Optimization of N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide via Reductive Amination

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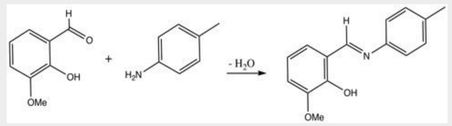
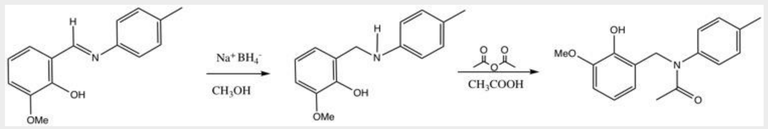
Introduction

- The synthesis of imines, amines and amides is fundamental to our understanding of biological pathways.[1]
- Several naturally occurring amines such as serotonin and epinephrine function as neurotransmitters in the body.
- Formation of amide bonds is one of the most important reactions in chemistry due to the pharmaceutical industry.
- An acetamide is an enanthic acid with an amide attached.[2]
- Acetamides are commonly used in syntheses as plasticizers
- Amination is the process of adding an amine group to a molecule and can be a powerful method of reducing functional groups.
- Reductive amination reduces imine to an amine.
- Proton and carbon-13 NMR are used to analyze the products and make preliminary judgements on the structure of the molecule.[3]
- IR spectroscopy is used to determine functional groups that would further classify the molecule.[4]



Scheme 1. Synthesis of 2-methoxy-6-(p-tolyliminomethyl)-phenol.

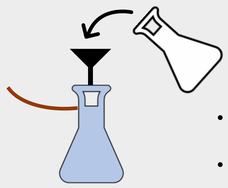


Scheme 2. Synthesis of N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide.

Methods

- p-toluidine & o-vanillin placed in beaker, mixed => orange spikes
- Imine dissolved in 95% methanol, stirred
- Reduced with sodium borohydride (added in small increments) => colorless

- Glacial acetic acid eliminates excess sodium borohydride, neutralizing the solution
- Reacted with acetic anhydride over steam bath for 15 minutes



- Reaction quenched with cold water, precipitated out of solution
- Vacuum filtration, isolation of colorless solid

Figure 1. Reductive Amination of N-(2-hydroxy-3-methobenzyl)-N-p-tolyacetamide.

Results

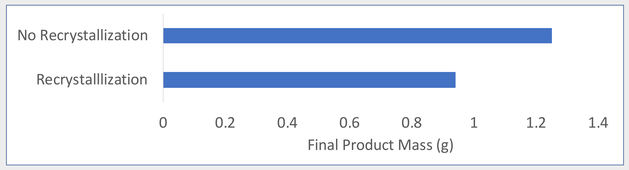


Figure 2: Comparison of final product yield as a result of recrystallization. Reaction without recrystallization yielded about 1.25g, while reaction with recrystallization yielded about 0.94g.

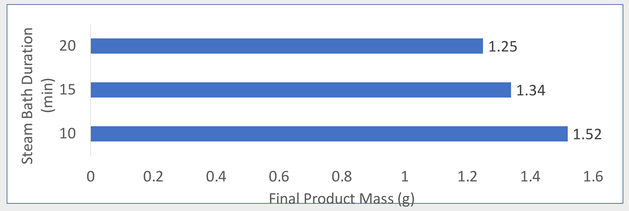


Figure 3: Comparison of resultant product yields as a result of different steam bath durations. 10 minute steam bath yielded 1.52g product, 15 minute bath yielded d1.34g, and 20 minute bath yielded 1.25g.

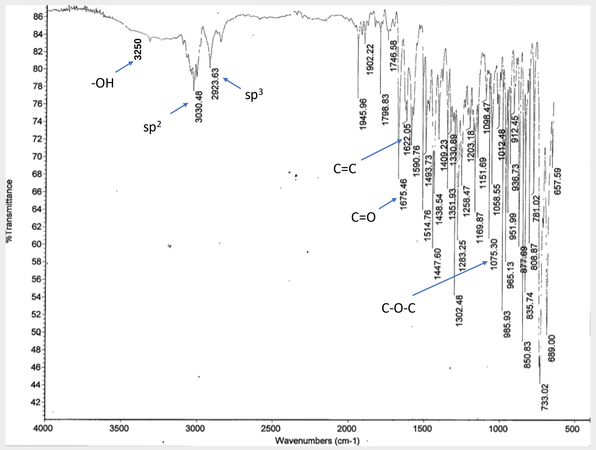


Figure 4: IR spectrum of product N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide.

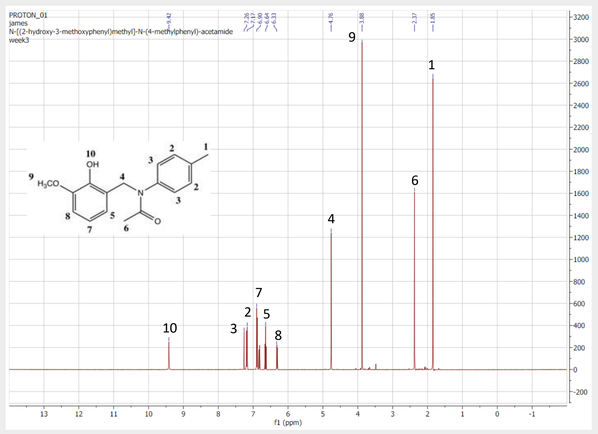


Figure 5. ^1H NMR spectrum of product N-(2-hydroxy-3-methoxybenzyl)-N-p-tolylacetamide.

Discussion

- Optimizations
  - I. Elimination of recrystallization as a means to prevent product loss
  - II. Methanol use rather than ethanol (the greener alternative) as a solvent system combined with recrystallization resulted in increased yield
  - III. Steam bath durations between ten and twenty minutes displayed close to full product yield
- Complications
  - I. Oiling out during reduction was prevented through constant stirring
  - II. Oil bath was difficult to control; steam bath produced much more even result

Summary and Conclusions

- Findings
  - I. Recrystallization is an unnecessary step to this procedure
  - II. Although it is not as environmentally-friendly as ethanol, methanol is the solvent of choice
  - III. 10 minutes is sufficient for reaction over steam bath
- Future Work:
  - I. Sodium cyanoborohydride could be used as reducing agent instead of sodium borohydride
  - II. An acid catalyst could be used to facilitate the formation of the imine
  - III. Recrystallization at the end of the filtration step to help further purify product

Acknowledgments

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References

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