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One-pot Conversion of Carboxylic Acids to Aldhydes

Hannah Khan
University of Louisville

Saurin Sutaria
University of Louisville

Michael Nantz PhD
University of Louisville

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Hannah Khan, Saurin Sutaria, and Michael H. Nantz
Biology major, University of Louisville

INTRODUCTION

There are many different ways to convert a carboxylic acid to an aldehyde.[1] A common way to accomplish this transformation is to use multiple steps (e.g., reduction of the carboxylic acid to the corresponding alcohol followed by selective oxidation to the aldehyde). Our success in reducing the diacid muconic acid (**1**) to muconaldehyde (**4**) in a relatively mild, one-pot process[2] has led us to examine whether the method can be expanded to other carboxylic acids. We report here our findings using benzoic acid as a representative substrate.

METHODS

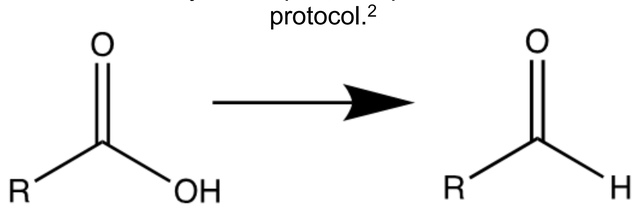
Activation: Carbodiimides are often used to activate carboxylic acids.[3] We used N,N'-diisopropylcarbodiimide (DIC, **5**) to activate the carboxylic acid group for selective addition of hydride. The initially formed acid-carbodiimide adduct rapidly undergoes rearrangement to form an N-acylurea intermediate, such as intermediate **2**.

Reduction: In the second stage of the reaction, the reducing agent, diisobutylaluminium hydride, **DIBAl-H** (**6**) was used to deliver a hydride anion to the intermediate. **6** was added drop-wise at -80 °C so the 1,2 addition chelate (**3**) does not eliminate and undergo further reduction.

Work-up/Purification: The reaction was quenched using **acetic acid**, and this will consume any excess **6**. The product was extracted into an organic layer and the aluminum impurities were removed in the aqueous layer. Potassium sodium tartrate (**Rochelle's salt**) coordinates aluminum to facilitate the separation of the two layers. The product was concentrated by removal of organic solvent through the evaporation under reduced pressure. The product was purified and collected using column chromatography.

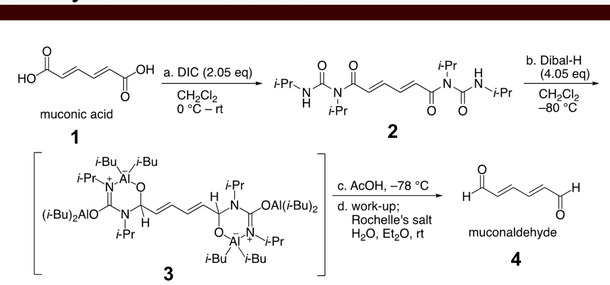
SPECIFIC AIM

Transform mono carboxylic acids to aldehydes using the recently developed, one pot DIC/DIBAl-H protocol.[2]

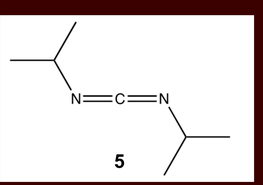


SYNTHESIS OF MUCONALDEHYDE

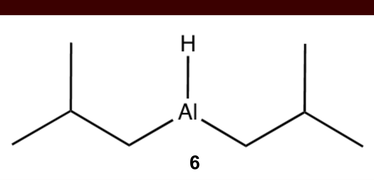
A Convenient Preparation of Muconaldehyde Using a One-PotAcid-to-Aldehyde Reduction Protocol



DIC



DIBAl-H



RESULTS

Benzoic Anhydride

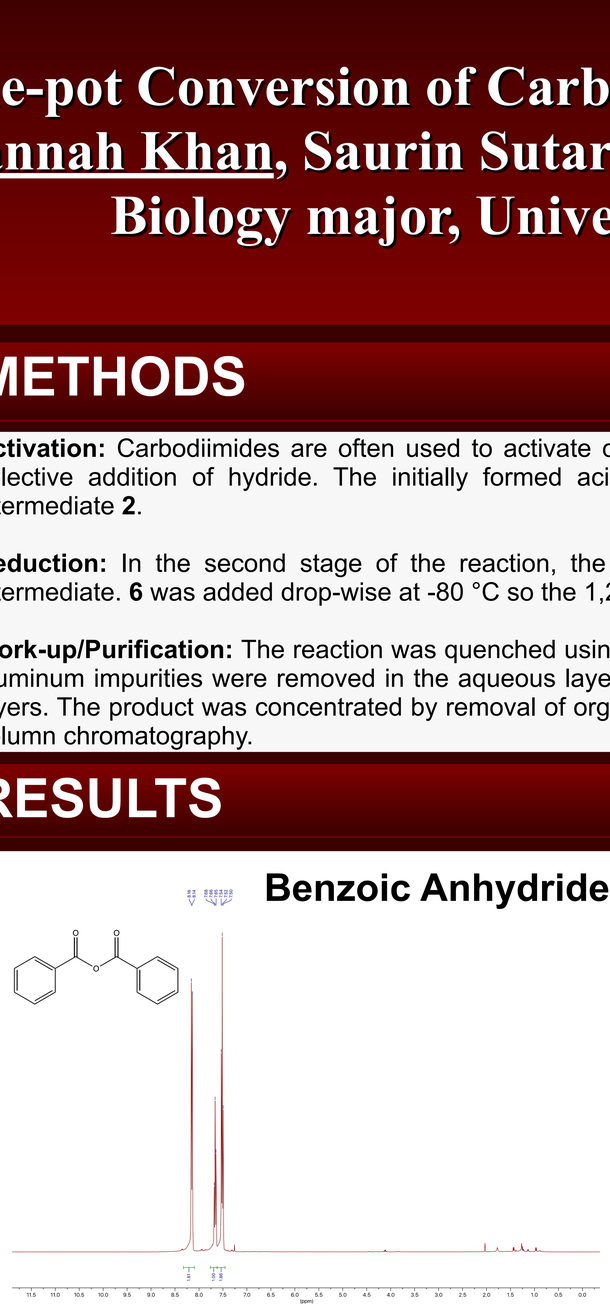


Figure 2. Crude ^{1}H NMR (400 MHz, $CDCl_3$) of side product after DIC addition

Benzoic Intermediate

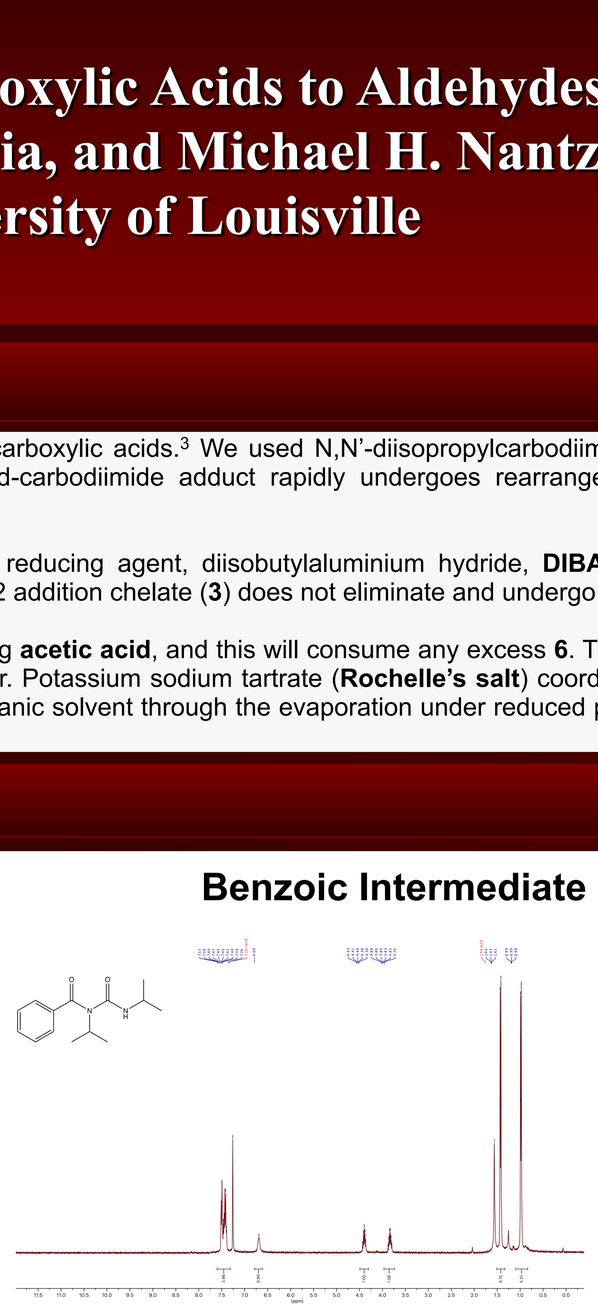


Figure 3. Crude ^{1}H NMR (400 MHz, $CDCl_3$) of product after DIC addition

Benzaldehyde

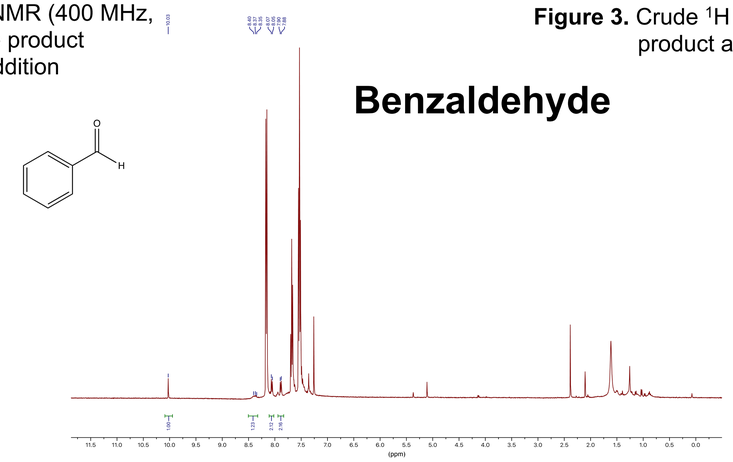


Figure 4. Crude ^{1}H NMR (400 MHz, $CDCl_3$) of the product obtained on work-up of the one-pot reduction of benzoic acid using the DIC/DIBAl-H protocol

CONCLUSION

The reduction of benzoic acid using the one-pot DIC/DIBAl-H method did not proceed as well as the reduction of muconic acid to muconaldehyde. In the benzoic acid activation step, benzoic anhydride (Figure 2) was formed in addition to the expected N-acylurea intermediate (Figure 3). Several experimental conditions were examined to prevent anhydride formation including varying the reaction temperature over a wide range (0 to -70 °C). Unfortunately, anhydride formation still remains a challenge. The product benzaldehyde (Figure 4) was formed in a small amount after varying the conditions (addition of **6** at -80 °C, followed by raising the temperature to -60 °C and stirring 1 h). Further optimization is still needed for this approach to be considered a general, one-pot reduction method.

REFERENCES

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2. Sutaria, S. R.; Nantz, M. H. A Convenient Preparation of Muconaldehyde Using a One-Pot Acid-to-Aldehyde Reduction Protocol. Org. Prep. Proced. Int. 2021, 53, In Press.

3. J. Kuo, D. A. Swann and G. D. Prestwich, Bioconjugate Chem., 2, 232 (1991). doi:10.1021/ bc00010a007.

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