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Development of New Arsenic Based Amidation Catalysts

Cameron Chrisman, Luc Boisvert

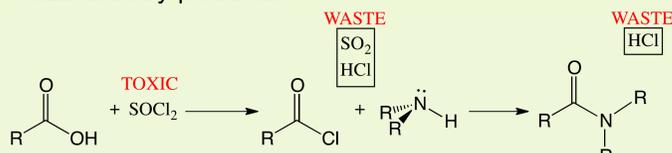
University of Puget Sound Chemistry Department, Summer 2013



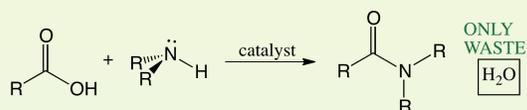
Background

In a 2006 survey of the pharmaceutical companies AstraZeneca, GlaxoSmithKline, and Pfizer, it was found that 12% of all reactions used in the synthesis of drugs were acyl addition reactions.¹ Of those, 66% were amidation reactions.

- The current method for generating amides requires the use of toxic reagents, along with the generation of hazardous by-products.

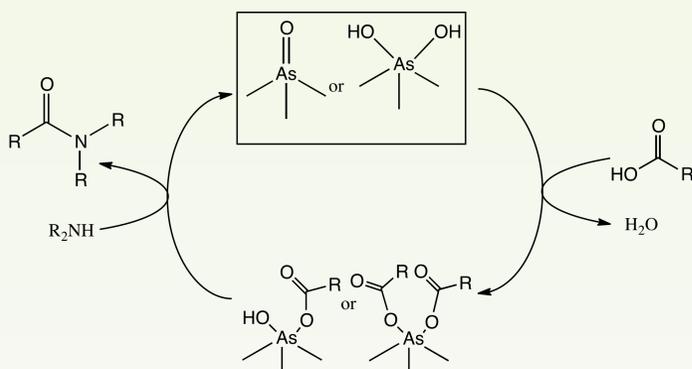


- The below figure illustrates how catalysis could eliminate any toxicity involved in amidation reactions.



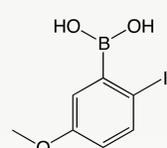
Objectives of the Research

- Synthesize arsenic catalysts building off the research done previously in the Boisvert Lab.
- Test these catalysts against the current most effective catalysts using ¹H NMR spectroscopy.



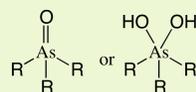
- Above is the proposed catalytic cycle for the arsenic-based catalysts.

Boronic Acid Catalysts



- The current most effective catalysts are the boronic acid compounds developed by Dennis Hall.²
- Disadvantages:
 - High catalyst loading
 - Long reaction times
 - Undesirable solvents

Previous Work in the Boisvert Lab

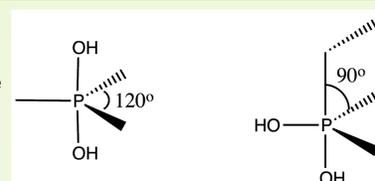


- The first examples of arsenic-based amidation catalysts were discovered.
- Several analogs of the tri-alkyl arsine oxides and dihydroxy compounds were synthesized.
- These were then tested by NMR with several amine, carboxylic acid combinations. Even the most effective catalyst was not active enough to continue pursuing in this direction.
 - More active catalysts are needed.

Project: Ring-Constrained Arsenic Catalysts

Comparison to Phosphorus:

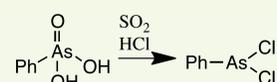
Phosphorus and arsenic have very similar properties. Since there has been much more research done on phosphorus compounds, using what is known about phosphorus was key in deciding what direction to go with the arsenic catalysts.



It has been found that constraining phosphorus in four and five membered rings can change the reactivity of the compounds by forcing electronegative groups into the axial-equatorial positions as opposed to the preferred axial-axial as seen in the figure above.³ This can significantly affect the reactivity of the OH groups. Therefore our research was focused on synthesizing similar molecules with arsenic centers.

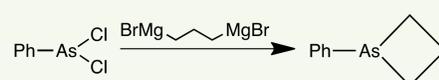
Synthesis of Four- and Five-Membered Rings:

1) Phenyl-dichloro arsine:



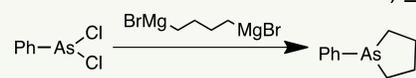
- 68.5% yield
- Yellow oil
- Very useful in many of the reactions attempted

2) Attempted synthesis of four-membered ring:

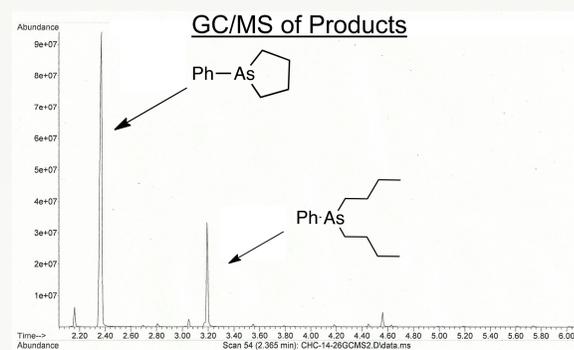
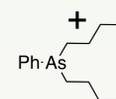


- Di-Grignard not stable and decomposed
- Grignard was difficult to work with so the 5-membered ring was pursued more.

3) Synthesis of five-membered ring:

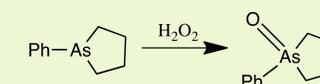


- Relatively successful reaction but there was also the presence of the di-alkylated compound shown below.



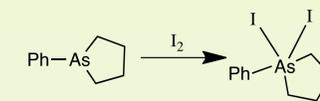
- By altering the conditions of the reaction the di-alkylated product was greatly reduced.
- The amount of the di-alkylated product relative to the desired product can be seen in the GC/MS to the left.
- It was found to be very difficult to isolate just the 5-membered ring as it has similar properties to the di-alkylated product.

4) Oxidation attempts of the five-membered ring:

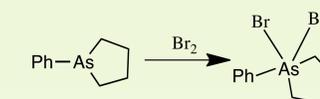


- Most effective

- Yielded what we propose as the polymerized compound since the GC/MS showed multiple broad peaks. Unable to actually isolate the compound for testing.

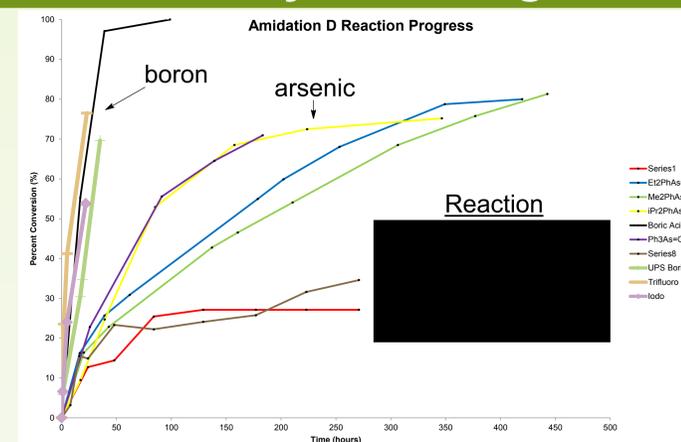


- None of the di-iodo compound formed.



- Compound seemed to form but wouldn't be isolated or purified

Catalytic Testing



- Three catalytic tests were run with boric acid and two of the boronic acid catalysts.
- The data was then compared to the data collected previously, of the current arsenic catalysts.
- Arsenic catalysts are not as active as boron catalysts.

Future work

More work isolating and testing the five-membered ring is needed. If it proves to have catalytic activity, more work should be dedicated to synthesizing the four membered ring among others.

Acknowledgments

I would first and foremost like to thank Professor Boisvert for all of the time he dedicated to helping me through my first research experience. I would also like to thank the University of Puget Sound for providing me with the funds to conduct my research.

Work Cited

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