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CYCLOADDITION OF NAPHTHALENYL AND ANTHRACENYL IMINES: INTERESTING ASPECTS OF THE STAUDINGER REACTION[↑]

Indrani Banik, Linda Hackfeld, and Bimal K. Banik*

Department of Molecular Pathology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA
E-mail: bbanik@mail.mdanderson.org

Abstract - Cycloaddition of imines derived from naphthalene and anthracene derivatives under Staudinger reaction conditions proceeded exceedingly well with remarkable control of stereochemistry to the corresponding β-lactams.

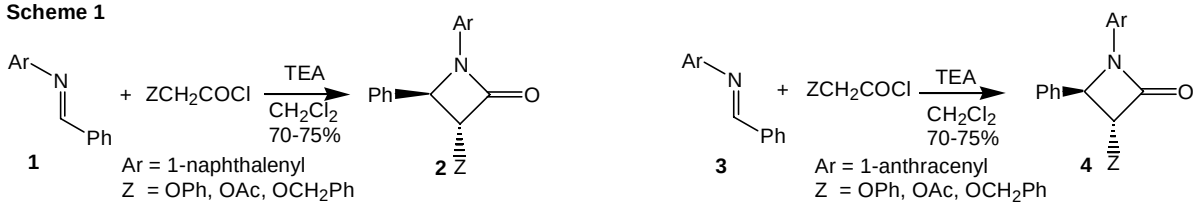
The Staudinger reaction, which was discovered more than 90 years ago is considered the best method of the construction of the β-lactam ring.[1] Because of the tremendous medicinal values of β-lactams, this cycloaddition reaction has been extensively investigated in the synthesis of *cis*- and *trans*- β-lactams.[2] From the enormous amount of data in the literature, some predictions about the stereochemistry of β-lactam ring formation have been made.[3] Some computer-assisted calculations have also been advanced to explain the stereochemistry of the β-lactams that form under Staudinger reaction or modified conditions.[4] In a continuation of our research of biologically active molecules derived from aromatic compounds,[5] we sought to use readily available naphthalenyl and anthracenyl compounds as the starting materials for the construction of β-lactam rings under Staudinger reaction conditions.[6] During this course of study, we uncovered an interesting aspect of this reaction regarding the stereochemistry of β-lactam formation. In this paper, we describe a new observation of stereochemistry control of the β-lactam ring using isomeric naphthalenyl and anthracenyl imines.

It is well established that the reaction of alkoxy- and acyloxy- containing acid chloride or equivalent with diaryl imines produces *cis*- β-lactam under Staudinger reaction conditions. However, slow addition of these types of acid chloride to the imine (**1**) derived from 1-aminonaphthalene and benzaldehyde at 0°C to room temperature produced *trans*- β-lactam (**2**) as the only product. A similar addition reaction with imine (**3**) derived from 1-aminoanthracene and benzaldehyde also produced a *trans* isomer as the only product (**4**). The results are surprising, because a *cis* product was expected. The reaction of aniline imines

[↑]Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

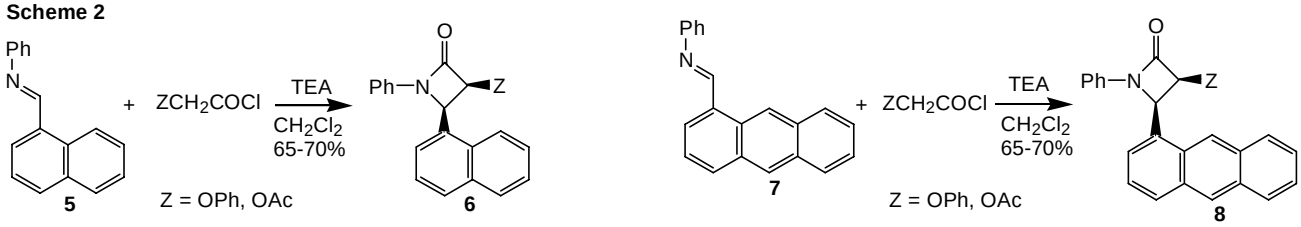
produced *cis* isomers under these conditions (**Scheme 1**).

Scheme 1



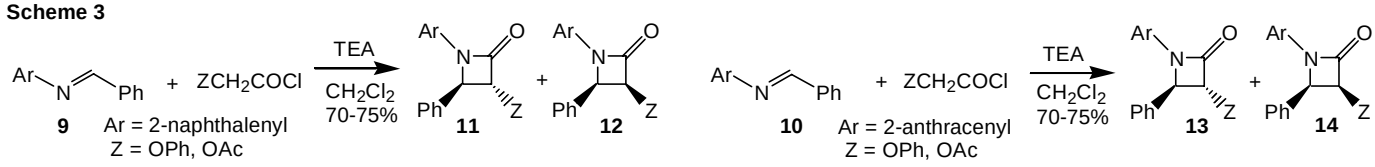
Having this stereochemical controversy, reaction with isomeric imines was investigated. For example, imines (**5**) and (**7**) derived from aniline and 1-naphthalenyl aldehyde and 1-anthracenyl aldehyde, however, produced *cis*- β-lactams (**6**) and (**8**) in excellent yield (**Scheme 2**).

Scheme 2



Encouraged by these results, we sought to test isomeric imines (**9**) and (**10**) obtained from naphthalene and anthracene. Reaction of these imines derived from 2-aminonaphthalene and anthracene with acid chloride produced predominantly *cis* isomers (**12**) and (**14**), although a small amount (10-20%) of *trans* isomers (**11**) and (**13**) were also formed (**Scheme 3**). The ratios and nature of the isomers were determined from ^{1}H NMR spectra.

Scheme 3

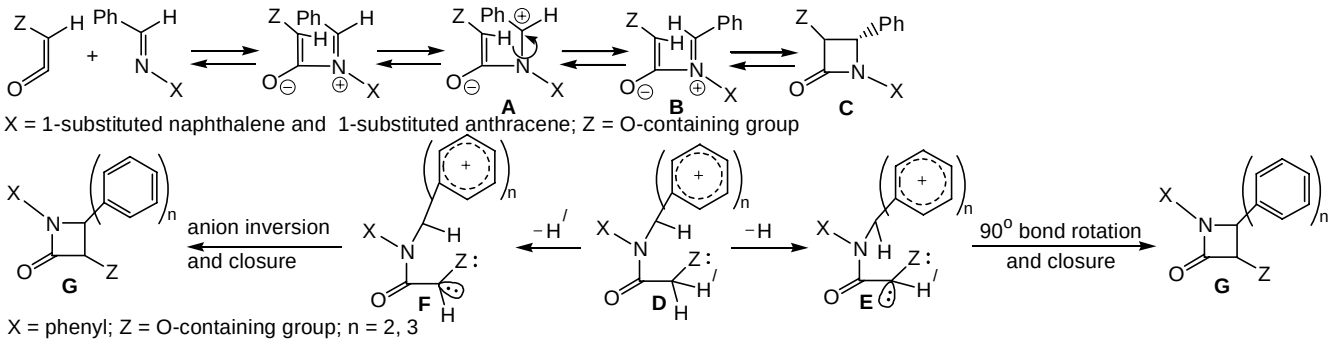


This indicated that by changing the location of the substituents in the imines or using isomeric imines it is possible to get different stereoisomeric β-lactams under identical experimental conditions. Until now, there has been no claim that this type of stereocontrol using positional isomers can be achieved in the field of β-lactam chemistry. Although this observation is simple and new to the literature, mechanistically, it is interesting in many ways.

The mechanism of β-lactam formation has been investigated by a number of researchers. For example, Georg and Ravikumar established some general rules regarding stereoselectivity in the formation of β-lactam rings.[3]Apart from this, a few computer-assisted calculations have been advanced to explain stereochemical results.[7] Additionally, low-temperature infrared spectroscopy was used by Lynch *et al.* to identify the reactive intermediates and explain the stereochemistry.[4] Based on the data in the literature, in general, two mechanisms have been proposed to explain the product distribution in β-lactam formation reactions under Staudinger reaction conditions. The first of these, the "ketene mechanism" was observed

in the low-temperature infrared spectroscopy study[4] while the second the "acylation of imine" mechanism was believed to be involved in many cases as described by some authors.[3] Interestingly, both of these mechanisms have been supported by much experimental evidence. In brief, it has been hypothesized that attacking of imines takes place from the least hindered side of the ketene, a process that generates zwitterionic intermediates. Subsequent conrotatory cyclization of these intermediates produces *cis*- and *trans*- β-lactams. The second mechanism proposes acylation of the imine by the acid chloride (or equivalent) to form *N*-acyliminium chloride, which produces an identical zwitterionic intermediate (**Scheme 4**).

Scheme 4



The formation of a *trans* isomer as observed in the present study can be explained through isomerization of the enolates (**Scheme 4**, **A** to **B**). The electron-withdrawing naphthalenyl and anthracenyl group at nitrogen stabilizes the iminium ion. As a result, rotation of the bond (**A** to **B**) takes place, resulting in *trans* β-lactam formation (**C**). Just *et al.* observed similar formation of a *trans* isomer having electron-withdrawing nitro-substituted imines.[8] It appears though, that the steric factors have no role. If a steric factor was involved, the isomeric imines would also produce the *trans*- β-lactams. In contrast with expectations, the exclusive formation of a *cis* β-lactam having naphthaneyl and anthracenyl at C_4 prompted us to develop a route suggested previously by Doyle *et al*.[9] In this context, extended conjugation of these systems at C_4 stabilizes the acyliminium ion (**D**), and subsequent proton abstraction from complex (**D**) would lead to *cis*- β-lactam (**G**) through **E** (90^o bond rotation and closure) or **F** (anion inversion and closure). This hypothesis has been supported by possible donor-acceptor complex formation as suggested by Bose *et al*.[10] This complex formation effectively stabilizes the transition states of the reaction and *cis*- β-lactam formation.

However, the most fascinating aspect of this study is with the isomeric imines as described in **Schemes 1** and **2**. If an electronic effect is involved, a *trans* isomer would have been expected with the 2-substituted isomer. The only precise structural difference between the isomers is the close proximity of peri hydrogen in the 1-substituted imines. The peri hydrogen is located relatively away from the imino group in the isomeric imines. Therefore, whether this peri hydrogen affects the transition state of the reaction

and product distribution remains in question.

These results indicate that the mechanism of β-lactam formation is very complex and that generalization of theories is still extremely difficult. Nevertheless, synthesis of stereo-defined β-lactams is absolutely necessary. In this case, the aromatic moieties can be oxidized to prepare some quinonoid compounds, and as a result of different stereoisomer formation, a clear approach to studying their bioactivity is highly feasible.

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