Development of A Novel One-pot Process for the Synthesis of Tolcapone

ARJUN BODKHE*, VILAS SUDRIK, DNYANESHWAR KARPE and SHAMRAO LAWANDE

1,2Department of Chemistry from Shri Chhatrapati Shivaji Mahavidyalaya, Shrigonda, Maharashtra, India.
*Corresponding author Email:arjunbodkhe@gmail.com

http://dx.doi.org/10.13005/ojc/380631

(Received: November 15, 2022; Accepted: December 16, 2022)

ABSTRACT

Novel one-pot process for the preparation of tolcapone., 2-methoxy anisole compound 9 treated with 4-methyl benzoyl chloride compound 10 using aluminium chloride gives 4-hydroxy-3-methoxy-4-methyl benzophenone compound 11 Further on nitration using new nitrating agent i.e. melamine nitrate to get corresponding nitro benzophenone compound 6. After demethylation using 48% HBr-Acetic acid to get pure Tolcapone 1 by the cost-effective and commercially feasible process.

Keywords: One-pot process, Melamine nitrate, Parkinson's disease, Tolcapone, Industrially feasible.

INTRODUCTION

Tolcapone FDA an approved drug used for Parkinson's disease. It inhibits the Enzyme Catechol-O methyltransferase (COMT). By inhibiting COMT, Tolcapone decreases the degradation of levodopa in the periphery, which allows more levodopa to reach the brain and potentially allows for a decrease in the dosage of levodopa. 1,2 Tolcapone is available in a tablet of 100 mg and 200 mg oral dose. 3 Overdose of Tolcapone cause liver toxicity. 4

Patients with Parkinson's disease will be identified in the society by their primary care physician, but further care should involve the efforts of an entire healthcare team. 5

Bernauer K.6,7 first disclosed tolcapone preparation in patents.6,7 (Scheme 1). Another method is described in the same patent as shown in Scheme 2.

Further Bruhin J.8 prepared tolcapone from 1,2-dimethoxybenzene and p-methyl benzoyl chloride as shown in Scheme 3 below.
Manikumar G.\textsuperscript{9} reported another method for tolcapone synthesis from 4-benzyloxy-3-methoxy benzaldehyde which is schematically represented below (Scheme 4).
Reddy B.S.\textsuperscript{10} discloses another route for synthesizing Tolcapone from 3-nitro 4, 5-dihydroxy benzoic acid as shown below (Scheme 5).

Irudayaraj V.P.R.\textsuperscript{11} prepared Tolcapone as per below (Scheme 6).

The above processes used hazardous chemicals, longer reaction times and more steps hence, not cost-effective and not commercially viable and the isolated yield was low.

Hence need to develop a less hazardous and cost-effective process of Tolcapone 1 which gives maximum conversion and purity.

We report here a one-pot process that is cost-effective and commercially viable.

**RESULTS AND DISCUSSION**

Our reported one-pot process is cost-effective and commercially viable to get pure Tolcapone 1 with maximum purity and conversion. (Scheme 7).

The prior art process involves purification processes during the preparation of Tolcapone, making it difficult and costlier on large-scale preparation. The impurities formed during the process, if not removed then it is undesirable in the active pharmaceutical product since they may harm the patient being treated. Hence, need to develop a less hazardous and cost-effective
process of Tolcapone 1. In this article, we disclosed cost-effective and commercially viable one-pot synthesis of tolcapone 1 from commercially available 1, 2 dimethoxy benzene.

Initially, treatment of 1,2-dimethoxy benzene 9 and 4-methyl benzoyl chloride 10 with aluminum chloride to form benzophenone derivative 11. Further on nitration using melamine nitrate in situ. By using 48% HBr-Acetic acid to produce pure Tolcapone 1.

Nitration of phenol gives a di-nitro compound by use of the nitrating mixture. To overcome this problem need to use a mild nitrating agent. For regioselective nitration of phenol, melamine nitrate is the best choice. This inspired us to think that melamine nitrate may be useful in Tolcapone synthesis. Before this nobody used melamine nitrate in tolcapone synthesis. So in this process, we used melamine nitrate for regioselective nitration.

Table 1: Screening in different solvents by use of melamine nitrate (step ii) and yield of Tolcapone 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrating agent</th>
<th>Solvent</th>
<th>Tolcapone 1 Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melamine nitrate</td>
<td>DCM</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Melamine nitrate</td>
<td>Chloroform</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Melamine nitrate</td>
<td>CCl₄</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Melamine nitrate</td>
<td>Acetone</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>Melamine nitrate</td>
<td>Methanol</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>Melamine nitrate</td>
<td>Ethanol</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Melamine nitrate</td>
<td>IPA</td>
<td>65</td>
</tr>
</tbody>
</table>

Reaction Condition: 4-hydroxy -3-methoxy-4-methyl benzophenone (in situ), melamine nitrate (10 mmoles), TsOH (0.14 mmole), Solvent- Acetone, maintaining 12 hrs 1 isolated yield.

We study the effect of the use of different solvents at low temp. i.e. 40°C and impact on the output of Tolcapone 1. In a variety of solvents and carried out Nitration using melamine nitrate (step ii) for our one-pot process and we got the following observations.

By use of DCM solvent, we got a 65% yield.
By use of chloroform solvent, we got a 62% yield.
By use of CCl₄ solvent, we got a 55% yield.
By use of acetone solvent, we got a maximum yield of 75% yield.

By use of methanol solvent, we got a 64% yield.
By use of ethanol solvent, we got a 68% yield.
By use of IPA solvent, we got a 65% yield. (Table 1)

Hence, acetone is an excellent solvent for nitration and we got a maximum yield of final Tolcapone 1 by comparing it with other solvents.

We study the effect of different temp. using acetone as a solvent for nitration using melamine nitrate (step ii) and to check the maximum yield of Tolcapone 1 for our one-pot process. We carried out several experiments and got the following observations.

Nitration at 30°C in acetone we got 75% yield.
Nitration at 35°C in acetone we got 70% yield.
Nitration at 40°C in acetone we got 75% yield.
Nitration at 45°C in acetone we got 70% yield.
Nitration at 50°C in acetone we got 60% yield.
Nitration at 55°C in acetone we got 55% yield.
Nitration at 60°C in acetone we got 50% of the yield.

Hence, by increasing temp. for the nitration step, the yield of tolcapone 1 decreases. Reaction favored at lowered temp. Hence, 40°C is the best temperature and got the maximum yield.

Table 2: Screening at different temp. in acetone solvent (step ii) and yield of Tolcapone 1

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Nitrating agent</th>
<th>Maintaining Time (h)</th>
<th>Temp. (°C)</th>
<th>Tolcapone 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>Melamine nitrate</td>
<td>12</td>
<td>60</td>
<td>50</td>
</tr>
</tbody>
</table>

Reaction Condition: 4-hydroxy -3-methoxy-4-methyl benzophenone (in situ), melamine nitrate (10 mmoles), TsOH (0.14 mmole), Solvent- Acetone, maintaining 12 h 1 isolated yield.

Table 3: Different Melamine nitrate concentration (step-ii) and yield of Tolcapone 1

<table>
<thead>
<tr>
<th>Amount of melamine nitrate (mmoles)</th>
<th>Reaction Time (h)</th>
<th>Tolcapone 1 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>7.9</td>
<td>18</td>
<td>62</td>
</tr>
<tr>
<td>8.6</td>
<td>15</td>
<td>71</td>
</tr>
<tr>
<td>9.3</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>10.8</td>
<td>12</td>
<td>75</td>
</tr>
</tbody>
</table>

Reaction Condition: 4-hydroxy -3-methoxy-4-methyl benzophenone (in situ), TsOH (0.14 mmole), Solvent-Acetone 1 isolated yield at 40°C

We study the effect of the use of different solvents at low temp. i.e. 40°C and impact on the output of Tolcapone 1. In a variety of solvents and carried out Nitration using melamine nitrate (step ii) for our one-pot process and we got the following observations.
Nitration was studied at different Melamine nitrate concentrations i.e. 7.2, 7.9, 8.6 and 9.3 mmoles at different maintaining times and checked the effect on the yield of Tolcapone 1. We got 55%, 62%, 71% and 75% yield, further increase of melamine concentration yield is the same. Based on optimization results by the use of 9.3 mmoles of melamine nitrate in acetone solvent maintaining the reaction at 40°C for 12 h stirring, we got maximum yield i.e.75%.

Table 4: Optimised conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrating agent</th>
<th>Solvent</th>
<th>Reaction Time (h)</th>
<th>Temp. (°C)</th>
<th>Tolcapone 1 Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melamine nitrate (9.3 mmoles)</td>
<td>Acetone</td>
<td>12</td>
<td>40</td>
<td>75</td>
</tr>
</tbody>
</table>

Some advantages of the one-pot process are like in situ process and the use of less hazardous reagents.

EXPERIMENTAL

Materials

All solvents and reagents used from analytical grade (A.R.) and purchased from Sigma Aldrich. 1,2-dimethoxy benzene, p-methyl benzoyl chloride, aluminum chloride, Melamine nitrate, 48% HBr-Acetic acid. Progress of reaction checked on Thin Layer Chromatography (TLC).

Instrumentation

The PMR spectra were recorded on 400MHz and CMR spectra on 100MHz Bruker Spectrophotometer in DMSO/CDCl₃ using a Bruker instrument. The chemical shift values in the δ scale. Tetramethylsilane was used as an internal standard.

Experimental procedure for Preparation of Tolcapone (1)

1, 2 dimethoxy benzene 9 (1.0 g, 7.2 mmol) dissolve in DCM (10 mL), cool it at 0-5°C then add dropwise p-methyl benzoyl chloride 10 (2.22 g, 1.4 mmol) in 10 minute. Followed by the addition of aluminium chloride (4.32 g, 32.4 mmol) and DCM (10 mL) and stirred for 1 h at 0-5°C temperature, monitoring reaction TLC. After completion of reaction raise temperature to 28°C and maintain for 8 hours. Again monitor the reaction by TLC. After completion of the reaction give 10 mL water washing to the organic layer. Concentrate organic layer to form residue 11. Add acetone (10 ml), melamine nitrate (1.77 g, 9.3 mmol) and PTSA (0.024 g, 0.14 mmol) at 25-30°C, heat reaction mass to 40°C and stirred for 12 h, monitor reaction by TLC. Concentrate acetone to get residue 6. To a concentrated reaction mass add Toluene (10 mL), 48% HBr-AcOH (2 mL) ad heat to 100°C for 3 h, cool to 25-30°C.

Distilled out toluene and add Chloroform (10 mL) and water (10 mL) stirred for 30 minute. at 25-30°C. Distilled out chloroform layer under vacuum. Add Chloroform (10 mL) to the reaction mass and stirred for 30 minute. at 0-5°C. Filter product and dry at 40-45°C under vacuum to get pure Tolcapone 1 (1.50 g; 75% yield) as a yellow solid.

Spectral data

HPLC purity=99.17% (m.p.147°C) (lit.11:146-148°C); IR (KBr cm⁻¹): 3392 (-OH), 2924 (-CH₃), 1629 (-CO), 1541 and 1363 (-NO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.43 (s, 3H), 7.38 (d, 2H), 7.48 (s, 1H), 7.65 (d, 2H), 7.67 (d 1H), ¹³C NMR, DMSO-d₆): δ 21.61, 118.29, 119.45, 127.43, 129.60, 130, 134.66, 137.09, 143.39, 146.25, 148.19, 193.30; Mass Spectra (EI): M⁺=273, m/z= 119 (+OC-Ph-CH₃), m/z= 91 (.Ph-CH₃).

CONCLUSION

In conclusion, we have developed an In-situ novel cost-effective and commercially feasible one-pot process for the preparation of pure Tolcapone 1 without the isolation of any intermediate.

ACKNOWLEDGEMENT

We thank the Principal and Management of Shri Chhatrapati Shivaji Mahavidyalaya, Shrigonda for providing infrastructure for this research work.
REFERENCES


11. Irudayaraj V. P. R.; Govindaraj Rao V.; Hanumantha D.; Gnanapragasam A.; Jayaraman B.; Thanukrishnan K. Tangirala V.; Sengodan S.; Ranganathan S., 201641042235, **2018**.