A new reaction to form hydroxamic acid derivatives using masked isocyanate reagents

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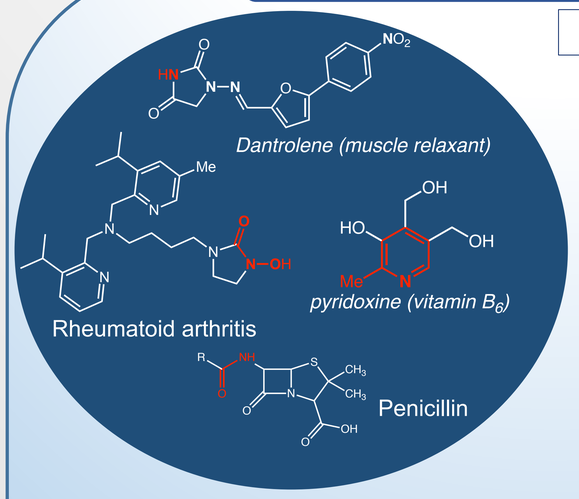
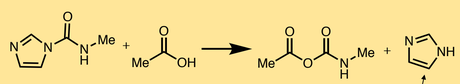
Introduction



Why hydroxamic acids?

- Present in bioactive molecules
- Vital for mode of action (metal binding)
- Useful reagents – amide synthesis
- **Can be hard to synthesize**

Previous studies



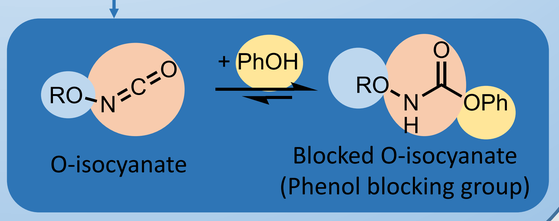
Production of imidazole

Previous studies showed amide formation with imidazole as the leaving group.(1)
This reactivity has not been exploited

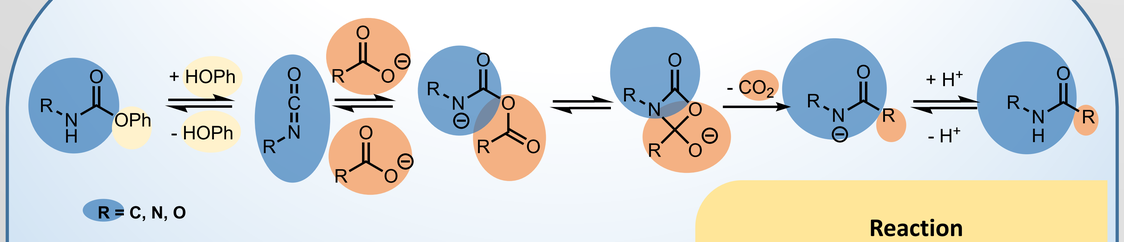
Why "masked reagents" with phenol?

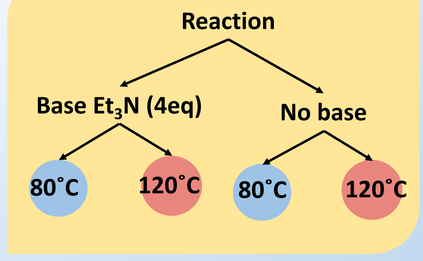
Blocked isocyanates…
- Increased functional group tolerance
- Reduced toxicity

Phenol…
- Using phenol as a blocking group has not been done before
- O and N substituted isocyanates have acidic protons which don't allow the use of imidazol based leaving group.



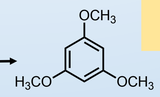
Method





Step 1: Setup the reactions
Temperature, Basicity
Anhydrous conditions - Argon

Step 2: NMR
Molecules identifications
Estimated yield with TMB standard

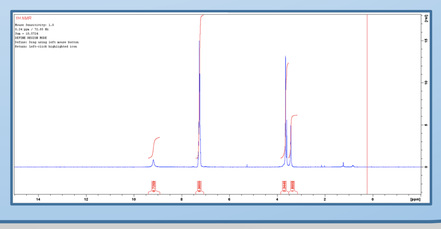


Step 3: Extraction
Separate the compound with aqueous and organic phase

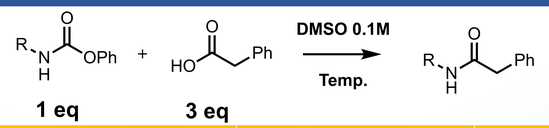
(2)

Step 4: Column
Isolate the product

Step 5: NMR
Identify the final isolated product

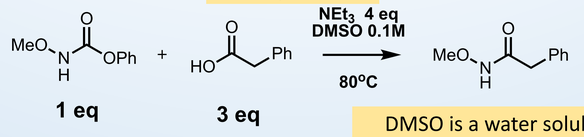


Results



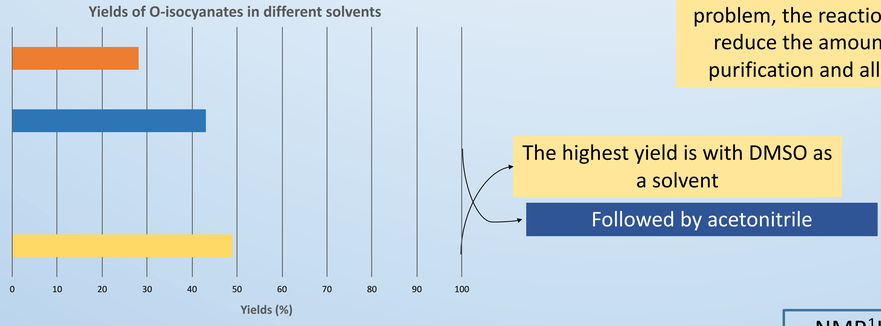
Conditions	Ph	Me, Me	Me, O
80°C	4%	0	0%
120°C	8%	0	0%
80°C w/ Et_3N (4 eq)	57%	0	**49%**
120°C w/ Et_3N (4 eq)	64%	0	0%

Scale up 0.6mmol



DMSO is a water soluble polar organic solvent with a high boiling point. Removing the DMSO from our compound requires a special workup involving several washes with water. This lead to significant loss of product. To address this problem, the reaction concentration was increased 10 fold to reduce the amount of DMSO present. This facilitated our purification and allowed us to isolate the desired product.

Yield of 63% for the isolated scaled up reaction

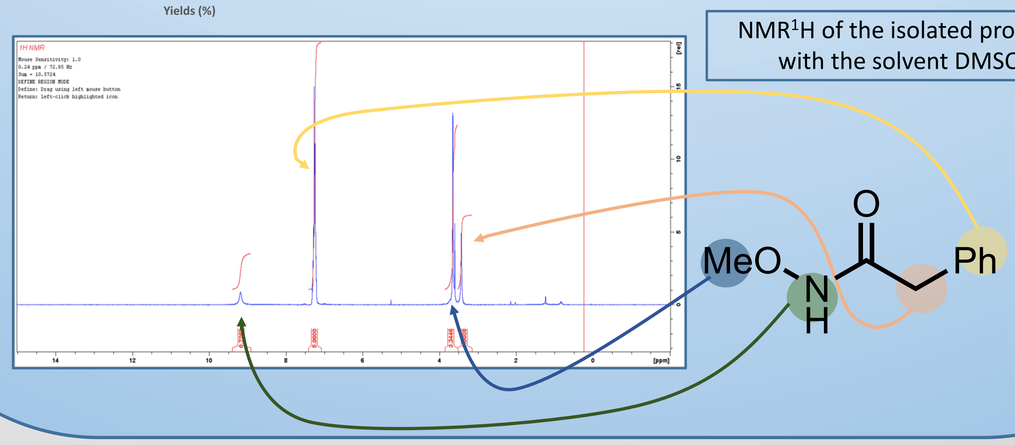


The highest yield is with DMSO as a solvent

Followed by acetonitrile

Acetonitrile works comparably to DMSO. This solvent is desirable because of its low boiling polar organic properties. It is easily removed from the product

NMR^{1}H of the isolated product with the solvent DMSO



Conclusion

The synthesis of amides with carboxylic acids and blocked O-isocyanate and C-isocyanate is possible

What does that tell us?
- This provides an alternative route to hydroxamic acid derivatives which have very limited synthetic routes
- This approach can likely be extended, allowing the synthesis of amides and hydrazides with other masked reagents
- Phenol is validated as a masking group in the synthesis of amide bonds from carbon and oxygen substituted isocyanates

Next steps
Optimization of reaction conditions (temperature, equivalents of starting material, additives…)

References

1. Yuan-Ye Jiang*, Tian-Tian Liu, Rui-Xue Zhang, Zhong-Yan Xu, Xue Sun, and Siwei Bi*. J. Org. Chem., **2018**, 83(5), 2676-2685
2. Lisa Nichols, "Organic chemistry laboratory techniques 2nd Edition", 2016

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