Improved Synthesis of Small Molecule Antioxidant OH-PyN_3

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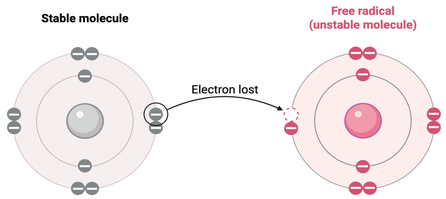
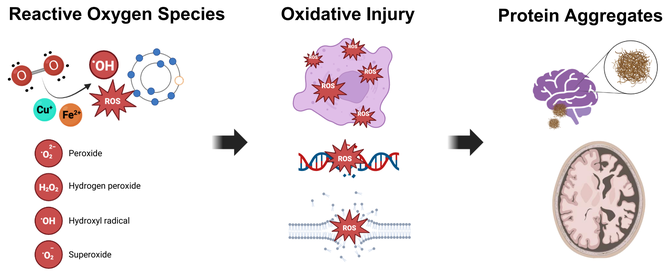
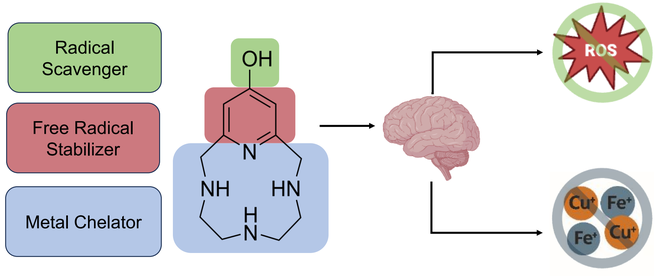
Abstract

Over seven million people are currently living with Alzheimer's disease (AD) in the United States today, with that number set to increase due to extended life expectancy. Studies have shown that **amyloid-beta (Aβ) plaque** accumulation, **tau tangles** in the brain, **metal-ion dysregulation**, and **oxidative stress are etiological hallmarks of AD**. Various treatment methods have been employed to reduce the effects of Alzheimer's disease, but these treatments aim to reduce Aβ plaque aggregates after they've formed, though this strategy focuses on symptom mediation as opposed to prevention. A different approach focuses on **preventative treatment of AD** to provide an antioxidant that can minimize the effects of oxidative stress through **scavenging reactive oxygen species**, which are known to lead to oxidative stress. Using this approach, a class of pyridinophanes has been synthesized as antioxidants and metal ion chelators to minimize the effects of oxidative stress through **biomimicry of enzymes such as superoxide dismutase**. The Green Group has presented multiple pyridinophanes that function as these biomimics, including **OH-PyN_3**. **Continued improvement of the synthesis of this small molecule** remains a focus, with the intent of a more **cost-effective synthesis** to facilitate clinical translation. Here we present an **improved synthetic scheme**, with optimizations to the chelidamic acid esterification and protection of the chelidamic acid and diethylenetriamine moieties. Through this synthetic scheme, the total chemical yield and reduce cost were doubled to 45% and decreased by 81%, respectively.

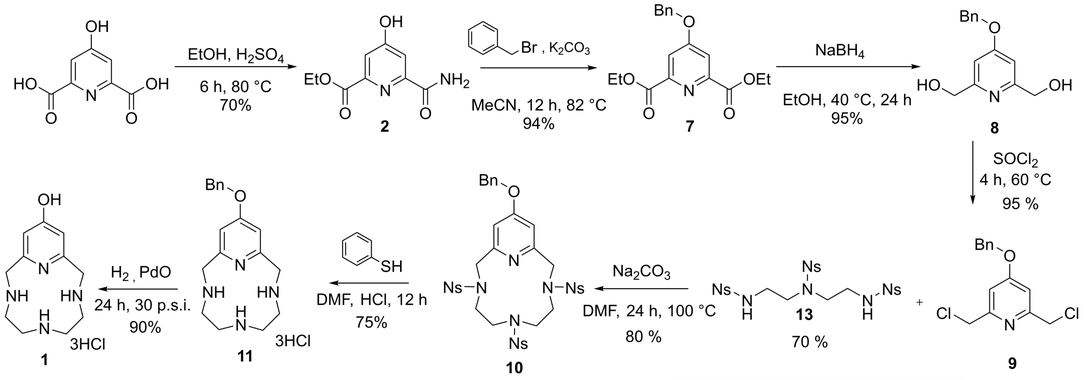
Background







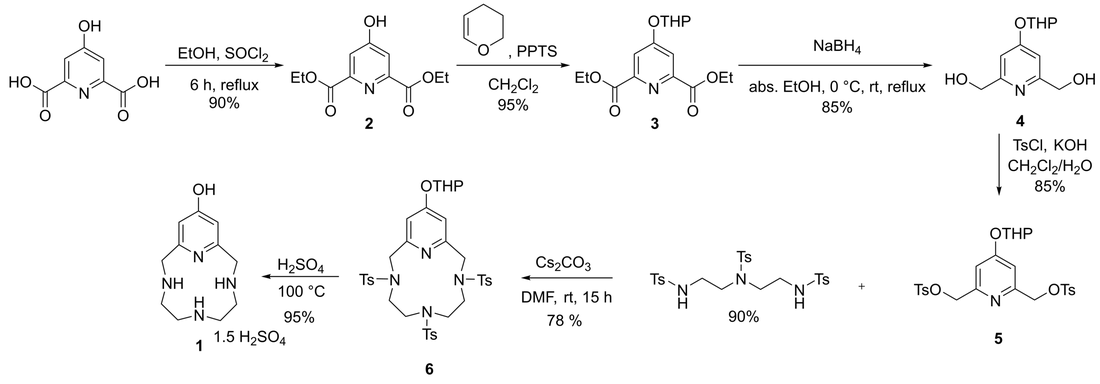
Previous Scheme



- Use of harsh thionyl chloride reagent as reagent makes Step 4 difficult
- Use of palladium-based catalyst leads to significant cost increase

Overall Yield 22.4%

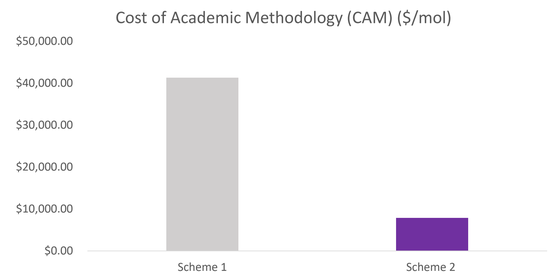
Current Scheme

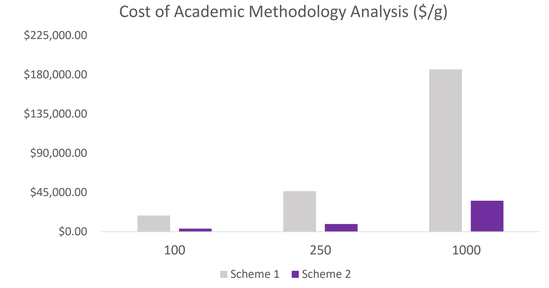


	Previous Synthesis	Improved Synthesis
Top Synthon Protecting Group	Benzyl (Bn) Ether	Tetrahydropyran (THP) Ether
Bottom Synthon Protecting Group	Nitrobenzenesulfonyl (Ns)	Toluenesulfonyl (Ts)
Use of Palladium Catalyst	Yes	No

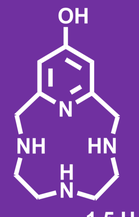
Overall Yield 45.7%

Cost Analysis





Conclusions



OH-PyN_3

Simplified Synthetic Approach:

- Removal of One Synthetic Step (6 Steps)
- Percent Yield: Increased to 45.7%
- Cost of Academic Methodology: $4/g
- Cost of Synthesis: Decreased by 81%

- Added benefit of removal of palladium metal catalyst, leading to significant cost minimization
- Future work on this synthesis includes the removal of potentially toxic reagents such as dichloromethane
- Additional future work includes translation of these techniques to the synthesis of other pyridinophane-based small molecules

Acknowledgements

Green Research Group

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