

CHEMISTRY SEMINAR

Advancements in the Manufacturing Route of Molnupiravir: A Promising Antiviral for COVID-19 Treatment

By Nicolle Elahian López '24 Chemistry

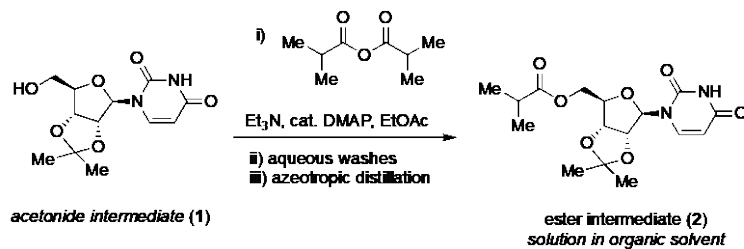
11:30 a.m.

April 4, 2024

Darrah Auditorium
McCreary 101

Abstract:

Molnupiravir (MK-4482) is a drug that surfaced as a promising antiviral agent for the treatment of COVID-19. The pandemic gave rise to an urgent search for the advancement of efficient and adaptable synthetic routes for the crucial medication. This presentation compares two synthetic approaches for Molnupiravir: the original five-step route from uridine and a novel biocatalytic cascade process. The original synthesis, developed by Merck & Co. Inc. and Ridgeback Biotherapeutics, involves the protection of uridine's secondary alcohols, esterification, activation of the amidic carbonyl, substitution with 1,2,4-triazole, conversion to oxime and final deprotection to yield Molnupiravir. Despite achieving a high-purity API, this method faced challenges such as low-yielding steps and lengthy operations.. API stands for Active Pharmaceutical Ingredient. It is the part of a pharmacological product that is physiologically active, it relates to Molnupiravir when used with COVID-19 antiviral medicines. The medication's medicinal effects are brought about via APIs. In response, an innovative biocatalytic route was developed, featuring engineered enzymes for ribosyl-1-phosphate synthesis and uracil incorporation. This new approach dramatically shortened the synthesis by 70% and increased the overall yield approximately seven-fold compared to the initial route. The innovative synthetic pathway received significant recognition, earning the prestigious 2022 EPA Green Chemistry Award. The presentation will examine the specifics of each synthetic strategy, comparing their overall yields, solvent usage, as well as environmental impact. The development of the biocatalytic route not only represents a significant advancement in the synthesis of Molnupiravir but also sets a precedent for the streamlined production of nucleoside-based therapeutics in the future.



Parameter	Original process	Improved process
EtOAc	8 L/kg	5 L/kg
Isobutyric acid	1.22 equiv	1.1 equiv
Et_3N	2.5 equiv	1.5 equiv
DMAP	5 mol%	2 mol%
Washes	water then brine, ca. 5% loss	water, ca. 2% loss
Isolation solvent	EtOAc; 2 poorly soluble	MeCN; 2 highly soluble

Figure 1. Comparison of the original and final processes for the preparation of the Ester Intermediate 2.

CHEMISTRY SEMINAR

Electrochemical CO₂ reduction using heterogenous metal-based catalysts

By Jenna King '24 Chemistry

11:30 a.m

April 4, 2024

Darrah Auditorium
McCreary 101

Abstract:

The reduction of CO₂ emissions is necessary for the prevention of further destruction to the environment and to improve air quality to overall benefit human health. Conversion of CO₂ to syngas, a mixture of CO and H₂, using the CO₂ reduction reaction (CO₂RR) represents a pathway for mitigating CO₂ emissions. Syngas is a feedstock for many thermochemical processes, including methanol synthesis and the Fischer-Tropsch process for long-chain liquid hydrocarbon synthesis.¹ By tuning the CO:H₂ ratio from the CO₂RR reactor to an optimal specification for the downstream thermochemical process, CO₂ can be converted to valuable products with potentially higher conversions and selectivities than electrocatalysis alone.¹ Using CO₂ as starting materials in the formation of syngas, green-house gases are consumed, while significant money is saved due to the abundance of CO₂ in the environment. Recent work has shown that Ag/, Au/, and Pd/C catalysts alongside KHCO₃ electrolyte showed promise in the simultaneous formation of CO and H₂.² Gas Chromatography (GC) was used to take continuous samples of the reaction's product formation which allowed for the calculation of Faradaic Efficiency (FE) of each catalyst. Data showed that an increase in KHCO₃ molarity caused an overall increase in H₂ formation, while catalysts Pd/C and Au/C had the potential to produce H₂:CO ratios of 1:1, 2:1 and 3:1 depending on current applied. Ag/C showed the lowest levels of CO formation out of all the catalysts. This information is helpful in finding which downstream reactions (e.g. methanol synthesis, Fischer-Tropsch process) are possible with the catalysts tested.

- (1) Garg, S.; Biswas, A. N.; Chen, J. G. Opportunities for CO₂ Upgrading to C₃ Oxygenates Using Tandem Electrocatalytic-Thermocatalytic Processes. *Carbon Future* **2024**, 1 (1), 9200002. <https://doi.org/10.26599/CF.2023.9200002>.
- (2) Tackett, B. M.; Lee, J. H.; Chen, J. G. Electrochemical Conversion of CO₂ to Syngas with Palladium-Based Electrocatalysts. *Acc. Chem. Res.* **2020**, 53 (8), 1535–1544. <https://doi.org/10.1021/acs.accounts.0c00277>.

CHEMISTRY SEMINAR

Producing High Yields of Pure Products from Iron-Catalyzed Alcohol Oxidations

By Cole Springer '25 Chemistry

11:30 a.m

April 4, 2024

Darrah Auditorium
McCreary 101

Abstract:

The oxidation of alcohols to their corresponding aldehydes or ketones is an important chemical reaction utilized often in synthetic organic chemistry. While there are many available methods to oxidize alcohols, they often use strong, reactive oxidants and produce toxic byproducts. Therefore, recent efforts are focused on creating safe, environmentally sustainable alcohol oxidations. Iron catalysts were found to be a promising alternative due to iron's high natural abundance, making these catalysts sustainable while still being similarly reactive. Previous work in our group led to the discovery that a simple compound in this class of iron catalysts could oxidize alcohols with furfural, a biomass waste product, as the stoichiometric oxidant/hydrogen acceptor. As a result, we are increasing the sustainability of alcohol oxidation methods. Our goal was to use the (tetraphenylcyclopentadienone)iron tricarbonyl catalyst (**1**) in the reaction shown in Figure 1 and find reaction workup conditions which would efficiently purify the products and afford them in the highest yields possible. The overarching goal of the project was, and still is, to prove our general method works by oxidizing a variety of primary and secondary alcohols and isolating their corresponding aldehydes or ketones. Trends indicated that, as previously discovered, secondary alcohols were oxidized more readily than primary alcohols, and alcohols with electron-donating groups were oxidized to greater yields than those with electron-withdrawing groups. Acetone was tested as an alternative hydrogen acceptor and solvent, but resulted in generally lower yields compared to furfural and toluene.

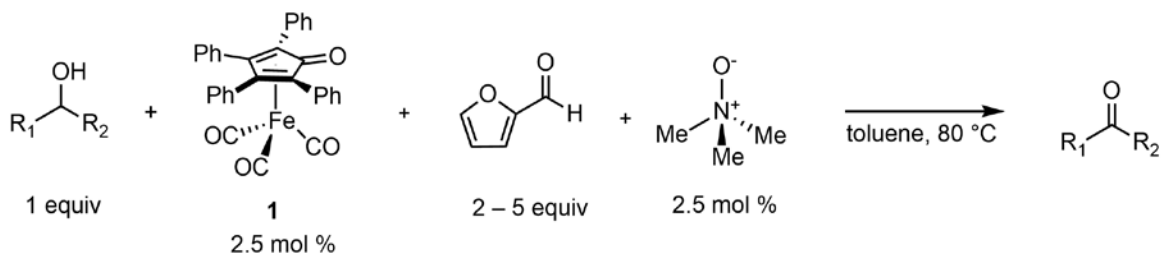


Figure 1: Oxidation of an alcohol using **1**.