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Stereoselective synthesis of β-lactams under diverse conditions: Unprecedented observations

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In this work we have investigated stereoselective synthesis of *cis* and/or *trans* β-lactams under diverse conditions. Ten different reaction conditions have been used for this study. It is important to note that the stereochemistry of the β-lactam formation reaction depends on the conditions of the experiments, structures of the imines and acid chlorides, order of addition of the reagents, reaction temperature and solvents. To summarize the results, mathematical graphs are plotted.

Keywords: β-Lactam, stereoselectivity, microwave.

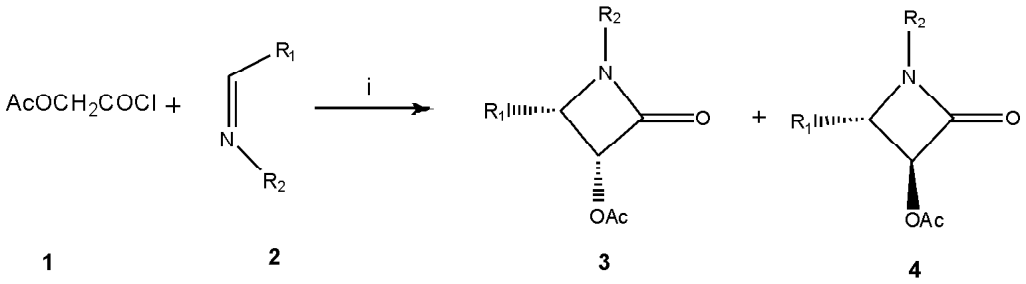
Introduction

β-Lactams are medicinally important compounds. Several groups have reported the anticancer[1], antibacterial[2], antifungal[3], cholesterol absorption inhibitors[4], anti-inflammatory[5], antihepatitis[6], analgesic activities[7] and antihyperglycemic[8] activities of β-lactams. Because of the wide range of medicinal activities of β-lactams, synthesis of these types of molecules as biologically active compounds is very crucial. A number of methods are currently available for the preparation of β-lactams, such as Staudinger cycloaddition reaction[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 synthesis[15]. Our group has demonstrated the synthesis of β-lactams by various methods extensively[16].

During our synthetic study, it has come to our attention that depending on the reactants and reaction conditions the stereochemistry of the products may alter and thus, various proportions or single stereoisomer (i.e. *cis* or *trans*) of β-lactam may result in from a particular reaction. Both the stereoisomers are equally important for pharmaceutical application. For example, *cis* amido β-lactam is the core part of penicillin and cephalosporin, but *trans* β-lactam is the core part of thienamycin and several other antibiotics. Thus, controlling diastereoselectivity (*cis* or *trans*) of the β-lactams formation is an important task during synthesis. This paper has described the stereoselective synthesis of diverse β-lactams following a variety of conditions through cycloaddition reaction of imines and acid chlorides. The results are also summarized by plotting the ratios of the two isomeric β-lactams formed with respect to time of the reaction required for completion. Despite a wide range of publications on the synthesis of β-lactams, mathematical graphs either in qualitative or quantitative forms have not been advanced.

Results with acetoxy derivative under different conditions

Staudinger cycloaddition reaction for the synthesis of monocyclic β-lactams was the method for our current investigation. This reaction mainly required an imine, a tertiary base and an acid chloride. As shown in Scheme 1, the reaction of an acid chloride (**1**) with a Schiff base/imine (**2**) in the



1 2 3 4

a: R_1 = Ph, R_2 = *p*-anisyl; b: R_1 = R_2 = Ph; c: R_1 = R_2 = *p*-anisyl.

Scheme 1. Synthesis of β-lactam isomers **3** and **4** under diverse conditions.

presence of a tertiary base under suitable conditions produced *cis* (**3**) and *trans* (**4**) isomers of β-lactams. The yield of the *cis* (**3**) and *trans* (**4**) isomers varied with reaction conditions. In this study we considered ten different reaction conditions including microwave-induced organic reaction enhancement (MORE) chemistry techniques and traditional synthesis/one pot synthesis. For microwave-induced synthesis, a domestic microwave oven is used for irradiation and a large Erlenmeyer flask was used as the reaction vessel. By the proper adjustments of the on-off cycle present in microwave and a 'heat sink', the temperature of the reaction mixture was kept always below 110°C, when chlorobenzene or DMF were the solvents. After the microwave irradiation was stopped the approximate temperature of the reaction was determined by using a thermometer.

Experiment number 1:

Irradiation of a solution of imine with acid chloride in benzene using a domestic microwave oven[17] produced a mixture of *cis* and *trans* β-lactams. Because of the high boiling, lower pKa (7.61) and good solubility in organic solvents, N-methylmorpholine (NMM) was used as a base for this reaction instead of trimethylamine (TEA). Non-polar solvent, for example, benzene was chosen as the reaction medium and reaction temperature was kept in between 45–50°C. It was observed that the reaction is not completed after 4 min and it produced a mixture of *cis* **3** (70%) and *trans* **4** (30%) β-lactams. Thus this reaction condition was favorable for the synthesis of *cis*-lactams, although all starting materials were not consumed. The ratios of the *cis* and *trans*-isomers were determined from the coupling constants of the C_3 and C_4 protons of the β-lactam rings. An identical procedure was followed to assign the stereochemistry of the β-lactams in the following experiments as well.

Experiment number 2:

In the second example, we also used microwave irradiation (MWI) for the formation of β-lactam derivatives from the solution of imine and acid chloride. To identify the effect of polarity of the solvent on stereoselectivity, chlorobenzene was used. Chlorobenzene absorbs microwave energy efficiently. NMM was chosen as a base for this reaction and reaction temperature was in between 95–100°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 favorable for the synthesis of *trans* β-lactams.

Experiment number 3:

To identify the effects of the solvent for the synthesis of lactam, 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 95–100°C in the presence of NMM. It was difficult to note the temperature when the reaction was performed with 1 mmol scale. However, it was done when the reaction was performed with 10 mmol of the substrates. The reaction was completed within 3 min and it produced a mixture of *cis* (5–10%) and *trans* (90–95%) isomers. It appeared that the solvent makes the reaction slower. A higher dilution of the reaction mixture probably was responsible for a slower reaction in the presence of solvent.

Experiment number 4:

In order to determine the effects of microwave irradiation on the stereochemistry and yield of the products, a method

was adopted with a preheated oil bath. For this purpose, an oil bath was preheated at 90°C. The reaction of imine with acid chloride in chlorobenzene and NMM at 90°C using the oil bath as the heating source was performed. The reaction was completed within 5 min and it produced a mixture of *cis* (5–10%) and *trans* (90–95%) β-lactams.

Experiment number 5:

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

Experiment number 6:

Another variation of this reaction was performed following a one-pot approach. In this experiment benzaldehyde **6** and *p*-anisidine **5** were used as the reactants, in the presence of clay. NMM, $AcOCH_2COCl$, and chlorobenzene were added to the reaction mixture. Upon irradiating the reaction mixture under a microwave for 2 min, *trans* isomer of β-lactams **4a** was only formed. The reaction produced the *cis* isomer **3a** without microwave irradiation in room temperature.

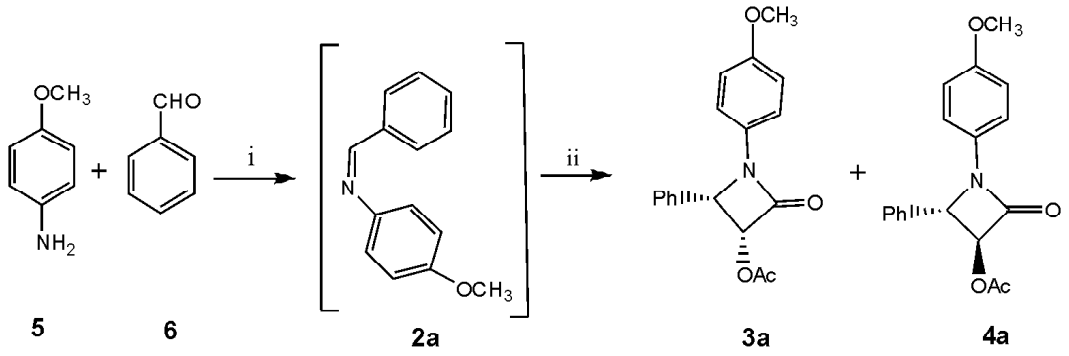
Table 1. Ratios of the *cis* **3** and *trans* **4** lactams under diverse conditions

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

†The conditions of the experiments were different as discussed in the text.

yield. While reaction conditions 1 and 6(b) were favorable for the synthesis of *cis* β-lactam in good yield. In contrast, reaction condition 5 was favorable for the synthesis of a mixture of *cis* and *trans* β-lactams. Graphical representation of the β-lactam formation under diverse conditions is shown in Fig. 1.

Also, it was observed that 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. These experiments established that there is no



Scheme 2. Reaction between benzaldehyde and *p*-anisidine. Reagents and conditions: (i) clay; (ii) $AcOCH_2COCl$, chlorobenzene, MWI.

3b and **4b**.

Discussions of the results with acetoxy derivative:

The results obtained under different reaction conditions were extremely intriguing since acetoxy β-lactams are important starting materials. The Table 1 showed the ratios of the *cis* and *trans* β-lactams under diverse conditions. The data indicated that the reaction conditions 2, 3, 4 and 6(a) were favorable for the synthesis of *trans* β-lactam in good isomerization of the *cis* β-lactams to the more thermodynamically stable *trans* β-lactams under microwave irradiation at a high temperature (Scheme 3).

The reaction was applied to phenyl-substituted (with bromo, **2b**) imine and similar ratios of the *cis* and *trans* isomers are formed (**3b** and **4b**). These compounds were characterized.

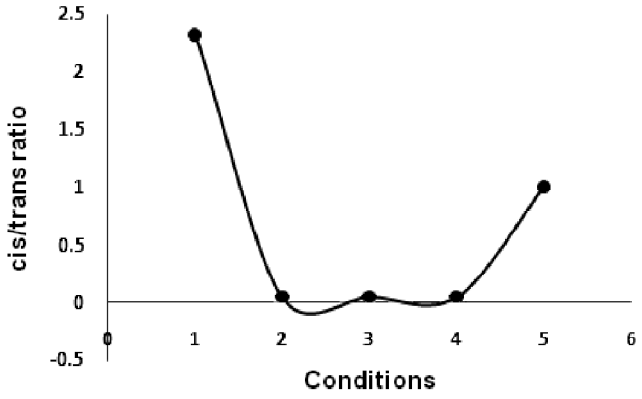


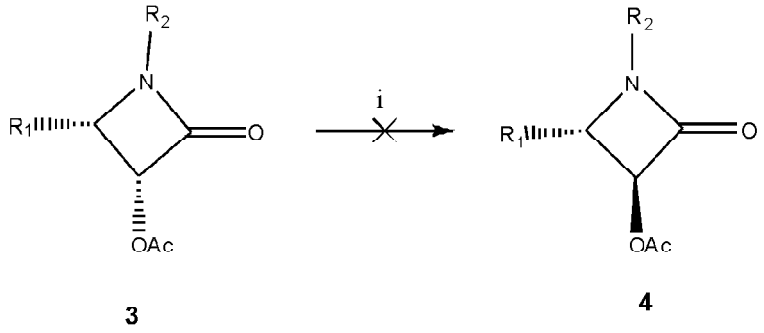
Fig. 1. Graphical representation of the β-lactam formation under 1-5 conditions.

Experiment number 7:

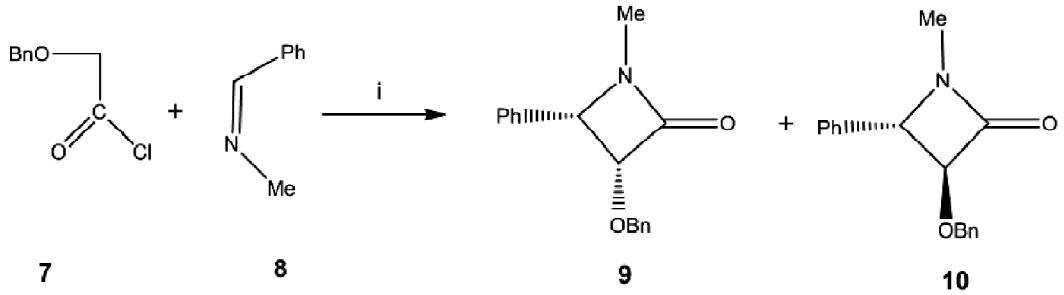
The reaction of benzyloxyacetyl chloride (**7**) with imine **8** in the presence of dimethylformamide (DMF) and NMM also produce a mixture of *cis* and *trans* β-lactam (**10** and **9**) in varying proportion (Scheme 4).

The Table 2 showed the *cis*/*trans* ratios during the time of irradiation at low power and high power of microwave irradiation. The data showed that *cis* lactams were formed when low power radiation was used. On the other hand, high power radiation favored *trans* lactams formation.

The Fig. 2 showed graphically the variation of the *cis* **9**



Scheme 3. Treatment of *cis* β-lactam with NMM in chlorobenzene. Reagents and conditions: (i) MWI, NMM, in chlorobenzene, RT–90°C, 2–4 min.



Scheme 4. Synthesis of β-lactam isomers **9** and **10** under microwave irradiation. Reagents and conditions: (i) DMF, NMM, MWI.

Table 2. Ratios of the *cis* **9** and *trans* **10** lactams with respect to time

Time (min)	Temp. (°C)	Power	*cis* (**9**)	*trans* (**10**)	*cis*/*trans* ratio
1	70	Low	85	15	85:15
2	75	Low	80	20	80:20
3	80	Low	60	40	60:40
4	95	Low	56	44	56:44
5	97	Low	55	45	55:45
4	110	High	45	55	45:55

and *trans* **10** ratios with irradiation time up to 5 min at low power mode. The data showed that *cis*/*trans* ratio decreases with time and finally stabilizes at 4–5 min.

Experiment number 8:

Microwave irradiation of activated phthalimido acetic acid **11** with imine **2** in the presence of chlorobenzene and NMM produced a mixture of corresponding *cis* and *trans* β-lactam (**12** and **13**) in varying proportions (**12a**:**13a** = 10:90, **12b**:**13b** = 10:90) (Scheme 5).

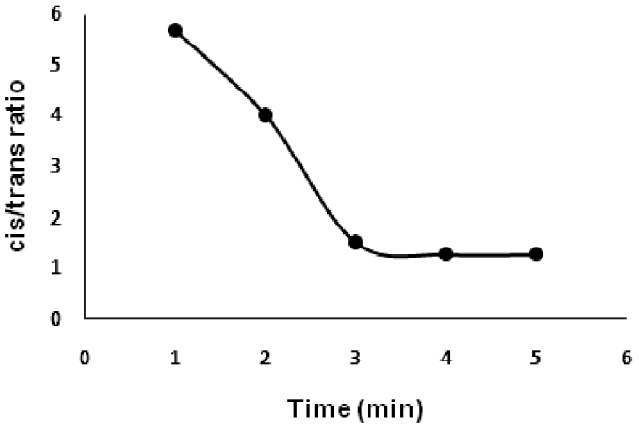


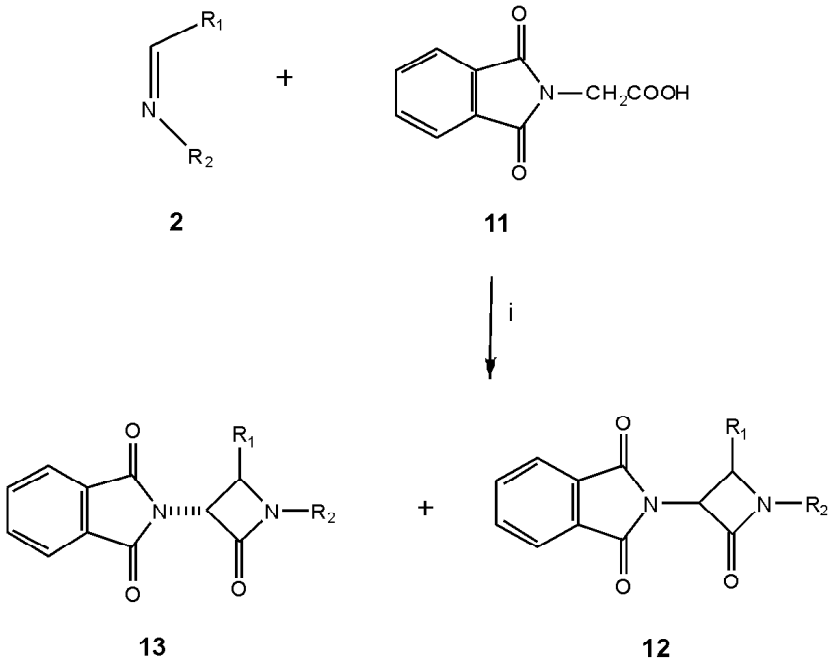
Fig. 2. Graphical representation of *cis/trans* ratio of β-lactam with time of irradiation.

Experiment number 10:

It was also observed that *trans* β-lactam **4** is formed in 100% yield by slow addition of NMM in ethylene dichloride to a refluxing solution of the Schiff base **2** and the acid chloride (**1**) (Scheme 7).

Mechanism

Our observations regarding the mechanism behind the formation of β-lactam isomers are shown in Scheme 8. Acid chloride in the presence of a tertiary base (NMM or TEA) produced a ketene intermediate **18**. The formation of the ketene was evidenced by a strong band at 2200 cm^{-1} in infrared spectra. The reaction of the ketene **18** with the imine

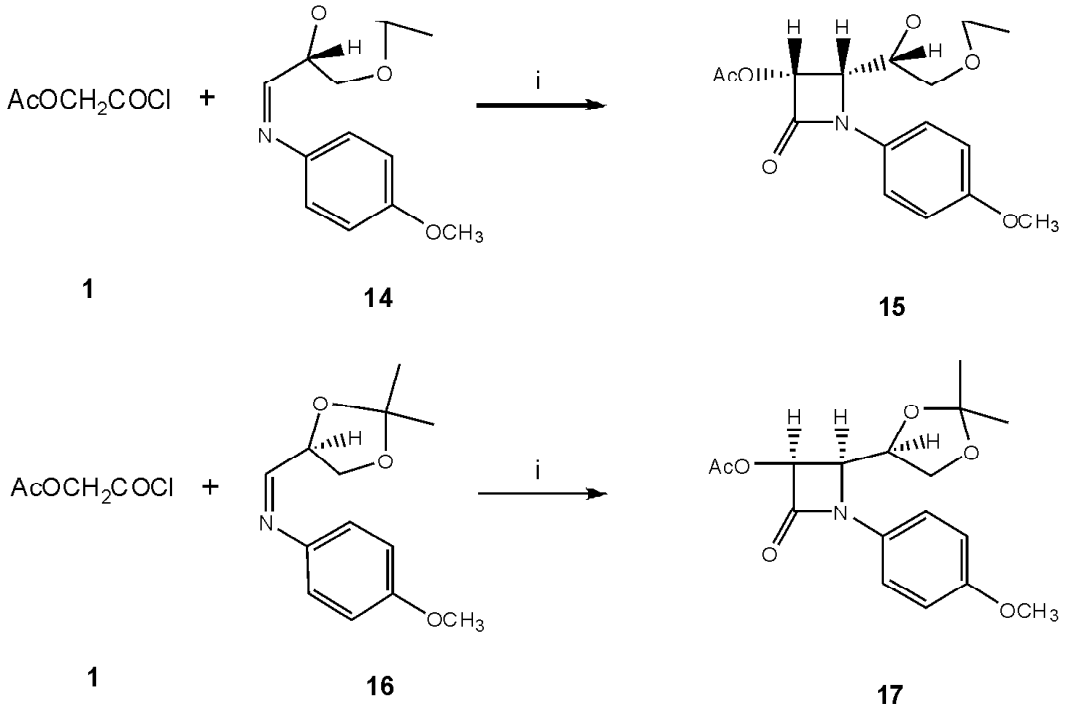


Scheme 5. Reagents and conditions: (i) chlorobenzene, NMM, MWI, 3 min. a: R_1 = Ph, R_2 = *p*-anisyl; b: R_1 = R_2 = *p*-anisyl.

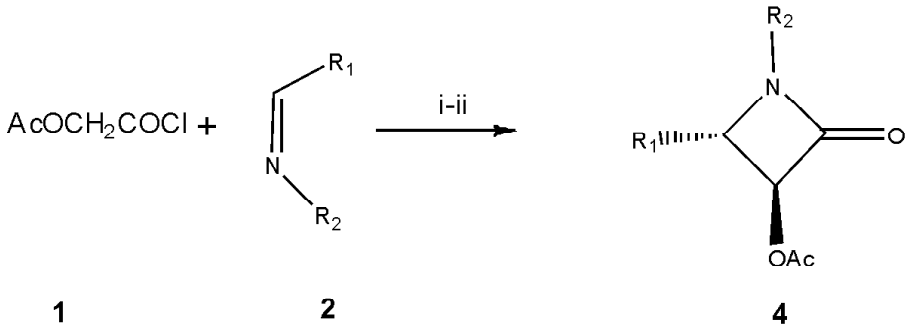
Experiment number 9:

Microwave irradiation of acid chloride (**1**) with imine **14** (obtained from D-glyceraldehyde) in the presence of chlorobenzene and NMM in 0–5 min produced only the corresponding *cis* β-lactam (**15**), while at the same reaction condition irradiation of acid chloride (**1**) with imine **16** (obtained from L-glyceraldehyde) produced *cis* β-lactam (**17**) with opposite absolute configuration in 100% yield (Scheme 6).

19 produces an ion (iminium ion) **21**. The stability of this ion **21** dictates the stereochemistry of the resulting products. If the ion undergoes reversible equilibrium with **22**, mixtures of β-lactams are formed. The relative proportions of these two β-lactams depend on the stability of the ions **21** and **22**. More stable **21** favors *cis* and the reverse is equally true for **22** (more *trans*). It is understandable that the ion **21** can alter its structure under the influence of the reaction conditions or



Scheme 6. Experiments 9. Reagents and conditions: (i) chlorobenzene, NMM, MWI, 0–5 min.



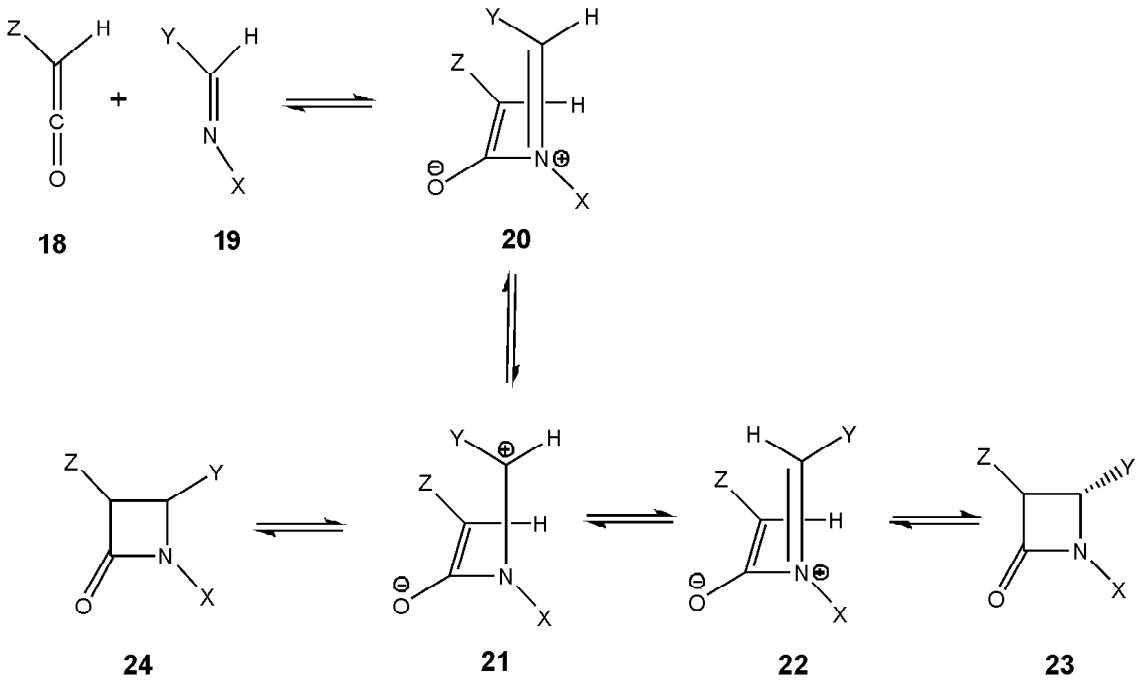
Scheme 7. Reagents and conditions: (i) ethylene dichloride, reflux, 80°C; (ii) NMM in ethylene dichloride dropwise at 8°C, 2 h.

because of the presence of certain specific groups in its structure. It is found that electron withdrawing aromatic groups at the nitrogen stabilizes the iminium ion and allows rotation of the bond in intermediates to form **22**. That results in isomerization of the intermediates **21** to **22** and eventually in the formation of a *trans* isomer **23** (nitro aromatics and polayaromatic groups at the nitrogen). Without this type of isomerization, the products become *cis* **24**. High power microwave irradiation and concentrated solution favors the formation of **22** even with imines that have electron donating groups (e.g. *p*-anisyl) as can be seen from this study. This stereochemical situation becomes highly complicated when electron withdrawing groups are present in C-3 of the system. Clearly, a rapid rise of temperature favors *trans* β-lactam formation through an isomerization process irrespective of the groups present in nitrogen. Microwave irradiation, polar solvent, concentrated solution and electron withdrawing groups at C_3 and an aryl group at C_4. Acetoxy and phthalimido groups have superior electron withdrawing capacity than benzyloxy group. These groups prefer to form the *trans* pro-

duct (for example, the acetoxy/phthalimido and benzyloxy at the C-3). The use of non-polar solvent retards the formation of the β-lactams under similar conditions. For example, the reactions are sluggish in benzene whereas they proceed at a significantly faster rate in the absence of any solvent (under neat conditions). The use of benzene as the solvent lowers the concentration of the reactants and intermediates. However, this explanation is not valid with imines derived from D and L-glyceraldehydes. The exclusive formation of *cis* products (single stereoisomer) with these two imines indicate rotation of the iminium ion structure is restricted due to the presence of a cyclic ketal group. The role of the ketal group in this type of reaction is not established. It can be assumed that the ketal group due to its cyclic structure forces the ion to adopt only one configuration. Inverse addition (base was added to the reaction mixture) of the base favors *trans* β-lactams formation with racemic imines. The proportion of the ketene in the reaction mixture is not sufficient in this type of reaction and thus the intermediate ion prefers to undergo an isomerization to the more stable structure at high temperature.

Preparation of these β-lactams following the procedures as described herein is simple and the isomers can be separated easily by column chromatography. Perhaps, the most significant observation is to complete these reactions within a few minutes with limited amounts of solvents. Clearly, this reaction proceeds in the absence of solvent with complete stereocontrol. The one-pot reaction in the presence of clay is also very interesting since it maintains the stereochemical outcome in a predictable way. The success of this reaction is because of the dehydrating power of the clay which helps to form the imines and stabilizes the iminium ion by stabilizing the system through its surface properties.

*(±)-cis-1-(4′-Bromophenyl)-3-acetoxy-4-phenylazetidin-2-one (**3b**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H, C*H*$_3$COO), 5.34 (d, *J* 4.85 Hz, 1H, C4-*H*), 5.95 (d, *J* 4.8 Hz, 1H, C3–*H*), 7.12–7.40 (m, 9H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 60.2, 83.3, 117.7, 125.8, 126.0, 128.0, 128.4, 130.9, 134.3, 161.25, 168.4. IR (neat): 1742 and 1605 cm^{-1}. Anal. Calcd. (%) for $C_{17}H_{14}BrNO_3$: C, 56.69; H, 3.92; N, 3.89. Found: C, 56.60; H, 3.79; N, 3.80.



Scheme 8. Mechanism of formation of β-lactam isomers.

*(±)-trans-1-(4′-Bromophenyl)-3-acetoxy-4-phenylazetidin-2-one (**4b**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H, C*H*$_3$COO), 4.82 (d, *J* 2.2 Hz, 1H, C4-*H*), 5.35 (d, *J* 1.9 Hz, 1H, C3-*H*), 7.10–7.34 (m, 9H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 62.8, 81.8, 118.8, 125.9, 126.9, 127.6, 129.5, 132.3, 133.8, 162.5, 169.0; Anal. Calcd. (%) for $C_{17}H_{14}BrNO_3$: C, 56.69; H, 3.92; N, 3.89. Found: C, 56.70; H, 3.84; N, 3.93.

Conclusions

In this work we investigated the stereochemistry (*cis* and/or *trans*) of the β-lactams synthesized under diverse conditions. We discussed ten different experiments and conditions for this study. The data showed that the reaction conditions 2, 3, 4, 6(a), 8, and 10 are favorable for synthesis of *trans* β-lactam in good yield. On the other hand, reaction conditions 1, 6(b), and 9 are favorable for synthesis of *cis* β-lactam in good yield. Moreover, reaction conditions 5 and 7 are favorable for the synthesis of a mixture of *cis* and *trans* β-lactam. Microwave-induced Organic Reaction Enhancement chemistry techniques and one pot synthesis have proven to be useful. It is clear from the observations that diastereoselectivity of the product β-lactams strongly depend on reactants and reaction conditions. The extensive data obtained from this study suggests that β-lactam formation reaction depends on two pathways: One is favored at high temperature and or concentrated solution/microwave-mediated reaction conditions. The graphical representation of the β-lactam formation and their stereochemical distribution deserves special comments as this is the first time such a plot is used to describe the results adequately.

Acknowledgements

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