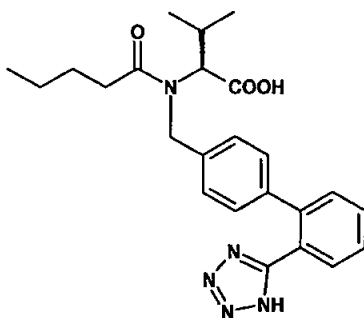
In a 50 ml steel autoclave, 3-methyl-2-[[1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-meth-(E/Z)-ylidene]-amino]-butyric acid (1.5 g; 3.2 mmol) and 5% Pt/C (7.5 mg, 5% wt/wt) is charged under argon. Then 15 ml methanol are added and the autoclave is sealed and flushed with argon and hydrogen. The pressure is set to 5 bars and the reaction stirred at room temperature. The reaction completion is monitored by HPLC. Then the autoclave is flushed with argon and the catalyst is filtered off. Further work-up and crystallisation are done similar to example 1 b2).

b5) Alternatively, (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid can be prepared e.g. as follows:

2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (0.79 g; 3.2 mmol) and L-Valine (0.4 g; 3.4 mmol) are suspended in 15 ml methanol. Then sodium hydroxide is added (0.27 g; 6.72 mmol) and the reaction mixture is stirred at room temperature until a clear solution is obtained. 5% Pt/C (15.8 mg; 2 wt/wt-%) is added. The autoclave is sealed and flushed with argon and hydrogen. The pressure is set to 5 bars and the reaction is stirred at 60°C. The

reaction completion is monitored by HPLC. Then the autoclave is flushed with argon and the catalyst is filtered off. Further work-up and crystallisation are done similar to example 1 b2). Enantiomeric excess (by HPLC): ee > 99.9 %.

c) Preparation of (S)-3-Methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid



A suspension of (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid (17.6 g; 50.0 mmol) in 1,2-dimethoxyethan (116 g) is cooled to -5°C , and valeroyl-chloride (9.9 ml; 80 mmol) is added, followed by slow addition of pyridine (6.0 ml; 75 mmol) diluted with 1,2-dimethoxyethane (60 ml). **[1]** After completion of the reaction, the reaction mixture is quenched with methanol (18 ml). Finally water (50 ml) is added at room temperature, and after stirring for 1 h, the mixture is adjusted to pH 7.5 by addition of aqueous sodium carbonate solution 10% (~ 116 ml, 120 mmol) at 0°C . The organic solvents are stripped off at 50°C in vacuo. Ethylacetate (125 ml) is added to the remaining aqueous concentrate, and the two-phase system is adjusted to pH 2 at $0-5^{\circ}\text{C}$ by addition of 2.0 M HCl (~ 98 ml). The organic phase is separated and concentrated at 45°C in vacuo (water is azeotropically removed). The crystallization of the product is initiated at 45°C and – after addition of cyclohexan (102 ml) – completed by cooling to -5°C . The solid is collected by filtration, and after drying at 50°C , (S)-3-methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid is received as a white powder.

Melting point: $108-110^{\circ}\text{C}$

Enantiomeric excess (by HPLC): ee > 99.5 %

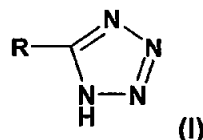
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- 57 -

[1] Alternatively pyridine and valeroylchloride can be added alternately: A suspension of (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid (25.5 g; 72.6 mmol) in 1,2-dimethoxyethane (126 g) is cooled to -10°C , and valeroylchloride (8.75 g; 72.6 mmol) is added over 15 min., followed by slow addition of a mixture (7.16 g) of pyridine (5.6 g) and water (1.5 g) over 61 min. After stirring for 30 min. valeroylchloride (5.3 g; 43.5 mmol) is added over 8 min., followed by slow addition over 30 min. of a mixture (4.3 g) of pyridine (3.4 g) and water (0.9 g). After each addition of pyridine the pH is controlled by sampling (hydrolyzed with water). The pH of the samples should always be below 2.5. The reaction is stirred for 25 min., then water (25.6 g) is added over 30 min. The mixture is stirred for another 30 min., then warmed to 23°C over 30 min. and stirred for another 2 hours. Adjustment of pH, remove of organic solvents by distillation, further work-up and crystallization is done as described in the example 1 c) above.

What is claimed is

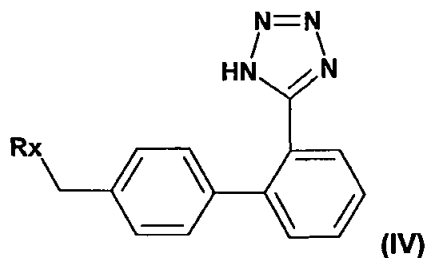
1. A process for the manufacture of a tetrazole of formula



or a tautomer or a salt thereof, wherein R represents an organic residue;
comprising

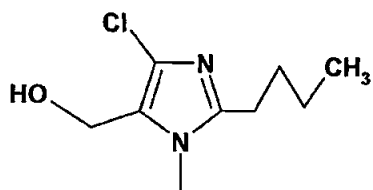
- (i) reacting a compound of formula **R-CN (II a)** with an azide of formula **(R₁)(R₂)M-N₃ (IIb)**, wherein R has the meaning as defined above; R₁ and R₂, independently of another, represent an organic residue such as an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or a heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted; and M is boron or aluminium; and
- (ii) isolating the resulting compound of formula (I).

2. A process according to claim 1 for the manufacture of said angiotensin II receptor antagonists having as structural feature a tetrazol ring, e.g. of formula (IV),

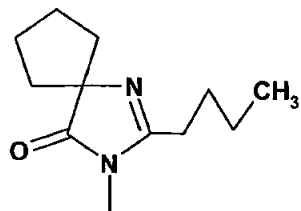


or a tautomeric form thereof, wherein Rx represents a structural element selected from the group consisting of

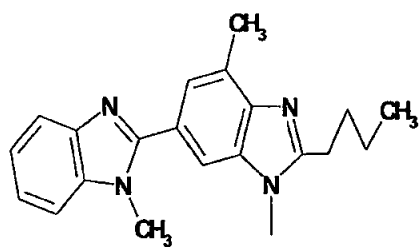
- 59 -



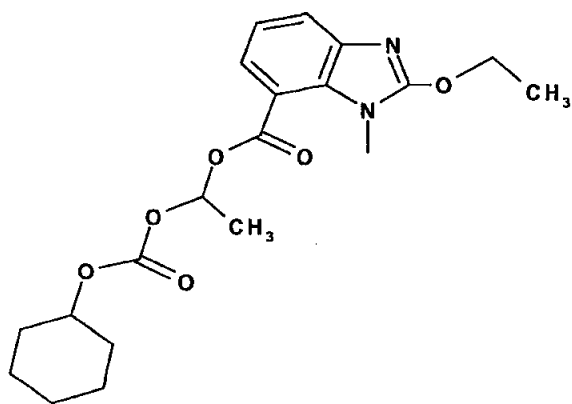
(derived from losartan - cf. EP 253310);



(derived from irbesartan - cf. EP 454511);

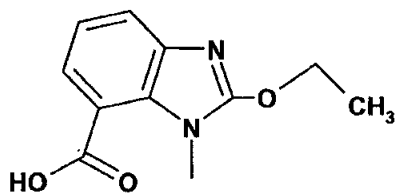


(derived from UR-7247);

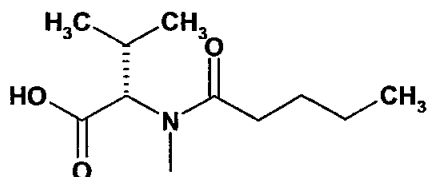


(derived from candesartan-cilexetil- EP

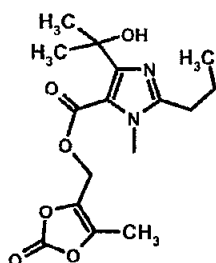
459136);



(derived from candesartan); and



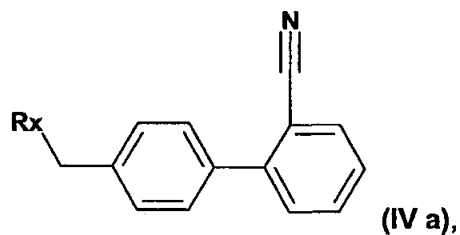
(derived from valsartan - cf. EP 443983);



(derived from olmesartan)

or, in each case, a salt thereof;

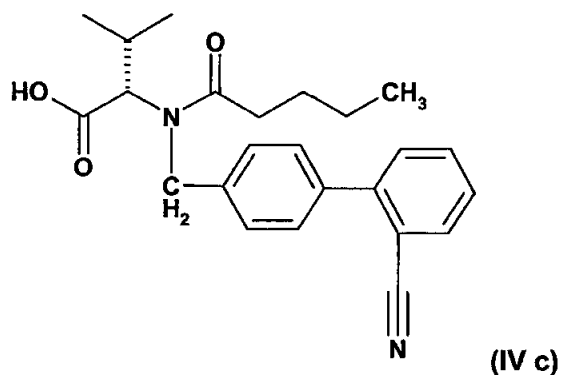
characterized by reacting a compound of formula (IV a)



wherein Rx has the meanings as given above,

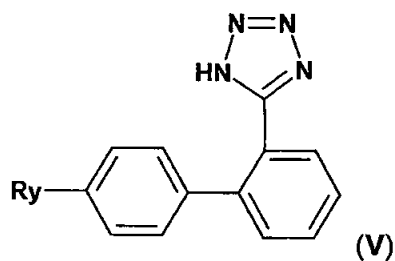
with a compound of formula $(R_1)(R_2)M-N_3$ (II b), wherein R_1 and R_2 , independently of one another, represent an organic residue; and isolating the resulting compound of formula (IV).

3. A process according to claim 1 for the manufacture of a compound of formula (IV b) comprising reacting a compound of formula (IV c)

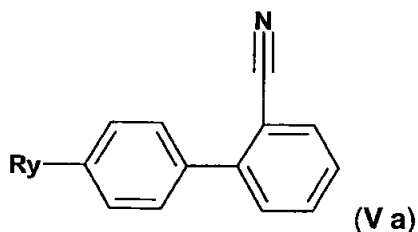


or an ester thereof with an azide of formula $(\text{R}_1)(\text{R}_2)\text{M}-\text{N}_3$ (IIb), wherein R_1 and R_2 , independently of each other, have the meanings as defined above, and isolating the compound of formula (IV b).

4. A process according to claim 1 for the manufacture of a compound of formula manufacture of a compound of formula

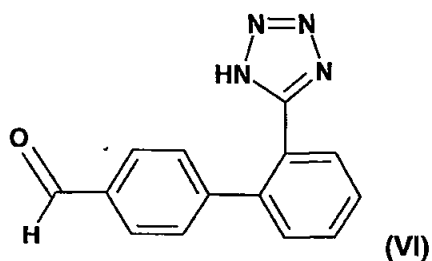


a tautomeric form thereof wherein R_y represents C_1 - C_8 -alkyl such as methyl; C_1 - C_8 -alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, or an acetal of formyl; and X_1 being in a benzylic position, comprising reacting a compound of formula (IV a)



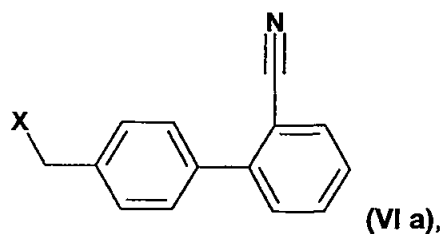
with a compound of formula $(\text{R}_1)(\text{R}_2)\text{M}-\text{N}_3$ (II b), wherein R_1 and R_2 , independently of one another, represent an organic residue; and isolating the resulting compound of formula (V).

5. A process for the manufacture of the compound of formula (VI)

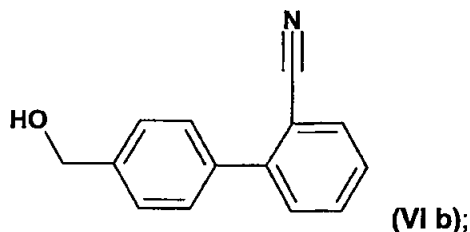


or a tautomer or salt thereof, comprising

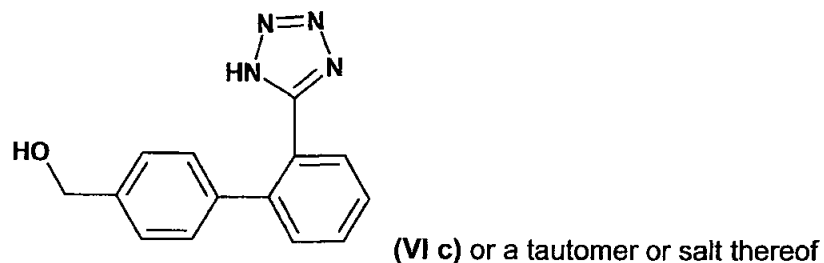
(a) treating a compound of formula (VI a)



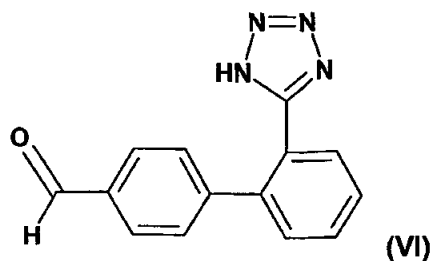
wherein X represents a leaving group, first with a nucleophilic agent and then with a "solvolytic" base resulting in a compound of formula (VI b)



(b) reacting a compound of formula (VI b) with an azide of formula $(R_1)(R_2)M-N_3$ (II b), wherein the variables R_1 and R_2 , independently of one another, have the meanings as defined above; resulting in a compound of formula (VI c)



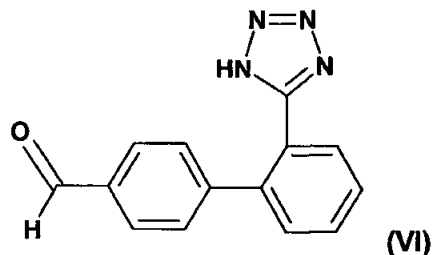
(c) oxidizing a compound of formula (VI c) or a tautomer or salt thereof resulting in a compound of formula (VI)



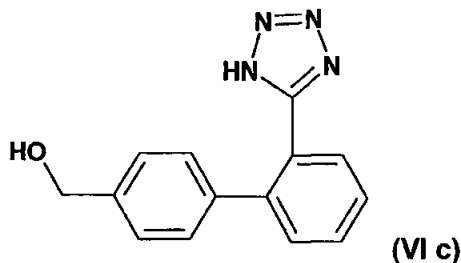
or a tautomer or salt thereof; and

(d) isolating the compound of formula (VI) or a tautomer or salt thereof.

6. A process for the manufacture of a compound of formula (V d)



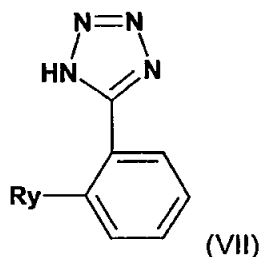
comprising oxidizing a compound of formula (VI c)



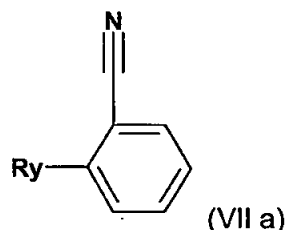
or a tautomer or salt thereof resulting in a compound of formula (VI) or a tautomer or salt thereof; and isolating a resulting compound of formula (VI).

7. A process according to claim 5 or 6, wherein the oxidation is carried out in the presence of an oxidation agent selected from the group consisting of HNO_2 , HNO_3 or a corresponding anhydride thereof, and a peroxodisulfate, and wherein as solvent an alkylated aromatic hydrocarbon solvent such as toluene is used.

8. A process according to claim 1 for the manufacture of a compound of formula



a tautomeric form thereof, wherein Ry represents C₁-C₈-alkyl such as methyl; C₁-C₈-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (VII a)



with a compound of formula **(R₁)(R₂)M-N₃ (II b)**, wherein R₁ and R₂, independently of one another, represent an organic residue; and isolating the resulting compound of formula (VI).

9. A process according to any one of claims 1 to 5 and 8, wherein a compound of formula **(R₁)(R₂)M-N₃ (II b)** is used, wherein M is aluminium or boron; and R₁ and R₂, independently of one another, is C₁-C₈-alkyl such as methyl, ethyl, propyl, diisobutyl, tert-butyl or n-octyl; C₃-C₇-alkenyl such as allyl or crotyl, C₃-C₇-cycloalkyl such as cyclohexyl; phenyl-C₁-C₄-alkyl such as benzyl or 2-phenethyl; phenyl-C₃-C₅-alkenyl such as cinnamyl, or C₃-C₈-cycloalkyl-C₁-C₈-alkyl such as cyclopropylmethyl or cyclohexylmethyl.

10. A compound of formula **(R₁)(R₂)M-N₃ (II b)**, wherein M is aluminium or boron; and R₁ and R₂, independently of one another, is C₃-C₇-alkenyl such as allyl or crotyl, C₃-C₇-cycloalkyl such as cyclohexyl; phenyl-C₁-C₄-alkyl such as benzyl or 2-phenethyl; phenyl-C₃-C₅-alkenyl such as cinnamyl, or C₃-C₈-cycloalkyl-C₁-C₈-alkyl such as cyclopropylmethyl or cyclohexylmethyl.

INTERNATIONAL SEARCH REPORT

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International Application No
EP2004/007980

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F5/06 C07F5/02 C07D257/04 C07D403/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAGISHITA S ET AL: "POTENT INHIBITORS OF SECRETORY PHOSPHOLIPASE A2: SYNTHESIS AND INHIBITORY ACTIVITIES OF INDOLIZINE AND INDENE DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 39, no. 19, 1996, pages 3636-3658, XP002921819 ISSN: 0022-2623 synthesis of compound 50b ----- -/-	1,10

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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10 November 2004

Date of mailing of the International search report

23/11/2004

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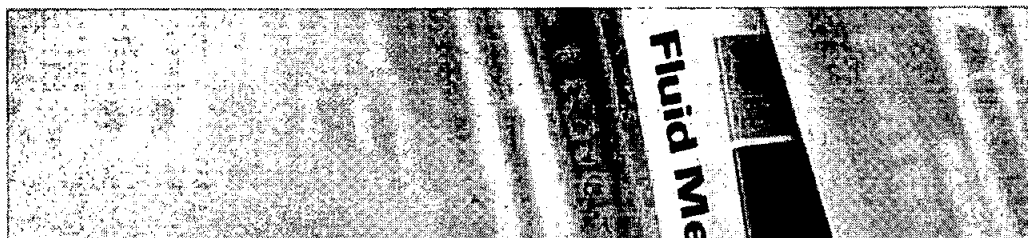
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NOVEL SYNTHESIS OF 5-SUBSTITUTED TETRAZOLES FROM NITRILES

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Why Is Tetrazole Formation by Addition of Azide to Organic Nitriles Catalyzed by Zinc(II) Salts?

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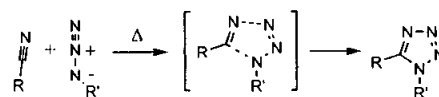
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Abstract: The mechanism by which zinc(II) catalyzes the union of an azide ion with organic nitriles to form tetrazoles is investigated by means of density functional theory using the hybrid functional B3LYP. The calculations indicate that coordination of the nitrile to the zinc ion is the dominant factor affecting the catalysis; this coordination substantially lowers the barrier for nucleophilic attack by azide. Relative reaction rates of catalyzed and uncatalyzed tetrazole formation also provide experimental support for this conclusion.

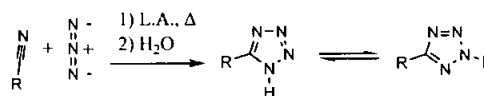
I. Introduction

Tetrazoles are an increasingly popular functionality¹ with wide ranging applications. They have found use in pharmaceuticals as lipophilic spacers² and carboxylic acid surrogates,³ in specialty explosives,⁴ photography, and information recording systems,⁵ not to mention as precursors to a variety of nitrogen containing heterocycles.⁶ The most direct method to form tetrazoles is via the concerted^{1,7} and highly regioselective⁸ [2 + 3] cycloaddition between an organic azide (R–N₃) and an organic nitrile (R–CN) as shown in Scheme 1.⁹ However, this cycloaddition is too slow to be synthetically useful except when potent electron-withdrawing groups activate the nitrile component.

Scheme 1. [2 + 3] Cycloaddition of an Organic Azide and an Organic Nitrile



Scheme 2. Addition of an Inorganic Azide to an Organic Nitrile

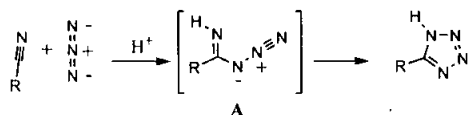


Of greater concern to us here is the mechanism behind the formally similar addition of azide salts and nitriles giving 1H-tetrazoles (Scheme 2). This variant is of greater synthetic interest since the range of nitriles which are competent dipolarophiles is much broader and a wide variety of metal-azide complexes can serve as azide donors.¹⁰ Mechanistically, however, these transformations are less straightforward. In the case where hydrazoic acid or an amine salt of hydrazoic acid acts as the dipole, both an anionic two step mechanism¹¹ and a concerted [2 + 3] cycloaddition¹² have been posited in the literature. More recently, we have suggested a different mechanism¹³ that involves the activation of the nitrile by protonation, proceeding through a previously unsuspected imidoil azide intermediate

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Scheme 3. Addition of an Azide Anion to a Nitrile through the Intermediacy of an Imidoyl Azide



(A, Scheme 3). This pathway is computed to be some 10 kcal/mol lower in energy than the concerted [2 + 3] mechanism. To the best of our knowledge, there are no reports concerning the mechanistic details for the cases where nonprotic Lewis acids are employed as catalysts for the addition of an azide ion to a nitrile.

It has been recently shown that zinc salts are excellent catalysts for this reaction;¹⁴ in fact, they function well even in aqueous media, thereby enabling a more environmentally friendly route to 1*H*-tetrazoles.¹⁵ When we follow this protocol, simple heating (80–170 °C) of an aqueous reaction mixture of nitrile, sodium azide, and catalytic zinc salt provides the 1*H*-tetrazole in good yield following acidic workup. Seeking to understand the mechanism of this catalysis, we have performed model calculations using density functional methods to investigate the role of zinc. A comparison of measured reaction rates of catalyzed with uncatalyzed tetrazole formation, for both intra- and intermolecular cases, seems to corroborate the computational findings.

II. Computational Details

All geometries and energies presented in the present study are computed using the B3LYP¹⁶ density functional theory method as implemented in the Gaussian98 program package.¹⁷ Geometry optimizations were performed using the triple- ζ plus polarization basis set 6-311G(d,p), followed by single-point energy calculations using the larger basis set 6-311+G(2d,2p). To evaluate the zero-point vibrational effects on energy, Hessians were calculated at the B3LYP/lan12dz level of theory.

Solvation energies were added as single-point calculations using the conductor-like solvation model COSMO¹⁸ at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by a polarizable dielectric continuum. The dielectric constant was chosen as the standard value for water,

$\epsilon = 80$. Some of the experiments were done in DMF, which has a dielectric constant of $\epsilon = 37$. As the solvation energy to a first approximation is proportional to $(1 - (3/2\epsilon))$ for dipoles and $(1 - (1/\epsilon))$ for charges for large ϵ ,¹⁹ the water and DMF values give almost identical solvation energies. Since we are mainly interested in reaction barriers (reactant – transition state) and relative barriers, the differences are not significant.

The energies presented here include solvation effects with $\epsilon = 80$, unless otherwise stated.

III. Experimental Details

To a solution of sodium azide (325 mg, 5 mmol) and zinc bromide (1.12 g, 5 mmol) in water (7 mL) and 2-propanol (3 mL) was added cyanopyrazine (21 mg, 0.2 mmol) and benzyl alcohol (21 mg). The reaction was stirred at 23 °C, and aliquots were removed, added to a biphasic solution of HCl (1 N, 1 mL) and ethyl acetate (5 mL), and shaken. The organic layer was injected onto a GC, and the extent of reaction was determined using benzyl alcohol as the internal standard. The data showed zeroth order kinetics, with a calculated nitrile half-life of 4.0 min. A second reaction was run as above except that no zinc was added, and the reaction was heated in an oil bath set to 80 °C. Zeroth order kinetics were observed again, and the computed half-life was 35 min.

A solution of 2-azidoethyl benzyleyanamide²⁰ (0.05 mmol) in DMF (5 mL) was heated in an oil bath set at 140 °C. Aliquots were removed and added to ethyl acetate (5 mL), washed with water, dried, evaporated, and analyzed by ¹H NMR. Zeroth order kinetics were observed, and a half-life of 24 h was calculated. In a similar experiment, zinc bromide was added to the aforementioned mixture to bring its concentration to 0.05 M, and the resulting solution was heated in an oil bath set to 75 °C. The half-life was found to be 18 h. In a third experiment, aluminum chloride was added to a solution of 2-azidoethyl benzyleyanamide (0.1 M) in 2-methyltetrahydrofuran (10 mL) to bring its concentration to 0.1 M, and the resulting solution was stirred at 23 °C. The half-life was found to be 24 h.

IV. Results and Discussion

The model calculations presented here will focus on the simplest nitrile, namely acetonitrile (CH₃CN). The conclusions should, however, be of direct relevance to nitriles in general.

Before discussing the results, the modeling of the Zn^{II} ligand sphere deserves comment. The zinc was modeled by either tetrahedral or octahedral coordination. These two models are electronically very similar, since Zn²⁺ presents an essentially degenerate coordination sphere. However, due to the different steric effects in these two systems, the results can differ somewhat, and the different possible mechanisms are considered individually below.

A. Azide Anion Bound to Zinc. Let us first consider the situation where the azide anion (N₃[−]) is bound to Zn^{II} and the acetonitrile undergoes the cycloaddition without coordinating to zinc. The optimized transition state structures for this [2 + 3] cycloaddition reaction, modeled using tetrahedrally coordinated zinc (three water ligands and the azide) or octahedrally coordinated zinc (5 water ligands and the azide), are displayed in Figure 1 (A and B, respectively). The energy barriers (enthalpy including solvation) for these reactions are calculated to 33.7 and 35.6 kcal/mol, respectively. Furthermore, making the overall system charge-neutral by substituting one of the water

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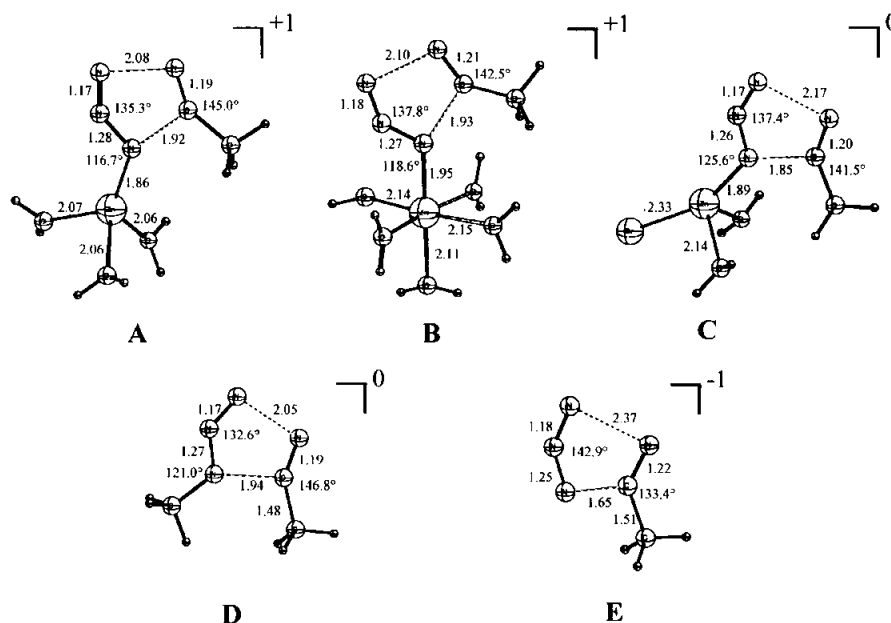


Figure 1. Optimized transition state structures for various models of the [2 + 3] tetrazole reaction. Bond lengths are given in angstrom. (A) (Tetrahedral zinc) $\Delta H^\ddagger = +33.7$ kcal/mol; (B) (octahedral zinc) $\Delta H^\ddagger = +35.6$ kcal/mol; (C) (neutral tetrahedral zinc) $\Delta H^\ddagger = +34.2$ kcal/mol; (D) (no zinc) $\Delta H^\ddagger = +31.6$ kcal/mol; (E) (no zinc, inorganic azide) $\Delta H^\ddagger = +33.8$ kcal/mol.

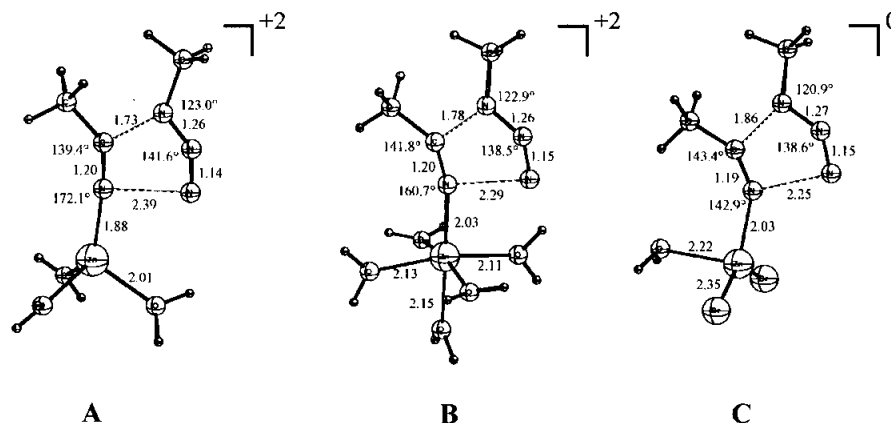


Figure 2. Optimized transition state structures for [2 + 3] cycloaddition reactions of methyl azide and acetonitrile coordinated to zinc. (A) (Tetrahedral zinc) $\Delta H^\ddagger = +25.3$ kcal/mol; (B) (octahedral zinc) $\Delta H^\ddagger = +28.7$ kcal/mol; (C) (neutral tetrahedral zinc) $\Delta H^\ddagger = +29.7$ kcal/mol.

ligands with a Br^- anion (C) gives almost the same barrier, 34.2 kcal/mol.

These barriers are to be compared to the 31.6 kcal/mol barrier for the uncatalyzed concerted cycloaddition of CH_3CN and CH_3N_3 (D) and the 33.8 kcal/mol barrier for [2 + 3] cycloaddition of CH_3CN and N_3^- (E). These calculations indicate that the coordination of an azide anion to Zn does not lead to any significant change in the barrier.

As seen from Figure 1, the local structure of the transition states around the azide and nitrile is quite similar in the zinc-coordinated cases (e.g., A) and in the parent zinc-free cases (D). The $\text{C}_{\text{nitrile}}-\text{N}_{\text{azide}}$ bond distance, for instance, is 1.92 Å in Figure 1A and is 1.94 Å in Figure 1D. The $\text{N}_{\text{nitrile}}-\text{N}_{\text{azide}}$ bond distance is 2.08 Å in Figure 1A and is 2.05 Å in Figure 1D.

B. Nitrile Bound to Zinc. Next, we consider the situation where the zinc ion is bound to the nitrile instead and methyl

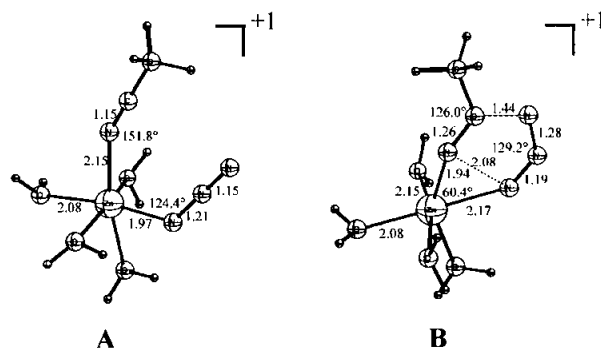


Figure 3. Optimized reactant (A) and transition state (B) structures for the formal [2 + 3] cycloaddition reaction of azide and acetonitrile, both bound to a zinc ion. (A) (Octahedral zinc) [reactant]; (B) (octahedral zinc) [transition state] $\Delta H^\ddagger = +27.3$ kcal/mol.

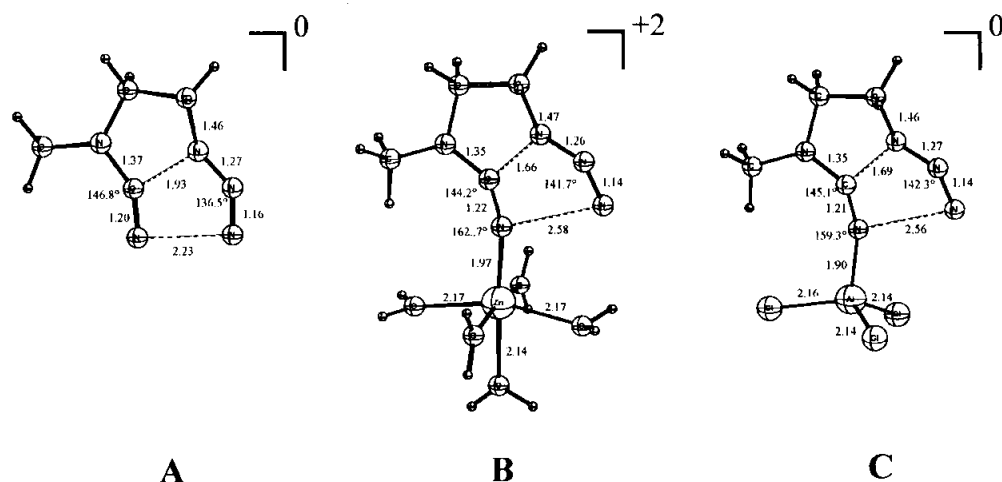
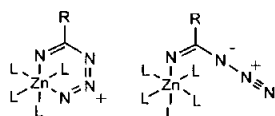


Figure 4. Optimized transition state structures for [2 + 3] intramolecular cycloaddition reaction. (A) Uncatalyzed, (B) octahedral zinc catalyzed, and (C) AlCl_3 catalyzed.

Chart 1. Potential Intermediates with the Nitrile Coordinated to Zinc



azide comes from outside the coordination sphere. Three optimized transition state structures modeling these reactions are displayed in Figure 2. In Figure 2A, the zinc is tetrahedral with three water ligands and the acetonitrile, in Figure 2B, the zinc is octahedral (5 water ligands and the acetonitrile), and finally, in Figure 2C, the zinc is tetrahedral (two bromine ligands, one water, and the acetonitrile). The calculated barriers for these reactions are, respectively, 25.3, 28.7, and 29.7 kcal/mol. All the models represent some lowering in the barrier compared to the reactions without the Zn, 31.6 kcal/mol for cycloaddition of CH_3CN and CH_3N_3 (Figure 1D) and 33.8 kcal/mol for cycloaddition of CH_3CN and N_3^- (Figure 1E).

For the structures shown in Figure 2, we notice that the local transition state geometries are more asymmetric than those of Figure 1A–D. The $\text{C}_{\text{nitrile}}-\text{N}_{\text{azide}}$ bond distance is shorter, and the $\text{N}_{\text{nitrile}}-\text{N}_{\text{azide}}$ bond distance is longer. This is reminiscent of the situation where the nitrile is attached to a strong electron-withdrawing group.¹³

C. Both Reactants Bound to Zinc. So far, the calculations indicate that coordination of the nitrile to Zn reduces the barrier somewhat, while binding of the azide to the Zn does not affect the barrier. What happens when both are bound to Zn?

The reactant and transition state for this cycloaddition reaction are shown in Figure 3. The calculated barrier is 27.3 kcal/mol, which is very close to the barriers obtained when the nitrile is bound to the Zn and the azide is not (e.g., Figure 2B). This suggests that the critical element of the catalysis is the activation of the nitrile by coordination to the metal ion.

As seen from Figure 3, the transition state structure is highly asymmetric, with the $\text{C}_{\text{nitrile}}-\text{N}_{\text{azide}}$ bond distance being as short as 1.44 Å. Finally, no intermediates of the type shown in Chart 1 could be located.

D. Experimental Corroboration. The results presented above indicate that coordination of the nitrile to the Zn is the

Scheme 4. Intramolecular [2 + 3] Cycloaddition between Azide and Nitrile

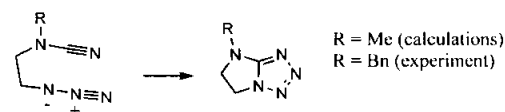


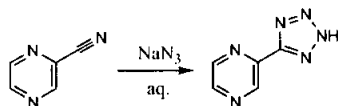
Table 1. Experimental and Theoretical Results of Intramolecular [2 + 3] Cycloaddition of Azide and Nitrile

additive	temperature (°C)	half life (h)	$\Delta G^\ddagger$ (kcal/mol) experimental	$\Delta H^\ddagger$ (kcal/mol) calculated
none	140	24	35.2 ± 0.2	31.6
ZnBr_2	75	18	29.3 ± 0.2	26.3
AlCl_3	23	24	25.0 ± 0.2	19.1

main source of catalysis. To test this hypothesis, and to further isolate the effect of zinc, we now consider the intramolecular cycloaddition of the azidoacyanamide shown in Scheme 4. This eliminates any possible effects of the charged inorganic zinc–azide complexes, as well as covalent coordination of the zinc and azide. We have calculated the transition states (optimized structures in Figure 4) and performed kinetic studies. The results are presented in Table 1. In the calculations, the benzyl group is substituted by a fully adequate methyl group. Experimentally, Zn^{2+} leads to a decrease in barrier of 5.9 kcal/mol. The calculated barrier reduction is 5.3 kcal/mol, in excellent agreement with experiment.

Zinc's Lewis acidity was previously suspected to be responsible for its catalysis in this reaction. Since most Lewis acids are not water stable, the intramolecular case allowed us to explore stronger, water sensitive Lewis acids. Aluminum chloride proved to be an even more potent catalyst for this reaction, lowering the reaction barrier by an additional 4.3 kcal/mol. The calculations predict a reduction of 7.2 kcal/mol compared to the Zn^{2+} ion.

The calculated absolute barriers are consistently lower than the experimental. The reason for this is that the entropy effect is not included in the calculations. The entropy effect on the intramolecular reaction is estimated from Hessian calculations to be ca. 12 cal/mol·K, corresponding to ca. 4 kcal/mol at room temperature, which when added to the calculated barriers leads

Scheme 5. Intermolecular Addition of Azide to Cyanopyrazine**Table 2.** Experimental Results of Intermolecular Addition of Azide to Cyanopyrazine

additive	temperature (°C)	half life (min)	$\Delta G^\ddagger$ (kcal/mol) experimental
none	80	35	27.2 ± 0.2
ZnBr ₂	23	4.3	21.5 ± 0.2

to excellent agreement with the experimental barriers. Note that an increase in catalyst concentration in these reactions was not found to significantly increase the rate of reaction.

However, the specific reaction mechanism we are trying to uncover is that for the aqueous conversion of a nitrile to a 1*H*-tetrazole by way of an inorganic azide salt. To assess the similarities of the case shown above, we also performed similar rate studies with the appropriate intermolecular reaction as shown in Scheme 5; the results are shown in Table 2. In this case, the experiments show that Zn reduces the activation barrier by 5.7 kcal/mol. The effect is virtually identical to the intramolecular case, supporting the hypothesis that nitrile coordination to the zinc is the key to catalysis.

V. Conclusions

The mechanism of the zinc catalyzed transformation of nitriles to 1*H*-tetrazoles, in which the presence of zinc lowers the energy barrier of reaction by 5 to 6 kcal/mol, has been studied. Synthetically, this corresponds to a rate acceleration of 3 to 4 orders of magnitude or the fact that the temperature required to achieve comparable rates reaction will drop by some 70–80 °C.

The data presented here strongly support the hypothesis that coordination of the nitrile substrate to the Lewis acidic zinc is the source of the catalysis in the formation of 1*H*-tetrazoles. This point is supported by model calculations using density functional theory and corroborated with experimental rate studies. We were also able to extend our knowledge of the system by looking at another Lewis acid, AlCl₃, which catalyzes the reaction to a greater extent than ZnBr₂.

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Mechanisms of Tetrazole Formation by Addition of Azide to Nitriles

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Abstract: It is well-known that azide salts can engage nitriles at elevated temperatures to yield tetrazoles; however, there is continued debate as to the mechanism of the reaction. Density functional theory calculations with the hybrid functional B3LYP have been performed to study different mechanisms of tetrazole formation, including concerted cycloaddition and stepwise addition of neutral or anionic azide species. The calculations presented here suggest a previously unsuspected nitrile activation step en route to an imido-yl azide, which then cyclizes to give the tetrazole. The activation barriers are found to correlate strongly with the electron-withdrawing potential of the substituent on the nitrile.

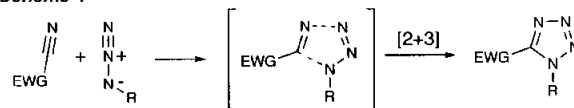
1. Introduction

Tetrazoles are an increasingly popular functionality¹ with wide-ranging applications. They have found use in pharmaceuticals as lipophilic spacers² and carboxylic acid surrogates,³ in specialty explosives⁴ and photography and information recording systems,⁵ not to mention as precursors to a variety of nitrogen-containing heterocycles.⁶ The most direct method to form tetrazoles is via the formal [2 + 3] cycloaddition of azides and nitriles. However, evidence in the literature indicates that the mechanism of the reaction is different for different azide species.

When an organic azide is used as the dipole, only certain highly activated nitriles are competent dipolarophiles.⁷ In these cases the reaction is regioselective, and only the 1-alkylated product is observed.⁸ It is commonly accepted that in these cases

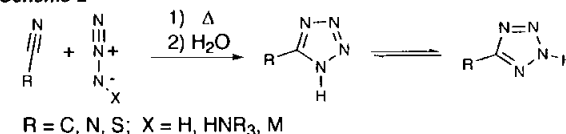
the reaction proceeds via a traditional [2 + 3] mechanism (see Scheme 1).^{1,9}

Scheme 1



Of greater interest to us here is the mechanism behind the formally similar addition of azide salts and nitriles to give 1H-tetrazoles. It has long been known¹⁰ that simple heating of certain azide salts with a nitrile in solution (typically 100–150 °C) produces the corresponding tetrazole in high yield (see Scheme 2). This variant is much more synthetically useful, as

Scheme 2



the scope of nitriles that are competent reactants in this reaction is very broad, in contrast with the case of organic azides. In addition, a wide variety of metal–azide complexes are competent azide donors.¹¹

Mechanistically, these cases are considerably more complicated: several possible reaction pathways can be envisioned.

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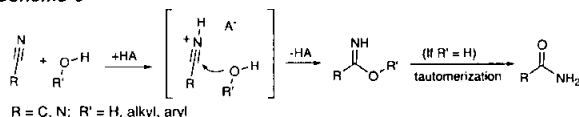
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Claims have been made for both an anionic two-step mechanism^{12,13} and a concerted [2 + 3] cycloaddition,¹⁴ but the data are not conclusive. Moreover, there is evidence against both of these mechanisms. For example, Koldobskii et al.^{14a} showed that while protic ammonium salts of azide are competent azide donors, tetraalkylammonium salts were *not*, refuting the strictly anionic two-step mechanism. Also, while virtually all nitriles are engaged by ammonium azide salts at elevated temperature, organic azides only react with the most activated nitriles.¹⁵ The fact that these azide salts and organic azides are electronically very similar, yet have significantly different reactivities, indicates that different mechanisms are likely in effect.

Other similar reactions involving nucleophilic attack on nitriles are known, including acidic hydrolysis of a nitrile to an amide,¹⁶ and the Pinner synthesis of imidates;¹⁷ relevant mechanistic studies prove illuminating. In these reactions, it has been shown that the rate-limiting step involves the activation of the nitrile by a protic acid to give an activated nitrile (see Scheme 3). Surprisingly, previous mechanistic work on tetrazole

Scheme 3



formation has not paid heed to these parallels. Is it possible that 1*H*-tetrazole formation follows a similar reaction pathway to these reactions, wherein the azide moiety engages the nitrile with the help of this protic nitrile activation step?

In the present study, we use quantum chemical calculations to probe the energetics of various reaction mechanisms for addition of azides to nitriles. This study will focus on hydrazoic acid as the dipole, and the simplest and most widely used¹⁸ procedure involving amine salts of hydrazoic acid.^{13,14,19} The theoretical method employed is the hybrid Hartree–Fock/density functional theory method B3LYP,²⁰ which has been applied extensively in organic chemistry in recent years.

II. Computational Details

All geometries and energies presented in the present study are computed with the B3LYP²⁰ density functional theory method as implemented in the Gaussian98 program package.²¹ Geometry optimizations were performed with the triple- ζ plus polarization basis set 6-311G(d,p), followed by single-point energy calculation using the larger basis set 6-311+G(2d,2p). Hessians were calculated at the B3LYP/6-311G(d,p) level of theory. Hessians provide a control that the stationary points localized are correct, with no imaginary frequencies

for minima and one imaginary frequency for transition states, and also to evaluate the zero-point vibrational effects on energy. Unless otherwise stated, solvation energies were added as single-point calculations by use of the conductorlike solvation model COSMO²² at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by polarizable dielectric continuum. The dielectric constant was chosen as the standard value for water, $\epsilon = 80$. Some of the experiments were done in DMF, which has a dielectric constant of $\epsilon = 37$. As the solvation energy to a first approximation is proportional to $(1 - 1/\epsilon)$ for large ϵ ,²³ the water and DMF values give almost identical solvation energies. Since we are mainly interested in reaction barriers (reactant – transition state) and relative barriers, the differences are not significant. This is probably best demonstrated by a numerical example. For the [2 + 3] cycloaddition of HN₃ to MeCN, the difference in solvation energy between $\epsilon = 37$ and $\epsilon = 80$ is 0.11 kcal/mol for the reactants and 0.19 kcal/mol for the transition state. The difference for the barrier is hence lower than 0.1 kcal/mol. Also, geometry optimization under solvation gives very small differences compared to optimization in gas phase and then addition of solvation energy as a single-point calculation.

The barriers reported in this paper are calculated relative to free reactants. In gas phase, this will introduce an error of several kilocalories per mole, since the depth of the hydrogen-bonding precursor is completely neglected. However, when solvation is included, the precursor complex has a very similar energy to the free reactants. Tests showed that the differences were on the order of 0.1 kcal/mol.

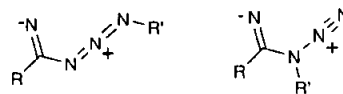
To be able to optimize the transition states, it was found crucial to start the optimization with a Hessian of a somewhat good quality; typically the HF/3-21G level was used.

All the energies presented in the present paper are enthalpies to which solvation energies are added. Zero-point energy (ZPE) effects are included.

III. Results and Discussion

A. Neutral Cycloaddition. When the azide is bound to an organic substrate, it seems clear that the reaction proceeds by a traditional concerted [2 + 3] mechanism (see Scheme 1). It is possible that azide salt species simply play the role of a covalently bound azide, a situation very similar electronically to that of organic azides. These two cases are considered in this section. Our calculations show that intermediates such as those shown in Chart 1 are not stable; thus, as previous studies

Chart 1



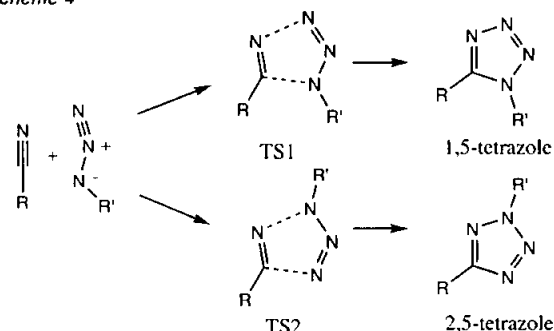
have shown, a concerted [2 + 3] cycloaddition is the most likely pathway for the bimolecular addition of nonionic azides to nitriles.

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In the context of the concerted cycloaddition, two different isomers of tetrazole, the 1,5- and 2,5-disubstituted, can be formed (see Scheme 4). We have calculated the transition states

Scheme 4



for the cycloaddition of methyl azide (MeN_3) and hydrazoic acid (HN_3) to a number of substituted nitriles, with substituents ranging from electron-donating (methyl) to very electron-withdrawing (fluorine). The barriers and reaction energies are presented in Table 1, and the transition-state and tetrazole

Table 1. Calculated Barriers and Exothermicities^a for Neutral [2 + 3] Cycloaddition Reaction of RCN with R'N₃

R	R'	TS1	TS2	$\Delta(\text{TS1} - \text{TS2})$	ΔH 1,5-tetrazole	ΔH 2,5-tetrazole	$\Delta\Delta H$
1 Me	Me	31.6	37.8	-6.2	-19.4	-19.0	-0.4
2 Ph	Me	32.5	37.8	-5.3	-17.4	-20.4	+3.0
3 tBu	Me	34.8	38.7	-3.9	-14.5	-17.3	+2.7
4 MeS	Me	28.5	33.6	-5.1	-20.4	-20.1	-0.3
5 MeO	Me	25.9	33.9	-8.0	-27.9	-28.3	+0.4
6 CH ₂ F	Me	27.8	33.5	-5.7	-22.9	-24.7	+1.8
7 CHF ₂	Me	23.3	29.7	-6.4	-31.8	-29.0	-2.8
8 CF ₃	Me	21.8	27.7	-5.9	-29.3	-31.9	+2.6
9 MeSO ₂	Me	20.4	26.1	-5.7	-26.4	-29.6	+3.2
10 F	Me	18.1	27.8	-9.7	-35.7	-38.9	+3.2
11 Me	H	35.1	41.7	-6.6	-13.7	-12.5	-1.2
12 MeSO ₂	H	23.7	29.7	-6.0	-21.1	-24.9	+3.8
13 F	H	21.9	31.9	-10.0	-29.5	-31.9	+2.3

^a Values are in kilocalories per mole.

geometries for two of these reactions (with methyl and methylsulfonium substituents) are displayed in Figure 1.

Of primary note is that all reactions are strongly exothermic, with the more electronegative substituents on the nitriles yielding greater exothermicities. The actual exothermicities are somewhat overestimated, as entropy effects are not included in the calculations.

Experimentally, the 1-substituted tetrazole is exclusively formed, as mentioned above. This is consistent with calculations which show that TS1, for all substituents, is considerably lower than TS2. The difference ranges from 9.7 kcal/mol for the extremely electron-poor fluoronitrile, to 3.9 kcal/mol for the relatively electron-rich and very bulky *tert*-butyl nitrile. A general trend is that the more activated the nitrile, the larger the difference between TS1 and TS2. Also, the size of the substituents affects the difference, as there is less steric repulsion in TS2 than in TS1.

From Table 1 we can see that the barriers for the [2 + 3] cycloaddition (TS1) are correlated with the electron-withdrawing power of the substituents. Accordingly, the lowest barriers are found for the very electronegative sulfonium and fluorine groups (lines 9 and 10). This effect is also seen in the series where the

substituents are $-\text{CH}_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, and $-\text{CF}_3$ (lines 1, 6, 7, and 8): the barriers for the reactions of these with methyl azide are 31.6, 27.8, 23.3, and 21.8 kcal/mol, respectively. A secondary factor is the steric bulk of the substituent. For instance, *tert*-butyl nitrile has a barrier 3.2 kcal/mol higher than that of methyl nitrile (34.8 vs 31.6 kcal/mol).

Transition-state geometries change slightly depending on the substituent. The $\text{C}_{\text{nitrile}}-\text{N}_{\text{azide}}$ distance of TS1, for example, varies between 1.80 and 1.99 Å, with the electronegative substituents causing shorter distances. The $\text{N}_{\text{nitrile}}-\text{N}_{\text{azide}}$ distance varies between 1.96 and 2.40 Å, with the electronegative substituents now causing longer distances. The angles adjust accordingly; the NNN angle of the azide varies between 131° and 139°, while the RCN angle varies between 139° and 147°. Hence, the more electron-withdrawing substituent has the more asymmetric transition state.

It is interesting to note that the energy needed to bend the RCN angle varies considerably with the substituents. For instance, the energy needed to bend the CCN angle in methyl nitrile from linear to 140° (the approximate angle at the transition state) is 13.5 kcal/mol, while the energy needed to bend the SCN angle in sulfonyl nitrile to the same degree is 6.4 kcal/mol. This explains in part the lower barrier found for the electronegative substituents.

It is also interesting to note that in gas phase, as previous studies have found,²⁴ the 2,5-tetrazoles are generally slightly more stable than the corresponding 1*H*-isomers. However, the 1,5-isomer has in general a higher dipole moment (6.2 vs 2.6 D for dimethyltetrazole, for example) and hence solvates better, which results in relative stabilities of the 1,5- vs 2,5-isomers very close to one another, in the range of ± 3 kcal/mol, depending on the size and electronegativity of the substituents.

B. Anionic Cycloaddition. In reactions where NaN_3 is added to nitrile in nonprotic organic solvents, such as dimethylformamide (DMF) or glyme,^{12,25} it has been found that yields are generally lower, and higher reaction temperatures are required. In these cases, there are two possible mechanisms, assuming the cation does not play a role, either a direct [2 + 3] cycloaddition or a two-step sequence wherein the azide first nucleophilically attacks the nitrile, followed by ring closure. In this section the barriers for the cycloaddition of the azide anion to nitriles have been calculated, with the same set of nitriles as in the previous section. The results are listed in Table 2, and

Table 2. Calculated Barriers and Exothermicities^a for Anionic [2 + 3] Cycloaddition Reaction of RCN with N_3^-

	R	barrier	tetrazole
1	Me	33.8	-14.8
2	Ph	32.4	-16.5
3	tBu	37.2	-11.3
4	MeS	26.5	-17.1
5	MeO	22.3	-24.2
6	CH ₂ F	24.6	-23.6
7	CHF ₂	18.9	-29.5
8	CF ₃	12.8	-34.0
9	MeSO ₂	10.7	-31.2
10	F	5.3	-39.5

^a Values are in kilocalories per mole.

two typical transition-state geometries are given in Figure 2.²⁶

As in the case of the neutral [2 + 3] cycloaddition, the barrier for anionic [2 + 3] cycloaddition decreases with increasing electron-withdrawing potential of the substituent on the nitrile.

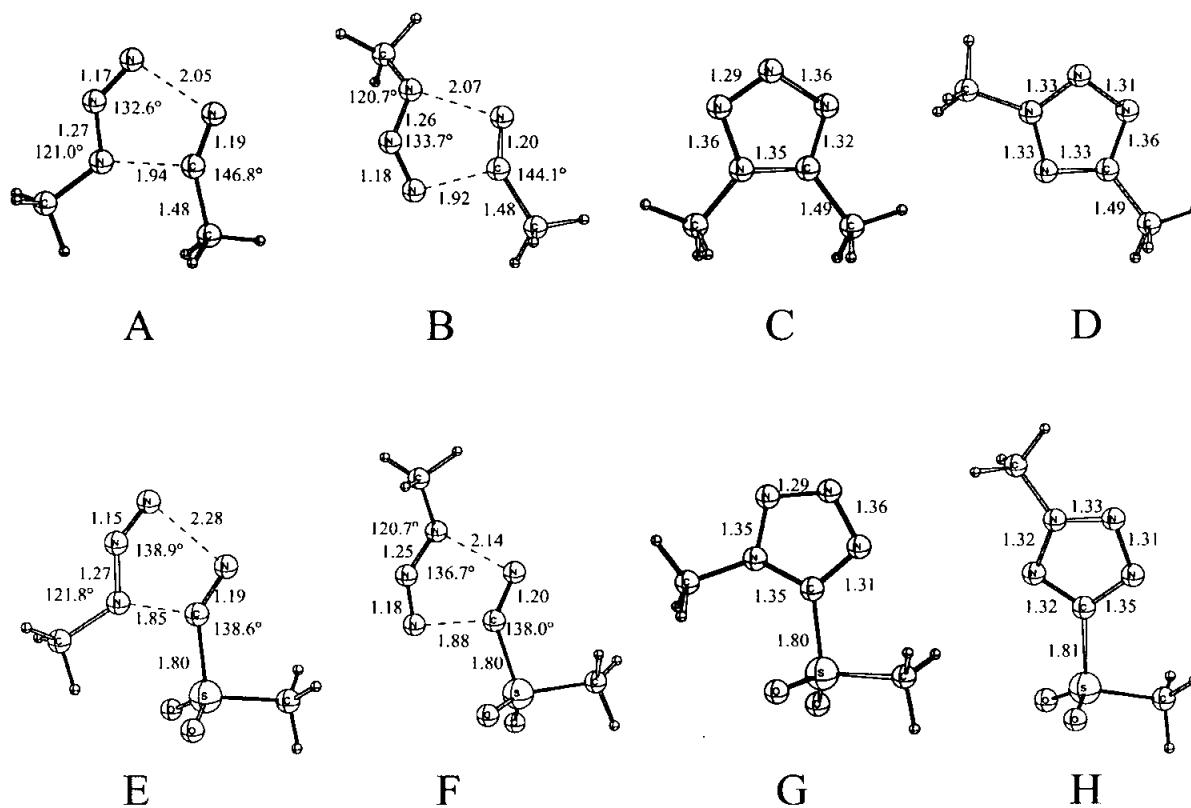


Figure 1. Optimized structures of transition states 1 (A, E) and 2 (B, F) and corresponding tetrazole products (C, D, G, H) formed from cycloaddition of methyl azide and acetonitrile (Table 1, line 1; structures A–D) or methyl azide and sulfoniumnitrile (Table 1, line 9; structures E–H). Bond lengths are given in angströms.

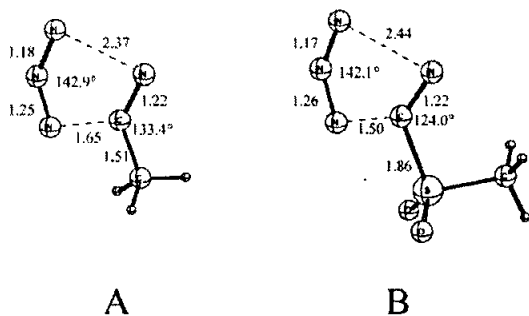


Figure 2. Optimized transition-state structures for addition of N_3^- to methylnitrile (A) and methanesulfonylnitrile (B).

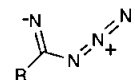
However, in this case, the slope of the change in barrier versus electronic character is greater (see Figure 6). For example, the barriers for the anionic reaction with the relatively electron-rich acetonitrile and *tert*-butylnitrile (Table 2, lines 1 and 3) are slightly more than 2 kcal/mol higher than for the concerted neutral reaction. The relatively electroneutral benzonitrile (Table 2, line 2) has an almost identical barrier, and the electron-poor methylcyanate (MeOCN) and extremely electron-poor methanesulfonyl cyanide (Table 2, lines 5 and 9) have barriers which

are 3.6 and 9.7 kcal/mol lower, respectively, than the comparable concerted neutral reaction.

The geometry of the transition state of anionic reaction is more asymmetric than for the neutral reaction; the $C_{\text{nitrile}}-N_{\text{azide}}$ distance is significantly shorter than the $N_{\text{nitrile}}-N_{\text{azide}}$ distance. The difference grows with the electron-withdrawing potential of the substituent. For acetonitrile, for example, the N–C distance is 1.65 Å and the N–N distance is 2.37 Å, while for sulfonyl cyanides the same distances are 1.50 and 2.44 Å, respectively.

For very strong electron-withdrawing groups, like F^- or RSO_2^- , an intermediate such as that found in Chart 2 could be

Chart 2

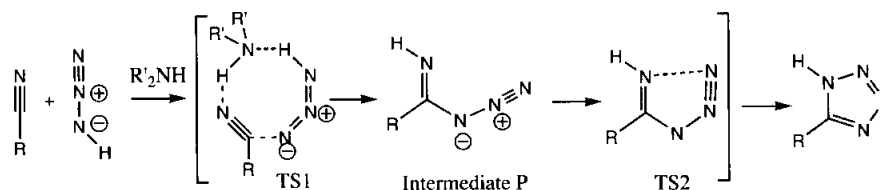


found. However, it is weakly bound, as seen for instance from the rather long N–C bond length (1.57 Å for FCN and 1.49 Å for CH_3SO_2CN). The intermediate is at about the same energy as the free reactants, with a very small barrier for its formation (transition state could not be optimized, but linear transit calculations gave an estimate of the barrier to be less than 4 kcal/mol). Despite the existence of this intermediate for the strongly activated nitriles, the transition state for the ring closing turns out to be identical to the concerted [2 + 3] transition state, indicating that the two pathways are essentially the same.

C. Proton Involvement. As mentioned in the Introduction, Koldobskii et al.^{14a} showed that only ammonium salts of azide

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 (26) A word of caution regarding the solvation energy of N_3^- is in place here. Negatively charged molecules of this small size tend usually to be undersolvated with the methods used here. This would mean that the barriers calculated here are somewhat underestimated. However, since the error is constant, this should not affect relative barriers.

Scheme 5



that contain a proton are competent dipoles; tetrabutylammonium azide does not work.⁵ What then is the role of the proton? Could it play the same role as it does in acid-catalyzed hydrolysis of nitriles or in the Pinner synthesis, namely, activation of the nitrile?

On the basis of the calculations, we propose that when a proton is available, the tetrazole reaction proceeds via intermediate P as in Scheme 5 (optimized geometries of the intermediate are shown in Figure 3A,C), instead of a direct [2 + 3] dipolar

substituent on the nitrile. For MeSO₂CN, for instance, the intermediate has as much as 11.4 kcal/mol lower energy than the free reactants.

From intermediate P, the barrier to close the ring and form 1-tetrazole is very feasible, ca. 15–19 kcal/mol (via TS2) with respect to intermediate P depending on the nature of the substituent (see Table 3). Hence, once the intermediate is created, the tetrazole can readily be formed.

How Then Is Intermediate P Formed? The transition states have been calculated for three scenarios for the creation of intermediate P. The first possibility considered is a direct concerted attack of HN₃ on the nitrile in which the proton is transferred to the nitrile nitrogen and at the same time the N–C bond is formed (typical six-membered ring transition-state structures are shown in Figure 4). This reaction, which assumes

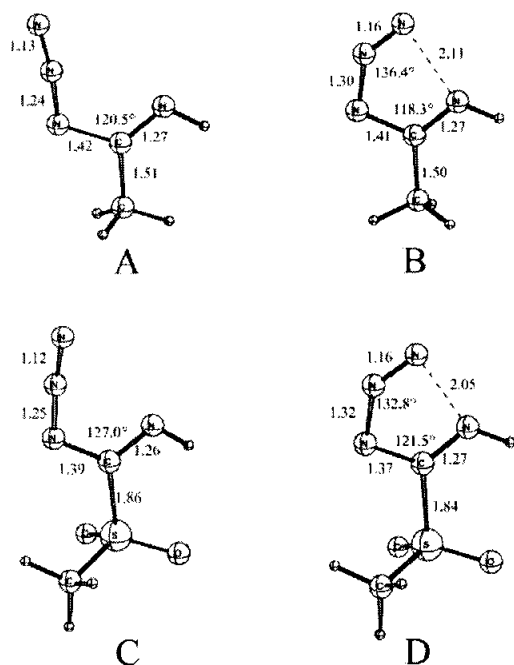


Figure 3. Optimized structures of intermediate P and the ring-closing transition states for methylnitrile (A, B) and methane sulfonylnitrile (C, D).

Table 3. Calculated Energy^a of Intermediate P Relative to HN₃ + RCN, and the Barrier for Ring Closing from There to Form the Tetrazole

R	intermediate P	ring closing barrier	barrier for formation of intermediate P		
			direct TS	NH ₄ ⁺ TS	water TS
1 Me	+3.3	+15.3	+31.0	+20.8	+26.8
2 MeS	−1.6	+15.9	+29.2	+15.5	+24.8
3 MeO	−12.0	+19.4	+29.1	+12.6	+24.1
4 MeSO ₂	−11.4	+17.8	+30.1	+5.3	+23.4

^a Values are in kilocalories per mole. Also included are the three models used to calculate the barrier for the formation of the intermediate, as discussed in the text.

cycloaddition. This intermediate is quite stable; for R = Me it is 3.3 kcal/mol less stable than the free reactants, HN₃ and MeCN. As seen in Table 3, the stability of the intermediate increases with the electron-withdrawing potential of the sub-

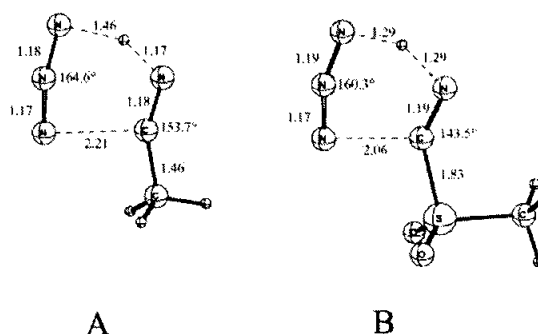


Figure 4. Optimized transition-state structures for the direct concerted attack of HN₃ on the methylnitrile (A) and methane sulfonylnitrile (B), to form intermediate P via a transition state with a six-membered ring.

stituent on the nitrile. For MeSO₂CN, for instance, the intermediate has as much as 11.4 kcal/mol lower energy than the free reactants.

Considered second is the mechanism where the proton comes from NH₄⁺. This reaction was modeled in two different ways, which, interestingly, gave very similar transition states and almost identical barriers. The first model starts from the neutral species HN₃ and RCN, and ammonia (NH₃) mediates the proton transfer from the azide to the nitrile, with the concomitant formation of the N–C bond. The optimized transition-state structure for R = Me is given in Figure 5A. The second model assumes a deprotonated azide ion (N₃[−]) and protonated ammonium species (NH₄⁺). Here the geometry optimization had to be performed under the solvation to circumvent the large charge separation that in the gas phase causes the moiety to collapse into neutral molecules. The optimized transition-state structure is given in Figure 5B.

The barriers for these two models are almost identical. For instance, for R = Me the neutral model yields a barrier of 20.8

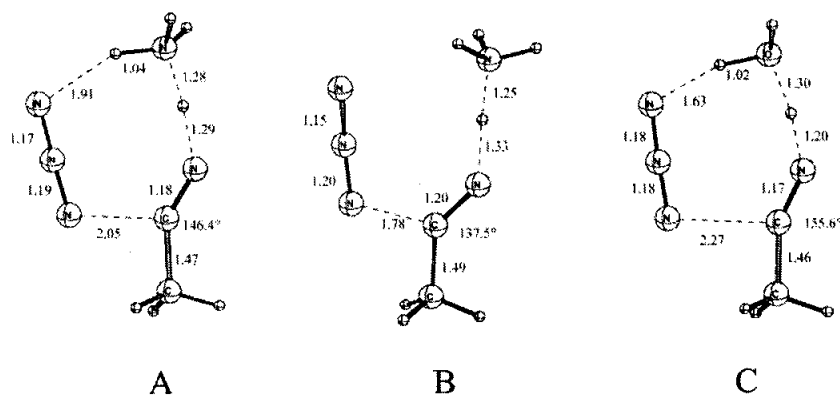


Figure 5. Optimized transition-state structures for the formation of intermediate P according to different models: a neutral model starting from HN_3 , NH_3 , and MeCN (A); an ionic model starting from N_3^- , NH_4^+ , and MeCN, geometry-optimized in solvent (B); and a neutral model starting from HN_3 , H_2O , and MeCN (C).

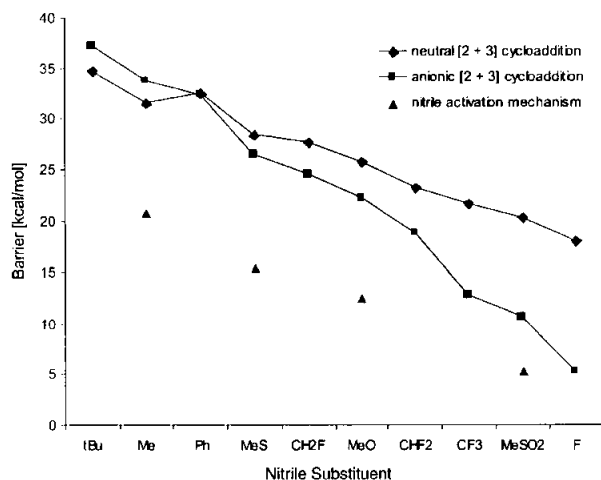


Figure 6. Summary of reaction barriers calculated in the present study. Note that triangles show the barrier only for formation of intermediate P and not for the subsequent ring closing, which has a barrier of ca. 15–19 kcal/mol depending on substituent group (see text and Table 3 for details).

kcal/mol, while the ionic model gives a barrier of 21.3 kcal/mol, i.e., a difference of only 0.5 kcal/mol. This barrier is considerably lower than all mechanisms previously considered in this paper. Compare these numbers with those for attack of hydrazoic acid through a six-membered transition state (31.0 kcal/mol), the neutral [2 + 3] cycloaddition of HN_3 to CH_3CN (35.1 kcal/mol), and the anionic [2 + 3] cycloaddition of N_3^- to CH_3CN (33.8 kcal/mol). The same conclusion applies to all other substitution patterns studied (see Table 3). When the nitrile is attached to a methoxy group (methyl cyanate), the ammonium-mediated reaction has a barrier (12.6 kcal/mol) significantly lower than that in the attack of HN_3 through the six-membered transition state (29.1 kcal/mol) or the [2 + 3] cycloaddition of HN_3 (25.9 kcal/mol) or the anionic [2 + 3] cycloaddition of N_3^- (22.3 kcal/mol). Within a few kilocalories per mole, the various mechanisms have the same entropy. Interestingly, as Table 3 indicates, for strongly electronegative substituents, the ring-closing step, which has a barrier of 16–19 kcal/mol, might become the rate-limiting step. However, the entropy effect for the creation of intermediate P should raise the barrier of that compared to the ring-closing step (estimated at ca. 5–7 kcal/mol).

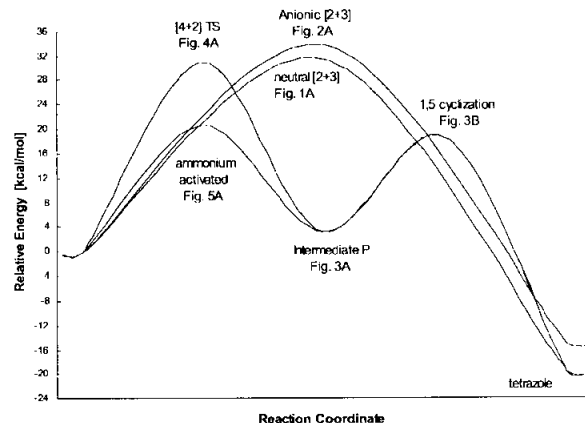


Figure 7. Calculated potential energy surfaces for the various mechanisms considered for the formation of tetrazole from azide and acetonitrile.

Last, we have investigated whether a water molecule can facilitate the reaction in the same way as ammonia (transition-state structure shown in Figure 5C). As seen from Table 3, although the water molecule reduces the barrier compared to the direct attack, it is still significantly higher than the ammonia-mediated reaction. Furthermore, the barrier shows a very modest decrease with the electronegativity of the substituent. While the barrier difference between $\text{R} = \text{Me}$ and $\text{R} = \text{MeSO}_2$ is only 3.4 kcal/mol in the water-catalyzed reaction, it is as large as 15.5 kcal/mol in the ammonium-catalyzed reaction.

To summarize this section, in situations where a proton is readily available, a stepwise reaction through intermediate P is more favorable than [2 + 3] cycloaddition reactions, either neutral or anionic. This mechanism is similar to the known mechanisms of acid-catalyzed nitrile hydrolysis and the Pinner synthesis, with the difference being that the nucleophile is an azide. The key to this mechanism's low-energy TS is that the nitrile is activated by a proton. Experimentally, this is provided by ammonium salt, but of course other proton sources could play the same role.

IV. Conclusions

In the present study we have examined the energetics of different mechanisms for formation of tetrazole from azide and nitriles. This has been done by means of the B3LYP density functional theory method. The barriers for the different mech-

anisms are summarized in Figures 6 and 7. The main result of the calculations is that when a proton is available, the reaction proceeds via the protonated intermediate P, as shown in Scheme 5. The transition state leading to the formation of intermediate P involves the activation of the nitrile by a proton, facilitating the attack of the azide on the carbon of the nitrile. From intermediate P, simple 1,5-cyclization occurs to give the 1*H*-tetrazole. This mechanism is consistent with available experimental results and with similar known mechanisms for related reactions involving nucleophilic attack on nitriles.

Addition reactions such as the ones studied in the present paper usually exhibit large entropic effects. These were not reported in the tables primarily because we are interested in trends and relative effects, and accurate determination of

entropies of bimolecular reactions in solution involves a number of subtle issues.²⁷

Acknowledgment. We thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384), the National Science Foundation (CHE-9985553), the Wenner-Gren Foundations (F.H.), the Skaggs Institute for Chemical Biology for a predoctoral fellowship (Z.P.D.), and the W. M. Keck Foundation for financial support. We thank Drs. D. Bashford and M. G. Finn for helpful discussions.

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Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures¹

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Sodium triacetoxyborohydride is presented as a general reducing agent for the reductive amination of aldehydes and ketones. Procedures for using this mild and selective reagent have been developed for a wide variety of substrates. The scope of the reaction includes aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, and primary and secondary amines including a variety of weakly basic and nonbasic amines. Limitations include reactions with aromatic and unsaturated ketones and some sterically hindered ketones and amines. 1,2-Dichloroethane (DCE) is the preferred reaction solvent, but reactions can also be carried out in tetrahydrofuran (THF) and occasionally in acetonitrile. Acetic acid may be used as catalyst with ketone reactions, but it is generally not needed with aldehydes. The procedure is carried out effectively in the presence of acid sensitive functional groups such as acetals and ketals; it can also be carried out in the presence of reducible functional groups such as C–C multiple bonds and cyano and nitro groups. Reactions are generally faster in DCE than in THF, and in both solvents, reactions are faster in the presence of AcOH. In comparison with other reductive amination procedures such as NaBH₃CN/MeOH, borane–pyridine, and catalytic hydrogenation, NaBH(OAc)₃ gave consistently higher yields and fewer side products. In the reductive amination of some aldehydes with primary amines where dialkylation is a problem we adopted a stepwise procedure involving imine formation in MeOH followed by reduction with NaBH₄.

Introduction

The reactions of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of the carbonyl compounds) or reductive alkylations (of the amines) are among the most useful and important tools in the synthesis of different kinds of amines. The reaction involves the initial formation of the intermediate carbinol amine **3** (Scheme 1) which dehydrates to form an imine. Under the reaction conditions, which are usually weakly acidic to neutral, the imine is protonated to form an iminium ion **4**.² Subsequent reduction of this iminium ion produces the alkylated amine product **5**. However, there are some reports that provide evidence suggesting a direct reduction of the carbinol amine **3** as a possible pathway leading to **5**.³ The choice of the reducing agent is very critical to the success of the reaction, since the reducing agent must reduce imines (or iminium ions) selectively over aldehydes or ketones under the reaction conditions.

The reductive amination reaction is described as a *direct* reaction when the carbonyl compound and the

amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. A *stepwise* or *indirect* reaction involves the preformation of the intermediate imine followed by reduction in a separate step.

The two most commonly used direct reductive amination methods differ in the nature of the reducing agent. The first method is catalytic hydrogenation with platinum, palladium, or nickel catalysts.^{2a,4} This is an economical and effective reductive amination method, particularly in large scale reactions. However, the reaction may give a mixture of products and low yields depending on the molar ratio and the structure of the reactants.⁵ Hydrogenation has limited use with compounds containing carbon–carbon multiple bonds and in the presence of reducible functional groups such as nitro^{6,7} and cyano⁷ groups. The catalyst may be inhibited by compounds containing divalent sulfur.⁸ The second method utilizes hydride reducing agents particularly sodium cyanoborohydride (NaBH₃CN) for reduction.⁹ The successful use of sodium cyanoborohydride is due to its stability in relatively strong acid solutions (~pH 3), its solubility in hydroxylic solvents such as methanol, and its different selectivities at different pH values.¹⁰ At pH

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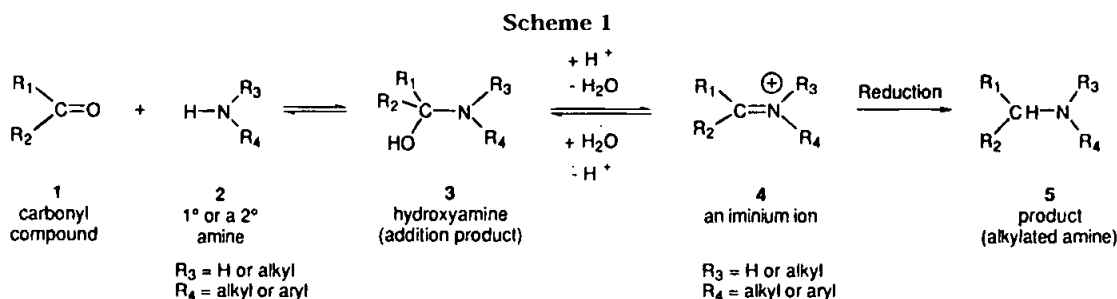
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3–4 it reduces aldehydes and ketones effectively, but this reduction becomes very slow at higher pH values.¹¹ At pH 6–8, the more basic imines are protonated preferentially and reduced faster than aldehydes or ketones.¹⁰ This selectivity allows for a convenient direct reductive amination procedure. The literature is replete with publications that document the use of sodium cyanoborohydride in reductive amination reactions.¹² Limitations are that the reaction may require up to a fivefold excess of the amine,¹⁰ is usually slow and sluggish with aromatic ketones¹⁰ and with weakly basic amines,¹³ and may result in the contamination of the product with cyanide.¹⁴ The reagent is highly toxic¹⁵ and produces toxic byproducts such as HCN and NaCN upon workup.

Other reported reductive amination reagents include borane-pyridine,^{13a} $\text{Ti}(\text{O}i\text{Pr})_4/\text{NaBH}_3\text{CN}$,^{13b} borohydride exchange resin,^{16a} Zn/AcOH ,^{16b} $\text{NaBH}_4/\text{Mg}(\text{ClO}_4)_2$,^{16c} and $\text{Zn}(\text{BH}_4)_2/\text{ZnCl}_2$.^{16d} In addition, there are some reports of electrochemical reductive amination reactions.¹⁷

In our work on hydride-induced reductive aminations of aldehydes and ketones, we sought an alternative to the toxic sodium cyanoborohydride to eliminate the risk of residual cyanide in the product and in the workup waste stream, particularly for large scale reactions. After surveying many of the commercially available hydride reagents, we selected sodium triacetoxyborohydride

[$\text{NaBH}(\text{OAc})_3$].¹⁸ This borohydride reagent is mild and exhibits remarkable selectivity as a reducing agent. It reduces aldehydes selectively over ketones,¹⁸ except for β -hydroxy ketones which can be reduced selectively to give 1,3-*trans* diols.¹⁹ The steric and the electron-withdrawing effects of the three acetoxy groups stabilize the boron–hydrogen bond and are responsible for its mild reducing properties.²⁰ Our selection was also based on the results of reductive alkylation of amines using sodium borohydride in neat liquid carboxylic acids reported earlier by Gribble *et al.*²¹

In this paper we report the results of our comprehensive investigation of the scope and limitations of sodium triacetoxyborohydride in a procedure for *direct* reductive amination of aldehydes and ketones with a variety of aliphatic and aromatic amines. This report also includes an alternative stepwise route for the reductive amination of aldehydes with primary amines which involves the preformation of imines and their subsequent reduction with NaBH_4 in one-pot reactions.

Results and Discussions

The direct reductive amination reactions were carried out in 1,2-dichloroethane (DCE), tetrahydrofuran (THF), or acetonitrile. The standard reaction conditions are as follows: a mixture of the carbonyl compound and the amine (0–5% molar excess) in the desired solvent is stirred with 1.3–1.6 equiv of sodium triacetoxyborohydride under a nitrogen atmosphere at room temperature. In some reactions, acetic acid (1–2 mol equiv) is added to the mixture. The progress of the reaction is followed by GC and GC/MS analysis. The results from various reductive amination reactions of ketones and aldehydes are listed in Tables 1 and 2, respectively. Solvents such as water or methanol are not recommended. Reactions in methanol resulted in a fast reduction of the carbonyl compound, and the reagent decomposed in water.

(a) Reductive Amination of Ketones. The results in Table 1 show that the reductive amination of a wide variety of cyclic and acyclic ketones with primary and

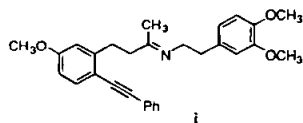
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(21) Earlier work by Gribble *et al.* demonstrated the potential of triacyloxyborohydrides generated from NaBH_4 in neat liquid carboxylic acids in reductive alkylation of amines: (a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766.

secondary amines was successful under the standard conditions and gave the desired products in good to excellent yields. The scope of the reaction includes different alicyclic ketones, from cyclobutanone to cyclododecanone (Table 1: entries 1–23), bicyclic ketones such as norcamphor and tropinone (Table 1: entries 24–30), saturated acyclic ketones (Table 1: entries 31–39), and keto esters (Table 1: entries 47–49). Nearly all primary and nonhindered secondary amines were used successfully in these reactions. For the same ketone, the rate of the reaction was dependent on the steric and electronic factors associated with the amines. In general, primary aliphatic amines reacted faster than primary aromatic and secondary aliphatic amines (Table 1: entries 10 vs 11; 14 and 15 vs 16 and 17; 24 vs 26 and 27). Cyclic secondary amines such as morpholine reacted faster than acyclic secondary amines such as diethylamine (Table 1: entry 33 vs 36) while the sterically hindered diisopropylamine did not react even after days (Table 1: entry 45). In some slow reactions (e.g., Table 1: entries 11, 27, 32, 34, and 36), small amounts of side products were formed (1–5% by GC area % analysis) from *N*-ethylation and *N*-acetylation of the starting amines.²² These impurities were easily removed in the workup or during the recrystallization of the salts.

The reaction conditions are very mild and can tolerate the presence of acid sensitive functional groups such as acetals and ketals. For example, the reductive amination of cyclohexanedione monoethylene ketal with primary and secondary amines afforded good to excellent isolated yields of the corresponding amines (Table 1: entries 14–18). Another example is the reductive alkylation of aminoacetaldehyde diethyl acetal with cyclododecanone (Table 1: entry 9). A particularly useful example is the reaction involving cyclohexanedione monoethylene ketal and aminoacetaldehyde diethyl acetal (Table 1: entry 18) which provides a secondary amine product containing protected aldehyde and ketone functionalities in a nearly quantitative yield.

Of all the ketones used in this study, small aliphatic cyclic ketones, ranging from cyclobutanone to cyclohexanone, were most reactive. Larger cyclic ketones such as cyclooctanone and cyclododecanone and acyclic ketones such as 2-heptanone reacted somewhat slower. Reactivity of cyclobutanone was so high that its reaction with benzylamine gave a mixture of mono- and dicyclobutylbenzylamines even with the use of excess amine (Table 1: entry 2). Clean formation of *N,N*-dicyclobutylbenzylamine resulted with the use of a 1:2 molar ratio of amine to ketone (Table 1: entry 1). The reactions with secondary amines were very effective since there was no dialkylation product (Table 1: entry 3).

The least reactive ketones were aromatic, α,β -unsaturated, and sterically hindered ketones. Aromatic and α,β -unsaturated ketones reacted very slowly (Table 1: entries 40, 41, and 43). Experimentally, a saturated aliphatic ketone was reductively aminated, selectively, and quantitatively in the presence of an aromatic or α,β -unsaturated ketone (Table 1: entries 42 and 44). The unreacted ketones were recovered unchanged except for the formation of trace amounts of their imines (as determined by GC/MS analysis of the reaction mixture). Sterically hindered ketones were even less reactive than aromatic

and α,β -unsaturated ketones, e.g., camphor showed no reaction with benzylamine after four days (Table 1: entry 46). The steric factors associated with both ketones and amines seem to be very important in determining the outcome of the reaction.

In reactions where the formation of diastereomers was possible, we observed varying degrees of selectivity. Reductive amination of 4-*tert*-butylcyclohexanone with pyrrolidine and cyclohexylamine occurred with a moderate diastereoselectivity to give the thermodynamically less favored *cis* products. This results from equatorial attack by the hydride reagent on the intermediate imine, to form the axial amine (Table 1: entries 19 and 20).²³ The reductive amination of androstanolone with isopropylamine gave a mixture of 3 α - and 3 β -(isopropylamino)-androstan-17 β -ol in about 25:75 ratio (Table 1: entry 21). The reactions involving bicyclic ketones showed higher degrees of diastereoselectivity. For example, the reductive aminations of norcamphor led to the exclusive formation of the *endo* products, from *exo* attack by the hydride reagent. The reductive amination of norcamphor with benzylamine (Table 1: entry 24) produced a single product. This product was identical to that obtained from the reductive amination of benzaldehyde with *endo*-2-aminonorborene (Table 2: entry 13), thus confirming the *endo* stereochemistry of the product.

Reductive amination of tropinone with primary amines such as benzylamine and aniline (Table 1: entries 28 and 29) was accomplished in good yield and high diastereoselectivity giving the *endo* isomer as the major product (determined by ¹H NMR).²⁴ The reaction with benzylamine gave the *endo* and *exo* products in approximately 20:1 ratio while the reaction with aniline showed no detectable *exo* product. The reaction of tropinone with piperidine was extremely sluggish giving low conversion to about a 1:1 mixture of the *exo*- and *endo*-products after four days of reaction (Table 1: entry 30).

The poor solubility of ammonium acetate in DCE, THF, or CH₃CN limits its use in the reductive amination of ketones to prepare primary amines. The initial primary amine product is much more soluble than ammonium acetate and reacts faster with the ketone to generate dialkylamines, so this reaction can be used for the preparation of symmetrical dialkylamines. The amination reaction is relatively slow and some ketone reduction may occur if AcOH is added. Even the use of a large excess (10 equiv) of ammonium acetate in THF, DCE, or CH₃CN, in the presence of Et₃N, did not favor the formation of the monoalkylamine, the only product formed was dicycloheptylamine (Table 1: entries 22 and 23).

N-Substituted α -amino esters were prepared by the reductive amination of α -keto esters with primary and

(23) This result is consistent with literature reports on the reduction of 4-substituted cyclohexanone imines or iminium salts which concluded that bulky hydride reagents such as *L*-Selectride attack preferentially from the less hindered equatorial side to give the *cis*-products, while less bulky hydride reagents such as NaBH₄ and NaBH₃CN slightly favor the axial approach, see: (a) Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, 22, 3447. (b) Hutchins, R. O.; Markowitz, M. *J. Org. Chem.* **1981**, 46, 3571. (c) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, 48, 3412. (d) Hutchins, R. O.; Adams, J.; Rutledge, M. C. *J. Org. Chem.* **1995**, 60, 7396.

(24) Chemical shift assignments of individual protons were arrived at by COSY, HETCOR, and Inverse HMBN NMR experiments. The stereochemistry of *N*-phenyl-3-aminotropone and *N*-benzyl-3-aminotropone was assigned based on 1D NOE and coupling experiments. The assignments were in line with other literature reports; cf. Bagley, J. R.; Riley, T. N. *J. Heterocycl. Chem.* **1977**, 14, 599 and references therein.

(22) The *N*-ethylation of amines is a major process in reaction of amines with sodium borohydride in neat acetic acid and is believed to proceed through an acetaldehyde formation.^{21a}

Table 1. Reductive Amination of Ketones

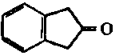
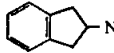
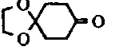
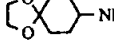
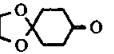
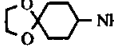
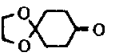
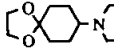
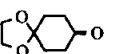
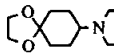
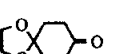
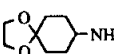
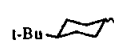
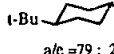
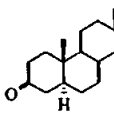
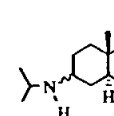
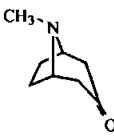
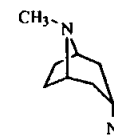
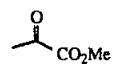
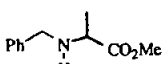
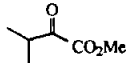
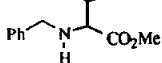
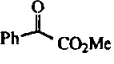
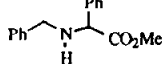
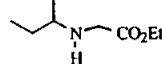
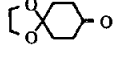
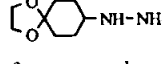
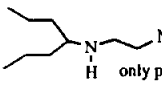
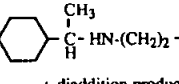
Entry	KETONE	AMINE	Method ^a	Time	PRODUCT	YIELD(%)	
						Base ^b	Salt ^c
1.	Cyclobutanone (2 mol)	Benzylamine (1 mol)	I	2 h	<i>N,N</i> -Dicyclobutylbenzylamine	98	90 (HCl)
2.	Cyclobutanone (1 mol)	Benzylamine (1 mol)	II	2 h	<i>N,N</i> -Dicyclobutylbenzylamine + <i>N</i> -Cyclobutylbenzylamine (1 : 1)	88	—
3.	Cyclobutanone	1-Phenylpiperazine	II	2 h	1-Cyclobutyl-4-phenylpiperazine	96	86 (ox)
4.	Cyclopentanone	Hexamethyleneimine	I	24 h	<i>N</i> -Cyclopentylhexamethylenimine	96	86 (ox)
5.	Cyclohexanone	Morpholine	I	2 h	<i>N</i> -Cyclohexylmorpholine	96	86 (HCl) 76 (pic)
6.	Cycloheptanone	1-Propylamine	IV	23 h	<i>N</i> -(1-propyl)aminocycloheptane	96	69 (HCl)
7.	Cycloheptanone	1-Propylamine	I	3 h	<i>N</i> -(1-propyl)aminocycloheptane	—	88 (HCl)
8.	Cyclooctanone	<i>m</i> -Methoxybenzylamine	I	36 h	<i>N</i> -Cyclooctyl- <i>m</i> -methoxybenzylamine	95	87 (HCl)
9.	Cyclododecanone	$\text{H}_2\text{NCH}_2-\text{C}(\text{OC}_2\text{H}_5)_2$	II	24 h	$\text{c-C}_{12}\text{H}_{23}-\text{NH}-\text{CH}_2-\text{C}(\text{OC}_2\text{H}_5)_2$	88	77 (ox)
10.	β -Tetralone	Cyclohexylamine	IV	24 h	<i>N</i> -Cyclohexyl-1,2,3,4-tetrahydro-2-aminonaphthalene	—	85 (HCl)
11.	β -Tetralone	Morpholine	III	120 h	2-(Morpholin-4-yl)-1,2,3,4-tetrahydronaphthalene	58	54 (HCl)
12.	β -Tetralone	Aniline	I	24 h	<i>N</i> -Phenyl-1,2,3,4-tetrahydro-2-aminonaphthalene	—	87 (HCl)
13.		$\text{H}_2\text{N-Ph}$	I	6 h		—	85 (HCl)
14.		Benzylamine	I	20 m		98	92 (ox)
15.		Cyclobutylamine	I	25 m		98	82 (HCl)
16.		Piperidine	I	75 m		85	66 (HCl)
17.		1-Phenylpiperazine	I	4 h		78	—
18.		$\text{H}_2\text{NCH}_2-\text{C}(\text{OC}_2\text{H}_5)_2$	II	4 h		—	99 (ox)
19.	4- <i>t</i> -Butylcyclohexanone	Pyrolidine	II	10 m	 a/c = 71 : 29	98	—
20.	4- <i>t</i> -Butylcyclohexanone	Cyclohexylamine	II	30 m	 a/c = 79 : 21	91	—
21.		Isopropylamine	I	24 h	 $\alpha/\beta = 25 : 75$	91	—
22.	Cycloheptanone	NH_4OAc (10 eq.)	II, ^d IV ^d	48 h	Dicycloheptylamine	—	80 (HCl)
23.	Cycloheptanone	NH_4OAc (10 eq.)	V ^d	30 h	Dicycloheptylamine	—	70 (HCl)
24.	Norcamphor	Benzylamine	IV	6 h	<i>endo-N</i> -Benzyl-2-aminonorbornane	95	82 (pic)
25.	Norcamphor	Aniline	III	48 h	<i>N</i> -Phenyl-2-aminonorbornane	80	75 (HCl)
26.	Norcamphor	Aniline	I	24 h	<i>N</i> -Phenyl-2-aminonorbornane	—	76 (HCl)
27.	Norcamphor	Diethylamine	I	96 h	<i>N,N</i> -Diethyl-2-aminonorbornane	—	79 (HCl)
28.		$\text{H}_2\text{N-CH}_2\text{-Ph}$	I	18 h	 NHCH ₂ Ph	99	80 (ox)
29.	"	Aniline	I	72 h	<i>endo</i> -3-(<i>N</i> -Phenylamino)tropane	96	65 (ox)
30.	"	Piperidine	I	4 d	about 1:1 mixture of <i>endo</i> + <i>exo</i> products	60 ^e	—

Table 1. (Continued)

Entry	KETONE	AMINE	Method ^a	Time	PRODUCT	YIELD(%)	
						Base ^b	Salt ^c
31.	2-Heptanone	Cyclohexylamine	IV	24 h	<i>N</i> -Cyclohexyl-2-aminoheptane	99	84 (ox)
32.	2-Heptanone	Aniline	IV	96 h	<i>N</i> -Phenyl-2-aminoheptane	90	89 (ox)
33.	2-Heptanone	Morpholine	III	27 h	<i>N</i> -(2-Heptyl)morpholine	-	73 (HCl)
34.	2-Heptanone	Piperidine	IV	48 h	<i>N</i> -(2-Heptyl)piperidine	67	35 (HCl)
35.	2-Heptanone	Piperidine	I	48 h	<i>N</i> -(2-Heptyl)piperidine	-	65 (HCl)
36.	2-Heptanone	Diethylamine	III	192 h	<i>N,N</i> -Diethyl-2-aminoheptane	-	44 (HCl)
37.	Acetylcyclohexane	Benzylamine	II	24 h	<i>N</i> -(1-(Cyclohexyl)ethyl)benzylamine	91	71 (HCl)
38.	1-Phenyl-2-propanone	Aniline	II	30 h	<i>N</i> -(3-Phenyl-2-propyl)aniline	-	80 (HCl)
39.	4-Heptanone	Propargylamine	II	12 h	<i>N</i> -(4-Heptyl)propargylamine	99	84 (HCl)
40.	Acetophenone	Benzylamine	I	10 d	<i>N</i> -Benzyl-1-phenylethylamine	55 ^e	-
41.	Acetophenone	Cyclohexylamine	I, III	1 d	<i>N</i> -Cyclohexyl-1-phenylethylamine	15 ^e	-
42.	Acetophenone Cyclohexanone	Benzylamine	I	1 h	<i>N</i> -Benzylcyclohexylamine Acetophenone (92 %)	98	97 (HCl)
43.	1-Acetylcyclohexene	Morpholine	II	4 d	<i>N</i> -[1-(1-Cyclohexenyl)ethyl]morpholine	10 ^e	-
44.	1-Acetylcyclohexane 1-Acetylcyclohexene	Benzylamine	I	4 h	<i>N</i> -[1-(Cyclohexyl)ethyl]benzylamine 1-Acetylcyclohexene	-	85 (HCl)
45.	Cycloheptanone	Diisopropylamine	IV	4 d	no reaction	-	-
46.	Camphor	Benzylamine	I	4 d	no reaction	-	-
47.		H ₂ N-CH ₂ -Ph	II	0.5 h		90	61 (HCl)
48.		H ₂ N-CH ₂ -Ph	VI	42 h		-	80 (HCl)
49.		H ₂ N-CH ₂ -Ph	VI	5 h		-	58 (HCl)
50.		H ₂ N-CH ₂ -CO ₂ Et	I	4 h		-	88 (HCl)
51.		H ₂ N-NH-Ph	I	4 h		98	71 (ox)
52.	Cyclohexanone	H ₂ N-NH-Ph	I	1 h	<i>N</i> ² -Cyclohexyl- <i>N</i> ¹ -phenylhydrazine	96 ^f	-
53.	2-Heptanone	H ₂ N-NH-Ph	I	8 h	<i>N</i> ² -2-Heptyl- <i>N</i> ¹ -phenylhydrazine	98 ^f	37 (ox)
54.	Cyclooctanone	H ₂ N-OH	I	72 h	Oxime formation, no reduction.	-	-
55.	4-Heptanone	H ₂ N-CH ₂ -CH ₂ -NH-Ph	II	30 h	 only product	99	79 (HCl)
56.	Acetylcyclohexane	H ₂ N-(CH ₂) ₂ -N 	II	12 h	 + diaddition product 94 : 6	98	83 (ox)

a) Methods: I: DCE, AcOH (1-2 eq.), NaBH(OAc)₃ (1.3-1.6 eq.); II: DCE, NaBH(OAc)₃ (1.3-1.6 eq.); III: THF, AcOH (1-2 eq.), NaBH(OAc)₃ (1.3-1.6 eq.); IV: THF, NaBH(OAc)₃ (1.3-1.6 eq.); V: CH₃CN, NaBH(OAc)₃ (1.3-1.6 eq.); VI: DCE, amine (1 eq.), AcOH (2-4 eq.), NaBH(OAc)₃ (2-5 eq.), ketone (2-5 eq.)

b) Salts: pic = picrate, ox = oxalate c) Yield of crude product determined to be > 96% pure by GC.

d) Reaction was carried out in presence of 1.5-2 equiv of Et₃N.

e) Yields were determined by GC and products were only characterized by GC/MS.

f) crude product contained about 15-31% byproduct(s), determined by area% GC analysis.

secondary amines. The reductive amination of methyl pyruvate with benzylamine was a fast and efficient reaction under the standard conditions that gave *N*-benzylalanine methyl ester in an excellent yield (Table 1: entry 47). The reaction was slower with hindered keto esters such as methyl 3-methyl-2-oxobutanoate (Table

1: entry 48), and the competing ketone reduction was a major reaction. The aromatic keto ester, methyl benzoyl formate reacted even slower with benzylamine and was also accompanied by considerable ketone reduction (Table 1: entry 49). Reactions involving other less reactive amines such as aniline or morpholine were much slower

and gave increasing amounts of ketone reductions. Whenever ketone reduction was a problem, the conditions were modified to use the amines as limiting reagents. The excess ketones were completely reduced to the corresponding alcohols which required the occasional addition of excess reducing agent. *N*-Substituted α -amino esters were also prepared by the reductive amination of α -amino esters with ketones, e.g., *N*-(2-butyl)glycine ethyl ester was prepared in very good yield from ethyl glycinate and 2-butanone (Table 1: entry 50).

The reductive amination of cyclohexanedione monoethylene ketal with phenylhydrazine gave cleanly the *N*-substituted phenylhydrazine (Table 1: entry 51) in nearly quantitative yield. Other ketones such as cyclohexanone and 2-heptanone reacted to give similar products (Table 1: entries 52 and 53); however, there were some competing side reactions. The crude products showed the formation of byproducts, about 15% with cyclohexanone and 31% with 2-heptanone. Attempted reductive amination of cyclooctanone with hydroxylamine was not successful and resulted in the oxime formation (Table 1: entry 54).

Reductive aminations in which diamines containing both primary and secondary amino groups were studied and in general, primary amines reacted faster. In the case where the primary amino group was aliphatic and the secondary group was aromatic, e.g., *N*-phenylethylenediamine, there was a clear difference in reactivity between the two amines. The reaction with 4-heptanone gave a quantitative yield of the product resulting from exclusive reaction with the primary amine (Table 1: entry 55). In the case where both amino groups were aliphatic, such as 1-(2-aminoethyl)piperazine, there was a high selectivity (94:6) for the primary group in reaction with acetylcyclohexane (Table 1: entry 56).

(b) Reductive Amination of Aldehydes. Unlike ketones, aldehydes can be reduced with sodium triacetoxyborohydride.¹⁸ Thus, the possibility exists that the reduction of the aldehyde would compete with the reductive amination process under the standard conditions. However, these conditions were so selective that the reductive aminations with aldehydes occurred very effectively and resulted in fast reactions with no aldehyde reductions in most cases studied (Table 2). One case in which aldehyde reduction was detected involved a reaction with the very sterically hindered diisopropylamine (Table 2: entry 6). All other examples in Table 2 resulted in fast and efficient reductive aminations with a variety of aliphatic primary and secondary amines as well as aniline with no detectable aldehyde reductions. Both aliphatic and aromatic aldehydes were very reactive and gave reductive amination products with a broad variety of primary and secondary amines. The reaction times ranged from 20 min to 24 h. The mildness of the reaction conditions is well illustrated in the reductive amination of 1,1',2-tris-nor-squalene aldehyde with diethylamine and diisopropylamine (Table 2: entries 19 and 20). The aldehyde was cleanly converted to the corresponding amines in high yields with no detectable side reactions.

In the reductive amination of aldehydes with primary amines, formation of dialkylated amines is a common side reaction.⁵ This side reaction was rarely a problem in most reactions reported in Table 2. In the few cases when it was detected, it was suppressed by the addition of up to 5% molar excess of the primary amine. However, the dialkylation of amines remained a problem with

certain substrates.²⁵ An alternative stepwise procedure for such systems is discussed later in this paper.

Some aldehydes, such as formaldehyde and glutaraldehyde are only available commercially as aqueous solutions which may restrict their use under the above reaction conditions because of the decomposition of the hydride reagent with water. However, the reaction may be carried out in DCE with excess hydride reagent, e.g., the reductive amination of either aqueous glutaraldehyde or formaldehyde with 1-phenylpiperazine and about 4 hydride equivalents was carried out on 10 mmol scale (Table 2: entries 21 and 22) and gave nearly quantitative yields of the corresponding amines. This, however, may not be suitable for large scale reactions.

The use of phenylhydrazine in reductive amination of benzaldehyde was not successful, resulting only in hydrazone formation.

Generally, with either ketones or aldehydes, reactions in DCE were noticeably faster than those carried out in THF (e.g., Table 1: entries 6 vs 7; 25 vs 26 and Table 2: entries 3 vs 4; 9 vs 10). Also, in the same solvent, reactions were consistently faster in the presence of 1 (or more) mol equiv of acetic acid. For most ketones, reactions were improved in the presence of acetic acid. However, the addition of acetic acid is not always advantageous to the reaction. Most reactions with aldehydes are fast and do not require addition of AcOH. Addition of AcOH to a slow reaction, e.g., cyclohexanecarboxaldehyde with diisopropylamine, resulted in a fast reaction accompanied with about 25% aldehyde reduction, and the yield of the isolated desired product was only 41%. When the reaction was carried out in the absence of AcOH, the reaction was slower; however, the aldehyde reduction was only about 5%, and the isolated yield of the purified reductive amination product increased to 75% (Table 2: entries 6 and 7). Direct comparisons were made between reactions in DCE and THF and with or without added acetic acid in representative reactions. The rate of product formation was determined quantitatively²⁶ in each case. The results of these comparisons were in agreement with the above observations.

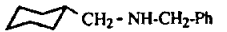
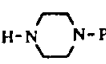
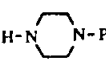
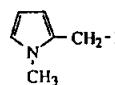
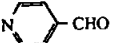
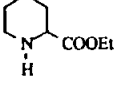
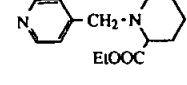
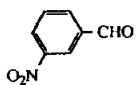
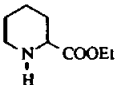
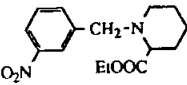
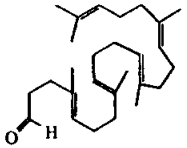
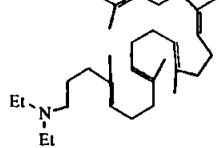
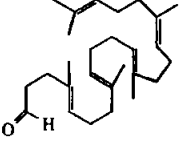
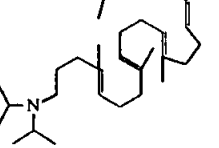
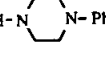
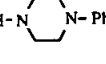
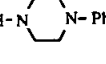
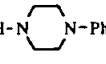
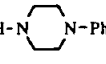
(c) Reductive Amination with Weakly Basic and Nonbasic Amines. Few literature references have dealt with aromatic amines containing electron withdrawing substituents in reductive amination reactions.^{13,21a} Catalytic hydrogenation conditions do not allow the presence of many of the easily reduced electron-withdrawing substituents such as cyano and nitro groups, since these substituents are often reduced under catalytic hydrogenation conditions.^{6,7} On the other hand, we and others^{13a,b} have found the most used hydride reagent, sodium cyanoborohydride [NaBH₃CN], to be sluggish and inefficient when used with these weak bases in reductive amination reactions.

As a consequence of substitution by electron-withdrawing substituents, these amines are both poor nucleophiles and weak bases (e.g., pK_a 3.98 for 4-chloroaniline, 1.02 for 4-nitroaniline, -0.29 for 2-nitroaniline, -4.26 for 2,4-dinitroaniline).²⁷ This slows the initial nucleophilic at-

(25) For a discussion of the dialkylation side reactions involving γ - and δ -amino esters with aldehydes and a mechanistic explanation, see: Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.

(26) The progress of these reactions was followed by GC. Linear standard curves of the response factors by GC areas of starting materials and expected products were determined to allow the quantitative measurements of their concentrations in the reaction mixtures.

Table 2. Reductive Amination of Aldehydes

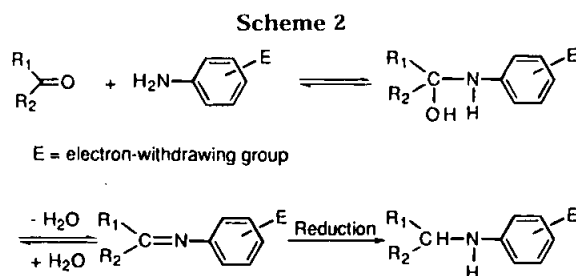
Entry	ALDEHYDE	AMINE	Method ^a	Time	PRODUCT	YIELD (%)	
						Base ^b	Salt ^c
1.	 CHO	Benzylamine	II	1 h		98	80 (HCl)
2.	"	Aniline	II	24 h	<i>N</i> -(Cyclohexylmethyl)aniline	95	85 (HCl)
3.	"	Morpholine	IV	2 h	<i>N</i> -(Cyclohexylmethyl)morpholine	74	63 (HCl)
4.	"	Morpholine	II	1 h	<i>N</i> -(Cyclohexylmethyl)morpholine	86	80 (HCl)
5.	"	Et ₂ NH	II	30 min	<i>N</i> -(Cyclohexylmethyl)diethylamine	95	84 (HCl)
6.	"	(<i>i</i> -Pr) ₂ NH	I	3 h	<i>c</i> -C ₆ H ₁₁ -CH ₂ -N(<i>i</i> Pr) ₂	68	41 (HCl)
7.	"	(<i>i</i> -Pr) ₂ NH	II	8 h	<i>c</i> -C ₆ H ₁₁ -CH ₂ -N(<i>i</i> Pr) ₂	88	75 (HCl)
8.	Hexanal	H-N  N-Ph	I	1 h	C ₆ H ₁₃ -N  N-Ph	95	85 (ox)
9.	<i>m</i> -Anisaldehyde	Aniline	III	24 h	<i>m</i> -CH ₃ O-C ₆ H ₄ -CH ₂ -NH-Ph	88	88 (HCl)
10.	<i>m</i> -Anisaldehyde	Aniline	I	20 min	<i>m</i> -CH ₃ O-C ₆ H ₄ -CH ₂ -NH-Ph	-	95 (HCl)
11.	<i>m</i> -Anisaldehyde	Morpholine	IV	6 h	4-(3-Methoxybenzyl)morpholine	88	74 (HCl)
12.	Benzaldehyde	<i>tert</i> -Bu NH ₂	I	3 h	<i>N</i> -(<i>tert</i> -Butyl) Benzylamine	95	92 (HCl)
13.	Benzaldehyde	<i>endo</i> -2-Aminonorbomane	II ^d	0.5 h	<i>endo</i> - <i>N</i> -Benzyl-2-aminonorbomane	97	85 (HCl)
14.	Benzaldehyde	<i>exo</i> -2-Aminonorbomane	I	3 h	<i>exo</i> - <i>N</i> -Benzyl-2-aminonorbomane	92	84 (HCl)
15.	Benzaldehyde	1-Adamantanamine	I	24 h	<i>N</i> -Benzyl-1-adamantanamine	—	66 (HCl)
16.	 CHO	H-N 	III	1.5 h		—	91 (ox)
17.	 CHO		II	1.5 h		95	—
18.	 CHO		II	1.5 h		96	—
19.		Et ₂ NH ₂	II	1.5 h		98	—
20.		H-N 	II	1.5 h		91	—
21.	 CHO 25% in H ₂ O	H-N  N-Ph	II	1 h	Ph-N  N-(CH ₂) ₅ -N  N-Ph	98	85 (ox)
22.	HCHO 30% in H ₂ O	H-N  N-Ph	II	1 h	CH ₃ -N  N-Ph	98	82 (ox.)
23.	Benzaldehyde	Phenyl hydrazine	I	96 h	Hydrazone formation, No reduction	—	—

a) Methods: I: DCE, AcOH (1-2 eq.), NaBH(OAc)₃ (1.3-1.6 eq.); II: DCE, NaBH(OAc)₃ (1.3-1.6 eq.); III: THF, AcOH (1-2 eq.), NaBH(OAc)₃ (1.3-1.6 eq.); IV: THF, NaBH(OAc)₃ (1.3-1.6 eq.).

b) Yield of crude product determined to be > 96% pure by GC. c) ox = oxalate.
d) Reaction was carried out in presence of 1.5-2 equiv of Et₃N.

tack on the carbonyl carbon and leads to slower overall reaction rates (Scheme 2). In addition, the carbonyl group now competes effectively with the less basic intermediate imine for protonation and subsequently for the hydride in the reduction step.^{2b} This may lead to a

significant carbonyl reduction, consumption of both the carbonyl compound and the reducing agent and low yields of the reductive amination products. The reducing agent and reaction conditions should be chosen carefully to minimize such side reactions.



Sodium triacetoxyborohydride is very efficient in reductive amination reactions with such unreactive amines. The results from several reactions are listed in Table 3. In several cases such as monosubstituted anilines (e.g., *p*-nitro-*p*-carbomethoxy-, and *p*-cyanoanilines), the standard reaction conditions described previously (about 1:1 ratio of carbonyl compound to amine, 1.4 equiv of NaBH(OAc)₃ with 1 equiv of acetic acid) were adequate. However, with less basic amines such as *o*-nitroaniline, 2,4-dichloroaniline, or 2-aminothiazole, the reaction conditions were modified to compensate for the aforementioned effects and to maximize the yields of the reductive amination products. The optimum conditions included the use of the amine as the limiting reagent with 1.5–2 mol equiv of the carbonyl compound, 2–3 equiv of NaBH(OAc)₃, and 2–5 equiv of AcOH in 1,2-dichloroethane. Under these conditions, a variety of weakly basic amines were successfully employed in the reductive aminations of ketones and aldehydes in isolated yields ranging from 60% to 96%. The reaction is convenient and the conditions are mild and show a high degree of tolerance for a variety of functional groups including nitro, cyano, halo, carboxy, and carbomethoxy groups.

Ketones reacted effectively with *p*-monosubstituted anilines to give good yields of the reductive amination products (Table 3: entries 1–8). The reaction was slightly slower with 2,4-dichloroaniline and gave a high yield of the desired reductive amination product in addition to some ketone reduction and the formation of about 3% of *N*-ethyl-2,4-dichloroaniline (Table 3: entry 9). The reaction became very slow with *o*-nitroaniline which progressed only to about 30% conversion to the reductive amination product and 17% of *N*-ethyl-2-nitroaniline after 6 days (Table 3: entry 10). The reaction stopped completely when both *ortho* positions were substituted as in 2,6-dibromo- and 2,4,6-trichloroanilines (Table 3: entries 11 and 12).

The reactions with aldehydes were faster than those with ketones and gave higher yields from similar reactions. Aldehyde reductions occurred only with the least reactive amines. In the reductive amination of aldehydes with *p*-carboxyaniline and *p*-nitroaniline (Table 3: entries 13, 14, and 18), no competing aldehyde reduction was observed. In these cases, the standard conditions were used. With weaker amines such as 2,4-dichloroaniline and *o*-nitroaniline (Table 3: entries 15 and 16), the conditions were modified to use the amine as a limiting reagent since aldehyde reduction occurred to the extent of 10–30%. This procedure was applied to other weakly basic primary amines such as 2-aminothiazole (Table 3: entries 22 and 23) and secondary amines such as iminostilbene (Table 3: entry 24). While imi-

nostilbene reacted with hexanal to give a high yield of the *N*-hexyl product, the dihydro analogue iminodibenzyl gave no reaction under the same conditions (Table 3: entry 25).

One of the most unique reactions, however, was the reductive alkylation of *p*-toluenesulfonamide with benzaldehyde to give the *N*-benzyl derivative (Table 3: entry 26). The reaction is carried out initially under the standard conditions in the presence of Et₃N (2 equiv). The aldehyde is usually consumed in about 24 h to give a mixture of *N*-benzyl *p*-toluenesulfonamide and *N*-benzal *p*-toluenesulfonamide. The reaction mixture is then treated with AcOH (2.5 equiv) and additional NaBH(OAc)₃ (1 equiv) to finish the reduction. The reaction, however, was not successful with ketones or carboxamides.

The least reactive amines, 2,4-dinitroaniline and 2,4,6-trichloroaniline failed to undergo reductive amination with benzaldehyde (Table 3: entries 20 and 21). Cyclohexanecarboxaldehyde, on the other hand, reacted slowly with these two amines to give the corresponding reductive amination products. In these two reactions, the aldehyde reduction became a major reaction process. To assure the presence of enough aldehyde to react with the amine, the reaction required occasional additions of aldehyde and reducing agent, up to 5 equiv each and over a two to four day period (Scheme 3). The reactions progressed to reach 90–92% conversion (as determined by GC) and gave 61% and 58% isolated yields, respectively, after chromatography. It is possible that these reactions proceed via initial formation of intermediate enamines rather than imines which may explain the lack of reactivity of aromatic aldehydes which cannot form enamines.

(d) Comparison with Other Reducing Agents. In general, the results of reductive amination employing sodium triacetoxyborohydride were as good as or better than most comparable reported results whether done using hydrogenation or hydride reagents. However, in many cases, our results were far superior to others. For example, we compared the reductive amination of cyclohexanone with morpholine using NaBH₃CN vs NaBH(OAc)₃. The reaction with NaBH₃CN (6 hydride equiv) in methanol and in the absence of AcOH was only 34% complete after 23 h with the formation of about 10% of the corresponding enamine. The conversion improved to 50% in 23 h with AcOH (1 equiv) with no enamine formation. The reaction using the standard NaBH(OAc)₃ conditions was 99.8% complete in 3 h without a trace of enamine formation (Table 1: entry 5). In another comparison, the reductive amination of 1-carbomethoxy-4-piperidinone with *p*-chloroaniline was only 45% complete with NaBH₃CN after 22 h but was >96% with NaBH(OAc)₃ in 2.5 h (Table 3: entry 4).

An impressive result was obtained in the reductive amination of 1,1',2-tris-nor-squalene aldehyde with diethylamine and isopropylamine. These reactions were reported to give about 5% yield under regular Borch conditions.²⁸ The yields were improved to 46 and 42%, respectively, when the reactions were carried out with NaBH₃CN in anhydrous THF in the presence of HCl (pH 3).²⁹ Under our standard conditions, these reactions gave

(27) (a) Albert, A.; Serjeant, E. P. In *The Determination of Ionization Constants*; Chapman and Hall: London, 1971; p 91. (b) Yates, K.; Wai, H. J. *Am. Chem. Soc.* **1964**, *86*, 5408.

(28) Duriatti, A.; Bouvier-Nave, P.; Benveniste, P.; Schuber, F.; Delprino, L.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34*, 2765.

(29) Ceruti, M.; Balliano, G.; Viola, F.; Cattel, L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199.

Table 3. Reductive Amination with Weakly Basic Amines

Entry	CARBONYL COMPOUND	AMINE	Method ^a	Time	PRODUCT	YIELD ^b (%)
1.	Cyclopentanone	<i>p</i> -Bromoaniline	I	48 h	<i>N</i> -(Cyclopentyl)- <i>p</i> -bromoaniline	89 (HCl)
2.	Cyclohexanone	<i>p</i> -Nitroaniline	VI	23 h	<i>N</i> -(Cyclohexyl)- <i>p</i> -nitroaniline	66
3.	Cyclohexanone	<i>p</i> -Chloroaniline	I	3.3 h	<i>N</i> -(Cyclohexyl)- <i>p</i> -chloroaniline	90 (HCl)
4.	EtO ₂ C-N $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -C(=O)-OEt	Cl- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	I	3.5 h	EtO ₂ C-N $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -Cl	85
5.	EtO ₂ C-N $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -C(=O)-OEt	O ₂ N- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	VI	18 h	EtO ₂ C-N $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NO ₂	60
6.	Cycloheptanone	<i>p</i> -Carboxyaniline	VI	22 h	<i>p</i> -Carboxy- <i>N</i> -cycloheptylaniline	79
7.	Cycloheptanone	<i>p</i> -Cyananiline	VI	24 h	<i>p</i> -Cyano- <i>N</i> -cycloheptylaniline	71
8.	2-Heptanone	<i>p</i> -Carbomethoxyaniline	I	14 h	<i>p</i> -Carbomethoxy- <i>N</i> -(2-heptyl)aniline	66
9.	Cyclohexanone	2,4-Dichloroaniline	VI	37 h	<i>N</i> -Cyclohexyl-2,4-dichloroaniline	95
10.	Cyclohexanone	<i>o</i> -Nitroaniline	VI	144 h	<i>N</i> -Cyclohexyl-2-nitroaniline	30 ^c
11.	4-Heptanone	2,6-Dibromoaniline	VI	24 h	No Reaction	
12.	Cycloheptanone	2,4,6-Trichloroaniline	VI	24 h	No Reaction	
13.	c-C ₆ H ₁₁ -CHO	<i>p</i> -Nitroaniline	I	1.5 h	<i>p</i> -Nitro- <i>N</i> -(cyclohexylmethyl)aniline	95
14.	c-C ₆ H ₁₁ -CHO	<i>p</i> -Carboxyaniline	I	0.5 h	<i>p</i> -Carboxy- <i>N</i> -(cyclohexylmethyl)aniline	85
15.	c-C ₆ H ₁₁ -CHO	2,4-Dichloroaniline	VI	0.6 h	2,4-Dichloro- <i>N</i> -cyclohexylmethylaniline	96
16.	c-C ₆ H ₁₁ -CHO	<i>o</i> -Nitroaniline	VI	1.5 h	<i>o</i> -Nitro- <i>N</i> -cyclohexylmethylaniline	95
17.	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CH ₂ CH ₂ CHO	Cl- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	VI	1.5 h	Cl- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH-(CH ₂) ₃ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$	70 ^d (HCl)
18.	Benzaldehyde	<i>p</i> -Nitroaniline	I	1.5 h	<i>p</i> -Nitro- <i>N</i> -benzylaniline	85
19.	O ₂ N- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CHO	CF ₃ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	I	1.5 h	CF ₃ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH-CH ₂ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NO ₂	75
20.	Benzaldehyde	2,4-Dinitroaniline	VI	24 h	No Reaction	
21.	Benzaldehyde	2,4,6-Trichloroaniline	VI	24 h	No Reaction	
22.	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CHO	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	VI	72h	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH-CH ₂ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$	60
23.	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CHO	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH ₂	VI	16h	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -NH-CH ₂ - $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$	85
24.	C ₅ H ₁₁ -CHO	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$	VI	10 h	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ C ₆ H ₁₃	82
25.	C ₅ H ₁₁ -CHO	$\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$	VI	24 h	No Reaction	
26.	Benzaldehyde	H ₂ N-S(=O)(=O)- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CH ₃	VI ^e	48 h	PhCH ₂ -HN-S(=O)(=O)- $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ -CH ₃	80
27.	Benzaldehyde	Benzamide	I	24 h	No reaction	

a) Methods: I: DCE, AcOH (1 eq.), NaBH(OAc)₃ (1.4 eq.); VI: DCE, amine (1 eq.), AcOH (2–5 eq.), NaBH(OAc)₃ (2–2.8 eq.), carbonyl compound (1.5–2 eq.)

b) Yield of isolated product, > 96% by GC area % analysis. Except for the cases indicated, all isolated as free bases.

c) Yield was determined by GC and the product was only characterized by GC/MS.

d) Crude product contained about 5% dialkylated amine.

e) Reaction was carried out in presence of 2 equiv of Et₃N.

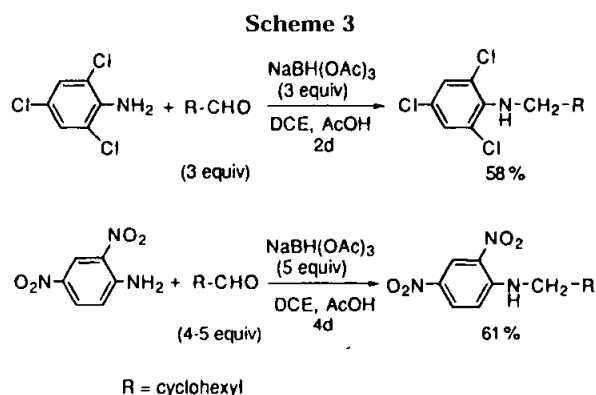
98 and 90% yield of products in high purity without chromatography (Table 2: entries 19 and 20).

The reductive amination of either 2-indanone, β -tetralone, or phenylacetone with aniline was reported to work when aniline was used as solvent under catalytic hydrogenation conditions and gave 72%, 54%, and 21% yield of products, respectively.³⁰ We obtained 85%, 87%, and 80% yield of these products using stoichiometric

amounts of reagents under the standard conditions (Table 1: entries 12, 13, and 38).

Borane–pyridine is another reducing agent used for reductive amination reactions.^{13a} Its use in the reductive amination of either pyridine-4-carboxaldehyde or *m*-nitrobenzaldehyde with ethyl piperidine-2-carboxylate

(30) Campbell, J. B.; Lavagnino, E. P. In *Catalysis in Organic Syntheses*; Jones, W. H., Ed.; Academic Press: New York, 1980; p 43.



gave 12% and 13% yield of isolated reductive amination products, respectively, and considerable aldehyde reduction.^{14b} Under our standard conditions, we did not observe any aldehyde reduction, and the isolated yields were nearly quantitative (Table 2: entries 17 and 18).

(e) Stepwise (Indirect) Reductive Amination of Aldehydes. Occasionally, some reactions of aldehydes and primary amines gave considerable amounts of dialkylation or other side products. As we mentioned previously, the addition of a slight excess of the primary amine may suppress this side reaction. However, the dialkylation of certain primary amines such as γ - or δ -amino esters and cyclobutylamine, remained a problem. This also occurred when certain aldehydes were used, such as cinnamaldehyde, hydrocinnamaldehyde, and some straight chain aldehydes. Those particular cases gave mixtures of monoalkylated and dialkylated amines in ratios ranging from 5:1 and up to 1:1 under the standard reaction conditions. Surprisingly, in some reactions, the dialkylation side reaction happened even when excess amine was used or when the reaction was carried out with a "preformed imine" and no excess aldehyde present. A discussion and a possible explanation of some of these results in case of γ - and δ -amino esters was reported.²⁵ We developed an alternative procedure for such reactions which involves the fast reduction of *preformed imines*. Imine formation, however, is a reversible reaction and requires long reaction times and the use of a dehydrating agent such as molecular sieves or azeotropic removal of water to drive the reaction to completion. We studied the relative rates of imine formation from aldehydes and primary amines in different solvents, namely THF, DCE, and methanol without added catalysts or dehydrating agents. A comparison of the relative rates of imine formation in the three solvents is listed in Table 4. The relative ratio of product imine to reactant aldehyde was determined by GC analysis of the reaction mixture and confirmed in some cases by ¹H NMR in CD₃OD, THF-*d*₈, or CDCl₃. In all the cases listed in Table 4, reactions in methanol were consistently faster and gave nearly quantitative conversions relative to those carried out in THF or DCE. The imine formation was slower for ketones in all three solvents; however, the reaction was still faster in methanol (Table 4: entry 7).

The reduction of the aldimines was carried out directly in methanol with sodium borohydride to give the corresponding secondary amines in very high yields and very short reaction times. Thus, this stepwise (or indirect) one-pot procedure involving imine formation in methanol followed by *in situ* reduction with sodium borohydride is

a very convenient and efficient alternative for carrying out reductive aminations on substrates which tend to give significant amounts of dialkylated products using the direct procedure.

A similar transformation along the lines of prior formation of the imine is prior formation and then reduction of the enamine. We have found that sodium triacetoxyborohydride reduces enamines quickly and efficiently in DCE to give products in high yields (Table 5: entries 6 and 7), making it a useful reagent for this stepwise procedure.

Another very efficient stepwise reductive amination procedure was developed by Mattson *et al.*^{13b} In this procedure, the amine and the carbonyl compound are mixed in neat titanium(IV) isopropoxide and the resulting intermediate is reduced with NaBH₃CN in ethanol. The authors reported the formation of a carbinol amine intermediate (see Table 5: entries 8–10) rather than the usual iminium ion. The method is applicable to primary and secondary amines. We modified this procedure to reduce the intermediate with NaBH₄ in methanol (instead of NaBH₃CN/ethanol).³¹ This modified reduction is very fast and gives the desired amine in very good yield and high purity, e.g., the reductive amination of the unsaturated ketone 1-acetylcyclohexene with benzylamine, which was very slow under our standard conditions, proceeded very fast under these modified conditions to give a quantitative yield of the reductive amination product (Table 5: entry 8). Of particular interest, the reductive amination of tropinone with benzylamine using this procedure which gave a near quantitative yield of a 3:2 mixture of the *endo*- and *exo* products (Table 5: entry 10). As reported earlier, this reaction gave approximately 20:1 ratio of the *endo* and *exo* products using NaBH(OAc)₃ (Table 1: entry 28). Attempts to achieve a reaction between tropinone and aniline using this modified system resulted in incomplete reactions. In regards to secondary amines, Mattson *et al.*^{13b} reported a successful reductive amination of tropinone with piperidine in 58% yield; however, the stereochemistry of the product was not disclosed. Our modified conditions gave the product in a 90% crude yield as a mixture of the *endo*- and *exo*-products in about 1:7 ratio. The pure oxalate salt of the *exo* product was isolated in 66% yield (Table 5: entry 9). The *exo*-stereoselectivity of this reaction is opposite to that obtained from the primary amines. We are examining these systems to better understand their mechanistic pathway.

Summary and Conclusions

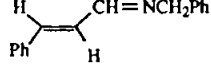
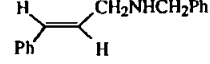
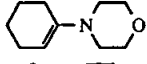
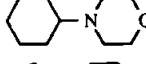
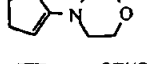
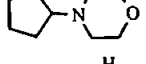
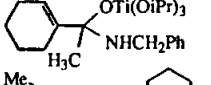
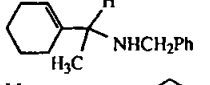
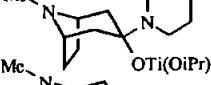
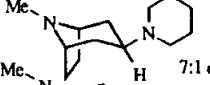
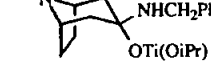
The results presented here indicate that sodium triacetoxyborohydride is a synthetically useful reagent for reductive aminations of aldehydes and ketones. It is a mild, commercially available reagent, and it is a reagent of choice for reductive amination of carbonyl compounds. The scope of the reaction covers all aldehydes and unhindered aliphatic ketones. Aliphatic ketones (and aldehydes) can be selectively reductively aminated in the

(31) (a) We reported the use of this modification of Mattson's procedure [Ti(OiPr)₄-NaBH₄/MeOH, rt] at the 198th ACS National Meeting, Miami Beach, FL, September 1989; paper ORGN 154 and at The International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December 1989; paper ORGN 409, Abdel-Magid, A. F.; Maryanoff, C. A.; Sorgi, K. L.; Carson, K. G. A similar modification [Ti(OiPr)₄-NaBH₄ in diglyme at 60 °C or in ethanol at 25 °C] was reported recently: (b) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, 35, 2401. (c) Bhattacharyya, S. *Synlett* **1994**, 1029; (d) Bhattacharyya, S. *Synth. Commun.* **1995**, 25, 9.

Table 4. Imine Formation from Aldehydes and Primary Amines

Entry	Aldehyde	Amine	Time (h)	Yield (%)	
				by GC (solvent)	by ¹ H NMR (solvent)
1	benzaldehyde	<i>tert</i> -BuNH ₂	22	84 (DCE)	80 (CDCl ₃)
			22	95 (THF)	98 (THF- <i>c</i> ₆ H ₆)
			4	97 (MeOH)	97 (CD ₃ OD)
2	benzaldehyde	aniline	4.2	81 (DCE)	90 (CDCl ₃)
			4.3	74 (THF)	75 (THF- <i>c</i> ₆ H ₆)
			1.5	99 (MeOH)	97 (CD ₃ OD)
3	<i>m</i> -anisaldehyde	aniline	24	92 (DCE)	
			26	84 (THF)	
			2.4	99 (MeOH)	
4	<i>m</i> -anisaldehyde	2-(3,4-dimethoxyphenyl)ethylamine	2	97 (DCE)	100 (CDCl ₃)
			0.24	95 (THF)	100 (THF- <i>c</i> ₆ H ₆)
			0.25	98 (MeOH)	100 (CD ₃ OD)
5	<i>c</i> -C ₆ H ₁₁ CHO	aniline	5.4	89 (DCE)	
			5.3	90 (THF)	
			2.7	96 (MeOH)	
6	<i>c</i> -C ₆ H ₁₁ CHO	<i>tert</i> -BuNH ₂	4.6	89 (DCE)	
			5.3	90 (THF)	
			2.7	94 (MeOH)	
7	cycloheptanone	benzylamine	23	53 (DCE)	
			23	75 (THF)	
			23	85 (MeOH)	

Table 5. Stepwise Reductive Amination Reactions

Entry	SUBSTRATE	Time	Method ^a	PRODUCT	Yield (%)	
					base	salt ^b
1	<i>c</i> -C ₆ H ₁₁ - CH = NPh	10 min	A	<i>c</i> -C ₆ H ₁₁ - CH ₂ - NHPh	95	90 (HCl)
2	<i>m</i> -CH ₃ O-C ₆ H ₄ - CH = N-Ph	10 min	A	<i>m</i> -CH ₃ O-C ₆ H ₄ - CH ₂ - NH-Ph	-	84 (HCl)
3	<i>c</i> -C ₆ H ₁₁ - CH = N- <i>t</i> -Bu	10 min	A	<i>c</i> -C ₆ H ₁₁ - CH ₂ - NH- <i>t</i> -Bu	-	83 (HCl)
4	<i>p</i> -Cl-C ₆ H ₅ - CH = N- 	10 min	A	<i>p</i> -Cl-C ₆ H ₅ - CH ₂ - N- 	98	89 (HCl)
5	 CH = NCH ₂ Ph	15 min	A		-	85 (HCl)
6		10 min	B		99	91 (HCl)
7		20 min	B		99	80 (HCl)
8		5 min	C		qu	83 (HCl)
9		20 min	C		90	66 (ox)
10		10 min	C		93	--

a) Methods

A: Imine formation followed by NaBH₄ reduction in methanol.

B: Reduction of enamine with NaBH(OAc)₃ in DCE, 1 equiv of AcOH.

C: Mixing of carbonyl compound and amine in neat Ti(OiPr)₄ for 2-3 h, dilution with methanol and reduction with NaBH₄.

The nature of the intermediates is uncertain, structures in entries 8-10 are proposed in reference 14b.

b) ox = oxalate, qu = quantitative

presence of aromatic and α,β -unsaturated ketones. Aliphatic and aromatic primary and sterically unhindered secondary amines can be used in these reactions. The procedure was superior with weakly basic and nonbasic amines. In representative comparisons with other commonly used reducing reagents, sodium triacetoxyborohydride reacted consistently faster, gave better yields, and produced fewer side products. Methanol allows a rapid formation of imines from aldehydes and primary amines. Aldimines formed in methanol

were efficiently reduced to their corresponding amines using NaBH₄.

Experimental Section

Melting points are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at 400 MHz. The chemical shifts are expressed as δ units with Me₄Si as the internal standard. IR spectra were recorded on an FT-IR spectrometer and absorptions are reported in wave numbers (cm⁻¹). GC-MS (EI) were recorded on a GC/MSD instrument using a cross linked methyl

silicone 12 m $\times$ 0.2 mm $\times$ 0.33 mm capillary column. Mass spectra were recorded as CI or FAB. Accurate mass measurements were carried out using a double-focusing instrument of EB configuration (where E is an electric sector and B is a magnet). The reported accurate mass (mass-to-charge ratio) measurement values (mean $\pm$ 3 σ) are for the [MH]⁺ ions of the analytes of interest and are the average of nine individual determinations. The deviation of the experimental determinations from the theoretical values are expressed in parts-per-million (ppm). GC analyses were carried out on a cross linked methyl silicone 12 m $\times$ 0.2 mm $\times$ 0.33 μ m capillary column or DB-17; 15 m $\times$ 0.2 mm $\times$ 0.25 μ m. Sodium triacetoxyborohydride was purchased from Aldrich Chemical Company, Inc. Most reagents were commercially available reagent grade chemicals and used without further purification.

Procedures. 1. Direct Reductive Amination Methods.

General Notes. (a) The amine and the carbonyl compound are mixed in 1,2-dichloroethane and treated with NaBH(OAc)₃. THF, CH₂Cl₂, or CH₃CN may also be used as solvents.

(b) Acetic acid (1–2 mol equiv) may be used in reactions of ketones but is not necessary with most aldehydes.

(c) Reactions are normally carried out using the free amines; however, the amine salt may be used. In this case, 1–2 equiv of Et₃N is added to the reaction mixture. The Et₃N must be removed from basified product prior to salt formation.

(d) The progress of the reaction is followed by GC analysis in most cases. A small aliquot is withdrawn from the reaction mixture, quenched with aqueous NaOH or aqueous NaHCO₃ and extracted with ether or any other suitable solvent and injected into the GC. In case of high MW or heat-sensitive compounds HPLC or TLC could be used.

(e) The reactions are usually quenched with aqueous 1 N NaOH. In the presence of esters, or other alkali hydroxide sensitive functional groups, aqueous NaHCO₃ is used for quench. Reactive amines such as benzylamine may dissolve in aqueous NaHCO₃ and that may give a false indication of their consumption.

(f) Most amines form HCl salts cleanly in ether with ethereal HCl, and most of these salts are recrystallized from EtOAc/MeOH. Some aromatic HCl salts may turn dark and a few aliphatic amine salts may be difficult to crystallize or may be hygroscopic; in these cases the oxalate salts are prepared, usually in MeOH. Picrate salts are prepared in ethanol.

Method I. This procedure is used for most ketone reactions: A representative example is the reductive amination of cyclopentanone with hexamethyleneimine (Table 1: entry 4): Hexamethyleneimine (1.0 g, 10 mmol) and cyclopentanone (0.84 g, 10 mmol) were mixed in 1,2-dichloroethane (35 mL) and then treated with sodium triacetoxyborohydride (3.0 g, 14 mmol) and AcOH (0.6 g, 10 mmol). The mixture was stirred at rt under a N₂ atmosphere for 24 h until the reactants were consumed as determined by GC analysis. The reaction mixture was quenched by adding 1 N NaOH, and the product was extracted with ether. The ether extract was washed with brine and dried (MgSO₄). The solvent was evaporated to give the crude free base (1.60 g, 96%). The oxalate salt was prepared in EtOAc/MeOH as shiny white crystals (2.2 g, 85.5%); mp 171–172 °C; FT-IR (KBr) 3435 (w), 2934 (s), 2872 (m), 2683 (m), 2648 (m), 2585 (m), 2524 (m), 1720 (m), 1623 (m), 1455 (m), 1404 (m), 1204 (m), 1116 (m), 717 (m), 499 (m), 466 (m) cm⁻¹; ¹H NMR (free base, CDCl₃) δ 2.94–2.83 (m, 1H), 2.68–2.65 (m, 4H), 1.87–1.25 (m, 16H); ¹³C NMR (free base, CDCl₃) δ 65.9 (CH), 53.6 (CH₂), 30.2 (CH₂), 27.9 (CH₂), 26.9 (CH₂), 24.1 (CH₂); EI MS *m/z* (relative intensity) 167 (M⁺, 15), 138 (100), 124 (17), 110 (24), 96 (9), 82 (7), 55 (16). Anal. Calcd for C₁₃H₂₃NO₄: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.69; H, 9.03; N, 5.44.

Method II. The above procedure is followed without the addition of glacial acetic acid. The reaction mixture remains cloudy throughout the reaction. This procedure is more appropriate with most aldehydes and unhindered aliphatic ketones. A representative example is the reductive amination of 4-pyridinecarboxaldehyde with ethyl 2-piperidinecarboxylate (Table 2: entry 17): Ethyl-2-piperidinecarboxylate (1.57 g, 10 mmol) and 4-pyridinecarboxaldehyde (1.07 g, 10 mmol) were mixed in 1,2-dichloroethane (35 mL) and then treated with

sodium triacetoxyborohydride (3.0 g, 14 mmol). The mixture was stirred at rt under a N₂ atmosphere for 1.5 h. The GC analysis showed >90% conversion in 30 min, but the remainder of the time was needed for the complete conversion. The reaction mixture was quenched by adding aqueous saturated NaHCO₃, and the product was extracted with EtOAc. The EtOAc extract was dried (MgSO₄), and the solvent was evaporated to give the crude free base (2.40 g, 96.7%), >98% pure by area % GC analysis. A small portion was converted to the dioxalate salt: an off-white solid, mp 109–111 °C (EtOAc/MeOH); FT-IR (KBr) 3076 (w), 2968 (w), 2870 (w), 2521 (m), 1738 (s), 1603 (s), 1504 (m), 1460 (w), 1372 (w), 1204 (s), 999 (w), 714 (m) cm⁻¹; ¹H NMR (free base, CDCl₃) δ 8.52 (d, *J* = 5.2 Hz, 2H), 7.29 (d, *J* = 5.2 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 14.4 Hz, 1H), 3.43 (d, *J* = 14.4 Hz, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.20 (m, 1H), 1.85 (m, 2H), 1.55 (m, 3H), 1.45 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (free base, CDCl₃) δ 174.1 (C), 153.3 (C), 149.7 (CH), 125.8 (CH), 64.8 (CH), 61.8 (CH₂), 59.9 (CH₂), 51.0 (CH₂), 30.5 (CH₂), 26.4 (CH₂), 23.1 (CH₂), 15.8 (CH₃); EI MS *m/z* (relative intensity) 175 (M⁺ – CO₂Et, 100), 147 (4), 93 (5), 92 (25), 82 (5), 65 (15). Anal. Calcd for C₁₈H₂₄N₂O₁₀: C, 50.47; H, 5.65; N, 6.54. Found: C, 50.26; H, 5.74; N, 6.44.

Method III. Same as Method I except for using THF as a solvent. An example is the reductive amination of 2-heptanone with morpholine (Table 1: entry 33): 2-Heptanone (2.28 g, 20 mmol) and morpholine (1.92 g, 22 mmol) were mixed in THF (80 mL) at rt under N₂. Sodium triacetoxyborohydride (6.36 g, 30 mmol) and glacial AcOH (1.20 g, 20 mmol) were added, and the mixture was stirred at rt for 27 h. The reaction mixture was quenched with aqueous saturated NaHCO₃ solution, and the product was extracted with Et₂O. The Et₂O extract was dried (MgSO₄) and cooled in an ice bath and then treated with ethereal HCl. The product precipitated as a white solid. The solid was collected by filtration and dried; yield: 3.24 g, 73% (>98% by GC area % analysis) mp 150–151 °C. The analytical sample was obtained as a white crystalline solid by recrystallization from EtOAc/MeOH: mp 151–153 °C; FT-IR (KBr) 3410 (m), 2924 (s), 2863 (s), 2656 (s), 2604 (s), 2462 (m), 1434 (m), 1266 (m), 1114 (s), 1073 (m), 928 (m), 881 (m); ¹H NMR (CDCl₃) δ 12.60 (bs, 1H), 4.43 (dt, *J* = 12.8, 2.1 Hz, 2H), 3.98 (dd, *J* = 12.8, 3.0 Hz, 2H), 3.30–3.16 (m, 3H), 3.09–2.95 (m, 2H), 2.15–2.06 (m, 1H), 1.64–1.10 (m, 10H), 1.44 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃) δ 63.43 (CH₂), 63.37 (CH₂), 62.5 (CH), 47.9 (CH₂), 47.4 (CH₂), 31.2 (CH₂), 30.0 (CH₂), 25.8 (CH₂), 22.2 (CH₂), 13.7 (CH₃), 13.4 (CH₃); EI MS *m/z* (relative intensity) 185 (M⁺, 5), 170 (28), 115 (31), 114 (100), 86 (7), 84 (7), 70 (28). Anal. Calcd for C₁₁H₂₄ClNO: C, 59.58; H, 10.91; N, 6.32; Cl, 15.99. Found: C, 59.66; H, 11.00; N, 6.42; Cl, 16.09.

Method IV. Same as method II except for using THF as a solvent. An example is the reductive amination of β -tetralone with cyclohexylamine (Table 1: entry 10): Cyclohexylamine (1.09 g, 11 mmol) and β -tetralone (1.46 g, 10 mmol) were mixed in THF (50 mL) at rt under N₂. The mixture changed in about 1 min from yellow to dark blue in color. Sodium triacetoxyborohydride (3.18 g, 15 mmol) was added and the mixture stirred at rt under a N₂ atmosphere for 24 h. The color of the reaction mixture became light pink at the end of the reaction time. The reaction mixture was quenched by adding aqueous 3 N NaOH (the color changed to dark green), and the product was extracted with Et₂O. The Et₂O extract was dried (MgSO₄) and cooled in an ice bath and then treated with ethereal HCl. The product precipitated as a white solid with a light pink shade. The solid was collected by filtration and dried; yield: 2.27 g, 85% (>98% by GC area % analysis). The analytical sample was obtained as a white solid by recrystallization from EtOAc/MeOH: mp 230–233 °C; FT-IR (KBr) 3415 (s), 2941 (s), 2819 (s), 2679 (m), 2506 (w), 2430 (w), 1452 (m), 742 (m) cm⁻¹; ¹H NMR (CDCl₃) δ 9.60 (bs, 2H), 7.16–7.02 (m, 4H), 3.62–3.45 (m, 1H), 3.43–3.12 (m, 3H), 2.91–2.80 (m, 2H), 2.61–2.50 (m, 1H), 2.40–2.17 (m, 3H), 1.91–1.60 (m, 6H), 1.39–1.18 (m, 3H); ¹³C NMR (CDCl₃) δ 134.6 (C), 132.4 (C), 129.2 (CH), 128.6 (CH), 126.5 (CH), 126.1 (CH), 54.2 (CH), 51.0 (CH), 32.3 (CH₂), 29.5 (CH₂), 28.9 (CH₂), 27.9 (CH₂), 26.0 (CH₂), 24.7 (CH₂); EI MS *m/z* (relative intensity) 229 (M⁺, 46), 187

(13), 186 (85), 158 (12), 132 (11), 131 (77), 130 (100), 129 (34), 128 (20), 116 (14), 115 (26), 104 (23), 100 (17), 91 (35), 78 (11), 77 (12), 56 (28), 55 (31). Anal. Calcd for $C_{10}H_{12}ClN$: C, 72.29; H, 9.10; N, 5.27; Cl, 13.34. Found: C, 72.41; H, 9.27; N, 5.17; Cl, 13.53.

Method V. This method is similar to methods I and II except for the use of acetonitrile as a solvent.

Method VI. This method was used with those reactions involving hindered α -keto esters or weakly basic amines in which a competitive reduction of the carbonyl compounds occur. The amine is used as a limiting reagent. A representative example of the α -keto esters is the reductive amination of methyl 3-methyl-2-oxobutanoate with benzylamine (Table 1: entry 48): methyl 3-methyl-2-oxobutanoate (1.8 g, 12.48 mmol) and benzylamine (0.446 g, 4.16 mmol) in DCE (14 mL) was treated with sodium triacetoxyborohydride (1.76 g, 8.32 mmol) at 0 °C. After stirring 21 h, GC analysis showed total consumption of the benzylamine with the presence of the product amine and the intermediate imine in an 8:1 relative ratio. The reaction was then treated with additional sodium triacetoxyborohydride (0.88 g, 4.16 mmol). After stirring an additional 21 h, GC analysis showed completion of the reaction. The reaction mixture was diluted with EtOAc (20 mL) and quenched with distilled water (10 mL). After further dilution with EtOAc (20 mL), the pH of the water layer was adjusted to 7 with saturated aqueous $NaHCO_3$. The EtOAc layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product (2.45 g). The crude product was dissolved in ether and treated with ethereal HCl to give the HCl salt, 0.92 g, 81% yield, as a white solid: mp 190–191 °C; FT-IR (KBr) 2966 (m), 2806 (m), 2696 (m), 1742 (s), 1565 (m), 1469 (m), 1424 (m), 1249 (s), 1030 (m), 753 (m), 704 (m) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 10.65 (bs, 1H), 10.00 (bs, 1H), 7.66–7.63 (m, 2H), 7.41–7.38 (m, 3H), 4.40 (d, J = 13.3 Hz, 1H), 4.25 (d, J = 13.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.45–3.35 (m, 1H), 2.75–2.60 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7 (C), 130.9 (CH), 129.5 (CH), 129.0 (CH), 63.1 (CH), 62.2 (CH₂), 50.3 (CH₂), 29.4 (CH), 19.5 (CH₃), 17.6 (CH₃), 14.0 (CH₃); EI MS m/z (rel intensity) 236 (M^+ , 100), 162 (38), 91 (20). Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.94; H, 8.21; N, 5.05.

An example of the use of weakly basic amines is the reductive amination of 1-Carbethoxy-4-piperidone with *p*-nitroaniline (Table 3: entry 5): 1-Carbethoxy-4-piperidone (3.2 g, 19 mmol), *p*-nitroaniline (1.4 g, 10 mmol), and glacial AcOH (3.6 g, 60 mmol) were mixed in 1,2-dichloroethane (45 mL). Sodium triacetoxyborohydride (6.0 g, 28 mmol) was added to the above solution and the reaction mixture stirred at room temperature under N_2 for 18 h (GC analysis indicated a complete reaction in addition to ca 20% ketone reduction). The reaction was quenched with saturated aqueous $NaHCO_3$, and the product was extracted with EtOAc (3 $\times$ 75 mL). The EtOAc extract was dried ($MgSO_4$), and the solvent was evaporated to give a yellow semisolid (4.7 g). The semisolid was triturated with ether/hexane (7:3) to dissolve the excess piperidone and the piperidol byproduct. The yellow solid was collected by filtration and dried (1.75 g, 60%), >99% pure by GC area % analysis. The analytical sample was obtained by recrystallization from EtOAc/hexane: mp 172–174 °C; FT-IR (KBr) 3327 (s), 3182 (s), 3097 (w), 2929 (w), 2870 (m), 2398 (m), 1679 (s), 1600 (s), 1546 (m), 1460 (s), 1387 (m), 1296 (s), 1234 (m), 1184 (m), 1144 (m), 1105 (s), 1033 (m), 937 (m); ^1H NMR ($CDCl_3/d_6$ -DMSO) δ 8.03 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.14 (d, J = 7.5 Hz, 1H), 4.16–4.10 (m, 4H), 3.58–3.50 (m, 1H), 3.02 (m, 2H), 2.04–2.00 (m, 2H), 1.51–1.42 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3/d_6$ -DMSO) δ 154.9 (C), 152.5 (C), 136.4 (C), 125.9 (CH), 110.6 (CH), 60.8 (CH₂), 49.0 (CH), 41.9 (CH₂), 31.0 (CH₂), 14.2 (CH₃); MS (EI), 293 (95), 277 (15), 276 (76), 264 (9), 248 (12), 220 (23), 177 (19), 156 (29), 155 (100), 154 (9), 131 (10), 130 (23), 129 (16), 128 (13), 127 (37), 126 (41), 117 (14), 100 (21), 96 (19), 82 (28), 57 (18), 56 (57). Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.27; H, 6.54; N, 14.21.

2. Stepwise Procedures. Aldimine Formation/Reduction in Methanol. An example is the preparation of *N*-cy-

clobutyl-4-chlorobenzylamine (Table 5: entry 4): *p*-Chlorobenzaldehyde (1.40 g, 10 mmol) and cyclobutylamine (0.75 g, 10.6 mmol) were mixed in MeOH (40 mL) at rt under a N_2 atmosphere. The mixture was stirred at rt for 3 h, until the aldimine formation was completed (determined by GC). The aldimine in MeOH was carefully treated with solid $NaBH_4$ (0.6 g, 16 mmol). The reaction mixture was stirred for 10 min and quenched with 1 M NaOH. The product was extracted with ether. The ether extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was evaporated to give the crude product as a nearly colorless oil (1.92 g, 98%) which was >97% pure by area % GC analysis. The oil was dissolved in ether and treated with ethereal HCl to give the HCl salt which was recrystallized from EtOAc/MeOH as white crystals, 2.07 g, 89%, mp 237–238 °C; FT-IR (KBr) 2917 (s), 2804 (s), 2762 (s), 2435 (m), 1497 (m), 1432 (m), 1092 (m), 808 (m), 520 (m) cm^{-1} ; ^1H NMR (free base, $CDCl_3$) δ 7.25–7.22 (m, 4H), 3.64 (s, 2H), 3.28–3.21 (m, 1H), 2.23–2.16 (m, 2H), 1.71–1.63 (m, 4H), 1.38 (bs, 1H); ^1H NMR (HCl salt, $CDCl_3 + CD_3OD$) δ 9.70 (bs, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 3.94 (s, 2H), 3.52 (q, J = 8.15 Hz, 1H), 2.95 (bs, 2H), 2.41–2.35 (m, 2H), 2.22–2.13 (m, 2H), 1.99–1.89 (m, 1H), 1.83–1.73 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) δ 138.9 (C), 132.4 (C), 130.1 (CH), 129.4 (CH), 50.2 (CH), 53.4 (CH₂), 30.9 (2 CH₂), 14.6 (CH₂); EI MS m/z (relative intensity) 196 (M^+), 167 (48), 125 (100), 89 (26), 39, (18). Anal. Calcd for $C_{11}H_{15}Cl_2N$: C, 56.91; H, 6.51; N, 6.03; Cl, 30.54. Found: C, 56.89; H, 6.45; N, 5.87; Cl, 30.82.

Reduction of Enamines. An example is the reduction of 1-morpholino-1-cyclohexene (Table 5, entry 6 and Table 1, entry 5): 1-Morpholino-1-cyclohexene (1.67 g, 10 mmol) in DCE (30 mL) and AcOH (0.61 g, 10 mmol) was treated with sodium triacetoxyborohydride (3.0 g, 14 mmol) and stirred under argon. The GC analysis determined that the reduction was complete after 10 min. The reaction was quenched by adding 1 M NaOH, and the product was extracted with ether. The ether extract was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the crude product as a colorless oil (1.70 g). The oil was dissolved in ether (50 mL), cooled in an ice bath, and treated with ethereal HCl to give the HCl salt as a white solid. The solid was collected by filtration air-dried, and then recrystallized from EtOAc/MeOH to give the purified product (1.88 g, 91.4%): mp 260–262 °C. Picrate salt: a yellow solid, mp 174–175 °C (ethanol) [lit.¹¹ 176–177 °C]; FT-IR (HCl salt, KBr) 3425 (s), 2937 (s), 2861 (m), 2672 (s), 2606 (s), 2478 (m), 1448 (m), 1399 (w), 1267 (w), 1110 (s), 1070 (w), 950 (w) cm^{-1} ; ^1H NMR (free base, $CDCl_3$) δ 3.74 (t, J = 5.0 Hz, 4H), 2.43 (t, J = 5.0 Hz, 4H), 2.29 (m, 1H), 1.88 (d, J = 10.0 Hz, 4H), 1.61 (d, J = 13.0 Hz, 1H), 1.28 (m, 5H); ^{13}C NMR (free base, $CDCl_3$) δ 66.9 (CH₂), 63.4 (CH), 49.3 (CH₂), 28.4 (CH₂), 25.9 (CH₂), 25.4 (CH₂); EI MS m/z (relative intensity) 169 (M^+ , 16), 127 (11), 126 (100), 98 (7), 83 (10), 82 (12), 68 (10), 56 (19), 55 (36). Anal. Calcd for $C_{10}H_{12}ClNO$: C, 58.38; H, 9.80; N, 6.81; Cl, 17.23. Found: C, 58.22; H, 9.69; N, 6.72; Cl, 17.25.

The Use of Titanium(IV) Isopropoxide. An example is the synthesis of *N*-[1-(1-cyclohexenyl)ethyl]benzylamine (Table 5, entry 8): 1-Acetylcyclohexene (1.24 g, 10 mmol) and benzylamine (1.2 g, 11.2 mmol) were mixed in neat titanium(IV) isopropoxide (4.78 g, 16.8 mmol) and stirred under nitrogen for 3 h. Methanol (45 mL) was added followed by careful addition of $NaBH_4$ (0.6 g, 16 mmol). Analysis of the reaction mixture after 5 min by GC indicated a complete reduction to the amine. The reaction was quenched by adding 0.1 N NaOH. The resulting mixture was filtered through Celite, and the residue was washed with ether (2 $\times$ 50 mL) and with CH_2Cl_2 (50 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product (2.2 g). The crude product was dissolved in ether and treated with ethereal HCl to give the HCl salt as a white solid. The solid was purified by recrystallization from EtOAc/MeOH to give 2.1 g, 83%, of white crystals: mp 215–217 °C; FT-IR (KBr) 3417 (m), 2932 (vs), 2835 (m), 2782 (s), 2732 (s), 2481 (w), 2422 (w), 1581 (m), 1454 (m), 1381 (w), 748 (m), 680 (m) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 9.65 (bs, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H),

7.29 (d, $J = 7.0$ Hz, 1H), 5.73 (s, 1H), 3.95–3.92 (m, 1H), 3.78–3.72 (m, 1H), 3.44 (bs, 1H), 2.25–2.21 (m, 1H), 2.05–1.95 (m, 3H), 1.72–1.51 (m, 4H), 1.52 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 132.6 (C), 130.6 (CH), 130.5 (C), 129.9 (CH), 128.9 (CH), 128.7 (CH), 59.0 (CH), 48.3 (CH₂), 25.1 (CH₂), 23.8 (CH₂), 22.2 (CH₂), 21.9 (CH₂), 17.4 (CH₃); EI MS m/z (relative intensity) 215 (M^+ , 4), 201 (16), 200 (83), 134 (17), 109 (4), 108 (4), 105 (10), 93 (5), 92 (13), 91 (100), 79 (13), 77 (11). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{ClN}$: C, 71.55; H, 8.81; N, 5.56; Cl, 14.08. Found: C, 71.73; H, 8.92; N, 5.40; Cl, 13.96.

Acknowledgment. We are grateful to the PRI spectroscopy group for their help and assistance: D. Gauthier, G. Leo, and P. McDonnell for NMR spectra, J. Masucci and W. Jones for the FT-IR and mass spectra, and X. Xiang, D. Burinsky, and R. Dunphy for

the high resolution mass spectra. We also thank Dr. Norman Santora, the chemical information specialist, for his valuable help with the library search. We thank professor Robert O. Hutchins (Drexel University) for helpful discussions and for supplying some authentic samples.

Supporting Information Available: Supporting data for nearly all products are available including mp, FT-IR, ^1H NMR, ^{13}C NMR, MS, and elemental analysis (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Sodium borohydride on wet clay: Solvent-free reductive amination of carbonyl compounds using microwaves^{*1}

Rajender S. Varma and Rajender Dahiya

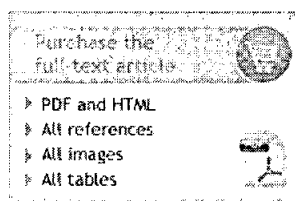
Department of Chemistry, Sam Houston State University, Huntsville, Texas 77341-2117, USA

Texas Research Institute for Environmental Studies (TRIES), Sam Houston State University, Huntsville, Texas 77341-2117, USA

Received 28 January 1998; accepted 7 April 1998. ; Available online 7 July 1998.

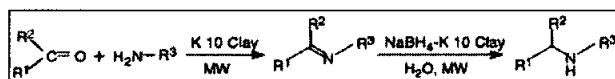
Abstract

A solvent-free reductive amination of carbonyl compounds by wet montmorillonite K 10 clay supported sodium borohydride is described; microwave irradiation facilitates the procedure.



Graphical Abstract

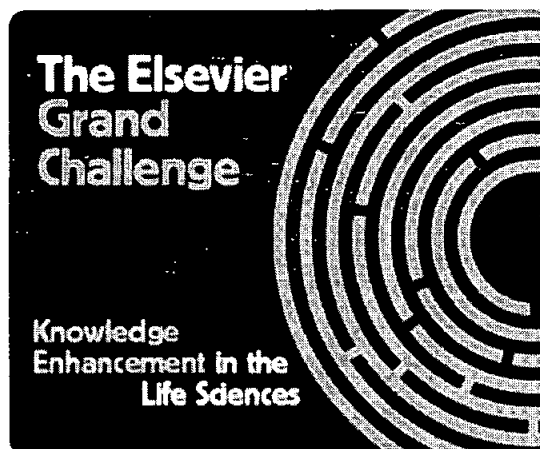
A solvent-free reductive amination of carbonyl compounds by wet montmorillonite K 10 clay supported sodium borohydride is described; microwave irradiation facilitates the procedure.



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The rate of coupling of oligosaccharides having aldose end groups to protein by reductive amination was significantly increased by changing the temperature and pH of the reaction, and even more significantly by the addition of borate ions. Under optimized conditions half of the lysine residues of bovine serum albumin could be derivatized by lactose in 7 h and their complete derivatization was achieved in approximately 24 h. All attempts to carry out similar reductive amination procedures using oligosaccharides having ketose (D-fructose, 3-deoxy-D-manno-octulosonic acid (KDO), and sialic acid) failed owing to the slowness of the reaction. Model studies on the coupling of D-fructose and KDO to glycine indicate that any coupling procedure based on reductive amination of ketose residues would of necessity require the prior introduction of a small functionalized spacer molecule.

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Expedient syntheses of neoglycoproteins using phase transfer catalysis and reductive amination as key reactions. [Glycoconj J. 1991]

Synthesis of glycoconjugates derived from various lipopolysaccharides of the *Vibrio* species. [Glycoconj J. 1989]

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del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: -----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
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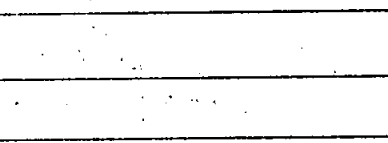
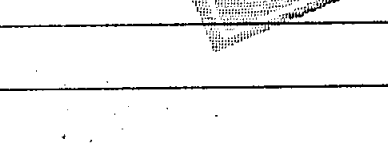
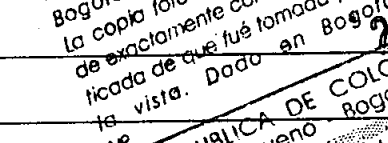
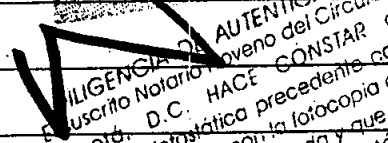
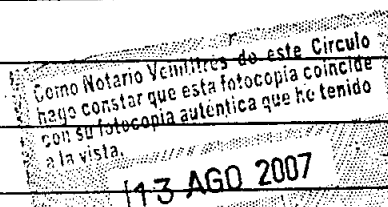
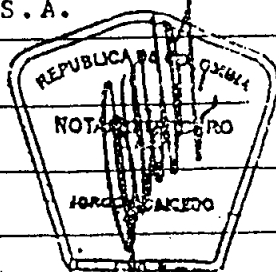
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9/ *Juan m. Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali Nº

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

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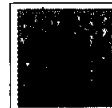
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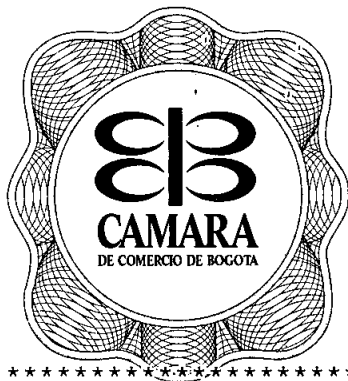
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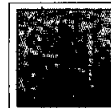
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E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970
41379			
E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI	14/10/1971
44154			
E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI	10/11/1971
44367			
E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971
44716			
E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI	15/10/1973
5505 IX			
E.P. 8741	31/12/1973	NOTARIA SEGUNDA DE CALI	08/03/1974

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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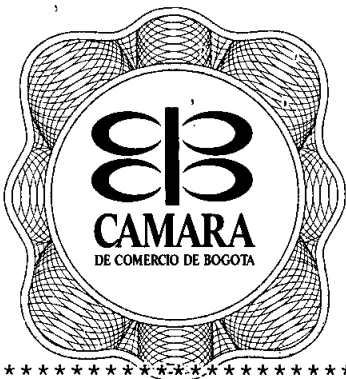
PAGINA No. 4

7636	IX	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	31/01/1975
E.P. 9270	IX	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	31/01/1975
11772	IX	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	04/04/1975
E.P. 9504	IX	31/12/1974	NOTARIA	SEGUNDA	DE	CALI	04/04/1975
12441	IX	05/12/1975	NOTARIA	SEGUNDA	DE	CALI	09/01/1976
E.P. 7566	IX	05/12/1975	NOTARIA	SEGUNDA	DE	CALI	09/01/1976
15581	IX	09/05/1980	NOTARIA	SEGUNDA	DE	CALI	22/10/1980
E.P. 2671	IX	09/05/1980	NOTARIA	SEGUNDA	DE	CALI	22/10/1980
41529	IX	10/03/1982	NOTARIA	DECIMA	DE	CALI	03/08/1982
E.P. 779	IX	10/03/1982	NOTARIA	DECIMA	DE	CALI	03/08/1982
54655	IX	10/11/1982	NOTARIA	DECIMA	DE	CALI	30/06/1983
E.P. 4324	IX	10/11/1982	NOTARIA	DECIMA	DE	CALI	30/06/1983
61172	IX	18/03/1986	NOTARIA	DECIMA	DE	CALI	01/04/1986
E.P. 1269	IX	18/03/1986	NOTARIA	DECIMA	DE	CALI	01/04/1986
83730	IX	24/09/1986	NOTARIA	DECIMA	DE	CALI	29/09/1986
E.P. 5089	IX	24/09/1986	NOTARIA	DECIMA	DE	CALI	29/09/1986
87933	IX	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
E.P. 7064	IX	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
2552	IX	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
E.P. 7065	IX	04/11/1987	NOTARIA	DECIMA	DE	CALI	19/11/1987
2553	IX	14/07/1989	NOTARIA	DECIMA	DE	CALI	26/07/1989
E.P. 5929	IX	14/07/1989	NOTARIA	DECIMA	DE	CALI	26/07/1989
20225	IX	29/09/1989	NOTARIA	DECIMA	DE	CALI	02/10/1989
E.P. 8569	IX	29/09/1989	NOTARIA	DECIMA	DE	CALI	02/10/1989
22250	IX	04/12/1992	NOTARIA	DECIMA	DE	CALI	15/12/1992
E.P. 10571	IX	04/12/1992	NOTARIA	DECIMA	DE	CALI	15/12/1992
60929	IX	18/12/1995	NOTARIA	DECIMA	DE	CALI	20/12/1995
E.P. 10249	IX	18/12/1995	NOTARIA	DECIMA	DE	CALI	20/12/1995
10214	IX	22/05/1997	NOTARIA	TERCERA	DE	CALI	27/05/1997
E.P. 2359	IX	22/05/1997	NOTARIA	TERCERA	DE	CALI	27/05/1997
3813	IX	30/06/2000	NOTARIA	TERCERA	DE	CALI	07/07/2000
E.P. 2624	IX	30/06/2000	NOTARIA	TERCERA	DE	CALI	07/07/2000
4740	IX	15/09/2000	NOTARIA	TERCERA	DE	CALI	18/09/2000
E.P. 3814	IX	15/09/2000	NOTARIA	TERCERA	DE	CALI	18/09/2000
6381	IX	30/07/2004	NOTARIA	TERCERA	DE	CALI	04/08/2004
E.P. 3588	IX	30/07/2004	NOTARIA	TERCERA	DE	CALI	04/08/2004
8542	IX	24/05/2006	NOTARIA	TERCERA	DE	CALI	30/05/2006
E.P. 2224	IX	24/05/2006	NOTARIA	TERCERA	DE	CALI	30/05/2006
6565	IX	08/05/2008	NOTARIA	TERCERA	DE	CALI	16/05/2008
E.P. 1675	IX	08/05/2008	NOTARIA	TERCERA	DE	CALI	16/05/2008
5362	IX						

CERTIFICA:

VIGENCIA: 01 DE JANUARY DEL A?O 2057

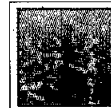
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CERTIFICADO NACIONAL

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PAGINA No. 5

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS. D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO, INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION. PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES

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PAGINA No. 6

EJECUTIVOS

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSI?N DE LA SOCIEDAD, SU TRANSFORMACI?N, LA ENAJENACI?N O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCI?N O LA PRORROGA Y CUALQUIER REFORMA; AMPLIACI?N MODIFICACI?N DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICI?N DE ACCIONES PROPIAS, CON SUJECI?N A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTER?S DE LA SOCIEDAD.

LA JUNTA DIRECTIVA SE COMPONE DE SEIS (6) MIEMBROS PRINCIPALES O DIRECTORES, ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS PARA PER?ODOS DE DOS A?OS, SIN PERJUICIO DE QUE PUEDAN SER REMOVIDOS LIBREMENTE POR LA ASAMBLEA O REELEGIDOS INDEFINIDAMENTE. SIMULT?NEAMENTE CON LA ELECCI?N DE LOS PRINCIPALES, LA ASAMBLEA ELEGIR? SEIS (6) SUPLENTE NUM?RICOS LOS CUALES, EN EL ORDEN DE DESIGNACI?N, REEMPLAZAR?N A LOS PRINCIPALES EN SUS FALTAS ABSOLUTAS, ACCIDENTALES O TEMPORALES.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDR? ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDR? LAS SIGUIENTES FUNCIONES (ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POL?TICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECON?MICA Y LABORAL; APROBAR PLANES DE INVERSI?N Y DE PRODUCCI?N; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCI?N Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEM?S ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACI?N Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACI?N QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CAR?CTER DE RESERVAS DE INVERSI?N, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RA?CES CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANT?A O SUPERIOR A CIEN MIL D?LARES AMERICANOS (\$US100.000.00). 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD, LOS REPRESENTANTES LEGALES CUANDO SU CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A US\$300.000.00. L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPA?A A LA CELEBRACI?N DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M)

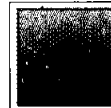
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CERTIFICADO NACIONAL

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PAGINA No. 7

SERVIR-DE-?RGANO-CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPA??A.

LA ADMINISTRACI?N INMEDIATA DE LA COMPA??A, SU REPRESENTACI?N LEGAL Y LA GESTI?N DE LOS NEGOCIOS SOCIALES ESTAR?N A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN A?O, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODR?N ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPA??A CON EXCEPCI?N DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTAR?N SOMETIDOS EN EL DESEMPE?O DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACI?N INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACI?N LEGAL DE LA COMPA??A, LA GESTI?N COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCI?N ADMINISTRATIVA, LA COORDINACI?N Y LA SUPERVISI?N GENERAL DE LA EMPRESA, LAS CUALES CUMPLIR?N CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECI?N A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

COMO REPRESENTANTES LEGALES DE LA COMPA??A EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CAR?CTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACI?N DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSAS ADMINISTRATIVAS EN QUE LA COMPA??A TENGA INTER?S E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CR?DITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PAR?GRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACI?N Y SIN REQUERIR AUTORIZACI?N PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACI?N, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACI?N DE CUANT?A ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOM?A MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080626

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PAGINA No. 8

DOCUMENTO: ACTA No. 393 DEL 20 DE JANUARY DE 1993
ORIGEN: JUNTA DIRECTIVA
INSCRIPCION: 26 DE JANUARY DE 1993 No. 62203 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

PRESIDENTE EJECUTIVO
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

VICEPRESIDENTE EJECUTIVO
JUAN MANUEL BARBERI OSPINA
C.C.14949561

VICEPRESIDENTE EJECUTIVO
JUAN BAUTISTA DE LOS RIOS GUTIERREZ
C.C.17108621

VICEPRESIDENTE EJECUTIVO
EMILIO SARDI APARICIO
C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 67 DEL 28 DE MARCH DE 2008
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 16 DE MAY DE 2008 No. 5363 DEL LIBRO IX

FUE(ON) NOMBRADO(S)

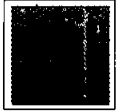
JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

SEGUNDO RENGLON
JUAN MANUEL BARBERI OSPINA
C.C.14949561

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PAGINA No. 9

TERCER RENGLON
EMILIO SARDI APARICIO
C.C.14434582

CUARTO RENGLON
ANTONIO JAIRO RAMIREZ ECHAVE
C.C.16741040

QUINTO RENGLON
DIEGO HUMBERTO QUIJANO REISSNER
C.C.16615708

SEXTO RENGLON
ALONSO BOTERO PARDO
C.C.16830282

SUPLENTE

PRIMER RENGLON
VICTOR RICARDO ROSA GARCIA
C.C.6811102

SEGUNDO RENGLON
ERNESTO TRUJILLO PEREZ
C.C.14984104

TERCER RENGLON
ANA MARIA ALVAREZ ROBLEDO
C.C.31170896

CUARTO RENGLON
GUSTAVO ADOLFO SANCHEZ LESMES
C.C.16625960

QUINTO RENGLON
JORGE ENRIQUE ARIZA BERNAL
C.C.19494493

SEXTO RENGLON
MARTHA LUZ GONZALEZ TORRES
C.C.31854671

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARCH DE 2003

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080626

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Operacion : 02NA40626030

PAGINA No. 10

ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL
DELOITTE & TOUCHE LTDA D & T LTDA
NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AUGUST DE 2004
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 30 DE AUGUST DE 2004 No. 9417 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
LUIS FERNANDO QUICENO BENAVIDES
C.C.6106227

REVISOR FISCAL SUPLENTE
JESUS DARIO LOPEZ CASELLA
C.C.16789097

CERTIFICA:

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULY DE 1996 NOTARIA DECIMA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULY DE 1996 BAJO EL NRO. 144 DEL
LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A
CARLOS ALBERTO QUINTERO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO
CON LA CEDULA DE CIUDADANIA NRO.

14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA
PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN
LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA
SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL
IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y
TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA
ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER
OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR.

B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A

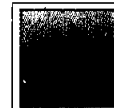
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PAGINA No. 11

TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE JANUARY DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRUARY DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CÉDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: 1o.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORQUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR

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PAGINA No. 12

 CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTAR A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTAR A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAY DE 1995 NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTAR A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA; E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS,

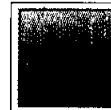
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PAGINA No. 13

PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DECEMBER DE 2004 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE JANUARY DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. EL APODERADO SE CE?IRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

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PAGINA No. 14

CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTEMBER DE 2005 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTOBER DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SEÑOR JUAN BAUTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621 DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C.; PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

EL PRESENTE PODER SE CONFIERE PARA QUE LOS APODERADOS ACTUEN ANTE CUALQUIER PERSONA O AUTORIDAD ADMINISTRATIVA DEL ORDEN NACIONAL, DEPARTAMENTAL, DISTRITAL Y LOCAL; ANTE LAS AUTORIDADES CONTENCIOSO ADMINISTRATIVAS Y JUDICIALES, PARA OBTENER LA PROTECCION DE NUESTRA PROPIEDAD INTELECTUAL Y CONTRA LAS PRACTICAS RESTRICTIVAS DE LA COMPETENCIA Y LOS ASUNTOS DE COMPETENCIA DESLEAL, A CUYO EFECTO LA AUTORIZO, EN TODO LO CONCERNIENTE A LOS SIGUIENTES ASUNTOS: A) OBTENCION DE PATENTES DE INVENCION, DE MODELO DE UTILIDAD, ESQUEMAS DE TRAZADOS DE CIRCUITOS INTEGRADOS, DISEÑOS INDUSTRIALES, EL REGISTRO DE MARCAS DE PRODUCTOS O SERVICIOS; LEMAS COMERCIALES; DEPOSITO DE NOMBRES Y ENSEÑAS COMERCIALES, INDICACIONES GEOGRAFICAS; RENOVACION DE SIGNOS DISTINTIVOS, RENOVACIONES, AFECTACIONES AL REGISTRO, INSCRIPCION DE CONTRATOS, SOLICITUD Y RENOVACION DE NOMBRES DE DOMINIO; B) PRESENTACION DE OPOSICIONES AL REGISTRO DE MARCAS DE TERCERO, PRESENTACION DE ALEGATOS EN DEFENSA DE OPOSICIONES AL REGISTRO, ACCION DE CANCELACION, ACCION POR INFRACCION DE DERECHOS, REVOCATORIA DIRECTA, ACCION DE NULIDAD, ACCION DE NULIDAD Y RESTABLECIMIENTO DEL DERECHO, ACCION REIVINDICATORIA, ACCIONES DE TUTELA, POPULARES, DE GRUPO, DE CLASE; ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; C) AGOTAMIENTO DE LA VIA GUBERNATIVA, EJERCICIO DEL DERECHO DE PETICION ANTE CUALQUIER PERSONA O AUTORIDAD; D) SOLICITUD DE MEDIDAS CAUTELARES, PRESENTACION DE ACCIONES MEDIANTE PROCESOS CIVILES, PENALES, ADMINISTRATIVOS O CONTENCIOSO ADMINISTRATIVOS RELACIONADOS CON ESTOS DERECHOS U OTROS DE DIFERENTE NATURALEZA, MEDIDAS EN FRONTERA, ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; E) OBTENER Y TRAMITAR TODO LO RELACIONADO CON EL RECONOCIMIENTO DE DERECHOS DE AUTOR, DERECHOS CONEXOS Y NUEVAS TECNOLOGIAS Y SU PROTECCION LEGAL; F) SOLICITUD DE REGISTRO Y RENOVACION DE CONTRATOS DE TRANSFERENCIA DE TECNOLOGIA; G) OBTENER Y TRAMITAR TODO LO RELACIONADO CON

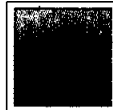
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PAGINA No. 15

LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES. RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I) SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 22 DE MAY DE 2008 DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE JUNE DE 2008 BAJO EL NRO. 90 DEL LIBRO V SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

1. ANA MAR?A ?LVAREZ R. CON C.C. 31.170.896 DE CALI Y JORGE ENRIQUE GIRALDO, CON C.C. 16.784.794 DE CALI, OBRARAN COMO APODERADOS ESPECIALES PARA EL DESARROLLO DE LAS SIGUIENTES FACULTADES:

A. SUSCRIBIR LOS CONTRATOS DE TRABAJO, SUS MODIFICACIONES Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE A TECNOQU?MICAS S.A.

B. COMPARECER DIRECTAMENTE U OTORGAR PODER PARA ATENDER RECLAMACIONES Y PROCESOS DE ORDEN LABORAL BIEN SEA DE CAR?CTER ADMINISTRATIVO O JUDICIAL ANTE LAS OFICINAS REGIONALES DE TRABAJO, MINISTERIO DE LA PROTECCI?N SOCIAL Y ANTE CUALQUIER OTRA AUTORIDAD O ENTIDAD ANTE LA QUE SE INICIE Y TRAMITE PROCEDIMIENTOS DE CAR?CTER LABORAL O RELACIONADOS CON TEMAS DE LA SEGURIDAD SOCIAL.

C. FIRMAR TODOS LOS DOCUMENTOS Y ATENDER TODOS LOS TR?MITES ANTE LAS CAJAS DE COMPENSACI?N FAMILIAR, EMPRESAS PRESTADORAS DE SERVICIOS DE SALUD (EPS), FONDOS DE PENSIONES Y CESANT?AS, ADMINISTRADORA DE RIESGOS PROFESIONALES (ARP), INSTITUTO DE LOS SEGUROS SOCIALES (ISS). ESTA FACULTAD TAMBI?N COMPRENDE LA DESIGNACI?N DE APODERADOS.

D. ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACI?N, DECLARACIONES DE PARTE Y RENDICI?N DE TESTIMONIOS DENTRO DE LOS PROCESOS DE LA JURISDICCI?N LABORAL Y TR?MITES ADMINISTRATIVOS, CUANDO ELLO SEA REQUERIDO.

E. RESPONDER LAS DEMANDAS DE TUTELA DIRECTAMENTE O A TRAV?S DE APODERADO ESPECIAL.

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G. SUSCRIBIR LOS CONTRATOS DE TODO TIPO CON ENTIDADES EDUCATIVAS DE TODO ORDEN, SIN LIMITACION DE CUANTIA.

H. SUSCRIBIR LOS DOCUMENTOS Y ESCRITURAS DE DONACION QUE SEAN AUTORIZADAS POR LA JUNTA DIRECTIVA, SIN LIMITACION ALGUNA.

I. SUSCRIBIR TODOS LOS CONTRATOS DE CONSTRUCCION, INSTALACION, SERVICIOS, REPARACIONES Y ADECUACIONES QUE SE REALICEN Y PRESTEN EN LA PLANTA Y SEDE ADMINISTRATIVA DE TECNOQUIMICAS S.A. LOCALIZADAS EN CALI, HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MINIMOS LEGALES MENSUALES, DARLOS POR TERMINADO POR CUALQUIER CAUSA, PRESENTAR RECLAMOS ANTE LAS COMPANIAS ASEGURADORAS, EXIGIR EL PAGO DE MULTAS E INDEMNIZACIONES DE CUALQUIER TIPO QUE ESTEN PACTADAS EN LOS RESPECTIVOS CONTRATOS Y EL CUMPLIMIENTO DE ELLOS.

J. ANTE EL MINISTERIO DEL MEDIO AMBIENTE Y ORGANISMOS DE CONTROL AMBIENTAL DEL ORDEN NACIONAL, DEPARTAMENTAL Y MUNICIPAL O DISTRITAL: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRAMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTE ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARACTER JUDICIAL O GUBERNATIVO.

K. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS ANTE CUALQUIER AUTORIDAD.

PARAGRAFO 1. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPANIAS ASEGURADORAS.

PARAGRAFO II. LOS APODERADOS EJERCERAN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACION.

2. JORGE ENRIQUE ARIZA BERNAL, IDENTIFICADO CON LA Cedula DE CIUDADANIA NO. 19.494.493 DE BOGOTA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES:

A. ANTE EL MINISTERIO DEL MEDIO AMBIENTE: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRAMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTE ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARACTER JUDICIAL O GUBERNATIVO.

B. ANTE LA SUPERINTENDENCIA DE VIGILANCIA: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, OTORGAR PODERES, RENDIR DECLARACIONES, ATENDER VISITAS, FIRMAR LAS ACTAS CORRESPONDIENTES Y NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRAMITES QUE

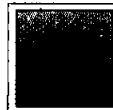
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080626

Hora Certificado 15:05:44

Operacion : 02NA40626030

PAGINA No. 17

LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA

ADELANTAR ANTE LA ENTIDAD, AS? COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

C. ANTE EL FONDO NACIONAL DE ESTUPEFACIENTES Y DIRECCI?N NACIONAL DE ESTUPEFACIENTES FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LAS CITADAS ENTIDADES, SUSCRIBIR LAS ACTAS DE VISITA, Y DESIGNAR APODERADOS PARA NOTIFICARSE DE ACTOS ADMINISTRATIVOS, INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

D. EN TODO LO RELACIONADO CON LOS TR?MITES DE IMPORTACIONES Y EXPORTACIONES, SEG?N SE INDICA:

I. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS ADMINISTRACIONES DE ADUANAS DE LA DIRECCI?N DE IMPUESTOS Y ADUANAS - DIAN - AS? COMO RENDIR DECLARACIONES, ATENDER VISITAS E INSPECCIONES Y FIRMAS LAS CORRESPONDIENTES ACTAS ATENDER DIRECTAMENTE, CUANDO ELLO SEA REQUERIDO Y EN GENERAL OBRAR COMO APODERADO ESPECIAL ANTE LAS AUTORIDADES ADUANERAS EN TODAS LAS OPERACIONES RELACIONADAS CON EL COMERCIO EXTERIOR.

II. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS SOCIEDADES PORTUARIAS DE BUENAVENTURA, CARTAGENA Y BARRANQUILLA, AS? COMO RESPONDER Y ATENDER LOS TR?MITES DIRECTAMENTE O A TRAV?S DE APODERADOS.

III- OTORGAR PODERES ESPECIALES Y GENERALES, OTORGAR GARANT?AS Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS NAVIERAS Y EMPRESAS ADMINISTRADORAS DE CONTENEDORES PARA EL MANEJO Y RETIRO DE ELLOS.

IV. OTORGAR PODERES ESPECIALES Y GENERALES A LAS SOCIEDADES DE INTERMEDIACI?N ADUANERA - SIA- Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN DE ACUERDA CON LA NORMATIVIDAD LEGAL SOBRE LA MATERIA.

V. SUSCRIBIR LAS CARTAS DE ANTINARC?TICOS QUE SE PRESENTAN ANTE LA POLIC?A AEROPORTUARIA BIEN DIRECTAMENTE O AUTORIZANDO A LOS JEFES DE BODEGA DE YUMBO Y JAMUND? PARA ESE TR?MITE DOCUMENTOS DENTRO DE LOS TR?MITES DE EXPORTACIONES O REEMBARQUES DE MERCANC?AS, Y EN GENERAL ATENDER TODAS LAS DILIGENCIAS DIRECTAMENTE U OTORGAR PODER AUN TERCERO.

D. SUSCRIBIR CONTRATOS DE CONSTRUCCI?N Y DE OBRA QUE SE REALICEN Y PRESTEN EN LAS PLANTAS DE TECNOQU?MICAS S.A. LOCALIZADAS EN JAMUND?, YUMBO Y VILLA RICA (DEPARTAMENTO DEL CAUCA EN EL CONJUNTO INDUSTRIAL PARQUESUR) HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS M?NIMOS LEGALES MENSUALES.

E. SUSCRIBIR CONTRATOS, SIN LIMITACI?N DE CUANT?A QUE TENGA QUE VER CON LA ADQUISICI?N DE EQUIPO Y MAQUINARIA, REPARACI?N, ADECUACI?N, INSTALACI?N,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 18

SERVICIOS TÉCNICOS Y DE ASESORIA.

E. SUSCRIBIR CONTRATOS DE FABRICACIÓN CON TERCEROS BIEN SEA QUE TECNOQUÍMICAS OBTenga COMO FABRICANTE O COMO PROPIETARIO.

PARAGRAFO. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

3. MARÍA TERESA CAJÓN DE GUZMAN, IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA NO. 31.238.104 DE CALI, CARLOS ARTURO PEÑA NIETO IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 19.483.439 DE BOGOTÁ Y ANGELA MARÍA CORREA CARDONA IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA NO. 66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL, EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A TECNOQUÍMICAS S.A. EN:

A. EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CRÉDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LAS CUENTAS CORRIENTES DE COMPENSACIÓN, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRÉSTAMOS EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICIÓN DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS, DECLARACIONES O RESPUESTAS A REQUERIMIENTOS QUE DEBAN HACERSE ANTE EL BANCO DE LA REPÚBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO.

LOS APODERADOS SUSCRIBIRÁN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMAN LA PERSONERÍA A NOMBRE DE TECNOQUÍMICAS S.A., BIEN SEA DIRECTAMENTE O A TRAVÉS DE APODERADO, SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGÚN CASO QUEDE SIN LA DEBIDA REPRESENTACIÓN EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARÁCTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER.

B. EN RELACIÓN CON SECTOR FINANCIERO:

I. SUSCRIBIR LOS CONTRATOS DE CRÉDITO Y LEASING CON LOS BANCOS, ENTIDADES FINANCIERAS, COMPAÑÍAS DE FINANCIAMIENTO COMERCIAL, DE ACUERDO CON LOS CUPOS FIJADOS POR LA JUNTA DIRECTIVA, ASÍ COMO LOS PAGARÉS, LOS CONTRATOS DE GARANTÍA PRENDARIA E HIPOTECARIA, LA CONFIRMACIÓN DE FORWARDS Y TODOS LOS DEMÁS DOCUMENTOS QUE SEAN REQUERIDOS PARA LA CULMINACIÓN Y FORMALIZACIÓN DE ESTOS TRÁMITES.

ESTAS FACULTADES IGUALMENTE APLICAN PARA TODOS LOS CRÉDITOS QUE OTORQUE EL BANCO DE COMERCIO EXTERIOR DE COLOMBIA - BANCOLEX.

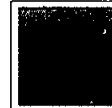
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PAGINA No. 19

II. SUSCRIBIR LOS FORMATOS Y CONTRATOS DE APERTURAS DE CUENTAS CORRIENTES, AHORROS, SERVICIOS DE BANCA VIRTUAL, LOS FORMATOS DE PROVEEDORES PARA PAGOS POR TRANSFERENCIA ELECTRÓNICA Y LOS FORMULADOS TÉCNICOS DE CONOCIMIENTO DE PERSONA JURÍDICA QUE EXIGE EL SECTOR FINANCIERO.

III. SUSCRIBIR LAS LETRAS DE COBRANZA Y LAS CARTAS DE CRÉDITO.

C. SOLICITAR TIDIS Y FIRMAR TODOS LOS DOCUMENTOS RELACIONADOS CON ESTE TRÁMITE.

D. EN RELACIÓN CON LA COMPAGNÍAS ASEGURADORAS:

I. SUSCRIBIR DOCUMENTOS DE RECLAMACIÓN Y OTORGAR PODERES PARA QUE COMPAREZCAN A LAS AUDIENCIAS DE RECLAMACIONES, ASÍ COMO LOS DOCUMENTOS DE TRANSACCIÓN. ESTAS FACULTADES SE OTORGAN SIN LIMITACIÓN DE CUANTÍA.

II. SUSCRIBIR LAS CARTAS DE NO RECLAMACIÓN A LAS COMPAGNÍAS ASEGURADORAS POR OCURRENCIA DE SINIESTROS Y LAS RESPECTIVAS CONSTANCIAS.

III. SUSCRIBIR LOS DOCUMENTOS REQUERIDOS POR EL SISTEMA DE INFORMACIÓN PARA LA PREVENCIÓN DE LAVADO DE ACTIVOS (SIPLA).

E. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS.

PARAGRAFO 1. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

PARAGRAFO II. LOS APODERADOS EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN.

4. ADRIANA JIMÉNEZ MERA, IDENTIFICADA CON LA C.C. 31.174.077 DE PALMIRA, PARA EL DESARROLLO DE LAS SIGUIENTES FUNCIONES:

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACIÓN DE LA CARTERA, SIN LIMITACIÓN DE CUANTÍA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACIÓN, CON AUTORIZACIÓN PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON LAS DEUDAS A FAVOR DE TECNOQUÍMICAS S. A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACIÓN Y O TERMINACIÓN, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACIÓN DE CUANTÍA. ESTA FUNCIÓN LA PODRÁ EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACIÓN DE APODERADOS.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 20

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACION DE CREACION DE CLIENTES Y
PROVEEDORES DE LA-EMPRESA.

D. EN RELACION CON LOS VEHICULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE
TECNOQUIMICAS, TIENE LA FACULTAD DE SUSCRIBIR LOS FORMULARIOS OFICIALES PARA
TODO TIPO DE TRAMITE, ENTRE ELLOS EL TRASPASO, QUE SE REQUIERA REALIZAR, ANTE
LAS SECRETARIAS DE TRANSITO Y ANTE LAS AUTORIDADES DE TRANSITO Y TRANSPORTE DE
CUALQUIER ORDEN, ASÍ COMO FIRMAR TODO TIPO DE CONTRATOS RELACIONADOS CON LOS
VEHICULOS.

PARAGRAFO. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD
DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O
HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER
ORDEN.

ESTOS PODERES ESTARÁN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS
EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

CAPITAL AUTORIZADO: \$27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: \$500
CAPITAL SUSCRITO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500
CAPITAL PAGADO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA
DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.158 DEL LIBRO IX, EN LA
CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

CONTROLADA: INDUGRAFICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INDUGRAFICAS S.A. CORRESPONDEN AL DESARROLLO DE

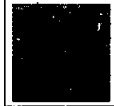
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 21

NEGOCIOS RELACIONADOS CON LAS ARTES GRAFICAS, LA DISTRIBUCION DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO EN EL INTERNACIONAL.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS E INDUGRAFICAS S.A. EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.159 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

CONTROLADA: TECNOFAR TQ S.A.

DOMICILIO: VILLA, RICA DEPARTAMENTO DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOFAR TQ S.A. CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PRODUCTOS VETERINARIOS Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR, PRODUCTOS DE ASEO PARA EL HOGAR Y LA FABRICACION Y DISTRIBUCION DE ENVASES PLASTICOS PARA TODO TIPO DE USO.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS Y TECNOFAR, EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE EL 27 DE MARZO DE 2001 BAJO EL NRO. 1979 DEL LIBRO IX, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA MARZO 21 DE 2001, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR LA SOCIEDAD TECNOQUIMICAS S.A.

MATRIZ: TECNOQUIMICAS S.A.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 22

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PANALES, PRODUCTOS VETERINARIO Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR Y PRODUCTOS DE ASEO PARA EL HOGAR.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.- ADHINTER S.A. DOMICILIO: CALI VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE ADHINTER S.A. SE DESARROLLAN EXCLUSIVAMENTE EN LA ZONA FRANCA DEL PACIFICO CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION EN EL MERCADO NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES TALES COMO CURAS, VENDITAS, ESPARADRAPOS, PARCHES, VENDAS; ADHESIVOS PARA USO EN OFICINA TALES COMO CINTAS, PEGANTES, PAPELES ADHESIVOS Y CINTAS ADHESIVAS PARA USO INDUSTRIAL.

PRESUPUESTO DE CONTROL: TECNOQUIMICAS S.A., TIENE SUSCRITAS EN LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A. ADHINTER S.A., LA CANTIDAD DE DOS MILLONES CUATROCIENTOS TREINTA MIL (2.430.000) ACCIONES ORDINARIAS DE VALOR NOMINAL DE CIEN PESOS (\$100.00) SOBRE UN TOTAL DE TRES MILLONES (3.000.000) DE ACCIONES ORDINARIAS SUSCRITAS QUE REPRESENTA UNA PARTICIPACION DIRECTA DEL 81% SOBRE EL TOTAL DEL CAPITAL SUSCRITO Y PAGADO DE LA SOCIEDAD.

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: ---C 23 7 39 DE CALI
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -K 7 22 122 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311235-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02NA40626030

PAGINA No. 23

UBICADO EN: --C-23-4-66-DE CALI

FECHA MATRICULA : 22 DE ABRIL DE 1992

RENOVO : POR EL AÑO 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI
UBICADO EN: --CARRETERA JAMUNDI KM. 23 DE JAMUNDI
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL AÑO 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO
UBICADO EN: --CL. 15 NRO. 30 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL AÑO 2008

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE MARCH DE 2008 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 26 DIAS DEL MES DE JUNE DEL AÑO 2008 HORA: 03:05:40

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

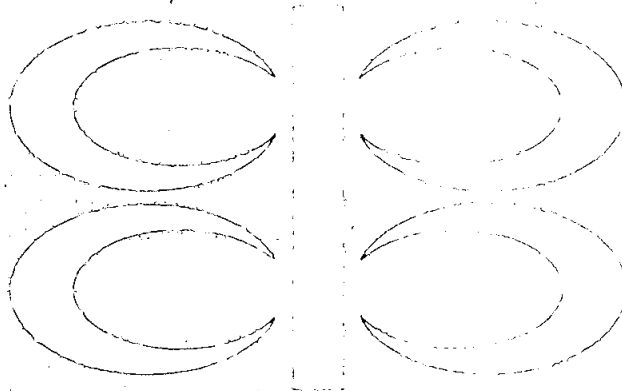
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Operacion : 02NA40626030

PAGINA No. 24


DIEGO FERNANDO OLAMPO GARCIA



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 08 - 50,765
FECHA : JUNIO 24 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-002341- -00002-0000

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Act. 400 OPOSIOBSERVTER Folios: 140

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	4640086	23/06/2008	1,023,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES
			266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 50,768
FECHA : JUNIO 24 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 140

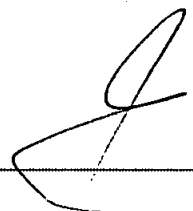
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	4640086	23/06/2008	1,023,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS
			75,000.00
		TOTAL :	\$ 75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE : 

140

2020
Bogotá, D.C.,

Doctor:
Carlos Reinaldo Olarte García
Apoderado

Oficio N°: 12804

ASUNTO: Radicación PCT N° 08-2341
Trámite 011
Evento 379
Actuación 440
Folios 143

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.

10 OCT. 2008

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

202021