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

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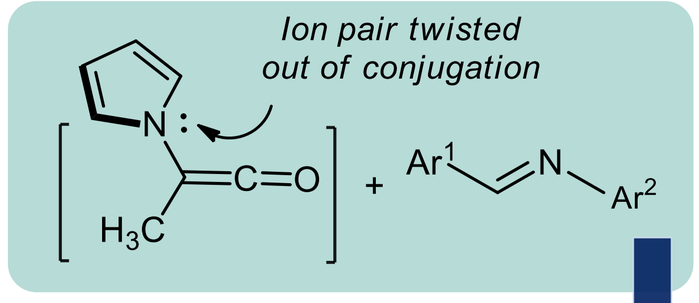
Introduction

β-Lactams are widely recognized for their role in medicinal chemistry, particularly as the backbone of many antibiotics [1]. One of the most efficient ways to synthesize these strained four-membered rings is via the [2+2] cycloaddition of ketenes with imines. In many cases, however, aryl ketenes are stabilized by π-conjugation, which reduces their electrophilicity and slows the reaction [2].

In this work, main focus is on an electronically destabilized *N*-pyrrolylketene. The nitrogen ione pair of pyrrole is twisted out of conjugation with the ketenyl π-system, eliminating resonance stabilization. This subtle structural change significantly increases reactivity and allows the cycloaddition to proceed under mild conditions.

Aims

- Develop a stereoselective and mild *β*-lactam synthesis using *N*-pyrrolylketene as a highly reactive, electronically destabilized intermediate, while clarifying whether the reaction follows a concerted pericyclic pathway or a stepwise polar sequence involving a zwitterionic intermediate.
- Assess the influence of imine electronic properties on both reactivity and stereochemical outcome, establishing ketene destabilization as a general design principle for strained-ring synthesis.



Destabilized Ketene

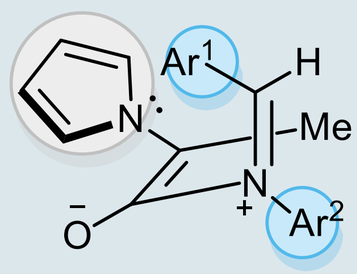
↓

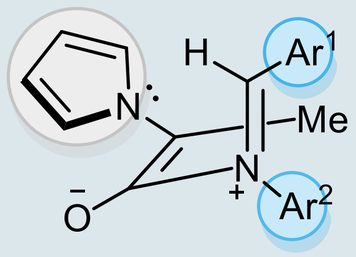
Enhanced reactivity
+
Stereocontrol

Method

- N-Pyrrolylpropanoic acid, prepared from L-alanine and dimethoxytetrahydrofuran, was converted in situ to the corresponding ketene using Mukaiyama reagent and triethylamine under mild conditions, as reported by Babaei et al. [3]. Because of its intrinsic instability, the ketene was not isolated but reacted directly with aromatic imines to afford β-lactams.
- In this study, reported data on yields, substituent effects, and stereochemical outcomes were analyzed. Frontier molecular orbital (FMO) considerations were applied to rationalize the role of π-conjugation disruption in enhancing ketene reactivity and in directing the observed preference for trans products.

***A** : Significant steric repulsion*





***B** : Favorable steric orientation*

Results

The reaction consistently favored trans-*β*-lactams, with some substrates producing exclusively trans products. For example, the combination of *N*-pyrrolylketene with *N*-benzylideneaniline (Ph_Ph) afforded only the trans isomer. Imines bearing strong electron-withdrawing groups (e.g., 4-Cl, 4-Br) reacted faster and delivered purely trans products, whereas those with electron-donating groups (4-MeO, 4-Me) reacted more slowly and gave small amounts of the cis isomer.

EWGs (e.g., 4-Cl, 4-Br):

- Faster reaction, exclusive trans products.

EDGs (e.g., 4-MeO, 4-Me):

- slower reaction, small cis fraction observed.
- The stereochemistry appears to be determined during the initial *N*-attack step.

Discussion: Mechanistic & Pericyclic Analysis

From a pericyclic perspective, this is a [π2s + π2a] thermal cycloaddition, but in reality, the strong polarization of *N*-pyrrolylketene shifts the reaction toward a polar, asynchronous pathway.

Stepwise mechanism proposal:

✓ Nucleophilic attack: **HOMO of imine nitrogen → LUMO of ketene carbonyl carbon**, forming zwitterion.
✓ Conformational relaxation: **A** → **B** to minimize steric clash between Ar^1 and Ar^2.
✓ Ring closure: Intramolecular C–C bond formation yields β-lactam.

Conclusion

We have demonstrated a mild, stereoselective route to *β*-lactams via the cycloaddition of a destabilized *N*-pyrrolylketene with aromatic imines. Mechanistic and Frontiers Molecular Orbitals analysis supports a polar, asynchronous [2+2] cycloaddition pathway. By breaking π-conjugation in the ketene, we enhance its reactivity and control stereochemistry, a strategy that holds promise for broader applications in synthetic organic chemistry.

Future work

- Investigate solvent effects on the stability of zwitterionic intermediates.
- Extend the methodology to include aliphatic imines and heteroaryl ketenes.
- Apply the strategy toward the synthesis of β-lactam analogs with potential medicinal relevance.

https://sciforum.net/event/ecsoc-29

References

[1] Lima, L. M., da Silva, B. N. M., Barbosa, G., & Barreiro, E. J. (2020). β-lactam antibiotics: An overview from a medicinal chemistry perspective. European journal of medicinal chemistry, 208, 112829.

[2] Fu, N., & Tidwell, T. T. (2008). Preparation of β-lactams by [2+ 2] cycloaddition of ketenes and imines. Tetrahedron, 64(46), 10465-10496.

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