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Calle 94 A No.7ª-09  
Bogotá-Colombia

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-078811- -00008-0000

Fecha: 2009-04-24 14:18:54 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 444 RESPUESTAREQUE Folios: 11

Señora

**Jefe de la División de Nuevas Creaciones**

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 05.078.811

Solicitud del examen de patentabilidad para: "PROCEDIMIENTO PARA  
PREPARAR DERIVADOS DE AMINOCETALES SUSTITUIDOS CON  
PIRIDINA"

Solicitante: SANOFI AVENTIS DEUTSCHLAND GMBH

### **RESPUESTA AL EXAMEN DE BUSQUEDA DE ANTERIORIDADES**

**LUIS PATIÑO LEYVA**, mayor de edad, identificado y domiciliado como aparece al  
pie de mi firma, en atención a su oficio No. 1116 notificado el 30 de enero de 2009,  
atentamente me permito presentar los documentos abajo relacionados, que fueron  
solicitados por su Despacho bajo el artículo 46 de la Decisión 486.

• DATABASE CASREACT 'Online!

CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;

LAMATTIMA, JHON L. ET AL: "Alpha.-Amino acetals 2,2-Diethoxy-2-(4-  
pyridyl)ethylamine"

XP002289290

Retrieved from STN

Databese accession no. 106:138221

Abstracts an reactions

& ORGANIC SYNTHESSES, 64, 16-26 CODEN:

ORSYAT; ISSN: 0078-6209, 1986

130  
134

- DATABASE CASREACT 'Online!  
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;  
SHARGHI, HASHEM ET AL: "Selective synthesis of E and Z isomers of oximes"  
XP002289291  
Retrieved from STN  
Database accession no. 134:280369  
Abstract an reactions  
& SYNLETT, (1), 99-101 CODEN:  
SYNLES; ISSN: 0936-5214, 2001,

- CHUNG, JHON Y. L. ET AL: "Practical chemoenzimatic synthesis of a 3-pyridylethanolamino .beta.3 adrenergic receptor agonist"  
TETRAHEDRON LETTERS, Vol. 40, no.37, 1999, pages 6739-6743,  
XP002289288  
scheme 1: steps a1, a2 and b

Cumplido así con lo dispuesto, atentamente solicito a Ud. se continúe con el trámite correspondiente a esta solicitud de Patente de Invención.

De la Señora Jefe,



**Luis Patiño Leyva**

C.C. No. 2.930.616 de Bogotá  
T.P.A. No.2698 del C. Sup. de la Judicatura  
Calle 94 A No. 7A-09 Bogotá D.C.  
Teléfonos: 6107420

Bogotá, D.C.

PATENTES/P20064/MEMORIAL ART 46

XP-002289290

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2-4 4

131  
135

(C) FILE CASREACT

STN CA Caesar accession number : 1014

AN - 106:138221 CASREACT

TI - .alpha.-Amino acetals. 2,2-Diethoxy-2-(4-pyridyl)ethylamine

AU - LaMattina, John L.; Suleske, R. T.

CS - USA

SO - Organic Syntheses (1986), 64, 19-26

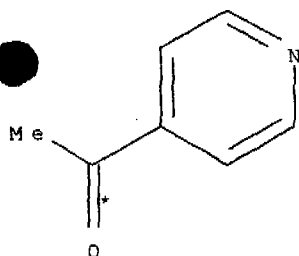
CODEN: ORSYAT; ISSN: 0078-6209

DT - Journal

LA - English

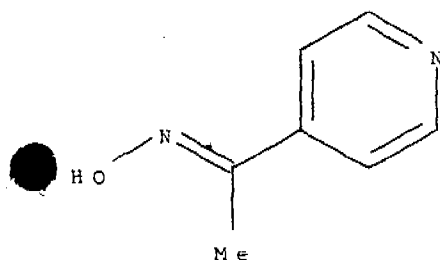
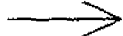
AB - Oximation of RAc (R = 2-, 3-, 4-pyridyl, p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, p-BrC<sub>6</sub>H<sub>4</sub>) gave RC(:NOH)Me, which was tosylated, treated with EtOK, and then with HCl-EtOH to give 53-92% RC(OEt)2CH<sub>2</sub>NH<sub>2</sub>.

RX(1) OF 11 2 \*\*\*A\*\*\* ==> \*\*\*B\*\*\* + C...

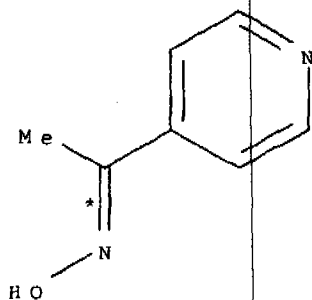


2 A

(1)



B

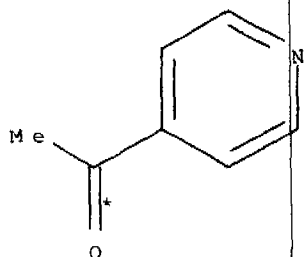


C

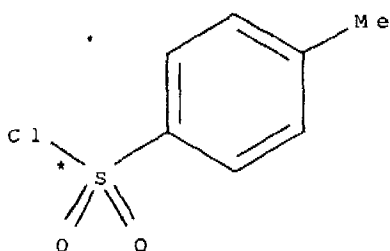
RX(1) RCT A \*\*\*1122-54-9\*\*\*  
 RGT D 1310-73-2 NaOH, E 5470-11-1 H2NOH-HCl  
 PRO B \*\*\*107445-21-6\*\*\* , C 1194-99-6  
 SOL 7732-18-5 Water

RX(9) OF 11 COMPOSED OF RX(1), RX(2)

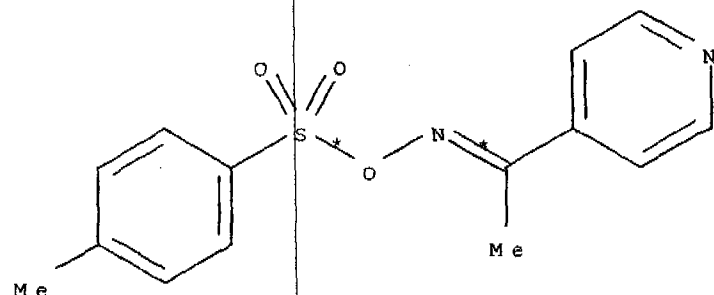
RX(9) 2 \*\*\*A\*\*\* + G ==> \*\*\*H\*\*\*



2 A



G



H  
 YIELD 95%

2  
 STEPS  
 →

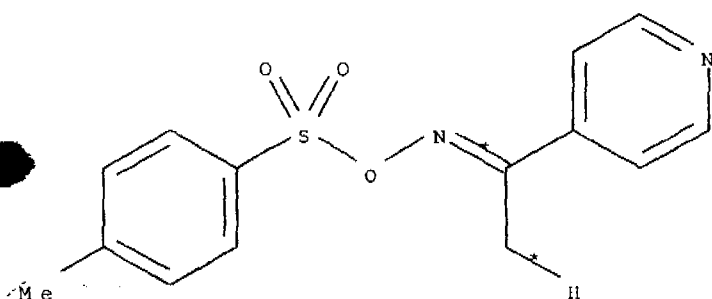
RX(1) RCT A \*\*\*1122-54-9\*\*\*  
 RGT D 1310-73-2 NaOH, E 5470-11-1 H2NOH-HCl  
 PRO B 107445-21-6, C 1194-99-6

✓  
132  
136

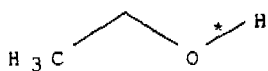
SOL 7732-18-5 Water

RX(2) RCT B 107445-21-6, G 98-59-9  
PRO H \*\*\*107445-22-7\*\*\*  
SOL 110-86-1 Pyridine

RX(3) OF 11 ... \*\*\*H\*\*\* + 2 J ==> \*\*\*K\*\*\*

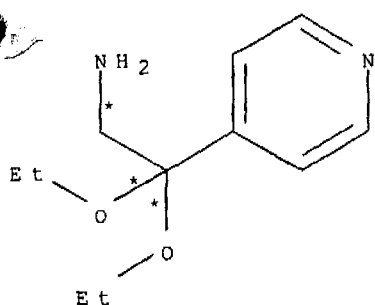
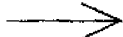


H



2 J

(3)



K

YIELD 74%

RX(3) RCT H \*\*\*107445-22-7\*\*\* , J 64-17-5

STAGE(1)

RGT L 7440-09-7 K

SOL 64-17-5 EtOH

STAGE(2)

RGT M 7647-01-0 HCl

SOL 64-17-5 EtOH, 60-29-7 Et2O

PRO . K \*\*\*74209-44-2\*\*\*

XP-002289291

|               |   |
|---------------|---|
| P.D. DO-DO-DO | 2 |
| P. 1-2        |   |

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D4  
133  
132

(C) FILE CASREACT

STN CA Caesar accession number : 1002

AN - 134:280369 CASREACT

TI - Selective synthesis of E and Z isomers of oximes

AU - Sharghi, Hashem; Sarvari, Mona Hosseini

CS - Department of Chemistry, College of Science, Shiraz University,  
Shiraz, 71454, Iran

SO - Synlett (2001), (1), 99-101

CODEN: SYNLES; ISSN: 0936-5214

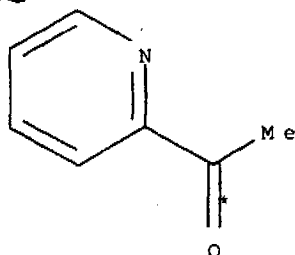
PB - Georg Thieme Verlag

DT - Journal

LA - English

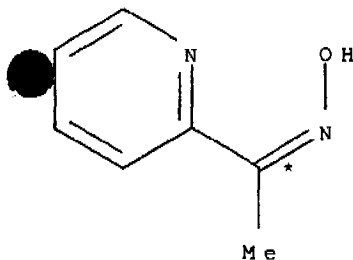
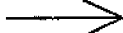
AB - The highly stereoselective conversion of aldehydes and ketones to their corresponding E- and Z-oximes with  $\text{NH}_2\text{OH} \cdot \text{HCl}$  is catalyzed by  $\text{CuSO}_4$  and  $\text{K}_2\text{CO}_3$ , resp. This method occurs under mild reaction conditions with high yields.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



AS

(27)

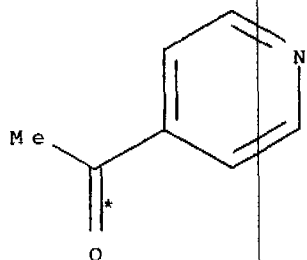


AT

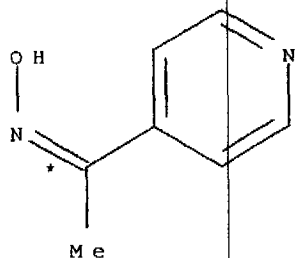
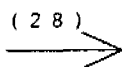
YIELD 90%

RX(27) RCT AS \*\*\*1122-62-9\*\*\*  
RGT C 5470-11-1  $\text{H}_2\text{NOH} \cdot \text{HCl}$   
PRO AT \*\*\*81563-77-1\*\*\*  
CAT 584-08-7  $\text{K}_2\text{CO}_3$

NTE stereoselective; solid state



A U



A V

YIELD 85%

RX(28)    RCT   AU   \*\*\*1122-54-9\*\*\*  
         RGT   C 5470-11-1 H2NOH-HCl  
         PRO   AV   \*\*\*107492-79-5\*\*\*  
         CAT   584-08-7 K2CO3  
         NTE   stereoselective; solid state

Selective Synthesis of *E* and *Z* Isomers of Oximes

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Received 14 September 2000

**Abstract:** The highly stereoselective conversion of aldehydes and ketones to their corresponding oximes with hydroxylamine hydrochloride are catalyzed by  $\text{CuSO}_4$  and  $\text{K}_2\text{CO}_3$ . This method occurs under mild reaction conditions with high yields.

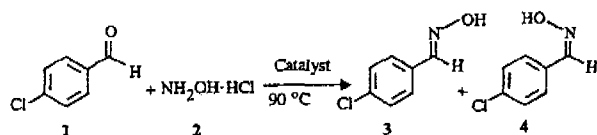
**Key words:** *E* and *Z* Isomers, oxime, hydroxylamine hydrochloride,  $\text{CuSO}_4$ ,  $\text{K}_2\text{CO}_3$

The addition of hydroxylamine hydrochloride to carbonyls to yield oximes is not only one of the best understood examples of a nonenzymatic addition-elimination reaction<sup>1</sup> but also an important reaction in organic synthesis.<sup>2</sup> Except in the case of symmetrical ketones, both isomeric oximes (*Z* and *E*) are usually produced which have different physical properties and biological activities<sup>3</sup> and should be separated by chromatography or recrystallization techniques.

Very few methods are available for the synthesis of *E* and *Z* isomer of oximes.<sup>4,5</sup> In many cases, *E* isomers were obtained from the *Z* forms by either the hydrochloride method<sup>6</sup> or purified by column chromatography.<sup>7</sup> The reagents which have been used for oximation of aldehydes<sup>8,9</sup> and ketones, also catalyze the interconversion of *Z* and *E* isomers. The rate of equilibration of a mixture of *Z* and *E* isomers and the position of the equilibrium is temperature dependent,<sup>8</sup> therefore, temperature control of the experiment is critical.

Having the above facts in mind, we wish to report a convenient method for controlling the stereochemistry of the reaction of hydroxylamine hydrochloride with aldehydes or ketones in solid state.

In order to find a simple and suitable catalyst for controlling the stereochemistry of oximes, the reaction of 4-chlorobenzaldehyde (1) with hydroxylamine hydrochloride (2) was chosen as a model and its behavior was studied under a variety of conditions via TLC and <sup>1</sup>H NMR spectroscopy (Scheme 1, Table 1).



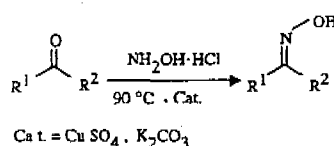
Scheme 1

Table 1 Reaction of (1) with (2) in the presence of different catalysts.

| Entry | Catalyst                 | Time (min) | Ratio of product <sup>a</sup> (3) : (4) | Yields based on NMR & TLC(%) |
|-------|--------------------------|------------|-----------------------------------------|------------------------------|
| 1     | $\text{SiO}_2$           | 30         | 1 : 1                                   | 100                          |
| 2     | $\text{MgO}$             | 30         | 1 : 4                                   | 100                          |
| 3     | $\text{Al}_2\text{O}_3$  | 30         | 1 : 2                                   | 100                          |
| 4     | $\text{CaO}^{18}$        | 5          | 1 : 4                                   | 100                          |
| 5     | $\text{CuCO}_3$          | 30         | 1 : 4                                   | 100                          |
| 6     | $\text{Na}_2\text{SO}_4$ | 30         | 1 : 4                                   | 100                          |
| 7     | $\text{K}_2\text{CO}_3$  | 60         | 0 : 1                                   | 100                          |
| 8     | $\text{CuSO}_4$          | 60         | 1 : 0                                   | 100                          |

a) Ratio of products was determined by <sup>1</sup>H NMR.

As shown in Table 1 (Entries 1-6), a mixture of *Z* and *E* isomer of 4-chlorobenzaldoxime was obtained by the use of various types of catalysts. In the comparison, the reaction proceeded rapidly to give exclusively the corresponding *Z/E* isomer of 4-chlorobenzaldoxime (3,4) in excellent yields when  $\text{K}_2\text{CO}_3$  /  $\text{CuSO}_4$  were employed (Table 1, Entries 7,8). Similarly, as shown in Scheme 2 and in Tables 2 and 3, the reactions of hydroxylamine hydrochloride with different aldehydes and ketones, including those with electron-withdrawing and donating substituents in the presence of these new catalysts, gave oximes in high yields and stereoselectivity.



Scheme 2

As shown in Table 2, various types of aromatic aldehydes with electron donating and withdrawing groups were cleanly and rapidly condensed with hydroxylamine hydrochloride at 90 °C, giving the corresponding *E*-isomer of oximes (OH *anti* to aryl) in excellent yields in the presence of  $\text{CuSO}_4$  (Entries 1-12). However, aromatic ketones such as benzophenone and others did not afford the corresponding oximes under these conditions. In order to show the chemoselectivity of the presented reagent toward the condensation of different carbonyl groups, a mixture of benzophenone and benzaldehyde was treated with hydroxylamine hydrochloride in the presence of  $\text{CuSO}_4$  at



Table 2 Conversion of aldehydes and ketones to *E*-isomer oximes using CuSO<sub>4</sub>.

| Entry | R <sup>1</sup>                                          | R <sup>2</sup> | Time (min.) | Mp.(lit.)                                | <sup>1</sup> H Chemical shifts of H <sub>A</sub> | Yields (%) <sup>a</sup> |
|-------|---------------------------------------------------------|----------------|-------------|------------------------------------------|--------------------------------------------------|-------------------------|
| 1     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>               | H              | 60          | 110 (110 <sup>9,12</sup> )               | 7.97                                             | 80                      |
| 2     | <i>p</i> -HOC <sub>6</sub> H <sub>4</sub>               | H              | 30          | 112 (112 <sup>13</sup> )                 | 7.81                                             | 70                      |
| 3     | <i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | H              | 30          | 120 (131 <sup>12</sup> )                 | 7.48                                             | 90                      |
| 4     | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>               | H              | 30          | 110 (110 <sup>10</sup> )                 | 7.27                                             | 90                      |
| 5     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>              | H              | 30          | 63-64 (65 <sup>9,12</sup> )              | 6.97                                             | 70                      |
| 6     | <i>m</i> -ClC <sub>6</sub> H <sub>4</sub>               | H              | 30          | 80 (71-72 <sup>12</sup> )                | 7.75                                             | 95                      |
| 7     | <i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | H              | 15          | 120 (124 <sup>12</sup> )                 | 7.64                                             | 95                      |
| 8     | <i>m</i> -MeC <sub>6</sub> H <sub>4</sub>               | H              | 30          | 58 (60 <sup>12</sup> )                   | 7.41                                             | 90                      |
| 9     | <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>              | H              | 30          | 40 (40 <sup>12</sup> )                   | 7.19                                             | 90                      |
| 10    | <i>m</i> -HOC <sub>6</sub> H <sub>4</sub>               | H              | 30          | 70 (88 <sup>10</sup> )                   | 7.12                                             | 70                      |
| 11    | Ph                                                      | H              | 60          | 32 (30 <sup>9</sup> , 35 <sup>12</sup> ) | 7.40                                             | 90                      |
| 12    |                                                         | H              | 120         | 110 (113 <sup>10</sup> )                 | 7.32                                             | 85                      |
| 13    | Ph                                                      | Me             | 360         |                                          |                                                  | no reaction             |
| 14    |                                                         | Me             | 360         |                                          |                                                  | no reaction             |
| 15    |                                                         | Me             | 360         |                                          |                                                  | no reaction             |
| 16    | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>               | Ph             | 360         |                                          |                                                  | no reaction             |

a) <sup>1</sup>H NMR yields.Table 3 Conversion of aldehydes and ketones to *Z*-isomer oximes using K<sub>2</sub>CO<sub>3</sub>.

| Entry | R <sup>1</sup> | R <sup>2</sup>                                          | Time (min.) | Mp.(lit.)                                    | <sup>1</sup> H Chemical shifts of H <sub>A</sub> | Yields <sup>a</sup> (%) |
|-------|----------------|---------------------------------------------------------|-------------|----------------------------------------------|--------------------------------------------------|-------------------------|
| 1     | H              | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>               | 60          | 72 (80 <sup>10</sup> )                       | 8.49                                             | 90                      |
| 2     | H              | <i>m</i> -MeC <sub>6</sub> H <sub>4</sub>               | 60          | 56 (60 <sup>10</sup> )                       | 8.13                                             | 90                      |
| 4     | H              | <i>p</i> -HOC <sub>6</sub> H <sub>4</sub>               | 60          | 94 (72 <sup>10</sup> )                       | 8.07                                             | 85                      |
| 5     | H              | <i>m</i> -HOC <sub>6</sub> H <sub>4</sub>               | 120         | 90 (90 <sup>10</sup> )                       | 8.09                                             | 90                      |
| 6     | H              | <i>o</i> -HOC <sub>6</sub> H <sub>4</sub>               | 15          | 63 (63 <sup>10</sup> )                       | 8.22                                             | 90                      |
| 7     | H              | <i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> | 120         | 100 (129 <sup>16</sup> )                     | 8.21                                             | 80                      |
| 8     | H              | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>               | 120         | 146 (145 <sup>9</sup> )                      | 8.12                                             | 85                      |
| 9     | H              | <i>m</i> -ClC <sub>6</sub> H <sub>4</sub>               | 120         | 100 (118 <sup>14</sup> )                     | 8.11                                             | 85                      |
| 10    | H              | <i>o</i> -ClC <sub>6</sub> H <sub>4</sub>               | 300         | 103 (100 <sup>17</sup> )                     | 8.57                                             | 90                      |
| 11    | H              | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>              | 60          | 132 (133 <sup>9,12</sup> )                   | 8.00                                             | 90                      |
| 12    | H              | <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>              | 15          | 110 (112 <sup>10</sup> )                     | 8.10                                             | 85                      |
| 13    | H              | Ph                                                      | 60          | 120 (128 <sup>9</sup> )                      | 8.17                                             | 90                      |
| 14    | H              | 2,6-di-ClC <sub>6</sub> H <sub>3</sub>                  | 300         | 132 (150 <sup>9</sup> )                      | 8.40                                             | 90                      |
| 15    | H              |                                                         | 15          | 130 (133 <sup>10</sup> )                     | 7.73                                             | 80                      |
| 16    | Me             |                                                         | 15          | 114 (114 <sup>10</sup> )                     | .....                                            | 90                      |
| 17    | Me             |                                                         | 60          | 142 (132 <sup>15</sup> , 130 <sup>11</sup> ) | .....                                            | 85                      |
| 18    | Ph             | Me                                                      | 300         | 140 (144 <sup>10</sup> )                     | .....                                            | 80                      |

a) <sup>1</sup>H NMR yields.

90 °C for 30 min. The *E*-benzaldoxime was obtained in 85% yield and benzophenone was recovered unchanged.

Table 3 also shows that various types of aromatic aldehydes and ketones with electron-donating and electron-withdrawing groups were cleanly and rapidly condensed with hydroxylamine hydrochloride at 90 °C, giving their corresponding *Z* oximes (OH *cis* to aryl) in high yields in the presence of K<sub>2</sub>CO<sub>3</sub> (Entries 1-18).

The advantages of the presented methods may be summarized as: use of commercial and available catalysts, mild reaction conditions, and high stereoselectivities good yields of the desired products.

#### General Procedure for preparation of *E* isomer of aldoximes in the presence of CuSO<sub>4</sub>:

Hydroxylamine hydrochloride (0.6 g, 8.6 mmol) was added to a stirred mixture of CuSO<sub>4</sub> (1 g) and aldehydes (1 mmol) at 90 °C in an oil bath. The progress of reaction was monitored by TLC. After complete disappearance of the starting material, the reaction mixture was cooled, and washed with cold diethyl ether and filtered to remove CuSO<sub>4</sub>. Then the mixture was poured into ice-water and extract with cold diethyl ether (2 × 25 mL). The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated over ice to give the crude *E* oximes. The process of work-up was carried out at 0 °C, otherwise, the *Z* isomer was obtained.

#### General procedure for preparation of *Z* isomer of aldoximes and ketoximes in the presence of K<sub>2</sub>CO<sub>3</sub>:

Hydroxylamine hydrochloride (0.6 g 8.6 mmol) was added to a stirred mixture of K<sub>2</sub>CO<sub>3</sub> (1 g) and aldehydes or ketones (1 mmol) in an oil bath at 90 °C for the periods of time reported in Table 3. Then, the reaction mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL) and water (2 × 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the crude *Z* isomer of oxime. The products were identified by comparison of their physical data with those prepared in accordance with the literature procedures.

#### Acknowledgement

We gratefully acknowledge the support of this work by the Shiraz University Research Council.

#### References and Notes

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- (2) Sandler, S. R.; Karo, W. *Organic Functional Group Preparation*, Academic Press: New York 1983; vol.III, Chapter 11.
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(6) Hauser, C. R.; Hoffenberg, D. S. *J. Org. Chem.* 1955, 20, 1491.  
(7) Vogel, A.I. *Text Book of Practical Organic Chemistry* 1986, 1113.  
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Article Identifier:

1437-2096,E;2001,0,01,099,0101,fx,en;L17500ST.pdf

2008/08/21





Pergamon

Tetrahedron Letters 40 (1999) 6739-6743

TETRAHEDRON  
LETTERS

## Practical chemoenzymatic synthesis of a 3-pyridylethanolamino $\beta_3$ adrenergic receptor agonist

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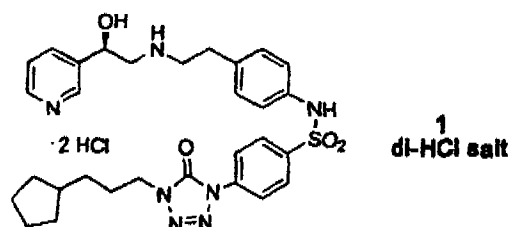
Received 11 June 1999; revised 28 June 1999; accepted 29 June 1999

### Abstract

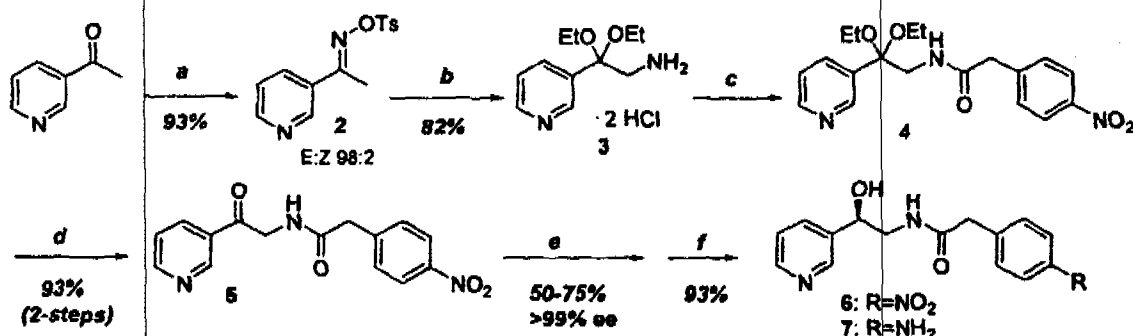
A chemoenzymatic synthesis of  $\beta_3$  agonist **1** suitable for large scale preparation is described. The key chiral 3-pyridylethanolamine intermediate (*R*)-**7** was prepared via an improved Neber rearrangement and a yeast-mediated asymmetric reduction. The tetrazolone fragment of the molecule was constructed via a dipolar cycloaddition between 1-(cyclopentyl)-3-propylazide and *p*-chlorosulfonyl phenylisocyanate. Sulfonamide coupling of these two intermediates under Shotten-Baumann conditions, followed by a borane reduction of the amide afforded **1** in 20–32% overall yield from 3-acetylpyridine. © 1999 Elsevier Science Ltd. All rights reserved.

Obesity affects approximately 30% of the adult population, and is closely associated with the development of type II diabetes, coronary artery diseases, and hypertension. The morbidities associated with these diseases are sometimes reversed by weight loss.<sup>1</sup> Compound **1** is proposed to act by a novel mechanism elevating metabolic rate through thermogenesis resulting from the stimulation of  $\beta_3$  adrenergic receptors (AR) in brown adipose tissue.<sup>2</sup> The elevation of metabolic rate, in the absence of increased food intake, will lead to weight loss over time.  $\beta_3$  AR agonists have also demonstrated a direct improvement on glucose tolerance and therefore may be very important in the treatment of type II diabetes.<sup>1</sup> In order to carry out further studies with this compound, we required a practical chiral synthesis. This paper describes the process used to provide kilogram quantities of compound **1**, a potent, selective  $\beta_3$  AR agonist.<sup>3</sup>

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Compound **1** consists of a chiral *N*-alkylated 3-pyridylethanolamine fragment and a tetrazolone sulfonyl fragment connected through a sulfonamide bond. Previous synthesis of the pyridyl ethanolamine portion involved a (–)-DIP-Cl asymmetric reduction of 3-pyridyl chloromethyl ketone, followed by epoxide formation of the resulting chlorohydrin, and then opening of the epoxide with the appropriate amine.<sup>2</sup> For our synthesis, we took a different approach where the amine moiety was incorporated in the form of amide early in the synthesis prior to introduction of the chiral alcohol. The synthesis of **7** is outlined in Scheme 1.



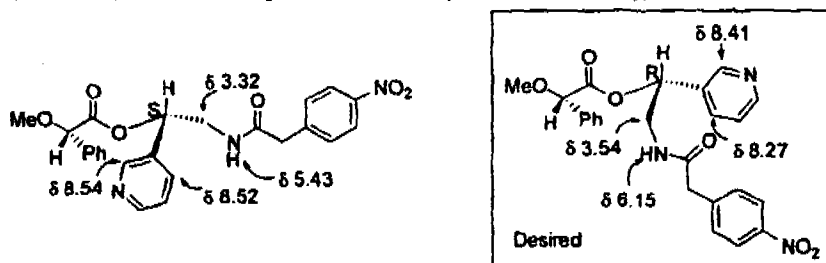
Scheme 1. a. 1.  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ; 2.  $\text{TsCl}$ , pyr; b. 1.  $\text{EtOK}$ ,  $\text{EtOH}$ ; 2.  $\text{HCl}$ ,  $\text{MTBE}$ ; c.  $\text{EDC}$ ,  $\text{THF}$ ,  $\text{H}_2\text{O}$ , pH 5.5, *p*-nitrophenyl acetic acid; d. aq.  $\text{HCl}$ ; e. yeast-mediated bioreduction; f.  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{MeOH}$ ,  $\text{NH}_4\text{OH}$

We have improved significantly upon an organic synthesis procedure<sup>4</sup> for the preparation of 3-pyridyl-aminomethyl ketal **3** via a Neber rearrangement reaction, and also noted some safety issues.<sup>5</sup> Compound **3** was prepared in 76% overall yield from 3-acetylpyridine in three steps via tosyl oxime **2**. The oxime formation and the tosylation steps<sup>5</sup> (93% overall yield) were carried out in a one-pot fashion using pyridine as the solvent. Under such conditions, the *E*-isomer of oxime predominates (>97:3). Water was removed by azeotropic distillation prior to the tosylation. Tosyl oxime **2** was crystallized from the reaction mixture by addition of water, and the wet cake was used directly in the Neber rearrangement by adding  $\text{EtOK}$  to a mixture of **2** in  $\text{EtOH}$  at 10–30°C. After removal of the  $\text{TsOK}$  salt,<sup>6</sup> the filtrate was treated with gaseous  $\text{HCl}$  (final pH 1–2) to precipitate the amino ketal di- $\text{HCl}$  salt **3** (82%). A carbodiimide-mediated coupling of **3** with *p*-nitrophenylacetic acid in  $\text{THF}/\text{H}_2\text{O}$  followed by a selective hydrolysis of the resulting amide-ketal **4** with concomitant removal of ethanol afforded pyridyl ketone **5** (93% for the two steps).<sup>12</sup>

With ketone **5** in hand, we screened methods for the key asymmetric reduction of the ketone to the chiral alcohol. Unfortunately, preliminary results from most known methods gave poor enantioselectivity and in some cases reduction of pyridine ring was observed (e.g. asymmetric hydrogenation with (*S*)- $\text{tol-BiNAP-RuCl}_2\text{-Et}_3\text{N}$  complex afforded the reduced pyridine vinylogous amide as the major product, with **6** as the minor product in only 6% ee). Alternatively, initial results using Baker's yeast (*Saccharomyces cerevisiae*) were encouraging,<sup>7</sup> which provided product in 70–80% ee. Subsequently, a microbial screen identified the yeast *Candida sorbophila* as a suitable biocatalyst,<sup>8</sup> which furnished the

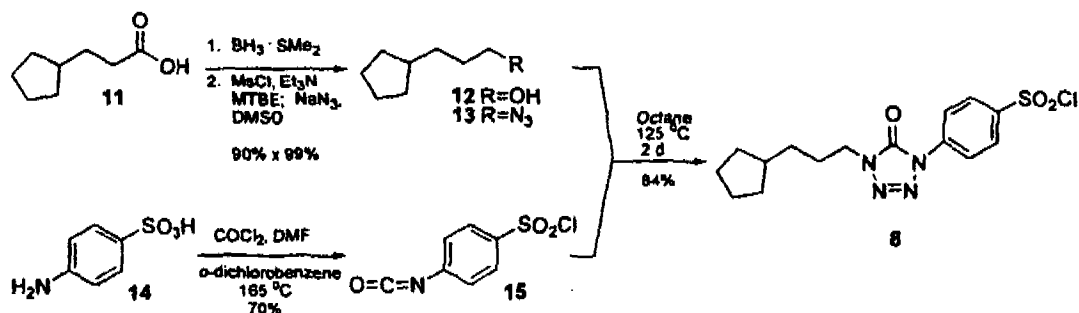
chiral alcohol **6**<sup>12</sup> in ~98% ee and 70–90% conversion after incubation for 2 days at 28°C. The material was routinely isolated in ~75% yield and >99.5% ee.<sup>9</sup> The absolute configuration of the secondary alcohol produced in the yeast-mediated reduction of ketone **5** was determined to be the desired *R*-enantiomer by NMR analysis of the (*S*)-methoxyphenylacetate esters based on Trost's method<sup>10</sup> and by comparison with materials derived from Shih's synthesis using (–)-DIP-Cl.<sup>2</sup> As shown below, the chemical shifts of the pyridyl protons of the *R*-isomer was shielded by the mandelate phenyl ring by 0.11–0.25 ppm relative to the *S*-isomer (at +20°C).

The optical purities of the crude **6** in the fermentation broth and the isolated **6** were determined to be >97.5% ee and >99.5% ee, respectively, by chiral HPLC using Chiralcel OD-H (20/80 IPA/hexanes, 0.8 mL/min, 254 nm; or SFC, 300 bar CO<sub>2</sub>, 16% MeOH (20 mM *i*PrNH<sub>2</sub>), 1.0 mL/min, 35°C).



Nitro compound **6** was hydrogenated (20 psi H<sub>2</sub>) over 5% Pd/C (4 wt%) in methanol with 1.7 equiv. NH<sub>4</sub>OH, conditions which minimized impurities derived from the intermediary nitroso compound. The reaction was run at 40°C for ~3 h until the uptake of H<sub>2</sub> had stopped. Aniline **7** was crystallized in high yield (96–97%) and purity (>99 A%).<sup>12</sup>

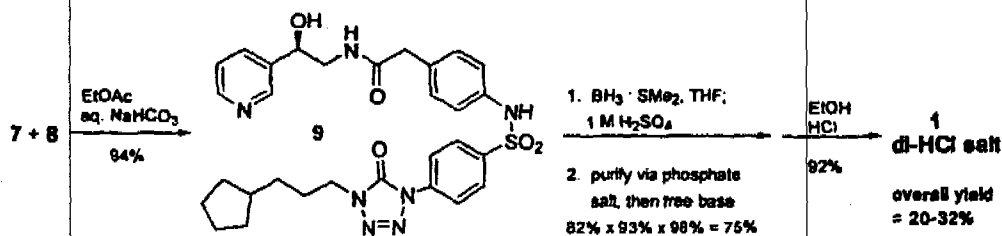
The southern half of the molecule was constructed as shown in Scheme 2. The cycloaddition between azide **13** and isocyanate **15** took place at 125°C to provide the tetrazolone **8** in 84% yield.<sup>11</sup>



Scheme 2.

Subsequent coupling of aniline **7** and sulfonyl chloride **8** under Schotten–Baumann conditions afforded the penultimate amide **9** in 94% yield (Scheme 3). Selective reduction of the amide with BH<sub>3</sub>·SMe<sub>2</sub> (7 equiv.) at +20°C followed by 1 M H<sub>2</sub>SO<sub>4</sub> work up at +50°C to break up the borane complexes afforded the crude **1** free base in 82% yield after neutralization. This material was purified to >99% pure by crystallization of the corresponding phosphate salt (93%) followed by free basing (98%), since the di-HCl salt gave poor rejection of the impurities. Finally, the di-HCl salt was prepared from ethanolic HCl in 92% yield.<sup>12</sup>

In summary, we have developed a practical synthesis of β<sub>3</sub> AR agonists **1** and have demonstrated it on kilogram scale. The key chiral pyridyl alcohol intermediate (*R*)-**7** was prepared via an improved Neber rearrangement and a yeast-mediated asymmetric reduction. The key dipolar cycloaddition between azide **15** and isocyanate **17** provided an efficient one-step synthesis of the tetrazolone sulfonyl chloride.



Scheme 3.

Coupling of the aniline and the sulfonyl chloride followed by borane reduction of the amide completed the synthesis of 1 in 20–32% overall yield from 3-acetylpyridine.

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- CAUTION. The tosylation reaction and isolated tosyl oxime 2 both showed exothermic activity beginning at +40°C. The dried tosylate 2 also showed evidence of possible low-level shock sensitivity (discoloration) at 250 kg cm and above. It is recommend that tosyl chloride is added with temperature control, and the batch temperature is kept between +30–35°C, and the product 2 was preferably handled as a wet cake. Upon tosylation completion, water was added to crystallize the product. The supernatant was removed by a filter stick and the wet cake was washed with cold iPrOH until <1.5 wt% water. Ethanol was then added to the wet cake and used directly in the next step. The Neber rearrangement step can tolerate up to 30 mol% of water without effecting the yield.
- Addition of MTBE and solka floc before filtration significantly improved the filtration rate.
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- The bioconversion assay yield ranged from 70–90% depending on the initial concentrations of ketone 5 (5–50 g/L). The isolation involved removal of cells by centrifugation/ultrafiltration and crystallization of alcohol 6 by neutralization of an acidic aqueous solution. The overall yields from the ketone were 52–76%. The purity of the alcohol ranged from 94–95 wt% and 99.5–99.7% ee.
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- All the new compounds were well characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and elemental analysis. Data for compounds 3, 5, 7, 8, and 1 are listed below. For compounds 2, 4, 6, and 9 data are readily available upon request. Amino ketal 3:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.07 (d,  $J=1.9$  Hz, 1H), 8.99 (d,  $J=6.0$  Hz, 1H), 8.83 (dt,  $J=8.3, 1.6$  Hz, 1H), 8.26 (dd,  $J=8.3, 6.0$ , 1H), 3.61 (m, 2H), 3.59 (brs, 2H), 3.46 (m, 2H), 1.30 (t,  $J=7$  Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  147.1, 143.8, 142.5, 139.9, 129.3, 99.9, 59.2, 44.5, 15.0. Anal. calcd for  $\text{C}_{11}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2 \cdot 3/4 \text{ KCl}$ : C, 38.96; H, 5.94; N, 8.26. Found: C, 38.81; H, 5.83; N, 8.00. Keto-amide 5:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.17 (d,  $J=1.7$  Hz, 1H), 8.84 (dd,  $J=4.8, 1.7$  Hz, 1H), 8.22 (d,  $J=8.7$  Hz, 2H), 8.23 (m, 1H), 7.52 (d,  $J=8.7$  Hz, 2H), 7.47 (m, 1H), 6.60 (brs, NH), 4.78 (d,  $J=4.4$  Hz, 2H), 3.78 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  193.1, 169.3, 154.7, 149.3, 147.3, 141.8, 135.2, 130.3, 129.7, 124.0, 123.9, 46.7, 43.0. Anal. calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$ : C, 60.20; H, 4.38; N, 14.04. Found: C, 59.82; H, 4.24; N, 13.83. Aniline-alcohol 7:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.49 (d,  $J=2.0$  Hz,

1H), 8.40 (dd, J=4.9, 1.6 Hz, 1H), 7.72 (dt, J=8.0, 1.6 Hz, 1H), 7.34 (dd, J=7.8, 5.0 Hz, 1H), 6.94 (d, J=8.4 Hz, 2H), 6.66 (d, J=8.4 Hz, 2H), 4.78 (t, J=6.1 Hz, 1H), 3.42 (d, J=6.1 Hz, 2H), 3.31 (s, 2H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 175.2, 149.1, 148.3, 147.7, 140.2, 136.3, 130.8, 125.9, 125.1, 116.8, 71.1, 47.5, 43.1. Anal. calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.07; H, 6.35; N, 15.29. Tetrazole sulfonyl chloride 8: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.35 (d, J=9.1 Hz, 2H), 8.16 (d, J=9.1 Hz, 2H), 4.03 (t, J=7.2 Hz, 2H), 1.90 (m, 2H), 1.85–1.70 (m, 3H), 1.65–1.45 (m, 4H), 1.40 (m, 2H), 1.08 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 148.7, 142.2, 139.9, 128.7, 118.8, 45.6, 39.5, 32.7, 32.6, 27.6, 25.1. Anal. calcd for C<sub>15</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>3</sub>S: C, 48.58; H, 5.16; Cl, 9.56; N, 15.11. Found: C, 48.87; H, 5.21; Cl, 9.29; N, 14.90. 1·2HCl: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 9.01 (d, J=1.2 Hz, 1H), 8.86 (d, J=5.6 Hz, 1H), 8.76 (dt, J=8.1, 1.5 Hz, 1H), 8.14 (dd, J=8.1, 5.6 Hz, 1H), 8.06 (d, J=8.9 Hz, 2H), 7.88 (d, J=8.9 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 5.37 (dd, J=9.8, 3.1 Hz, 1H), 4.00 (t, J=7.1 Hz, 2H), 3.49 (dd, J=12.8, 3.3 Hz, 1H), 3.35–3.20 (m, 3H), 3.00 (m, 2H), 1.92–1.70 (m, 5H), 1.70–1.45 (m, 4H), 1.45–1.30 (m, 2H), 1.10 (m, 2H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 150.1, 145.9, 143.3, 142.5, 141.1, 139.7, 139.4, 137.8, 134.4, 130.7, 129.7, 128.7, 122.8, 120.0, 66.9, 53.7, 50.0, 46.4, 40.9, 33.9, 33.6, 32.4, 28.6, 26.1. Anal. calcd for C<sub>30</sub>H<sub>36</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>4</sub>S: C, 54.21; H, 5.91; Cl, 10.67; N, 14.75; S, 4.82. Found: C, 54.35; H, 5.90; Cl, 10.78; N, 14.64; S, 4.87.