Process for producing 6-(2,3-dichlorophenyl)-1,2,4-triazine 3,5-diamine (Lamotrigine) and identification, characterization of a new N-methyl impurity

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ABSTRACT

Disclosed herein is the industrial scalable process for producing the 6-(2,3-dichloro-phenyl)-1,2,4-triazine-3,5-diamine (Lamotrigine) with 99.9% HPLC purity and high yield in neutral conditions as compared to basic and acidic reaction conditions. The major impurities, A, B, C, D, E, F and G, are listed in European & US pharmacopoeias. We are reporting, an investigated and characterized new impurity (N-methyl impurity) and besides a way to control during the process.

Keywords: Lamotrigine, New N-methyl impurity, NOSEY studies, different pH conditions, 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile.

INTRODUCTION

6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine, sold as Lamotrigine [1] (Fig 1), is an anticonvulsant drug used in the treatment of epilepsy [2] and bipolar disorder. [3-4] It is used to treat partial, primary and secondary tonic-clonic seizures, also seizures associated with Lennox-Gastaut syndrome besides acting as a mood stabilizer.

[Chemical structure of Lamotrigine (1) is shown here]
There are several processes, reported in literature [1C-5] for the preparation of Lamotrigine, and involves cyclisation of 2-(2,3-dichlorophenyl)-2-(amino guanidine) acetonitrile, in an aliphatic alcohol under reflux temperature in the presence of a strong inorganic bases like potassium hydroxide or sodium hydroxide. Yet another route [6] (1 involves photochemically induced reaction of the intermediate with an expensive and hazardous reagent rendering it unsuitable for industrial scale production of Lamotrigine with desired pharmacopeia purity. The cyclization reaction of compound 3 is performed in a highly basic condition results in generating the undesirable impurity [7] 2 (3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4H)-one) (Fig 2) as a result of hydrolysis during Lamotrigine synthesis. High volumes of organic solvents for reaction completion and final isolation and multiple crystallization results in lowered yields as well.

![Figure-2](image-url)

There exists a need to develop an improved process for producing Lamotrigine that reduces the manufacturing cost and batch cycle time. Moreover the process should produce Lamotrigine in high yield with minimal impurities and should be amenable for large scale production. The present invention described herein overcomes the above drawbacks of prior art process.

**MATERIALS AND METHODS**

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), $^1$H and $^{13}$C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-$d_6$ and CDCl$_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

**New process for the Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (1).** A suspension of 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile (3, 500.0 g, 1.95 mol) in methanol (9.0 L) was stirred at reflux for about 2 h to get a clear solution. Activated carbon (10.0 g) was added to the solution and stirred at 63-65°C for 15 min. The hot solution was filtered through celite at 60-65°C. The filtrate was heated to reflux and maintained for about 15 h. After
completion of the reaction the reaction mass was cooled to 10°C and stirred for an hour maintains the same temperature. The solid material was filtered and washed with chilled methanol. The product was dried under vacuum at 70-75°C to yield 470.0 g (94%) of product of the title 1. $^1$H NMR (DMSO-d_6): $\delta$ 7.66 (d, 1H), 7.42(t, 1H), 7.32 (d, 1H), 6.64 (br, 2H, NH$_2$), 6.40 (br s, 2H, NH$_2$).

**Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (1)**. A suspension of 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile (3, 10.0 g, 0.039 mol) in methanol (180 mL) was stirred at reflux for about 2 h to get a clear solution. Activated carbon (0.2 g) was added to the solution and stirred at 63-65°C for 15 min. The hot solution was filtered through celite at 60-65°C. The filtrate was heated to reflux and maintained for about 15 h. After completion of the reaction the reaction mass was cooled to room temperature and stirred for 1 h at the same temperature. The solid material was filtered and washed with methanol. The product was dried under vacuum at 70-75°C to yield 8.4 g (84%) of product of the title 1.

**Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (1) in basic condition**. A suspension of 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile (3, 10.0 g, 0.039 mol) in methanol (180 mL) was added ~3 drops of 0.1 N NaOH solution and stirred at reflux for 1-2 h to get a clear solution. Activated carbon (0.2 g) was added to the solution and stirred at 63-65°C for 15 min. The hot solution was filtered through celite at 60-65°C. The filtrate was heated to reflux and maintained for about 15 h. After completion of the reaction the reaction mass was cooled to 10°C and stirred for 1 h at same temperature. The solid material was filtered and product washed with chilled methanol. The product was dried under vacuum at 70-75°C to yield 8.6 g (86%) of product of the title 1.

**Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (1) in acidic condition**. A suspension of 2-(2,3-dichlorophenyl)-2-(aminoguanidine) acetonitrile (3, 10.0 g, 0.039 mol) in methanol (180 mL) was added ~3 drops of sulphuric acid and stirred at reflux for 1-2 h to get a clear solution. Activated carbon (0.2 g) was added to the solution and stirred at 63-65°C for 15 min. The hot solution was filtered through celite at 60-65°C. The filtrate was heated to reflux and maintained for about 15 h. After completion of the reaction the reaction mass was cooled to 10°C and stirred for 1 h at same temperature. The solid material was filtered and product washed with chilled methanol. The product was dried under vacuum at 70-75°C to yield 8.0 g (80%) of title compound 1.

**RESULTS AND DISCUSSION**

In the present communication, we restrict the formation of 2 during the cyclisation of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile, 3 by carrying it out out in the absence of a base and using methanol at reflux temperature (Scheme 1). The progress of reaction was monitored by HPLC. The reaction was completed in about 15 h with no formation of Impurity 2 and formation of desired product in > 97% with much less impurities.

In the course of our ongoing efforts to increase the yield and further simplification of the process from a commercial aspect, improvements have been made, by charcoaling the reaction mixture at intermediate stage to reduce the solvent consumption and avoiding multiple recrystallizations.
The process disclosed herein, the suspension is stirred under reflux for 2 to 4 h to attain the equilibrium stage. The equilibrium stage was attained when a clear solution of said suspension is obtained. Further, the clear solution is treated with activated carbon at a temperature preferably between 60-65°C. The filtrate was further refluxed for about 14 h for completion of the reaction.

![Chemical structures](image)

Scheme 1: Synthesis of Lamotrigine, 1

During the process optimization we have studied the effects of different pH conditions and role of the same. We have done the cyclisation of 3 in methanol under acidic condition (pH 1-2) and monitored the progress of reaction by HPLC and observed the formation of one new impurity about 6.9% at RRT 1.7 which is not captured in European & US pharmacopoeias. The same cyclisation reaction performed under basic condition (pH 8-9) and at neutral conditions (pH 6-7) results in the formation of the said impurity but only to an extent of 1.0% and 0.9% by HPLC. Due to the formation of unknown impurity under acidic conditions isolated yield of lamotrigine (1) was low (80%) compared to isolated yield (94%) in neutral reaction conditions. However, in basic medium the yield was 86%, may be due to the higher solubility of Lamotrigine. The results are tabulated in Table 1.

Table 1. Preparation of Lamotrigine (1) under different pH conditions

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>pH</th>
<th>HPLC (Area %) details</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During reaction progress</td>
<td>After Crystallization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>~7.0</td>
<td>97.70</td>
<td>0.90</td>
</tr>
<tr>
<td>2</td>
<td>7-8</td>
<td>97.50</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>6-7</td>
<td>92.27</td>
<td>6.87</td>
</tr>
</tbody>
</table>

*ND= Not detectable

To find the reason behind the formation of impurity, we have isolated the unknown impurity using column chromatography and characterized it by physical and spectral analyses (mp, IR, Mass spectroscopy, NMR spectroscopy (1H, 13C, and NOESY)). The response of aromatic proton during irradiation of N-methyl proton (singlet) and vice-versa was observed. It concludes the
presence of methyl (on amine), which is nearer to the aromatic system (ie) N^5 position of Lamotrigine (1) rather than the amine away from the aromatic substitution (ie, amine at 3rd position). Based on all the spectral data we confirmed the unknown impurity as 6-(2,3-dichlorophenyl)-N^5-methyl-1,2,4-triazine-3,5-diamine (4). See also figures 1, 2, 3, 4 and 5 given in supporting information.

Scheme 2: Synthesis of N-methyl impurity of Lamotrigine

Impurity 4 physical and spectral data. mp: 244° C – 248° C; IR spectrum (KBr): 3395, 3315, 3109, 2949, 2746, 1648, 1561, 1510, 1438, 1136, 799; MS: m/z 271 (M+1); ^1H NMR (300 MHz, DMSO-d6): δ 7.74 (dd, 1H), 7.47 (d, H), 7.45 (s, 1H), 7.30 (br s, NH2); 3.86 (s, 3H); ^13C-NMR (300 MHz, DMSO-d6): δ 162.6, 160.5, 139.7, 135.8, 131.7, 131.1, 130.7, 130.4, 128.2, 53.4; HPLC purity: 98.30%.

The single solvent was used in the process that is easily recyclable, reduces the consumption of solvent and makes the process more cost-effective and environment friendly. The invention is further explained in detail in the following examples.

CONCLUSION

In conclusion, a cost-effective and commercial process for preparation of Lamotrigine (1) with improved yield, purity and shorter reaction time was reported. This process also avoids the isolation of crude and involves single step purification process to get pure Lamotrigine which is having 99.9% purity by HPLC and high yield (94%).

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REFERENCES

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