Supporting Information

Accelerated Formation of Trioximes through Confined Volume Reactors and Scale-up using Thin Film Methods

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Table of Contents

Experimental

Cylcohexane-1,3,5-trione trioxime synthesis:

Phloroglucinol, hydroxylamine solution (50% wt in H_2O), and methanol were purchased from Sigma Aldrich (St. Louis, MO). Traditional synthesis to form cyclohexane-1,3,5-trione trioxime using the procedure described by Bottaro et. al. was performed to obtain pure product for comparative analysis.[1] Briefly, phloroglucinol (~8 g) was added to hydroxylamine (29.2 g) and allowed to stand at room temperature for 1 hour. The solution was gently agitated then set at room temperature for another 2 hours. The product was filtered, washed with water, and then dried.

Phloroglucinol (~0.02 g) was added to 60 µL hydroxylamine and 1 mL methanol. This reaction mixture was used for all accelerated methods and the respective bulk reactions (500 µL each), except the electrospinner and rotavap thin film techniques. The reaction mixture for the electrospinner reactions consisted of ~0.1 g phloroglucinol, 600 µL hydroxylamine, and 9.4 mL of methanol. Methanol was added to improve desolvation of the microdroplets formed using these techniques. The reaction mixture for the rotavap reactions consisted of ~1 g phloroglucinol and 6.5 mL hydroxylamine. The bulk for the rotavap contained ~0.02 g phloroglucinol and 1 mL of hydroxylamine. Accelerated methods were directly compared to their corresponding bulk reactions prepared under the same conditions.

Easy ambient sonic-spray ionization (EASI) and Electrosonic spray ionization (ESSI)

A custom ESI source previously described in Brown et al.[2] was used to generate microdroplets for both EASI and ESSI techniques. The reaction mixture (250 µL) was pushed through a silica capillary at 50 µL/min (PHD Ultra syringe pump; Harvard Apparatus; Holliston, MA) for the preset reaction time, 5 minutes. EASI droplets are generated after desolvation gas is applied, whereas ESSI both desolvation gas and high voltage are applied. Nitrogen sheath gas (100 psi) was used for desolvation. High voltage (4 kV) for ESSI experiments was applied to the syringe needle from an external power supply (Spellman Bertan; Model 205B-10R; Hauppauge, NY). The reaction mixture was sprayed into a 15 mL conical tube (Falcon, Fisher Scientific, Waltham, MA) for 5 minutes and product was collected on glass wool inside the tube (spray distance 7.5 cm). The product was extracted from the glass wool using 2 mL of methanol. The bulk reaction mixture (250 µL) reacted in a glass vial for the same reaction time and then was added to 1.75 mL of methanol for mass spectrometry analysis.

Nano-electrospray ionization (nESI)

A custom nano-electrospray (nESI) previously described in Brown et al.[2] was used to generate microdroplets for nESI. The reaction mixture (125 µL) was pushed through a silica capillary at 25 µL/min for the preset reaction time, 5 minutes. nESI droplets are generated after high voltage is applied. High voltage (3.5 kV) for nESI experiments was applied to a conductive wire wrapped around the emitter from an external power supply. The reaction mixture was sprayed onto glass wool (spray distance 3.5 cm) atop a stainless-steel L-bracket that was electrically grounded. The product was extracted from the glass wool using 2 mL of methanol. The bulk reaction mixture (125 µL) reacted in a glass vial for the same reaction time and then was added to 1.875 mL of methanol for mass spectrometry analysis.

Paper Spray Ionization (PSI)

PPG Teslin® SP600 substrate (Monroeville, PA) was used for all paper spray experiments. A ring stand and a copper clip were used to hold the Teslin® substrate in front of the mass spectrometer. The copper clip is also attached to the instrument's high voltage supply. The reaction mixture was prepped in a glass vial, and a 10 µL aliquot was spotted onto the tip of the paper substrate. The spot was allowed to dry on the paper for 5 minutes, while the corresponding bulk reacted in the glass vial for the same amount of time. Once dry, the paper was positioned in front of the mass spectrometer inlet to be analyzed. Methanol (60 µL) and high voltage (4kV) were applied to create the spray plume. For the bulk reaction, after the reaction mixture react in the vial, 10 µL was spotted on the substrate but not allowed to dry. Methanol and high voltage were applied immediately after spotting. Once the spray was formed, spectra were collected for each reaction condition.

Leidenfrost (LF)

For the Leidenfrost experiments, a glass spot plate (Pyrex, 7220-85; Corning Inc.; Corning, NY) was heated to 540°C on a hot plate (Fisher Isotemp; Fisher Scientific; Waltham, MA). The initial droplet was formed by adding the reaction mixture (500 µL) dropwise to a single well. Methanol was constantly supplied (2.5 mL syringe, 180 µL/min) to the well

to replenish evaporated solvent and maintain the droplet for 5 minutes. After the reaction, the droplet was collected from the well and added to 2 mL of methanol. Bulk reaction mixtures (500 µL) were refluxed for 5 minutes at 200°C. The resulting solution was then added to 2 mL of methanol.

Electrospinner

A Nanon-01A Electrospinning System (MECC Co., LTD. Fukuoka, Japan) was used to deposit the reaction mixture onto Teslin paper substrate. The reaction solution was added to a disposable syringe and infused at 3 mL/hr. Teflon tubing was fed from the syringe and connected to a 27-gauge needle. High voltage (5 kV) was applied to the needle to initiate the spray. Strips of Teslin paper were taped to the spinning drum to collect product during the 5-minute reaction time. **Figure S1** shows the Teslin paper on the drum with the product visible due to the color change of the reaction (clear to yellow solution). The spray distance between the needle and the drum was 50 mm. The drum's rotational speed was set to 100 rpm.

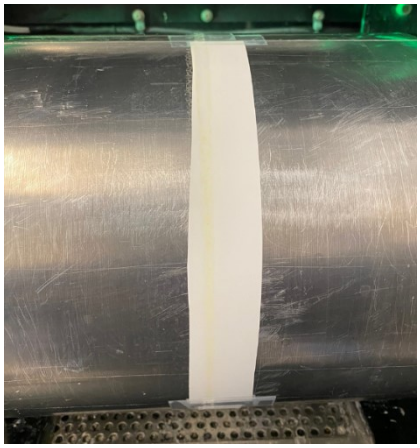

Figure S1. Teslin paper taped to rotating drum inside the electrospinner. After the 5-minute reaction time a visible line of product (yellow) is seen on the surface of the paper.

Rotary Evaporator (Rotavap)

Phloroglucinol and hydroxylamine were added to a 250 mL round-bottom flask (Corning Pyrex, Corning, NY). The reaction mixture was swirled several times to mix the phloroglucinol and hydroxylamine (milky white mixture, see **Figure S2** below). The round-bottom flask was attached to the bump trap on a R-300 Rotavapor (Buchi, New Castle, DE). The water bath was set to 45°C. The rotational speed was set to 225 rpm. After 5 minutes under vacuum pressure (20 in. Hg; PTFE diaphragm pump; Chemglass Scientific Apparatus; Vineland, NJ) and removing solvent, the product remaining in the round-bottom flask was removed. A 100 µL aliquot was removed and added to 1 mL of methanol for MS analysis. The bulk was sampled in the same way. The remaining

Figure S2. Reaction mixture in the round-bottom flask attached to the bump trap of the rotavap. The flask was submerged in a water bath set to 45°C. Initially the solution is milky white (shown in the picture) but is a clear brown solution after the 5-minute reaction time.

product was rinsed with water, vacuum filtered and then dried in a vacuum oven overnight at 65°C. TLC, FTIR, and NMR were performed to characterize the rotavap product and compare it to the traditionally synthesized product.

Thin Layer Chromatography (TLC)

The rotavap product, traditional product, and starting material were analyzed by TLC. Each solid was dissolved in isopropanol (IPA) then spotted on the silica gel TLC plate. Toluene-IPA 1:1 was used the mobile phase solvent. Each plate was developed using I_2 vapors. The resulting spots are shown in **Figure S4**.

Fourier-Transform Infrared Spectroscopy (FTIR)

The rotavap and traditionally synthesized products were analyzed on a Thermo Nicolet 6700 FTIR Spectrometer (Thermo Fisher Scientific; Waltham, MA) equipped with a single-bounce germanium internal reflective element (IRE), a liquid N_2 cooled MCTA detector, and Omnic software. The spectrum is averaged over 32 scans with 4 cm^{-1} resolution. Background subtraction and baseline correction were applied.

Nuclear Magnetic Resonance (NMR)

All NMR spectra of the rotavap and traditional synthesis products were obtained using a 500 MHz Bruker Avance HD-III NMR spectrometer (Billerica, MA) at room temperature. The samples were dissolved in and all spectra were referenced to d6-DMSO. The ^{1}H NMR spectra were obtained using a 30-degree pulse with 8 transients and 2 sec. relaxation delay. The ^{1}H-decoupled ^{13}C NMR spectra were obtained using a 30-degree ^{13}C pulse and 2 sec. relaxation delay.

Mass Spectrometry

A Thermo LTQ mass spectrometer (Waltham, MA) was used for all mass spectrometry analysis. The front-end of the instrument was modified to allow for ambient ionization sources to be used. The product collected from each experiment were analyzed using nanospray ionization (Warner Instruments electrode holder, ESW-M15P 64-1017, Holliston, MA) except for the reactions deposited onto paper. Product from PSI thin films and the electrospinner reactions were analyzed by MS directly from the paper described above. Spectra were collected in full scan, positive ionization mode. High voltage (2.5 kV nanospray, 4 kV PSI) was supplied from the instrument and the capillary temperature was set to 300°C.

Calculation of Apparent Acceleration Factor

Apparent acceleration factors (AAF) were calculated to determine the degree of acceleration that occurred and compare across confined-volume techniques. The intensity of the starting material and product were obtained from the average spectra for both the confined-volume system and the bulk reaction. AAF were calculated using **Equation S1** below. Each reaction was analyzed in triplicate and average AAFs were calculated (**Table 1**).

*Equation S1.*Formula for calculating apparent acceleration factors (AAF). Signal intensity comes from averaged mass spectra.

$$AAF = \frac{\left(\frac{\text{Product Intensity}}{\text{Reactant Intensity}}\right)_{droplet}}{\left(\frac{\text{Product Intensity}}{\text{Reactant Intensity}}\right)_{bulk}} = \frac{\left(\frac{P}{R}\right)_{droplet}}{\left(\frac{P}{R}\right)_{bulk}}$$

Calculation of Conversion Ratio

Conversion ratios (CR) were calculated for both confined-volume systems and the bulk reactions to estimate the yield. The ratio accounts for intermediates as well as the starting material and product. CR were calculated for each reaction using **Equation S2** below. Each reaction was analyzed in triplicate and the average CR are reported in **Table 1**. Note: these values are estimated values of the yield and do not correct for differences in ionization efficiency.

Equation S2. Formula for calculating conversion ratios (CR). Signal intensity comes from average mass spectra.

$$CR = \frac{\text{Product Intensity}}{(Reactant\ Intensity + Intermediate\ Intensity + Product\ Intensity)} = \frac{P}{(R + I + P)}$$

Supplemental Figures

Accelerated Techniques vs Bulk Mass Spectra

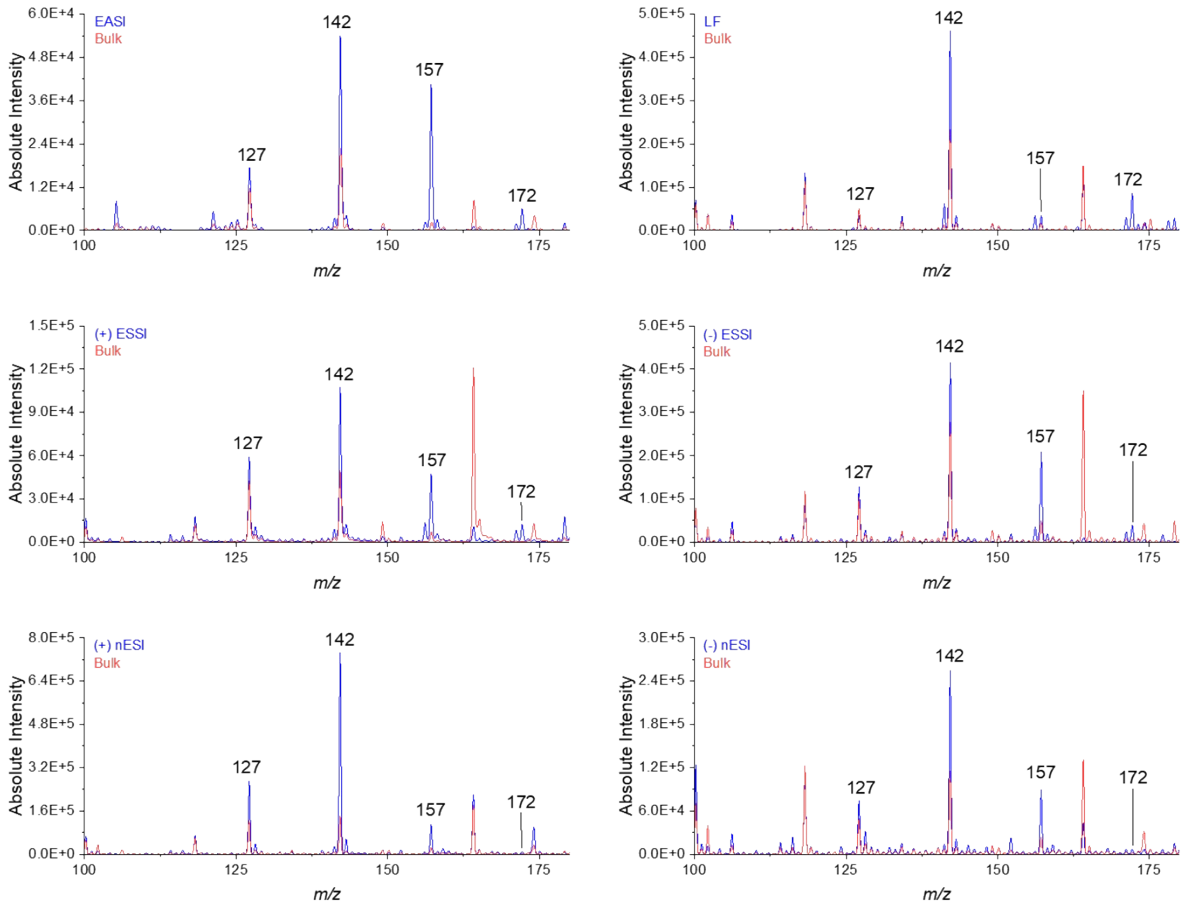

Figure S3. Overlaid spectra comparing each accelerated method (blue) to their respective bulk reaction (red) for reaction step 1. Includes the spray-based confined-volume techniques (EASI, ESSI, nESI) and Leidenfrost. Phloroglucinol, starting material, is observed at *m/z* 127, two intermediates 3,5-dihydroxycyclohexa-2,4-dien-1-one oxime (*m/z* 142) and 5-hydroxycyclohex-4-ene-1,3-dione dioxime (*m/z* 157), and the trioxime product at *m/z* 172.

TLC: Rotavap Product vs. Traditional Product and Starting Material

Figure S4. Picture of TLC plate results. (A) Traditionally prepared trioxime product (left) compared to the trioxime product formed in the rotavap (right). (B) Starting material, phloroglucinol (left), compared to the trioxime product formed in the rotavap (right).

FTIR: Rotavap vs. Traditional Product

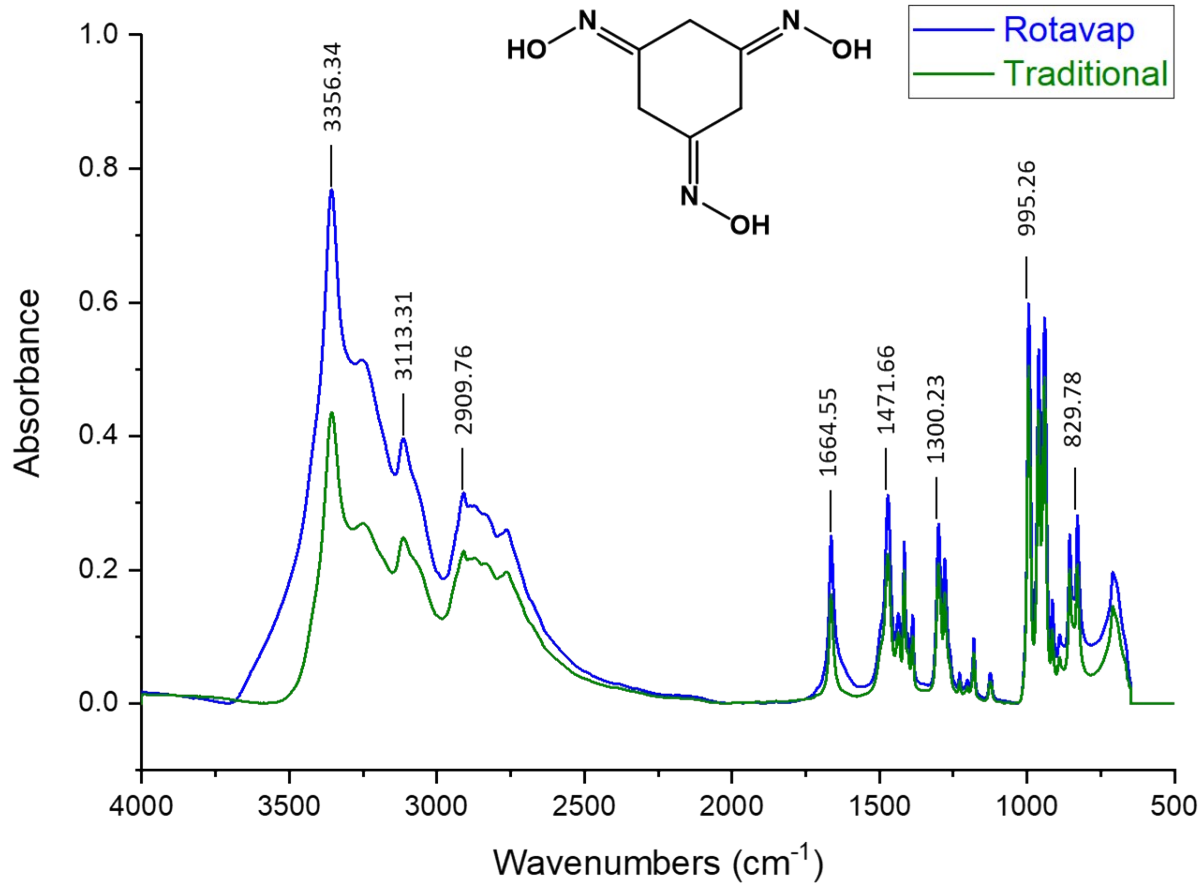

Figure S5. FTIR spectra comparing the traditionally made trioxime product (green) to the trioxime product made in the rotavap (blue). Indicative peaks include 3356 cm^{-1} corresponding to the O-H stretch, 2909 cm^{-1} corresponding to the C-H stretch, and 1664 cm^{-1} for the C=N stretch.

Proton NMR: Rotavap vs. Traditional Product

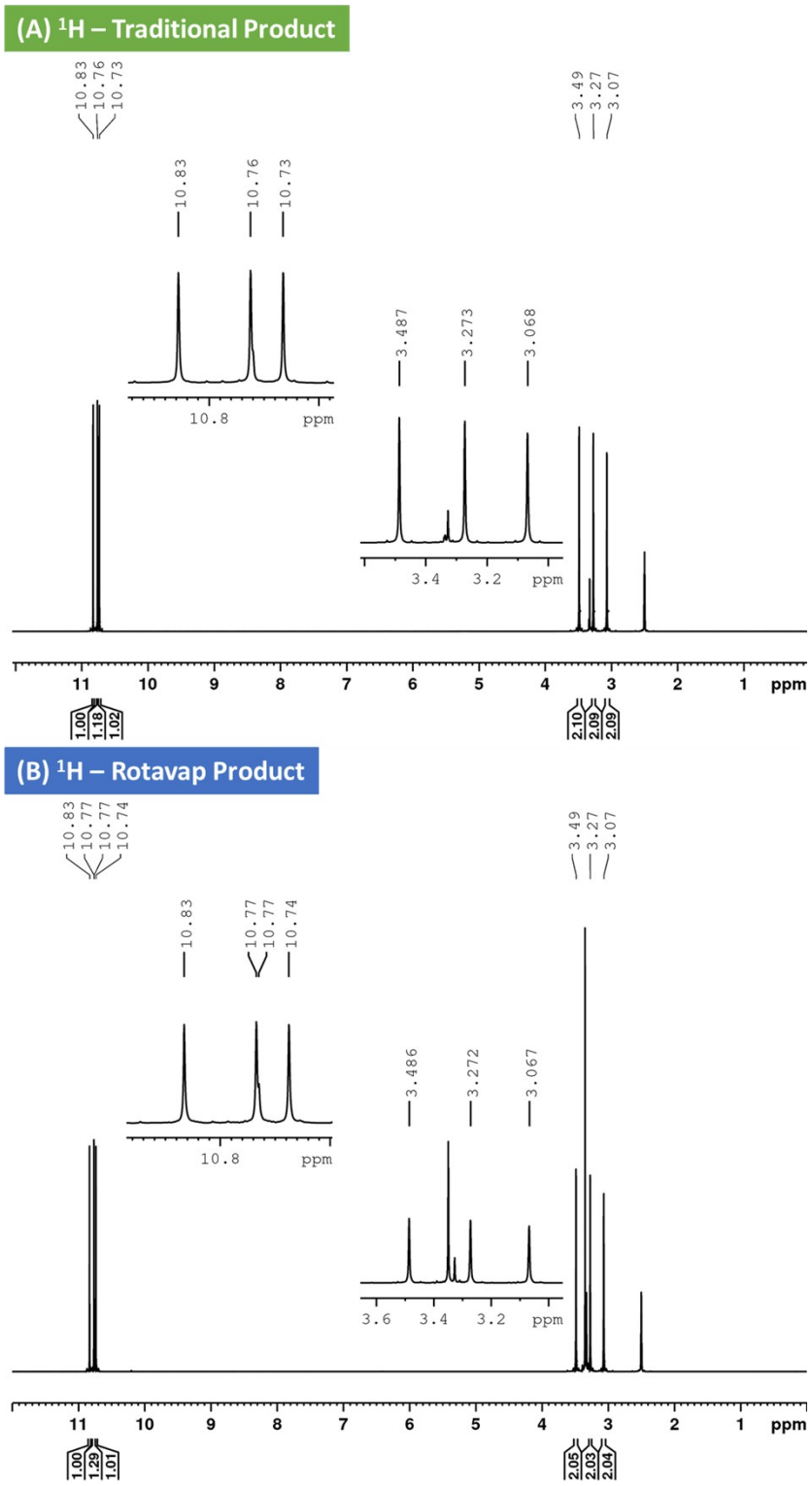

Figure S6. Proton NMR spectra comparing the traditionally synthesized product (A) to the product synthesized in the rotavap (B). DMSO-d6 was used as the solvent in both spectra. Three peaks at 3.4, 3.2, and 3.0 ppm correspond to the aliphatic protons. Three peaks at 10.8, 10.77, and 10.74 ppm correspond to the oxime hydroxyl protons.

Proton NMR: Rotovap Product dried in Vacuum Oven

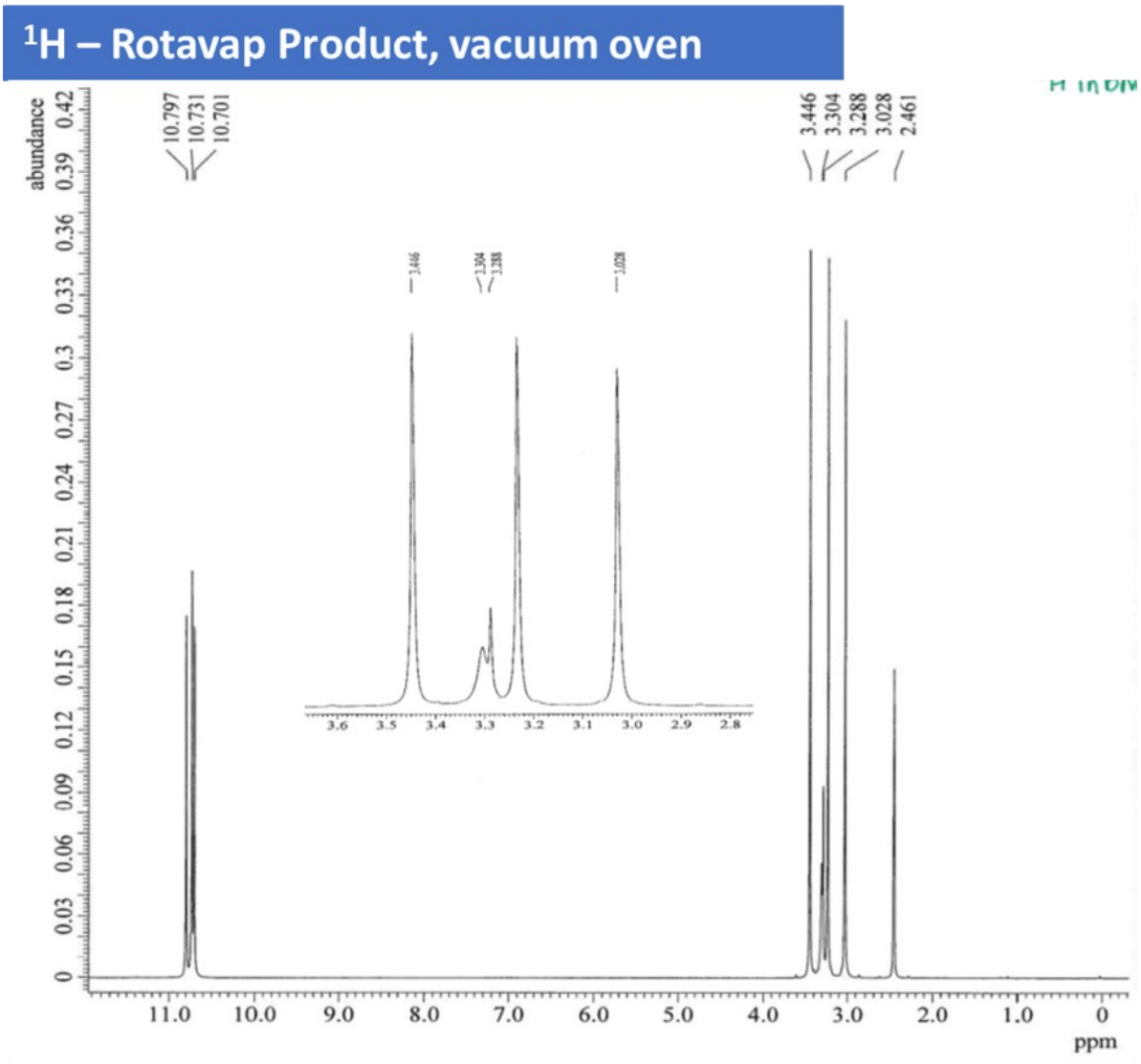

Figure S7. Proton NMR spectra of the product synthesized in the rotavap after being dried in a vacuum oven. DMSO-d6 was used as the solvent. Peak at ~3.3 ppm is reduced compared to previous ^{1}H NMR before being dried completely.

Carbon NMR: Rotavap vs. Traditional Product

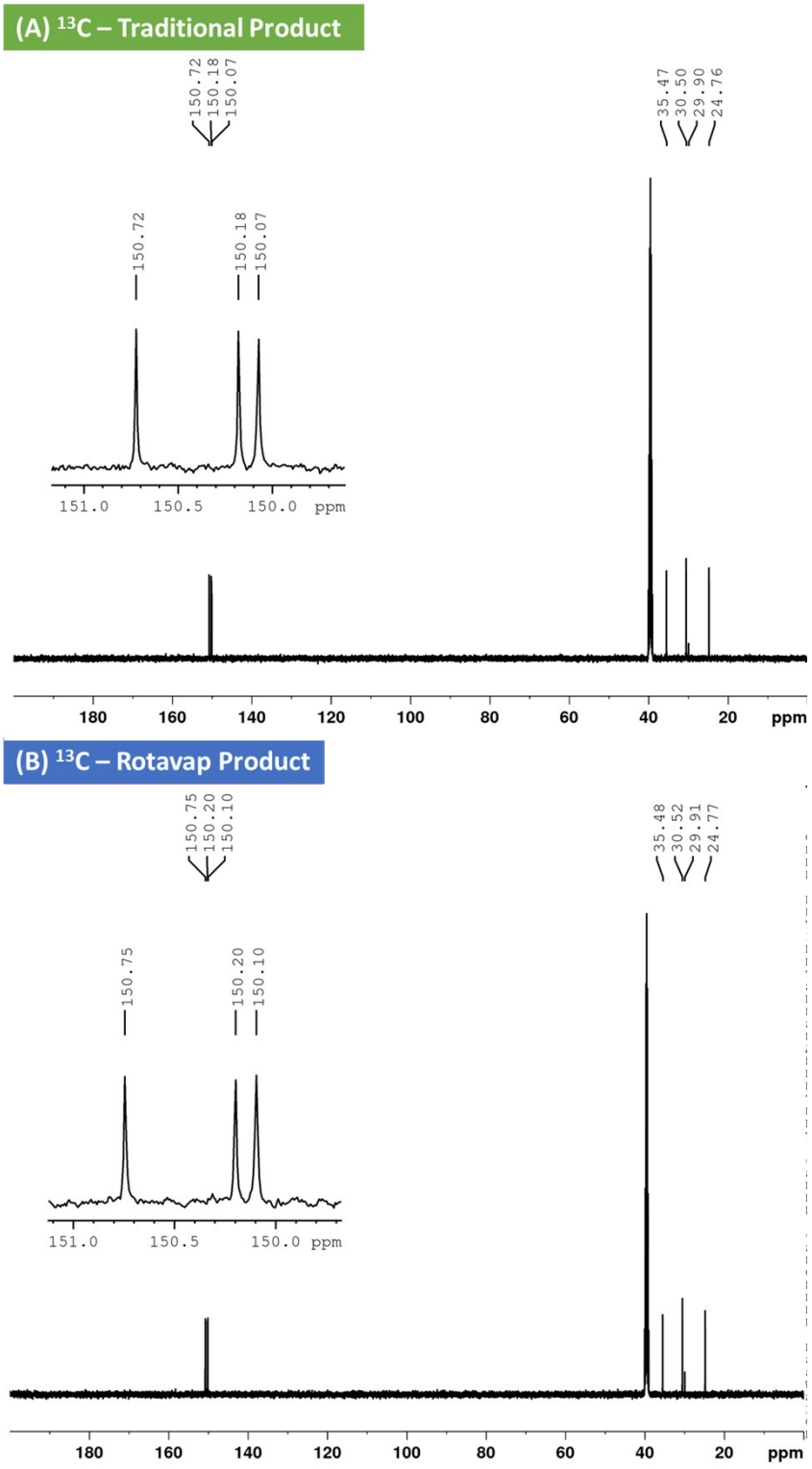

Figure S8. Carbon NMR spectra comparing the traditionally synthesized product (A) to the product synthesized in the rotavap (B). DMSO-d6 was used as the solvent in both spectra. Three peaks around 30 ppm correspond to the aliphatic carbons. Three peaks around 150 ppm correspond to the oxime carbon (C=N).

References

[1] J. C. Bottaro, R. Malhotra, A. Dodge, *Synthesis* **2004**, *2004*, 499-500.
[2] H. M. Brown, K. R. Doppalapudi, P. W. Fedick, *Scientific Reports* **2021**, *11*, 24093.