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Cycloaddition Reaction of Imines with Acid Chlorides in the Presence of a Tertiary Base: Variation of the Methods for the Synthesis of Beta Lactams

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Abstract

Cycloaddition of optically active and racemic imines with diverse acid chlorides in the presence of a tertiary amine has been studied extensively for the synthesis of beta lactams. The conditions of the experiments have profound influence on the course of the reaction and stereochemistry of the products. Numerous methods are adopted for this cycloaddition reaction in order to control the yields, stereochemistry of the products, and durations of the reactions. This perspective demonstrates a few methods that are used for the synthesis of numerous beta lactams by cycloaddition reaction of imines and acid chlorides in the presence of a tertiary amine. The beta lactams are one of the most challenging heterocyclic compounds discovered in the world.

Keywords: Cycloaddtion; Beta lactam; Variation of the methods; Imines, Acid chloride; Stereochemistry

Introduction

Rapid synthesis of organic compounds with defined stereochemistry in a simple way is a very challenging objective. It is necessary to isolate the product from a reaction mixture when the reaction is completed without going through exhaustive process. Many scientists keep a reaction mixture for overnight even when the reaction is completed after a certain period of time. This has become a common practice to stir or continue the reaction "overnight" (sometimes reflux) although it is not necessary. This additional time of stirring or refluxing may harm the yields of the products, alter the stereochemistry of the products, rearrange the initially formed products to something else, decompose the products and the products may undergo further reactions with unused reagents present in the reaction mixture. Moreover, heating and extra time certainly can change the color and texture of the products and therefore, additional purification and separation are necessary to obtain pure products. This lowers the overall yields of the final compound. This is particularly very crucial when synthesis of a 4-membered heterocyclic ring system, for example beta lactam is the target [1-7]. The use of beta lactam for diverse purposes is well-known [1-7]. In addition to different types of medicinal applications, many heterocyclic compounds are obtained from them by chemical manipulations. Consequently, numerous methods are available for the synthesis of diverse medicinally active beta lactams [8-16]. A single method is not the choice for the preparation of all types of beta lactams. However, Staudinger Cycloaddition reaction remains the most popular and attractive methods for the preparation of beta lactams. This reaction is discovered more than 100 years ago. Nevertheless, scientists are highly interested in performing cycloaddition chemistry for this purpose. In this perspective several variations of cycloaddition chemistry with imines and acid chlorides in the presence of a tertiary amine are discussed.

Results and Discussions

Method 1: Addition of acid chloride to imine in the presence of a tertiary base

The most common method for the synthesis of beta lactams is performed by the addition of acid chloride to a solution of an imine in the presence of triethylamine at cold conditions (0-5°C) and then continuing the reaction at room temperature. Certainly, this reaction does not require 24 hours stirring at room temperature or high temperature (approximately 50°C). Some imines with electronegative groups at the -N or -C or non-activated acid chloride require longer reaction time/high temperature. The stereochemistry of the products depends on the structure of the starting compounds and in most of the instances, the stereochemistry of the products is found to be cis. A few reactions with reactive components may complete within 30 minutes at 0-5°C.

Method 2: Addition of a tertiary base to acid chloride and imine solution

This procedure is also widely used when opposite stereochemically pure trans beta lactams is needed. This is called inverse addition method. This reaction is conducted at cold conditions, room temperature and reflux temperature. However, the stereochemistry of the products from this method is mostly found opposite to that obtained following the above method.

These two methods are widely used for the preparation of 3, 4-disubstituted Beta-lactams, 3, 3/, 4-trisubstituted beta lactams and 3, 4, 4/-trisustituted beta lactams. Imines derived from primary aromatic amines, primary aliphatic amines and primary heterocyclic amines are used with success. Aromatic carbonyl compounds, heterocyclic carbonyl compounds and aliphatic carbonyl compounds (aldehydes and ketones) are used as the other component for the imine preparation. Different types of acid chlorides, for example, acetoxyacetyl chloride, phthalimido acid chloride, methoxyacetyl chloride, benzyloxyacetyl chloride, crotonyl chloride and

phenoxyacetyl chloride and a tertiary base (triethylamine and N-methylmorpholine) are used with varying successes [8-16]. The nature of the imines affect the time of the reaction. Imines derived from monocyclic primary aromatic amines react much faster than imines obtained from bicyclic aromatic amines. Similarly, imines obtained from monocyclic aromatic aldehydes react faster than the imines synthesized from bicyclic analogues. Sterically hindered imines react slower than the non-sterically hindered imines in an identical series of compounds. Electron donating groups at -N or -C in the imines helps to form the beta lactam in a shorter reaction time. In contrast, electron withdrawing groups at the same two centers considerably retard the reaction.

Method 3: Addition of imine solution to acid chloride and tertiary amine solution

Imine solution in dichloromethane, toluene, dichloroethane and dimethylformamide is added to acid chloride and tertiary amine solution (in the same solvent) following the conditions described above in method 1 and 2. The reaction takes more or less the same time as described in methods 1 and 2. The distribution of stereochemical isomers remains the same as described in method number 1.

Method 4: Microwave-induced methods

Since many beta lactams are synthesized at relatively high temperature or stirring at room temperature for a long time, microwave-induced reaction can be used to accelerate the rate of reaction. The reaction under microwave becomes very rapid and clean. The synthesis of beta lactams is performed under domestic and automated microwave and excellent yields are also obtained. In some instances, mixtures of beta lactams are formed because of rapid rise in reaction temperature [17-20]. This isomer formation is not due to isomerization of the cis beta lactams to the more stable trans beta lactams under basic reaction conditions. Probably, microwave reaction follows two different pathways: one pathway is favored over the other and they are temperature dependent. Any procedures described under methods 1-3 can be used in microwave depending upon the target molecules. This method can be easily performed using 50 mg-50 gm scale. The exact cause of acceleration under microwave condition is not properly understood. It is argued that rapid rise of temperature causes acceleration of the reaction rate. Some authors believe that the microwave radiation is responsible for the acceleration of the reaction rates.

Method 5: Ultasound-induced methods

Ultrasound-induced reactions of imines with acid chloride in the presence of triethylamine produces beta lactams at a much faster rate than the method described under methods 1-3. The stereochemistry of the resulting beta lactam remains the same as that of the products obtained by methods 1-3. It is known that ultrasound can accelerate the vibration of the reactants and therefore, can collide to each other more effectively.

Method 6: Light-induced methods

An exposure of the reactants (imine, acid chloride and triethylamine in dichloroethane) with domestic light bulbs (100 watts) helps the formation of beta lactam at a faster rate than that obtained following the methods 1-3. The visible light can cause acceleration of the reaction rate due to photo effects or an increase of the reaction temperature of the reactants.

Method 7: Grinding methods without solvent

The reactions among imine, acid chloride and triethylamine can produce beta lactam in the absence of any solvent by grinding the reactants in a mortar-pestle. If the grinding is continued, the rate of the reaction can be significantly accelerated. The stereochemical results remain identical as described in methods 1-3. Appropriate level of grinding can create friction among the molecules in a much better way, particularly in a very concentrated media.

Conclusions

Synthesis of beta lactams is achieved by a number of methods. Each method has its own benefits and disadvantages. It does not take many hours or days to complete a beta lactam synthesis. However, care must be taken in conducting the beta lactam synthesis using the starting compounds mentioned in this paper. All of these reactions should be performed in a well-ventilated hood with complete body protection. The starting materials used for the preparation of beta lactams are toxic and health hazards. Students are advised to take help from experienced researchers when conducting these types of reactions as described here.

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