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Exploiting the Reactivity of Destabilized Pyrrolylketene for the Stereoselective Synthesis of β-Lactams †

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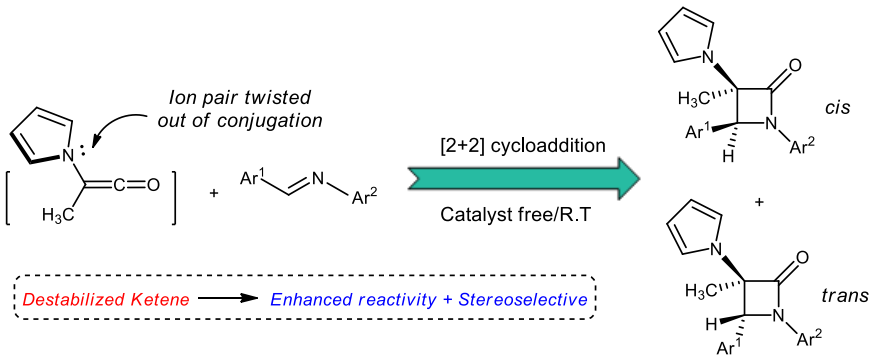
Abstract

β-Lactams are key scaffolds in synthetic and medicinal chemistry, valued for both therapeutic relevance and synthetic utility. Classical ketene-imine [2+2] cycloadditions often employ stabilized aryl ketenes, which display reduced reactivity and modest stereoselective. Disruption of π-conjugation in *N*-pyrrolylketene has been shown to enhance electrophilicity and direct stereochemical outcome in reactions with aromatic imines. The ketene, generated in situ from *N*-pyrrolylpropanoic acid, undergoes cycloaddition under mild conditions to give β-lactams with a strong preference for the trans isomer. Frontier molecular orbital analysis and mechanistic interpretation suggest a polar asynchronous pathway, highlighting ketene destabilization as a practical strategy for stereoselective β-lactam synthesis.

Keywords: β-lactams; [2+2] cycloaddition; *N*-pyrrolylketene; ketene reactivity; stereoselectivity; frontier molecular orbital analysis; heterocyclic synthesis



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1. Introduction

β-Lactams represent one of the most valuable classes of heterocycles in organic and medicinal chemistry, best known as the core structure of widely used antibiotics and other bioactive agents [1–4]. The stereochemical arrangement within the β-lactam ring plays a crucial role in determining biological activity, making the development of selective and efficient synthetic methods an important objective [5,6]. Traditionally, β-lactams have been accessed through the Staudinger reaction, a [2+2] cycloaddition between ketenes and imines [7–10]. While this transformation has proven highly versatile, it often suffers from

reduced reactivity when stabilized aryl ketenes are employed, and the stereochemical outcome can be difficult to control. Recent studies have demonstrated that disruption of π-conjugation in *N*-pyrrolylketenes produces "destabilized" intermediates with enhanced electrophilicity, enabling more efficient and stereoselective cycloadditions with aromatic imines [11–14]. This approach has provided *β*-lactams in good yields with a pronounced preference for the trans isomer, offering a significant improvement over conventional methods. Ongoing challenges in this area include balancing reactivity with stereoselective, since small changes in electronic or steric properties of the substrates can affect the diastereomeric outcome [15]. Moreover, although some metal-assisted and multicomponent strategies have been explored to improve efficiency [16–18], the search for mild, catalyst-free methods remain highly relevant in the context of sustainable synthesis [19]. Taken together, the growing body of research highlights destabilized *N*-pyrrolylketenes as powerful intermediates in *β*-lactam synthesis [12]. Their ability to combine high reactivity with stereochemical control represents an important conceptual advance and provides a promising platform for addressing current challenges in drug discovery and development.

The aim of this work is to analyze and discuss the reactivity of destabilized *N*-pyrrolylketenes in the stereoselective synthesis of *β*-lactams. By focusing on mechanistic interpretations, frontier molecular orbital analysis, and reported experimental results, this study seeks to clarify the role of ketene destabilization as a general strategy for controlling both reactivity and stereochemistry in [2+2] cycloadditions.

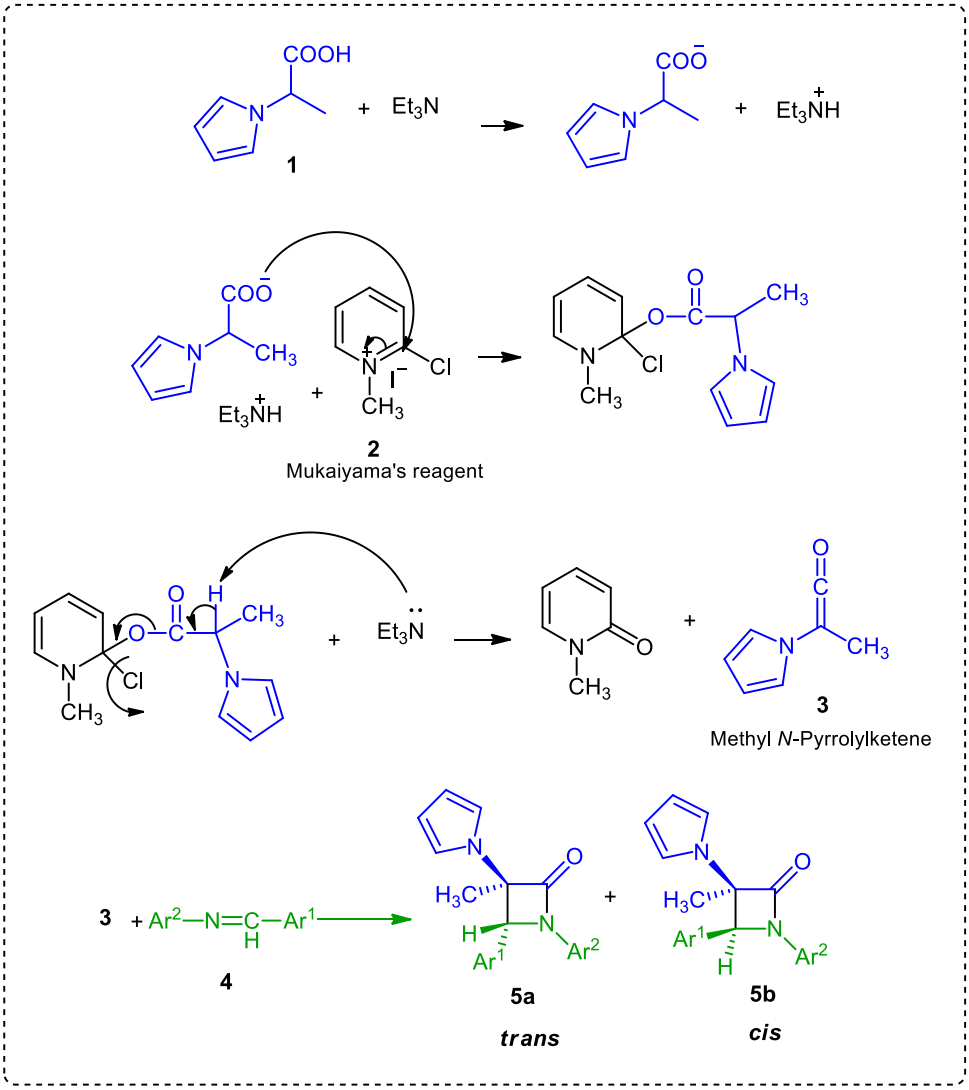
2. Methodology and Approach

This study is based on previously reported investigations of *N*-pyrrolylketenes, most notably the cycloaddition reactions with aromatic imines described by Babaei and co-workers [12], along with related literature on ketene-imine chemistry [20,21]. Reported yields, stereochemical data, and substrate scope serve as the basis for further mechanistic interpretation. Frontier molecular orbital (FMO) analysis is employed to rationalize the electronic features governing the [2+2] cycloaddition [22–24], with particular attention to the role of π-conjugation disruption in enhancing ketene electrophilicity and stereochemical control. By integrating experimental precedent with theoretical considerations [25], the present approach provides a framework for analyzing the reactivity and stereoselectivity of destabilized ketenes.

3. Results

3.1. In Situ Generation and Cycloaddition of N-Pyrrolylketene

Destabilized *N*-pyrrolylketene was obtained in situ from *N*-pyrrolylpropanoic acid, which itself was synthesized starting from alanine and dimethoxytetrahydrofuran following established protocols [26,27]. In the procedure reported by Babaei and co-workers, activation of the acid with Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) in the presence of triethylamine promoted the elimination step to generate the ketene intermediate [12]. Because of its instability, the ketene was not isolated and was used directly in [2+2] cycloaddition with aromatic imines. Under mild, catalyst-free conditions, the reactions afforded *β*-lactams in moderate to good yields and showed tolerance toward both electron-donating and electron-withdrawing substituents. These outcomes demonstrate the high reactivity of destabilized *N*-pyrrolylketenes. The proposed pathway is shown in Scheme 1.



Scheme 1. In situ generation of destabilized *N*-pyrrolylketene and its [2+2] cycloaddition with aromatic imines.

3.2. Substituent Effects and Stereochemical Preferences

The cycloaddition reactions predominantly furnished trans-*β*-lactams, with several substrates affording the trans isomer exclusively. For example, *N*-pyrrolylketene combined with *N*-benzylideneaniline (Ph_Ph) to give only the trans product. Substituent effects on the imine partner were evident: electron-withdrawing groups (4-Cl, 4-Br) accelerated the reaction and consistently produced trans products, while electron-donating substituents (4-MeO, 4-Me) led to slower reactions and small amounts of the cis isomer alongside the major trans product. These findings indicate that stereoselectivity is determined during the initial nucleophilic attack of the imine nitrogen on the ketene carbon, favoring a transition state geometry that directs the reaction toward the trans configuration. Representative outcomes are summarized in Table 1.

Table 1. Representative outcomes of the [2+2] cycloaddition of *N*-pyrrolylketene with aromatic imines.

Entry	Imine Substituents (Ar^1_Ar^2)	Reaction Profile	Product Distribution
1	Ph_Ph	Moderate yield	trans only
2	4-ClC_6H_4_Ph	Fast	trans only
3	Ph_4-BrC_6H_4	Fast	trans only
4	Ph_4-$MeOC_6H_4$	Slow	trans major, cis minor
5	Ph_4-MeC_6H_4	Slow	trans major, cis minor
6	Ph_4-ClC_6H_4	Moderate	trans major, cis minor

As summarized in Table 1, the cycloaddition of *N*-pyrrolylketene with aromatic imines consistently favored the formation of trans-*β*-lactams. In cases where the imines carried electron-withdrawing substituents (e.g., 4-Cl, 4-Br), the reactions proceeded rapidly and delivered exclusively trans products. In contrast, imines bearing electron-donating groups (e.g., 4-MeO, 4-Me) reacted more slowly, and minor amounts of the cis isomer were observed alongside the predominant trans product. The unsubstituted benzylideneaniline (Ph_Ph) provided only the trans isomer, albeit in moderate yield.

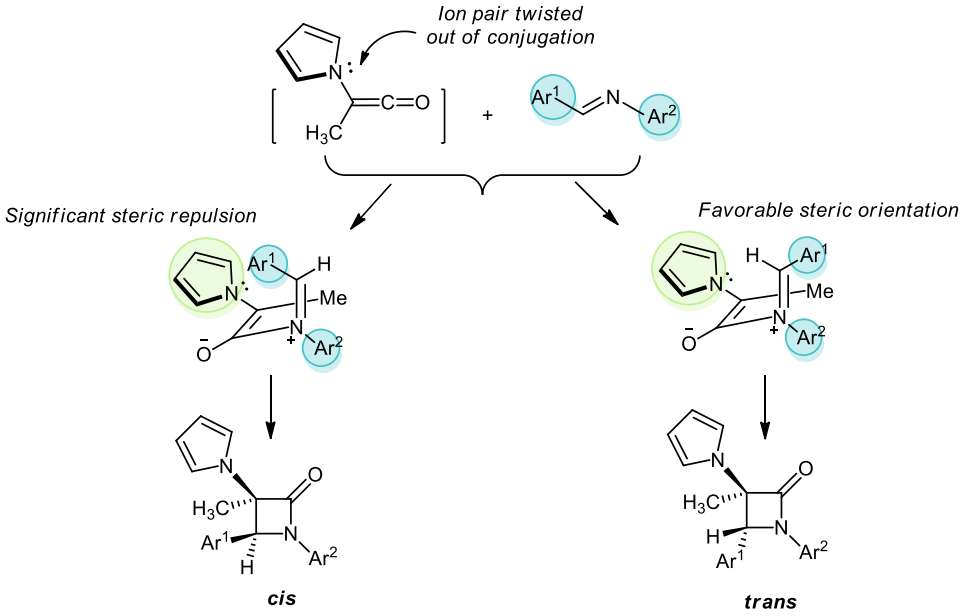
3.3. Mechanistic Considerations

Frontier molecular orbital (FMO) considerations suggest that the [2+2] cycloaddition proceeds through a polar asynchronous pathway. The reaction is initiated by overlap of the imine HOMO (nitrogen lone pair) with the ketene LUMO (π^* orbital), giving rise to a zwitterion-like transition structure in which N-C bond formation is more advanced than C-C bond formation. Subsequent closure of the four-membered ring affords the β-lactam framework.

A central electronic feature is the disruption of π-conjugation between the pyrrolyl substituent and the ketenyl group. Because the lone pair on the pyrrolyl nitrogen is twisted out of conjugation, effective overlap with the ketenyl π-system is prevented. This loss of delocalization destabilizes the ketene and increases the electrophilicity of the ketenyl carbon, thereby lowering the barrier for nucleophilic attack. In this sense, the enhanced reactivity of destabilized *N*-pyrrolylketenes can be directly attributed to their orbital alignment and electronic structure.

The stereochemical outcome is controlled primarily by steric effects. In a cis transition state, the pyrrolyl ring and the aryl substituent of the imine are forced into close proximity, generating significant steric repulsion. By contrast, the trans transition state positions these groups further apart, minimizing steric interactions and favoring the formation of the trans isomer.

Taken together, the interplay of orbital interactions (HOMO–LUMO overlap and conjugation loss) and steric control (repulsion minimized in the trans pathway) accounts for both the high reactivity of destabilized *N*-pyrrolylketenes and their consistent trans selectivity. The proposed pathway is summarized in Scheme 2.



Scheme 2. Proposed mechanistic pathway for the [2+2] cycloaddition of *N*-pyrrolylketene with aromatic imines, illustrating asynchronous bond formation and steric effects controlling trans selectivity.

4. Conclusions

The analysis of destabilized N-pyrrolylketenes has highlighted their unique role as reactive intermediates for the stereoselective construction of β-lactams. Disruption of π-conjugation between the pyrrolyl group and the ketenyl fragment was shown to increase the electrophilicity of the ketene carbon, thereby promoting efficient [2+2] cycloadditions under mild, catalyst-free conditions. The preference for trans isomers was attributed to steric factors in the transition state, where avoidance of unfavorable interactions between the pyrrolyl and aryl substituents favors the trans pathway. These combined electronic and steric effects establish ketene destabilization as a general concept for improving both reactivity and stereoselective in β-lactam synthesis.

Future directions include exploring solvent effects on the stability of zwitterionic intermediates, extending the methodology to encompass aliphatic imines and other heteroaryl ketenes, and applying this strategy to the preparation of β-lactam analogues with potential medicinal relevance. Taken together, these perspectives emphasize the broader utility of ketene destabilization as a guiding principle in synthetic and medicinal chemistry, while aligning with the goals of sustainable and catalyst-free methodologies.

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