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Catalytic Direct Amidation

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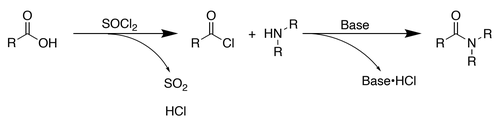
Abstract

- Traditionally, amides are synthesized by activating a carboxylic acid with reagents such as thionyl chloride and introducing the amine to the resulting acyl chloride (Scheme 1).
- Since thionyl chloride and acyl chlorides are strong electrophiles, they are highly toxic, water sensitive, and produce dangerous waste.

Traditional Formation of Amides



Scheme 1. Traditional formation of amides.

- Since 2019, the Boisvert lab has been working on utilizing boric acid ($B(OH)_3$) as a catalyst for amidation reactions.
- To increase the reactivity of boric acid, the Boisvert lab tested over 100 additives. Out of those additives, sulfuric acid and 1,2-aminoalcohols were found to noticeably increase the reactivity of boric acid.
- This summer, we tested these additives for reproducibility, and studied different substrates to show that this reaction is broadly applicable.

Ideal Reaction: Catalytic Formation of Amides

Scheme 2. Ideal formation of amides.

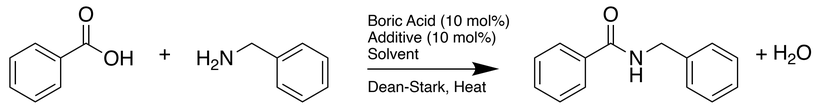
Objectives

My objectives were to complete data collection for the small-scale testing of the additives on the benchmark reaction (benzoic acid + benzylamine), and then carry out large scale reactions to confirm the efficacy and the scope of these results.

Small-Scale Results for *N*-Benzyl Benzylamide

^{1}H NMR spectroscopy was used to measure the amount of product formed by integrating protons unique to the amide vs the amine. An example of the integrations can be seen in Figure 1.

- Out of the 9 additives listed in Figure 2, diethylamino ethanol had the best reactant to product ratio at 10 mol%.
- To prove that 10 mol% was the ideal amount of additive, reactions were run with 5 and 20 mol%. Both those percents had worse average results than 10%.
- To also prove that diethylamino ethanol isn't itself a catalyst, a reaction was run without boric acid and the resulting ratio was significantly worse.
- Some of the additives such as catechol, 8-hydroxyquinoline and sodium iodide appear to hinder the reaction, compared to using no additive.
- Most of the additives made no discernable difference to the efficiency of reaction.



Scheme 3. Catalytic synthesis of *N*-benzylbenzylamide.

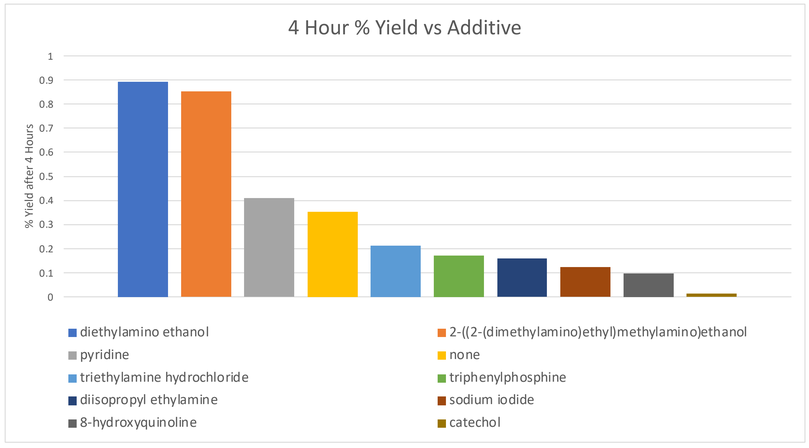


Figure 2. Percentage of product formed vs additive as determined by ^{1}H NMR spectroscopy.

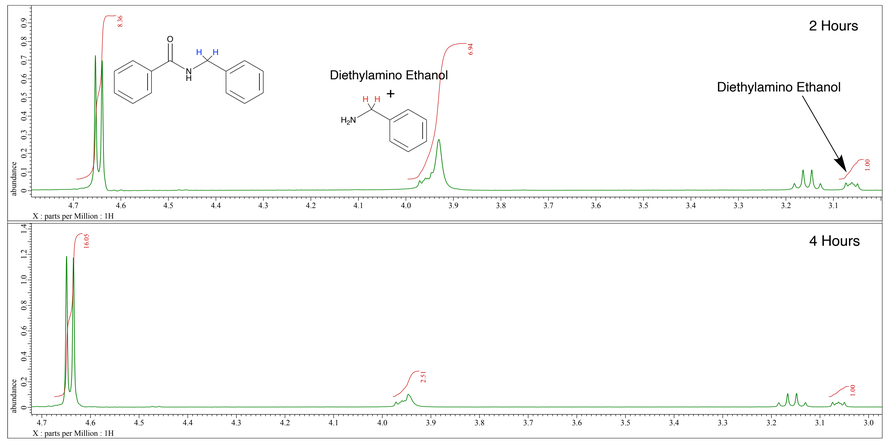


Figure 1. ^{1}H NMR spectrum of *N*-benzylbenzylamide and benzylamine with diethylamino ethanol. Top: after 2 hours, bottom: after 4 hours.

Conclusions

- According to the data from the 4 hour runs, reactions that have a combination of: a primary amine, acids and amines without heteroatoms, and acids with an aromatic group were the most positively affected by diethylamino ethanol.
- The overall results are a bit of a mixed bag though, the three most positively affected reactions had between a 221% and 243% increase, but the highest yield of those three was only 40%.
- The next three reactions had increases between 87% and 218% and much higher yields of 60% to 84%.
- Other reactions had high yields but low % increase, meaning the reaction was already decently efficient and wasn't much affected by the diethylamino ethanol.
- Then there were six reactions that had both poor yields and low, even negative increases. None of these "bad" reactions contained the exact combination of characteristics listed in the first bullet point.
- Hopefully next semester, I will get to study the mechanism of these reactions and establish a reliable pattern of characteristics that cause the best performing reactions.

References

Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem*. **2006**, *4*, 2337-2347.

Monks, B. M.; Whiting, A. Direct Amide Formation Avoiding Poor Atom Economy Reagents. In *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries,* 1st ed.; John Wiley & Sons, **2013**; pp 89-110.

Results for Other Substrates

- We then used diethylamino ethanol in large scale reactions and on other substrates.
- Figures 3 shows the average reaction progress of 2-thiophenecarboxylic acid and morpholine.
- Figure 4 shows the average reaction progress of phenylacetic acid and 2-aminopyridine.
- Both reactions demonstrated a significant increase in productivity when diethylamino ethanol was introduced.
- Other combinations, such as BOC-alanine-OH + benzylamine in Figure 5 didn't see much of an improvement with the additive.

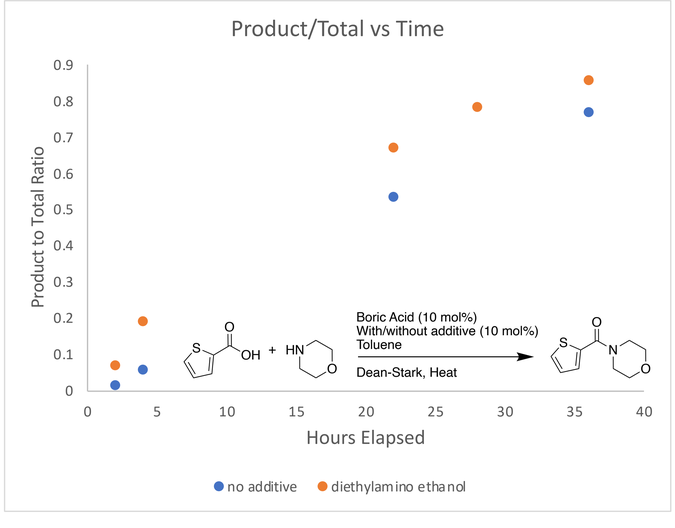


Figure 3. Results for 2-Thiophene Carboxylic acid + Morpholine as determined by ^{1}H NMR spectroscopy.

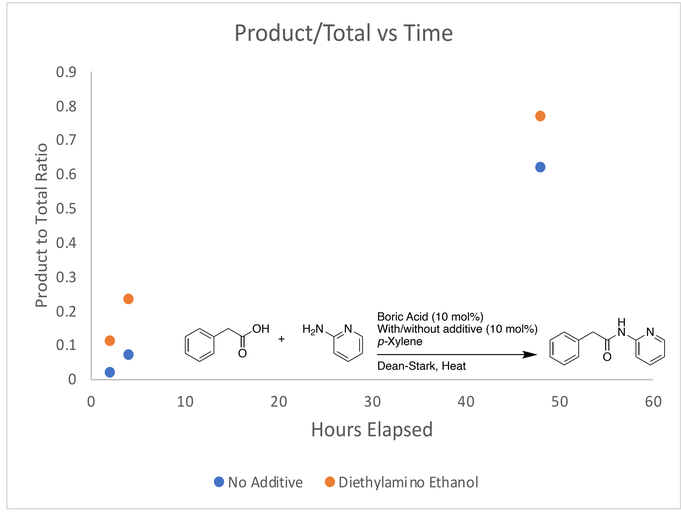


Figure 4. Results for phenylacetic acid and 2-aminopyridine as determined by ^{1}H NMR spectroscopy.

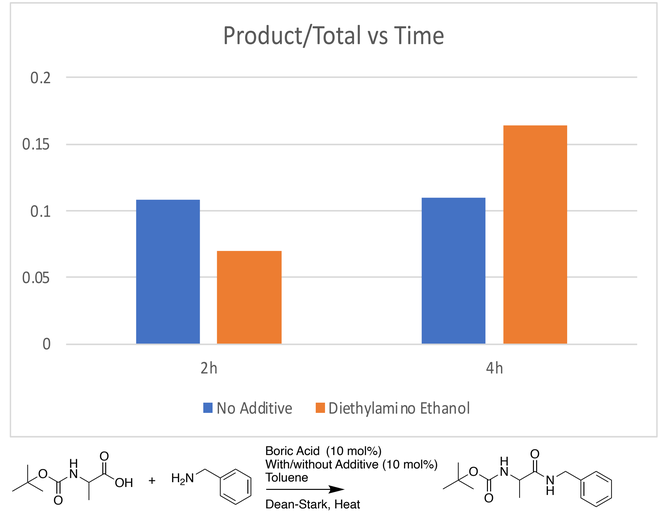


Figure 5. Results for Boc-Alanine-OH and Benzylamine as determined by ^{1}H NMR spectroscopy.