A NOVEL AND EFFICIENT METHOD TO SYNTHESIS MICONAZOLE ANALOGUE AND ITS INTERMEDIATES

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ABSTRACT

An alternative method for the preparation of Miconazole intermediate 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol is described, process involves the 2,4-Dichloroacetophenone as the key raw material from which the substituted 2-chloro-1-(2,4-dichlorophenyl)ethanone was prepared. 2-chloro-1-(2,4-dichlorophenyl)ethanone was reduced to 2-Chloro-1-(2,4-dichlorophenyl)ethanol and via SN2 reaction with imidazoles the 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol was obtained, further 1-(2-(2,4-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)1H-imidazole was synthesized.

Keywords: Miconazole, Antifungal, Imidazoles, Fungal infections

INTRODUCTION

Fungal infections on skin, mucosa and hair are due to dermatophytes, induced by pathogens collectively known as tinea, Candida albicans cause vulvovaginitis and oral candidiasis. The fungal infection has greatly increased as a consequence of various factors in immune-suppressed patients.\textsuperscript{1,2}

Patients with incompetent immune systems have a large contribution to both increased use of antifungals and the evolution of resistant organisms.\textsuperscript{3} In this setting, more efficient formulations are an attractive alternative to the systematic treatment of fungal diseases. Miconazole is one such medication as an antifungal drug for many fungal diseases.\textsuperscript{4-9}

Miconazole is a synthetic lipophilic compound that was initially for topical use, also it is used orally and intravenously,\textsuperscript{10-13} it was the first patented\textsuperscript{14} in 1968 and approved for medical use in 1971, World Health Organization considers it as one among the essential medicine, the most effective and safe medicines in health system.\textsuperscript{15}

Prior art on miconazole synthesis disclosed in patent\textsuperscript{14} in 1973 involves the 2,4-Dichloro phenacyl chloride as the key starting material reacting with imidazoles to yield intermediate 2-(1-Imidazolyl) 2,4-Dichloroacetophenone further reduced to ethanol. Sodium salt of ethanol reacted with substituted benzylchloride to yield miconazole. The later patents published involve the 2,4-Dichloro-alpha-chloroacetophenone or 2-Chloro-1-(2,4-dichlorophenyl) ethanol as key starting material.\textsuperscript{17} One of the recent Chinese patents discloses the synthesis of miconazole by preparing the 2,4-Dichloro-alpha-chloroacetophenone by halogenation of 2,4-Dichloroacetophenone.\textsuperscript{16,18} Remaining non-commercial synthetic route\textsuperscript{1,19,20} involves 2-(2,4-dichlorophenyl) oxirane and 2,4-Dichlorobenzaldehyde as the starting material.\textsuperscript{20}

The process or synthetic methods discussed above has shortcomings like a tedious process, side products, low yield, costly raw material. Therefore there is scope for the alternative method or to improve the process. Therefore we have developed a synthetic route starting from 2,4-dichloroacetophenone as Kew raw material.

EXPERIMENTAL

In the new method developed, the 2-chloro-1-(2,4-dichlorophenyl)ethanone(1) used as starting material for miconazole was prepared by carrying out fridalcraft acylation of m-Dichlorobenzene with chloroacetyl
chloride in presence of lewis acid anhydrous aluminium chloride at ambient temperature. However in previous attempts of bromination of 2,4-dichloroacetophenone which can also be used as starting material resulted in very low yield and side products.

In the newly developed process, 2-Chloro-1-(2,4-dichlorophenyl)ethanone was prepared by acylation at lower temperature 45-50 °C and m-dichlorobenzene (starting material) is used as solvent here the reaction temperature is low no additional solvent is used. The yield obtained is (95%).

The substitution reaction of 2-chloro-1-(2,4-dichlorophenyl)ethanone(1) with imidazoles did not result good yield and purity, therefore keto group present in 2-chloro-1-(2,4dichlorophenyl) ethanol was reduced to 2-Chloro-1-(2,4dichlorophenyl)ethanol(2) using NaBH₄ taking aqueous methanol as solvent, here instead of using only methanol or ethanol as solvent, Aqueous methanol is used as a solvent for the reduction reaction. The reduction reaction was carried out using different solvents and at different temperatures, the results are depicted in the following Table-1 to get a respected alcohol yield of the reduced product that can be varied in different conditions and solvents. In The above process reduction of compound 2-Chloro-1-(2,4-dichlorophenyl)ethanone was reduced to) 2-Chloro-1-(2,4dichlorophenyl)ethanol using NaBH₄ (0.50 mol) using less costly solvent aqueous methanol to Yield (86%) of product.

![Table-1](image)

Thus obtained 2-Chloro-1-(2,4-dichlorophenyl)ethanol was taken for amination with imidazole by employing weak base anhydrous K₂CO₃ and DMF as solvent by maintaining the reaction temperature at 55-60 °C for about 20 hours to give 1-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl) ethanol, the inorganic salts and solvent were removed by quenching reaction mass into ice water, the desired product precipitates out in good yield and purity.

In the second step formation of 2-(2,4-dichlorophenyl)oxirane as an intermediate which is low boiling and difficult to handle was avoided by carrying out a reaction at a lower temperature, in which imidazoles, it was condensed with the 2-Chloro-1-(2,4-dichlorophenyl)ethanol using mild base K₂CO₃ instead of sodium hydride or potassium hydride and DMF as a solvent, other solvents like benzene xylene are avoided.

Finally, the O-alkylation of the 1-(2-(benzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole done by converting it into alkali metal salt by treatment with Sodium hydride in DMF and reacting with benzylchloride yielded 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol isolated using the conventional method.

In the final stage, miconazole analogue was obtained by the nucleophilic substitution of benzylchloride with the above-obtained product. Literature survey on the synthesis of Miconazole suggest that nitrogen atmosphere and low temperature were the most required reaction conditions but the present method has not utilized such conditions instead at room temperature under normal atmospheric conditions the nucleophilic substitution was carried out.

Thus we have developed a new process which is economically viable, safe and User-friendly process and can be taken up in commercial purpose. The selected route of synthesis to prepare the title compound as outlined in the following Scheme-1.
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Table-2: Physical Parameters

<table>
<thead>
<tr>
<th>S. No.</th>
<th>IUPAC Names</th>
<th>Colour</th>
<th>Melting Point</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-chloro-1-(2,4-dichlorophenyl)ethanone</td>
<td>Colourless</td>
<td>57 -58 °C</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>2-Chloro-1-(2,4dichlorophenyl)ethanol</td>
<td>Colourless</td>
<td>47 -48 °C</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol</td>
<td>Pale yellow</td>
<td>116 -118 °C</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>1-(2-(benzylxoy)-2-(2,4dichlorophenyl)ethyl)-1H-imidazole</td>
<td>Brown</td>
<td>Gummy solid obtained (Melting point not checked).</td>
<td>62%</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

Melting points were determined by the open capillary method and are uncorrected. IR spectra were recorded on Perkin Elmer spectrum version 10.5.4. $^1$H-NMR was recorded on JEOL 400 MHz using CDCl$_3$ as a solvent and TMS as an internal standard. The chemical shifts are expressed in $\delta$ ppm. The purity of the compound was checked by TLC. Mass was recorded using Shimadzu GCMS-QP2010S. All the chemicals purchased were of analytical grade and were used without further purification unless otherwise stated.

**Spectral Data of 2-Chloro-1-(2,4-dichlorophenyl)ethanone (2)**

IR: (KBr: $\nu$/cm$^{-1}$): 1697 (C=O), 2996,2940(C-H stretching), 1580-154(C=C Aromatic), 1398 (CH$_2$ bending) $^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 4.604 (s, 2H CH$_2$Cl) 7.294 (d, 1H Ar-H), 7.408 (s. 1H Ar-H), 7.479 (d, 1H Ar-H).

**Spectral Data of 2-Chloro-1-(2,4-dichlorophenyl)ethanol(3)**

IR: (KBr: $\nu$/cm$^{-1}$): 1697 (C=O), (C-Cl), (C-H stretching),$^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 2.721 (bs, 1H OH), 5.263 (d, 1H CH), 3.528 (dd, 1H CH$_2$), 3.876 (dd, 1H 1H CH$_2$), 7.313 (dd, 1H, Ar-H), 7.579 (d, 1H, Ar-H), 7.380 (d, 1H, Ar-H).
Spectral Data of 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol (4)
IR: (KBr: ν/cm⁻¹): 1234 (C-N, C-O str), 1697 (C=O), 1588 (C=C aromatic), 2960 (C-H stretching), 3159 (O-H str)
H-NMR (δ ppm, DMSO-d6, 400 MHz): 3.88 (dd, 1H, CH₂), 4.196 (dd, 1H, CH₂), 5.29 (dd, 1H, CH), 6.822 (s, 1H, Imi-H), 6.884 (s, 1H, Imi-H), 7.248 (s, 1H, Imi-H), 7.278 (dd, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 7.37 (dd, 1H, Ar-H).
MS m/z: 256 (M⁺), 238 ((M-18), 73, 82 (alpha cleavage), 221 & 223 (M⁺ and M⁻² 2,4-dichlorophenyl).

Synthetic Procedure For the Synthesis of 2-Chloro-1-(2,4-dichlorophenyl)ethanol
First, m-Dichloro benzene (0.050mol) is charged into a clean and dry 250ml three-necked R.B. flask, anhydrous aluminium chloride (0.078mol) is added in lots. The reaction mixture was stirred for 10 minutes at R.T. Chloroacetyl chloride (0.065mol) was added in drops, the reaction mixture was stirred at 40-50°C for 4hrs. After the completion of the reaction mass was quenched into ice water, the product precipitated was filtered, dried, and recrystallized from 25ml n-hexane.

Synthetic Procedure For the Synthesis of 2-chloro-1-(2,4-dichlorophenyl)ethanol
2-chloro-1-(2,4-dichlorophenyl)ethanone (0.02237mol) was charged into a clean 100ml R.B. Flask, five-volume of 30% aqueous methanol was charged and is allowed to stir at room temperature. The reaction mixture was cooled to 0°C and sodium borohydride (0.01185mol) was added in lots. The above reaction mixture was allowed to stir for 3 hrs. After the completion of the reaction, methanol was evaporated under reduced pressure, quenched into crushed ice. The solid obtained was filtered and washed with water several times and dried. The crude product obtained was recrystallized using 25ml pet ether and is dried to get colorless crystals.

Synthetic Procedure For the Synthesis of 1-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl)ethanol:
The imidazole (0.0011mol) was dissolved in 5ml DMF in a clean and dry 100ml R.B. Flask, Potassium carbonate (0.00165mol) was added. allowed to stir for 40 minutes at room temperature, to the above reaction mass 2-chloro-1-(2,4-dichlorophenyl)ethanol (0.0011mol) was added. The reaction mixture was heated to 50-60°C for 20hrs. After the completion of the reaction, the reaction mixture was quenched into crushed ice. The pale yellow solid was obtained was filtered and washed several times and dried. The crude product was recrystallized using 25ml n-hexane and is dried to get pale yellow colored crystals.

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CONCLUSION
The 2-Chloro-1-(2,4-dichlorophenyl)ethanone was synthesized by Fridal Crafts acylation at ambient temperature in the present synthetic process rather than at an elevated temperature. The 2-chloro-1-(2,4-dichlorophenyl)ethanol was prepared by employing less expensive and environmentally benign conditions such as sodium borohydride and aqueous alcohol. Sodium borohydride resulted in the highly selective reduction of ketones thus increasing the yield and a mild, less expensive and easily handleable base K₂CO₃ was used instead of highly corrosive and expensive base like sodium hydride for the condensation of α-chloro secondary alcohol and imidazoles to yield 1-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl)ethanol, avoided completely low boiling epoxide intermediate. In the final step imidazolyl secondary alcohol and...
benzyl chloride have been made to react at room temperature and normal atmospheric conditions avoiding nitrogen atmosphere and low-temperature conditions. By observing all the above facts we are developed a new route for the synthesis of miconazole analogue.

ACKNOWLEDGEMENT

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REFERENCES


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