

Quantitation of reaction results for DPDS-mediated amide reductions

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BACKGROUND

Traditional transformations of amides to amines use aluminum or boron hydrides, which require complicated and expensive purification and produce hazardous waste. However, more selective, efficient, and environmentally friendly methods of reducing amides to amines are highly desired in industry¹, and a better understanding of reaction kinetics of these reductions is crucial to optimizing these processes. Methodologies of chemoselective, green amide reductions have been published recently by several groups, but the kinetics of these reactions are not well understood, reflecting a need for this type of research. While the research done by the Aldrich group in the Medicinal Chemistry department at the University of Minnesota Twin Cities is comprised largely of the synthesis and analysis of new chemical entities for the eradication of *M. tuberculosis*, the development of novel reactions enables the design of efficient synthetic campaigns to achieve these goals.

OBJECTIVES

Previous work done by researchers in the Aldrich group² explored silane-mediated reductions of phosphine oxides, and the kinetics of the reaction were studied using analytical NMR methods to determine the mechanistic underpinnings of the reaction. The culmination of this work resulted in the discovery of a novel silane reducing agent, 1,3-diphenyldisiloxane (DPDS), which can be combined with a zinc catalyst to transform amides to amines. This reaction presents unparalleled reactivity, allowing for the reduction of primary, secondary, and tertiary amides selectively based on the temperature of the reaction. This project aims to collaborate with a graduate student researcher in the Aldrich group to progress this methodology during an optimization campaign, which includes conducting a thorough analysis of its kinetics.

To begin, in this project, a tertiary amide was synthesized to conduct preliminary analyses and develop quantitation methods in high-performance liquid chromatography (HP-LC) and mass spectrometry (MS) instruments. The reaction scheme of the silane-mediated reduction studied is shown below.

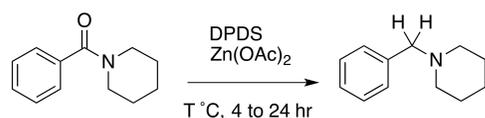


Figure 1. Scheme of reduction.

METHODS

LC-MS analysis methods were developed and optimized on instrumentation owned by the Aldrich group for these purposes. Calibration curves were constructed by preparing samples of the amide starting material and the amine product. In order to ensure that no remaining DPDS or Zn(OAc)_2 are contaminating the LC column, a brief work-up procedure was developed as part of the sample preparation process. Samples of both starting material and product were prepared in duplicate at seven different concentrations. After running the LC-MS method, data was collected and analyzed to construct the curves below.

Calibration curve of 254 nm analyte trace vs. amide concentration (averaged)

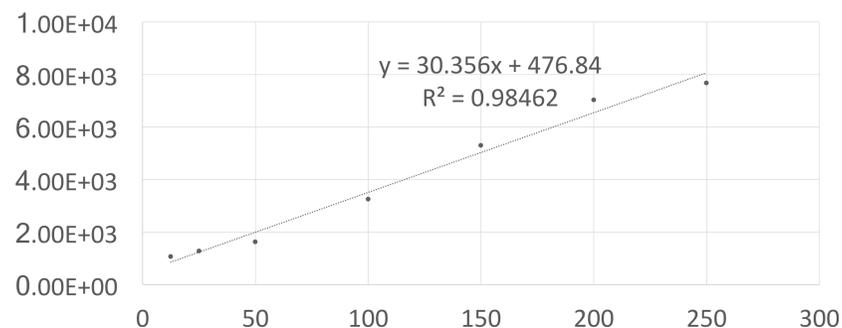


Figure 2. Calibration curve of 254 nm analyte trace vs. amide concentration.

Using the best-fit linear trendline added by Excel to the graph, the concentration of starting material amide in a sample run on the LC-MS instrument can be determined. Additionally, because the R^2 value is 0.99, the linearity and fit of the data are valid.

Calibration curve of MS analyte trace vs. amine concentration (averaged)

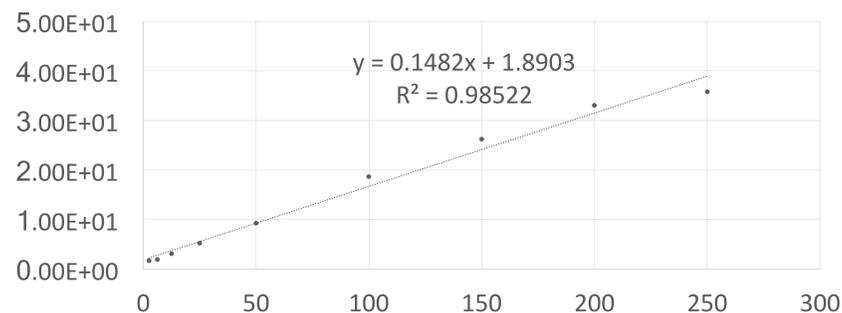


Figure 3. Calibration curve of MS analyte trace vs. amine concentration.

Similarly, the best-fit linear trendline added by Excel to the graph can be used to determine the concentration of starting material amide in a sample run on the LC-MS instrument. Additionally, because the R^2 value is 0.99, the linearity and fit of the data are valid.

FUTURE DIRECTIONS

Researchers in the Aldrich group are also working on determining the rate constant of this silane-mediated amide reduction. In general, first-order reaction kinetics obey the equation $rate = k [I]$, where k is the rate constant and $[I]$ is the concentration of substrate I in the reaction³. The rate constant k can be determined by plotting the changes in concentration of substrate I over time. To determine the concentrations of substrate and product, the calibration curves are used to relate instrument signal to concentration. These calibration curves were constructed using the tertiary amide and amine shown in Figure 1 to the left.

Three different experiments will be conducted. First, the temperature at which the reaction depicted in Figure 1 is conducted will be varied systematically in order to construct an Arrhenius plot for this reduction and determine the value of the activation energy E_a of the catalyst. Second, using the reagents in Figure 1, concentrations of the silane reducing agent will be varied throughout reactions and the substrate concentrations will be plotted against time for each reaction to determine whether the reduction behaves as a first order reaction with respect to the amide substrate. Finally, various withdrawing and donating functional groups will be installed on the aromatic ring of the amide substrate to construct a Hammett plot, and thus probe the requirements for reactivity in this reduction scheme.

In the process of constructing the Hammett plot, several different tertiary amide substrates will be synthesized and reduced using the system analyzed in this project. Yields from these reductions will also be reported, as they give valuable insight to the reactivity of this silane reducing agent.

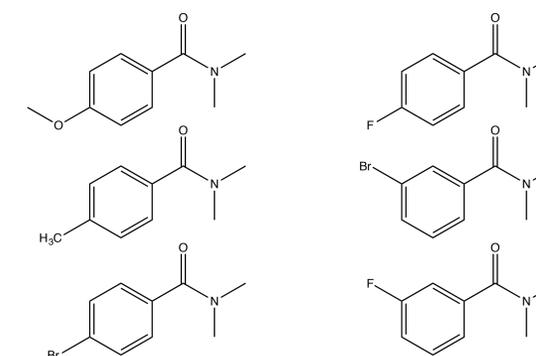


Figure 4. Substrates to be synthesized and reduced for Hammett plot and yields.

REFERENCES

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