

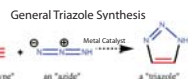
Optimization of Triazole Production Through Microwave-Assisted Synthesis

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Introduction

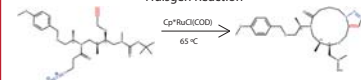
The goal of this project was to examine the effects of microwave irradiation on the production of triazoles. Triazoles are molecules formed when an alkyne containing a carbon-carbon triple bond, and an azide containing three nitrogen atoms, combine. Triazoles have many uses in medicine such as HIV-1 protease inhibitors, size specific ligands for mRNA hairpin loops, and fungicides.



Triazole based molecules are widely used in the diversity oriented synthesis (DOS) libraries at the Broad, mainly for their properties of being metabolically inert, having multiple hydrogen bond acceptor and donor regions, and acting as a peptide bond mimic. Triazoles and other DOS library molecules will eventually be used in chemical screens to evaluate their effects on biological processes.

The reaction done at the Broad for triazole synthesis is known as the Huisgen reaction. Scientists from the Chemical Biology Platform create custom in-house "SSR" substrate as the starting material for this reaction. The Huisgen reaction is intramolecular, meaning the reaction takes place within the molecule itself. Under optimal conditions, our substrate will not interact chemically with any molecule with the exception of the catalyst Cp*RuCl(COD).

Huisgen Reaction



In recent years, the use of microwave-assisted synthesis has attracted the attention of many organic chemists. Reactions that formerly took hours or days can be done in minutes via a microwave. In many thermal reactions, significant time is spent waiting for the heat to conduct from apparatus to solvent. Microwaves stimulate molecules in the solvent to resonate, thus allowing for much faster and efficient heating. The goal of our research is to see if microwave-assisted synthesis can be applied to our in-house substrates to increase efficiency and decrease reaction time.

Materials and Methods

Experiments were performed in a CEM Explorer 24 microwave. Methods were set up where the microwave would irradiate the reaction tube to heat to the desired temperature, and then keep the tube at that temperature for a specified amount of time. All tubes were sealed before entering the microwave.

The Explorer 24 Microwave Automation Module



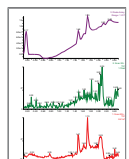
Results

Selecting a Solvent

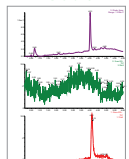
In order to have efficient heating through microwave irradiation, a solvent must be used as a medium to absorb the incoming microwaves. Thus a broad range of solvents with diverse properties such as boiling point, polarity, and ability to absorb microwaves (permittivity) were surveyed.

| Solvents | Boiling Point | Permittivity | Dielectric | Product Present (P) | Reactant Present (R) | Dimer Present (D) | P:R:D |
|--------------|---------------|--------------|------------|---------------------|----------------------|-------------------|-----------------|
| Acetone | 56 °C | 1.118 | 20.7 | run failed | run failed | run failed | run failed |
| Acetonitrile | 82 °C | 2.325 | 37.5 | 15.5% | 36.1% | 16.9% | 1 : 2.18 : 1.03 |
| Dioxane | 101.1 °C | 2.7 | 2.2 | 84.8% | 5.4% | 5.4% | 1 : 0.57 : 0.47 |
| DMP | 153 °C | 6.07 | 36.7 | 69.6% | 7.7% | 9.4% | 1 : 0.11 : 0.13 |
| Ethanol | 78 °C | 22.866 | 79 | 14.6% | 43.0% | negligible | 1 : 2.95 : 0.00 |
| Nitromethane | 100-103 °C | 2.304 | 35.87 | 24.0% | 67.3% | 2.0% | 1 : 2.80 : 0.08 |
| DMF | 66 °C | 0.348 | 7.6 | 46.3% | 45.4% | 2.2% | 1 : 0.97 : 0.40 |
| Toluene | 111 °C | 0.94 | 2.4 | 46.3% | 4.2% | 6.2% | 1 : 0.92 : 0.40 |

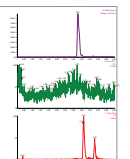
Ethanol



Dioxane



Toluene



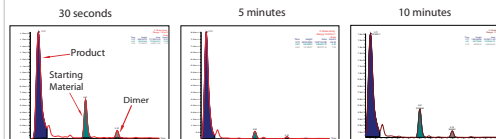
Optimizing Molar Percent

After obtaining the optimal solvents, testing began for optimal substrate concentration and catalyst mole percent. Our goal here was to find the highest substrate concentration and lowest amount of catalyst with an acceptable conversion rate.

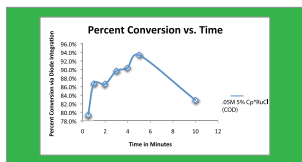
| Solvent | Substrate | Catalyst | Mole Percent | Product Present (P) | Reactant Present (R) | Dimer Present (D) | P:R:D |
|---------|-----------|----------|--------------|---------------------|----------------------|-------------------|-----------------|
| Dioxane | 0.01M | 5 | 5 | 81.8% | 7.8% | negligible | 1 : 0.10 : 0.00 |
| Toluene | 0.01M | 5 | 5 | 86.2% | 3.8% | negligible | 1 : 0.04 : 0.03 |
| Toluene | 0.01M | 15 | 5 | 95.1% | 3.4% | negligible | 1 : 0.04 : 0.00 |
| Toluene | 0.01M | 5 | 5 | 94.8% | 16.5% | 4.8% | 1 : 0.51 : 0.06 |
| Toluene | 0.1M | 5 | 5 | 79.3% | 16.0% | 4.5% | 1 : 0.23 : 0.09 |

Optimizing Reaction Time

We tested a range of times from 30 seconds to 10 minutes. From analyzing our solvent and concentration optimization, we decided to set the substrate molarity at .05M, set the catalyst mole percent at 5%, and use Toluene for the next set of experiments.

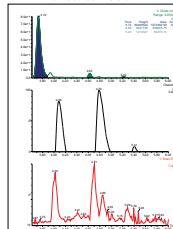


Integrated LC for .05M substrate 5% Cp*RuCl(COD) Reactions

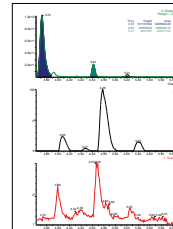


Moving to Large Scale

Small Scale 94.5% Conversion



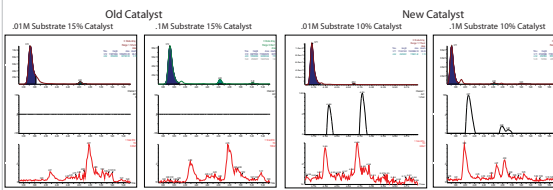
Large Scale 85.7% Conversion



Our next step was to see if our optimized conditions would translate on a larger scale. We tripled the amount of substrate while leaving substrate molarity, catalyst mole percent, and reaction time constant at .05M substrate 5% catalyst and 5 minute reaction time.

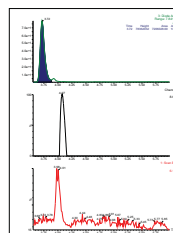
Changing Catalyst

We suspected that one of the problems with our catalyst, Cp*RuCl(COD), was that it was unstable in Toluene and decomposing in solution. Analysis of the time trial revealed that, in the 10 minute run, there was significantly more dimer, meaning our catalyst must have failed sometime in the middle of the reaction. We chose to try a different catalyst that is less stable under oxygen, but more stable in Toluene. We found that, under the same substrate concentration and reaction time, our new catalyst, Cp*(RuCl)4, produced more product than Cp*RuCl(COD).

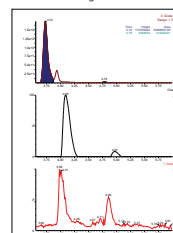


Maximizing Conversion

Small Scale



Large Scale



Using what we learned from solvent, molarity and catalyst optimization, we tried several reactions to maximize conversion. We found that the .01M substrate 15% Cp*(RuCl)4 gave us 100% conversion on a small scale. When we tripled the mass there was a corresponding 98.7% conversion.

Conclusions

- Microwaves are very effective in the cycloaddition of our 1,5 triazoles. Microwaves decreased the reaction time of this particular reaction by 200%.
- Longer reaction times correlate to more dimers, as the catalyst will decompose in solution, allowing the substrate to react intermolecularly.
- Though microwave-assisted cycloaddition is much faster than traditional thermal methods, thermal is still the most catalyst efficient, as it is able to completely convert the starting material with only 2 mole percent of Cp*(RuCl). We observed that only 15% Cp*(RuCl) was able to completely convert the starting material in the microwave-assisted reactions.

Future Research

- Optimize microwave heating through dynamic (multi-staged) heating methods. The microwave heating methods we used were set to hold our samples at a specified temperature for a specified amount of time. It has been observed that cycling between a high temperature and low temperature in a microwave prevents the sample from achieving equilibrium (where ΔE is zero), allowing the system to gradually increase in energy.
- Optimize all conditions (solvent, molarity, temperature, and reaction time) under which the microwave-assisted cycloaddition is able to fully convert starting material using 2% catalyst or less.
- Observe behavior of Cp*(RuCl)(PPh₃) as a catalyst in microwave assisted triazole synthesis. This catalyst is known to be more stable in air than Cp*RuCl(COD), and as stable in solution as Cp*(RuCl).
- Investigate the temperature extremes where the substrate and catalyst start to decompose. Future research can be done to determine if higher reaction temperature correlates with higher product yield and at what point diminishing returns occur.

Literature Cited

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