

CAVELIER

ABOGADO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

www.cavelier.com
cavelier@cavelier.com

EDIFICIO
CARRERA 41
BOGOTÁ 8, C



No. 06-055564-00003-0000

Fecha: 2008-05-20 16:40:14 Dep: 2020 NUEVAS CREACIONES
Tra: 11 PATENTE Ley: 379 BASE NACIONAL
Act: 538 PETICION Folios: 2

3611
8650
0860
9660

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

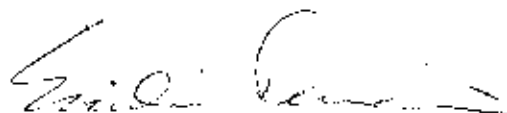
Trámite : 011
Evento : 379
Actuación : 538

Referencia : Expediente No. 06.055.564
Asunto : Solicitud de Patente para **PROCESO PARA LA RECUPERACION DE COMPUESTOS NITROXI, A PARTIR DE SOLUCIONES ORGANICAS Y PROCESO DE OXIDACION**
Solicitante : SCA HYGIENE PRODUCTS AB
Clase : C07B 041/000, C07B 063/000, C07D 207/046
Publicada en : La Gaceta No. 584 Del 31 de diciembre de 2007
Fecha de Solicitud : 8 de junio de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$210.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO-11256-841-065-9
ASG|SCT|ID-128807|WPC|11256
No. M-2008-128807|ASG

76 77

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-055564-00003-0000
Fecha: 2008-06-20 16:40:14 Dep. 2020 INSCRIPCION
Tm. 11 PATENTE/YY Evt. 379 TASENACION/II
Art. 53B PETICION Folia 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 00 - 45,904
FECHA : JUNIO 9 DE 2008

==== CONSIGNACION =====

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678328	09/06/2008	89,445,000.00

==== CONCEPTO =====

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
		TOTAL :	\$ 210,000.00

SOM: DOSCIENTOS DIEZ MIL PESOS



RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 11256-841-085-9

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-55564

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **584** DE

FECHA **31 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **31 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

Organic Oxoammonium Salts. 3.¹ A New Convenient Method for the Oxidation of Alcohols to Aldehydes and Ketones

Zhenkun Ma and James M. Bobbitt*

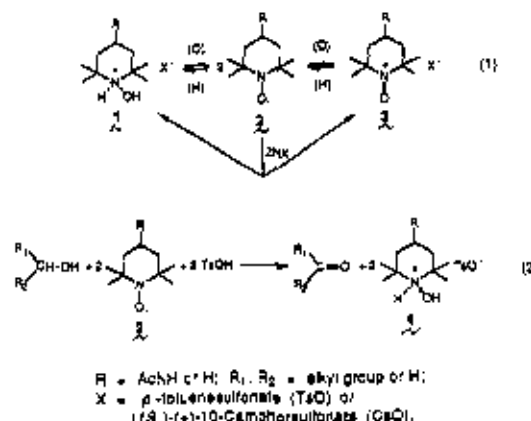
Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060

Received May 13, 1991

A new method for the selective oxidation of alcohols using organic oxoammonium salts generated by acid-promoted disproportionation of nitroxides in solution has been developed. Major advantages are high yields, ease of product isolation, and a high degree of selectivity in the presence of other functional groups.

Oxoammonium salts such as 3 have been used extensively for the oxidation of alcohols to aldehydes and ketones. The older literature has been summarized.² These reactions have been carried out in two modes. One is the use of synthetically prepared oxoammonium salts, and the other is the use of nitroxide catalysts (such as 2) in the presence of a primary oxidant, which will oxidize the nitroxides to oxoammonium salts. Recent papers have appeared on the oxidation of difunctional alcohols,³ ω -(benzoyloxy)alkanols,⁴ *N,N*-dialkylanilines,⁵ and poly(vinyl alcohol).⁶ Nitroxide-catalyzed oxidations of alcohols with hypochlorite,^{7a} bromite,^{7b} or electrolytically generated Br^+ ¹⁰ have been described. We have carried out the preparative oxidation of alcohols and thiols on graphite anodes coated with a nitroxide catalyst,¹¹ as have others.^{12,13} The field has been reviewed recently.¹⁴

In this paper, we would like to describe a third mode based upon the known acid-promoted disproportionation of nitroxides to oxoammonium salts and hydroxylamine salts (eq 1).¹⁵⁻¹⁷ Thus, treatment of the alcohol to be



oxidized in an organic solvent with a slight excess of a mixture of 2 equiv of nitroxide and 2 equiv of *p*-toluenesulfonic acid gives essentially quantitative yields of aldehydes from primary alcohols and ketones from secondary alcohols. The oxoammonium salt formed during the disproportionation is reduced, in the oxidation, to the same hydroxylamine salt formed during the disproportionation. The overall reaction is shown in eq 2. The sulfonate salt promotes the disproportionation and pulls the reaction to completion by salt formation, with the hydroxylamine salt precipitating in high yield when the solvent is CH_2Cl_2 . Product isolation involves the removal of the oxoammonium salt by filtration and the small amount of hydroxylamine salt by extraction and filtration. The product is the essentially pure aldehyde or ketone.

It is quite possible that some of the earlier catalyzed work involving peracids goes by a similar mechanism since Cella¹⁸ noted that his reaction required a strong acid such as H_2SO_4 . The strong acid catalyzed the disproportionation, and the peracid reacts with the hydroxylamine salt to give the product. Such a mechanism was proposed by Aurich.¹⁹ In support of this suggestion, there does not appear to be any report of the oxidation of nitroxide to oxoammonium salt with peracids, although the oxidation of hydroxylamines to nitroxides is well known.¹⁹

The advantages of this method are the high yields obtained and the convenience of the product isolation. It also avoids the presence of less selective oxidizing agents such as peracids and the halogen derivatives used in the various catalytic methods mentioned above⁷⁻¹³ and elsewhere.²

(1) Paper 2: Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* 1990, 30, 1131. Our previous papers have been published under the generic name "Nitroxonium Salts". At least five other names have been used: oxoammonium salts, oxoammonium salts, immonium salts, oximinium salts, and oxazonium salts. "Oxoammonium Salts" seems to be used by most authors. We will use the modified term "organic oxoammonium salts".

(2) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* 1988, 27, 509.
(3) Yamaguchi, M.; Takata, T.; Endo, T. *Tetrahedron Lett.* 1988, 29, 5671.

(4) Yamaguchi, M.; Takata, T.; Endo, T. *J. Org. Chem.* 1990, 55, 1490.
(5) Hunter, D. H.; Racco, J. S.; Ray, A. W.; Ponce, Y. Z. *J. Org. Chem.* 1988, 53, 1278.

(6) Yamaguchi, M.; Takata, T.; Endo, T. *Makromol. Chem., Rapid Commun.* 1988, 9, 203.

(7) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* 1989, 54, 2870 and references cited.

(8) Siedlecke, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* 1990, 31, 2177.

(9) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Terii, S. *J. Org. Chem.* 1990, 55, 462.

(10) Inokuchi, T.; Matsumoto, S.; Terii, S. *J. Org. Chem.* 1991, 56, 2418.

(11) (a) Osa, T.; Akiba, U.; Sugawa, I.; Bobbitt, J. M. *Chem. Lett.* 1988, 1423. (b) Osa, T.; Kashiwagi, Y.; Mukai, K.; Ohsawa, A.; Bobbitt, J. M. *Chem. Lett.* 1990, 78. (c) Kashiwagi, Y.; Ohsawa, Y.; Osa, T.; Ma, Z.; Bobbitt, J. M. *Chem. Lett.* 1991, 581. (d) Osa, T.; Kashiwagi, Y.; Bobbitt, J. M.; Ma, Z. *Festschrift Manual Boiser*; Marcel Dekker: New York, in press.

(12) MacCorquodale, F.; Crayston, J. A.; Walton, J. C.; Worsfold, D. *J. Tetrahedron Lett.* 1990, 31, 771.

(13) Derunzel, A.; Limolin, D.; Moutet, J.-C. *Electrochim. Acta* 1987, 32, 1843.

(14) Yamaguchi, M.; Miyazawa, T.; Takata, T.; Endo, T. *Pure Appl. Chem.* 1990, 62, 217.

(15) Meyer, K. H.; Rapp, W. *Ber.* 1931, 54, 327.

(16) (a) Golubev, V. A.; Zhdanov, R. I.; Gida, V. M.; Rozantsev, E. G. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* 1971, 20, 768. (b) Golubev, V. A.; Sen, V. D.; Kulyk, I. V.; Aleksandrov, A. L. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* 1978, 24, 2119.

(17) Ullman, E. F.; Olschki, J. H.; Boocock, D. G. B.; and Darcy, R. J. *Am. Chem. Soc.* 1972, 94, 7049.

(18) Cella, J. A.; Kellav, J. A.; Kenahan, E. F. *J. Org. Chem.* 1975, 40, 1880.

(19) Breuer, E.; Aurich, G. F.; Nielsen, A. *Nitroxides, Nitronates and Nitroxides*; John Wiley and Sons, Inc.: New York, 1988; pp 354-357.

Furthermore, no metal ions are involved, as in oxidations with the various chromium or manganese reagents.²⁰ In contrast to the Moffatt and Swern oxidation and similar reactions,²¹ anhydrous solvents are not required; the product isolation is simple; no dimethyl sulfide is given off. The main disadvantage is that 2 equiv of a, so far, noncommercially available nitroxide, 2, R = NHAc, is required. However, the nitroxide can be prepared in 97% yield and recovered in yields of over 98%.

It would appear logical to explore the reactions of the oxoammonium salt, 3, R = NHAc, itself rather than to prepare it as needed, and the reactions of many such compounds are known.² However, the salt did not precipitate under the various acid conditions normally used.¹ Since the nitroxides are much more stable than the oxoammonium salts, there seemed little reason to prepare 3, R = NHAc.

We have used two nitroxides, the commercially available 2,2,6,6-tetramethylpiperidinyl-1-oxyl (2, R = H (TEMPO)) and 4-acetylamino-TEMPO (2, R = AcNH). (Acetyl-amino)-TEMPO²² can be easily made in an overall yield of 97% by a modified two-step procedure, from the readily available and inexpensive 4-amino-2,2,6,6-tetramethylpiperidine. We prefer the acetylamino nitroxide for the following reason. The sulfonate salt of the hydroxylamine derived from TEMPO, 4, R = H, is more soluble in CH₂Cl₂ than the salt of 4-(acetylamino)-TEMPO, 4, R = AcNH. Thus, it is difficult to remove the TEMPO salt entirely, even with extensive water washing. The result is that there are nitroxide derived materials in the organic phase, which complicate the isolation procedure. If any TEMPO itself is present, it is volatile and distills with the products. In general, it was necessary to use short column flash chromatography for product isolation when TEMPO was used (see entries 3, 7, 9, and 11 in Table I).

Two sulfonic acids were used to generate the oxoammonium salt, *p*-toluenesulfonic acid, and (1S)-(+)-camphor-10-sulfonic acid. The camphorsulfonic acid was used for several oxidations (entries 12, 14, and 22 in Table I) to see whether any enantioselectivity could be obtained, as has been noted in enzyme work (specifically for entry 22).²³ None was observed.

We have used two procedures for the oxidation. In the first procedure (method A), the alcohol to be oxidized is dissolved in CH₂Cl₂, and the *p*-toluenesulfonic acid is added as a solid (the solubility was determined to be less than 36 mg/100 mL). The nitroxide, dissolved in CH₂Cl₂, is added slowly to the ice-cooled alcohol-acid. The sulfonic acid slowly goes into solution, generating the oxoammonium ion. As the oxoammonium ion is used up, the color is dispatched. At the end of the reaction, the solution is almost colorless, and the hydroxylamine salt precipitates, sometimes after a short time. In the second procedure (method B), the sulfonic acid and nitroxide are mixed together to form the oxoammonium ion in solution, and this is slowly added to the cooled alcohol solution. Again, the color is dispatched, and the salt precipitates. In method A, the concentration of the oxidizing agent is kept low to enhance selectivity, but there is some acid present that might catalyze undesired reactions. In method B, the concentration of oxidant is high, but the acid is minimal. A real difference was noted only in the oxidation of nerol

and geraniol to their respective aldehydes. Method B gave less isomerization around the 2,3 double bond than method A, although some was still observed.²⁴ Otherwise, there seem to be few differences between the methods.

The recovery of the nitroxide 2, R = NHAc, from the hydroxylamine salt is quite simple. The salt is dissolved in water, basified with K₂CO₃, and treated with either H₂O₂ or sodium perborate (NaBO₃). After 24 h, the nitroxide crystallizes. The overall recovery is about 98%. The salt 4, R = NHAc, is quite stable and can be stored for recovery at a later date.

The reaction has been investigated with a large array of alcohols as shown in Table I. Double bonds do not seem to interfere with the reaction, although there is some problem with entry 4 and cholesterol (not shown) in which there is a β - γ double bond. This is not understood and is under further study. Several diols were investigated in accord with previous studies,^{9-10,25} pure products were not obtained. As pointed out by Endo,⁴ alcohols having a β oxygen are not oxidized by oxoammonium salts, and those with a γ oxygen are slow. We have found that ethylene glycol is completely unreactive under our conditions, although 2,3-butanediol was found by Endo to give a poor yield of 3-hydroxy-2-butanone.²⁵ 5,6-Dodecanediol was oxidized in good yield by Torii using a similar method.¹⁰ Under our conditions, 2-phenoxyethanol reacts slowly and incompletely. Acid groups do not interface with the reaction, although base groups should, due to the reversal of eq 2.

The mechanisms of the reactions are not clear. Golubev suggested a mechanism for the acid-promoted disproportionation.^{16b} A concerted cyclic mechanism for oxoammonium salt oxidations was suggested by Semmelhack²⁶ and is shown in Scheme 1 (5 to 6 to 7). An alternate mechanism with an acyclic transition state is shown as 5 to 8 to 7. We favor the acyclic form for two reasons. First, it is probably less sterically confining than the cyclic form and there seem to be few steric effects in oxoammonium oxidations.² Second, the acyclic intermediate shows how a β oxygen may hinder the reaction by complexing with the positively charged nitrogen as shown in 9. This is less likely to occur in 6 because of the negative oxygen. The complex formation as shown in 9 may hinder or slow the reaction in two ways. It may reduce the positive charge on nitrogen and therefore reduce the driving force of the reaction. Or, alternatively, complex formation may force the hydrogen being lost out of the planar conformation required for reaction.

Experimental Section

General Procedures. Gas chromatography-mass spectra were

- (20) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph 186, American Chemical Society: Washington DC, 1990; pp 116-120.
 (21) Tidwell, T. T. *J. Org. Chem.* 1990, 55, 387.
 (22) Rosantsev, E. G.; Kokhanov, Y. V. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* 1966, 15, 1422.
 (23) Jakovac, L. J.; Goodbrand, R. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* 1982, 104, 4659.

- (24) Such isomerization is normal in the oxidations of these compounds. In only one case has an oxidation been reported with no isomerization (Guzic, F. S., Jr.; Luzzio, P. A. *J. Org. Chem.* 1982, 47, 1787).
 (25) Miyazawa, T.; Endo, T. *J. Org. Chem.* 1985, 50, 3930.
 (26) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A. *Tetrahedron Lett.* 1986, 27, 1119.
 (27) Stephen, H. *J. Chem. Soc.* 1925, 1875.
 (28) Bly, R. S.; Konizer, G. B. *J. Org. Chem.* 1969, 34, 2348.
 (29) Booth, A. B., U.S. Patent, 2815496, Dec. 22, 1959; *Chem. Abstr.* 1960, 54, 7780.
 (30) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* 1955, 77, 1905.
 (31) Smedley, R. P. A.; Turner, R. B. *J. Am. Chem. Soc.* 1955, 77, 190.
 (32) Feigee, P. C. *Bull. Soc. Chem. Fr.* 1954, 1882.
 (33) Nollan, C. R.; Adams, R. J. *J. Am. Chem. Soc.* 1924, 46, 1889.
 (34) Corson, B. B.; Sanborn, N. E.; Van Es, P. R. *J. Am. Chem. Soc.* 1930, 52, 1823.
 (35) Andrews, L. J.; Linden, S. L. *J. Am. Chem. Soc.* 1947, 69, 2081.
 (36) Davis, J. B.; Jackson, L. M.; Siddons, P. T.; Weedon, B. C. L. *J. Chem. Soc. C* 1968, 2154.
 (37) Russell, A.; Kenyon, R. L. *Org. Synth.* 1943, 23, 78.
 (38) Chen, C.-Y.; Le Pevre, R. J. *J. Chem. Soc.* 1963, 5528.

Table I. Oxidation of Alcohols by Oxoammonium Salts 8 (*R* = H or AcNH, *X* = TsO or CsO)

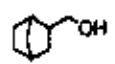
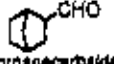
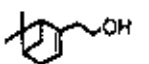
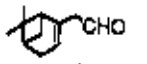
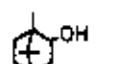
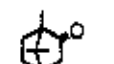
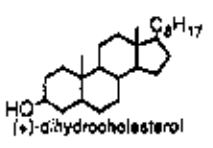
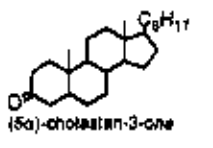
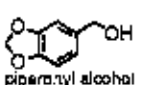
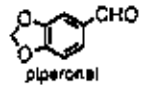
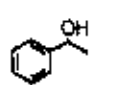
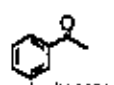
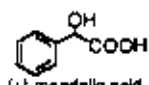
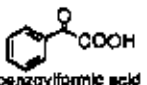
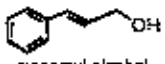
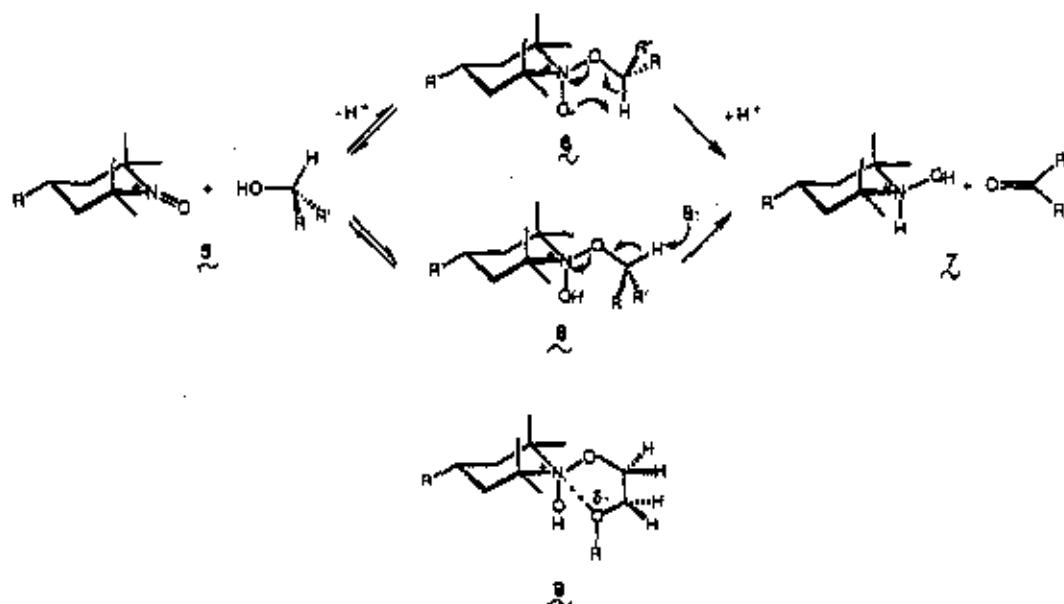
reaction number	substrate	oxidant	method (time)	product	yield, % ^(a) (purification method) ^(b)	bp, °C / mmHg or mp, °C (lit.)	ref.
1	<chem>CH3(CH2)14CH2OH</chem> 1-hexadecanol	<i>R</i> = AcNH <i>X</i> = TsO	A (2.5 h)	<chem>CH3(CH2)14CHO</chem> hexadecanal	100 (FCC)	33-35 (34)	27
2	 (±)-2-norbornanol- methanol	<i>R</i> = AcNH <i>X</i> = TsO	A (2 h)	 2-norbornanecarbaldehyde (endo and exo)	94 (Dis.)	35-38 / 1.0 (89-70 / 13)	28
3	.	<i>R</i> = H <i>X</i> = TsO	A (2 h)	.	92 (FCC and Dis.)	36-38 / 1.0 (69-70 / 13)	28
4	 (1 <i>R</i>)-(-)-nopol	<i>R</i> = AcNH <i>X</i> = TsO	A (2.5 h)	 nopal	78 (Dis.)	66-71 / 1.0 (94 / 10)	29
5	 (±)-isoborneol	<i>R</i> = AcNH <i>X</i> = TsO	A (1.5 h)	 (±)-camphor	97 (Rec., sq. EtOH)	177-178 (177-178)	30
6	 (+)-dihydrocholesterol	<i>R</i> = AcNH <i>X</i> = TsO	A (1 h)	 (5α)-cholestan-3-one	98 (Rec., EtOH)	130-131 (128-130)	31
7	.	<i>R</i> = H <i>X</i> = TsO	A (1 h)	.	100 (FCC)	128-130 (128-130)	31
8	 piperonyl alcohol	<i>R</i> = AcNH <i>X</i> = TsO	A (1 h)	 piperonal	99 (no purification)	34-36 (35-37)	32
9	.	<i>R</i> = H <i>X</i> = TsO	A (1 h)	.	96 (FCC)	34-37 (35-37)	32
10	 sec-phenethyl alcohol	<i>R</i> = AcNH <i>X</i> = TsO	A (2 h)	 acetophenone	100 (Dis.)	60-61 / 2.0 (68 / 16)	33
11	.	<i>R</i> = H <i>X</i> = TsO	A (1.5 h)	.	95 (FCC and Dis.)	62-64 / 13 (58 / 16)	33
12	.	<i>R</i> = AcNH (c) <i>X</i> = CsO	A (1.5 h)	.	83 (d) (FCC and Dis.)	60-62 / 2.0 (58 / 16)	33
13	 (±)-mandelic acid	<i>R</i> = AcNH <i>X</i> = TsO	A (6 h)	 benzoylformic acid	91 (Rec., CCl ₄)	84-88 (86)	34
14	.	<i>R</i> = AcNH (c) <i>X</i> = CsO	A (8 h)	.	82 (d) (derivative) (e)	193-195 (195-197)	34
15	 cinnamyl alcohol	<i>R</i> = AcNH <i>X</i> = TsO	A (1 h)	 cinnamaldehyde	96 (Dis.)	88-92 / 1.2 (135-136 / 25)	35

Table I (Continued)

reaction number	substrate	oxidant	method (time)	product	yield, % ^(a) (purification method) ^(b)	bp, °C / mmHg or mp, °C (lit.)	ref.
16		R = AcNH X = TsO	A (1 h)		88 (Dis.)	128-134 / 1.0 (135-155 / 2)	36
17		R = AcNH X = TsO	A (2 h)		91 (Dis.)	73-74 / 1.2 (84-85 / 2)	37
18	.	R = AcNH X = TsO	B (1.5 h)	(92) (8) (1)	91 (Dis.)	73-75 / 1.2 (84-85 / 2)	37
19		R = AcNH X = TsO	A (2 h)		90 (Dis.)	70-72 / 1.2 (84-85 / 2)	38
20	.	R = AcNH X = TsO	B (1.5 h)	(94) (8) (1)	95 (Dis.)	74-75 / 1.4 (84-85 / 2)	36
21		R = AcNH (g) X = TsO	A (2 h)		89 (Dis.)	88-90 / 1.2 (72-77 / 0.5)	23
22	.	R = AcNH (g) X = CsO	A (2 h)	.	90 (Dis.)	90-93 / 0.5 (72-77 / 0.5)	23

^a Isolated yield of purified product. ^b FCC: flash column chromatography on silica gel. Dis.: distillation. Rec.: recrystallization. ^c Half amount of oxidant used to check for enantioselectivity. ^d Yield based on 4-(acetylaminio)-TEMPO. ^e (2,4-Dinitrophenyl)hydrazones derivative. ^f The ratios were estimated by gas chromatography and ¹H NMR spectroscopy. ^g Two equivalents of oxidant used to produce lactone.

Scheme I



obtained on a Hewlett Packard 5870G system equipped with a 12 M HP-1 capillary column. Elemental analyses were performed by Galbraith Laboratories, Inc., Memphis, TN.

The 4-amino-2,2,6,6-tetramethylpiperidine was obtained from Fluka Chemical Co., Ronkonkoma, NY, and the various alcohols were all commercial samples used without purification.

4-(Acetylamino)-TEMPO (2, R = NHAc). Acetic anhydride (70.0 g, 0.686 mol) was added, dropwise, to a solution of 34.8 g (0.221 mol) of 4-amino-2,2,6,6-tetramethylpiperidine dissolved in 100 mL of anhydrous ether that had been cooled to 0 °C. After addition was complete (about 1 h), the solution was stirred for 30 min at room temperature. The precipitate was removed by filtration and washed with 20 mL of ether to give 56.6 g (98%) of 4-(acetylamino)-2,2,6,6-tetramethylpiperidinium acetate, mp 175 °C subl.

The acetate was dissolved in 400 mL of water and basified with 50.0 g of K₂CO₃·1.5 H₂O (0.303 mol). To this solution was added 80 mL of 30% H₂O₂, 4.00 g of sodium tungstate, and 4.00 g of ethylenediaminetetraacetic acid, tetrasodium salt. The mixture was stirred at room temperature for 72 h. The red precipitate was removed by filtration and washed with 20 mL of H₂O to give 38.6 g of product, which melted at 146–147 °C, lit.²² mp 147.5 °C. The filtrate was saturated with solid K₂CO₃ and extracted with two 100-mL portions of CH₂Cl₂. The organic phase was washed with saturated aqueous sodium chloride, dried over Na₂SO₄, and evaporated to give 7.1 g more of product, mp 145–147 °C. The combined yield was 45.7 g (overall yield for the two steps, 97%).

General Procedure for Alcohol Oxidation. Method A. *p*-Toluenesulfonic acid monohydrate (4.00 g, 21 mmol) was suspended in 30 mL of CH₂Cl₂ containing 10 mmol of the alcohol to be oxidized and cooled to 0 °C. A solution of 4.47 g (21 mmol) of nitroxide 2, R = NHAc, in 30 mL of CH₂Cl₂ was added dropwise over 30 min. This addition could be much slower if there were a problem with selectivity. The solution was stirred at 0 °C for 1 h and then at room temperature until it was almost completely decolorized. During the last of the reaction or sometimes after color was gone, a heavy white precipitate formed. The mixture was cooled in ice, and the precipitate was removed by filtration and washed with 10 mL of cold CH₂Cl₂ to give the salt 4 in essentially quantitative yield. The filtrate was washed with 50 mL of H₂O and 50 mL of saturated aqueous NaCl and dried over Na₂SO₄. After removal of the solvent, the product was purified by distillation or crystallization. The products were identified by MS, IR, and NMR spectroscopy, and in some cases by derivative formation (Table I).

General Procedure for Alcohol Oxidation. Method B. A solution of oxoammonium salt 3, R = NHAc, was prepared by stirring a suspension of 4.00 g (21.0 mmol) of *p*-toluenesulfonic acid monohydrate with 4.47 g (21.0 mmol) of nitroxide 2, R = NHAc, in 30 mL of CH₂Cl₂ for 20 min at 0 °C. An intense red color developed from the oxoammonium salt. This solution was added dropwise to 10 mmol of the alcohol to be oxidized in 30 mL of cold CH₂Cl₂ over 30 min. The orange solution was then stirred at room temperature until the color was essentially gone and a dense white precipitate formed. The reaction mixture was then processed as described in method A.

4-(Acetylamino)-2,2,6,6-tetramethyl-1-hydroxypiperidinium *p*-Toluenesulfonate (4). The salt, as recovered from the oxidation reactions, melted at 188–171 °C when the temperature was slowly raised. When the temperature was raised quickly, a second melting point at about 146 °C was observed, almost surely corresponding to a loss of water. The compound was recrystallized from water with no change in mp. Anal. Calcd for C₁₉H₃₀N₂O₆S·H₂O: C, 53.44; H, 7.97; N, 6.97. Found: C, 53.72; H, 8.05; N, 6.89.

Recovery of Nitroxide 2, R = NHAc, from Salt 4, R = NHAc. A solution of 22.8 g (60 mmol) of 4 in 300 mL of H₂O was made basic with 19.8 g of K₂CO₃·1.5 H₂O (120 mmol). Hydrogen peroxide, 20 mL of 30% (170 mmol), or 27.8 g of sodium perborate tetrahydrate (170 mmol) was added, and the solution was stirred at room temperature for 24 h to give an intense red solution. The solution was saturated with solid K₂CO₃, and a red precipitate formed. The precipitate was removed by filtration to give 11.99 g (98%) of 2, R = NHAc, mp 146–147 °C. The purity was sufficient for use in further oxidations.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also acknowledge financial support from the University of Connecticut Research Foundation.

Direct Conversion of (1*S*,2*S*)-2-Amino-1-[(4-methylthio)phenyl]-1,3-propanediol into Its Enantiomer for Efficient Synthesis of Thiamphenicol and Florfenicol

Claudio Giordano,* Silvia Cavicchioli, Silvio Levi, and Marco Villa*

Istituto di Ricerca Chimica "G. Zamboni", Zamboni Group S.p.A., Via Cimabue, 26/28, 20032 Corsico,
Milan, Italy

Received April 30, 1991

The usual synthesis of thiamphenicol and florfenicol involves the resolution of racemic threo-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol into its 1*S*,2*S* and 1*R*,2*R* isomers ((+)-3 and (–)-3), of which only the latter is a useful precursor. An efficient conversion of the 1*S*,2*S* isomer into the 1*R*,2*R* enantiomer in high yield, is described.

Thiamphenicol, threo-(1*R*,2*R*)-2-(dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (1),¹ and florfenicol (2),² the 3-fluoro derivative of 1, are broad-spectrum antibiotics (Figure 1).

Current manufacturing processes for 1 and 2 involve an optical resolution at some stage of the synthesis. In most cases, entrainment resolution³ is performed on racemic threo-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol⁴ to afford the 1*R*,2*R* isomer (–)-3 (the precursor of 1 and

(1) (a) Ellis, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapman and Hall: London, 1990; T-00179. (b) Outler, R. A.; Stenger, R. J.; Suter, C. M. *J. Am. Chem. Soc.* 1982, 74, 5475.

(2) (a) Ellis, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapman and Hall: London, 1990; F-00124. (b) Schumacher, D. P.; Clark, J. E.; Murphy, B. L.; Fischer, F. A. *J. Org. Chem.* 1990, 55, 5291.

(3) (a) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley & Sons: New York, 1981. (b) Collet, A.; Brienne, M. J.; Jacques, J. *Bull. Soc. Chim. Fr.* 1972, 127.

(4) Entrainment resolution of (±)-3: Long, L. M. U.S. Pat. 2,767,213, 1956; *Chem. Abstr.* 1957, 51, 7414b.



US 2002/0151431A1

(19) **United States**(12) **Patent Application Publication**

Thornton et al.

(10) **Pub. No.: US 2002/0151431 A1**(47) **Pub. Date: Oct. 17, 2002**(54) **RECOVERY METHOD****Related U.S. Application Data**

(79) Inventors: Jeff Thornton, Al Heizer (NL); Arle Besemer, CC Amerongen (NL); Bas Schraven, Nymegen (NL)

(60) Provisional application No. 60/264,018, filed on Jan. 26, 2001.

Publication Classification

Correspondence Address:

William C. Rowland

BURNS, DOANE, SWECKER & MATHIS,
L.L.P.

P.O. Box 1404

Alexandria, VA 22313-1404 (US)

(51) Int. Cl.⁷ B01J 31/00

(52) U.S. Cl. 502/150; 502/159

(57) **ABSTRACT**

The present invention relates to a method for obtaining a catalytically active mixture based on stable nitroxyl radicals. The invention is characterized in that the stable nitroxyl radicals are hydrophobic and are selectively separated from a reaction mixture by means of hydrophobic interactions.

(21) Appl. No.: 10/053,646

(22) Filed: Jan. 24, 2002

1. *Introduction*
 2. *Methodology*
 3. *Results*
 4. *Discussion*
 5. *Conclusion*
 6. *References*
 7. *Appendix*
 8. *Index*
 9. *Table of Contents*
 10. *Abstract*
 11. *Keywords*
 12. *Summary*
 13. *Notes*
 14. *References*
 15. *Appendix*
 16. *Index*
 17. *Table of Contents*
 18. *Abstract*
 19. *Keywords*
 20. *Summary*
 21. *Notes*
 22. *References*
 23. *Appendix*
 24. *Index*
 25. *Table of Contents*
 26. *Abstract*
 27. *Keywords*
 28. *Summary*
 29. *Notes*
 30. *References*
 31. *Appendix*
 32. *Index*
 33. *Table of Contents*
 34. *Abstract*
 35. *Keywords*
 36. *Summary*
 37. *Notes*
 38. *References*
 39. *Appendix*
 40. *Index*
 41. *Table of Contents*
 42. *Abstract*
 43. *Keywords*
 44. *Summary*
 45. *Notes*
 46. *References*
 47. *Appendix*
 48. *Index*
 49. *Table of Contents*
 50. *Abstract*
 51. *Keywords*
 52. *Summary*
 53. *Notes*
 54. *References*
 55. *Appendix*
 56. *Index*
 57. *Table of Contents*
 58. *Abstract*
 59. *Keywords*
 60. *Summary*
 61. *Notes*
 62. *References*
 63. *Appendix*
 64. *Index*
 65. *Table of Contents*
 66. *Abstract*
 67. *Keywords*
 68. *Summary*
 69. *Notes*
 70. *References*
 71. *Appendix*
 72. *Index*
 73. *Table of Contents*
 74. *Abstract*
 75. *Keywords*
 76. *Summary*
 77. *Notes*
 78. *References*
 79. *Appendix*
 80. *Index*
 81. *Table of Contents*
 82. *Abstract*
 83. *Keywords*
 84. *Summary*
 85. *Notes*
 86. *References*
 87. *Appendix*
 88. *Index*
 89. *Table of Contents*
 90. *Abstract*
 91. *Keywords*
 92. *Summary*
 93. *Notes*
 94. *References*
 95. *Appendix*
 96. *Index*
 97. *Table of Contents*
 98. *Abstract*
 99. *Keywords*
 100. *Summary*
 101. *Notes*
 102. *References*
 103. *Appendix*
 104. *Index*
 105. *Table of Contents*
 106. *Abstract*
 107. *Keywords*
 108. *Summary*
 109. *Notes*
 110. *References*
 111. *Appendix*
 112. *Index*
 113. *Table of Contents*
 114. *Abstract*
 115. *Keywords*
 116. *Summary*
 117. *Notes*
 118. *References*
 119. *Appendix*
 120. *Index*
 121. *Table of Contents*
 122. *Abstract*
 123. *Keywords*
 124. *Summary*
 125. *Notes*
 126. *References*
 127. *Appendix*
 128. *Index*
 129. *Table of Contents*
 130. *Abstract*
 131. *Keywords*
 132. *Summary*
 133. *Notes*
 134. *References*
 135. *Appendix*
 136. *Index*
 137. *Table of Contents*
 138. *Abstract*
 139. *Keywords*
 140. *Summary*
 141. *Notes*
 142. *References*
 143. *Appendix*
 144. *Index*
 145. *Table of Contents*
 146. *Abstract*
 147. *Keywords*
 148. *Summary*
 149. *Notes*
 150. *References*
 151. *Appendix*
 152. *Index*
 153. *Table of Contents*
 154. *Abstract*
 155. *Keywords*
 156. *Summary*
 157. *Notes*
 158. *References*
 159. *Appendix*
 160. *Index*
 161. *Table of Contents*
 162. *Abstract*
 163. *Keywords*
 164. *Summary*
 165. *Notes*
 166. *References*
 167. *Appendix*
 168. *Index*
 169. *Table of Contents*
 170. *Abstract*
 171. *Keywords*
 172. *Summary*
 173. *Notes*
 174. *References*
 175. *Appendix*
 176. *Index*
 177. *Table of Contents*
 178. *Abstract*
 179. *Keywords*
 180. *Summary*
 181. *Notes*
 182. *References*
 183. *Appendix*
 184. *Index*
 185. *Table of Contents*
 186. *Abstract*
 187. *Keywords*
 188. *Summary*
 189. *Notes*
 190. *References*
 191. *Appendix*
 192. *Index*
 193. *Table of Contents*
 194. *Abstract*
 195. *Keywords*
 196. *Summary*
 197. *Notes*
 198. *References*
 199. *Appendix*
 200. *Index*
 201. *Table of Contents*
 202. *Abstract*
 203. *Keywords*
 204. *Summary*
 205. *Notes*
 206. *References*
 207. *Appendix*
 208. *Index*
 209. *Table of Contents*
 210. *Abstract*
 211. *Keywords*
 212. *Summary*
 213. *Notes*
 214. *References*
 215. *Appendix*
 216. *Index*
 217. *Table of Contents*
 218. *Abstract*
 219. *Keywords*
 220. *Summary*
 221. *Notes*
 222. *References*
 223. *Appendix*
 224. *Index*
 225. *Table of Contents*
 226. *Abstract*
 227. *Keywords*
 228. *Summary*
 229. *Notes*
 230. *References*
 231. *Appendix*
 232. *Index*
 233. *Table of Contents*
 234. *Abstract*
 235. *Keywords*
 236. *Summary*
 237. *Notes*
 238. *References*
 239. *Appendix*
 240. *Index*
 241. *Table of Contents*
 242. *Abstract*
 243. *Keywords*
 244. *Summary*
 245. *Notes*
 246. *References*
 247. *Appendix*
 248. *Index*
 249. *Table of Contents*
 250. *Abstract*
 251. *Keywords*
 252. *Summary*
 253. *Notes*
 254. *References*
 255. *Appendix*
 256. *Index*
 257. *Table*

1. *Phylogenetic relationships* among the studied species were determined using the maximum parsimony method. The analysis was performed using the PAUP 4.0 software package (Felsenstein, 1993). The tree was rooted using the outgroup species, *Phytophthora infestans* (M. & S.). The bootstrap values were calculated using 1000 replicates. The tree was drawn using the TreeView 1.6.6 software package (Tamura & Nei, 1993).

(The following text is mirrored bleed-through from the reverse side of the page and is largely illegible due to being upside down.)

11. A worker in a clothing store is exposed to a mixture of formaldehyde and acetaldehyde vapors. The formaldehyde concentration is 0.1 ppm and the acetaldehyde concentration is 0.05 ppm. The worker is exposed to this mixture for 8 hours per day, 5 days per week. The TLV for formaldehyde is 0.1 ppm and the TLV for acetaldehyde is 0.05 ppm. Is this exposure acceptable? Why or why not?
12. A worker in a paint store is exposed to a mixture of toluene and xylene vapors. The toluene concentration is 100 ppm and the xylene concentration is 50 ppm. The worker is exposed to this mixture for 8 hours per day, 5 days per week. The TLV for toluene is 100 ppm and the TLV for xylene is 50 ppm. Is this exposure acceptable? Why or why not?
13. A worker in a chemical plant is exposed to a mixture of benzene and toluene vapors. The benzene concentration is 10 ppm and the toluene concentration is 50 ppm. The worker is exposed to this mixture for 8 hours per day, 5 days per week. The TLV for benzene is 10 ppm and the TLV for toluene is 50 ppm. Is this exposure acceptable? Why or why not?

1. **Договор** заключается в письменной форме и подписывается уполномоченными лицами обеих сторон. Договор должен быть заверен печатью каждой из сторон.
 2. **Стороны** обязуются соблюдать все условия договора и нести ответственность за неисполнение обязательств.
 3. **Срок действия** договора составляет 12 месяцев с даты подписания.
 4. **Изменения** к договору могут быть внесены только по взаимному согласию сторон.
 5. **Решение споров** принимается путем переговоров. В случае невозможности достижения соглашения спор передается в арбитражный суд.
 6. **Договор** вступает в силу с момента подписания.
 7. **Договор** составлен в двух экземплярах, имеющих равную юридическую силу.
 8. **Подпись** и печать являются обязательными для вступления договора в силу.
 9. **Договор** действует до момента его расторжения.
 10. **Договор** является неотъемлемой частью договора.

1. A method according to any one of the preceding claims, wherein the method is performed by a computer system.

Nº	Documento	Título	Fecha de publicación
D1	ART. 1	ORGANIC OXOAMMONIUM SALTS. 3. A NEW CONVENIENT METHOD FOR THE OXIDATION OF ALCOHOLS TO ALDEHYDES AND KETONES	1991-05-13
D2	US2002151431	RECOVERY METHOD	2002-10-17

ART 1.: Journal of Organic Chemistry 1991, 56, 6110-6114.

4. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Novedad (artículo 16 D486)

Respecto a la reivindicación 1:

La reivindicación 1 dice "Proceso para la recuperación de un compuesto nitroso orgánico de una solución de este compuesto nitroso en un solvente orgánico o una mezcla de solvente orgánico miscible en agua y agua, el proceso se caracteriza porque comprende las etapas de:

- Ajustar el pH de la solución a un valor menor que 4, para generar un ión nitrosonio y la hidroxilamina protonada,
- Retirar el solvente orgánico hasta que se forma un residuo que contiene el ión nitrosonio y la hidroxilamina protonada,
- De ser necesario, redisolvió el residuo obtenido en agua, y
- Neutralizar la solución acuosa resultante para recuperar el compuesto nitroso."

Respecto al estado de la técnica:

D1 describe un nuevo método para la oxidación selectiva de alcoholes usando sales orgánicas de oxoamonio generadas por desproporción de nitroxidos promovida por ácidos en solución (Resumen).

Respecto a la solicitud en estudio:

De acuerdo con la reivindicación independiente 1 de la solicitud en estudio el principio técnico de esta es un proceso para la recuperación de un compuesto orgánico. No obstante D1 describe proceso basado en la desproporción de nitroxidos a sales de oxoamonio y sales hidroxilamina promovidos por ácidos, así:

- Desproporción de nitroxidos a sales de oxoamonio y sales hidroxilamina promovidos por ácidos (Pág. 6110, Col 2 párrafo 1),
- Remover la sal por filtración, secado, concentración y destilación o cristalización (Pág. 6110, Col 2 párrafo 1),
- Recuperación fácil del nitroxido de la sales de hidroxilamina donde la sal es disuelta en agua, y (Pág. 6111, Col 2 párrafo 2)
- Neutralización de la sal con K_2CO_3 y tratada con peróxido y perborato (Pág. 6111, Col 2 párrafo 2).

Dado lo anterior, el objeto de la invención recogido en la reivindicación 1 ha sido divulgado idénticamente en la anterioridad D1, por lo tanto esta reivindicación y sus dependientes no pueden considerarse nuevas.

Respecto a la reivindicación 7:

La reivindicación 7 dice "Proceso para la oxidación de un compuesto hidroxi en la presencia de un compuesto nitroxil, que comprende las etapas de

- i) Oxidar un compuesto hidroxi en la presencia de un compuesto nitroxil y opcionalmente un oxidante primario en un medio de reacción que contiene agua,
- ii) Separar el compuesto nitroxil restante en la mezcla de reacción con una resina hidrofóbica,
- iii) Retirar el compuesto hidroxi de la resina hidrofóbica al eluir la misma con un solvente orgánico o una mezcla de agua y un solvente orgánico miscible en agua, la mezcla tiene menor polaridad que el medio de reacción
- iv) Recuperar el compuesto nitroxil de la solución resultante por el proceso de la reivindicación 1,
- v) Reciclar el compuesto nitroxil obtenido de esta a la etapa (i)

Respecto al estado de la técnica:

D2 describe un método para obtener el activo catalítico de una mezcla basada en un radical estable nitroxil. Este consiste en poner en contacto la mezcla de reacción que comprende radicales estables de nitroxil con una fase sólida o líquida que exhiben hidrofobicidad.

Respecto a la reivindicación en estudio:

De acuerdo con la reivindicación independiente 7 de la solicitud en estudio el principio técnico de esta es un proceso para la oxidación de un compuesto hidroxi en presencia de un compuesto nitroxil. No obstante D2 describe la oxidación de soluciones orgánicas y la recuperación del los compuestos nitroxil por separación cromatográfica, específicamente en el Ej. 4.

D2 no menciona la recuperación de los compuestos nitroxil por desproporción de nitroxidos. Sin embargo en el estado de la técnica ya era conocido el proceso de recuperación de nitroxidos por desproporción como lo reporta D1.

Es así como un experto en la materia que tuviera acceso a los documentos D2 y D1, podría verse motivado a un proceso de oxidación de compuestos hidroxi en presencia de compuestos nitroxil y su final recuperación por medio de desproporción de nitroxidos tal como lo propone la solicitud en estudio.

Dado lo anterior, las características técnicas del proceso de oxidación de esta solicitud, no representa un avance tecnológico sobre el estado de la técnica.

En conclusión, esta reivindicación y sus dependientes se encuentran afectadas en su nivel inventivo ya que se derivan de manera evidente del estado de la técnica y pueden ser obvias para un experto en la materia.

89

90

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	ART. 1	1-6	Novedad
		7-11	Nivel Inventivo
D2	US2002151431	7-11	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente. 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 Nº 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
09 OCT. 2009

CONCEPTO TÉCNICO Nº 3372	EXAMINADOR TÉCNICO Código Nº 202090
------------------------------------	---