Industrial process for OXICONAZOLE

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BIOSCIENCE RESEARCH CENTRE- VISAKHAPATNAM

Introduction-Oxiconazole inhibits ergosterol biosynthesis, which is required for cytoplasmic membrane integrity of fungi. It acts to destabilize the fungal cytochrome P450 51 enzyme (also known as Lanosterol 14-alpha demethylase). This is vital in the cell membrane structure of the fungus. Its inhibition leads to cell lysis. Oxiconazole has also been shown to inhibit DNA synthesis and suppress intracellular concentrations of ATP. Like other imidazole antifungals, Oxiconazole can increase membrane permeability to zinc, augmenting its cytotoxicity.

Oxiconazole

Information of Nitrate salt
CAS No: [64211-46-7]
IUPAC Name: (Z)-1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone O-[(2,4-dichlorophenyl)methyl]oxime mononitrate
M. P.: 137-38 °C
MW: 492.14

Drug information:- Oxiconazole is an anti-microbial drug further classified as anti-fungal agent. This imidazole compound is used in the treatment of infections caused due to fungus such as athlete's foot, jock itch and ringworm. It is also available as skin ointments.

Oxiconazole nitrate -Synthesis

The reaction of 2’, 4’-dichloro-2-imidazol-1-yl-acetophenone (I) with hydroxylamine (II) in refluxing ethanol pyridine gives the corresponding oxime (III). Which is condensed with 2,4-dichlorobenzyl chloride (IV) by means of NaH in hot DMF.
Synthesis of 091133: The reaction of 2', 4'-dichloro-2-imidazol-1-yl-acetophenone (I) with hydroxylamine (II) in refluxing ethanol pyridine gives the corresponding oxime (III). Which is condensed with 2, 4-dichlorobenzyl chloride (IV) by means of NaH in hot DMF (1,2). (Scheme 09113301a) Description mp 137-8° (1). Manufacturer Siegfried AG (Switzerland). References 1. Mixich, G. et al. (Siegfried AG); US 4124767. 2. Mixich, G and Thiele, K.; Ein beitrag zur stereospezifischen Synthese von antimykotisch wirksamen imidazolyloximathern; Arzneim-Forsch 1979, 29, 1510-13. Arzneim-Forsch Drug Res Synthetic route
The reaction of 2', 4'-dichloro-2-imidazol-1-yl-acetophenone (I) with hydroxylamine (II) in refluxing ethanol pyridine gives the corresponding oxime (III). Which is condensed with 2,4-dichlorobenzyl chloride (IV) by means of NaH in hot DMF.


DE 2657578; FR 2336129; GB 1514870; JP 52102276; US 4124767

Synthetic route
Title  Imidazolyl-oxime ethers having anti-mycotic and bactericidal activity

Synthesis - The reaction of 2', 4'-dichloro-2-imidazol-1-yl-acetophenone (I) with hydroxylamine (II) in refluxing ethanol pyridine gives the corresponding oxime (III).

Which is condensed with 2,4-dichlorobenzyl chloride (IV) by means of NaH in hot DMF.

Author  Mixich, G.; et al. (Siegfried AG)

Scheme Oxiconazole

Stage -I

2,2,4'-tri-choloroaceto-phenone  imidazole  1-(2,4-dichlorophenacyl)-imidazole
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**Stage - II**

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[+ \quad \text{NH}_2\text{OH}-\]

1-(2,4-dichlorophenacyl)-hydroxylamine

(Z)-1-(2,4-dichlorophenyl)-2-imidadole

ethanone oxime

**Stage-III**

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

\[+ \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

2,4-Dichlorobenzyl chloride

Oxiconazole

**Stage-IV**

Oxiconazole \[\rightarrow\] Oxiconazole nitrate
Brief Process Description

In step-I 2,2’4’-tri-chloroacetophenone, Imidazole reacted in presence of acetonitrile to form 1-(2,4-dichlorophenacyl)-imidazole (I). Which is then reacted with hydroxylamine hydrochloride to give (Z)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethanone oxime (II). It is further reacted with 2,4-Dichlorobenzyl chloride in presence of sodium hydride to give (III) Oxiconazole and finally salt formation with nitric acid.

OXICONAZOLE

Stage1 :

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of chemical</th>
<th>Mol. Wt.</th>
<th>Qty.</th>
<th>Moles</th>
<th>Mole eq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2’,2,4-trichloroacetophenone</td>
<td>223.5</td>
<td>100.0 gm</td>
<td>0.45</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Imidazole</td>
<td>68.0</td>
<td>76.15 gm</td>
<td>1.12</td>
<td>2.49</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>----</td>
<td>100.0 ml</td>
<td>----</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>---</td>
<td>400.0 ml</td>
<td>----</td>
<td>---</td>
</tr>
</tbody>
</table>

Practical yield w/w : 0.75
Theor. Yield : 1.14

Procedure :

In 1000.0 ml 4-neck RBF
Charge 100.0 gm 2’,2, 4-trichloro acetophenone in 100.0 ml acetonitrile at 30-35°C.
Charge 76.15 gm imidazole slowly exotherm observed temp. rises to 54°C.
Cool reaction mass to 30-35°C.
Stir & maintain reaction mass for 3.0 hrs. at same temp.
Check TLC

Mobile Phase : Ethyl acetate

If TLC is OK

Distill out acetonitrile under vac. below 40°C.
Charge 300 ml methanol in undistilled material at 30-35°C
Stir at same temp. for 30.0 min.
Cool the reaction mass to 10°C & maintain reaction mass for 30 min.
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Filter the reaction mass at 10°C
Slurry wash with 2X50 ml chilled methanol.

Wet wt. : 86.0 gm
Dry at 50°C

Dry wt. : 75.0 gm
Mpt. : 80-86°C

Stage2 :

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of chemical</th>
<th>Mol. Wt.</th>
<th>Qty.</th>
<th>Moles</th>
<th>Mole eq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stage 1</td>
<td>255.0</td>
<td>100.0 gm</td>
<td>0.39</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Hydroxyl amine.HCl</td>
<td>69.5</td>
<td>41.4 gm</td>
<td>0.59</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>-----</td>
<td>730.0 ml</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pyridine</td>
<td>79.0</td>
<td>73.0 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Aq. Ammonia</td>
<td>-----</td>
<td>4.0 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>-----</td>
<td>300.0 ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Practical yield w/w : 0.5-0.52
Theor. Yield : 1.05

Procedure :

In 1000.0 ml 4 neck RBF

Charge Stage 1 100.0 gm, 730.0 ml methanol & 73.0 ml pyridine.
Heat to 60°C to dissolve the material.
Add hydroxyl amine.HCl 41.40 gm in reaction mass .
Heat reaction mass to reflux.
Maintain reaction mass to reflux for 3.0 hrs.
Check TLC
Mobile phase Ethyl acetate : Acetic acid 9 : 1

If TLC OK
Cool reaction mass to 40°C.
Distill out methanol under vac. completely. (Methanol recovery 550 ml) (GC -70.0 %)
Cool reaction mass to 30-35°C.
Add 300 ml water in undistilled material at 40°C.
Stir reaction mass at 25-30°C for 30 min.
Filter the reaction mass at 25-30°C.  
Suck dry and wash with 75 ml water.  
Charge wet cake in 300.0 ml water  
Adjust pH 7.0-8.0 by aq. ammonia (approx. 4.0 ml)  
Stir at 25-30°C for 30-60 min.  
Filter the reaction mass.  
Suck dry.  
Wash with 75.0 ml water.  
Suck dry and unload wet wt.  

Wet wt. :  280.0 gm  

Dry at 60-65°C  
Dry wt. :  242.0 gm  

**Purification** :  
Charge 242.0 gm material in 750.0 ml DMF.  
Heat reaction mass to 90-95°C.  
Maintain reaction mass for 60.0 min. clear soln.  
Cool reaction mass to 0-5°C  
Stir reaction mass for 30 min at 0-5°C  
Filter the reaction mass and suck dry.  
Wash with 25.0 ml DMF at 0-5°C.  
Suck dry and unload.  

Wet wt. :  162.0 gm  

Dry at 60-65°C  
Dry wt. :  125.0 – 130.0 gm  

**Stage 3** :  

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of chemical</th>
<th>Mol. Wt.</th>
<th>Qty.</th>
<th>Moles</th>
<th>Mole eq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stage 2</td>
<td>270.0</td>
<td>100.0 gm</td>
<td>0.37</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>2,4-dichloro benzyl chloride (2,4-DBC)</td>
<td>195.5</td>
<td>72.36 gm</td>
<td>0.37</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>-----</td>
<td>2000.0 ml</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sodium hydride 60.0%</td>
<td>24.0</td>
<td>13.32 gm</td>
<td>0.37</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>IPA</td>
<td>-----</td>
<td>750.0 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2N Nitric acid</td>
<td>63.0</td>
<td>850.0 ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Practical yield w/w :  1.1  
Theor. Yield :  1.82
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Procedure:

In 1000.0 ml 4 neck RBF
Charge stage 2 100.0 gm in 2.0 lit. DMF.
Heat reaction mass to 50°C to dissolve.
Cool reaction mass to 35°C.
Add 2,4-DBC slowly at 30-35°C.
Stir for 30.0 min. at 30-35°C.
Add 13.32 gm NaH 60.0% at 30-35°C. Exotherm observed temp. rises to 40°C
Stir reaction mass for 30.0 min. at 30-35°C.
Heat to 50-55°C and maintain reaction mass for 2.0 hrs.

Check TLC

Mobile phase MDC: EtOAc : formic acid : ethanol : water
9 : 8 : 2 : 1 : 0.2

If TLC OK
Distill out complete DMF at 40-45°C under high Vac. Recovery 3.8 lit GC 99.7%
After complete distillation cool undistill material to 30-35°C.
Add 750.0 ml IPA stir reaction mass to 30-35°C for 30 min.
Filter reaction mass to 30-35°C
Collect filtrate
Add 2N HNO3 2960.0 ml slowly in 30 min. at 30-35°C
Stir reaction mass for 4-5 hrs. at 30-35°C
Filter & suck dry Slurry wash with 100.0 ml water
Suck dry.
Wet wt. : 200.0 gm
Dry at 50-55°C
Dry material : 155.0 gm

Purification:
Charge above material in 750.0 ml IPA.
Heat to 70-75°C to dissolve.
Add 5.0 gm activated carbon.
Maintain reaction mass for 30.0 min. and clarify the soln.
Collect filtrate.
Cool reaction mass to 25-30°C.
Stir & maintain reaction mass for 1.0 hrs.
Filter the reaction mass and suck dry.
Slurry wash with 2X50.0 ml IPA.
Suck dry.
Wet wt. : 115.0 gm
Dry at 50-55°C
Dry wt. : 90.0 gm
If isomer is present upto 20-30%

Charge above material in 1240.0 ml DNS
Heat to reflux add 5.0 gm Carbon
Clarify Collect filtrate.
Cool to 30-35°C
Stir for 1.0 hrs
Filter collect filtrate cool to 0-5°C.
Filter and wash with 50 ml DNS 0-5°C.