Synthesis of β-Lactams

Definition

Stereoselective synthesis of cis and trans β-lactams under diverse conditions is performed. Numerous conditions are used for this study. The formation of β-lactam depends on the conditions of the experiments, structures of the imines and acid chlorides, order of addition of the reagents, reaction temperature, and solvents. A few mathematical graphs are plotted to explain the results.

1. Introduction

β-Lactams are medicinally active molecules. Several publications have disclosed the anticancer, antibacterial, antifungal, cholesterol absorption inhibitors, anti-inflammatory, anti-hepatitis, analgesic activities and antihyperglycemic properties of β-lactams. Many methods are available for the preparation of β-lactams, such as Staudinger cycloaddition, hydroxamate approach, ester enolate-imine condensation, alkene-isocyanate method, the alkyne-nitrone reaction (Kinugasa reaction), catalytic asymmetric synthesis and polymer-supported method. Our group has also demonstrated the synthesis of β-lactams.

Depending on the reactants and reaction conditions the stereochemistry of β-lactams may alter. Both the stereoisomers are important for medicinal applications. Thus, controlling diastereoselectivity (cis or trans) of the β-lactams is important. Stereoselective synthesis of diverse β-lactams following a variety of conditions through cycloaddition reaction of imines and acid chlorides is described. The results are also explained by plotting the ratios of the two isomeric β-lactams formed with respect to the time of the reaction.

2. Results with Acetoxy Derivative

The Staudinger reaction mainly required an imine, a tertiary base, and an acid chloride. The reaction of an acid chloride or equivalent with an imine in the presence of a tertiary produced cis and trans isomers of β-lactams. In this study, ten different reaction conditions including microwave-induced organic reaction enhancement (MORE) chemistry techniques and traditional synthesis/one-pot synthesis was adopted. A domestic microwave oven was used for irradiation and a large Erlenmeyer flask was used as the reaction vessel.

Experiment 1:

Microwave irradiation of a solution of imine with an acid chloride in chlorobenzene produced a mixture of cis and trans β-lactams. N-methylmorpholine (NMM) was used as a base for this reaction instead of trimethylamine (TEA). Non-polar solvent, benzene was chosen as the reaction medium and reaction temperature was kept in between 45°C-50°C. It was observed that the reaction is not completed after 4 min and it produced a mixture of cis (70%) and trans (30%) β-lactams. The ratios of the cis and trans-isomers were determined from the coupling constants of the C3 and C4 protons of the β-lactam rings.

Experiment 2:

To identify the effect of the polarity of the solvent on stereoselectivity, chlorobenzene was used. Chlorobenzene being a polar solvent absorbs microwave energy efficiently. NMM was chosen as a base and reaction temperature was between 95°C-100°C. The reaction was completed within 5 min and it produced
a mixture of cis (5-10%) and trans (90-95%). Thus this reaction condition was suitable for the preparation of trans β-lactams.

**Experiment 3:**

The third reaction was undertaken without any solvent. The reaction between the imine and acid chloride was conducted in a microwave oven at the temperature range of 95°C-100°C in the presence of NMM. The temperature was noted when the reaction was performed with 10 mmol of the substrates. The reaction produced a mixture of cis (5-10%) and trans (90-95%) isomers. It appeared that the solvent makes the reaction slower.

**Experiment 4:**

The reaction was conducted in a preheated oil bath at 90°C in the presence of NMM. The reaction was completed within 5 min and it gave a mixture of cis (5-10%) and trans (90-95%) β-lactams.

**Experiment 5:**

In another experiment, the oil bath was used, but the temperature was gradually increased from room temperature to 90°C. Chlorobenzene was chosen as the solvent and NMM was the base. The same reaction of the imine with acid chloride was performed and it was completed within 15 min. It produced a mixture of cis (50%) and trans (50%) β-lactams.

**Experiment 6:**

Another variation of this reaction was conducted using a one-pot method. In this experiment, benzaldehyde and p-anisidine were reacted in the presence of clay. NMM, AcOCH₂COCl, and chlorobenzene were added to it. Irradiating the reaction mixture in a microwave for 2 min, the trans isomer of β-lactam was formed. The reaction produced only the cis isomer in the absence of microwave irradiation at room temperature.

### 3. Results with Acetoxy Derivative:

The results obtained under different reaction conditions were extremely interesting. Table 1 showed the ratios of the cis and trans β-lactams obtained under different conditions. The data showed that reaction conditions 2, 3, 4, and 6(a) were helpful for the synthesis of trans β-lactam. In contrast, reaction conditions 1 and 6(b) were good for the synthesis of cis β-lactam. On the other hand, reaction condition 5 was perfect for the synthesis of a mixture of cis and trans β-lactams. The graphical representation of these observations under diverse conditions is shown in Figure 1.

**Table 1:** Ratios of the cis and trans lactams under diverse conditions.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Reaction temperature</th>
<th>Time</th>
<th>cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45°C-50°C</td>
<td>4 min</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>95°C-100°C</td>
<td>5 min</td>
<td>5:95</td>
</tr>
<tr>
<td>3</td>
<td>95°C-100°C</td>
<td>3 min</td>
<td>5:95</td>
</tr>
<tr>
<td>4</td>
<td>90°C</td>
<td>5 min</td>
<td>5:95</td>
</tr>
</tbody>
</table>
Table 2: Ratios of the cis and trans lactams with respect to time.

<table>
<thead>
<tr>
<th>Time</th>
<th>Temperature</th>
<th>Power</th>
<th>Cis</th>
<th>Trans</th>
<th>cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>70°C</td>
<td>Low</td>
<td>85</td>
<td>15</td>
<td>85:15</td>
</tr>
<tr>
<td>2 min</td>
<td>75°C</td>
<td>Low</td>
<td>80</td>
<td>20</td>
<td>80:20</td>
</tr>
<tr>
<td>3 min</td>
<td>80°C</td>
<td>Low</td>
<td>60</td>
<td>40</td>
<td>60:40</td>
</tr>
<tr>
<td>Time</td>
<td>Temperature</td>
<td>Power</td>
<td>Ratio 1</td>
<td>Ratio 2</td>
<td>Ratio</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>-------</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>4 min</td>
<td>95°C</td>
<td>Low</td>
<td>56</td>
<td>44</td>
<td>56:44</td>
</tr>
<tr>
<td>5 min</td>
<td>97°C</td>
<td>Low</td>
<td>55</td>
<td>45</td>
<td>55:45</td>
</tr>
<tr>
<td>4 min</td>
<td>110°C</td>
<td>High</td>
<td>45</td>
<td>55</td>
<td>45:55</td>
</tr>
</tbody>
</table>

Figure 2 represented graphically the variation of the cis and trans ratios with irradiation time up to 5 min at low power mode. The data indicated that the cis/trans ratio decreases with the progress of time and finally stabilizes at 4-5 min.

**Figure 2**: Graphical representation of the cis/trans ratio of β-lactam with the time of irradiation.

**Experiment 8**:
Microwave irradiation of activated phthalimido acetic acid with imine in the presence of chlorobenzene and NMM produced a mixture of cis and trans β-lactams.

**Experiment 9**:
Microwave irradiation of acid chloride with imine (produced from D-glyceraldehyde) in the presence of chlorobenzene and NMM in 0-5 min gave cis β-lactam. However, irradiation of acid chloride with imine (obtained from L-glyceraldehyde) gave cis β-lactam with opposite absolute stereochemistry.

**Experiment 10**:
trans β-Lactam was formed in 100% yield by slow addition of NMM in ethylene dichloride to a refluxing solution of imine and the acid chloride.

## 4. Conclusion
The stereochemistry (cis and/or trans) of the β-lactams under diverse conditions was analyzed. The data showed that some reaction conditions are favorable for the synthesis of trans β-lactams. On the other hand, some reaction conditions are favorable for the synthesis of cis β-lactams. A few reaction conditions are favorable for the synthesis of a mixture of cis and trans β-lactam. The diastereoselectivity of the β-lactam formation strongly depends on reactants and reaction conditions. The data suggest that the β-lactam formation reaction depends on two pathways. One pathway is favored at high temperatures and or concentrated solution/microwave-mediated reaction conditions.

**Contributors**
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References


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