

Exploration Into Copper Catalyzed and Copper-less Click Reactions with $\text{Re}(\text{CO})_3$ Complexes

Nicholas Naro, Adam Moore, and Paul Benny

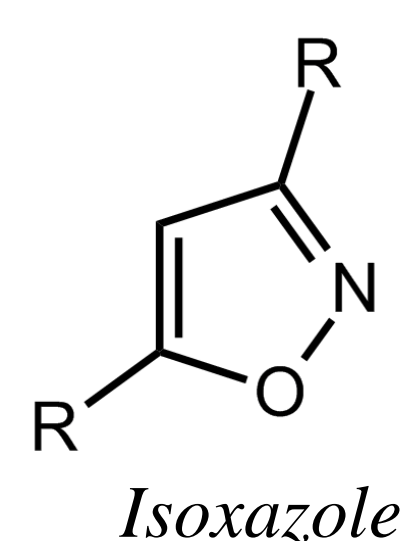
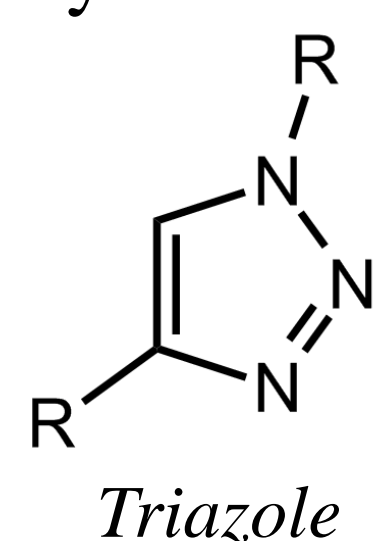
Washington State University, Department of Chemistry, Pullman, WA 99164

Nan27@pitt.edu

Introduction

“Click” chemistry is a rapidly developing field of chemistry, which allows two independent functionalities to be efficiently and selectively linked in near quantitative yields. This type of reaction is of particularly interest in the field of radiopharmacy, where novel methods are needed to improve radiolabeling of biomolecules (BM). In this application, a radioactive complex could be separately generated from radiometal and a ligand, then joined rapidly to a biological targeting molecule. This process separates the complexing conditions (i.e., pH, temperature) of the radiometal from the BM, which may adversely degrade or deactivate the BM.

The speed and efficiency of “click” reactions are particularly important to this application due to the short half-life of the most common medical radioisotope, $^{99\text{m}}\text{Tc}$ (half-life 6.0 hr, 140 KeV), that is utilized in 3D Single Photon Emission Computed Tomography imaging (SPECT). My research has focused on investigating a new type of click reaction that combines a alkyne and an oxime to generate a isoxazole cycloaddition product. Compared to the copper(I) catalyzed Huisgen alkyne and azide reaction to generate a triazole, this approach has potential by reducing the coordination strength cycloaddition product, which simplifies the number of possible complexes observed. In addition, isoxazole linkages have unknown effects on biologically active molecules and have been proposed under copperless conditions, making it a linkage of interest for further study.

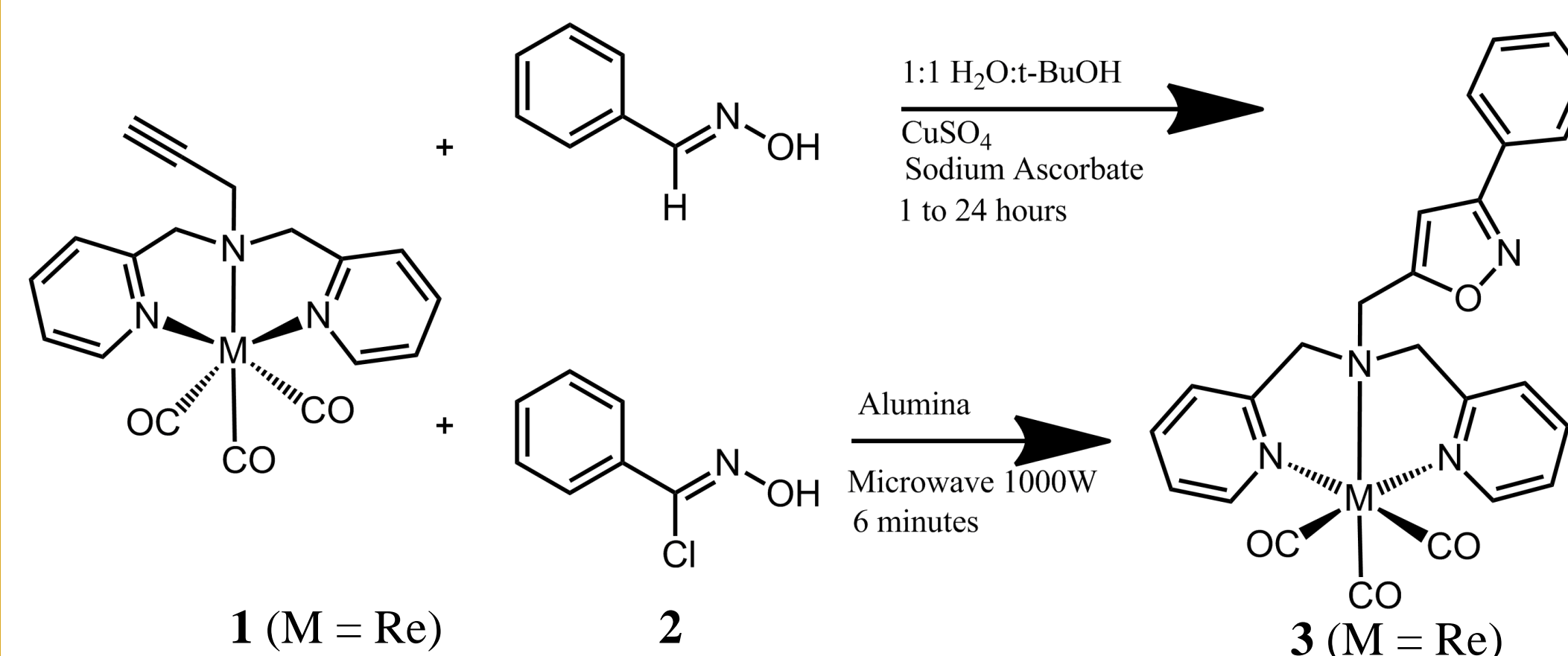


My Research

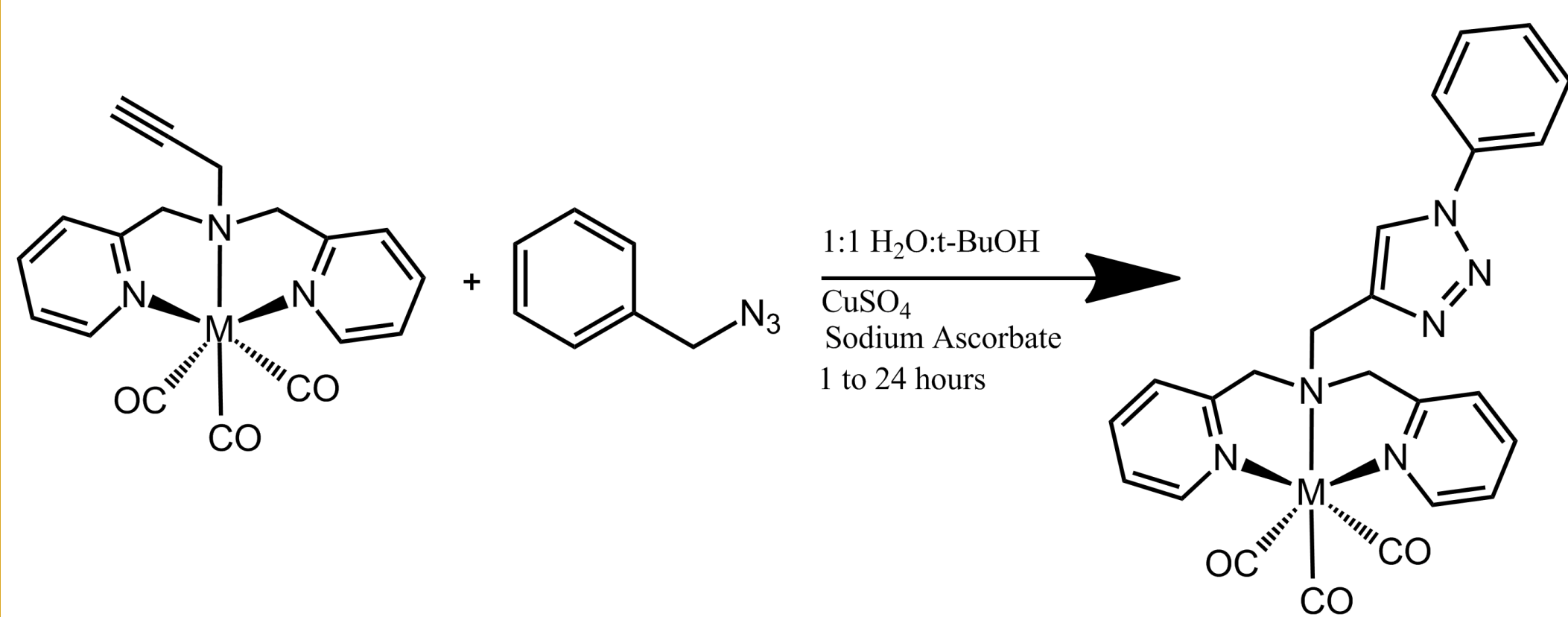
My research investigated the feasibility of two different approaches to the “click” chemistry linkage between the metal chelator and an oxime derivate of the biologically active molecule. One approach involves chlorinating the oxime and then proceeding with the typical copper(I) catalyzed “click” reaction procedure, while the other approach involves generating the chlorinated oxime *in situ* using a microwave and dispensing with the copper catalyst. In addition to removing a potentially toxic impurity *in vivo*, the copper-less method is greener, proceeds faster and requires fewer reagents.

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Click Chemistry Schema



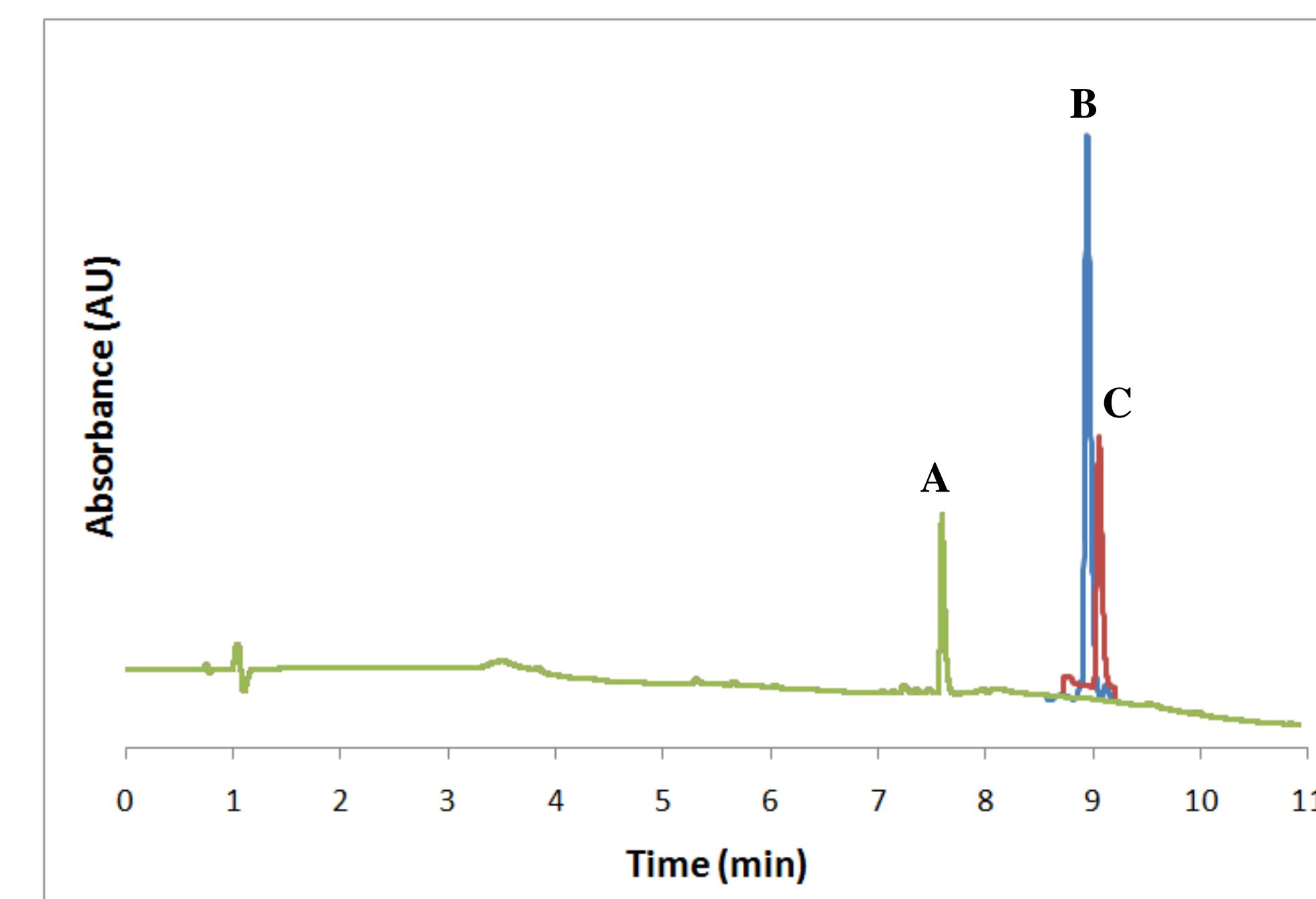
Copper catalyzed and copper-less isoxazole formation



Copper catalyzed triazole formation

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Representative HPLC Trace



Combined HPLC traces of 1, 2, and 3. ~ 7.58, 9.05, and 8.94, respectively.

A: Rhenium complex (1)
B: Click product (3)
C: Chlorinated oxime (2)

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Attempted Reactions

	Substrate /Solvent	Power	Time	Catalyst	Linkage Form	Results
1	1:1 H ₂ O:t-BuOH	-	24 hours	Copper/ Acetate	Isoxazole	Failed
2 [†]	Alumina	50%	3 min	NCS	Isoxazole	Trace
3 [†]	Alumina	50%	3 min	Copper/ Acetate	Triazole	90% yield by HPLC
4 [†]	Alumina	50%	9 min	None	Triazole	Failed
5 [†]	None	40%	3 min	NCS	Isoxazole	Failed
6 [†]	Alumina/ Carbonate	50%	3 min	NCS	Isoxazole	Trace
7	1:1 H ₂ O:t-BuOH	-	24 hours	Copper/ Acetate	Isoxazole	Strange peak at 5.6 min
8	1:1 H ₂ O:t-BuOH	-	24 hours	Copper/ Acetate	Isoxazole	Success! (New 2)

[†]: Reactions performed under microwave conditions

Conclusions and Future Work

- Isoxazole formation is possible using traditional “click” chemistry conditions, though it is neither as fast nor as high yielding as triazole formation
- Microwave Isoxazole formation is possible, though conditions such as time, power, concentration, and substrate need to be optimized
- Future work includes complexation studies using $^{99\text{m}}\text{Tc}$, replacement of the benzyl group used in this study with targeted biomolecules containing an oxime functionality, development and examination of this reaction’s effectiveness using different ligand systems, and optimization of conditions for the microwave assisted reaction.

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