

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-088020- -00007-0000

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Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y
Bogotá, D.C.

Re.: Expediente No. 06-88.020
Fase nacional de Solicitud
de Patente PCT
EURO-CELTIQUE S.A.
Código 011-378-444

En relación con el expediente de la referencia y dando cumplimiento a la última providencia recaída sobre este asunto por medio del presente escrito me permito manifestarles lo siguiente:

1. Adjunto un pliego reivindicatorio modificado donde se han eliminado las reivindicaciones 41-43 anteriores. Además, se ha incorporado la reivindicación 6 anterior en la reivindicación 1.
2. Con relación a que la reivindicación 1 se refiere a una composición mientras que la solicitud se refiere a un método mi representada afirma que una persona versada en la técnica puede comprender fácilmente que la composición de la reivindicación 1 es para usarse en la provisión de un aldehído o una cetona. De este modo, la persona versada puede comprender fácilmente el concepto de la reivindicación 1 independiente. Por lo tanto, la sociedad solicitante tiene un interés legítimo en mantener las reivindicaciones de composición tal como la reivindicación 1 independiente.
3. En cuanto a la observación relacionada con que hay varias reivindicaciones independientes la reivindicación 42 anterior se ha eliminado con el fin de superar esta parte de la objeción en particular. Como se dijo arriba, la reivindicación 1 independiente se refiere a una composición. La reivindicación 9 (antes reivindicación 10) independiente se refiere a un método para hacer una cetona y por lo tanto, no es apropiado introducir una dependencia en la

reivindicación 1 independiente en la reivindicación 9 teniendo en cuenta las diferentes categorías. La reivindicación 19 (antes reivindicación 20) se refiere a una composición para la provisión de una morfinona de la fórmula (II). La reivindicación 19 requiere el uso de un alcohol especial, es decir, un compuesto de la fórmula (I), y describe el uso de un compuesto que ocntenga cloro para oxidar el compuesto de la fórmula (I). De otra parte, la reivindicación 1 independiente no se limita a una morfinona de la fórmula (I), sino que requiere un alcohol primario o secundario para oxidación. Además, el reactivo que ocntenga cloro se limita, según la reivindicación 1, a ácido tricloroisocianúrico. En consecuencia, se justifica el formato independiente de las reivindicaciones 1 y 19. Finalmente, la reivindicación 25 (antes reivindicación 26) se refiere a la provisión de un carboxilato de dienol morfinona (III). De otra parte, las reivindicaciones 1-24 describen la oxidación de alcoholes a aldehídos o cetonas y no tienen que ver con la provisión de carboxilatos de dienol. Al contrario, los aldehídos o cetonas según las reivindicaciones 1-24 tal como el compuesto de la fórmula (II) pueden usarse como intermediarios para la provisión de carboxilatos de dienol morfinona de la fórmula (III).

Por lo tanto, la reivindicación 25 independiente comprende todas las características de las reivindicaciones referentes a la provisión de un compuesto de la fórmula (II), pero se distingue de esas reivindicaciones en el hecho de que se requiere otro paso adicional para proveer el carboxilato de dienol morfinona. Por ello, se debe justificar el formato independiente de la reivindicación 25 actual.

4. El Examinador objeta el grupo protector R₃. En particular, el uso de grupos protectores está bien establecido en síntesis orgánicas. Una persona versada en la técnica comprenderá esto fácilmente. Si esta persona encuentra alguna duda, se puede referir a las enseñanzas de la presente descripción o a las referencias que se citan allí, por ej: Green *et al.*, *Protective Groups in Organic Syntheses*, 143-140 (1991), que se cita en la página 32, líneas 15 y 16 de la publicación internacional de la presente solicitud. Igualmente, la solicitante considera además que la mayoría de las partes de la objeción deben superarse luego de eliminar la reivindicación 42.

5. Para evaluación de patentabilidad, el Examinador se refiere a dos documentos anteriores de la técnica, es decir, D1: US 6 013 769, y D2: US 5 821 374.

D1 ya era conocida por mis clientes por seguimiento a miembros correspondientes de familia de patentes. De otra parte parece que D2 se cita recientemente en la familia de patentes actual.

Para la evaluación del nivel inventivo, el Examinador se refiere especialmente a la reivindicación 15. Según el Examinador, la reivindicación 15 anterior se distingue de D1 en que ésta usa oxidación Swern, mientras que la presente solicitud se refiere a oxidación Corey/Kim. El análisis del Examinador a este respecto parece ser correcto.

6. Sin embargo, el Examinador considera que la deficiencia anterior es superada por D2. Por el contrario, D2 divulga la oxidación de alcoholes simples mediante el uso de ácido tricloroisocianúrico y un grupo hidroxilo que contiene catalizadores. D2 no divulga el uso de ácido tricloroisocianúrico en combinación con sulfuros. Además, el documento no divulga la oxidación de alcoholes bicíclicos posiblemente lábiles, tales como opioides.

Para argumentar el nivel inventivo de la reivindicación 1 y el objeto materia relacionado, la sociedad solicitante se refiere al documento adjunto de U. Tilstam *et al.*, citado en el *International Search Report*. Este documento describe la oxidación de sulfuros a sulfóxidos mediante el uso de ácido tricloroisocianúrico (cf.; páginas 392 y 193 del documento adjunto). En la técnica se conoce que una combinación de ácido tricloroisocianúrico y sulfuros resulta en sulfóxidos y no en la oxidación de alcoholes. El documento también reporta que NCS no reacciona con sulfuros para formar sulfóxidos. Considerando lo anterior, con respecto a la reivindicación 1 y el objeto materia relacionado, la persona experta asumiría que una combinación de ácido tricloroisocianúrico con sulfuros no conduciría a la oxidación deseada de alcoholes sino a la provisión de un sulfóxido.

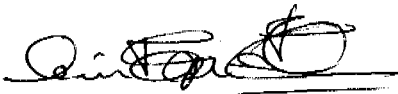
7. Además, nuevamente se adjunta un documento de Corey/Kim citado en la página 3, líneas 3 y 4 de la solicitud internacional. En la página 7587, Corey/Kim reportan que el método que usa sulfuros y NCS no es adecuado para la oxidación de alcoholes correspondiente a una carbocación estabilizada (como es el caso en el opioide de la fórmula (I)). Por lo tanto, la persona versada en la técnica no tendría ningún incentivo para aplicar el método de

oxidación Corey/Kim a alcoholes opioides bicíclicos correspondientes a una carbocación estabilizada.

8. D1 y D2 que cita el Examinador no pueden superar las deficiencias que se mencionan arriba. D1 ni siquiera usa la oxidación Corey/Kim. Además, D2 no supera el prejuicio existente en la técnica anterior en el sentido de que ácido tricloroisocianúrico en combinación con sulfuros resulta en la provisión de sulfóxidos (a diferencia de NCS). Por lo tanto, el objeto materia de las presentes reivindicaciones no es obvio por D1 y D2.
9. Teniendo en cuenta lo dispuesto por el Consejo de Estado en sentencia proferida dentro del Expediente No. 7684 el 22 de Octubre de 2004 y acogida por esa Superintendencia mediante memorando interno de fecha 22 de Diciembre de 2004 dirigido a los funcionarios de la Delegatura de Propiedad Industrial, no se hace necesario acompañar comprobante de pago por concepto de modificación de la solicitud por cuanto el nuevo pliego reivindicatorio se presenta a instancia de la Superintendencia en cumplimiento de lo ordenado por el artículo 45 de la Decisión 486.

Renuncio al término faltante de traslado, y les solicito conceder el privilegio de patente de invención aquí tramitado.

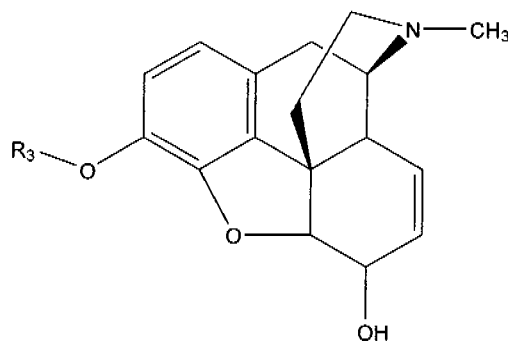
De Ustedes Atentamente,


LUIS FELIPE CASTILLO GIBSONE
T.P. No. 68.995 del C.S.J.

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Reivindicaciones

1. Una composición que comprende un compuesto de la fórmula R_1SR_2 , ácido tricloroisocianúrico y una base, en donde cada uno de R_1 y R_2 son independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o fenilo, que además comprende un alcohol primario o secundario.
2. La composición de la reivindicación 1, en donde R_1 es $-CH_3$ y R_2 es alquilo (C_1-C_{20}) y preferiblemente, R_1 es $-CH_3$ y R_2 es alquilo (C_{12}).
3. La composición de la reivindicación 1, en donde la cantidad del compuesto de la fórmula R_1SR_2 varía entre cerca de 1,0 a cerca de 9,0, entre cerca de 2,0 a cerca de 5,0, o entre cerca de 2,5 1,0 a cerca de 3,5 equivalentes molares por equivalente molar de ácido tricloroisocianúrico.
4. La composición de la reivindicación 1, en donde la base es una amina orgánica, y preferiblemente es trietilamina, diisopropiletilamina, piridina, dimetilpiridina o dimetilaminopiridina y más preferiblemente es trietilamina.
5. La composición de la reivindicación 1, en donde la cantidad de la base varía entre cerca de 1,0 a cerca de 15,0, entre cerca de 2,0 a cerca de 10,0, o entre cerca de 2,5 a cerca de 7,0 equivalentes molares por equivalente molar de ácido tricloroisocianúrico.
6. La composición de la reivindicación 5, en donde el alcohol secundario tiene la fórmula (I):



(I),

en donde R_3 es un grupo protector.

7. La composición de la reivindicación 5, en donde la cantidad del alcohol varía entre cerca de 1,0 a cerca de 9,0, de entre cerca de 2,0 a cerca de 5,9 o de entre cerca de 2,0 a cerca de 4,0 equivalentes molares por equivalente molar de ácido tricloroisocianúrico.

8. La composición de la reivindicación 1 que además comprende un solvente orgánico y el solvente orgánico es preferiblemente benceno, tolueno, xileno, mesitileno, clorobenceno, diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, dietil éter, dipropil éter, di-butil éter, metil-tert-butil éter, tetrahidrofurano, metiltetrahidrofurano, acetato de etilo, o cualquier combinación de lo anterior y más preferiblemente es diclorometano.

9. Un método para hacer una cetona, que comprende permitir a un alcohol secundario que reaccione en presencia de un compuesto de la fórmula R_1SR_2 , ácido tricloroisocianúrico y una base bajo condiciones suficientes para hacer la cetona, en donde cada uno de R_1 y R_2 es independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o -fenilo.

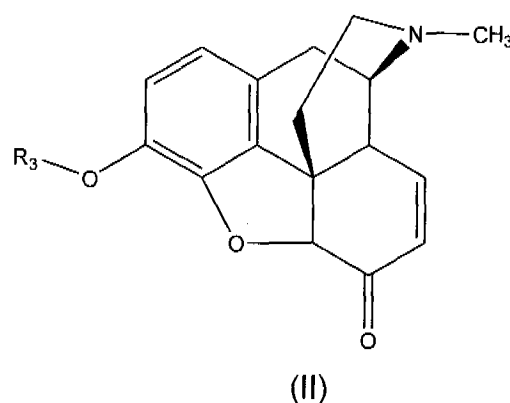
10. El método de la reivindicación 9, en donde R_1 es $-CH_3$ y R_2 es alquilo (C_1-C_{20}), y preferiblemente, R_1 es $-CH_3$ y R_2 es alquilo (C_{12}).

11. El método de la reivindicación 9, en donde la cantidad del compuesto de la fórmula R_1SR_2 varía de entre cerca de 1,0 a cerca de 9,0, de entre cerca de 2,0 a cerca de 5,0, o de entre cerca de 2,5 a cerca de 3,5 equivalentes molares por equivalente molar de ácido tricloroisocianúrico.

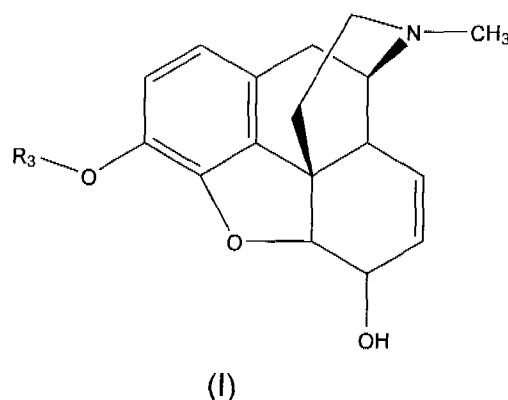
12. El método de la reivindicación 9, en donde la cantidad de base varía de entre cerca de 1,0 a cerca de 15,0, de entre cerca de 2,0 a cerca de 10,0, o de entre cerca de 2,5 a cerca de 7,9 equivalentes molares por equivalente molar de ácido tricloroisocianúrico.

13. Un método para hacer un aldehído, que comprende permitir que un alcohol primario reaccione en presencia de un compuesto de la fórmula R_1SR_2 , ácido tricloroisocianúrico y una base bajo condiciones suficientes para hacer el aldehído, en donde cada uno de R_1 and R_2 es independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o -fenilo.

14. Un método para hacer un compuesto de la fórmula (II):



que comprende permitir que un compuesto de la fórmula (I):



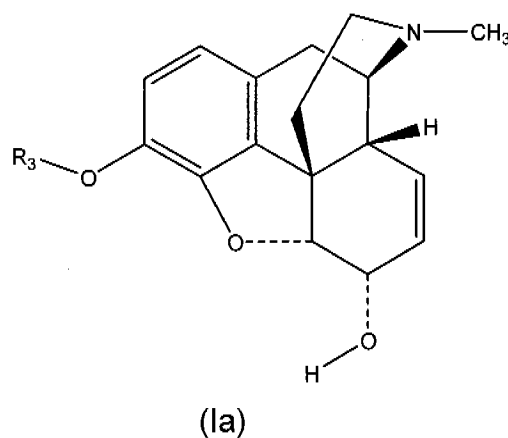
reaccione en presencia de un compuesto de la fórmula R_1SR_2 y un reactivo que contenga cloro bajo condiciones suficientes para hacer el compuesto de la fórmula (II); en donde

cada uno de R_1 y R_2 es independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o -fenilo; y

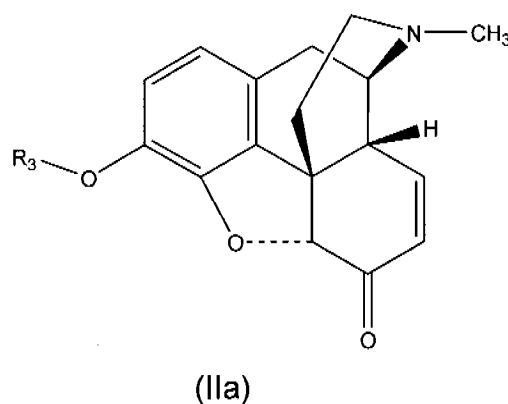
R_3 es un grupo protector.

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15. El método de la reivindicación 14, en donde el compuesto de la fórmula (I) es un compuesto de la fórmula (Ia):



el compuesto de la fórmula (II) es un compuesto de la fórmula (IIa):



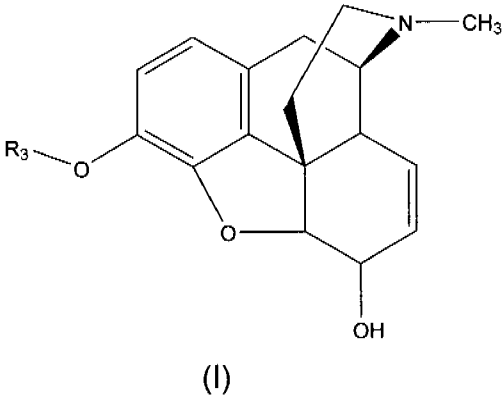
16. El método de la reivindicación 14, que además comprende el uso de una base.

17. El método de la reivindicación 16 o 9, en donde la base es una amina orgánica y preferiblemente es trietilamina, diisopropiletilamina, piridina, dimetilpiridina o dimetilaminopiridina, y más preferiblemente es trietilamina.

18. El método de la reivindicación 16, en donde la cantidad de base varía de entre cerca 1,0 a cerca de 15,0, de entre cerca de 2,0 a cerca de 10,0 o

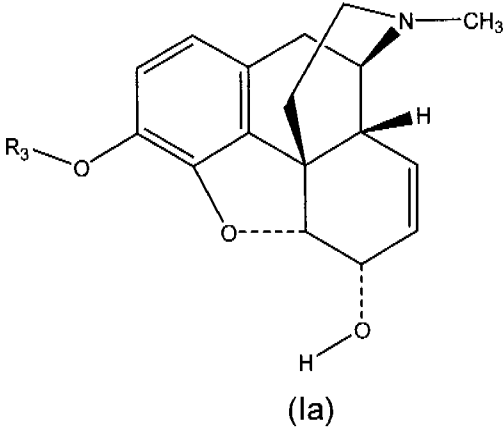
de entre cerca s,5 a cerca de 7, equivalentes molares por equivalente molar del reactivo que ocntenga cloro .

19. Una composición que comprende un compuesto de la fórmula (I):



un compuesto de la fórmula R_1SR_2 y un compuesto que contiene cloro ; en donde cada uno de R_1 y R_2 es independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o -fenilo; y R_3 es un grupo protector.

20. La composición de la reivindicación 19, en donde el compuesto de la fórmula (I) es un compuesto de la fórmula (Ia).



21. La composición de la reivindicación 19, en donde el reactivo que contiene cloro es ácido tricloroisocianúrico, N-clorosuccinimida, dicloroisocianurato de sodio, 1,3-dicloro-5,5-dimetilhidantoina, Cl_2 , hipoclorito de calcio, o cualquier mezcla de lo anterior y preferiblemente, es ácido tricloroisocianúrico, N-clorosuccinimida, Cl_2 , o cualquier mezcla de lo anterior y más preferiblemente, es ácido tricloroisocianúrico.

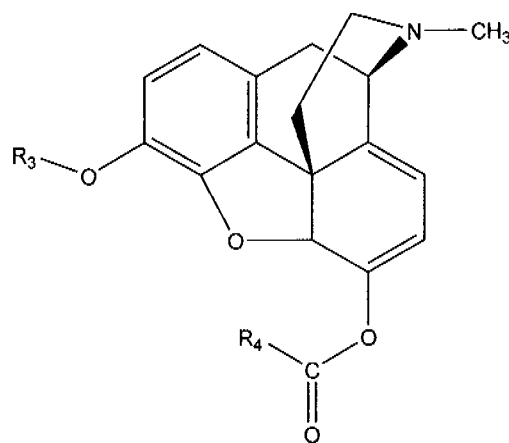
22. La composición de la reivindicación 6 o 19, en donde R_3 es alquilo (C_1-C_{10}), bencilo, alquilo $-C(O)(C_1-C_{10})$, alquilo $C(O)O(C_1-C_{10})$, $-Si(alquilo(C_1-C_{10}))_3$, $-Si(arilo)(alquilo C_1-C_{10})_2$, $-Si(arilo)_2(alquilo (C_1-C_{10}))$, $-P(O)(alquilo (C_1-C_{10}))_2$, $-P(S)(alquilo (C_1-C_{10}))_2$, o $S(O)OC_6H_4-p-CH_3$ y preferiblemente R_3 es

- a) $-CH_3$; o
- b) $-Si(alquilo (C_1-C_{10}))_3$, $-Si(arilo)(alquilo (C_1-C_{10}))_2$, o $-Si(arilo)_2alquilo (C_1-C_{10})$, ay preferiblemente es $Si(alquilo (C_1-C_{10}))_3$; y más preferiblemente es $Si(CH_3)_2(C(CH_3)_3)$.

23. La composición de la reivindicación 19 que además comprende una base.

24. La composición de la reivindicación 19 que además comprende un solvente orgánico.

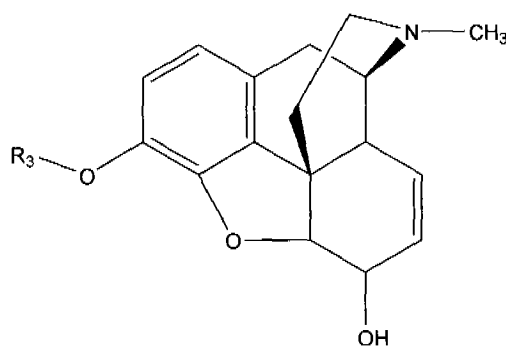
25. Un método para hacer un compuesto de la fórmula (III):



(III)

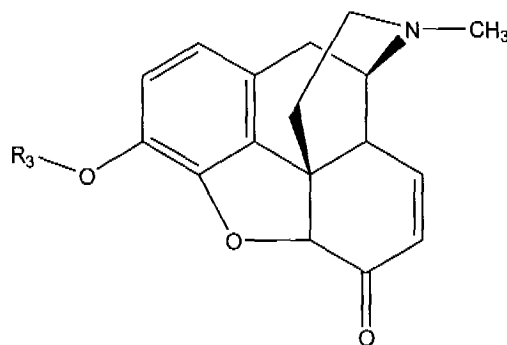
que comprende:

- (a) permitir a un compuesto de la fórmula (I):



(I)

que reacciones en presencia de un compuesto de la fórmula R_1SR_2 y un reactivo que contenga cloro, bajo condiciones suficientes para hacer un compuesto de la fórmula (II):



(II)

y

(b) permitir que el compuesto de la fórmula (II) reacciones con una primera base y un agente de acilación de la fórmula $R_4(C(O)OC(O)R_4$ o $R_4C(O)X$ bajo condiciones suficientes para hacer el compuesto de la fórmula (III), en donde :

cada uno de R_1 y R_2 es independientemente alquilo (C_1-C_{20}), cicloalquilo (C_3-C_8) o -fenilo;

R_3 es un grupo protector;

R_4 es alquilo (C_1-C_{10}); y

X es $-Cl$, $-Br$ o $-I$.

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26. El método de la reivindicación 25 o 14, en donde R_3 es alquilo (C_1-C_{10}), bencilo, alquilo $-C(O)(C_1-C_{10})$, alquilo $C(O)O(C_1-C_{10})$, $-Si(alquilo(C_1-C_{10}))_3$, $-Si(arilo)(alquilo C_1-C_{10})_2$, $-Si(arilo)_2(alquilo (C_1-C_{10}))$, $-P(O)(alquilo (C_1-C_{10}))_2$, $-P(S)(alquilo (C_1-C_{10}))_2$, o $S(O)OC_6H_4-p-CH_3$ y preferiblemente R_3 es

- a) $-CH_3$; o
- b) $-Si(alquilo (C_1-C_{10}))_3$, $-Si(arilo)(alquilo (C_1-C_{10}))_2$, o $-Si(arilo)_2alquilo (C_1-C_{10})$, ay preferiblemente es $-Si(alquilo (C_1-C_{10}))_3$; y más preferiblemente es $-Si(CH_3)_2(C(CH_3)_3)$.

27. El método de la reivindicación 25 o 14, en donde el reactivo que contiene cloro es ácido tricloroisocianúrico, N-clorosuccinimida, dicloroisocianurato de sodio, 1,3-dicloro-5,5-dimetilhidantoin, Cl_2 , hipoclorito de calcio, o cualquier mezcla de lo anterior, y preferiblemente, es ácido tricloroisocianúrico.

28. El método de la reivindicación 25 o 14, en donde la cantidad del compuesto de la fórmula (I) varía entre cerca de 1,0 a cerca de 9,0, entre cerca de 2,0 a cerca de 5,0 o entre cerca de 2,0 a cerca de 4,0 equivalentes molares por molar equivalente del reactivo que contiene cloro.

29. El método de la reivindicación 25 o 14, en donde R_1 es $-CH_3$ y R_2 es alquilo $-(C_1-C_{20})$, y preferiblemente, R_1 es $-CH_3$ y R_2 es alquilo (C_{12}).

30. El método de la reivindicación 25 o 14, en donde la cantidad del compuesto de la fórmula R_1SR_2 varía entre cerca de 1,0 a cerca de 9,0, entre cerca de 2,0 a cerca de 5,0 o entre cerca de 2,5 a cerca de 3,5 equivalentes molares por equivalente molar del reactivo que contiene cloro.

31. El método de la reivindicación 25, en donde el paso (a) comprende además el uso de una segunda base.

32. El método de la reivindicación 31, en donde la segunda base es una amina orgánica, y preferiblemente es trietilamina, diisopropiletilamina, piridina, diemetilpiridina o dimetilaminopiridina y más preferiblemente es trietilamina.

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33. El método de la reivindicación 31, en donde la cantidad de la segunda base varía entre cerca de 1,0 a cerca de 15,0, entre cerca de 2,0 a cerca de 10,0 o entre cerca de 2,5 a cerca de 7,0 equivalentes molares por equivalente molar del reactivo que contiene cloro.

34. El método de la reivindicación 25, en donde la primera base es una amina orgánica, y preferiblemente es trietilamina, diisopropiletilamina, piridina, dimetilpiridina o dimetilaminopiridina, y más preferiblemente es trietilamina.

35. El método de la reivindicación 25, en donde el agente de acilación es

a) $R_4C(O)OC(O)R_4$ y preferiblemente es $-CH_3C(O)OC(O)CH_3$; o

b) $R_4C(O)X$, y preferiblemente es $CH_3C(O)X$ y más preferiblemente es $CH_3C(O)Cl$.

36. El método de la reivindicación 25, en donde la cantidad de la cantidad de la primera base varía entre cerca de 1 a cerca de 10, entre cerca de 2 a cerca de 7 o entre cerca de 3 a cerca de 6 equivalentes molares por equivalente molar del agente de acilación.

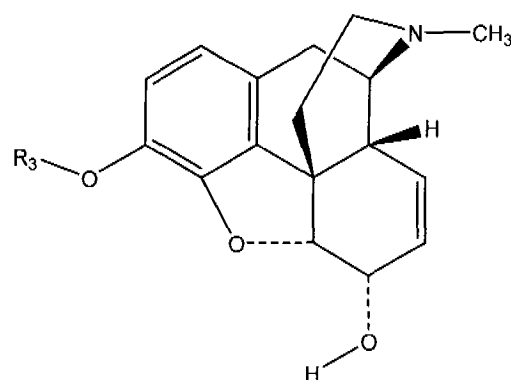
37. El método de la reivindicación 25, en donde la cantidad del agente de acilación varía entre cerca de 1 a cerca de 15, entre cerca de 1 a cerca de 10 o entre cerca de 2 a cerca de 7 equivalentes molares por equivalente molar del compuesto de la fórmula (II).

38. El método de la reivindicación 31, en donde la primera base y la segunda base son las mismas.

39. El método de la reivindicación 25, en donde
I. el paso (a) comprende además aislar el compuesto de la fórmula (II) antes de proceder a hacer el paso (b); o
II. el paso (b) se hace sin aislar primero el compuesto de la fórmula (II) preparada en el paso (a).

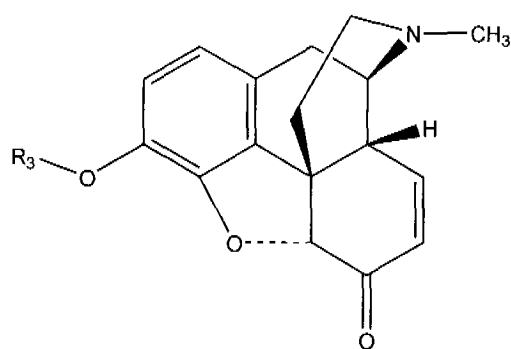
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40. El método de la reivindicación 25, en donde el compuesto de la fórmula (I) es un compuesto de la fórmula (Ia):



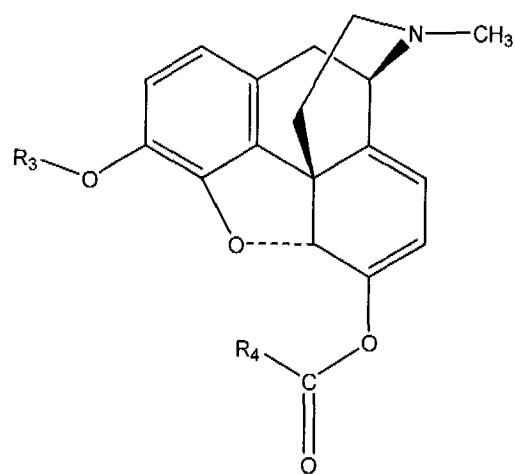
(Ia),

el compuesto de la fórmula (II) es un compuesto de la fórmula (IIa):



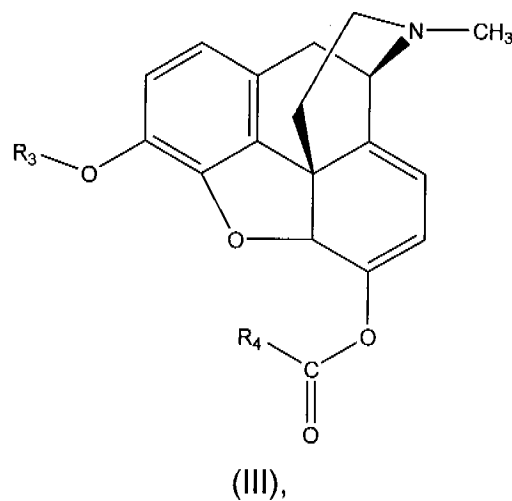
(IIa),

y el compuesto de la fórmula (III) es un compuesto de la fórmula (IIIa):



(IIIa).

41. Un compuesto de la fórmula (III):



en donde :

R₃ is Si((C₁-C₁₀)alkyl)₃, -Si(aryl)(C₁-C₁₀)alkyl)₂, or -Si(aryl)₂(C₁-C₁₀)alkyl); and
R₄ is -(C₁-C₁₀)alkyl.

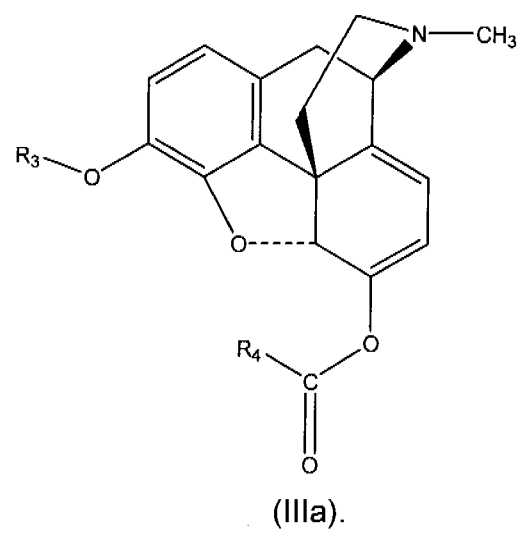
42. El compuesto de la reivindicación 41, en donde R₃ is Si(alquilo(C₁-C₁₀))₃, -Si(arilo)(alquilo C₁-C₁₀))₂, o Si(arilo)₂(alquilo (C₁-C₁₀)); y

R₄ es alquilo (C₁-C₁₀).

43. El compuesto de la reivindicación 41, en donde el compuesto de la fórmula (III) es a

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16

compuesto de la fórmula (IIIa):



Reviews

XP-002334135

Trichloroisocyanuric Acid: A Safe and Efficient Oxidant

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Abstract:

The literature on trichloroisocyanuric acid (TCCA) has been reviewed. TCCA is a safe and efficient reagent, useful for chlorination and oxidation even on large scale.

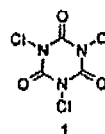
Introduction

Trichloroisocyanuric acid, 1,3,5-trichloro-1,3,5-2,4,6-(1H,3H,5H)-trione (TCCA, 1) (Scheme 1) with the commonly used trade names, Symclosene, ACL-85, or Chloreal,¹ was first reported in 1902 by Chattaway and Wadmore. The authors describe that trichloriminocyanuric acid is obtained in a quantitative yield from the reaction of the potassium salt of cyanuric acid (2) with chlorine gas² (Scheme 2). Later Birckenbach and Linhard described the synthesis of TCCA through cyclization of *N*-carbonyl-*N,N*-dichlorourea.³ After the microbiological activity of TCCA was discovered, Hands and Whitt reported the synthesis of TCCA through chlorination of cyanuric acid (2) with chlorine gas in aqueous NaOH. Thereafter, TCCA and its monosodium salt DCCA became industrially important.⁴ In 1952 Monsanto obtained a patent on the synthesis of TCCA.⁵ In 1960 W.R. Grace obtained a second patent on the synthesis of TCCA.⁶ Purex obtained in 1958 a patent on a method for the purification of TCCA through dissolution in concentrated H₂SO₄ and dilution with ice water.⁷

Over the years there has been some confusion about the correct structure of TCCA. In earlier volumes of Fieser and Fieser the structure of TCCA was confused with cyanuric chloride (3) the acid chloride of cyanuric acid (2) Scheme 3).

As seen from the structure TCCA belongs to the large group of *N*-chloroimides and amides which is a subgroup of the more general *N*-chloroamines. *N*-chloroamines are inorganic or organic nitrogen compounds with at least one chlorine atom attached to nitrogen. The oldest example is monochloroamine NH₂Cl known since the beginning of the

Scheme 1. Trichloroisocyanuric acid (1)



Scheme 2. Synthesis of TCCA



Scheme 3. Structure of TCCA (1) versus cyanuric chloride (3)



19th century. The solvent-free material, isolated at +70 °C, disproportionates violently at -50 °C to ammonium chloride and the explosive nitrogen trichloride.⁸

Chloroamines are used as bleaching agents, disinfectants, and bactericides, due to their function as chlorinating agents and oxidants. A few of them are also commonly used as chlorinating reagents and oxidants in organic synthesis. Many of the chloroamines show unstable or explosive properties. Many of their reactions are also extremely violent, for example, the reaction of *N*-chlorosuccinimide with aliphatic alcohols.⁹ Since chloroamines are easier to handle than chlorine gas or metal hypochlorites, they are widely used in the purification of drinking water and as sanitizing agents in swimming pools. Since the first large-scale manufacture of TCCA and its monosodium salt DCCA, they have gained a continuously growing share of these markets as important replacements of calcium hypochlorite, 1,3-dichloro-5,5-dimethylhydantoin (NDDH), and chloramine T.

The chemical synthesis of TCCA has not been that successful. The most commonly used reagent is *N*-chlorosuccinimide (NCS) 4. Another reagent commonly used is 1,3-dichloro-5,5-dimethylhydantoin (NDDH) 5¹⁰ (Scheme 4).

- (8) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann Ltd.: London, 1995; Vol. 1, Entry 3857, p 1259.
 (9) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann Ltd.: London, 1995; Vol. 2, p 158.

* Author for correspondence. Fax: +49-30-46892074. E-mail: ulf.tilstam@schering.de.

- (1) (a) Ura, Y.; Sakata, G. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, 2001. (b) *Merck Index*; Merck & Co.: Whitehouse Station, NJ, 1996.
 (2) Chattaway, F. D.; Wadmore, J. M. *J. Chem. Soc.* 1902, 81, 191.
 (3) Birckenbach, L. *Chem. Ber.* 1930, 63, 2528.
 (4) Hands, W. *J. Soc. Chem. Ind.* 1948, 67, 66.
 (5) Hardy, U.S. Patent 2,607,738, 1952.
 (6) Christian, U.S. Patent 2,956,056, 1960.
 (7) Lorenz, U.S. Patent 2,828,308, 1958.

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18

Scheme 4. Structure of NCS (4), NDDH (5), and TCCA (1)

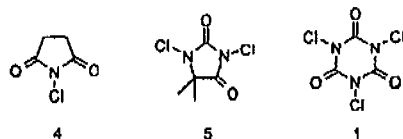


Table 1. Properties

reagent	NCS	NDDH	TCCA
physical properties	white solid 150–151 °C dec	white solid 132 °C dec	white solid 234 °C dec
active chlorine content	51%	78%	91.5%
oxidizing ability	5.82	4.40	4.84
decomposition enthalpy kJ/mol active chlorine	–129,8	–120,3	–120.0
toxicological properties (LD ₅₀)	2700*	542	1300
cost USD/kg active chlorine	164	58	44

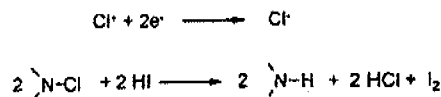
For chlorination and oxidation *tert*-butylhypochlorite has also been a very commonly used reagent. However, the use of *tert*-butylhypochlorite has been slowly vanishing over the last years due to reports of decomposition during transportation and explosions during production. The use of aqueous hypochlorite is still very common for various oxidations although only in cases where the use of an aqueous solution does not interfere with the reaction or the product. In organic synthesis the hypochlorites could also be substituted with *N*-chloroamines, especially when anhydrous conditions are necessary.

Properties of *N*-Chloroamines. At this point, it is important to state that all *N*-chloroamines are thermally unstable and can explode at elevated temperature. They can also react violently with amines, strong acids and bases, and easily oxidised organic material. *N*-Chlorosuccinimide has been reported to react violently with alcohols and benzylamine, 1,3-dichloro-5,5-dimethylhydantoin reacts violently with xylene, and trichloroisocyanuric acid has been reported to generate explosive nitrogen trichloride in concentrated acidic aqueous solution due to the attack of formed hypochlorous acid on the imine bond.¹¹

To get a comparative picture of the optimal use of different *N*-chloroamines in organic synthesis we have compared some of the properties of NCS, NDDH, and TCCA (see Table 1). In all *N*-chloroamines all chlorines are active, and in the case of TCCA we have found that all chlorines have comparable reactivity

All three *N*-chloroamines are white solids which decompose at elevated temperature. NDDH has a melting point with decomposition at 132 °C, NCS, at 150 °C, and TCCA, at 234 °C (Scheme 5). *N*-Chloroamines can act as oxidants by absorbing two electrons. Thus, *N*-chloroamine oxidises hydroiodic acid to liberate iodine which is used for quantitative analysis of the activity.

Scheme 5. Oxidation mechanism



The theoretical available chlorine content is expressed as twice the mass fraction of chlorine in the molecule or for practical purposes, the equivalent of elemental chlorine. This is a value for the atom efficiency of these reagents. The amount of active chlorine in NCS is 51%, in NDDH 78%, and TCCA has the highest amount of active chlorine with 91.5%.

The quantitative hydrolysis constant *K* is used to express the bactericidal power of *N*-chloroamines, which depends on the ability to generate hypochlorous acid in water. It is expressed as the total amount of hypochlorous acid produced through quantitative hydrolysis of the *N*-chloroamine in water, is expressed by the equation below, and is normally in the range 10^{–4}–10^{–10}; expressed as the p*K*-value, it is between 4 and 10. Among the three reagents NDDH has the highest oxidation potential with 4.40, TCCA with 4.84, and NCS with 5.82, which also indicates another property of these reagents. They are rather slowly hydrolysed in water. A well-known method for purification of NCS is through recrystallization from water.

$$K = \frac{C_{\text{RRNH}} \cdot C_{\text{HOCl}}}{C_{\text{RRNCl}}}$$

The bulk price of the different *N*-chloroamines in relationship to the amount of active chlorine is also important for large-scale synthesis. The price of NCS (\$164/kg) is almost 4 times the price of TCCA (\$44/kg). The price of NDDH is also in a moderate range with \$58/kg.

The toxicity of *N*-chloroamines is very important because of their widespread use in drinking water, swimming pools, and food processing. The toxicological data for TCCA, NCA, and NDDH are summarised in Table 1.¹²

Last, but not least important, is the solubility of reagents in organic solvents which is an important factor for scale-up and manufacture. During our research in the field of β -carboline we determined the solubilities of these three reagents in various solvents.

In organic solvents TCCA has the highest solubility of the three reagents. TCCA has a high solubility in acetone (350 g/L) and ethyl acetate (385 g/L) and a moderate solubility in toluene (70 g/L). In comparison the solubility of NCS in organic solvents is much lower than for TCCA (see Table 2). The difference in solubility between NCS and TCCA becomes even more striking when one compares the amount of active chlorine which is possible to dissolve per liter of solvent. After dissolving TCCA in ethyl acetate the solution is 5.0 M in active chlorine in comparison with NCS which only gives a 0.44 M solution. The picture is the same in acetone and other organic solvents where TCCA gives highly concentrated solutions, and NCS gives much more diluted ones.

(10) Larock, R. C. *Comprehensive Organic Transformations, A Guide to Functional Group Preparations*; VCH Publishers Inc.: New York, 1989.

(11) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann Ltd.: London, 1995.

(12) Ura, Y.; Sakata, G. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, 2001.

Table 2. Solubility

solvent (g/L) (mol active chlorine/L)	TCCA	NCS	NDDH
water	10 (0.13)	43 (0.32)	9 (0.09)
acetone	350 (4.56)	183 (1.37)	211 (1.83)
ethyl acetate	385 (5.02)	59 (0.44)	131 (1.14)
toluene	70 (0.91)	15 (0.07)	62 (0.53)

As it is possible to chlorinate ketones and esters in the α -position with TCCA, we investigated during our solubility test if any chlorination of the solvent could be determined. We did not observe any chlorination but it is still not recommended to store solutions of *N*-chloroamines in organic solvents.

The Main Use of TCCA. The worldwide production of TCCA and DCCA is about 100.000 t/year. The demand is increasing by 8–10% per year for swimming pools and 3–5% for food processing. They are used for many purposes such as disinfecting swimming pools, nonshrinking treatment of wool, cleaning and sterilizing bathrooms, and using in laundry bleach as well as for removing oil and protein in stainless steel. They are also recommended for dishwashing in hotels, hospitals, restaurants, and food factories; however, as reagents for organic synthesis the examples are rather rare.

Trichloroisocyanuric Acid in Organic Synthesis. Although TCCA has been produced on large scale for use in household and industry since the 1950s, it has never had a real breakthrough in organic chemistry laboratories. It also has not found its way into textbooks in organic chemistry and even books on heterocyclic chemistry fail to mention this very useful reagent. This probably has something to do with the early chlorination experiments which indicated a rather uncontrolled chlorination with TCCA in comparison to that using NCS and NBS.

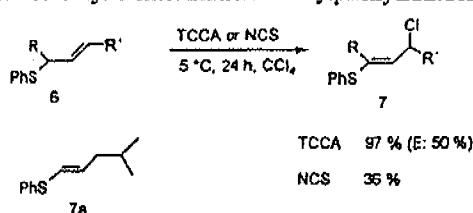
The main part of this contribution will concentrate on the chemistry of TCCA in organic synthesis that has been reported up to now. We do not intend to give a complete review over all reports that have been published on chemical synthesis with this reagent. When possible the uses of NCS and NDDH are compared, and the possibilities to substituting *tert*-butyl hypochlorite with TCCA are shown.

This part will be divided into:

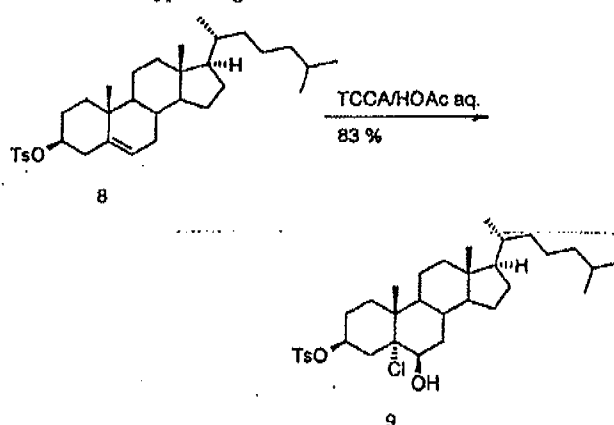
- A. Chlorination
- B. Oxidation
- C. Miscellaneous

A. Chlorination. In 1942 Ziegler and co-workers¹³ reported for the first time the use of trichloroisocyanuric acid as a reagent in organic synthesis for the α -chlorination of alkenes. During a detailed study about the allylic halogenation with different reagents TCCA was also studied under standard reaction conditions. The authors reported a very exothermic reaction with cyclohexene producing a mixture of products. The main product 3-chlorocyclohexene was obtained in a yield of 29%. No optimization of the reaction conditions was performed.

Scheme 6. Allylic chlorination of allylphenylsulfides



Scheme 7. Hypohalogenation of an alkene



In 1975 an allylic chlorination was used by Cohen et al.¹⁴ for the synthesis of 1-thiophenoxy-3-chloroalkenes (7) from allyl phenyl sulphides (6). The authors commented that the yield with TCCA approached quantitative in comparison to that of the far more expensive reagent *N*-chlorosuccinimide which was considerably less effective. When R = alkyl, the reaction conditions using NCS afforded mainly unreacted starting material. The yield of 7a was found to be quantitative with TCCA although as 1:1 mixture of *E/Z* (Scheme 6). The authors observed, though, that for substrates which reacted with NCS the stereoselectivity was better.

Under aqueous conditions in acetic acid it was possible to do a hypohalogenation to a Δ -5,6 double bond in a cholesterol derivative.¹⁵ Hypohalogenation has mainly been reported from the reaction of sodium hypochlorite reaction with alkenes (see, for instance, ref 16) or chlorine gas (see, for instance, ref 17) (Scheme 7). Also for the preparation of 9 α -chloro-11- β -formyloxypregnan derivative, 11, a type of hypohalogenation was used¹⁸ (Scheme 8).

A benzylic chlorination of *N*-heterocycles has been reported by Jeromin et al.¹⁹ Alkyl pyridine and methylquinoline which are normally difficult to chlorinate in the side chain were easily chlorinated with TCCA. In comparison to the fast and exothermic chlorination in chlorinated solvent with TCCA, the use of NCS or NDDH gave no complete reactions. The major product was always the monochloro derivative when TCCA was used in a stoichiometric amount.

(13) Ziegler, K.; Späth, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Anal. Chem.* 1942, 551, 80.

(14) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* 1975, 50, 4433.

(15) Mukawa, F. *Nippon Kagaku Zasshi* 1957, 78, 450; *Chem. Abstr.* 1960, 53, 5338.

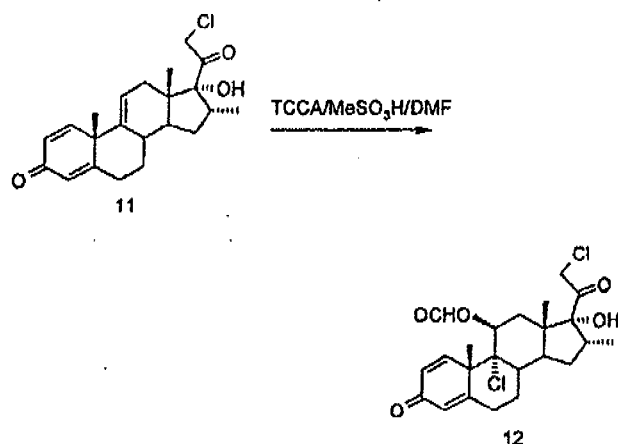
(16) Colonge, J.; Comet, L. *Bull. Soc. Chim. Fr.* 1947, 838.

(17) Mills, J. S. J. *Chem. Soc.* 1966, 2261.

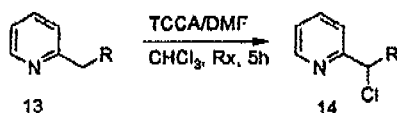
(18) Draper, R. W.; Vater, E. J. U.S. Patent 5,602,248 A, 1995.

(19) Jeromin, G. E.; Orth, W.; Rapp, B.; Weiss, W. *Chem. Ber.* 1987, 120, 649.

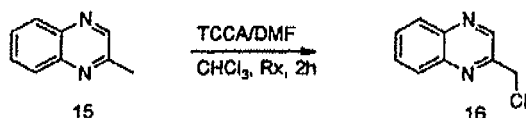
Scheme 8. Hypohalogenation of a pregnan derivative



Scheme 9. Benzylic chlorination of pyridines



Scheme 10. Benzylic chlorination of chinoxalin



Surprisingly no ring chlorination was observed under the reaction conditions (Scheme 9).

The authors found that adding a radical starter did not have any significant effect on the reaction which rules out a radical mechanism. Instead it was found that the addition of carboxylic amide like benzamide or DMF was beneficial for the start of the reaction. 2-Chloromethyl pyridines were obtained in fairly good yields. Another independent study of the benzylic chlorination of 13 ($R = H$) with NCS gave only 25% of 14 combined with 20% of the dichloro derivative.²⁰

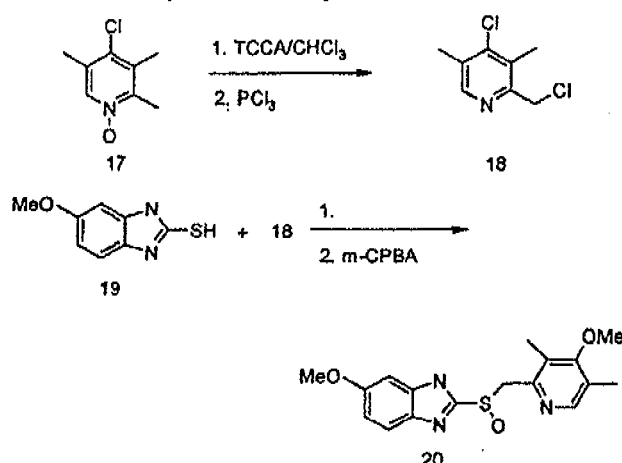
Also other alkyl-substituted *N*-heterocycles could be chlorinated, for instance, 2-methylchinoxalin (15), from which it was possible to obtain the monochloro derivative 16 in 75% (Scheme 10).

In this chlorination study only electron-deficient *N*-heterocycles were studied. Until now no benzylic chlorination of electron-rich heterocycles with TCCA has been reported.

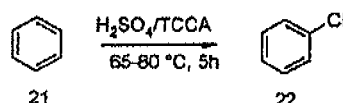
As part of the synthesis of omeprazole, the antiulcer drug from AstraZeneca, the benzylic chlorination of a pyridine derivative was the central transformation in a patented synthesis of A. Palomo Coll²¹ (Scheme 11).

As part of their continued study of the use of TCCA as a safe and convenient substitute for chlorine, Juenge et al.²² also observed that trichloroisocyanuric acid could be used for the chlorination of aromatic systems under polar and free radical conditions. When 50% H_2SO_4 was used as catalyst,

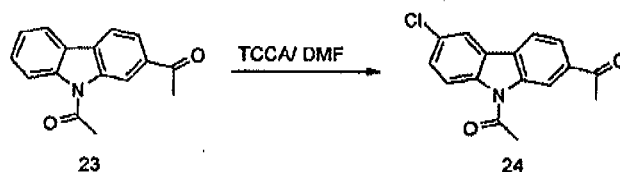
Scheme 11. Synthesis of omeprazole



Scheme 12. Aromatic chlorination



Scheme 13. Chlorination of a carbazole



it was possible to obtain a fairly good yield of chlorobenzene (80%) after 5 h at 65–80 °C.

Toluene gave the 2- and 4-chlorotoluenes under acidic reaction conditions (66%). The main regioisomer was the 4-chlorotoluene. With phenol and aniline the yield was lower, giving mainly the para isomer. With electron-withdrawing groups no reaction occurred (Scheme 12). Alternately, when benzoylperoxide was used as radical initiator, benzylchloride was obtained in 44% from toluene.

J. Rosevear and J. F. K. Wilshire reported in 1980 a study of the chlorination of some *N,N*-dimethylanilines with TCCA.²³ Under the reaction conditions, concentrated sulfuric acid at room temperature overnight, the reaction produced a complex mixture of chlorinated products. No attempt was made to optimise the reaction conditions.

In 1994 Manschand et al.²⁴ reported a selective chlorination in the 7-position of the carbazole 23 using TCCA in DMF or triethylphosphate at room temperature. Using these conditions a moderate yield of the chlorinated carbazole 24 was obtained. The authors claimed this to be the most selective chlorination system for this substrate (Scheme 13).

H. Suzuki published in 1998 a method for the chlorination of phenylphosphonic acid with TCCA in concentrated sulfuric acid.²⁵ Using this method it was also possible to

(20) Newkome, G. R.; Kiefer, G. E.; Xia, Y. J.; Gupta, V. K. *Synthesis* 1984, 676.

(21) Palomo Coll, A. Eur. Pat. 0484265, 1992.

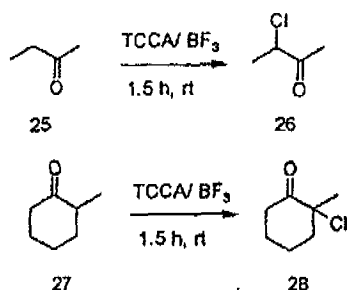
(22) Juenge, E. C.; Beal, D. A.; Duncan, W. P. *J. Org. Chem.* 1970, 35, 719.

(23) Rosevear, J.; Wilshire, J. F. K. *Aust. J. Chem.* 1980, 33, 843.

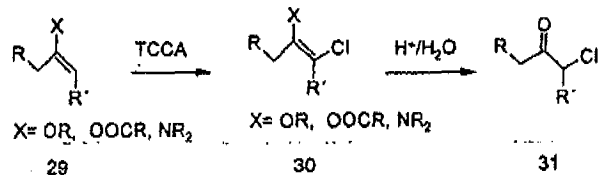
(24) Manschand, P. S.; Coffen, D. L.; Belica, P. S.; Wong, F.; Wong, H. S.; Berger, L. *Heterocycles* 1994, 39, 833.

(25) Suzuki, H. Japanese Patent 10045779 A2, 1998. *Chem. Abstr.* 1998, 128, 154222.

Scheme 14. Chlorination of ketones



Scheme 15. Chlorination of substituted alkenes



prepare tetrachlorophthalic anhydride from phthalic anhydride in 93.2% yield.²⁶

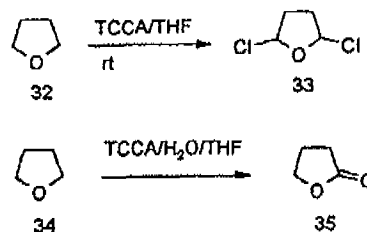
In 1985 Hiegel et al. reported for the first time the use of TCCA for the α -chlorination of ketones. The chlorination was performed under acid catalysis using BF_3 -etherate as catalyst. Under these conditions a monochlorination of the most substituted side chain was obtained in moderate-to-high yields. A drawback of this method is that the ketone has to be used in large excess. In the case of 2-propanone (25) a 17.4 excess was used, giving 58% of chloroketone 26. In the case of 2-methylcyclohexanone (27) a 1.98 excess was necessary to obtain the chloroketone 28 in 87% yield (Scheme 14).

In 1998 H. Rayle and R. Roemmele reported the chlorination of substituted alkenes 29 using trichloroisocyanuric acid.²⁷ The alkenes used were enoethers, enolesters, and enamines, and after hydrolysis the corresponding monosubstituted chloroketone 31 was obtained in good yield without using a large excess of the starting material (Scheme 15).

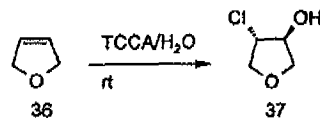
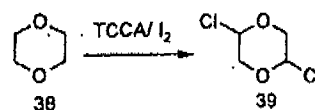
Juenge et al.²⁸ also reported in 1966 the chlorination of cyclic ethers. They investigated the reaction between tetrahydrofuran or tetrahydropyran with trichloroisocyanuric acid at 0 °C. The reaction afforded mainly *trans*-2,5 dichlorotetrahydrofuran (33) in 26% or *trans*-2,6-dichlorotetrahydropyran 28% yield. By a simple modification of the reaction conditions, namely, the addition of water, the reaction afforded instead γ -butyrolactone (35) from THF and δ -valerolactone from THP as the major product after an α -methylene oxidation probably via a hypochlorous acid oxidation. The liberation of hypochlorous acid from TCCA in contact with water is well-known²⁹ (Scheme 16).

Hypohalogenation was also found by Juenge et al. to occur with TCCA in the presence of water in the reaction with unsaturated cyclic ethers such as 2,5-dihydrofuran. By

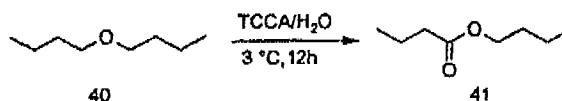
Scheme 16. Chlorination of cyclic ethers



Scheme 17. Hypohalogenation of unsaturated ethers

Scheme 18. α -Chlorination of ethers

Scheme 19. Oxidation of ethers



the reaction *trans*-3-chlor-4-hydroxy-tetrahydrofuran was obtained in about 30% yield. In this case no α -chlorination of the cyclic ether was observed (Scheme 17).

Later the scope and limitation of the chlorination of cyclic ethers was reported by Duncan et al.³⁰ studying also *p*-dioxane. The chlorination of dioxane at 80–85 °C with TCCA in dioxane as solvent and I_2 as catalyst was found to give a 9:1 mixture of *trans*- and *cis*-2,5-dichloro-*p*-dioxane (39) in 72% yield. The catalysis with ZnCl_2 also gave a rise in yield compared to that of the uncatalysed reaction although not as high as with iodine catalysis. It was also possible through iodine catalysis of the reaction with THF and THP to raise the yield of the dichloro derivatives to 54 and 56%, respectively (Scheme 18).

B. Oxidation. Oxidation of Ethers. In 1968 Juenge et al.³¹ described the direct oxidation of aliphatic ethers to esters utilizing TCCA in aqueous ether solution. The yield from the reaction was found to be extremely dependent on the structure of the ether. From diethyl ether ethyl acetate was obtained in 49%, but from dibutyl ether (40) butylvalerate (41) was obtained in a quantitative yield. From benzyl ethers the major product was benzaldehyde. As it is necessary to have at least 3 equiv of water compared to TCCA in the mixture to start the reaction, the actual oxidant is probably hypochlorous acid as described earlier for the synthesis of lactones from cyclic ethers (Scheme 19).

The oxidation of a thioether in a two-step process with TCCA and AgTFA for a short synthesis of sarkomycin (44) from cyclopentenone (42) has also been reported.³² (Scheme 20).

(26) Suzuki, H. Japanese Patent 09067359 A2, 1997. *Chem. Abstr.* 1997, 126, 277382.

(27) Rayle, H. L.; Roemmele, R. C. *Eur. Pat.* 0872463A1, 1998.

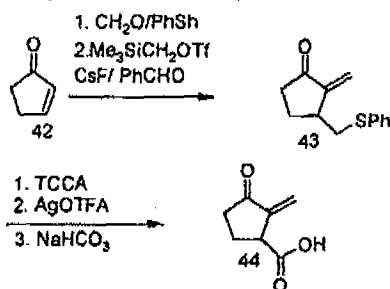
(28) Juenge, E. C.; Spangler, P. L.; Duncan, W. P. *J. Org. Chem.* 1966, 31, 3836.

(29) Brady, A. P.; Sancier, K. M.; Sirine, G. *J. Am. Chem. Soc.* 1963, 85, 3101.

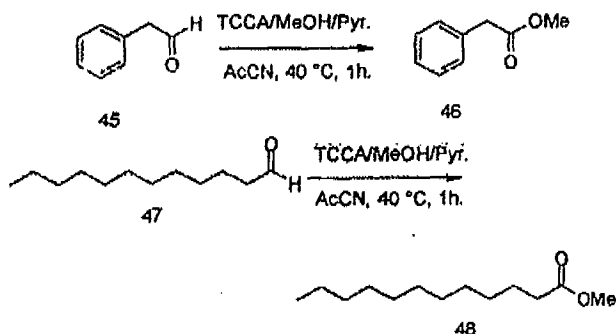
(30) Duncan, W. P.; Strate, G. D.; Adcock, B. G. *Org. Prepr. Proced. Int.* 1971, 3, 149.

(31) Juenge, E. C.; Beal, D. A. *Tetrahedron Lett.* 1968, 55, 5819.

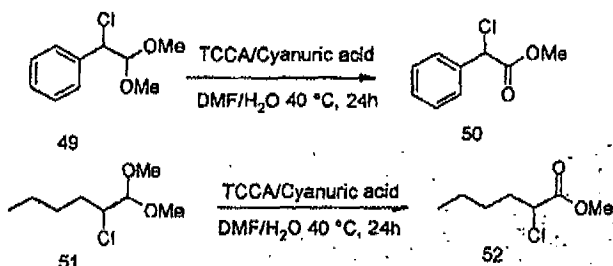
Scheme 20. Synthesis of sarkomycin



Scheme 21. Oxidation of aldehydes



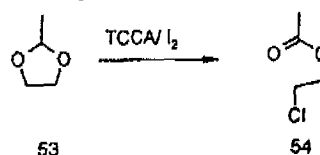
Scheme 22. Oxidation of 2-chloroacetals



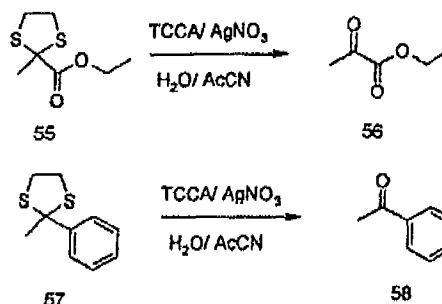
Oxidation of Aldehydes and Acetals. In 1980 Hiegel et al.³³ presented a simple method for the oxidation of aldehydes to methyl esters. A solution of TCCA, the aldehyde, methanol, and pyridine in acetonitrile gave the corresponding methylester. The authors suggested that the reaction probably goes through a hemiacetal which can be oxidised as a secondary alcohol. The methylesters were obtained from all examples in fairly good yields with yields ranging from methyl 2-phenylethanoate (46) in 68% yield to methyl dodecanoate (48) in 93% yield (Scheme 21). The oxidation of 2-chloroacetals with TCCA has also been reported to give the corresponding 2-chloroesters³⁴ (Scheme 22).

The reaction gives yields in the range from 42% of methyl 2-chloro-2-phenylethanoate (50) to 92% of methyl 2-chloro-2-(4-chlorophenyl)ethanoate (52). The authors reported that the addition of cyanuric acid to the reaction mixture was necessary to get the reaction started. The cyanuric acid probably functions as an acid catalyst for the formation of the hemiacetal which can be oxidised as a secondary alcohol.

Scheme 23. Cleavage of acetal



Scheme 24. Cleavage of thioacetal



Also the oxidation of α -acetoxyacetals has been reported by Ghelfi et al.³⁵ The reaction was performed under the same reaction conditions as with the chloro acetal except that no cyanuric acid was added to the reaction. The yields are also comparable with those obtained with the chloroacetals.

The α -chlorination of cyclic ethers with TCCA has also been used to open up cyclic acetals to the corresponding chlorine-substituted esters. In 1974 Gelas and Petrequin developed this reaction as an alternative for cleavage of acetals in sugar chemistry.³⁶ (Scheme 23)

The authors reported a 70% yield of 54 after distillation. The low yield was found to be due to the instability of the product during distillation. Prior to purification a yield of 90% was observed. The authors also compared the use of NCS for the reaction. It was found that the yield was much lower around 40–50%.

Later G. Olah et al. used the α -chlorination of sulfides with TCCA as a mild cleavage of ethandiyl *S,S*-acetals. The authors used an excess of TCCA together with silver nitrate in aqueous acetonitrile. The corresponding carbonyl compound was obtained in excellent yield after a reaction time of only 10 min (Scheme 24).

From the reaction it was possible to obtain ethyl pyruvate (56) in an almost quantitative yield (95%). The lowest yield was obtained from acetophenone (58) 93%. α -Chlorination of thioethers has also been reported to occur with NCS although in modest yield.³⁷

Oxidation of Alcohols. In 1957 the first use of TCCA for the oxidation of alcohols was reported.¹⁵ This was a small study over oxidation of steroid and terpene alcohols using TCCA.

In 1992 Hiegel and Nalbandy³⁸ reported a more detailed study over the use of TCCA for the oxidation of alcohols. They studied the oxidation of secondary alcohols in acetone

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(33) Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamshiro, G. S.; Hiberath, L. A. *Synth. Commun.* 1996, 26, 2633.

(34) Boni, M.; Ghelfi, F.; Pagoni, U. M.; Pinetti, A. *Bull. Soc. Chem. Jpn.* 1994, 67, 156.

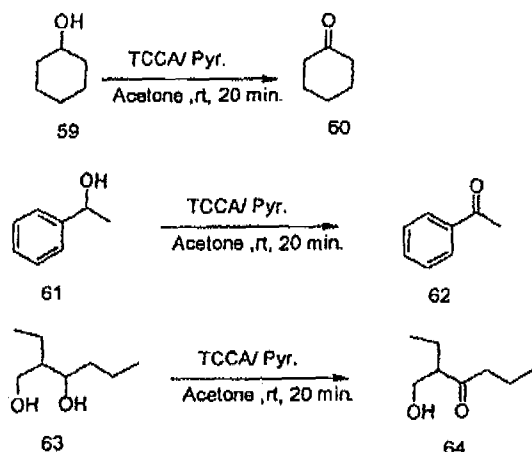
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(37) Muthusubramanian, L.; Mitra, R. B.; Rao V. S. S.; Raghavan, K. V. *Indian J. Chem., Sect. B* 1996, 35, 1331.

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Scheme 25. Oxidation of secondary alcohols



Scheme 26. Oxidation of diols



with TCCA and pyridine as base to scavenge the released hydrochloric acid. All ketones were obtained in good yields after 20 min at room temperature. During the course of the reaction in acetone only very limited amounts of chlorinated products were observed. When the reaction was run in acetonitrile, more chlorinated products were observed.

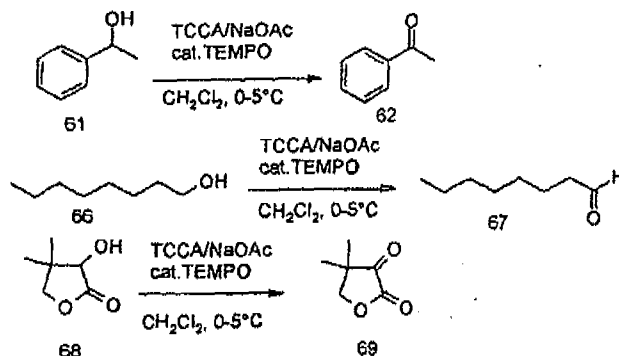
The authors also observed that secondary alcohols were oxidised considerably faster than primary alcohols in the presence of TCCA which allowed a selective oxidation of secondary alcohols in the presence of primary (Scheme 25).

The yield of ketone was more or less independent of the structure. The lowest yield of 68% was obtained from cyclohexanone (60), and the best, from acetophenone (62) with 90%. 2-Ethyl-1-hydroxy-3-hexanone was obtained in 72%.

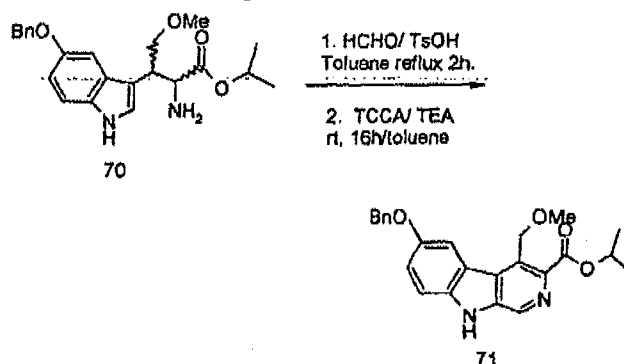
Kondo et al.³⁹ reported in 1995 the oxidation of diols for the synthesis of lactones using *N*-haloamides. The reaction was initially optimised with NCS. The optimal conditions for the reaction with 1,4-butanediol (65) were found to be room temperature in methylene chloride for 5 h. Under these conditions γ -butyrolactone (35) was obtained in 88% yield. The authors found that the reaction did not work at all in the presence of pyridine. For the reaction 3 equiv of NCS was necessary to force the reaction to completion. Using the optimum conditions other *N*-haloamides were compared to NCS. In these studies TCCA was the best, giving 35 in 85% yield. *N*-Bromoacetamide and *N,N*-dichlorobenzenesulfonamide also gave yields over 80%. With NBS the reaction did not work well, giving only 57% of 35 (Scheme 26).

A TEMPO-catalysed oxidation of alcohols with TCCA as primary oxidant has also been reported.⁴⁰ With this method it is possible to oxidise primary and secondary alcohols to the corresponding carbonyl compound in good-to-excellent

Scheme 27. TEMPO-catalysed oxidation of alcohols.



Scheme 28. Dehydrogenation of tetrahydro- β -carboline



yields. The standard procedure for the TEMPO-catalysed oxidation of alcohols utilises aqueous sodium hypochlorite as the primary oxidant.⁴¹ The major drawback of the standard method is that it is not possible to prepare aldehydes and ketones which are sensitive towards aqueous alkaline conditions. With the new method no water is necessary to reoxidise TEMPO (Scheme 27). The authors reported that after purification by distillation they obtained acetophenone (62) in 69% yield, octanal (67) in 91%, and 2-ketopantolacton (69) in 86% yield. Instead of TCCA dichlorodimethyl hydantoin NDDH could also be used without any difference in yield of the prepared product.

The TEMPO-catalysed oxidation of primary and secondary alcohols has also been reported for NCS.⁴²

Dehydrogenation of Amines. In 1998 we reported the use of TCCA in combination with triethylamine for the dehydrogenation of 3-carboxytetrahydro- β -carboline.⁴³ The method was developed during scale-up of the β -carboline abecarnil, 71. Due to reported problems of explosions during transport of *tert*-butyl hypochlorite, the method of choice for lab scale, it was decided to search for an alternative method. During this study two reagents were found to give high transformations: NCS and TCCA. Although NCS gave a very high yield of crude product, it was not possible to obtain a purified product after recrystallization due to the fact that the byproduct succinimide cocrystallises with 71. It was only possible to eliminate succinimide from the crude product through a chromatographic purification (Scheme 28).

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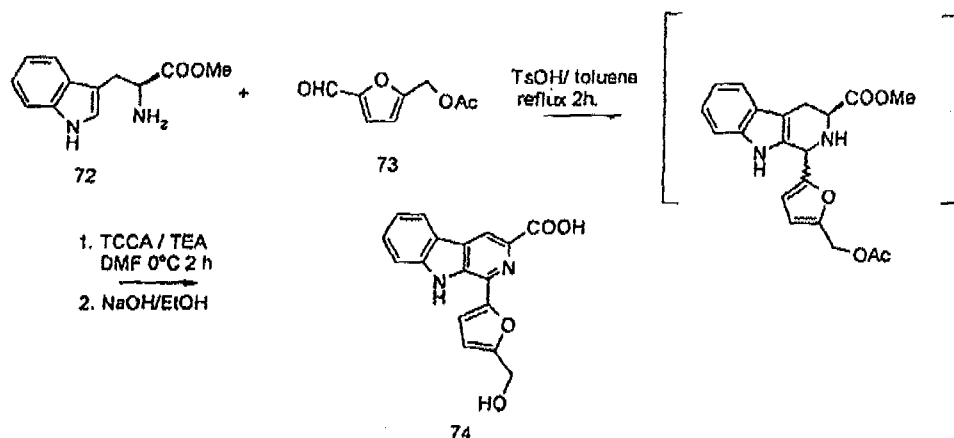
(40) Jenny, C. J.; Lohri, B.; Schlageter, M. *Eur. Pat.* 775684, 1997.

(41) Anelli, P. C.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* 1987, 52, 2559.

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Scheme 29. Synthesis of flazin



Using TCCA it was possible in the laboratory to obtain the **71** in 82% yield from the tryptophan derivative, **70**. For the sequence the yield from **71** using *t*-BuOCl as oxidant was 80%. The method was transferred to the pilot plant and could be safely scaled up to a 100-kg scale. During hazards evaluation of the process it was found that the addition of TCCA to the reaction mixture was best dose-controlled. The addition of TCCA to the reaction mixture was found to have a heat of reaction of -210 kJ/mol.

After the successful transfer to the pilot plant the scope and limitations of the process for the dehydrogenation of various tetrahydro- β -carboline were evaluated. During this evaluation it was also possible to perform a total synthesis of flazin (**74**) a natural product found in Japanese soy sauce.⁴⁴ The original aromatization was performed with Pu/C and oxygen in refluxing toluene (Scheme 29).

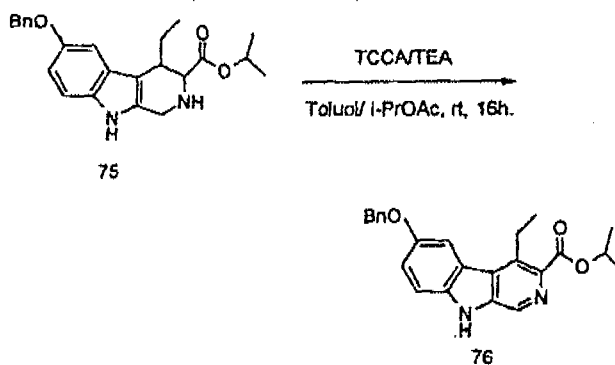
Tryptophan methyl ester was condensed with 5-(acetoxymethyl)furfuraldehyde under TsOH catalysis in refluxing toluene. The yield of flazin (**74**) from tryptophan methyl ester (**72**) was 85%. No benzylic oxidation or aromatic chlorination was observed under the reaction conditions, although the system contains an electron-rich benzylic position and two electron-rich heterocycles.

Also in another development project the aromatization of a tetrahydro- β -carboline (**75**) with TCCA and TEA was successfully used for scale-up to 15-kg scale in the pilot plant (Scheme 30). The aromatization method has lately also been reported for the synthesis of β -carboline on solid phase.⁴⁵

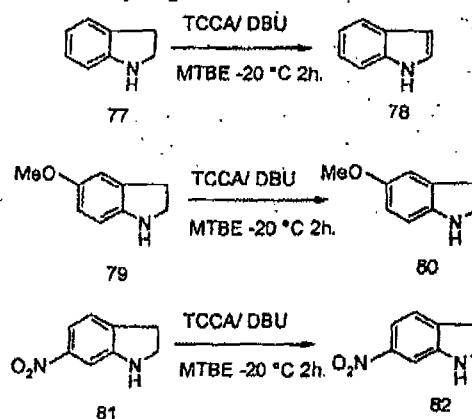
The conversion of indolines to indoles has been the subject of many oxidation studies over the years.⁴⁶ This theme seems to be trivial but has not been satisfactorily solved until we utilised TCCA for the conversion⁴⁷ (Scheme 31).

The reaction was optimised for indole (**78**); from this study it was found that the amount of oxidant and base for a complete conversion of indoline to indole was found to be a 10% molar excess of TCCA with 2 equiv of DBU. The best solvent being MtBE. Utilizing these reaction conditions

Scheme 30. Large-scale dehydrogenation



Scheme 31. Dehydrogenation of indolines



it was possible to obtain indole in 89% yield after workup and crystallization from petrol ether. Under these conditions it was possible to obtain 5-methoxyindole (**80**) in 83% yield and the electron-poor 6-nitro-indole (**82**) in 76% yield (Scheme 32).

During our laboratory investigation of dehydrogenation of β -carboline we also investigated the aromatization of the core system (**83**). Under these reaction conditions the dihydro- β -carboline (**84**) was the main product, although accompanied by the starting material and the β -carboline (**85**). This is probably due to disproportionation of the dihydro- β -carboline (**84**).

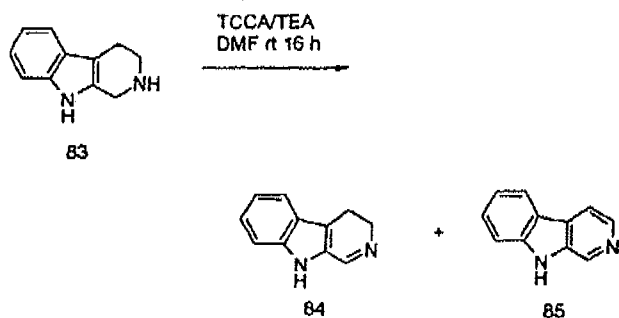
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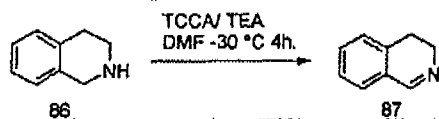
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(47) Tilstam, U.; Hare, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* 2001, 42, 5385.

Scheme 32. Dehydrogenation of tetrahydro- β -carboline



Scheme 33. Dehydrogenation of tetrahydroisoquinoline



Under the used reaction conditions it was not possible to obtain the β -carboline (85) selectively. This resistance of tryptamine derivatives towards oxidation is known from the literature.⁴⁸

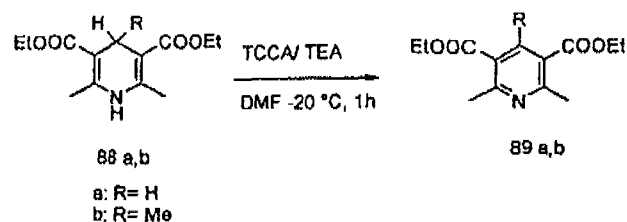
3,4-Dihydroisoquinoline (87) is a useful precursor for the synthesis of isoquinoline alkaloids. Using TCCA/TEA 3,4-dihydroisoquinoline (86) could easily be obtained in high yield under mild conditions without being contaminated with larger amounts of the corresponding isoquinoline or the 1,2,3,4-tetrahydroisoquinoline-1-one normally seen in oxidations of tetrahydroisoquinoline⁴⁹ (Scheme 33). 3,4-Dihydroisoquinoline (87) was obtained in 88% yield.

1,4-Dihydropyridines are intermediates in the Hantzsch pyridine synthesis, one of the most useful pyridine ring synthesis, and there is a demand for a general and convenient method for their oxidation to the corresponding pyridines. A variety of oxidizing agents, viz. HNO_3 , PCC, KMnO_4 , CAN, and *tert*-butylhydroperoxide, at elevated temperature have been reported.⁵⁰

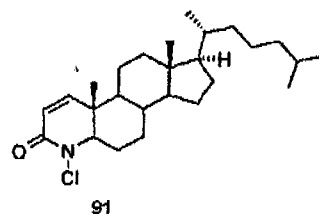
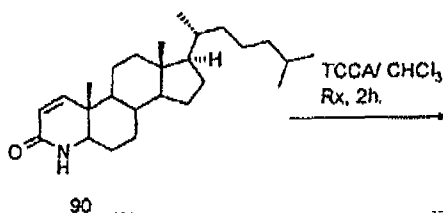
The use of TCCA/TEA was found to be very efficient for the dehydrogenation of 1,4-dihydropyridines.⁵¹ Until now we have studied two cases, 89a and b. In both cases we obtained almost a quantitative yield of the pyridine derivative 89a (92%) and 89b (95%). In the case of 89b no demethylation was observed, a major obstacle reported with other methods (Scheme 34).

C. Miscellaneous. In 1991 Back et al.⁵² reported the synthesis of some novel *N*-chloro- Δ^1 -4-azasteroids by efficient *N*-chlorination with TCCA. The authors compared the reaction time and the amount of reagent necessary for the reaction for TCCA and NCS. For instance for the chlorination of the azasteroid 90 0.5 mol equiv of TCCA was necessary to prepare the *N*-chloro-derivative 91 in 99% yield within 2 h in refluxing chloroform. With NCS 5.2 mol equiv was neces-

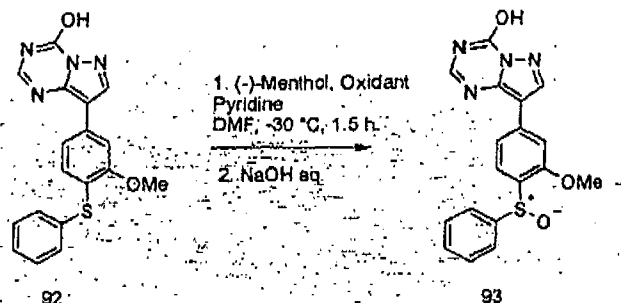
Scheme 34. Aromatization of dihydropyridines



Scheme 35. *N*-Chlorination of azasteroids



Scheme 36. Sulfide oxidation



sary for the conversion, which then took 12 h in refluxing chloroform. The yield of 91 from the reaction with NCS was 85%. Due to the huge excess a tedious chromatographic workup was necessary. The authors found also for other derivatives that TCCA is superior to NCS from the point of view of efficiency and convenience (Scheme 35). Matsugi et al. reported the use of various chlorine- and bromine-containing oxidants together with (-)-menthol for an enantioselective oxidation of sulfides to sulfoxides⁵³ (Scheme 36).

The reaction was studied on the pyrazolotriazine system 92 for the preparation of BOF-4272 (93), a potent xanthine oxidase/xanthine dehydrogenase antagonist. The method was first reported by Oae's group using *tert*-butylhypochlorite as oxidant and pyridine as base.⁵⁴ In the study from Matsugi et al. the influence of the type of oxidant, chiral alcohol, pyridine base, and solvent on the reaction was studied as a starting point. The best oxidant was selected from *tert*-butylhypochlorite, *N*-chlorobenzotriazole, TCCA, *N*-bro-

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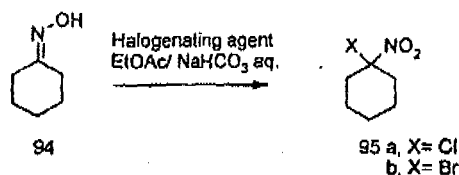
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Scheme 37. Oxidation of oximes



mobenzotriazole and NCS. *N*-bromobenzotriazole and NCS did not give the expected product. The other three gave almost the same yield and ee: *N*-chlorobenzotriazole (yield 87%, 43% ee), TCCA (yield 83%, 39% ee), and *tert*-butylhypochlorite (yield 87%, 38% ee). From these results *N*-chlorobenzotriazole was chosen for further optimization. DMF was found to be the best solvent, and 4-cyanopyridine was used as base. As chiral auxiliary 2-substituted cyclohexanols were effective. From (1*R*,2*S*)-(-)-2-phenylcyclohexanol an ee of 73% was obtained.

Later it was found that the best conditions were to isolate the intermediate menthoxy sulfonium salt from ethyl acetate (> 99% de) which afterwards was separately treated with sodium hydroxide.

In 1991 the use of DCCA, the monosodium salt of TCCA, *N,N*-dibromocyanuric acid and dibromodimethyl-hydantoin were studied for the oxidation of hydroxylamines to gem-halonitro compounds (Scheme 37).⁵⁵

The chloro compound 95a was obtained in 78% yield independently if TCCA or the monosodium salt was used as these are under the reaction conditions convertible. The bromo derivative 95b was obtained in 69% yield, utilizing dibromocyanuric acid.

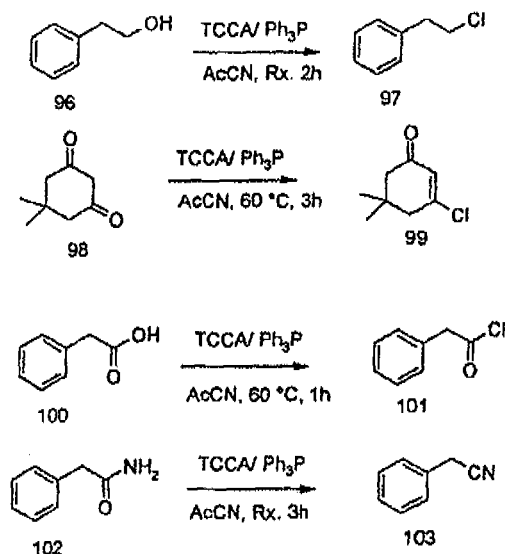
Alkyl chlorides, acid chlorides, and vinyl chlorides can be prepared from alcohols, carboxylic acids, and 1,3-diketones, respectively, by using phosphorus pentachloride, phosphorus trichloride, sulfonyl chloride, or dichlorotriphenylphosphorane ((C₆H₅)₃PCl₂). The same reagents can also convert amides into nitriles.⁵⁶ Hiegels group reported in 1999 that a mixture of TCCA and triphenylphosphine in anhydrous acetonitrile effectively carries out the same kinds of reactions described above⁵⁷ (Scheme 38).

All derivatives were obtained in fairly good yields after chromatographic purification except that the yield for the nitrile 103 was only 39%. 2-Phenylethyl chloride (97) was obtained in 74% yield, the vinyl chloride 99 in 82% yield, and the acid chloride 101 in 95% yield.

The most important advantage of this new method is that the two reagents triphenylphosphine and TCCA are stable until combined in anhydrous acetonitrile which makes the method attractive for large-scale preparations.

Chlorine-substitution reactions with alcohols has also been reported for NCS in combination with dimethyl sulfide.⁵⁸

Scheme 38. Chlorine-substitution reactions



Conclusions

In this literature review we have shown that trichloroisocyanuric acid (TCCA) is a safe and efficient reagent, useful for chlorination and oxidation reactions also on large scale.

Depending on the reaction conditions employed, it is possible to obtain either a selective chlorination (acidic conditions) or an oxidation (alkaline conditions).

For use in reactions all three chlorine atoms are active. In comparison to NCS, the most-used *N*-haloamide, TCCA is more atom economical and is also highly soluble in organic solvents as well as more economical, thus making it the better reagent for large-scale use.

TCCA shows in benzylic chlorinations a remarkable selectivity for the monochlorination of different electron-poor heterocycles. The selectivity for the monochlorination of cyclic ethers is also quite good, affording rather good yields of monochlorinated cyclic ethers when used in combination with a catalytic amount of iodine. The α -chlorination of ethers has also been successfully used for the ring-opening of acetals and thioketals. In combination with water, TCCA is a good reagent for hypohalogenation of alkenes. The monochlorination of ketones affords the more substituted α -chloroketone.

The use of TCCA for the oxidation of secondary alcohols has been shown to be a method to consider. The combination with TEMPO has been shown to be a remarkably good method for the oxidation of primary and secondary alcohols under nonaqueous conditions.

The use of TCCA for the dehydrogenation of various *N*-heterocycles has been shown to be not only selective but also very high-yielding.

Acknowledgment

Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 70th birthday.

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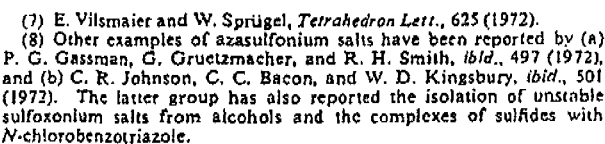
tions undergo elimination to form a carbonyl compound. This process would effectively allow an overall transformation such as: $RR'CHOH + Cl_2 \rightarrow RR'CO + 2HCl$, which is mediated by a sulfide. The operability of this scheme has now been demonstrated. For example, treatment of dimethyl sulfide in carbon tetrachloride at 0° with 1 equiv of chlorine in carbon tetrachloride at 0° results in rapid formation of the partially insoluble complex I, which when cooled to -25° (Dry Ice-carbon tetrachloride bath) and treated with cyclohexylcarbinol for 2 hr at -25° with stirring is converted to the sulfoxonium complex II. Addition of 2 equiv of triethylamine, removal of the cooling bath, and isolation after 5 min affords pure cyclohexylcarboxaldehyde in ca. 80% yield after distillation.

$$\begin{array}{c}
 (\text{CH}_3)_2\text{S} + \text{Cl}_2 \xrightarrow[0^\circ]{\text{CCl}_4} (\text{CH}_3)_2\text{S}^+\text{Cl}^- \text{Cl}^- \xrightarrow[-25^\circ]{\text{C}_6\text{H}_{11}\text{S-CH}_2\text{OH}} \\
 \text{I} \\
 \text{HCl} + \text{C}_6\text{H}_{11}\text{CH}_2\text{OS}(\text{CH}_3)_2 \text{Cl}^- \\
 \text{III} \quad \text{C}_6\text{H}_{11}\text{CH}_2\text{OS}(\text{CH}_3)_2 \text{Cl}^- \xrightarrow{\text{Et}_3\text{N}} \text{C}_6\text{H}_{11}\text{CHO} + (\text{CH}_3)_2\text{S}
 \end{array}$$

The oxidation of cyclohexylcarbinol can be effected even more cleanly and efficiently (93% yield) using the recently reported complex III from dimethyl sulfide and *N*-chlorosuccinimide^{7,8} under carefully controlled conditions. Most of this work has been performed using the complex III, since the use of *N*-chlorosuccinimide for small-scale laboratory work is convenient, since the formation of hydrogen chloride is avoided (in contrast to the use of I), giving a milder and probably more generally useful method, and, finally, since the reaction products are somewhat cleaner.

The simplicity and the key details of the new oxidation process are illustrated by the following procedures for the preparation of a ketone and an aldehyde.

A. 4-*tert*-Butylcyclohexanone. To a stirred solution of 400 mg (3.0 mmol) of *N*-chlorosuccinimide in 10 ml of toluene (analytical grade) was added at 0° 0.3 ml (4.1 mmol) of methyl sulfide under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to -25° (carbon tetrachloride-Dry Ice), and a solution of 312 mg (2.00 mmol) of 4-*tert*-butylcyclohexanol (mixture of *cis* and *trans*) in 2 ml of toluene was added dropwise. The stirring was continued for 2 hr at -25°, and then a solution of 303 mg (3.0 mmol) of triethylamine in 0.5 ml of toluene was added dropwise. The cooling bath was removed and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and twice with 15 ml of water. Removal of dried (magnesium sulfate) solvents produced 310 mg (~100%) of 4-*tert*-butylcyclohexanone as white



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- (5) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 67, 247 (1967).
- (6) See, for example, (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., New York, N. Y., p 48, and also (b) H. Meerwein, K. F. Zenner, and R. Gipp, *Justus Liebig's Ann. Chem.*, 687, 67 (1965). The question of tetravalent or sulfonyl sulfur in these complexes merits further study, but is not crucial to the present application.

plates which melted at 44–47° (an authentic sample from Aldrich Chemical Co. had mp 45–50°). The infrared and nmr spectra were identical with those of an authentic sample, and the nmr spectrum showed that no more than 1% of the methylthiomethyl ether of 4-*tert*-butylcyclohexanol was present. Vapor chromatographic analysis indicated a yield of 97% (xylene as internal standard with a 10% SE-30, 10-ft column).

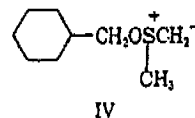
B. Octanal. The complex III (3 mmol) was generated following the procedure described above. To this stirred suspension of III was added a solution of 260 mg (2.0 mmol) of 1-octanol in 1 ml of toluene at –25°. After stirring at –25° for 90 min, a solution of 303 mg (3.0 mmol) of triethylamine in 1 ml of toluene was added. The cold bath was then removed, and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and then twice with 15 ml of water. The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure to 10 ml and analyzed by vapor phase chromatography (10% SE-30, 10-ft column with xylene as the internal standard) (96% yield). Removal of all solvents under reduced pressure produced 250 mg of 1-octanal as a colorless liquid which was spectroscopically identical with an authentic sample.

Using the method detailed above, benzyl alcohol and 2-octanol were converted respectively to benzaldehyde (90% yield) and 2-octanone (91% yield). 1,2-Diphenyl-1,2-propanediol gave 2-hydroxy-1,2-diphenyl-1-propanone in 86% yield indicating that the sulfonium method may be valuable for the avoidance of C–C bond cleavage in the oxidation of *sec,tert*- α -glycols to α -ketols.

An important limit on the scope of the new oxidation process has been observed, however. Benzhydrol and 2-cyclohexenol suffered replacement of hydroxyl by chlorine instead of oxidation using III under the standard conditions. The conversion of alcohols to halides is very efficient for such cases involving alcohols which correspond to stabilized carbocations.^{9,10} Fortunately the oxidation of allylic or benzylic alcohols is readily effected by other mild, highly selective oxidizing agents, including manganese dioxide and various quinones, and consequently there is no pressing need for the sulfonium reagents in such cases.

Still another reaction may occur in more polar media, *viz.* the transformation of the alcohol ROH to the corresponding methylthiomethyl ether ROCH₂SCH₃. Thus, although cyclohexylcarbinol is converted cleanly to the corresponding aldehyde using complex III at –25° in toluene with less than 1% of methylthiomethyl ether formation, the methylthiomethyl ether is formed to the extent of ca. 18% in methylene chloride at –25° and 45% in methylene chloride–dimethyl sulfoxide (1:1) at –25°. It seems likely that the ylide IV is an intermediate¹¹ in the formation of the methylthiomethyl ether

and that its formation and/or further reaction can be avoided in nonpolar media.



The oxidation process which is described herein should be extremely useful for complex or polyfunctional molecules, the reaction conditions being so mild as to minimize the possibility of involvement of most functional or protecting groups. As is clear from the examples cited above the yields of carbonyl compounds are remarkably high and there is little variation in optimal conditions.¹²

We are currently exploring other applications of reagents such as III, for example to carboxyl activation. The use of inexpensive halogen-derived reagents such as I for large scale oxidation is also under study.

Acknowledgment. This research was supported in part by grants from the National Science Foundation and the National Institutes of Health.

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E. J. Corey,* C. U. Kim

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received August 1, 1972

Photosensitized Aqueous Oxidation of the Hexacyanochromate(III) Ion. Evidence against the Doublet Mechanism

Sir:

Two principal mechanisms have been proposed in order to account for the photochemistry of Cr(III) complexes.¹ The first mechanism² assumes that the lowest spin-forbidden excited state (³E_g, Figure 1) is that one responsible for the photoreactivity, whereas the alternative mechanism³ involves the lowest quartet excited states (⁴T_{2g} and ⁴T_{1g}, Figure 1) as direct precursors to the photochemical reactions. Neither direct photolysis⁴ nor sensitization experiments⁴⁻⁶ has as yet given a definitive answer to the above alternative, whereas quenching experiments carried out on Cr(NH₃)₂(NCS)₄⁻ have clearly shown that its photoaquation originates, at least in part, from the lowest quartet excited state.⁷ These latter experiments as well as some studies^{7,8} on the temperature dependence of the phosphorescent lifetime for some

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(3) A. W. Adamson, *ibid.*, **71**, 798 (1967).

(4) A. W. Adamson, J. E. Martin, and F. D. Carnassey, *J. Amer. Chem. Soc.*, **91**, 7530 (1969); J. E. Martin and A. W. Adamson, *Theor. Chim. Acta*, **20**, 119 (1971).

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US005869669A

D3

United States Patent [19]**Huang et al.**[11] **Patent Number:** **5,869,669**[45] **Date of Patent:** **Feb. 9, 1999**[54] **PREPARATION OF 14-HYDROXYNORMORPHINONES FROM NORMORPHINONE DIENOL ACYLATES**[75] Inventors: **Bao-Shan Huang; Yansong Lu**, both of Edison, N.J.; **Ben-Yi Ji**, Brooklyn; **Aris P. Christodoulou**, New York, both of N.Y.[73] Assignee: **Penick Corporation**, Newark, N.J.[21] Appl. No.: **893,464**[22] Filed: **Jul. 11, 1997****Related U.S. Application Data**

[60] Provisional application No. 60/022,685 Jul. 26, 1996 and provisional application No. 60/045,081 Apr. 29, 1997.

[51] Int. Cl. ⁶ **C07D 489/08**[52] U.S. Cl. **546/45**[58] Field of Search **546/45**[56] **References Cited****U.S. PATENT DOCUMENTS**

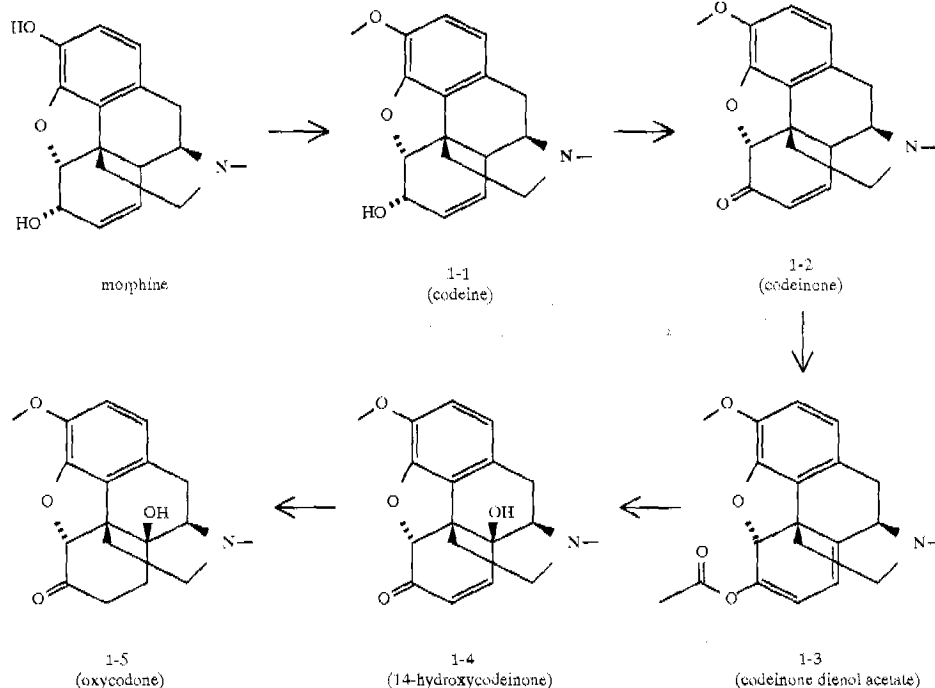
4,668,685	5/1987	Shami	514/279
4,795,813	1/1989	Schwartz	546/45
5,112,975	5/1992	Wallace	546/45

Primary Examiner—Alan L. Rotman*Assistant Examiner*—Charanjit S. Aulakh*Attorney, Agent, or Firm*—Burgess, Ryan & Wayne[57] **ABSTRACT**

The invention provides processes for the conversion of normorphinone and its derivatives, which can be synthesized from morphine, to the corresponding 14-hydroxynormorphinone and its derivatives including oxycodone, oxymorphone, noroxymorphone and naltrexone. Noroxymorphone is a key intermediate for the production of important narcotic analgesics and antagonists. The invention also provides certain novel intermediates.

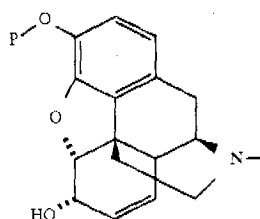
4 Claims, No Drawings

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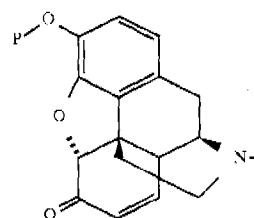
For the synthesis of oxymorphone from morphine in the present invention,

- (a) the first step is to protect the phenolic hydroxy on the 3-position of morphine to form the 3(O)-protected-morphine having the formula:



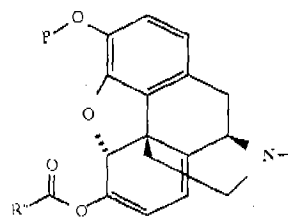
wherein $P=P_1$ or R_2 . P is a suitable protecting group which is stable under the reaction conditions and easily removable by mild hydrolysis with an acid or base (for P_1) or under catalytic hydrogenation (for P_2). P_1 includes acyl, benzoyl and alkoxycarbonyl. P_2 includes benzyl, substituted benzyl and benzyloxycarbonyl.

- (b) the second step is to oxidize the 3(O)-protected-morphine to 3(O)-protected-morphinone having the formula:



by any of the prior art methods such as Swern oxidation (DMSO/acid halide or acid unhydrite).

- (c) the third step is to convert the 3(O)-protected-morphinone to the 14-hydroxy-3-(O)-protected-morphinone using the techniques disclosed in this invention as set forth in the conversion of codeinone to 14-hydroxycodeinone in the synthesis of oxycodone. The intermediate, 3(O)-protected-codeinone dienol acylate, is a novel compound having the formula:



wherein P and R are as defined above; preferably P_1 is acetyl and P_2 is benzyl.

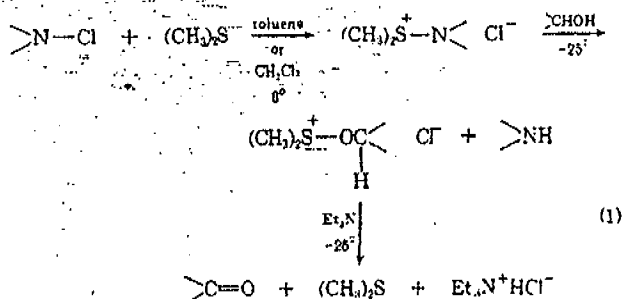
- (d) depending on the particular protection group, P_1 or P_2 , the fourth step is either (i) to first produce the 7,8-double bond of 3-(O)- P_1 -protected morphinone and then to remove the protection group by acid or base

(18) See, e.g., G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955); M. H. Mok and J. C. Polanyi, *J. Chem. Phys.*, **51**, 1451 (1969); and C. A. Parr and D. G. Truhlar, *J. Phys. Chem.*, **75**, 1844 (1971).

*Chemical Dynamics Laboratory, Department of Chemistry
University of Minnesota, Minneapolis, Minnesota 55455*

A New and Highly Effective Method for the Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

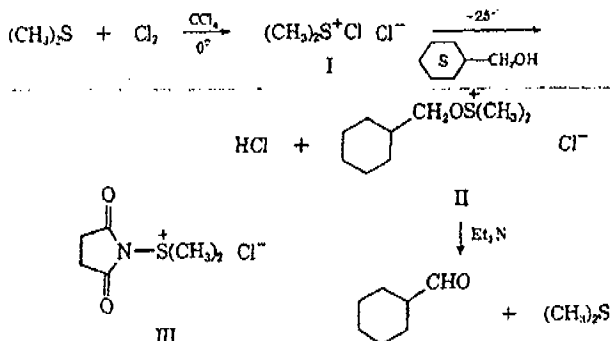
We report here a new process for the oxidation of alcohols to ketones or aldehydes which is operationally simple, highly selective, and efficient. It is expected that the method will find widespread use and that in many instances it will be found superior to currently important procedures such as those using the reagents CrO_3 -pyridine complex,¹ CrO_2 -acetone,² and dimethyl sulfoxide with various coreactants.³⁻⁵ An overall representation of the new method, which is clearly related to the dimethyl sulfoxide based processes, is given in sequence 1.



(1) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

- (2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemlin, *ibid.*, 2555 (1953).
- (3) K. E. Pfizner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 87, 5661 (1965); 88, 1762 (1966).
- (4) J. R. Parikh and W. von E. Doering, *ibid.*, 89, 5505 (1967).
- (5) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 67, 247 (1967).
- (6) See, for example, (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., New York, N. Y., p. 48, and also (b) H. Meerwein, K.-F. Zenner, and R. Gipp, *Justus Liebig's Ann. Chem.*, 687, 67 (1965). The question of tetravalent or sulfoxonium sulfur in these complexes merits further study, but is not crucial to the present application.

tions undergo elimination to form a carbonyl compound. This process would effectively allow an overall transformation such as: $RR'CHOH + Cl_2 \rightarrow RR'CO + 2HCl$, which is mediated by a sulfide. The operability of this scheme has now been demonstrated. For example, treatment of dimethyl sulfide in carbon tetrachloride at 0° with 1 equiv of chlorine in carbon tetrachloride at 0° results in rapid formation of the partially insoluble complex I, which when cooled to -25° (Dry Ice-carbon tetrachloride bath) and treated with cyclohexylcarbinol for 2 hr at -25° with stirring is converted to the sulfoxonium complex II. Addition of 2 equiv of triethylamine, removal of the cooling bath, and isolation after 5 min affords pure cyclohexylcarboxaldehyde in ca. 80% yield after distillation.



The oxidation of cyclohexylcarbinol can be effected even more cleanly and efficiently (93% yield) using the recently reported complex III from dimethyl sulfide and *N*-chlorosuccinimide^{7,8} under carefully controlled conditions. Most of this work has been performed using the complex III, since the use of *N*-chlorosuccinimide for small-scale laboratory work is convenient, since the formation of hydrogen chloride is avoided (in contrast to the use of I), giving a milder and probably more generally useful method, and, finally, since the reaction products are somewhat cleaner.

The simplicity and the key details of the new oxidation process are illustrated by the following procedures for the preparation of a ketone and an aldehyde.

A. **4-*tert*-Butylcyclohexanone.** To a stirred solution of 400 mg (3.0 mmol) of *N*-chlorosuccinimide in 10 ml of toluene (analytical grade) was added at 0° 0.3 ml (4.1 mmol) of methyl sulfide under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to -25° (carbon tetrachloride-Dry Ice), and a solution of 312 mg (2.00 mmol) of 4-*tert*-butylcyclohexanol (mixture of *cis* and *trans*) in 2 ml of toluene was added dropwise. The stirring was continued for 2 hr at -25°, and then a solution of 303 mg (3.0 mmol) of triethylamine in 0.5 ml of toluene was added dropwise. The cooling bath was removed and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and twice with 15 ml of water. Removal of dried (magnesium sulfate) solvents produced 310 mg (~100%) of 4-*tert*-butylcyclohexanone as white

- (8) Other examples of azasulfonium salts have been reported by (a) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *ibid.*, 497 (1972), and (b) C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *ibid.*, 501 (1972). The latter group has also reported the isolation of unstable sulfoxonium salts from alcohols and the complexes of sulfides with *N*-chlorobenzotriazole.

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plates which melted at 44–47° (an authentic sample from Aldrich Chemical Co. had mp 45–50°). The infrared and nmr spectra were identical with those of an authentic sample, and the nmr spectrum showed that no more than 1% of the methylthiomethyl ether of 4-*tert*-butylcyclohexanol was present. Vapor chromatographic analysis indicated a yield of 97% (xylene as internal standard with a 10% SE-30, 10-ft column).

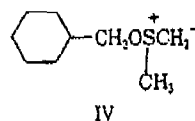
B. Octanal. The complex III (3 mmol) was generated following the procedure described above. To this stirred suspension of III was added a solution of 260 mg (2.0 mmol) of 1-octanol in 1 ml of toluene at –25°. After stirring at –25° for 90 min, a solution of 303 mg (3.0 mmol) of triethylamine in 1 ml of toluene was added. The cold bath was then removed, and after 5 min, 20 ml of ether was added. The organic layer was washed with 5 ml of 1% aqueous hydrochloric acid and then twice with 15 ml of water. The organic layer was dried (magnesium sulfate) and concentrated under reduced pressure to 10 ml and analyzed by vapor phase chromatography (10% SE-30, 10-ft column with xylene as the internal standard) (96% yield). Removal of all solvents under reduced pressure produced 250 mg of 1-octanal as a colorless liquid which was spectroscopically identical with an authentic sample.

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Received August 1, 1972

Photosensitized Aquation of the Hexacyanochromate(III) Ion. Evidence against the Doublet Mechanism

Sir:

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
LUIS FELIPE CASTILLO GIBSON
Apoderado

ASUNTO

Radicación	06-088020
Trámite	002
Evento	001
Actuación	430
Oficio	
Folios	12

10453

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/US2005/003390
Fecha de Presentación Internal. 04/02/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 7, 23 a 57 como se radicó inicialmente

Reivindicaciones: Folios 8 a 22 modificadas
Folios 58 a 72 modificadas
Folio 79 modificadas
Folios 112 a 123 modificadas

Prioridad: Folios: 01
06/02/2004, US, 60/542,711

Respuesta del solicitante: Folios: 108 a 111

2. Modificaciones

El solicitante modificó las reivindicaciones en fase nacional y no anexó el capítulo reivindicatorio tal como fue presentado en fase internacional.

3. Objeto de la Invención

Título de la invención: Métodos para elaborar morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos.

Problema Técnico Planteado: obtener métodos de preparación de morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos, sin la formación de productos que causen mal olor.

Solución: métodos de preparación de morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos, sin el empleo de oxidantes que causen mal olor

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192

durante la reacción.

IPC: C07D 489/02

4. De la solicitud de Patente

Descripción (artículo 28 D. 486)

Los Folios 27, 30 de la solicitud presentada se encuentran incompletos en el texto (ver parte inferior)

No se encuentra la suficiente información soportada para que un experto medio en la materia pueda desarrollar todas las reivindicaciones objeto de invención.

Reivindicaciones (artículo 30 D 486)

La reivindicación 1 se refiere a una composición, mientras que el objeto de la solicitud presentada es un método de preparación; por lo tanto se sugiere al solicitante reorganizar el capítulo reivindicatorio con sus respectivas dependencias de la reivindicación 1 y referido al método de preparación en forma clara y concisa, puesto que la composición se refiere a una mezcla de reactivos dentro de una etapa de síntesis química, sin evidenciarse que sea un producto obtenido. Las composiciones, como tal, no se encuentran sustentadas en la descripción.

No se evidencia en el capítulo reivindicatorio el empleo de un alcohol primario, para la producción de un aldehído.

Se sugiere al solicitante restringir de una manera razonable las reivindicaciones de acuerdo a lo sustentado en la descripción como es la síntesis del compuesto O-protegido y el acetato de dienol codeinona.

Las reivindicaciones referidas a un método para elaborar una cetona (Reivindicación 9) y un método para elaborar un aldehído (Reivindicación 13), se encuentran de forma general y amplia y no define la cetona o aldehído empleada.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: 06 de febrero de 2004

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 06/02/2004 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D3	US 5,869,669	Preparation of 14-hydroxynormorphinones from normorphinone dienol acylates	09/02/1999
D4	Journal of American Society, 94:21, 1972	A new and highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds	18/10/1972

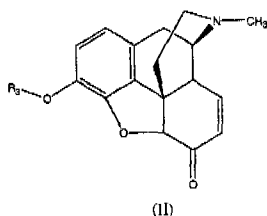
6. Análisis de Patentabilidad (Art 14 D486)

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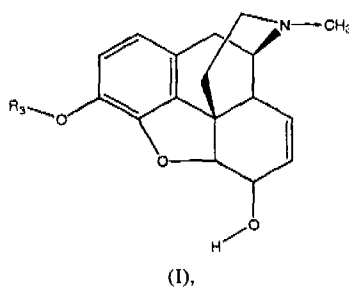
Nivel Inventivo (Art18 D486)

- La reivindicación 14 consiste en:

Un método para preparar un compuesto de la fórmula (II):

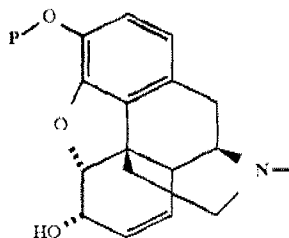


caracterizado porque comprende permitir que un compuesto de fórmula (I) reaccione en presencia de un compuesto de fórmula R_1SR_2 , y un reactivo que contiene cloro bajo condiciones suficientes para preparar el compuesto de la fórmula (II); en donde, R_1 y R_2 son cada uno independientemente $-(C_1-C_{20})$ alquil, $-(C_3-C_8)$ cicloalquil o $-$ fenilo y R_3 es un grupo protector.



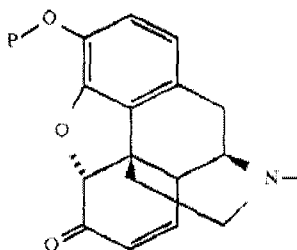
El Estado de la Técnica más cercano es **D3**, que enseña la preparación de 14-hidroxinormorfinonas de normorfinonas dienol acilatos (Ver resumen) y donde para la síntesis de oximorfona de morfina, realiza los siguientes pasos:

- a) Proteger el hidroxil fenólico en la posición 3-(O)-protegida de la morfina en el compuesto de fórmula I:



Donde $P=P_1$ o P_2 o R_2 . P es un grupo protector.

- b) Oxidar la morfina 3-(O)-protegida a 3-(O)-morfinona protegida con la siguiente fórmula, por cualquiera de cualquiera de los métodos como la oxidación de Swern (DMSO/haluro ácido o anhídrido ácido)



El método de preparación objeto de esta solicitud se diferencia del método de **D3**, en que se emplea una mezcla de un compuesto tioéter en presencia de un ácido triclorocianúrico y una base.

El hecho de incluir un compuesto tioéter en presencia de un ácido triclorocianúrico y una base, causa que durante el proceso de preparación de morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos, no se produzcan malos olores.

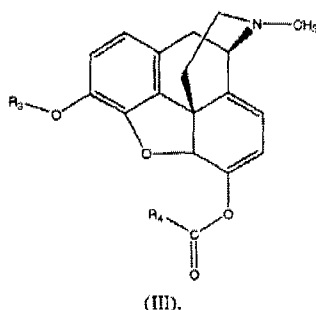
El Problema Técnico Objetivo era obtener métodos de preparación de morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos, sin la formación de productos que causen mal olor.

D4 describe una manera de solucionar el problema técnico, pues enseña la oxidación de alcoholes primarios o secundarios mediante el tratamiento de dimetilsulfuro en tetracloruro de carbono, cuya oxidación del ciclohexilcarbinol es del 93%.

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de "obtener métodos de preparación de morfinonas 3-O protegidas y carboxilatos dienol morfinona 3-O protegidos, sin la formación de productos que causen mal olor", incluiría "una mezcla oxidante de compuestos análogos al dimetilsulfuro en presencia de cloro", logrando de esta forma el método de preparación objeto de esta solicitud. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2 - 43, no mencionan alguna característica que haga inventiva a la composición de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

- La reivindicación 25 consiste en:

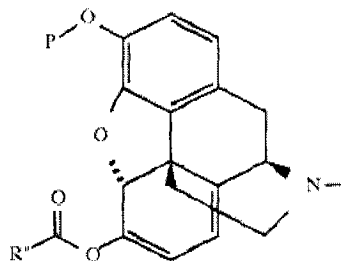
Un método para hacer un compuesto de la fórmula (III):



En la parte b) se refiere a: Permitir que el compuesto de la fórmula (II) reacciones con una primera base y agente de acilación de la fórmula $R_4(C(O)OC(O)R_4$ o $R_4C(O)X$ bajo condiciones suficientes para hacer el compuesto de la fórmula (III), en donde:

Cada uno de R¹ y R² es independientemente alquilo (C₁-C₂₀), cicloalquilo (C₃-C₈) o -fenilo, R³ es un grupo protector, R⁴ es alquilo (C₁-C₁₀), y X es -Cl, Br o I.

El Estado de la Técnica más cercano es **D3**, que enseña la preparación de 14-hidroxinormorfinonas de normorfinonas diénol acilatos (Ver resumen) y donde enseña el intermediario de codeinona 3-O protegida diénol acilato de fórmula y cuya preparación se encuentra referida en el ejemplo 2 (Ver columnas 9, 10, 11 y 12, columna 23, línea 10):



El método de preparación objeto de esta solicitud se diferencia del método de **D3**, en que no incluye la preparación del compuesto de fórmula I y II, en la reivindicación 25.

Esta diferencia no le concede un efecto técnico superior a dicha reivindicación, pues el experto en la materia derivaría de forma obvia del estado de la técnica la parte b) de la reivindicación 25. Por lo tanto carece de nivel inventivo.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D3	US 5,869,669	1-43	Nivel Inventivo
D4	Journal of American Society, 94:21, 1972	1-43	Nivel Inventivo

9. Respuesta a los argumentos del solicitante:

El solicitante se refiere en el Folio 108: "la composición de la reivindicación 1 es para usarse en la provisión de un aldehído o una cetona. De este modo, la persona versada puede comprender fácilmente el concepto de la reivindicación 1 independiente"

En cuanto a lo anterior claramente el solicitante está presentando la composición en mezcla para ser usada en un proceso de síntesis, lo cual no representa la elaboración de un producto final. Las composiciones no se encuentran sustentadas como tal en el capítulo descriptivo, el simple hecho de nombrarlas no evidencia su sustento o su aplicación industrial como producto terminado. Por lo tanto, las reivindicaciones de composición no son aceptadas.

El solicitante en el Folio 109, desarrolla las reivindicaciones y sus dependencias, sin embargo se sugiere realizar la correspondiente restricción de acuerdo a la materia sustentada en la descripción de forma tal que posea unidad de invención. Se sugiere nuevamente revisar la descripción y sus folios, en cuanto a los textos faltantes.

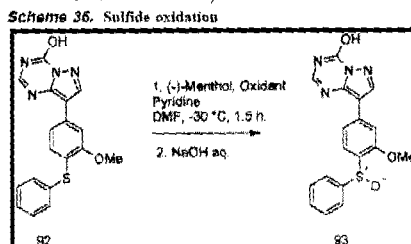
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El solicitante en el Folio 109 argumenta: "El Examinador objeta el grupo protector R³"

El solicitante restringió y definió a lo largo del capítulo reivindicatorio los grupos protector que se pueden emplear en el método de preparación, encontrándose superada esta objeción.

El solicitante en el Folio 110 afirma y lo reitera en el Folio 111: "En la técnica se conoce que una combinación de ácido tricloroisocianúrico y sulfuros resulta en sulfóxidos y no en la oxidación de alcoholes"

Una vez revisadas las páginas 392 y 393 del documento adjunto por el solicitante, se encuentra que la producción de sulfóxidos se presenta sobre la estructura del compuesto a oxidar que contiene azufre (Ver esquema 36), y la codeína no presenta azufre en su molécula. Por lo tanto esta reacción no corresponde con la de solicitud, la cual es la oxidación partir de alcoholes.



El solicitante se refiere en el Folio 110: "En la página 7587, Corey/Kim reportan que el método que usa sulfuros y NCS no es adecuado para la oxidación de alcoholes correspondiente a una carbocación (sic) estabilizada (como es el caso en el opioide de fórmula (I))

El argumento del solicitante, no es aceptado puesto que este documento se refiere a carbocationes estabilizados, donde la oxidación es más eficiente. Esto se evidencia con la estructura química de la codeína estabilizada como carbocatión con el grupo protector, donde se esperaría con éxito su oxidación eficiente.

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 sesenta 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 N° 10 de 2001.

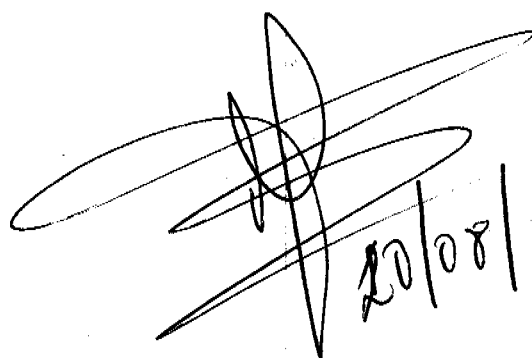
ALIX CARMENZA CÉSPEDES DE VERGEL
Dirección de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

28 AGO 2010

CONCEPTO TÉCNICO No. 02437

EXAMINADOR TÉCNICO
Código No. 202070


20/08/0