

Synthesis of β -Lactams

Subjects: [Chemistry](#), [Organic](#)

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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.

β -Lactam

Stereoselectivity

Microwave

1. Introduction

β -Lactams are medicinally active molecules. Several publications have disclosed the anticancer ^[1], antibacterial ^[2], antifungal ^[3], cholesterol absorption inhibitors ^[4], anti-inflammatory ^[5], anti-hepatitis ^[6], analgesic activities ^[7] and antihyperglycemic ^[8] properties of β -lactams. Many methods are available for the preparation of β -lactams, such as Staudinger cycloaddition ^[9], hydroxamate approach ^[10], ester enolate-imine condensation ^[11], alkene-isocyanate method ^[12], the alkyne-nitrone reaction (Kinugasa reaction) ^[13], catalytic asymmetric synthesis ^[14] and polymer-supported method ^[15]. Our group has also demonstrated the synthesis of β -lactams ^[16].

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 [17] 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.

Experiments	Reaction temperature	Time	<i>cis/trans</i> ratio
1	45°C-50°C	4 min	70:30
2	95°C-100°C	5 min	5:95
3	95°C-100°C	3 min	5:95
4	90°C	5 min	5:95
5	RT-90°C	15 min	50:50
6 (a) [†]	95°C-100°C	5-10 min	0:100
6 (b) [†]	0°C-RT	Overnight	100:0

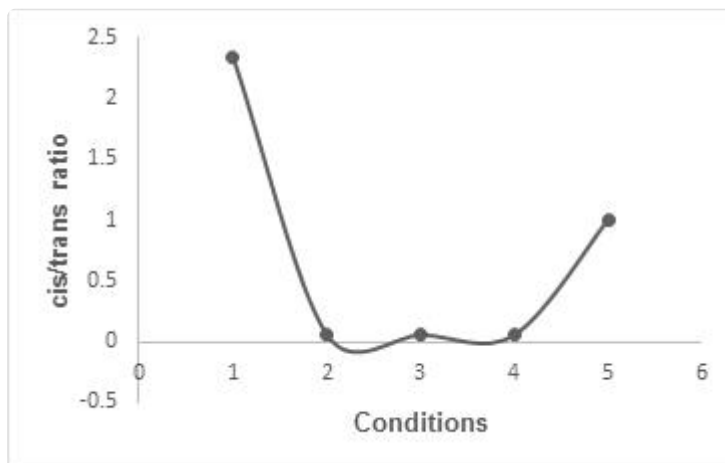


Figure 1: Graphical representation of the β -lactam formation under diverse conditions.

Also, the *cis* β -lactams did not change to *trans* β -lactams when they were treated with NMM in chlorobenzene in a domestic microwave oven for 2-3 min even at 90°C. This experiment established that there is no isomerization of the *cis* β -lactams to the more thermodynamically stable *trans* β -lactams under microwave irradiation at a high temperature.

The reaction was performed with phenyl-substituted imine and similar ratios of the *cis* and *trans* isomers were formed.

Experiment 7:

The reaction of benzyloxyacetyl chloride with imine in the presence of dimethyl-formamide (DMF) and NMM also yielded a mixture of *cis* and *trans*- β -lactam in varying proportions.

Table 2 showed the *cis/trans* ratios during the time of microwave irradiation. The results showed that *cis* lactams were formed with low power radiation. On the other hand, high power radiation generated *trans* lactams formation preferentially.

Table 2: Ratios of the *cis* and *trans* lactams with respect to time.

Time	Temperature	Power	Cis	Trans	cis/trans ratio
1 min	70°C	Low	85	15	85:15
2 min	75°C	Low	80	20	80:20

3 min	80°C	Low	60	40	60:40
4 min	95°C	Low	56	44	56:44
5 min	97°C	Low	55	45	55:45
4 min	110°C	High	45	55	45:55

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.

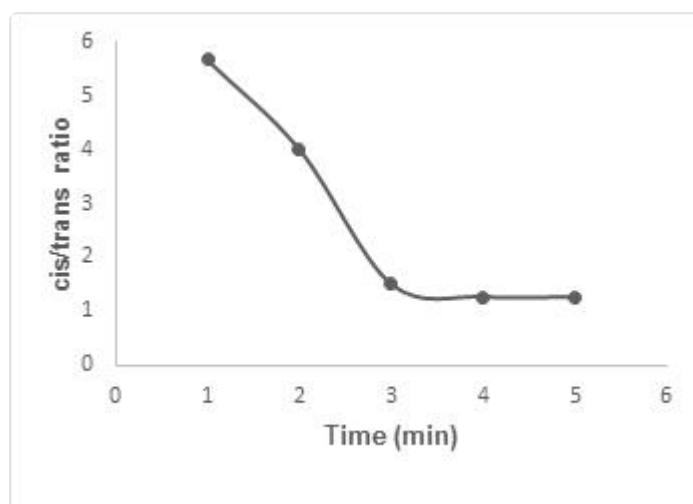


Figure 2: Graphical representation of the *cis/trans* ratio of β -lactam with the time of irradiation.

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.

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