Developing an Ortho-metalation Organic Synthesis Laboratory Activity with Applications to Agriculture

THOMPSON RIVERS UNIVERSITY

Connor Johnson, Dr. Jessica Allingham, Dr. Bruno Cinel and Dr. Norman Reed

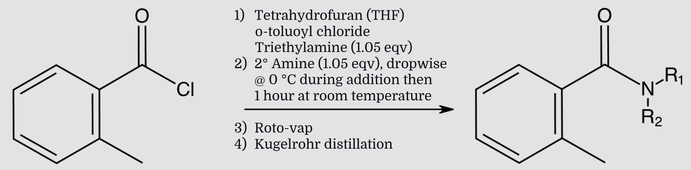
Thompson Rivers University, Chemistry Department

Introduction

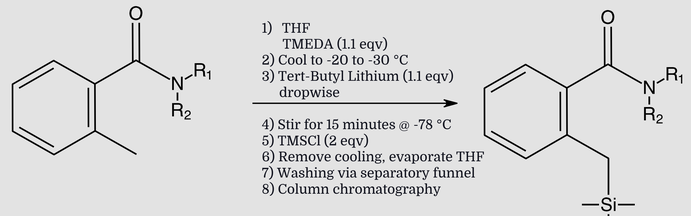
- Monsanto discovered that the substituted tertiary benzamide was active against *Gaeumannomyces graminis*, a fungus that attacks wheat and other crops.[1]
- Dr. Norman Reed at the University of Waterloo in Waterloo Ontario found that the substituted tertiary benzamide could be achieved through sequential directed *ortho* metalation reactions.[2]
- Monsanto researched the most effective method of producing the tertiary benzamide and created the novel wheat fungicide "silthiofam" for the market.
- Improvements were made in the synthesis of silthiofam, but the sterically crowded relationship of the amide and the trimethylsilyl group is believed to be the root cause of fungicide efficacy.
- Through the lithiation of the *ortho* benzylic position, a stabilized structure is formed between the methyl and the neighbouring tertiary amide which acts as an effective directing group, allowing for easy metalation reactions to occur.

Reaction Scheme

Step 1: Synthesis of Tertiary Amide



Step 2: Benzylic Lithiation and Electrophile Reaction



Conclusion

- Successfully synthesized 4 tertiary amides with percent yields from 29.47-95.87%.
- Can utilize the scent of tertiary amides as a potential marker to ensure the product is correct before proceeding.
- Unable to create *ortho*-metalated analogues, scans from ^{1}H nuclear magnetic resonance spectroscopy (NMR) suggest that the metalation step was not successful.
- Integrated important and useful organic synthesis techniques, and found a useful method of small-scale distillation through the Kugelrohr, and column chromatography to purify the final product. The use of these unique procedures would be impactful in a fourth-year undergraduate laboratory.

Methodology

Figure 1. Kugelrohr distillation of a tertiary amide.

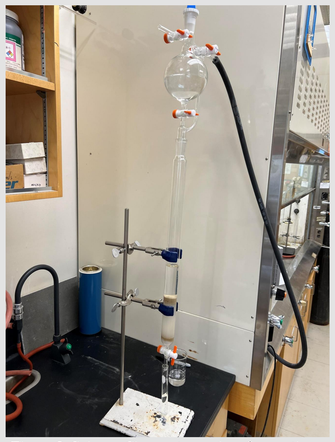


Figure 2. Column Chromatography of an *ortho*-metalated product.

- A rudimentary Kugelrohr (**Figure 1**) is used in Step 1 of the experiment, which distills and purifies the tertiary amide product. The Kugelrohr is attached to a high-power vacuum to reduce the pressure on the round-bottomed flask during distillation.
- Column Chromatography (**Figure 2**) is used at the end of Step 2 to purify the *ortho*-metalated product by separation based on polarity.
- A rotary evaporator was used frequently throughout the experiment to remove any excess solvent to check the purity throughout the experiment.

Results

Table 1. List of products from Step 1 of the reaction scheme. *Product names will be named as the amine added for ease of reference.

Product name*	Percent Yield	Melting Point (°C)	Description
Diethyl amide (DEA)	77.88%	< 25	Essence of grape flavouring, clear oil.
Diisopropyl amide (DIPA)	29.47%	80-84	Essence of grape flavouring, clear crystals.
Di-sec-butyl amide (DSBA)	73.94%	< 25	Essence of dusty fruit, clear oil.
Ethylbutyl amide (EBA)	95.87%	< 25	Essence of dusty cabinet, clear oil.

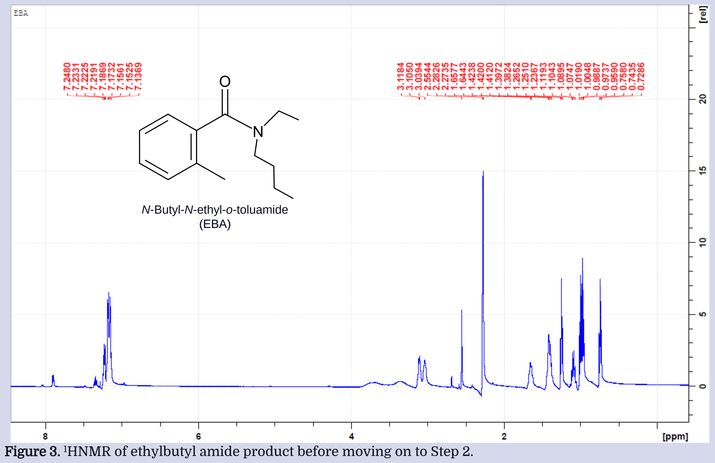


Figure 3. ^{1}HNMR of ethylbutyl amide product before moving on to Step 2.

Future Work

- More work will have to be done for additional *ortho*-metalated products, as well as find the percent yield and characterization of said products through melting point (if solid), infrared spectroscopy (IR) and ^{1}HNMR
- The lab procedure will have to be properly detailed and finalized with a list of secondary amines to pair with *o*-toluoyl chloride and include expected percent yields as a benchmark for the fourth-year undergraduate laboratory activity.
- Testing of *ortho*-metalated analogues for effectiveness as herbicides and fungicides.

References

(1) Phillips, G.; Fevig, T. L., Lau, P. H., Klemm, G. H., Mao, M. K., Ma C., Gloeckner, J. A., Clark, A. S. Org. Process Res. Dev. 2002, 6, 357.

(2) (a) Reed, J. N. Ph. D. Thesis, University of Waterloo, 1985. *(b) Mills, R. J.; Taylor, N. J.; Snieckus, V. J. Org. Chem. 1989, 54, 4372.