The Novel Synthesis of 3,5-disubstituted Δ^2-isoxazoline Through a Metal Mediated Cyclization-Coupling Reaction

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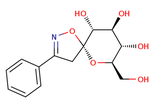
Abstract

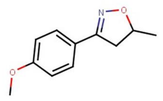
The main focus of this research is to find a cost-effective pathway to synthesize 3,5-disubstituted Δ^2-isoxazoline with relatively high yields. 3,5-disubstituted Δ^2-isoxazoline contains an isoxazole ring, which is an essential structure in some anti-diabetic medications [1][3]. This synthesis relies on a metal catalyst that converts an oxime into an isoxazoline by forming an isoxazole ring. Palladium (II) Chloride is a current metal mediator for this reaction and is being tested against Nickel (II) Chloride in varying amounts as well as Lead (II) Acetate. It is hypothesized that all three metal-mediated cyclizations will produce 3,5-disubstituted Δ^2-isoxazoline. After performing the reactions to synthesize the 3,5-disubstituted Δ^2-isoxazoline, Lead (II) Acetate was deemed to be the most viable and promising option for future research. Nickel (II) Chloride produced traces of 3,5-disubstituted Δ^2-isoxazoline, meaning that it is also a feasible option. In future experimentation, both processes will be refined to optimize results. Lead (II) Acetate and Nickel (II) Chloride are also substantially cheaper than Palladium (II) Chloride which will strengthen their viability for usage in the pharmaceutical industry.

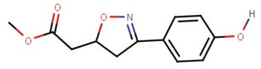
Introduction

- Type II Diabetes affects 29.1 million people, and it is projected that 84.1 million people will be affected in the coming years [4]
- Current treatment consists of the prescription drug metformin, which can cause a fatal condition called lactic acidosis [5]
- An emerging treatment for Type II Diabetes consists of glucose-derived spiro-isoxazolines (below left) [3]



- An isoxazole ring structure (above right) is an important part of glucose-derived spiro-isoxazolines
- However, current production methods are extremely costly
- Finding a cost-effective way to synthesize the 3,5-disubstituted Δ^2-isoxazoline, a precursor to the spiro-isoxazolines, will allow for widespread production and distribution





- Another version of isoxazoline is ISO-1 (above right)
- It inhibits Macrophage Migration Inhibitory Factor (MIF) which plays a role in promoting inflammation in Type I Diabetes [1]
- 3,5-disubstituted Δ^2-isoxazoline (above left) is very similar in structure to ISO-1, and it is probable that it will mimic ISO-1's effects

The research focuses on synthesizing 3,5-disubstituted Δ^2-isoxazoline in a cost-effective manner that could mimic the effect or be a precursor to both spiro-isoxazolines and ISO-1.

Methodology

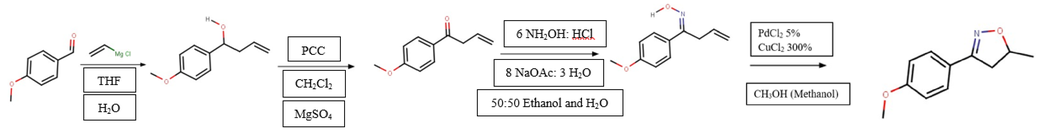
Reactions in the synthesis of 3,5-disubstituted Δ^2-isoxazoline

Grignard Reaction
Changed P.Anisaldehyde into 1-(4-Methoxyphenyl)-3-buten-1-ol

Oxidation Reaction
Changes 1-(4-Methoxyphenyl)-3-buten-1-ol into ketone

Oximation Reaction
Changes the ketone into oxime

Cyclization Reaction
Changes the oxime into 3,5-disubstituted Δ^2-isoxazoline



Cyclization Reaction Overview

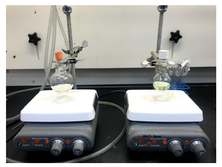


Figure 1: Cyclizations using Lead (II) Acetate and Nickel (II) Chloride (respectively) as the metal mediators.

- The metal mediator was varied in the different cyclizations
- The amounts of each particular metal mediator were also varied in some of the different cyclizations
- Specifically, Nickel (II) Chloride and also Lead (II) Acetate were used in the in the various experimental cyclizations
- In the cyclizations pictured on the right, 300% Copper (II) Chloride was also added to re-oxidize the metals

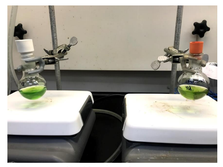
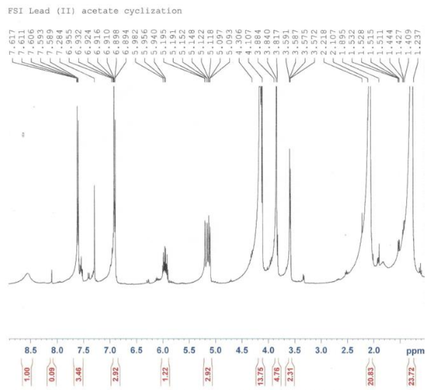


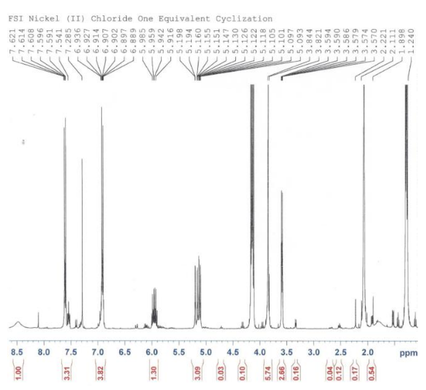
Figure 2: Cyclizations using 5% Nickel (II) Chloride and a 5% Palladium (II) Chloride (respectively) as the metal mediators.

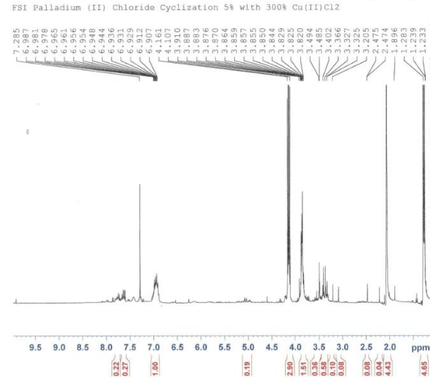
Results

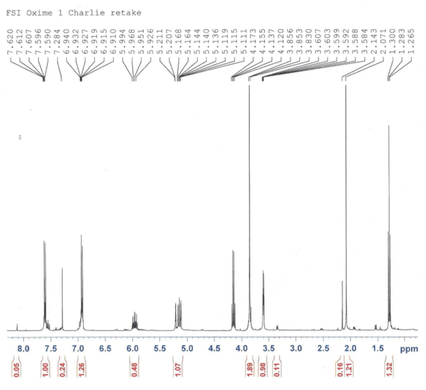
- The defining structure of the 3,5-disubstituted Δ^2-isoxazoline is the symmetric couplets of peaks from the 2.5 ppm to 3.4 ppm range.
  - The Lead (II) Acetate reaction had the strongest signals in this area
  - The Nickel (II) Chloride one equivalent showed traces of this signal
  - The Palladium (II) Chloride may have had traces, but the peaks were indistinguishable
- The couplet of symmetric peaks at 6.9 ppm and 7.6 ppm on the x-axis represent the benzene ring, which is shown to be destroyed in the Palladium (II) Chloride catalyzed reaction
  - Only the two cyclizations with Copper (II) Chloride (5% Nickel (II) Chloride and 5% Palladium (II) Chloride) had their benzene rings disintegrated

The oxime is shown for comparison to show the differences between the structures.









Discussion

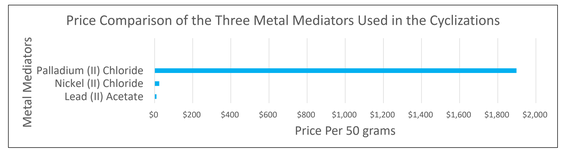
Analysis

- The Lead (II) Acetate and one equivalent Nickel (II) Chloride cyclizations supported the hypothesis that 3,5-disubstituted Δ^2-isoxazoline would be synthesized
- There were two cyclizations (5% Palladium (II) Chloride and 5% Nickel (II) Chloride) that did not support the hypothesis
- Interestingly, these two cyclizations used 300% Copper (II) Chloride to re-oxidize the metal mediators
- It is probable that the Copper (II) Chloride caused these cyclizations to overreact, which then caused the isoxazoline to break down

Future Work

- Attempt these failed cyclizations with either less Copper (II) Chloride or none of it at all.
- Let the reactions with Copper (II) Chloride to react for shorter periods of time such as 3 hours compared to the 24 hours that entailed these cyclizations.
- Refine the Lead (II) Acetate Cyclization

Implications



- As seen in the chart above, Lead (II) Acetate is drastically cheaper than Nickel (II) Chloride and especially Palladium (II) Chloride
- Lead (II) Acetate also produced higher yields of 3,5-disubstituted Δ^2-isoxazoline making it a promising target for ISO-1 and spiro-isoxazoline development
- This would also allow for production and distribution in the pharmaceutical industry

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